TARGETS IN HETEROCYCLIC SYSTEMS

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Preface

This book is dedicated to the memory of our friend Carlo Dell'Erba

(Ω November 12, 2005)

Heterocyclic derivatives are important in organic chemistry as products (including natural) and/or useful tools in the construction of more complicated molecular entities. Their utilization in polymeric, medicinal and agricultural chemistry is widely documented. Both dyestuff structures and life molecules frequently involve heterocyclic rings that play an important role in several biochemical processes.

Volume 10 (2006) keeps the international standard of THS series and contains fifteen chapters, covering the synthesis, reactivity, activity (including medicinal) and mass spectrometry of different heterorings. Authors from Brazil, Egypt, France, Germany, Italy, Poland, Portugal, Russia, and Switzerland are present in this book.

Comprehensive Reviews reporting the overall state of the art on wide fields as well as personal Accounts highlighting significative advances by research groups dealing with their specific themes have been solicited from leading Authors. The submission of articles having the above-mentioned aims and concerning highly specialistic topics is strongly urged. The publication of Chapters in THS is free of charge. Firstly, a brief layout of the contribution proposed, and then the subsequent manuscript, may be forwarded either to a Member of the Editorial Board or to one of the Editors.

The Authors, who contributed most competently to the realization of this Volume, and the Referees, who cooperated unselfishly (often with great patience) spending valuable attention and time in the review of the manuscripts, are gratefully acknowledged.

The Editors thank very much Dr. Lucia De Crescentini for her precious help in the editorial revision of the book.

Orazio A. Attanasi and Domenico Spinelli

Editors

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2,3-DINITRO-1,3-BUTADIENES: VERSATILE BUILDING-BLOCKS FROM THE RING OPENING OF 3,4-DINITROTHIOPHENE

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Dedicated to the memory of Carlo Dell'Erba, Angelo Mugnoli and Marino Novi: teachers, colleagues and friends, without whose contribution this review would have never been written.

Abstract. *Since its discovery in 1968, the ring opening of 3,4-dinitrothiophene (**1**) with amines has represented the first step in a number of valuable synthetic pathways. As a matter of fact, the dinitrobutadienediamines (**7** or **8**) which smoothly form in ethanol at room temperature as a result of a clear example of the non-benzenoid behaviour of **1**, are highly-functionalized unsaturated systems whose versatility as building-blocks has so far been exploited for the preparation of linear as well as of homo- and hetero-cyclic molecules. In particular, target heterocycles encompass pyrroles, pyrrolidines, isoxazolines, isoxazoles, oxadiazoles, triazoles: i.e. systems endowed with high potentialities both in synthesis and in pharmacology.*

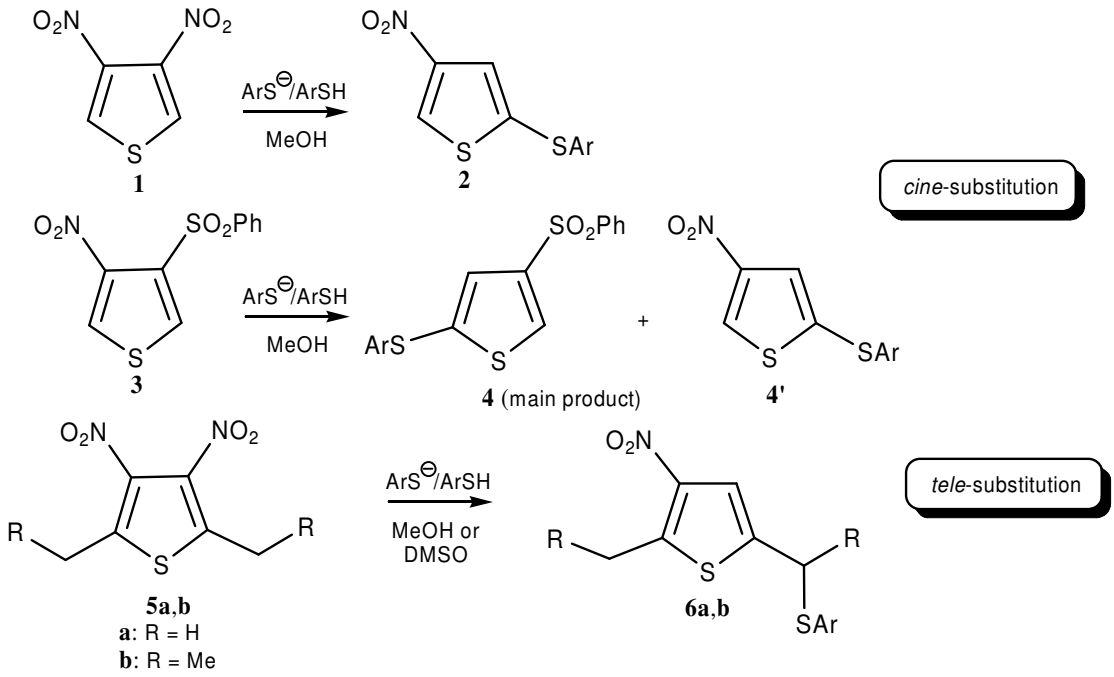
Contents

1. Introduction

The relatively low aromaticity degree of thiophene [testified by a resonance energy which lags significantly behind that of benzene (24-29 *vs.* 36 Kcal/mol)] and the π-electron-density distribution within the ring [determining an enhanced double-bond character for the C(2)-C(3) and C(4)-C(5) bonds (hyper-*ortho* relation) and, conversely, a marked single-bond character for the C(3)-C(4) bond (hypo-*ortho* relation)], are responsible for a number of appealing reactivity outcomes which have no counterpart in the benzene chemistry.[1]

An older classical example of such "non-benzenoid" behaviour is represented by the reductive cleavage with *e.g.* nickel-Raney.[2] Moreover the preliminary oxidation of sulfur to sulfur dioxide has in turn been reported to further weaken the C-S bonds, favouring their subsequent breakage in a number of synthetically useful processes.[3]

More recently, non-conventional nucleophilic substitutions[4] for the reactions of sulfur nucleophiles with 3,4-dinitro- (3,4-DNT, **1**)[4a,b] and 3-nitro-4-(phenylsulfonyl)thiophene (**3**) (*cine*-substitutions),[4c] or with 2,5-dialkyl-3,4-dinitrothiophenes (**5**) (*tele*-substitutions)[4d] (Scheme 1), have been reported from our laboratories.



Scheme 1

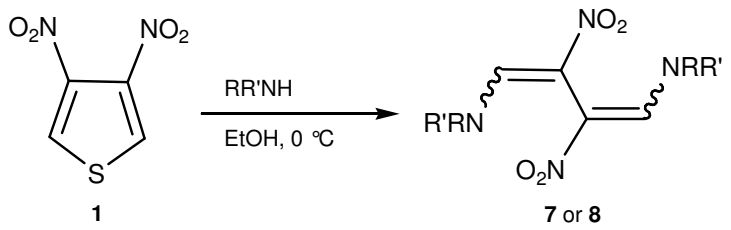
2. Ring opening of 3,4-dinitrothiophene to 2,3-dinitro-1,3-butadiene-1,4-diamines

Contemporaneously with the first report on its *cine*-substitution cited above,[4a] 3,4-DNT was also found[4a,5] to react smoothly with excess primary or secondary amines in EtOH at 0 °C to provide the 2,3-dinitro-1,3-butadiene-1,4-diamines **7** and **8** respectively (Scheme 2): such derivatives, whose most valuable aspect is the presence of two conjugated nitroenaminic moieties, promised to be useful synthetic fragments.

Accordingly, since its discovery in 1968,[4a] the reaction, which represents a clear example of the non-benzenoid character of nitrothiophenes, has been deeply investigated by our group in order to simplify the experimental procedures and to optimize the yields in the ring-opening products.[6]

The most convenient experimental conditions were eventually identified in the treatment of a suspension of the substrate in ethanol with a little excess of the amine (2.2 mol equiv.).[6a] The reaction

proceeds with hydrogen sulfide evolution, and, after completion, the insoluble dinitrobutadienediamine **7** or **8** can be simply collected by filtration in usually satisfactory yields.



1 **7** or **8**

7: R = H, R' = alkyl or aryl: av. yield 85%
8: R = R' = alkyl or R, R' = -$(CH_2)_n$- (n = 4, 5): av. yield 68%

Scheme 2

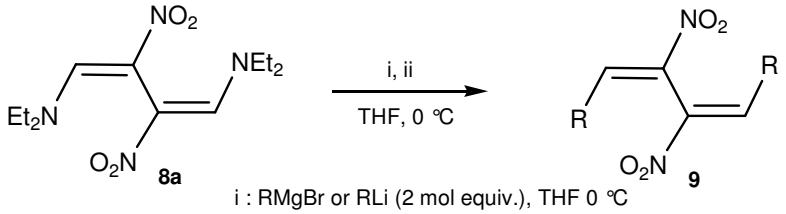
As far as the stereochemistry of the ring opening is concerned, while the NMR analysis invariably showed an (*E,E*) configuration for **8**, compounds **7** displayed in solution an equilibrium among the three configurational isomers (*E,E*), (*E,Z*), and (*Z,Z*); in particular, the (*Z,Z*) isomers predominate in chloroform, where intramolecular hydrogen bonding between NH and the nearest nitrogroup provides stabilization, while in DMSO, a more polar and hydrogen-bond-accepting solvent, the (*E,E*) isomers are largely favoured.[6b]

Compounds **8** show, in particular, the very interesting structural feature represented by the presence of two adjacent tertiary nitroenaminic functionalities. They are well known to possess wide synthetic potentialities,[7,8] *e.g.* as far as their reactivity with carbon nucleophiles is concerned,[8] and it was our interest to verify whether and to what extent compounds **8** would display the typical reactivity of monofunctional nitroenamines.

3. Access to 1,4-dialkyl- or 1,4-diaryl-2,3-dinitro-1,3-butadienes

3.1. Reaction of 2,3-dinitro-1,3-butadiene-1,4-diamines with alkyl or aryl Grignard reagents

At first, an investigation on the reaction of compounds **8** with carbon nucleophiles such as Grignard and/or organolithium reagents has been performed,[6,9] using the bis(diethylamino) derivative **8a** as the model substrate, as it resulted to be the best compromise between easy accessibility and reactivity towards organometals. The treatment of **8a** with two molar equivalents of an organometal in THF, followed by acidic quenching, furnishes the results collected in Table 1, thus fulfilling our expectations and proving to represent an excellent access to the 1,4-dialkyl- and 1,4-diaryl-2,3-dinitro-1,3-butadienes **9** (Scheme 3).



8a **9**

i : RMgBr or RLi (2 mol equiv.), THF 0 °C
ii : ice-3% HCl quench

Scheme 3

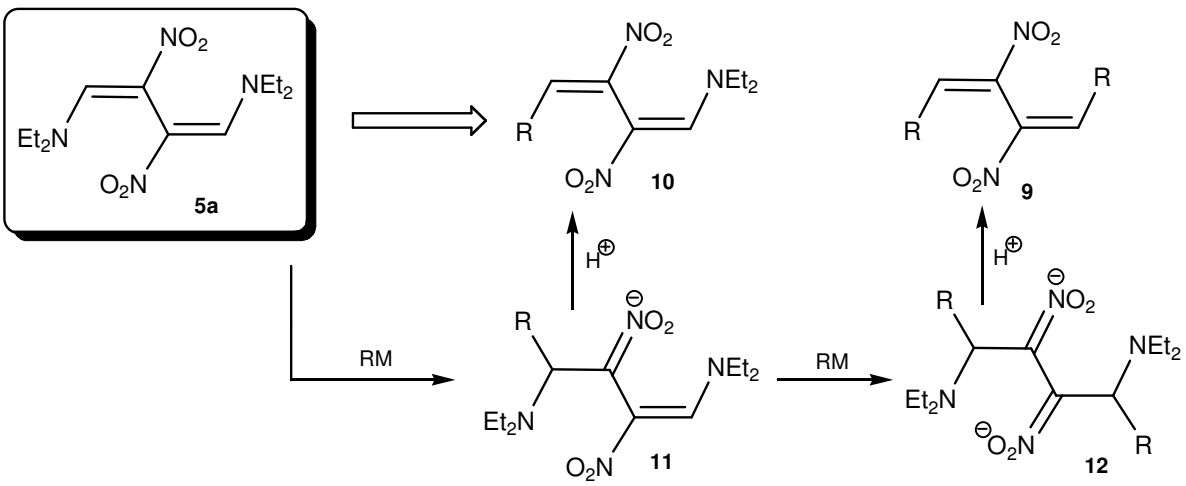
As far as the stereochemistry of the products is concerned, the NMR analysis of the crude showed that the formation of (*E,E*) isomers is generally predominant. When extending the reaction to particular typologies of Grignard reagents (*e.g.* vinyl,[10] benzyl[11]) we observed peculiar behaviours, which will be discussed separately.

Table 1. Yields of **9** from the reactions of **8a** with RMgBr in THF at 0 °C (Scheme 3).

R	**9** (Yield %)
Phenyl	88[a]
1-Naphthyl	87
2-Thienyl	86[a]
2-MeC_6H_4	87
4-MeC_6H_4	95
4-$MeOC_6H_4$	90
3-ClC_6H_4	95
2,4,6-$Me_3C_6H_2$	35[b]
Me	73
Et	94
n-Bu	97[a]
sec-Bu	51[b]
Cyclohexyl	90

[a]Comparable yields were obtained using the corresponding organolithium reagent.
[b]The monosubstitution product **10** was also isolated (see further in the text).

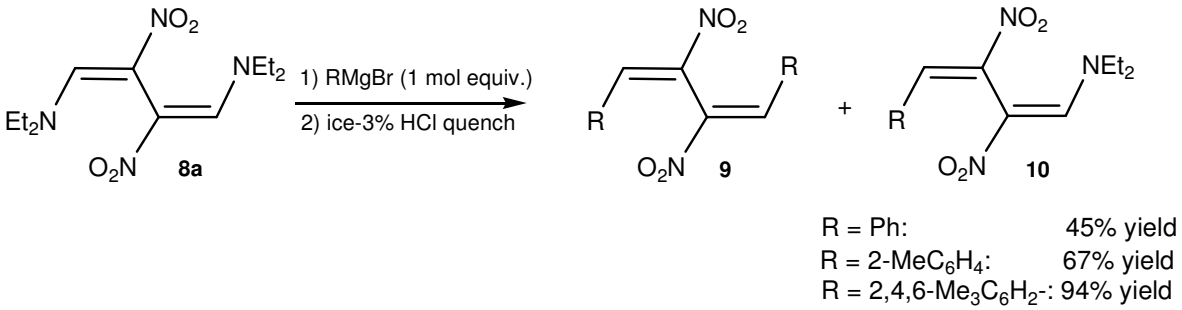
From the mechanistic point of view, in agreement with the behaviour of simple nitroenamines[7,8] the transformation of **8a** into the dinitrobutadienes **9** proceeds most likely through two successive 1,4-additions of the organometal to the nitroenamine moieties, followed by elimination of two diethylamine molecules after acidic quenching (Scheme 4). Accordingly, when **8a** was reacted with 1.1 equivalents of PhMgBr, the final reaction mixture contained, together with some unreacted substrate (30%), both **9a** (38%) and **10a** (31%), the latter evidently deriving from the intermediate mono-nitronate **11a**. On the grounds of the relative percentages above, it is possible to calculate a ratio of 0.8 between the rates of the first and of the second addition step.



Scheme 4

As compounds **10** are in turn of evident interest, possessing a nitroenaminic system coupled with a nitroalkene functionality, we investigated more in detail the possibility of obtaining the monosubstituted product by reaction with 1 mol equivalent both of alkyl and of aryl Grignard reagents.[9]

The results obtained are strongly dependent on the nature of the Grignard reagent employed: yields are not quite acceptable for R = alkyl (**10**: 16-25%), but become satisfactory for R = aryl (**10**: 43-94%). Furthermore, within the *series* of aryl substituted **10**, we observed a strong steric effect, as the relative yield of the monosubstitution product significantly increases when increasing the steric demand of the reagent (see yields in Scheme 5).



Scheme 5

The so obtained 4-aryl-2,3-dinitro-1,3-butadiene-1-diethylamines **10** (R = aryl) are easily converted into the asymmetrically-substituted 1,4-diaryl derivatives **13** (Figure 1) by reaction with a second, different Grignard reagent in a completely regioselective way.[9]

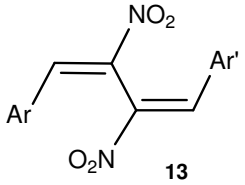


Figure 1

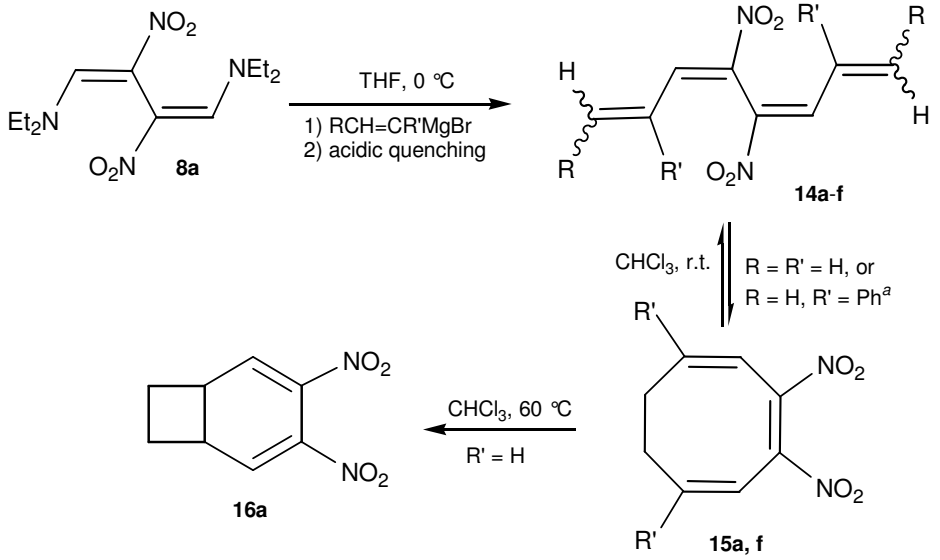
It is necessary to underline that it was found impossible to realize a similar sequence with alkyl Grignard reagents, because complex mixtures containing degradation and/or polimerization products are usually obtained.

3.2. Reaction of 2,3-dinitro-1,3-butadiene-1,4-diamines with vinyl Grignard reagents

The extension of the reactivity above to vinylic Grignard reagents has furnished likewise interesting and, in some cases, unexpected results (Scheme 6 and Table 2).[10] Actually, when **8a** was reacted with vinylmagnesium bromide in THF at 0 °C, the tetraene **14a** (R = R′ = H) could be isolated in satisfactory yields only by a careful work-up of the crude, as it is prone to mass polymerization above room temperature. Moreover, in chloroform solution at room temperature, **14a** slowly equilibrates, *via* an effective 8π-electrocyclization, with its cycloisomer **15a**, which in turn can be transformed, by gentle heating in the same solvent, into its valence tautomer bicyclooctadiene **16a** by a 6π-electrocyclization. All three compounds could be isolated and characterized.

The reaction was then applied to 2-substituted vinylmagnesium bromides, and good yields of the relevant 1,8-disubstituted-4,5-dinitro-1,3,5,7-octatetraene **14b-e** as diastereomeric mixtures were obtained in

every case (Table 2, entries 2-5): as a matter of fact, while the configurations of the C(3)-C(4) and C(5)-C(6) double bonds are completely retained (with respect to **8a**), those of the terminal double bonds depend on the extent of retention of the stereochemistry when preparing the Grignard reagent from the appropriate vinyl bromide. Anyway, the (*E,E,E,E*) stereoisomer has been isolated by chromatography as the main stereoisomer in all cases but one (entry 5). Interestingly enough, no cycloisomerization was observed for the tetraenes **14b-e**, bearing substituents at the terminal positions (R ≠ H).



[a]The tetraene **14f** could not be isolated.

Scheme 6

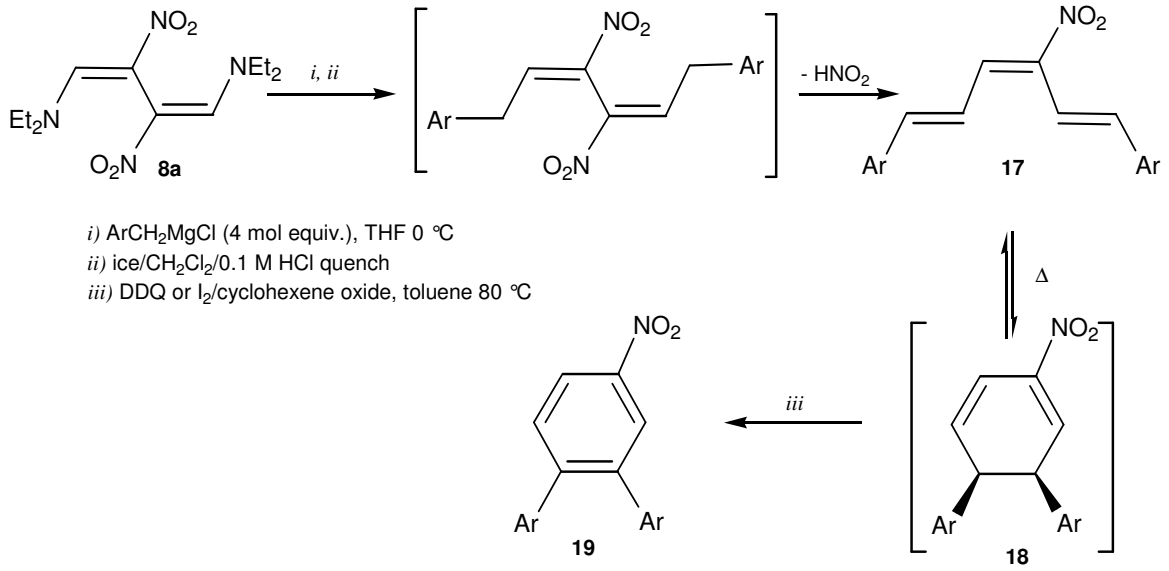
Table 2. Reactions of **8a** with vinyl Grignard reagents in THF at 0 °C (Scheme 6).

Entry	Grignard reagent from	Product (Yield %)	Diastereomeric ratio
1	CH_2=CHBr	**14a**: 47	*E,E*
2	PhCH=CHBr (*E*)/(*Z*) = 86:14	**14b**: 60	(*E,E,E,E*)/(*Z,E,E,E*) = 48:52
3	(*E*)-4-MeC_6H_4-CH=CHBr	**14c**: 84	(*E,E,E,E*)/(*Z,E,E,E*) = 70:30
4	(*E*)-4-MeOC_6H_4-CH=CHBr	**14d**: 86	(*E,E,E,E*)/(*Z,E,E,E*) = 83:17
5	(*Z*)-Me-CH=CH-Br	**14e**: 56	(*E,E,E,E*)/(*Z,E,E,Z*) = 36:64
6	CH_2=C(Ph)Br	**15f**: 69	-

A different behaviour was finally shown by the reaction of **8a** with 1-phenylvinylmagnesium bromide (Table 2, entry 6): actually in this case the only isolated product was the 3,4-dinitro-1,6-diphenyl-1,3,5-cyclooctatriene **15f**, probably originating by a fast cycloisomerization of the corresponding (never isolated) **14f**.

3.3. Reaction of 2,3-dinitro-1,3-butadiene-1,4-diamines with benzyl Grignard reagents

Within the context of the reactivity of **8a** with organometallic reagents, another peculiar behaviour was observed in its reaction with benzyl Grignard reagents.[11] Actually compounds like **9** (R = benzyl), *i.e.* the expected substitution products, were never detected, while the isolated products were the nitrotrienes **17**, conceivably due to fast HNO_2 elimination from the relevant dibenzyldinitrobutadienic precursors (Scheme 7).



Scheme 7

The stereochemistry of trienes **17** was assigned as (*E,E,E*) on the grounds of ^{1}H NMR analysis: such a result is in agreement with a *trans*-configuration at the C(3)-C(4) double bond, which corresponds to the proper geometric arrangement when considering the possibility for trienes **17** to undergo a 6π-electrocyclization. Such process was at first observed by ^{1}H NMR, when heating samples of **17** in $CDCl_3$ at 60 °C in the NMR tube. The electrocyclization was evidenced by the progressive formation of the cyclohexadienes **18**, characterized by a *cis* relationship between the two adjacent benzylic protons, well in agreement with the disrotatory nature of the thermic 6π-electrocyclization. No attempt was made to isolate such cyclohexadienes, while their conversion to the *o*-terphenyls **19** was realized by two different methods (DDQ or iodine/cyclohexene oxide, in toluene at 80 °C), always obtaining satisfactory yields (Table 3).

Table 3. Yields of hexatrienes **17** and 1,2-diaryl-4-nitrobenzenes **19** from Scheme 7.

Entry	Ar in $ArCH_2MgCl$	**17** (Yield %)	**19** (Yield %)	
			Method A[a]	Method B[a]
1	Ph	76	75	92
2	4-MeC_6H_4	72	88	96
3	3-$MeOC_6H_4$	78	84	80
4	4-$MeOC_6H_4$	73	78	85
5	2-Thienyl	41	-	95
6	3-Thienyl	45	83	98

[a]Cyclization methodology, in toluene at 80 °C: A = DDQ, B = I_2/cyclohexene oxide.

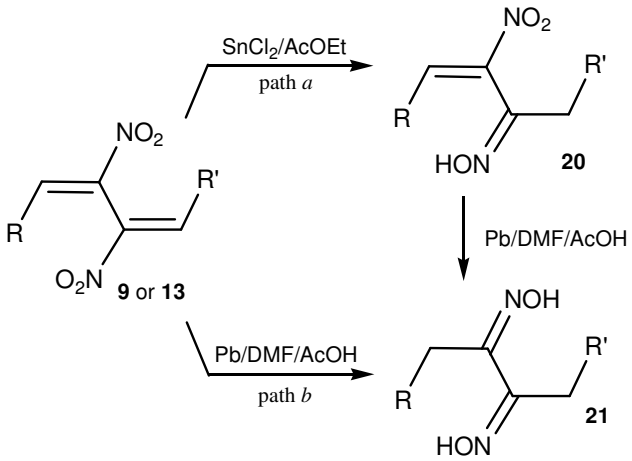
4. Synthetic exploitation of 1,4-disubstituted 2,3-dinitro-1,3-butadienes 9 or 13

4.1. Reduction products and heterocyclic compounds therefrom

The behaviour of 1-nitroalkenes in reduction reactions has been extensively studied,[7c,12-14] realizing their conversion to various, differently-functionalized compounds like nitroalkanes, carbonyl compounds, amines, hydroxylamines and oximes. So it was of interest to verify how our systems would behave in reductive conditions.

4.1.1. Monooximes and dioximes as precursors of nitrogen/oxygen heterocycles

The selective reduction of a single nitrovinyl moiety of compounds **9** to an hydroxyiminoethyl fragment could be realized employing stannous chloride in ethyl acetate.[15] If stoichiometric amounts of the reductant are used, it is possible to limit the formation of the corresponding dioxime to traces (Scheme 8). Yields of the mono-reduction products are usually good, as far as 1,4-diaryldinitrobutadienes are concerned (**9**, R = aryl, or **13**), but are lower for the 1,4-dialkyl derivatives (**9**, R = alkyl) (Table 4). It should be noted that the formation of monooximes is usually accompanied by an average 30% of unreacted **9** due to the complexation that oximes exert on Sn(II) ions. Nevertheless, the use of such a reducing agent is justified by the high degree of selectivity obtained. Further reduction of the monooxime to the dioxime may be obtained[15] with lead powder in DMF/acetic acid, a reducing system that may also be directly applied on **9** if dioximes are the desired products, both in the case of dialkyl and of diaryl derivatives.[6b]



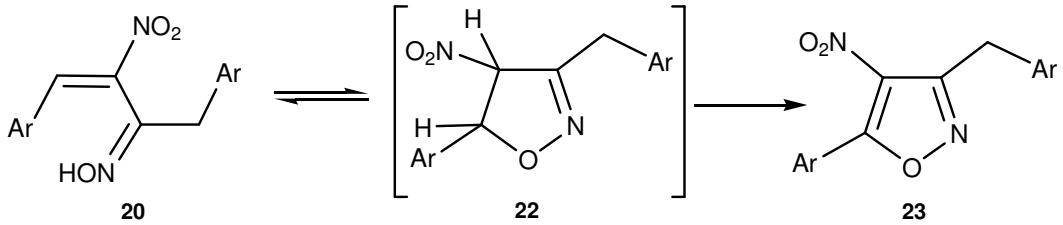
Scheme 8

Table 4. Reduction of dinitrobutadienes **9** (R = R′) or **13** (R ≠ R′) to monooximes **20** ($SnCl_2$/AcOEt; Scheme 8, path *a*) or to dioximes **21** (Pb/DMF/AcOH, Scheme 8, path *b*).

R	R′	**20** (Yield %)	**21** (Yield %)
Phenyl	Phenyl	74	81
1-Naphthyl	1-Naphthyl	70	72
2-MeC_6H_4	2-MeC_6H_4	78	68
4-MeC_6H_4	4-MeC_6H_4	75	75
4-$MeOC_6H_4$	4-$MeOC_6H_4$	-	80
Et	Et	35	72
C_6H_{11}	C_6H_{11}	57	84
2-MeC_6H_4	3-ClC_6H_4		85
2,4,6-$Me_3C_6H_2$	C_6H_5		79

The method represents a valid access to a class of compounds of wide synthetic applicability:[16] in particular oximes **20** and **21** have been conveniently employed for the synthesis of different nitrogen/oxygen heterocycles.

For instance, monooximes **20** undergo[15] an oxidative cyclization (Scheme 9) to the corresponding 3,5-disubstituted-4-nitroisoxazoles **23** *via* an intramolecular Michael addition of the hydroxyimino group of **20** onto the nitroactivated double bond,[17] to give the corresponding 4,5-dihydroisoxazoles **22** as non-isolated intermediates. The aromatization of **22** can be realized (Table 5) with DDQ[18] or γ-MnO_2[19] in dioxane (methods A and B, respectively), or, alternatively, by the Buchi method (method C: aqueous THF in the presence of $NaHCO_3$, I_2 and KI);[20] this last method allows to obtain comparable or better yields within shorter reaction times.



Scheme 9

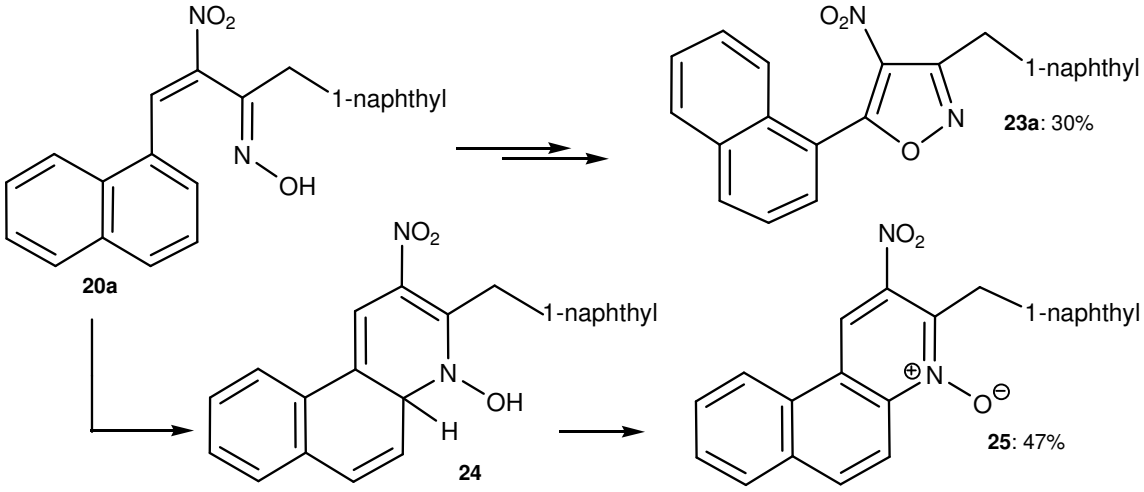
When Ar (in **20**) is 1-naphthyl, a competitive route leads to a quite different reaction product, namely the benzoquinoline *N*-oxide **25** shown in Scheme 10. The formation of this compound can be rationalized by means of a nucleophilic attack of the hydroxyimino nitrogen on the β carbon of the naphthalene ring activated by the nitrogroup in a vinylogous position; the intermediate **24** then aromatizes in the oxidative reaction conditions.

Table 5. Cyclization reaction of **20** to **23** (Scheme 9).

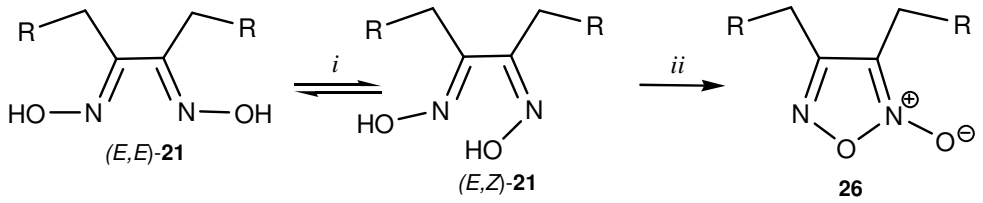
	23 (Yield %)[a]		
Ar	Method A	Method B	Method C
Phenyl	61	40	50
2-MeC_6H_4	57		
4-MeC_6H_4	50		
1-Naphthyl	5		30
2-Thienyl	7		20
Et	12		20
Cyclohexyl	15		48

[a]Method A: DDQ/dioxane; method B: γ-MnO_2/dioxane; method C: $NaHCO_3$, I_2/KI, THF.

As far as dioximes **21** are concerned, it has been ascertained[21] that they can be conveniently transformed into different nitrogen/oxygen heterocycles, depending on the reaction conditions. Thus, a gentle warming of **21** (isolated in *E,E* configuration) in basic ethanol induces the preliminary stereomutation to the (*E,Z*) configuration necessary for the cyclization, and the following treatment at 0 °C with aqueous NaClO leads to the 1,2,5-oxadiazole 2-oxides (furoxans) **26**, always isolated in high yields (Scheme 11, Table 6).



Scheme 10



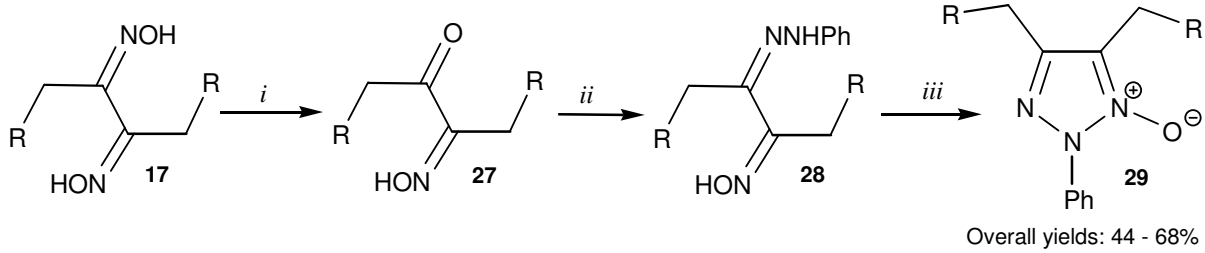
i: gentle warming in EtOH/NaOH. *ii*: $NaClO/H_2O$, 0 °C.

Scheme 11

On the other hand, the hydrolysis of **21** to the monoketooximes **27**, followed by conversion of the latter into the corresponding hydrazonooximes **28**, leads to the 1,2,3-triazole 1-oxides (furazans) **29** (Scheme 12) in more than satisfactory yields (Table 7).

Table 6. Yields of compounds **26** starting from the corresponding **21** (Scheme 11).

R	**26** (Yield %)
Phenyl	95
2-MeC_6H_4	98
4-MeC_6H_4	71
4-$MeOC_6H_4$	88
1-Naphthyl	81
Cyclohexyl	96



Overall yields: 44 - 68%

i: Dioxane/diluted HCl, reflux. *ii*: $PhNHNH_2$ in EtOH/AcOH, reflux. *iii*: $CuSO_4$ in aq. pyridine, reflux.

Scheme 12

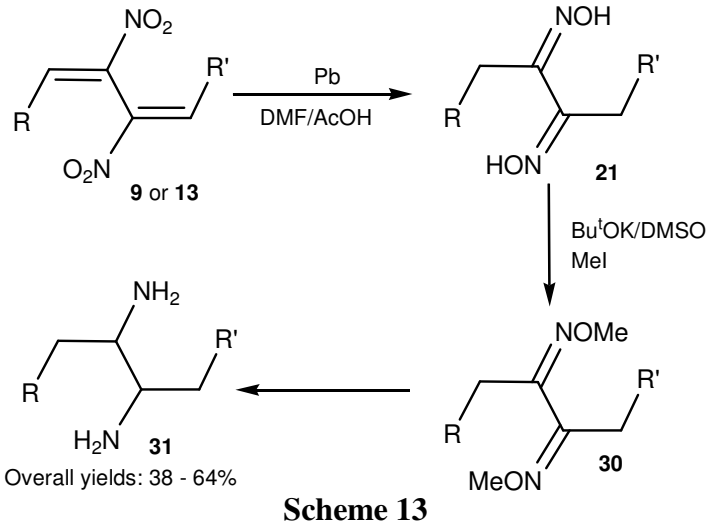
Table 7. Yields obtained along the synthesis of compounds **29** starting from the corresponding **17** (Scheme 12).

R	**17** → **27** (Yield %)	**27** → **28** (Yield %)	**28** → **29** (Yield %)
Phenyl	80	86	97
2-MeC_6H_4	65	80	90
4-MeC_6H_4	60	88	96
4-$MeOC_6H_4$	60	90	96
1-Naphthyl	63	85	82
Cyclohexyl	77	91	97

4.1.2. Diamines

The complete reduction[9] of the dinitrobutadiene system of compounds **9** or **13** to the diaminobutanes **31** has been initially attempted by employing proper modifications of procedures already applied to 1-nitroalkenes.[22] Anyway, such methods, which usually require $LiAlH_4$ or $NaBH_4$, did not provide fully satisfactory results in terms of yields and purity of the desired products. Better results could be definitely obtained following the three-step procedure of Scheme 13. Compounds **9** were first reduced to the dioximes **21** (following the method already described), which were then methylated at both oxygens with methyl iodide after salification with potassium *tert*-butoxide in DMSO. The obtained 1,4-disubstituted 2,3-bis(methoxyimino)butanes **30** were finally reduced with excess borane-THF complex in refluxing THF, an appropriate modification of a literature method employed for the reduction of monooxime ethers.[23] The desired diaminobutanes were isolated as pure mixtures of diastereomers (Table 8).

The method represents a valid alternative access to variously substituted 1,2-diamines, a class of compounds of interest in synthesis,[24,25] and a structural unit present in various naturally-occurring compounds and pharmacologically-active molecules.[25,26]



Scheme 13

Table 8. Synthesis of diaminobutanes **31** from dinitrobutadienes **9** (R = R′) or **13** (R ≠ R′), according to Scheme 13.

R	R′	**9** (or **13**) → **21** (Yield %)	**21** → **30** (Yield %)	**30** → **31** (Yield %)
Ph	Ph	81	83	93
1-Naphthyl	1-Naphthyl	72	77	69
2-MeC_6H_4	2-MeC_6H_4	68	90	84
4-MeC_6H_4	4-MeC_6H_4	75	83	93
4-$MeOC_6H_4$	4-$MeOC_6H_4$	80	87	70
3-ClC_6H_4	3-ClC_6H_4	83	96	80
Et	Et	72	75	80
n-Bu	*n*-Bu	85	84	77
Cyclohexyl	Cyclohexyl	84	83	82
2-MeC_6H_4	3-ClC_6H_4	85	85	73
2,4,6-$Me_3C_6H_2$	Ph	79	76	70

4.1.3. Nitroalkanes and ketones

In the reduction processes described in the previous paragraphs, the two nitrovinyl moieties of dinitrobutadienes **9** and **13** have been shown to behave as isolated nitroethenyl functional groups, undergoing transformations whose outcome is not influenced in any way by their proximity. Thus, for instance, as outlined in paragraph 4.1.1. above, monooximes (**20**) or dioximes (**21**) can be selectively obtained with a proper choice of the reducing agent and/or of the experimental conditions, while vicinal diamines (**31**) can be best obtained from (**21**) *via* the two-step procedure of Scheme 13.

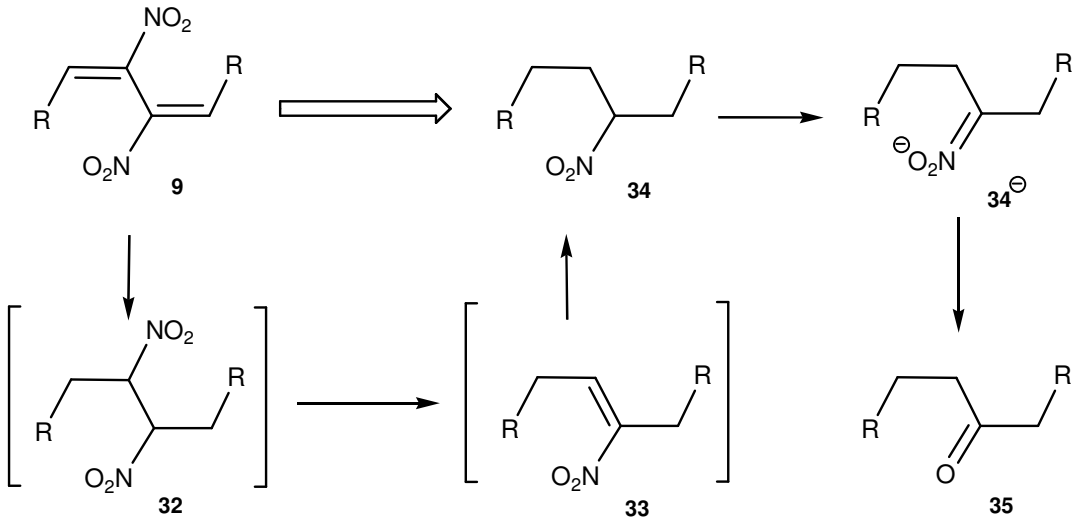
As a matter of fact, such an "independent" behaviour of two conjugated functionalities can afterward result in the exploitability of the bifunctionality of the relevant products, leading *e.g.* to the interesting heterocycles **23**, **25**, **26** or **29** *via* intramolecular processes allowed by a proper distance between the two functional groups themselves.

In the present and in the next paragraphs we will describe, instead, chemical processes which take direct advantage of the proximity between the two nitroethenyl moieties of **9**, definitely expanding the synthetic interest attached to such polyfunctionalized building-blocks.

Thus, for instance, when dinitrobutadienes **9** are treated with polymer-supported borohydride reagents, the isolable products are the relevant nitroalkanes **34** (Scheme 14).[27]

It is reasonable to admit that the initial reduction product, namely the dinitrobutane **32**, does not survive in the experimental conditions, eliminating nitrous acid to give the new nitroalkene **33**, which can in turn be reduced to give the ultimate reaction product, **34**.[28] As an alternative,[29] without isolation of the

nitroalkane, the final reaction solution can be conveniently filtered from the polymer, added with sodium methoxide in methanol (to generate the corresponding nitronate **34**$^{-}$) and then with hydrochloric acid (Nef reaction[30]) to give good yields of 1,4-disubstituted-2-butanones **35** (Table 9).



Scheme 14

Table 9. Yields obtained in the synthesis of nitrobutanes **34** and ketones **35** from dinitrobutadienes **9**, according to Scheme 14.

R	**9** → **34** (Yield %)	**34** → **35** (Yield %)	**9** → **35** (Yield %)[a,b]
Ph	76	72	85
1-Naphthyl	79		
2-Thienyl	75	51	
2-MeC_6H_4	75		
4-MeC_6H_4	79	93	
4-MeOC_6H_4	93	85	94
Et	45	51	
n-Bu	72	73	
Cyclohexyl	91	90	

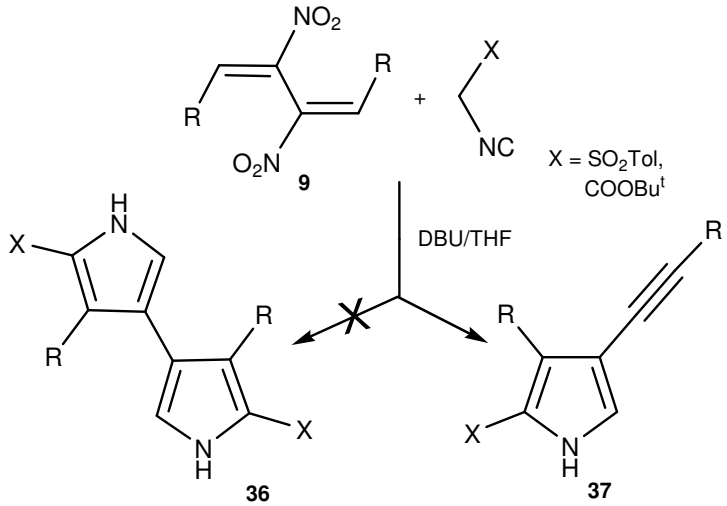
[a]Unpublished results.
[b]Without isolation of the intermediate **34**.

4.2. Cyclization products

The 1,4-diaryl- and 1,4-dialkyl-2,3-dinitro-1,3-butadienes **9** have been conveniently employed as precursors of heterocycles within an overall ring-opening (starting from **1**)/ring-closing process: actually, the protocol has so far proved to be a very fertile field and a number of appealing applications have been optimized in the last few years. It should be once more underlined that in the examples to follow, the two nitrovinyl functionalities do not react independently, but show interesting cooperative/synergic effects.

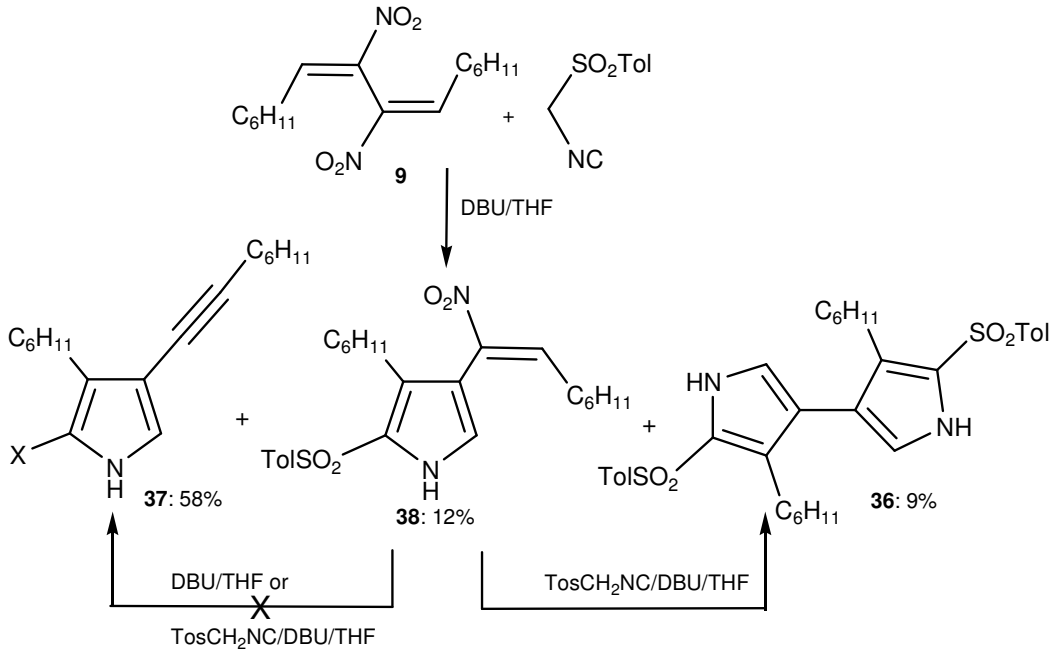
4.2.1. Ethynylpyrroles

An interesting example of the just described synthetic methodology is the reaction of dinitrobutadienes **9** with isocyanides (X-CH_2-NC; X = Tos, $COOBu^t$) in basic conditions.[31] It should be recalled that starting from simple 1-nitroalkenes, the conditions above allow to obtain substituted pyrroles *via* a base-induced cycloaddition, followed by nitrite elimination.[32] Nevertheless, when applied to dinitrobutadienes **9**, instead of the expected 3,3'-dipyrroles **36** the only products observed (in all cases but one) were, as depicted in Scheme 15, the 3-aryl-4-arylethynyl-2-X-pyrroles **37**.



Scheme 15

Apparently, the formation of compounds **37** involves a cycloaddition-elimination process upon one of the nitrovinyl moieties of **9**, accompanied by formal nitrous acid elimination from the second unsaturated moiety. Interesting information on the mechanism of this process was obtained from the results of experiments involving the 1,4-bis(cyclohexyl)-2,3-dinitro-1,3-butadiene. Actually, this is the only case where, beside to the ethynylpyrrole **37** (58%), the nitrovinylpyrrole **38** and the bis-pyrrole **36** were also isolated, even if only in low yields (12% and 9% respectively) (Scheme 16).

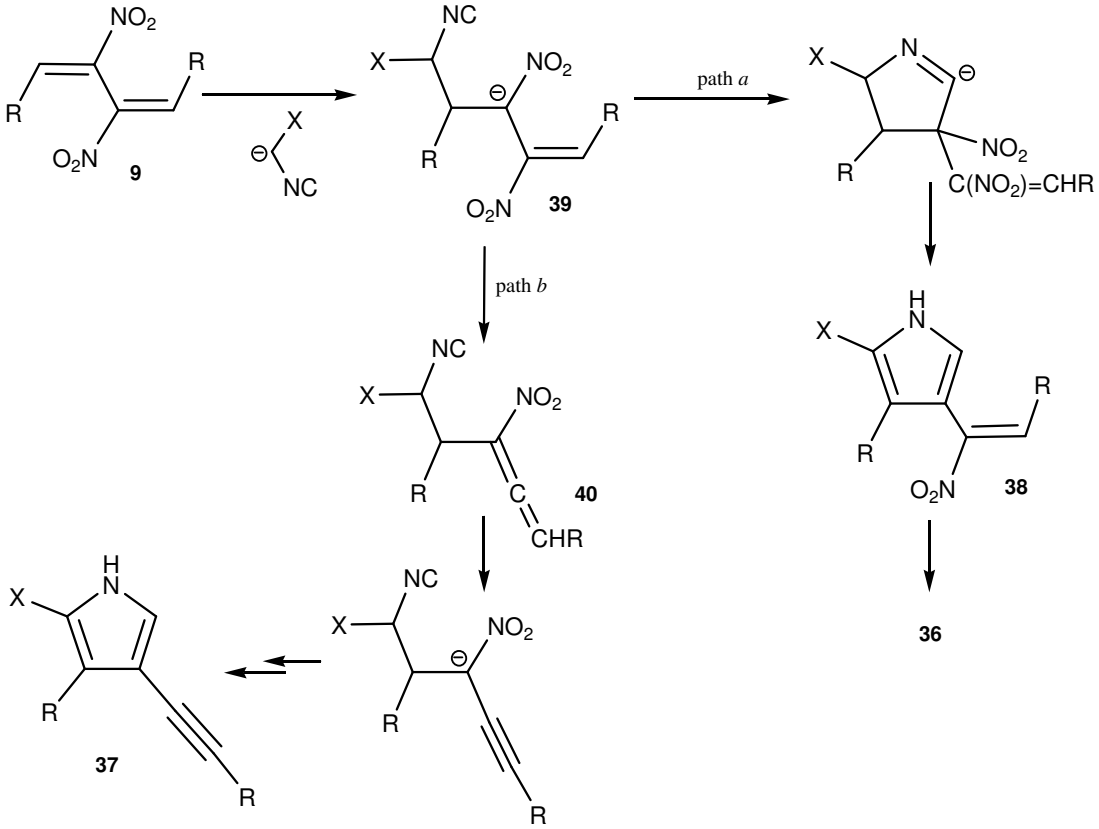


Scheme 16

Furthermore, as ascertained by independent experiments, the nitrovinylpyrrole **38** is a precursor of the bis-pyrrole **36** but not of the ethynylpyrrole **37**.

Table 10. Yields of pyrroles **37** from dinitrobutadienes **9** and X-CH_2NC in basic conditions, according to Scheme 15.

R in **9**	**37** (Yield %)	
	X = SO_2Tol	X = $COOBu^t$
Phenyl	72	63
2-MeC_6H_4	82	82
4-MeC_6H_4	76	70
4-$MeOC_6H_4$	71	67
1-Naphthyl	59	30
2-Thienyl	40	17
Cyclohexyl	58	67
Ethyl	11	-



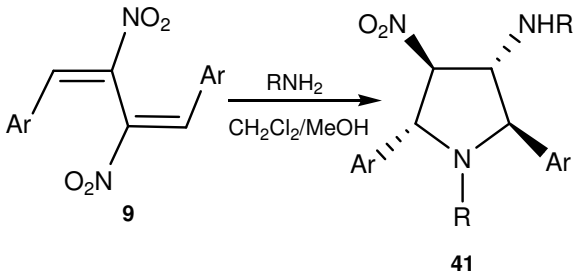
Scheme 17

On the grounds of these results, a mechanism was formulated which, starting from the initially formed nitronate anion **39**, involves, competitively with the cyclization of path *a* (that would eventually produce **38**

and **36**), the unexpected formation (path *b*) of the nitroallenic intermediate **40**, converted, in the basic conditions employed, into a propargyl nitronate, which cyclizes at last to the final product **37** (Scheme 17).[31]

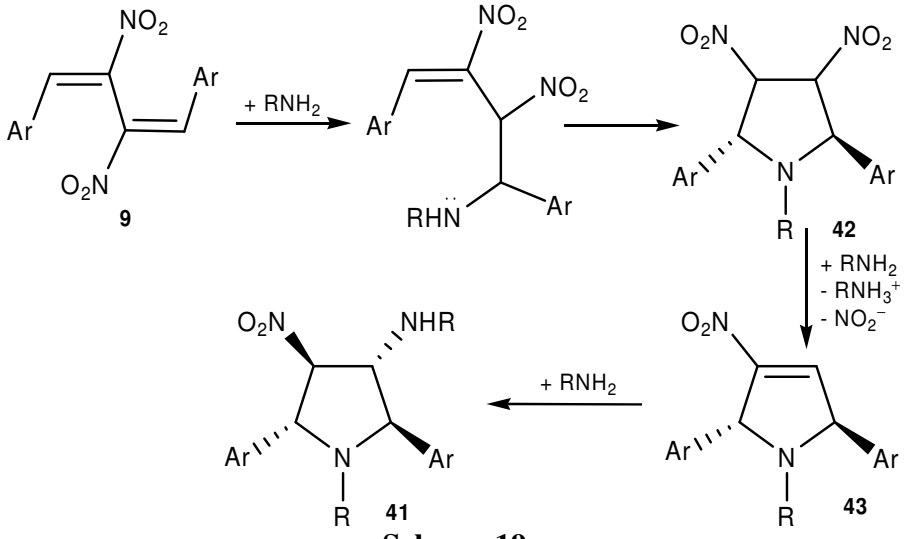
4.2.2. Pyrrolidines, pyrrolines and pyrroles

Another remarkable example of the employment of butadienes **9** in the synthesis of heterocyclic compounds is their reaction with primary amines (Scheme 18), which provides the highly-substituted pyrrolidines **41**, in very mild conditions, high yields (see Table 11) and complete diastereoselectivity.[33] The reaction is a further performance of the cooperative/synergic effects played by the two adjacent nitrovinylic moieties.



Scheme 18

According with the ascertained stoichiometry, which requires three molar equivalents of amine, the most likely path from **9** to **41** involves (Scheme 19) an initial Michael addition of the nucleophilic amine to one of the nitrovinylic moieties of **9**, followed by a second intramolecular conjugate addition that requires a "disfavoured" *5-endo-trig* ring closure.[34] The ensuing pyrrolidine **42** undergoes a fast base-induced nitrous acid elimination, to give the pyrroline **43**; this cannot be isolated in the reaction conditions because of a fast reaction with a third molecule of amine, to give the ultimate product **41**.



Scheme 19

It should be underlined that pyrrolidines **41** are always obtained as a single racemic diastereoisomer, whose definitive stereochemical characterization was obtained thanks to an X-ray crystal structure analysis; due to the fact that **41** are usually oils or glassy solids, suitable crystals were obtained (for Ar = 4-methylphenyl and R = methyl) only after *N*-acetylation at the 3-NHMe group. The all-*trans* stereochemistry

so ascertained was confidently assigned also to all the other pyrrolidines **41**, on the grounds of the analogies in the NMR spectra.

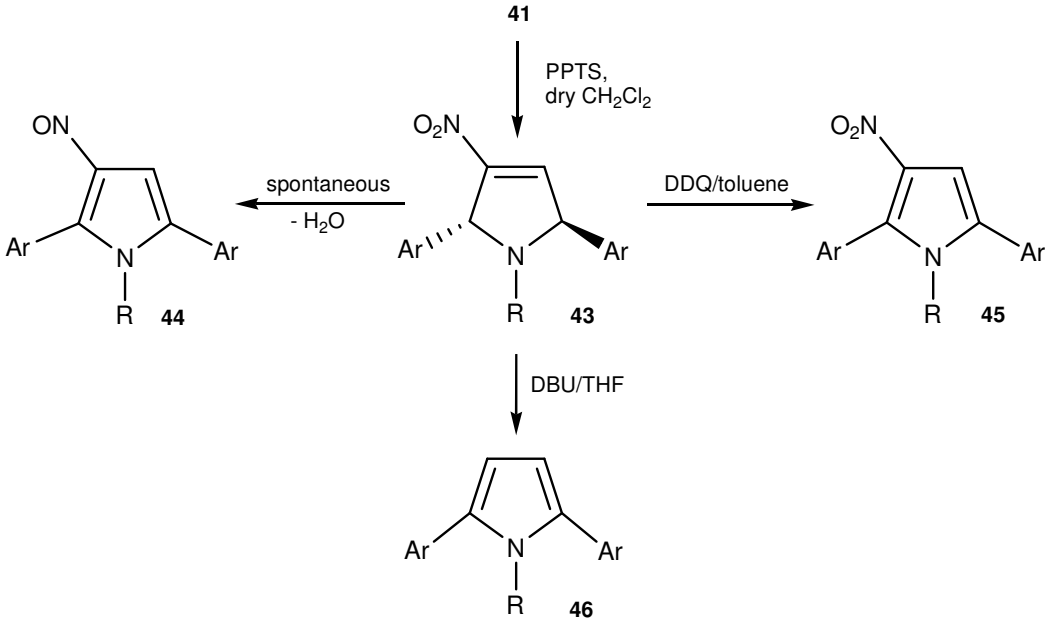
Table 11. Yields of pyrrolidines **41** according to Schemes 18 or 19, and of pyrrolines **43** and pyrroles **45** according to Scheme 20.

Ar in **9**	R in RNH_2	**41** (Yield %)	**43** (Yield %)	**45** (Yield %)
4-MeC_6H_4	Methyl	98	61	83
	Butyl	98	74	86
	Benzyl	98	63	98
	CH_2-CH=CH_2	98	55	60
	CH_2-C≡CH	98	32	98
	Cyclohexyl	98	20	62
	CH_2-CH_2OH	98	35	92
4-$MeOC_6H_4$	Methyl	98	50	98
	Butyl	90	41	61
	Benzyl	98	36	73
2-Thienyl	Methyl	98	35	85
	Butyl	98	35	80
	Benzyl	98	60	60
1-Naphthyl	Methyl	85	77	77
	Butyl	42	72	70
	Benzyl	45	54	80

Interestingly, pyrrolines **43** can be re-obtained from **41** by treatment with PPTS (pyridinium *p*-toluenesulfonate) in dry CH_2Cl_2, even if yields are generally lowered by the contemporaneous presence of the corresponding nitrosopyrroles **44** in variable amounts (Scheme 20, Table 11). From **43** two further transformations can be easily performed: aromatization with DDQ in toluene, to give the diarylnitropyrroles **45**, or treatment with DBU to obtain the diaryl pyrroles **46** (Scheme 20).

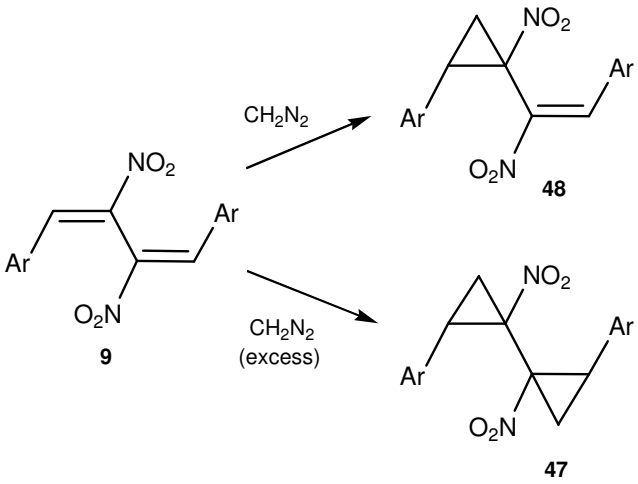
4.2.3. Monocyclopropanes, bis(cyclopropyl)s and heterocycles therefrom

The reaction of dinitrobutadienes **9** with diazomethane represents the starting point for the synthesis of a number of homo- or hetero-cyclic derivatives (cyclopropanes, isoxazoline *N*-oxides, isoxazolines, isoxazoles) whose importance in applicative fields is well documented.[35]



Scheme 20

Cyclopropanation could be limited to a single nitrovinyl moiety or extended to both, depending on the reaction conditions:[36] thus, the bis(cyclopropyl) derivatives **47** (by using an eccess of diazomethane) or the monocyclopropanes **48** (by using 1.1 molar equiv. of diazomethane) were obtained (Scheme 21). Relevant results are reported in Table 12.



Scheme 21

Bis(cyclopropyl)s **47** are characterized by two pairs of chemically equivalent stereocenters, and in principle the reaction could generate six pairs of enantiomers and two *meso* forms; nevertheless, the final reaction mixture always contains only two diastereomeric products: a *d,l* couple and a *meso*-form. Such a diastereoselectivity provides evidence for two concerted *syn*-stereospecific cyclopropanations, which could involve carbene singlet as the reactive species, although intermediacy of pyrazolines (whose formation was anyway never observed) cannot be in principle excluded.

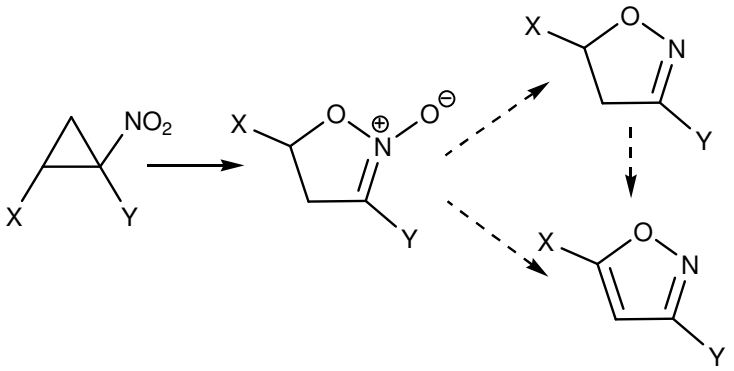
As far as the monocyclopropanation of **9** is concerned, the most convenient experimental conditions, in order to minimize the formation of **47**, were found to require the progressive addition of fractional molar amounts of diazomethane, up to a slight final molar excess with respect to **9**. Both **47** and **48** are interesting compounds, because of the presence of the cyclopropane ring, whose chemical reactivity and biological

activity is well documented.[35] Among the transformations they may undergo, the nitrocyclopropane to five-membered nitronate isomerization[37] represents an appealing access to isoxazoline *N*-oxides and, eventually, to isoxazoles (Scheme 22).

Table 12. Yields and diastereomeric ratios obtained in the reaction of bis-cyclopropanation and of mono-cyclopropanation of compounds **9**.

	Bis-cyclopropanation		**Mono-cyclopropanation**	
Ar	**47** (Yield %) *d,l; meso*	*d,l/meso* *molar ratio*	**48** (Yield %)	**47** (Yield %)
Ph	23; 54	30:70	77	14
4-MeC_6H_4	24; 54	31:69	67	20
4-$MeOC_6H_4$	92[a]	38:62	65	10
3-ClC_6H_4	52; 40	57:43	70	9
1-Naphthyl	21; 70	23:77	71	15
2-Thienyl	90[a]	62:38	42	22

[a]The two diastereoisomers could not be separated.



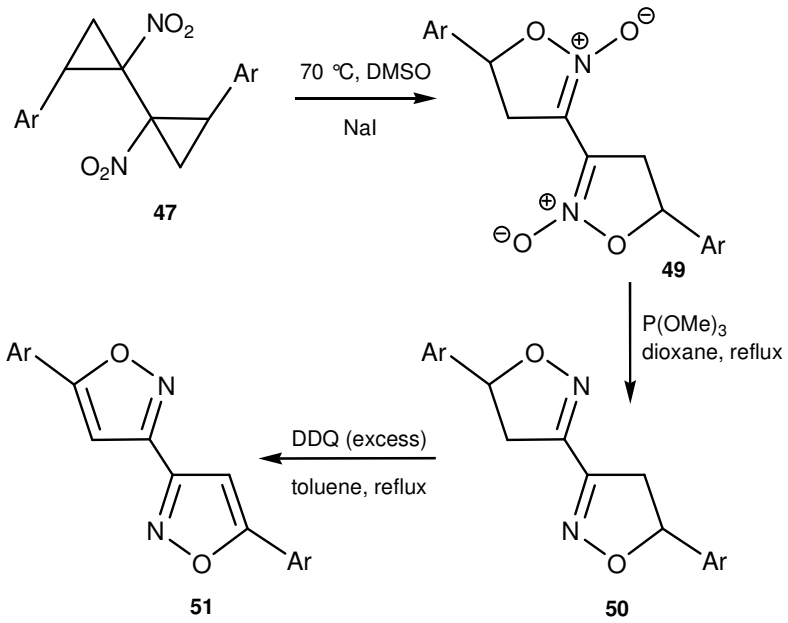
Scheme 22

In the literature, similar isomerizations have been reported in conditions of thermal activation, or electrophilic or nucleophilic catalysis,[38] proceeding in every case through the selective breakage of the more substituted bond of the cyclopropane ring. In our systems, the bis(cyclopropyl)s **47** were gently warmed at 70 °C in DMSO, in the presence of NaI, whose nucleophilic activation allows reasonable reaction times, at temperatures low enough to avoid undesired decomposition processes (Scheme 23). The bis(isoxazoline *N*-oxide)s **49** were obtained in high yields and with complete stereospecificity (see Table 13): *d,l*-**47** furnishing *d,l*-**49**, and conversely *meso*-**47** furnishing *meso*-**49**.[37]

The mechanism proposed for this iodide-assisted isomerization involves a double S_N2 nucleophilic displacement at the benzylic chiral carbon atom, with final retention of configuration at the two surviving stereocenters.[37]

The successive deoxygenation step (from **49** to **50**, Scheme 23) was conveniently performed with $P(OMe)_3$ in dioxane at reflux, with results always more than satisfactory (see Table 13) and, as expected, complete retention of configuration.

Finally, the aromatization of the bis(isoxazoline)s **50** to give the bis(isoxazole)s **51** was realized by means of a previously reported procedure: an excess of DDQ in dry toluene at reflux was usually effective (see Table 13), although prolonged reaction times were necessary in the case of the 1-naphthyl derivatives.



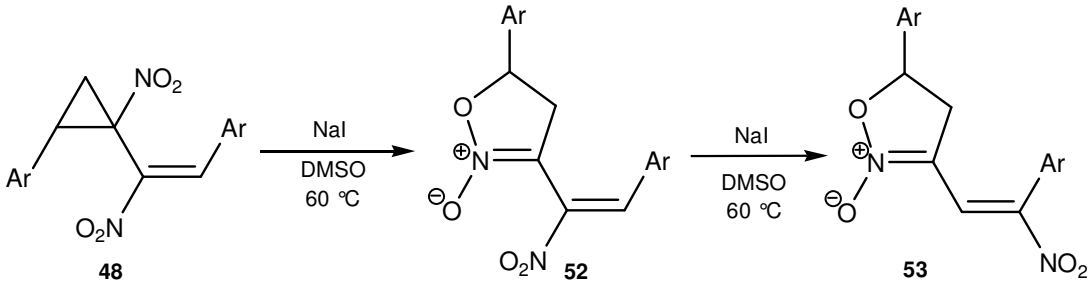
Scheme 23

Table 13. Yields of bis(isoxazoline *N*-oxide)s **49**, bis(isoxazoline)s **50** and bis(isoxazole)s **51**, according to Scheme 23.

Ar	Diastereoisomer	**49** (Yield %)	**50** (Yield %)	**51** (Yield %)
4-MeC_6H_4	*d,l*	80	95	77
4-MeC_6H_4	*meso*	87	91	81
1-Naphthyl	*d,l*	87	86	62
1-Naphthyl	*meso*	74	89	59
2-Thienyl	*d,l*	74	96	73
2-Thienyl	*meso*	37	93	68

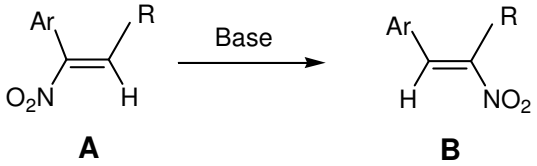
As a prosecution of this study, we have more recently considered the possibility of applying such a reactivity also to the nitrovinyl-substituted monocyclopropanes **48**.[39]

As a matter of fact, the **48** to **52** isomerization effectively occurs in experimental conditions analogous to those applied to **49** (Scheme 24), although prolonged reaction times unveiled a subsequent, unexpected and very interesting migration of the second nitrogroup, to yield the final isolable derivative **53**.[39] Of course, **52** can be in turn isolated in good yields by work-up of the reaction mixture at appropriate times.[39]



Scheme 24

To our knowledge, the migration of a nitrogroup within an arylnitroethenyl moiety usually proceeds in the direction which allows the onset of through conjugation between the aryl and the nitrogroup (*i.e.* from **A** to **B** in Scheme 25).[40]



Scheme 25

In our systems, the unprecedented migration of the nitrogroup in the opposite direction can be reasonably explained by means of a) the release of repulsive interactions of steric and/or stereoelectronic nature between the cyclic nitronate moiety and the nitrogroup in compounds **52**, and b) the replacement of a preexisting conjugation with an extended one, between the nitronate and the nitrogroup.

Further exploitation of either **52** or **53** for the synthesis of variously functionalized heterocycles is presently under way.

5. Conclusions

The almost fourty-years' chemistry of the ring opening of 3,4-dinitrothiophene with nitrogen nucleophiles has definitely brought to evidence the versatility of the polyfunctional butadienes generated by the formal sulfur extrusion from the heteroring. As a matter of fact, a proper modification of the existing functionalities has provided a number of valuable intermediates in turn endowed with synthetic potentialities, biological interest or pharmacological activity.[41]

Yet it is our feeling that what is reported above is only a partial sight of the panorama of synthetic possibilities such appealing building blocks are provided of: accordingly, particular attention will be paid in the next future to the optimization of new synthetic routes, *e.g.* in the field of heterocyclic chemistry, within an overall ring-opening/ring-closing protocol, with the aim of providing new molecular arrangements of possible wide interest.

Acknowledgments

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MACROCYCLIC PEPTOIDS: *N*-ALKYLATED CYCLOPEPTIDES AND DEPSIPEPTIDES

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Contents

1. Introduction

Peptides are among both the main lead structures and the main chemical targets in the development of new therapeutic agents. Their participation in many biological and physiological processes renders them prime candidates as models for medicinally more attractive lead compounds. Unfortunately the application of these biopolymers as drugs is limited due to poor oral availability, low metabolic stability and often low membrane permeability. Another factor is the undesirable side effects caused by their interaction with several receptors.[1] To overcome these limitations, compounds that can either stabilize or mimic the structure and properties of peptides, without loosing the biological activity, have been developed during the last decades.

Important goals in the design of stabilized peptides and peptidomimetics are to improve the pharmacological properties and bioavailability, as well as to increase their metabolic stability, *e.g.* against catabolic and hydrolytic enzymes. Of the many ways to achieve these goals, two are commonly used by nature: cyclization, which avoids attack of exo-peptidases, and *N*-methylation, which imposes more flexibility, lipophilicity, and to some extent endopeptidase stability. In this article, we will concentrate on such compounds: macrocyclic[2] at least partially *N*-alkylated peptides emanating from both natural and laboratory synthesis.

Compounds wherein the side chains have been shifted from the α-position to the amide nitrogen belong to a family of peptidomimetics called peptoids. Originally, the term peptoids[3] was exclusively employed for oligomers of *N*-substituted glycines, which have no substitution at the α carbon and, consequently, no stereogenic center. The *N*-substitution thereby commonly reflects common amino acid side chains. However, nowadays the term peptoid often is more generally applied to any oligopeptide that has substituted nitrogen atoms, *i.e.* tertiary amides. Indeed, this term in its extented meaning also applies to natural and synthetic *N*-methyl cyclopeptides and *N*-methyl depsipeptides. Commonly, peptide-peptoid-chimaeric compounds are also reported. In principle the extended definition of a peptoid must also include proline and the homologous six-membered pipecolic acid. Oxidized derivatives of these cyclic amino acids are commonly found in bioactive peptides, and thus collagen with its (proline-hydroxyproline-glycine)$_n$ repetitve element qualifies to be the most widespread (linear) peptoid unit in nature.

The introduction of a substitution at the amide nitrogen atom reduces the number of intramolecular hydrogen bonds, thus enhancing membrane permeability by passive diffusion.[4] This modification also stabilizes peptides towards the action of proteases, thereby amplifying their pharmacological potential.[5] Additionally, it has been observed that the *N*-methylation of peptides reduces the energy barrier between the *cis* and the *trans* configuration of the amide bond provoking conformational changes or faster interconversion compared to the original peptide.[5] This is similar to the effect of the only proteinogenic (ribosomal) "peptoid" amino acid proline. Biological and structural studies of varied peptoids have demonstrated that they possess great enzymatic stability,[6] membrane permeability[7] and high conformational flexibility. These features render the peptoid backbone an excellent option for lead design.

Another modification that improves the pharmacological properties of peptides and peptidomimetics is cyclization.[8,9] Cyclic peptides are also more resistant to hydrolysis and proteolic degradation than their linear analogues.[8] The intramolecular hydrogen bonding and the steric protection of the amido groups from solvation are important factors that favour membrane permeability of these compounds.[10] Likewise, it is known that the lower conformational freedom of cyclopeptides can increase their affinity towards protein domains due to a lower entropy loss upon binding.[11]

The possibility of combining cyclic structures and *N*-substitutions in the peptide skeleton is an interesting prospect in the design of potential therapeutic compounds. Consequently, cyclic peptoids have been considered important leads in drug discovery and development during the last years. Although many interesting reports of isolation, synthesis, and bioactivity evaluation of compounds fitting the (extended) definition of cyclic peptoids can be found; it is noteworthy that to our knowledge, there is no publication reviewing this interesting class of molecules.

This review describes the most important variations of cyclic peptoids reported in the literature up to date, including natural and synthetic *N*-alkyl cyclopeptides and depsipeptides, as well as selected proline-containing cyclopeptides. In order to structure the review, cyclopeptoids were classified based on the

N-substitution. They were divided in: *N*-methyl, higher *N*-alkyl, and proline derivatives. Subsequently, these three groups were subclassified according to the cyclization type, *i.e.*, compounds bearing disulfide bridges, cyclopeptides, cyclodepsipeptides, and bidirectional lactams. Finally, all these subgroups were divided in natural and synthetic cyclopeptoids. Some structural groups possess only very few members, whereas others, especially proline containing cyclopeptides and depsipeptides, are too numerous in number to include all examples. In those large groups a selection had to be made. Selected were more recently published examples that allow the reader to obtain an insight into the most common structural features and principles, interesting biological activity, and that provide an entry into the literature.

Especially in cyclopeptides (ringsize <18) and depsipeptides (ringsize <19) with less than six amino acids, transannular reactivity can constitute a problem. Indeed such smaller species are less common in nature, unless some special measures, *e.g.* ansa bridges, stabilize the structure.[2a] Thus in synthetic paragraphs, special emphasis is given to the macrocyclization step as this is crucial to avoid possible side reactions such as transannular reaction or formation of diketopiperazines.

2. *N*-Methyl cyclopeptides and depsipeptides

2.1. Purely *N*-heterocyclic peptides

2.1.1. Natural purely *N*-heterocyclic peptides

Tentoxin (**1**, Figure 1), a phytotoxic metabolite isolated from the pathogenic fungus *Alternaria tenuis* Ness,[12] is a cyclic tetrapeptide with interesting features, such as its strained 12-membered ring system and the presence of a didehydroamino acid (DDAA), also present in cyclosporine. Its ability to induce chlorosis in many dicotyledoneous plants makes it a potential selective herbicide.[13]

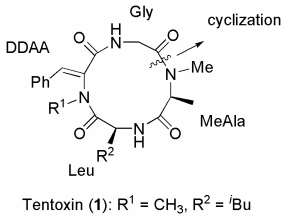


Figure 1. Structure of tentoxin.

The only synthesis described for this molecule uses a solid phase strategy during which dehydration to form the DDAA residue and selective *N*-methylation (K_2CO_3, MeI, 18-crown-6, DMF) were successfully carried out.[14] Four different sequences of amino acids were studied for the cyclization step which considered the risk of epimerization, the difficulty of cyclization and diketopiperazine (DKP) formation. The sequence of choice involved *N*-MeAla and Gly as N and O termini, respectively (Figure 1). The cyclization was accomplished after cleavage from the Wang resin in a yield of 41% after purification, using the DIPCDI/HOBt method. Using this same strategy, seven other derivatives of tentoxin were synthesized varying both R^1 and R^2 groups.

The cyclic pentapeptide argifin (**2**, Figure 2) was isolated from a *Gliocadium* fungal culture[15] and was found to be a low micromolar inhibitor of several family 18 chitinases,[16] being a potential fungicide and insecticide.[17]

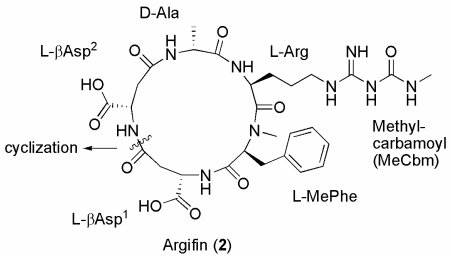


Figure 2. Structure of argifin.

Egglestone and coworkers reported an Fmoc-based solid phase synthesis of argifin using 2-chlorotrityl polystyrene resin.[18] After the synthesis of the linear pentapeptide, the resin was removed and the cyclization was efficiently performed on a dilute (1 nM) DCM solution using PyBOP activation and DIPEA as base (96% yield). Argifin was then obtained in 17% overall yield from the linear peptide after removal of the protective groups and introduction of the *N*-methyl carbamoyl group onto the N^{ω}-position of the Arg side chain. This group proved to be very important for the binding of Argifin to family 18 chitinases.[19] In its absence, no inhibition was observed against the secreted chitinase B1 from *Aspergillus fumigatus* (AfChiB1) up to a concentration of 1 mM whereas synthetic argifin inhibited the enzyme competitively with a K_i of 17 nM.

Motuporin (**3**, Figure 3) was isolated in 1992 from the marine sponge *Theonella swinhoei* Gray collected in Papua New Guinea.[20] Its structure comprises a cyclic pentapeptide that contains some unusual amino acids, such as (2*S*, 3*S*, 8*S*, 9*S*, 4*E*, 6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda). It shows strong *in vitro* cytotoxicity against a variety of human cancer cells (IC_{50} < 1.0 nM) being one of the most potent PP1 (protein phosphatase 1) inhibitors known. The crystal structure of motuporin bound to PP1-c recently has been published.[21]

Several syntheses have been published for this interesting molecule since its isolation. The first one was described by Schreiber and Valentekovich[22] in 1995 which used D-threonine as a chiral building block in the synthesis of the three unusual amino acids. Common amino acids and D-mandelic acid were used to build the stereocenters of the molecule. In 1999, three other syntheses were reported almost simultaneously by the groups of Panek,[23] Toogood,[24] and Armstrong.[25] The former turned out to be the most efficient one not only in convergence (28 steps, with a longest linear sequence of 16 steps, 15.8% overall yield) but also in the cyclization step which was performed in the presence of HATU and *N*-ethyl-morpholine (79% yield).

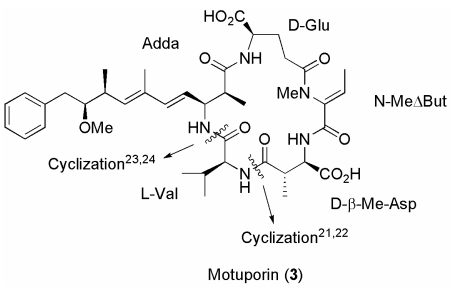


Figure 3. Structure of motuporin.

The last two groups reported low yields and also mixtures of epimers during the cyclization using either HATU/DIPEA or the pentafluorophenyl ester method (the same used by Schreiber[22] in 1995). These differences can be attributed to the proper choice of the C and N termini for the cyclization as illustrated in Figure 3.

Cyclomarin C (**4**, Figure 4) is an anti-inflammatory cyclic heptapeptide isolated along with cyclomarins A and B as a metabolite from a marine bacterium collected in the vicinity of San Diego.[26] The main feature of these structures is the presence of four noncoded amino acids in each.

The only synthesis of cyclomarin C was reported by Yao and coworkers[27] using a convergent 4 + 3 fragment condensation strategy (Figure 4). The cyclization step was achieved in 63% yield using the PyBOP method[28] in dilute DCM solution (1.4 mM). Several different ring closure possibilities were screened to determine optimum conditions.

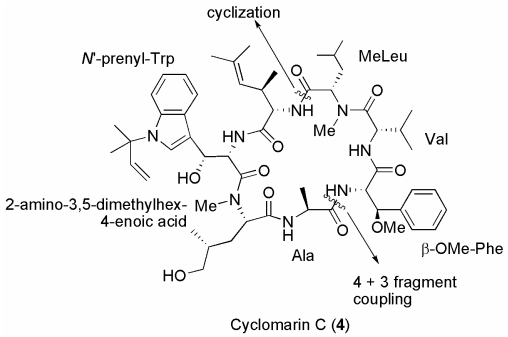


Figure 4. Structure of cyclomarin C.

Cyclosporin O (CsO, **5**) is a cyclic undecapeptide, containing 6 *N*-methyl amino acids, isolated from *Tolypocladium inflatum* Gams[29] (Figure 5). It belongs to the cyclosporins (Cs) family of which CsA is the most important member. CsO shows strong immunosuppressive activity[29] and is much less nephrotoxic than CsA.[30] Xu and Li described the synthesis of CsO both in solution and in solid phase through a 7 + 4 fragment condensation.[31] CsO was obtained in 20-23% overall yield from the corresponding amino acid derivatives using BEMT, BDMP and BEP as coupling agents. Cyclization of the linear undecapeptide was achieved in dilute solution (0.2 mM) using HAPyU or BDMP to give CsO in 68-84% yield.

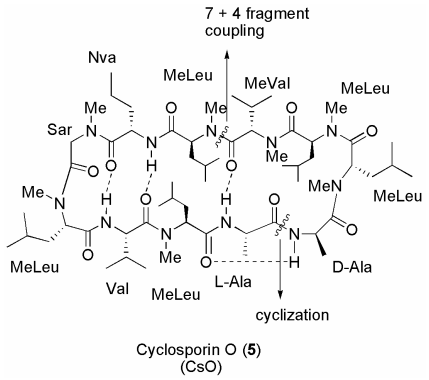


Figure 5. Structure of cyclosporin O.

Other representative examples of recently described natural cyclic peptides with varying biological activities are shown in Figure 6. Hirsutide (**6**) is a *Hirsutella* metabolite isolated from an infected spider and displayed moderate cytotoxic activity (IC_{50} = 11 μg/mL) against P388 murine leukemia cells.[32] Cordyheptapeptide A (**10**) was isolated from an entomopathogenic fungus of the genus *Cordyceps* and showed antimalarial activity against *Plasmodium falciparum* K1.[33] Brunsvicamides A-C (**7-9**) were isolated from the cyanobacterium *Tychonema sp.*[34] Except for brunsvicamide A (**7**), they act as potent selective

inhibitors for Mycobacterium tuberculosis protein tyrosine phosphatase B (MptpB), being potential candidates for tuberculosis therapy. Interestingly, brunsvicamide C (**9**) is so far the only cyclic peptide that contains the unusual amino acid residue *N*-methyl-*N'*-formylkyrunenine. Omphalotin A (**11**) was isolated from the basidiomycete *Omphalotus olearius*[35] and shows nematicidal properties. Recently, a solid-phase synthesis of this compound was published.[36]

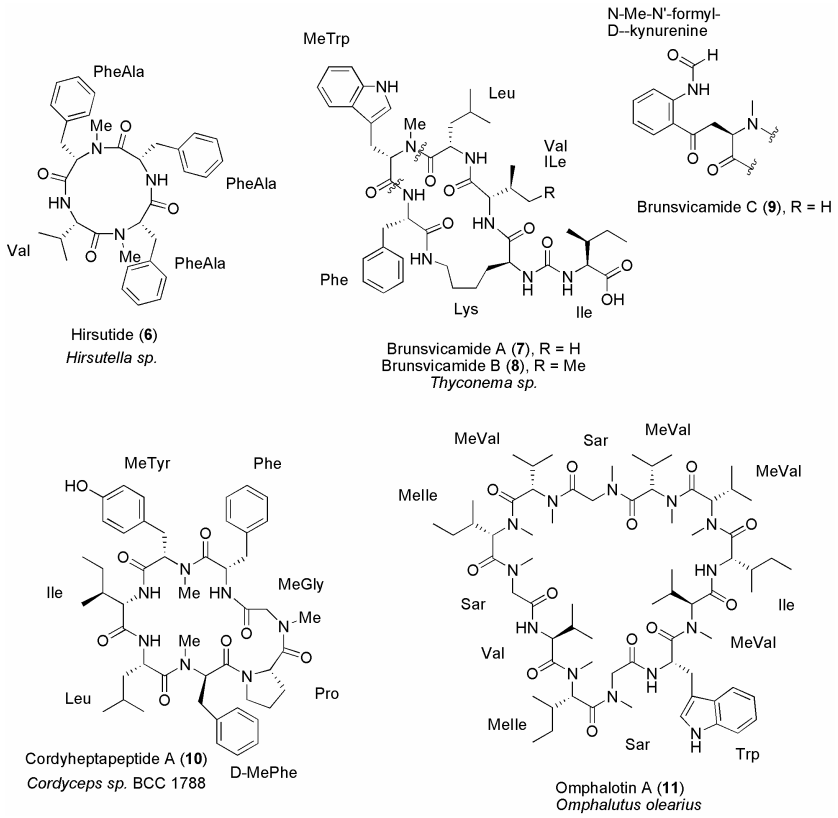


Figure 6. Representative examples of other *N*-methylated cyclic natural peptides.

2.1.2. Synthetic *N*-methylated cyclopeptides

Sansalvamide A (San A) is a cyclic pentadepsipeptide produced by a marine fungus of the genus *Fusarium*, found in Bahamas, with antitumor activity.[37] Its structure (**12**, Figure 7) shows four hydrophobic amino acids and one hydrophobic hydroxy acid.

McAlpine and coworkers synthesized 14 novel derivatives of San A, 10 of them bearing *N*-methyl amino acids in their structures.[38] This work led to the discovery of two compounds more active than the natural product itself showing high cytotoxicity against cancer cells lines (HCT-116). One of them is the San A peptide (**13**)[39] and the other is the *N*-methylated derivative **14** (Figure 7).

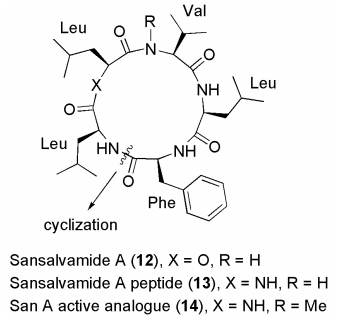
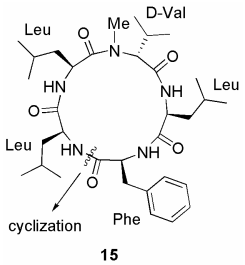


Figure 7. Structures of sansalvamide A (**12**) and analogues.

The authors used a combinatorial-type strategy in a convergent approach. The macrocyclization reactions were slow (~ 4 days) due to the high dilution conditions (5 – 10 mM) used and the yields obtained were low (20-35%). These reactions involved the intermediacy of several coupling reagents.

Shortly afterwards, a more efficient protocol was developed which substantially increased the macrocyclization yields by using HCl to deprotect both the amine and the acid without forming insoluble salts.[40] The cyclizations were then realized as mentioned above at a much faster rate.

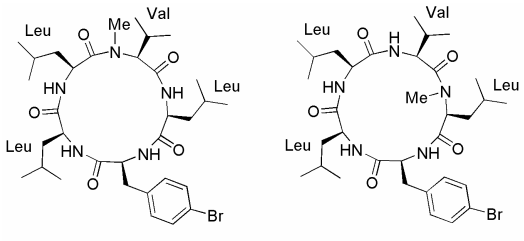
A further study of McAlpine and coworkers determined the structure-activity relationship (SAR) of 36 San A derivatives (18 new compounds) towards the MSI colon cancer cell line HT-29.[41] They observed that, except for one compound, *N*-methylation does not significantly alter the potency which is substantially increased when a single L-amino acid (L-Val) is exchanged to the enantiomeric D-amino acid. Compound **15** was almost as potent as 5-fluorouracil (5-FU), a current drug on the market (Figure 8). All compounds were prepared by solution phase synthesis as described above.



15

Figure 8. Structure of a synthetic peptide active against colon cancer cells (HT-29).

The *N*-methyl San A peptide analogues **16** and **17** were also synthesized by Silverman and coworkers[42] by a solid phase approach and tested against human cancer cells. *N*-Methylation of the amino acids was realized through activation of the amino groups by trifluoroacetylation followed by deprotonation with K_2CO_3 and addition of MeI. Differently from most reported cyclopeptide syntheses,[2] the resin was removed at the last stage of the synthesis after the macrocyclization which proceeded in good yields using PyBOP as coupling agent in the presence of DIPEA. It was observed that *N*-methylation in combination with *p*-bromination of the aromatic ring were beneficial for increasing the activity as compared to San A against human prostate and breast cancer cells (Figure 9).



16 17

Figure 9. Synthetic compounds active against human prostate (PC-3) and breast cancer cells (MDA-MB231).

A library of 30 different *N*-methylated peptides with the basic sequence cyclo(-D-Ala-L-Ala_4-) was designed and synthesized employing a usual solid phase strategy by Kessler and coworkers to identify peptides with a preferred conformation in solution that could be used as templates for biologically active

peptides.[43] The cyclizations were performed in solution using diphenylphosphoryl azide (DPPA) and $NaHCO_3$ in DMF. Only seven peptides adopted a preferred conformation by NMR analysis, and out of these, six had the D-residue *N*-methylated (Figure 10). According to the authors, the most promising compounds are the ones with mono- and di-*N*-methylation whereas multiple *N*-methylation led to an equilibrium between different conformations.

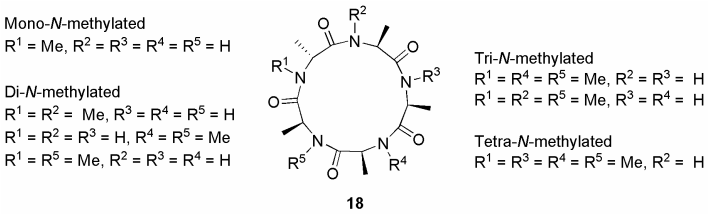


Figure 10. Structures of synthetic *N*-methylated pentaalanine peptides.

Other representative works involving synthetic cyclic peptides deal with the solid-phase synthesis of a somatostatin antagonist,[44] the synthesis of gramicidin S derivatives[45] and the study of a new class of peptide nanotubes.[46]

2.2. *N*-Methylated depsipeptides

2.2.1. Natural *N*-methylated depsipeptides

IB-01212 (**19**) is a cytotoxic symmetric octadepsipeptide isolated from the mycelium extract of *Clonostachys sp.* ESNA-A009 (Figure 11).[47] It showed GI_{50} (growth inhibition) in the order of 10^{-8} M against Ln-CAP (prostate cancer), SK-BR3 (breast cancer), HT29 (colon cancer) and HELA (cervix cancer). Albericio and coworkers[48] reported three solid-phase strategies for the synthesis of IB-01212 of which the convergent method proved to be the best one. In this strategy, two tetrapeptide fragments were prepared separately on two different resins, released and then coupled together. The cyclization step was carried out in solution *via* ester bond formation using MSNT, NMI, and DIPEA in DCM/DMF and the cyclized product was obtained in low yield (14%) but in high purity (96%).

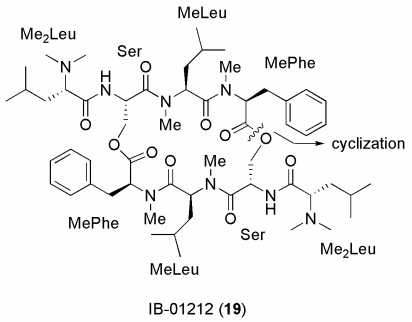
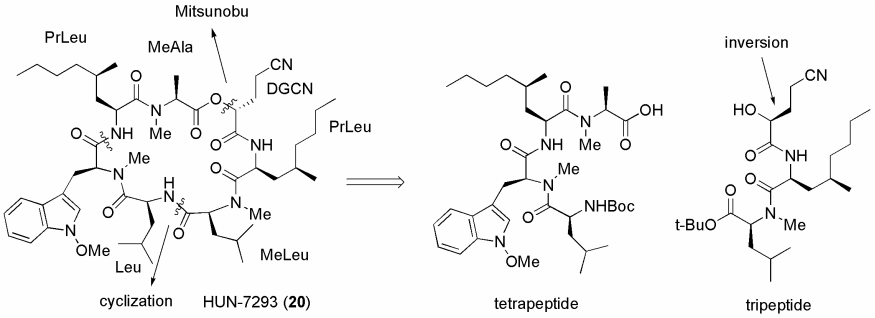


Figure 11. Structure of IB-01212.

HUN-7293 (**20**) is a cyclic heptadepsipeptide isolated from a fungal broth which is able to act as an anti-inflammatory due to its potent inhibition of the vascular cell adhesion molecule 1 expression (VCAM-1)[49] (Scheme 1). It contains six L-amino acids residues and a D-hydroxy carboxylic acid residue (DGCN). Two transannular H-bonds confer stability and rigidity to its structure.

Boger and coworkers[50] reported the first total synthesis of HUN-7293 (**20**) in a solid phase convergent strategy using a 4 + 3 fragment condensation (Scheme 1). The cyclization step affording HUN-7293 proceeded in 71% yield at 0 ºC using EDCI-HOAt and $NaHCO_3$. The synthetic compound was identical in all aspects to the natural product including the results of biological activity. Shortly afterwards, the same group reported the solution-phase parallel synthesis of a pharmacophore library of HUN-7293 analogues.[51] They realized an alanine scan and *N*-methyl deletion of each residue of the natural product searching for the key sites responsible for the biological properties. For instance, when the methyl group of the *N'*-methoxy tryptophane residue was removed, a complete loss of activity (> 10,000 fold) was observed.



Scheme 1. Retrosynthetic analysis of HUN-7293.

The cyclic pentadepsipeptide obyanamide (**21**, Figure 12) was isolated from the marine cyanobacterium *Lyngbya confervoides* by Moore and coworkers[52] and showed cytotoxicity against KB and LoVo cells with IC_{50} values of 1 and 5 μM, respectively. It contains two *N*-methyl amino acids, an Ala-thiazol unit and a β-amino acid. It is closely related to other cyclodepsipeptides known as guineamides A and B[53] and ulongamides A-E.[54]

The total synthesis of obyanamide was accomplished by Li and coworkers[55] who reassigned the stereochemistry at carbon 3 based on spectroscopic data. Macrocyclization was achieved using HATU and DIPEA in THF (59%). The compound with the wrong stereochemistry at carbon 3 was also synthesized and showed no inhibition on several cancer cell lines tested.

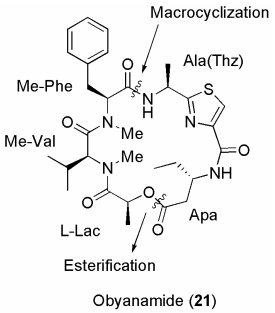


Figure 12. Structure of obyanamide.

Apratoxins A-C (**22**-**24**) are depsipeptides isolated from cyanobacterial *Lingbya spp*. collected in Palau and Guam by Moore, Paul and coworkers.[56] The interesting point about these compounds is the presence of both polypeptide and polyketide domains (Figure 13). Apratoxins A (**22**) and C (**24**) showed high levels of cytotoxicity *in vitro* against KB and LoVo cancer cells. Apratoxin B (**23**), with one *N*-methylation less, was somewhat less potent.

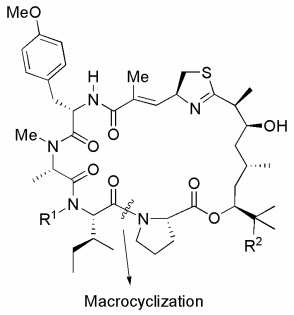
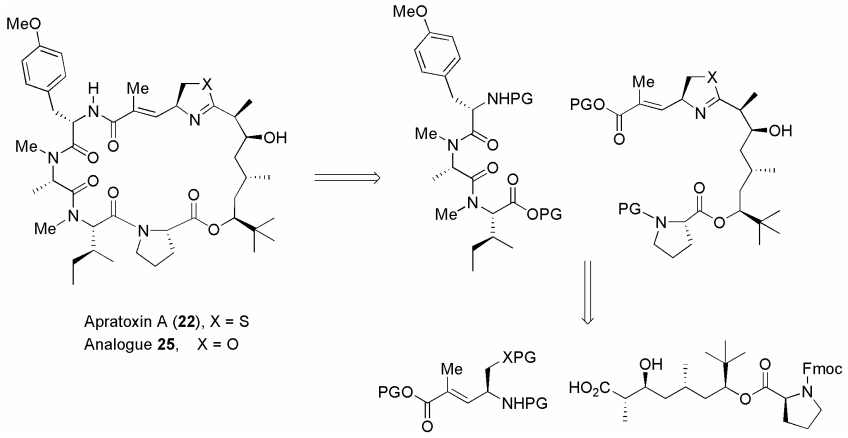


Figure 13. Structures of apratoxin A-C.

Forsyth and Chen[57] reported the first total synthesis of apratoxin A (**22**) in which the sensitive 2,4-disubstituted thiazoline moiety was installed at a later stage under neutral conditions using a one-pot Staudinger reduction-intramolecular aza-Wittig process. The macrocyclization was efficiently mediated by PyAOP and DIPEA in CH_2Cl_2 furnishing the macrocycle in good yield (73% including the ester hydrolysis step).

Another synthesis of apratoxin A (**22**) was recently described by Ma, Liu and coworkers[58] using a different approach (Scheme 2). The polyketide fragment was assembled *via* two asymmetric aldol reactions and the thiazoline moiety by Kelly's biomimetic method.[59] An oxazoline analogue (**25**) of apratoxin A was also synthesized and showed nearly the same potency in inhibiting proliferation of the human cervical cancer cell line HeLa.

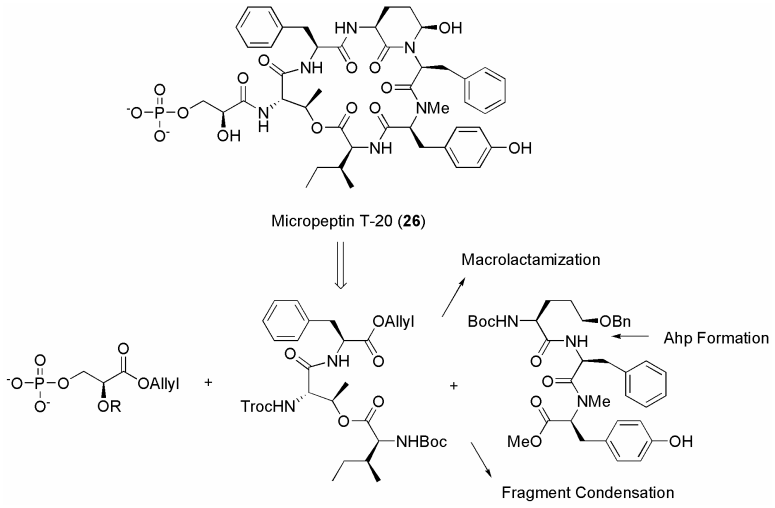


Scheme 2. Retrosynthetic analysis of apratoxin A (**22**) and its oxazoline analogue **25**.

The hexadepsipeptide micropeptin T-20 (**26**) was isolated from the cyanobacterium *Microcystis aeruginosa* collected in Thailand by Kaya and coworkers (Scheme 3).[60] Beside the presence of the 3-amino-6-hydroxy-2-piperidone (Ahp) unit, which is very common in depsipeptides derived from cyanobacteria,[61] its structure bears three hydroxyl groups and a phosphate function which are responsible for its high polarity. Shioiri and coworkers reported a synthesis for micropeptin T-20.[62] Scheme 3 illustrates the retrosynthetic analysis.

The crucial step of the synthetic strategy involved the preparation of the Ahp unit which was done at a later stage of the synthesis through an amide-aldehyde cyclization. Macrolactamization occurred under high dilution conditions (2 mM) mediated by pentafluorophenyl diphenylphospinate (FDPP) and DIPEA in

CH_2Cl_2 (84% yield). Surprisingly, the synthetic compound showed different spectroscopic data from the natural one indicating that a revision on the structure of micropeptin T-20 is necessary.



Scheme 3. Retrosynthetic analysis of micropeptin T-20.

The antibiotic enopeptides **27** were isolated from *Streptomyces sp.* RK-1051 and *S. hawaiiensis*, and have been studied in detail by pharma companies. Medicinal chemistry programs could increase activity, solubility and stability, the latter *e.g.* by substitution of the lightsensitive polyene side chain.[63a] The compounds are active against several Gram-positive bacteria, impair cell devision and induce filamentation in *Bacillus subtilis*. Two hydrogen bridges between side chain and macrocycle impose a cage-like structure in crystals.

Further depsipeptides were isolated from streptomycetes (**28**)[63] or marine sources (coral,[64] sponges[65] and cyanobacteria[66]) and selected structures are presented in Figures 14-16. It should be noted that in some cases the original producer of the compounds may be endosymbiotic microorganisms associated to, *e.g.*, sponges.

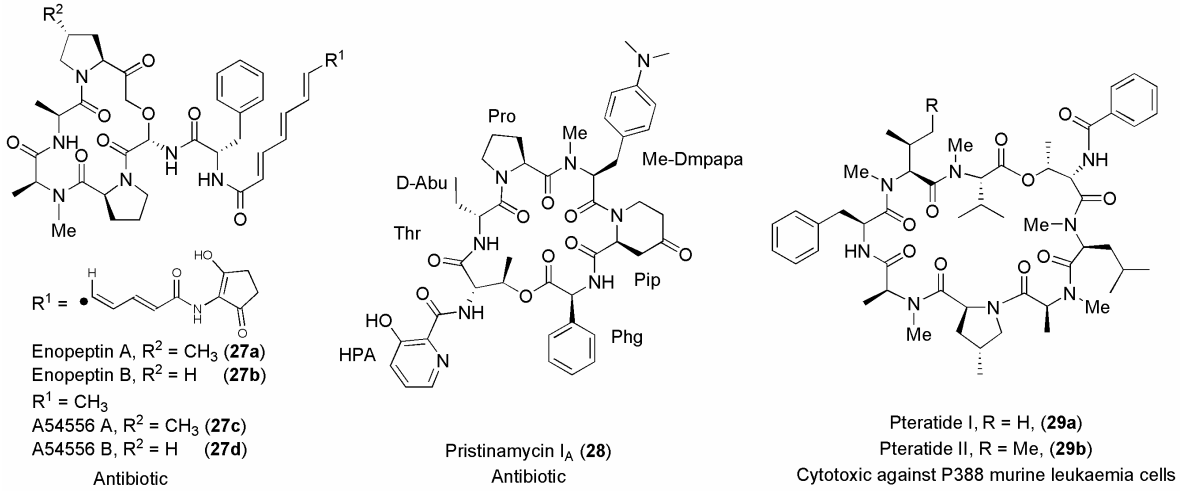


Figure 14. Depsipeptides isolated from streptomycetes (**27**-**28**) and corals (**29**).[63,64]

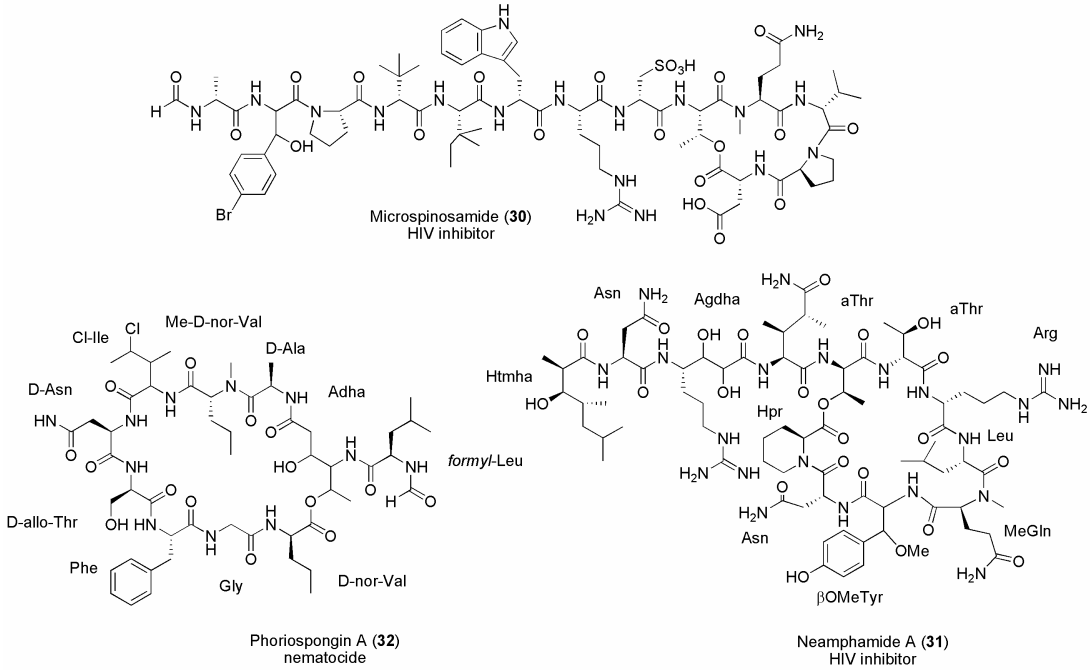


Figure 15. Depsipeptides isolated from sponges.[65,66c]

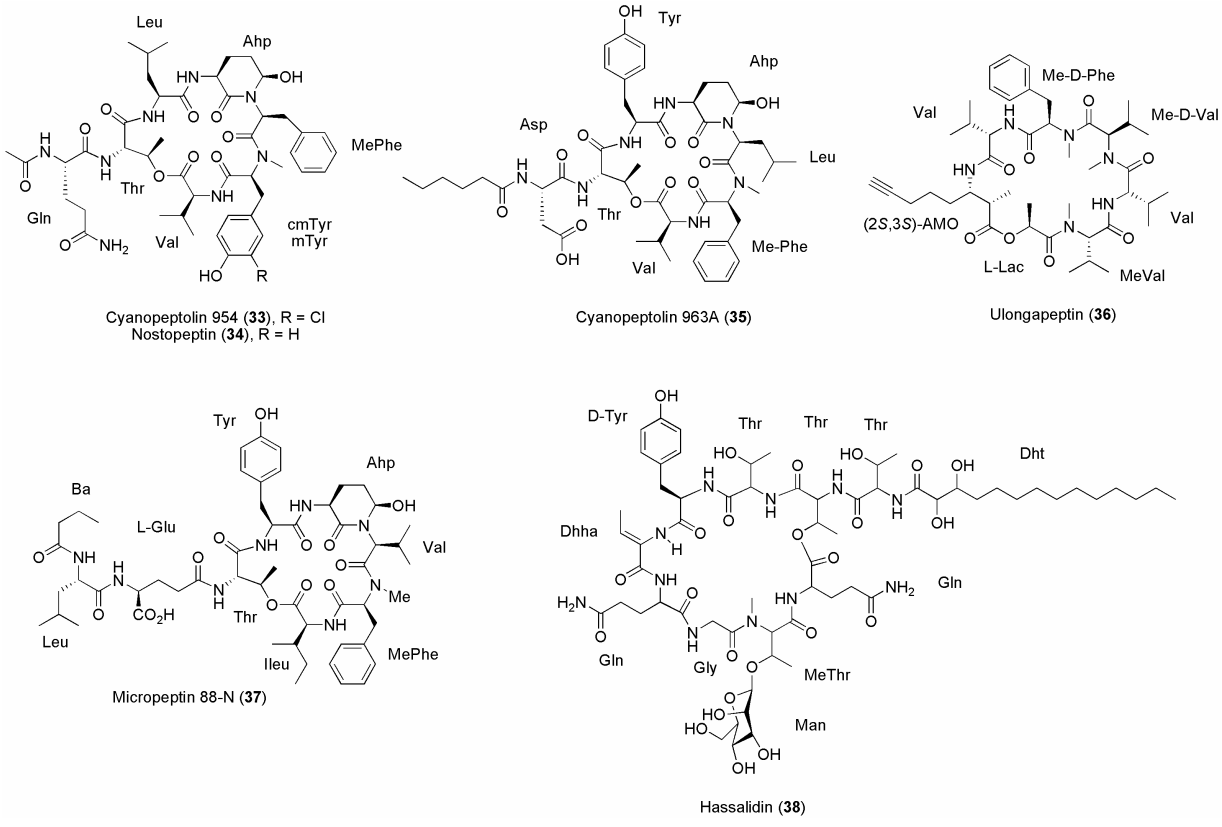


Figure 16. Depsipeptides isolated from cyanobacteria.[66]

2.2.2. Synthetic *N*-methylated depsipeptides

Jasplakinolide (**39**) is a natural cyclotetradepsipeptide with a polyketide moiety isolated from a *Jaspis* sp. Sponge[67] and shows potent antifungal, insecticidal, and antitumor activity (Figure 17). A related compound is geodiamolide A (**40**) isolated from the marine sponge *Geodia* sp.[68] These peptides possess a ω-hydroxy acid moiety whose preparation on a large scale can be costly. Aiming to prepare simpler

analogues of these compounds, Maier and coworkers[69] reported the synthesis of four new cyclic depsipeptides, two of them are *N*-methylated (Figure 18).

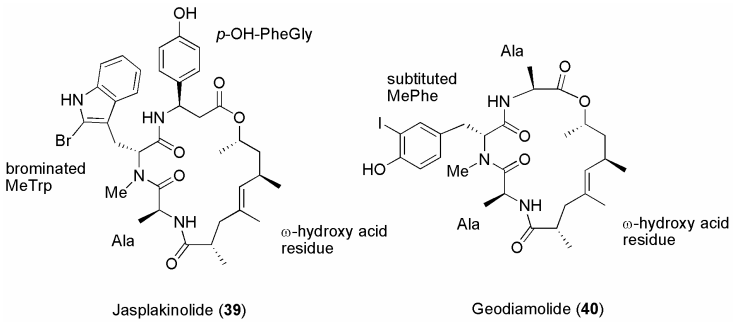


Figure 17. Structures of jasplakinolide and geodiamolide.

Conformational analysis showed a good agreement between the structures of the analogues and those of the natural compounds. The macrolactam formation involved the use of TBTU, HOBt and DIPEA in DMF (65% yield for compound **41** and 45% for compound **42**). In biological studies, compound **42** was inactive towards L929 mouse fibroblasts and ovary cancer cell line SKOV-3 whereas compound **41** showed moderate activity.

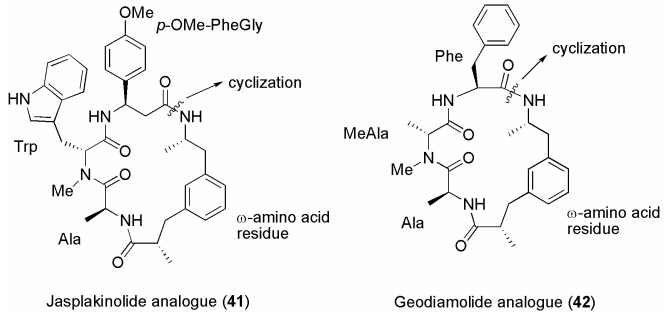


Figure 18. Structures of synthetic jasplakinolide and geodiamolide analogues.

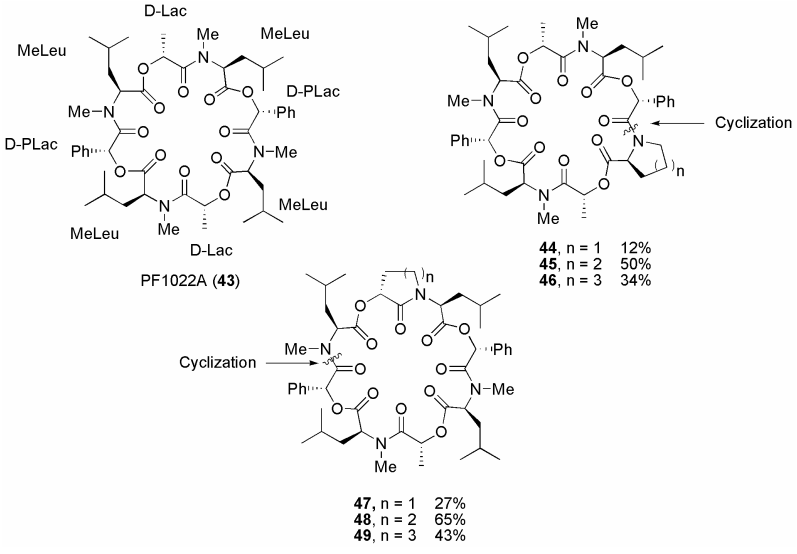


Figure 19. Structure of PF1022A and its analogues.

The compound known as PF1022A (**43**, Figure 19) is a cyclic octadepsipeptide with antihelmintic properties, isolated from the fungus *Mycelia sterilia* PF1022.[70] In order to reduce the number of conformations which the floppy 24-membered ring can adopt, aiming to increase both potency and selectivity of the natural product, Lee and coworkers[71] synthesized six analogues bearing a small ring fused to the macrocycle (Figure 19).[72]

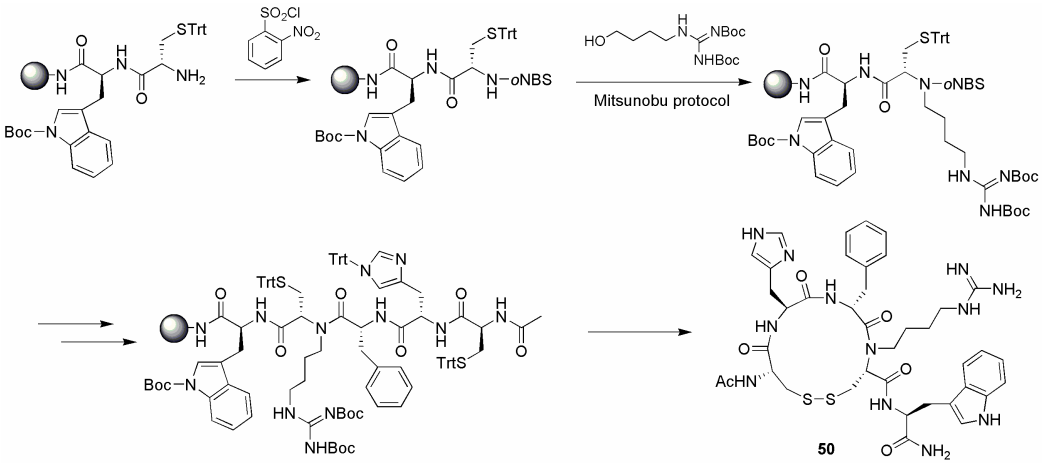
The peptides were prepared by macrolactamization with BOP reagent at high dilution (1 mM) except for compounds **45** and **46** which underwent cyclization at moderate dilution (4-7 mM) using 1-methyl-2-chloropyridinium iodide in CH_2Cl_2. The yields of this crucial step varied from low to moderate. A reduced biological activity was observed for compound **47** which possesses a five-membered ring lactam. As the size of this small ring increases the biological activity tends to be restored. Of the derivatives prepared, compound **45** showed the best activity and **46** was essentially inactive. The authors suggested that this lack of antihelmintic activity may be related to the deleterious replacement of a leucine residue, as reported earlier.[72f] Molecular modeling studies indicated that a close to symmetric conformation is necessary for biological activity. Other representative examples involving the syntheses of non-natural cyclic depsipeptides are published elsewhere.[73]

3. Higher *N*-alkyl cyclopeptides and depsipeptides

All cyclopeptides with linear *N*-alkyl residues larger than methyl appear to be synthetic. We could not retrieve a natural cyclopeptide with other *N*-substitution than methylation or a proline or pipecolic acid moiety.

3.1. Synthetic higher N-alkyl cyclopeptides with disulfide bridge

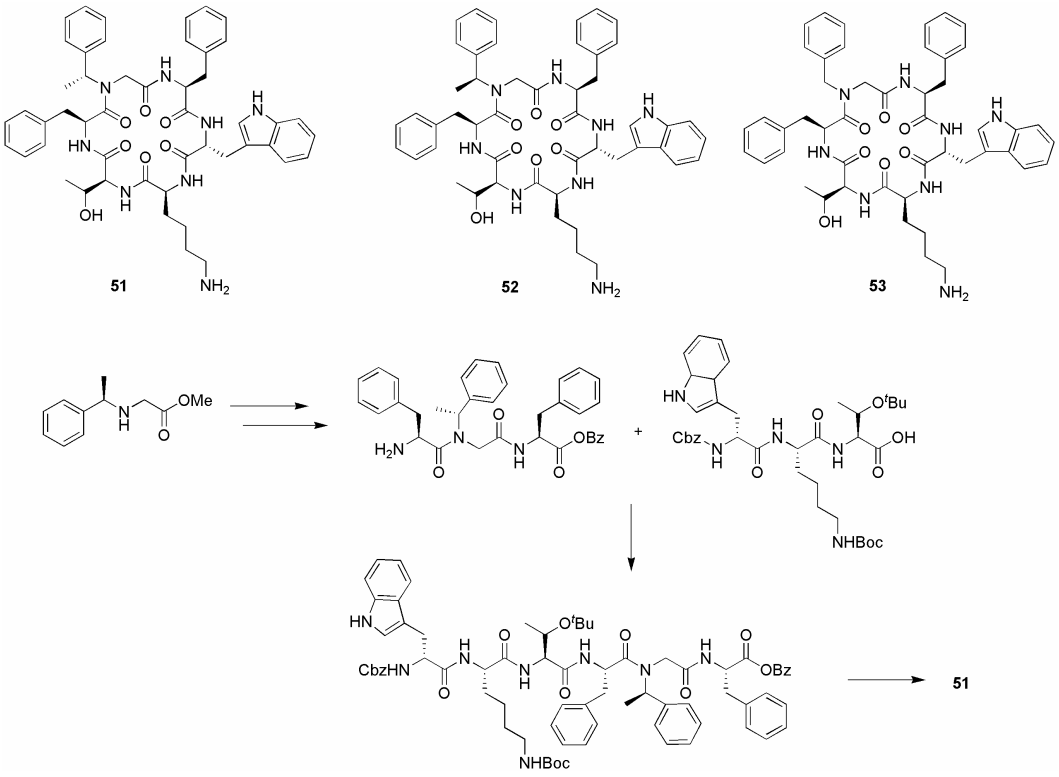
Cyclopeptide **50** and seven more derivatives were designed and synthesized by Ying and coworkers[74] as cyclic melanotropin analogues selective for the human melanocortin-4 receptor (Scheme 4). Cyclization was used to introduce conformational constrains and the *N*-substitution was chosen to mimic an arginine side chain. Three of the compounds exhibited antagonistic activity showing high selectivity towards the human melancortin-4 receptor. All cyclopeptoids were generated by standard solid-phase peptide synthesis. The *N*-alkylation step was accomplished by using *N,N'*-di-Boc-guanidinylbutanol in a standard Mitsunobu protocol. Sulfide cyclopeptides also have been reported (v.i.).[82,92]



Scheme 4. Synthesis of cyclopeptoid **50**.

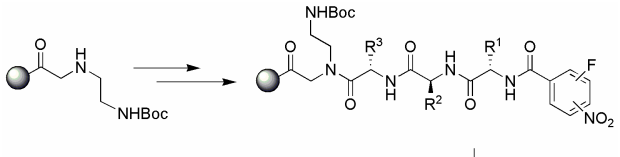
3.2. Synthetic higher *N*-alkyl cyclopeptides

In synthetic studies directed towards bioactive somatostatin analogues,[75] three new cyclopeptoids were prepared. Phenylethylamine-peptoids **51**-**53** were synthesized in solution phase by consecutive peptide couplings of the previously *N*-alkylated moiety with mono-protected amino acids and peptides, followed by the final ring-closing step (Scheme 5). Thus, benzyl, (*R*)-α-methylbenzyl and (*S*)-α-methylbenzylamines were alkylated with ethyl 2-bromoacetate giving rise to the *N*-alkylated amino acids, a process known as submonomer approach in sequential linear peptoid synthesis.[76] These *N*-alkyl amino acids were coupled to *N*-Boc-phenylalanine and phenylalanine benzyl ester to afford the intermediate *N*-alkylated tripeptide, which was additionally coupled to the tripeptide Cbz-D-Trp-Lys(Boc)-Thr(t-Bu)-OH. The final cyclization of the *N*-alkylated hexapeptide was accomplished under high dilution conditions by using DPPA/K_2HPO_4 as the coupling reagents. Conformational analysis[77] of the resulting cyclopeptoids showed that the *N*-alkylation provoked a modification in the bridging region that resulted in an enhanced selectivity to the human somatostatin receptor subtype hsst2. These compounds proved to selectively inhibit the release of growth hormone (GH), but they were found to have no effect on the inhibition of insulin compared to other peptide inhibitors of GH and insulin.

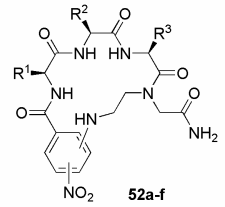


Scheme 5. Structures of somastostatin analogues **51-53** and representative synthesis of cyclopeptoid **51**.

In an attempt to develop an efficient strategy to cyclize tripeptides, Kofod-Hansen and coworkers[78] synthesized six new cyclic tetrapeptoids (Scheme 6). The precursor linear peptoids were prepared by Fmoc solid-phase synthesis and then cyclized by aromatic nucleophilic substitution as shown in Scheme 6. Different amino acids were employed in this synthetic approach, thus providing a high diversity of cyclic peptoids. Both the *N*-substitution and the nonpeptide tether are responsible for the high flexibility of these molecules. This feature was proved by the high number of low energy conformers found in conformational studies.

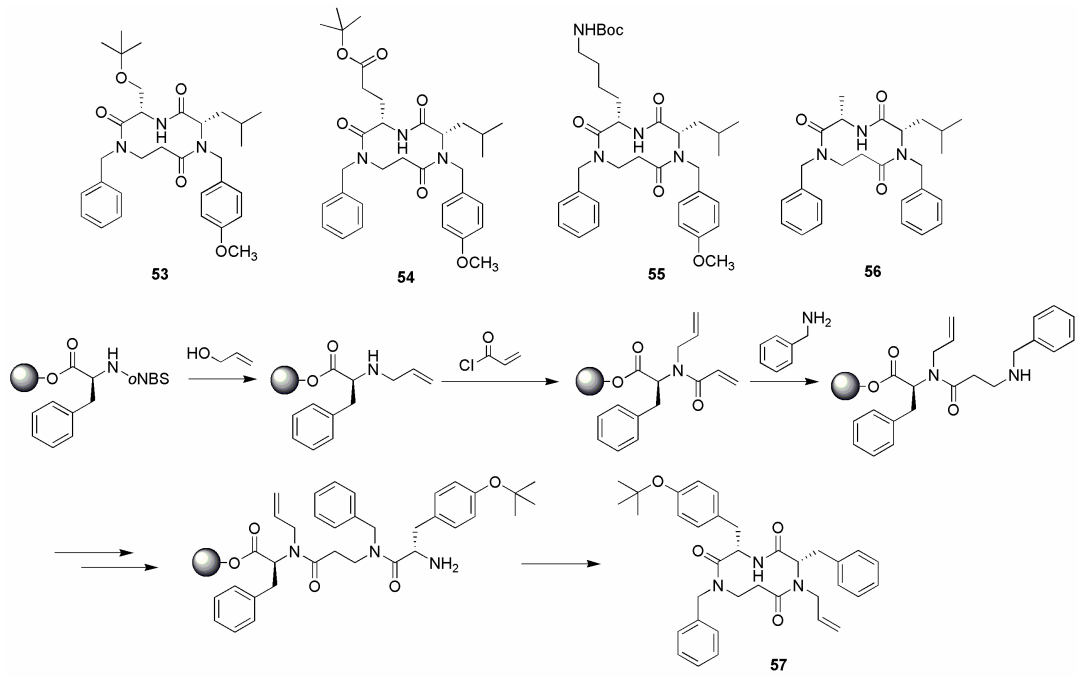


Compound	R^1	R^2	R^3
52a	Gly	Leu	Pro
52b	Gly	Arg	Ala
52c	Met	Pro	Ala
52d	Ala	Trp	Ala
52e	Lys	Pro	Ala
52f	Ala	Ser	Leu



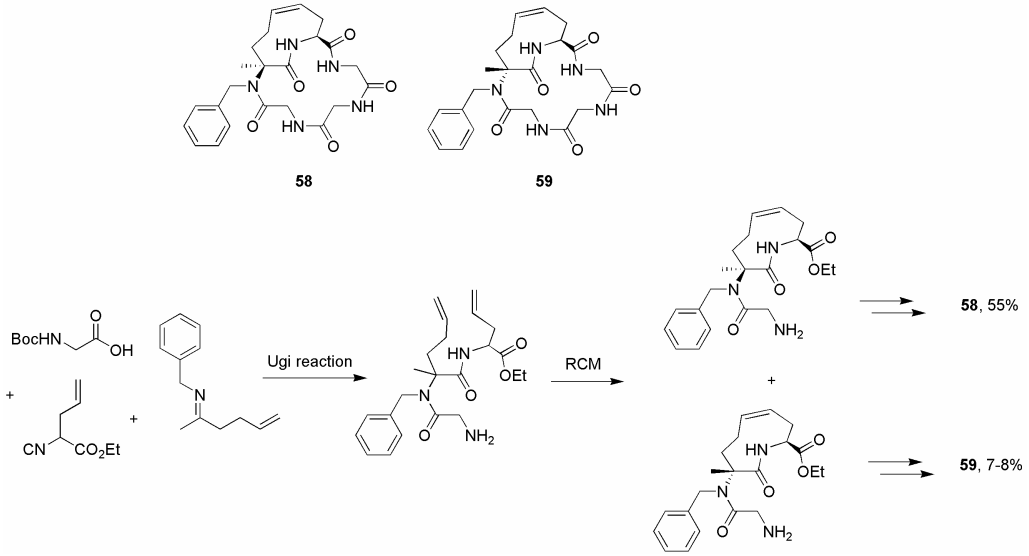
Scheme 6. Synthesis of cyclic peptoids by aromatic nucleophilic substitution of peptoid side chains.

A small array of cyclic peptoids with potential features as β-turn mimetics was produced by Liskamp and coworkers (Scheme 7).[79] Due to the presence of the *N*-substitution, the conversion between the *trans* and the *cis* rotamers was facilitated, thus allowing the cyclization to occur leading to ten-membered ring derivatives. Likewise, the replacement of a natural β-turn elements by a β-peptoid residue provides a covalent control of the turn structure and facilitates the rotation around the amide bond. These cyclopeptoids were synthesized on solid-phase by a Michael addition of a primary amine to a resin-bound acrylate. *N*-Alkylation was accomplished by a Mitsunobu reaction prior to the Michael addition. After coupling with an amino acid, the linear trimer was released from the resin and the cyclization was performed at a concentration of 1 mM. Once more, it must be noted that the challenging ring closure was only possible due to the energetically facile rotation of the tertiary amide bond in peptoids. It also appears to prevent trans-annular cyclization, as "normal"cyclotri- and -tetrapeptides are not stable. A small library of sulfonamide-containing peptoids was also synthesized by employing the same methodology.[80]

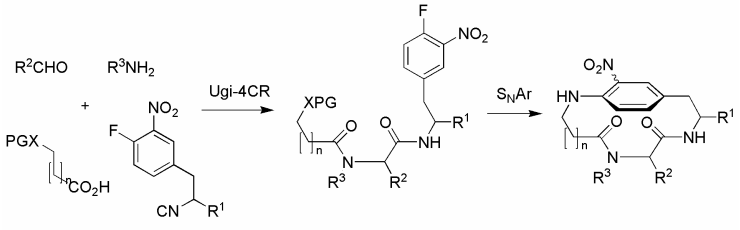


Scheme 7. Synthesis of ten-membered cyclopeptoids.

In a very interesting entry to the field, conformationally restricted cyclic pentapeptoids **58** and **59** were obtained by a tandem Ugi four component reaction/ring closing metathesis (RCM) procedure (Scheme 8). By this reaction sequence, the cyclopeptoid moiety results fused to an unsaturated nine-membered cyclolactam, a feature that decreases the conformational freedom of the system as a whole.[81] The initial *N*-alkylated dipeptide moiety was formed in the Ugi reaction, which after the RCM reaction rendered the functionalized nine-membered lactam as a diasteromeric mixture. This latter mixture was coupled to diglycine methyl ester, followed by removal of the protecting groups and final peptide coupling furnished the cyclic pentapeptoid. Interestingly, only peptoid **58** with *cis* configuration was capable to cyclize in good yield. Although this cyclopeptoid has no biological activity, it was useful to study the macrocyclization of this kind of compound without an interference of more complex substituents.



Scheme 8. Synthesis of conformationally restricted cyclopeptoids by tandem Ugi four component reaction/RCM.



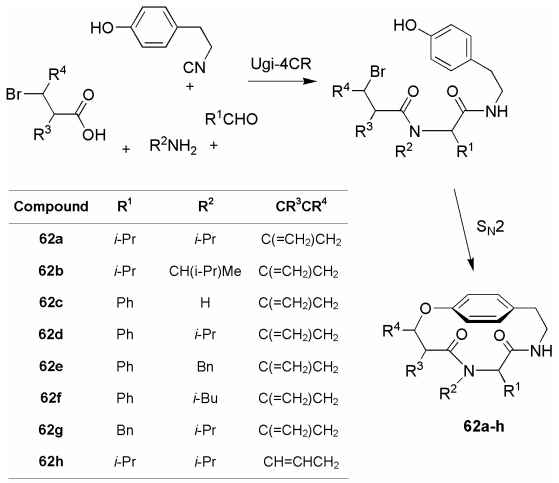
Compound	X	R^1	R^2	R^3
60a	NH	H	*n*-C_6H_{13}	Bn
60b	NH	CO_2Me	Ph	*p*-MeOPh
60c	NH	CO_2Et	*n*-C_6H_{13}	*n*-C_5H_{11}
60d	NH	CO_2Et	*n*-C_6H_{13}	Cyclohexyl
60e	S	CO_2Et	*n*-C_6H_{13}	*n*-C_5H_{11}

Compound	R^1	R^2
61a	*i*-Pr	Bn
61b	CH_2Bn	(CH_2)-2,3DMB

Scheme 9. Zhu-synthesis of *para*-cyclophanes by consecutive Ugi reaction/S_NAr.

The most recent examples of synthetic *N*-alkyl cyclopeptides has been reported by Zhu and co-workers[82] and Wessjohann and coworkers.[83] The corresponding ansa-cyclopeptoids are inspired by natural cyclopeptides alkaloid.[84] The first group synthesized a variety of *para*-cyclophanes using a reaction sequence consisting in an Ugi reaction followed by an intramolecular S_NAr cyclization (Scheme 9). The *N*-alkylation was achieved during the Ugi reaction by employing varied primary amines. This synthetic planning allowed the introduction of four points of diversity within the resulting scaffolds, thus producing a small library of cyclopeptoids.

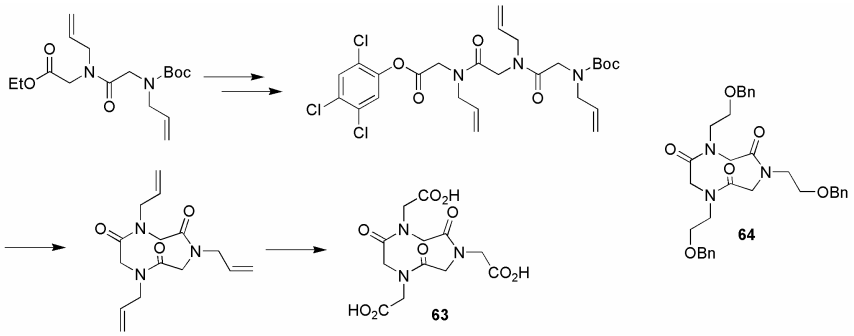
A similar type of compounds, without the nitro group, was achieved by Wessjohann and coworkers (Scheme 10).[83] Their approach also uses the Ugi reaction to build the linear peptoid intermediates, but a nucleophilic substitution is employed for the ring closure.



Compound	R^1	R^2	CR^3CR^4
62a	*i*-Pr	*i*-Pr	$C(=CH_2)CH_2$
62b	*i*-Pr	CH(i-Pr)Me	$C(=CH_2)CH_2$
62c	Ph	H	$C(=CH_2)CH_2$
62d	Ph	*i*-Pr	$C(=CH_2)CH_2$
62e	Ph	Bn	$C(=CH_2)CH_2$
62f	Ph	*i*-Bu	$C(=CH_2)CH_2$
62g	Bn	*i*-Pr	$C(=CH_2)CH_2$
62h	*i*-Pr	*i*-Pr	$CH=CHCH_2$

Scheme 10. Wessjohann-synthesis of *para*-cyclophanes by Ugi reaction/intramolecular ether bond formation.

To our knowledge, the only example of a designed "pure" cyclopeptoid, *i.e.*, a cyclo *N*-alkyl oligoglycine found in the literature is a report of Hioki *et al.* (Scheme 11).[85] Thus, *N,N',N''*-trisubstituted cyclotriglycines **63** and **64** were produced by a typical solution-phase peptide coupling followed by cyclization under high dilution conditions. The desired cyclopeptoids were obtained along with the cyclic dimer (*i.e.*, diketopiperazine) and a substantial amount of the cyclic hexamer. Remarkably, derivatives of compound **63** showed high affinity towards calcium ions, demonstrating that this type of cyclic skeleton can be considered as a template for the development of novel host compounds.



Scheme 11. Synthesis of *N,N',N''*-trisubstituted cyclo triglycines.

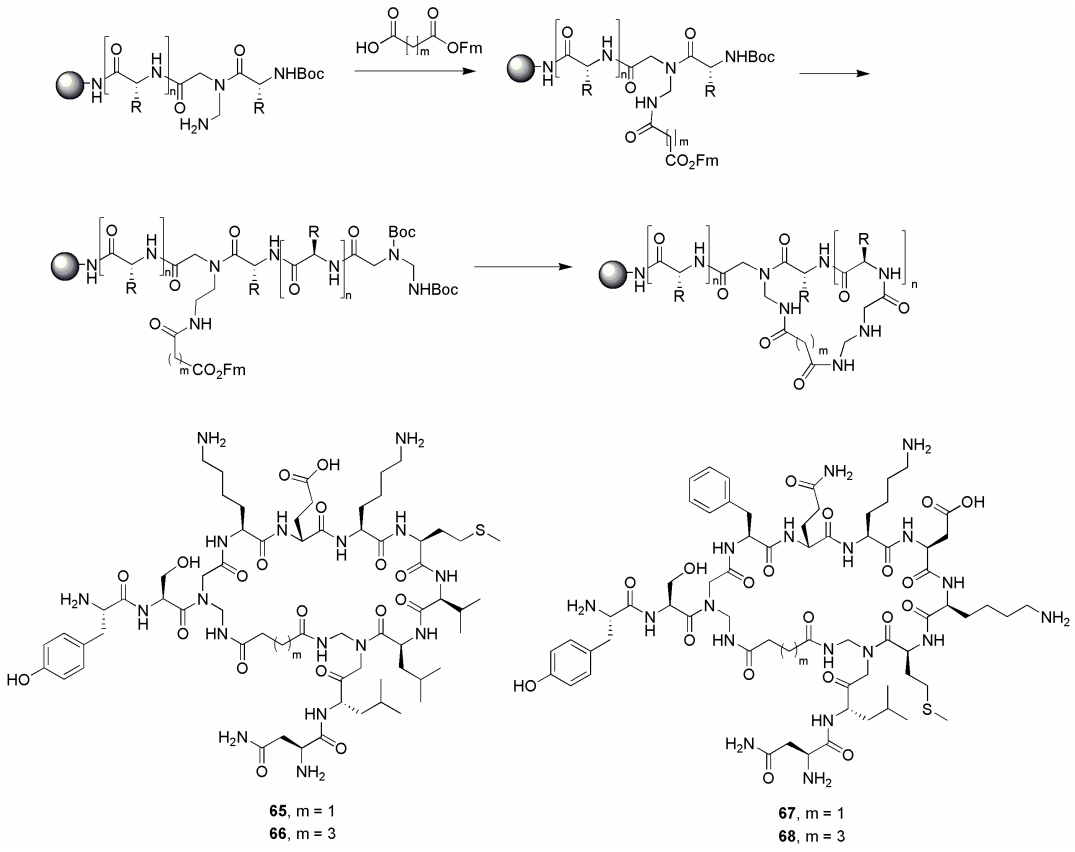
Finally, Failli *et al.* were the first to cyclize oligoglycines by an Ugi reaction generating cyclopeptides with exo-*N*-alkyl moieties.[86]

3.3. Depsipeptides

No higher *N*-substituted depsipeptides of medicinal interest were identified in addition to the previously mentioned *N*-methyl depsipeptides.

3.4. Other synthetic cyclopeptoids

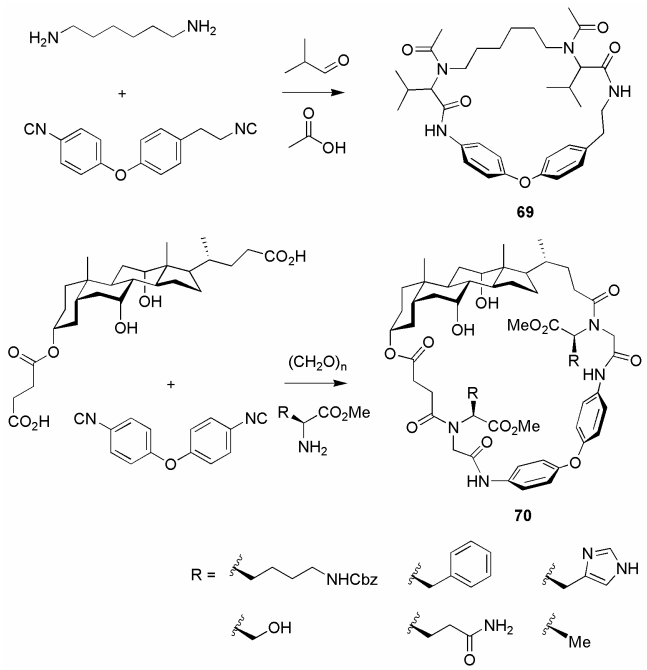
Cyclopeptoids useful for the design of anti-malarial synthetic vaccines were prepared by cyclization of the central part of the 42-61 *N*-terminal of the parasitic Merozoiote Surface Protein 1 (MSP-1) fragment (Scheme 12).[87] As the cycle is a combination of a peptide with tether chains derived from aliphatic diacids or diamines, it cannot be included as a cyclopeptide. Cyclization was performed by introducing the aminoethylglycine subunits into the peptide sequence, linked by diacid bridges of different lengths. The peptide sequences were synthesized by Boc solid-phase peptide synthesis. All cyclopeptoids showed immunological activity, whereas the linear analogues exhibited no activity at all. This finding suggested that the conformational constrain introduced by the cyclization process is important for epitope immunogenicity.



Scheme 12. Synthesis of potential anti-malarial cyclopeptoids.

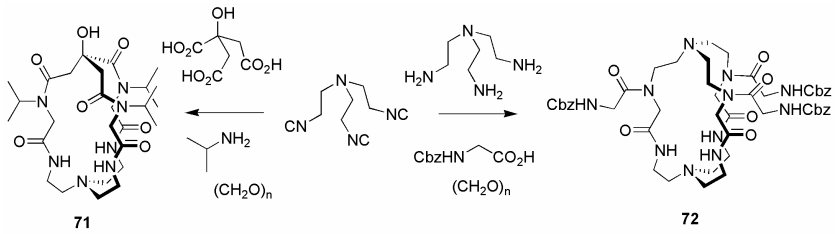
A library of peptoid-containing steroid-biarylether hybrid macrocycles was prepared by multiple multicomponent macrocyclization including bifunctional building blocks (MiB). This synthetic strategy, developed in the Wessjohann group proved suitable for the diversity-oriented synthesis of macrocycles (Scheme 13).[88-90] The macrocyclization was achieved by combining two Ugi reactions that include two

bifunctional building blocks into the final hybrid scaffolds. Additionally, the methodology showed to be very straightforward and versatile to generate libraries of cyclic peptoids with functional and skeletal diversity. Natural product-inspired biaryl ether-cyclopeptoid macrocycles were also obtained by this methodology.[89,90]



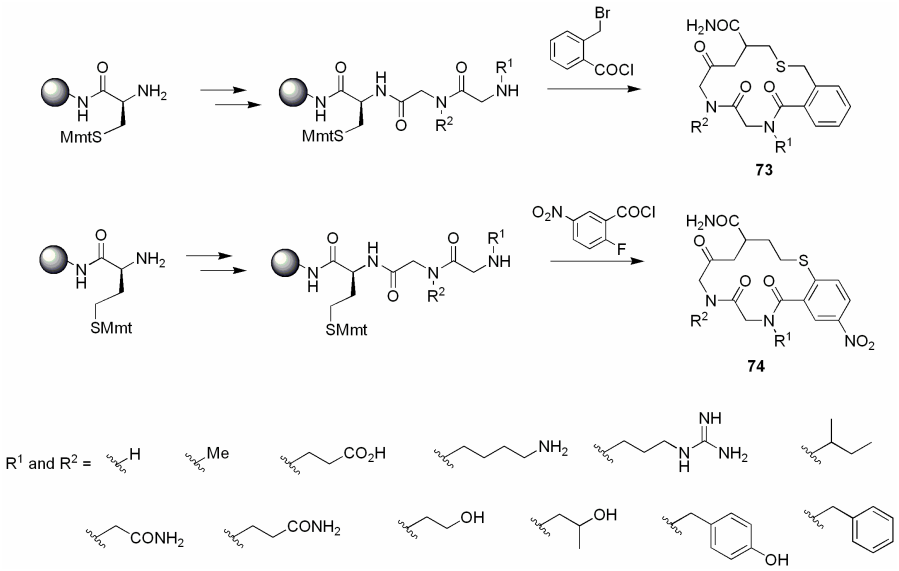
Scheme 13. Library of peptoid-biaryl ether hybrid macrocycles produced by double multicomponent macrocyclizations.

Using the same strategy, but with polyfunctional building blocks, a variety of peptoid-based cryptands, cages and cryptophanes was synthesized by the Wessjohann group (Scheme 14).[91] These complex macrobicycles were assembled by the incorporation of 8 building blocks, forming 12 new bonds in a one-pot reaction.



Scheme 14. Macrobicycles prepared by threefold multicomponent macrocyclizations.

Burgess and Nnanabu synthesized a small library of peptoid-organic hybrid macrocycles featuring the general structures **73** and **74** (Scheme 15).[92] The peptoid moiety was assembled by a mixture of microwave-assisted submonomer and monomer protocols. The cyclization was accomplished by a microwave-assisted S_N2 ring closure reaction on-resin. For peptoids of structures such as **74**, a microwave-assisted S_NAr reaction was used for the cyclization step. These compounds were expected to have improved pharmacological properties compared to peptides and linear peptoids.



Scheme 15. Synthesis of sulfide peptoid-organic hybrid macrocycles.

4. Proline-containing cyclopeptides and depsipeptides

Proline-containing cyclopeptides may be considered a special type of peptoid because the tertiary amide bond present in these compounds is not only restricted in rotationfrom the macrocyclic conformational constraints, but additionally and often more severely along the N-Cα--bond by the five-membered ring. Also, in principle, it is accessible by ribosomal peptide synthesis of a linear precursor, although small cyclic peptides are often formed by non-ribosomal peptide synthases (NRPS) as has been reviewed elsewhere.[2a] Accordingly, proline is the most abundant "peptoid" moiety in nature (cf. collagen). Herein, just a few but representative examples of this important class of cyclopeptides are shown.

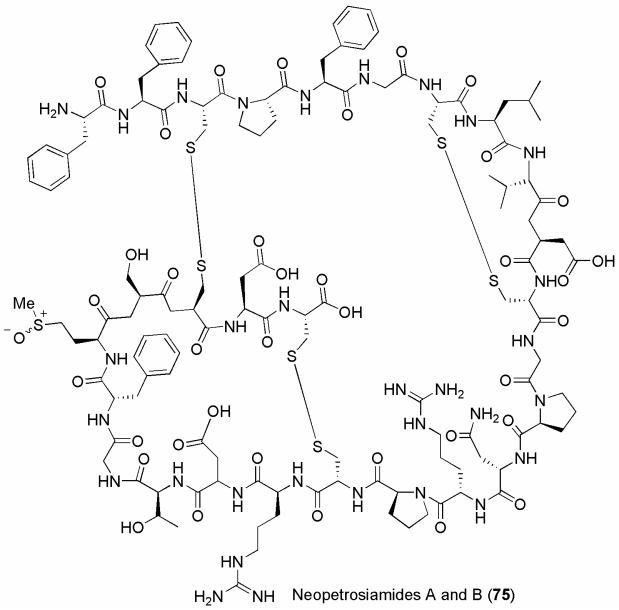


Figure 20. Structure of Neopetrosiamides A and B.

Besides proline, cyclo(depsi)peptides with a pipecolic acid residue underly similar constraints. However, they are more flexible, have different favorable angles than proline and, of course, are not "ribosomal". There are several examples where the six-membered pipecolic acid moiety cannot be

substituted by the cheaper building block proline,[53a,72] *e.g.* in enopeptide derivatives where *N*-methylalanine can be substiuted by pipecolic acid but not by proline without losing activity. Since pipecolic acid is also commonly found in *N*-methylated compounds, some relevant examples were already discussed above.

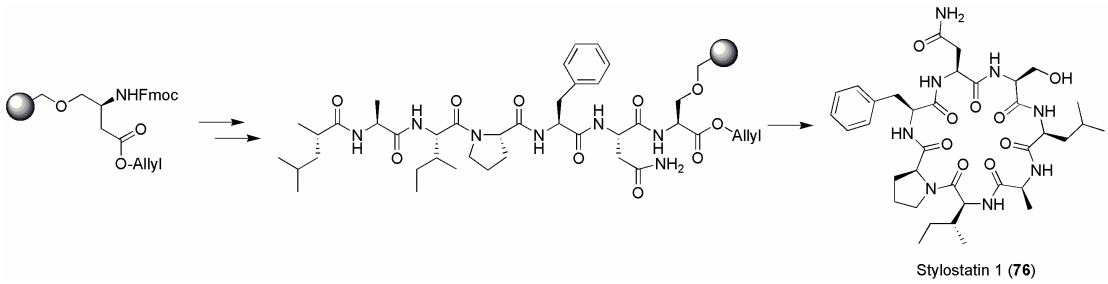
4.1. Natural disulfide bridge proline-containing cyclopeptides

Recently, Neopetrosiamides A and B (**75**) were isolated from the marina sponge *Neopetrosia* sp. collected in Papua New Guinea (Figure 20).[93] These compounds are tricyclic peptides including three proline and containing three disulfide bridges. They proved to be potential inhibitors of amoeboid tumor invasion. So far, no synthesis of this family of compounds has been reported.

4.2. Proline-containing cyclopeptides

4.2.1. Natural derivatives

The cyclic heptapeptide Stylostatin 1 (**76**) was isolated from *Stylotella aurantium* and has one proline residue within its structure (Scheme 16).[94] The most recent synthesis of this peptide used a solid-phase strategy wherein the resin was anchored by the serine side chain.[95] After attachment of Fmoc-serine to the resin, the peptide was grown using the Fmoc solid-phase synthetic protocol and cyclized on-resin. Another synthesis was also performed by a Boc solid-phase peptide synthesis strategy.[96]



Scheme 16. Synthesis on-resin of Stylostatin 1.

Diandrines A-D (**77**-**79**) were isolated from *Drymaria diandra* and were identified as cyclopeptides containing two proline residues in their structures (Figure 21).[97] Diandrine A (**77**) was the only cyclopeptide in the series in which the amide bonds of proline adopt a *cis* configuration. The other three cyclopeptides isolated had a *trans* configuration in both proline residues. Only diandrine A exhibited inhibition against collagen-induced platelet aggregation and seems to be the first cyclopeptide that shows this kind of selectivity.

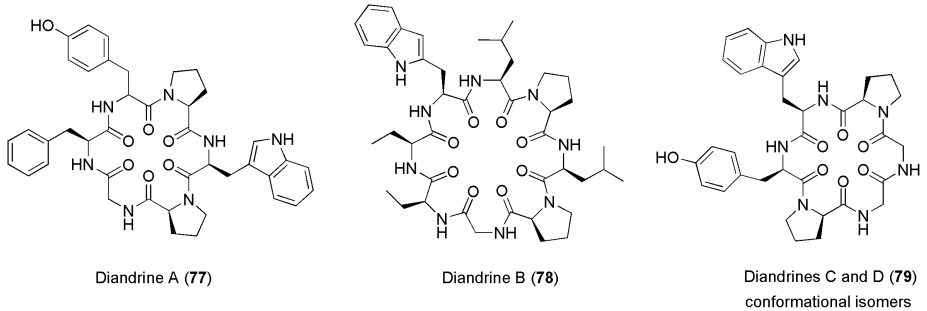


Figure 21. Structures of diandrines A-D.

Cyclosenegalin A (**80**) and B (**81**) were isolated from the seeds of *Annona senegalensis* and have one and three proline residues in their structures, respectively (Figure 22).[98] In a similar way as shown for other cyclopeptides, the presence of proline showed to have a marked influence on the conformational constrains of such compounds.

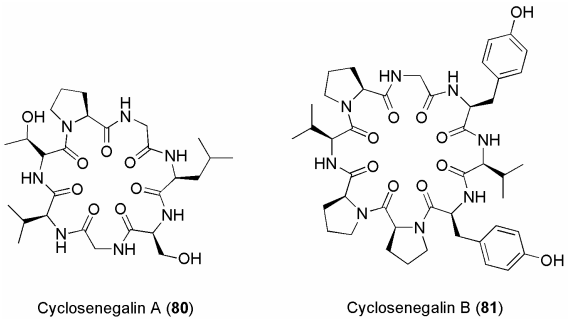


Figure 22. Structures of cyclosenengalins A and B.

Hymenamide C (**82**) was isolated from marine sponge *Axinella carteri* and is a cyclopeptide that contains two proline units (Figure 23).[99] This peptide was synthesized by solid-phase synthesis, where the resin was attached to the glutamine side chain. After peptide elongation, the heptapeptide was cyclized on-resin. The compound showed interfering activities with immune cells, more specifically, inhibition of the elastase degranulation release.

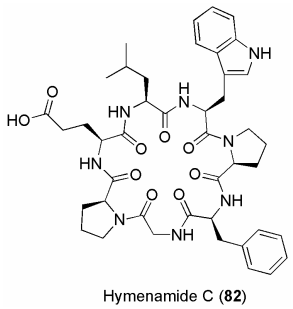


Figure 23. Structure of hymenamide C.

4.2.2. Synthetic derivatives

Cyclopeptides of the general formula **83** are regioselectively addressable functionalized templates (RAFT[100]) (Figure 24).

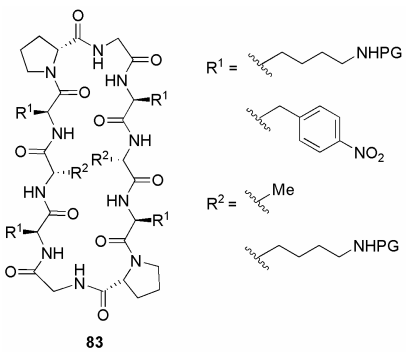


Figure 24. Structure of RAFT cyclopeptides.

These compounds incorporate two proline-glycine sequences as β-turn inducers to constrain the backbone conformation into an antiparallel β-sheet.[101] Cyclopeptides **83** were synthesized by a Fmoc solid-phase peptide synthesis protocol and the cyclization was accomplished in solution phase after the release from the resin. These topological templates represent a powerful tool in protein design and mimicry.

4.3. Natural proline-containing depsipeptides

Petrosifungins A (**84**) and B (**85**) are depsipeptides isolated from a sponge-derived strain of *Penicillium brevicompactum* that have one proline and two pipecolic acid residues (Figure 25).[102] An interesting feature of these two compounds is the presence of three cyclic amino acids in sequence, a characteristic never before observed in natural cyclopeptides.

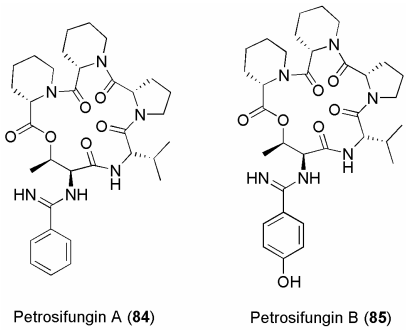
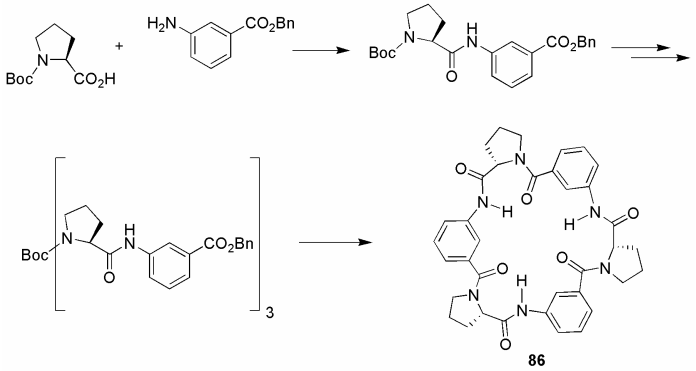


Figure 25. Structures of petrosifungins A and B.

4.4. Synthetic proline-containing cyclopeptoids

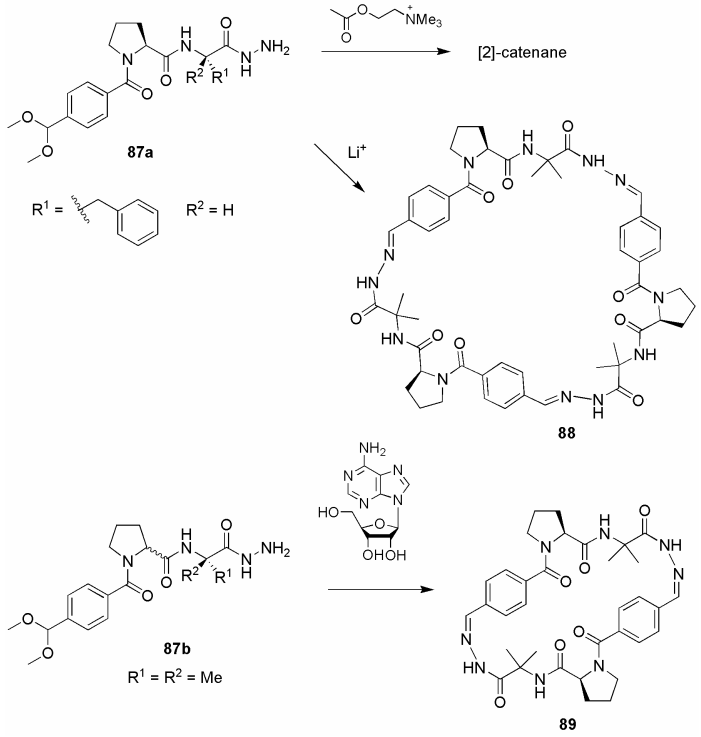
Cyclopeptoid **86** is composed of (L)-proline and 3-amino benzoic acid subunits was obtained by Kubik and Goddard and can act as ion receptor (Scheme 17).[103] The compound was synthesized by coupling Boc-(L)-proline with benzyl-3-aminobenzoate followed by peptide sequence elongation up to the tetra- and hexapeptides. The cyclization was accomplished under high dilution conditions by normal peptide coupling. Proline amide bonds adopted a *trans* configuration in solid and solution state. It was demonstrated that the proline subunits have a significant effect on the conformational behavior and binding properties of these molecules. Cyclopeptoids with similar structures were also synthesized and shown to act as receptors towards varied guests.[104-106]



Scheme 17. Synthesis of a proline-containing ion receptor.

By using dynamic combinatorial libraries (DCL) based on hydrazone exchange, different proline-containing peptoid macrocycles were obtained from building block **87** (Scheme 18). Interestingly, the

formation propensity of different macrocycles was determined by the addition of varied guests to bias the DCL. *E.g*, by utilizing Li^+ as template the DCL was shifted towards the macrocyclic trimer **88**.[107] However, when acetylcholine was employed as template, a [2]-catenane containing two interlocked 42-membered rings was preferentially formed over the days.[108] On the other hand, the stereoselectively pure macrocyclic dimer **89** was favored over the racemic building block **87b** by using (-)-adenosine as a template.[109] Indeed, the use of proline as a turn element plays an important role in the formation of the macrocyclic hosts, which are amplified under thermodynamic control within the DCL.



Scheme 18. Synthesis of different macrocycles by template-induced dynamic combinatorial library (DCL).

5. Conclusions

Many naturally occurring and synthetic *N*-alkylated cyclopeptides are known and some have been reviewed herein with an emphasis on recent work. Most natural compounds presented have interesting biological activities, even without knowing their natural purpose. Proline appears to have a similar role as in linear peptides. More unique is the role of *N*-methylation, which not only facilitates amide *cis*/*trans* isomerization, but also imposes biological (metabolic) as well as chemical (transannular) stability. Another important issue that must not be underestimated is the increased lipophilicity and thus bioavailability and altered tissue distribution induced by *N*-alkylation. It is also noteworthy that many synthetic cyclopeptoids, apart from biological mimicry, also can act like receptors or host molecules. These properties also can be modified by *N*-alkylation, that brings great conformational changes into the structure of a peptide. *E.g.*, with the decrease of the energy barrier between *cis* and *trans* configuration of amide bonds, sometimes improvements in the inner space and binding properties of these compounds are observed.

Cyclopeptoids encompass a class of target molecules very attractive either in drug discovery or for the achievement of synthetic receptors. It is remarkable that only very few cyclo *N*-alkyl polyglycines are found in the literature. This shows that the field is quite unexplored yet, but based on the many active natural

products related, it may become a relevant topic of research. The major challenge in the design of new lead compounds based on this type of scaffolds is the achievement of derivatives with enhanced bioavailability and metabolic stability without the lost of biological activity. A crucial issue to success is understanding the volatile folding characteristics of (cyclic) peptoids and peptide-peptoid chimaerics, as so efficiently started by Kessler.[9]

List of abbreviations

Adda: (2*S*, 3*S*, 8*S*, 9*S*, 4*E*, 6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid
Ahp: 3-amino-6-hydroxy-2-piperidone
BDMP: 5-(1*H*-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2*H*-pyrrolium hexachloroantimonate
BEMT: 2-bromo-3-ethyl-4-methylthiazolium tetrafluoroborate
BEP: 2-bromo-1-ethyl-pyridinium tetrafluoroborate
Boc: *t*-butoxy-carbonyl
BOP: benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
Cbz: benzyloxycarbonyl
DCL: dynamic combinatorial library
DCM: dichlorometane
DDAA: didehydroamino acid
DGCN: (*R*)-2-hydroxy-4-cyanobutyric acid
DIPEA: diisopropylethyl amine
DIPCDI: *N,N*'-diisopropyl carbodiimide
DKP:diketopiperazine
DMF: *N,N*-dimethyl formamide
DPPA: diphenylphosphoryl azide
EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FDPP: pentafluorophenyl diphenylphosphinate
Fmoc: 9-fluorenylmethyloxycarbonyl
GH: growth hormone
HAPyU: 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium *N*-oxide hexafluorophosphate
HATU: *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HIV: human immunodeficiency virus
HOAt: 1-hydroxy-7-azabenzotriazole
HOBt: 1-hydroxy-1*H*-benzotriazole
MSI: microsatellite instability
MSNT: 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole
NMI: *N*-methylimidazole
NMR: nuclear magnetic resonance
*o*NBS: orto-nitrobenzyl sulfonyl
PyAOP: (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
PyBOP: benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

PP1: protein phosphatase 1

SAR: structure-activity relationship

RCM: ring closing metathesis

S_NAr: aromatic nucleophilic substitution

S_N2: bimolecular nucleophilc substitution

TBTU: *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate

THF: tetrahydrofurane

Trt: trityl = triphenylmethyl

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MULTI-COMPONENT SYNTHESES OF HETEROCYCLES BY VIRTUE OF PALLADIUM CATALYZED GENERATION OF ALKYNONES AND CHALCONES

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Dedicated to Prof. Dr. Klaus Hafner on the occasion of his 80th birthday

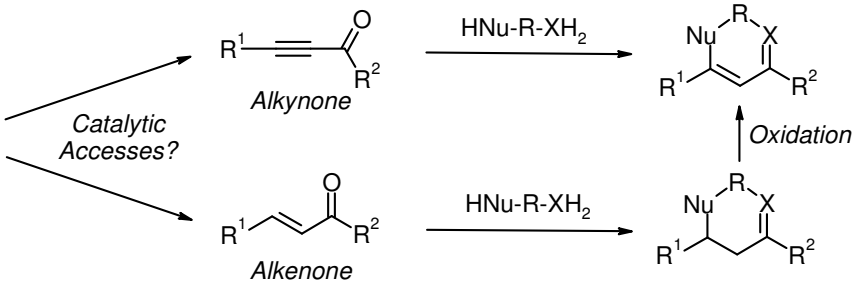
Abstract. *Alkynones and chalcones are of paramount importance in heterocyclic chemistry as three-carbon building blocks. In a very efficient manner, they can be easily generated by palladium-copper catalyzed reactions: ynones are formed from acid chlorides and terminal alkynes, and chalcones are synthesized in the sense of a coupling-isomerization sequence from (hetero)aryl halides and propargyl alcohols. Mild reaction conditions now open entries to sequential and consecutive transformations to heterocycles, such as furans, 3-halo furans, pyrroles, pyrazoles, substituted and annelated pyridines, pyridimines, benzoheteroazepines and tetrahydro-β-carbolines, by consecutive coupling-cyclocondensation or coupling-isomerization-cyclocondensation sequences, as new diversity oriented routes to heterocycles.*

Contents

1. Introduction

An increasing demand for rapid syntheses of functional molecules has stimulated synthetic chemists to seek and devise fruitful strategies that inevitably address the very fundamental principles of efficiency and efficacy. Besides chemo-, regio- and stereoselectivity, they also encompass economical and ecological aspects. Therefore, the intellectual challenge to create concise, elegant and conceptually novel synthetic routes has become a steadily accelerating driving force both in academia and industry. In the past decade the productive concepts of multi-component processes have considerably stimulated the synthetic scientific community.[1,2] In particular, these diversity oriented syntheses[3] are demanding challenges for synthetic efficiency and reaction design. Mastering unusual combinations of elementary organic reactions under similar conditions is the major conceptual defiance in engineering novel types of sequences. From a practical point of view combinatorial chemistry[4] also offers manifold opportunities for conducting diversity oriented syntheses. Thus, the prospect of expanding one-pot reactions into combinatorial and solid phase syntheses[2d,5] promises multiple opportunities for developing novel lead structures of pharmaceuticals, catalysts and even novel molecule based materials.

Classically, five-, six-, and seven-membered heterocycles can be synthesized from reactive three-carbon building blocks such as alkynones[6-9] and 1,3-diaryl propenones (chalcones),[10-12] which can react with bifunctional nucleophiles in a sequence of Michael addition and cyclocondensation (Scheme 1). As a consequence, this general strategy has found broad application. However, standard syntheses of alkynones[13] and chalcones[14] are often harsh and require either strongly basic or strongly Lewis or Brønsted acidic conditions. Therefore, the application in one-pot methodology, where delicately balanced reaction conditions are prerequisite, is largely excluded.

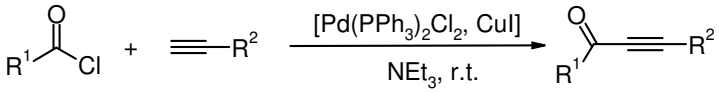


Scheme 1. Ynones and enones as three-carbon building blocks in heterocycle synthesis.

Hence, mild reaction conditions for the catalytic generation of ynones and enones, which are compatible with following transformations, are highly desirable. In particular, transition metal catalysis opens many opportunities for functional group tolerant product formations. This account summarizes a concept developed in recent years, where palladium-copper catalyzed coupling reactions are used for generation of ynones and enones as an entry to consecutive multi-component syntheses of heterocycles.

2. Multi-component syntheses of heterocycles *via* alkynones by coupling-addition sequences

Sonogashira coupling,[15] a palladium-copper catalyzed alkynylation of (hetero)aryl halides, is particularly mild alkyne synthesis and, hence, alkynones **3** can be easily prepared from acid chlorides **1** with terminal alkynes **2** (Scheme 2).[16]



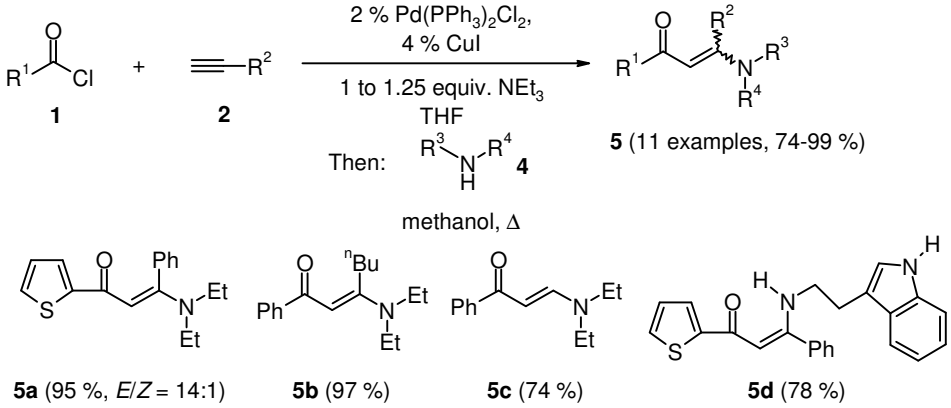
1 **2** **3**

Scheme 2. Alkynones by Sonogashira coupling.

Upon optimization we found that only one equivalent of triethylamine, necessary for binding hydrochloric acid, is actually needed for complete conversion. This not only reduces the amount of base but also leads to an essentially base-free reaction medium after the cross-coupling event.[17] With this methodological improvement in hand the stage was set for the generation of alkynones under conditions and in media where consecutive reactions in a one-pot fashion could easily follow.

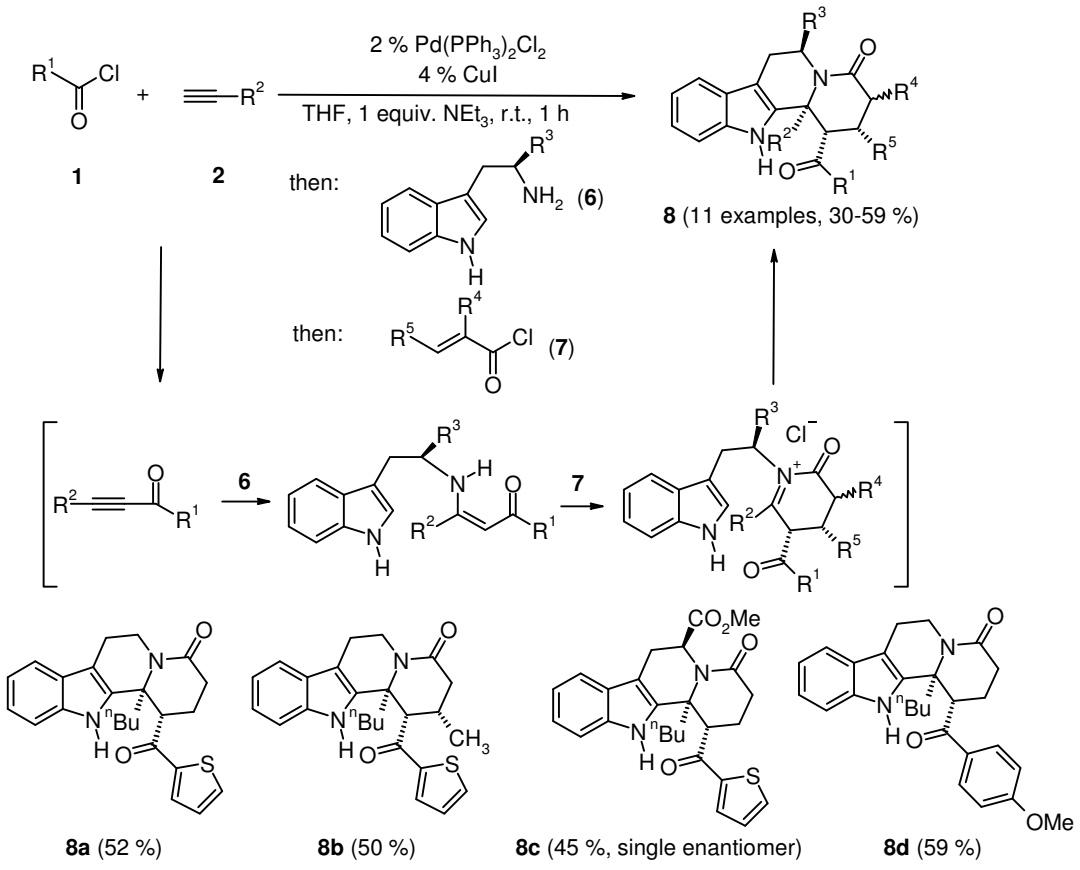
In the sense of a consecutive three-component one-pot reaction, after reacting various acid chlorides **1** with terminal alkynes **2** under modified Sonogashira conditions to furnish the desired alkynones and subsequent addition of primary and secondary amines **4**, heating for several hours furnishes the enaminones **5** in good to excellent yields (Scheme 3).[17,18] Primary amines give rise to the formation *Z*-enaminones **5** (R^4 = H), whereas secondary amines furnish *E*-enaminones **5** ($R^4 \neq$ H) in good *E*/*Z*-selectivity. This one-pot

coupling-addition enaminone synthesis is of a fairly broad scope and of excellent chemoselectivity. *E.g.*, tryptamine (example **5d**) neither needs to be protected at the indole nitrogen nor any enamine side reaction can be detected.



Scheme 3. Three-component synthesis of enaminones **5**.

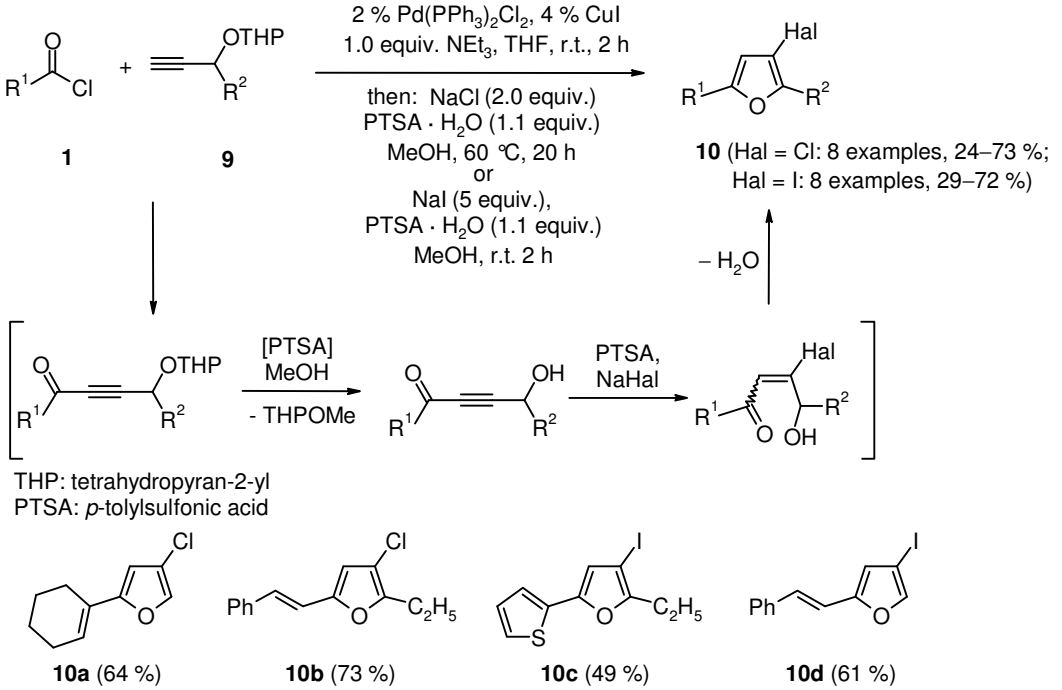
In agreement with the fundamental principles of multi-component reactions, products of consecutive transformations are to contain substantial fragments of all starting materials, thus providing a high degree of atom-efficiency. Hence, the use of β-enaminones **5** in the heterocyclic synthesis as synthetic equivalents of 1,3-dicarbonyl compounds would only result in an additional step in a reaction sequence, since ynones react with binucleophiles as well giving rise to the same products. On the other hand, it could be even more useful to take advantage of the unique electronically amphoteric reactivity of β-enaminones **5** trying to conserve all atoms in the final product, including the enamino nitrogen atom.



Scheme 4. Four-component synthesis of tetrahydro-β-carbolines **8**.

With this respect we have developed a consecutive four-component synthesis of tetrahydro-β-carbolines **8** that can be rationalized as a coupling-aza-annulation-Pictet-Spengler (CAAPS) sequence (Scheme 4).[19] After the formation of the alkynone **3**, a tryptamine derivative **6** is added to give the corresponding enaminone. Then, the addition of the α,β-unsaturated acid chloride **7** generates in an aza-annulation step an acyliminium ion that is prone to undergo a Pictet-Spengler cyclization.

As mentioned before, only one stoichiometrically necessary equivalent of triethylamine is consumed in the alkynone synthesis, the reaction medium is essentially base free. These peculiar circumstances have now paved the way to subsequent steps under Brønsted or Lewis acidic conditions, yet in a one pot fashion. Therefore, in the sense of a sequence of Sonogashira coupling of acid chlorides **1** and THP-protected propargyl alcohols **9** and acid-mediated nucleophilic addition to the ynone intermediate with concomitant deprotection and cyclocondensation 3-halo furans **10** can be obtained in moderate to good yields (Scheme 5).[20]



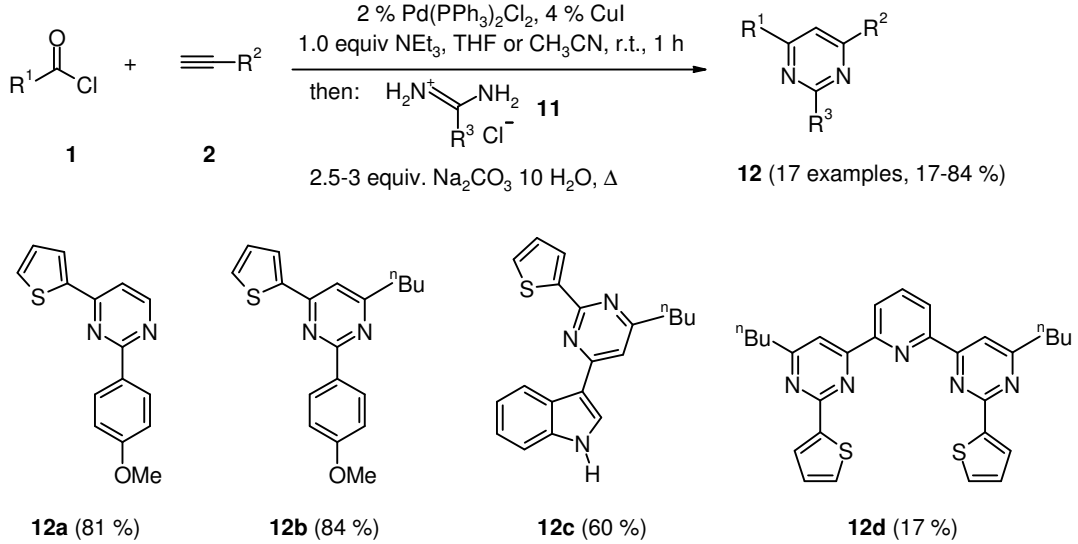
Scheme 5. Three-component synthesis of 3-halo furans **10**.

Likewise, iodine monochloride as an electrophile opens a straightforward access to 3-chloro-4-iodo furans.[20b] It is noteworthy to mention that the 3-iodo furans **10** (Hal = I) can be coupled with boronic acids in a Sonogashira-addition-cyclocondensation-Suzuki sequence in a pot fashion, since the palladium catalyst is still active after the acid-mediated Michael addition.[20a]

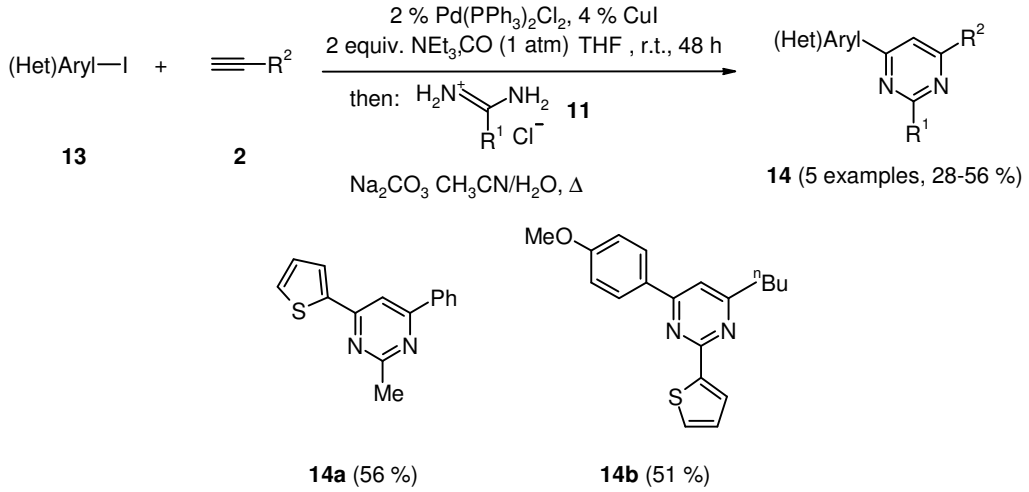
As already indicated, alkynones **3** could be reacted without isolation with difunctional nucleophiles to furnish heterocycles. Therefore, a consecutive three-component synthesis of 2,4-disubstituted and 2,4,6-tri-substituted pyrimidines **12** is based upon the sequence of Sonogashira coupling and subsequent cyclocondensation with amidinium salts **11** (Scheme 6).[17,18] Interestingly, this one-pot reaction can also be applied to furnish complex pyrimidines such as the ligand type system **12d**.

An alternative approach to alkynones, yet with only little literature precedence, is the carbonylative alkynylation.[21] We have adapted our modified Sonogashira protocol to the carbonylative coupling of (hetero)aryl iodides **13** and alkynes **2** and subsequent cyclocondensation with amidinium salts **11** to furnish

2,4,6-trisubstituted pyrimidines **14** in moderate yields in the sense of a four-component one-pot reaction (Scheme 7).[22] Additionally, we have applied this approach, however, as a two step carbonylative alkynylation-cyclocondensation sequence to concise syntheses of naturally occurring and highly biologically active meridianines.



Scheme 6. Three-component synthesis of pyrimidines **12**.



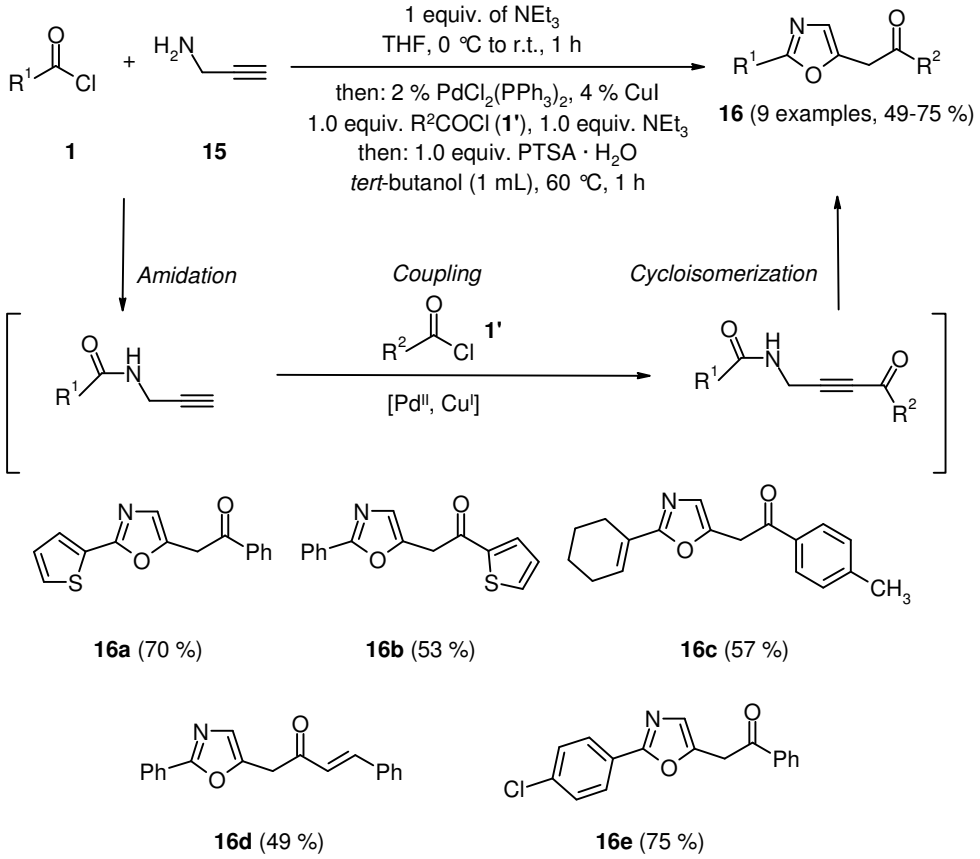
Scheme 7. Four-component synthesis of pyrimidines **14**.

Finally, the intermediacy of functionalized alkynones generated by the coupling of acid chlorides **1'** and propargyl amides, that have been prepared in the same pot in a preceding amidation of propargyl amine (**15**) with acid chlorides **1**, can also undergo a cycloisomerization to give functionalized oxazoles **16** in good yields in the sense of a amidation-coupling-cycloisomerization sequence (Scheme 8).[23]

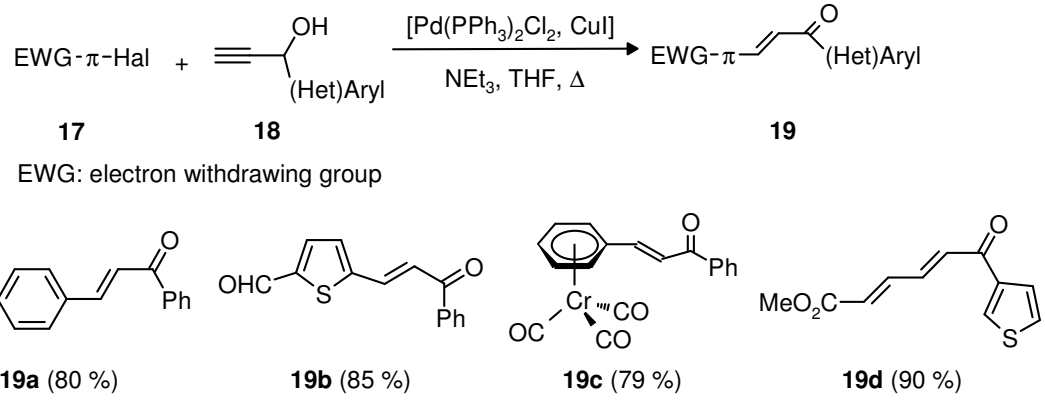
3. Multi-component syntheses of heterocycles *via* chalcones by coupling-isomerization sequences

As pointed out before enones and, in particular, chalcones (1,3-diaryl propenones) are predominantly synthesized under aldol conditions, which are relatively harsh and not always suitable for establishing multi-component synthesis. However, a couple of years ago we have disclosed a new mode of alkyne activation towards isomerization as a detouring outcome of the Sonogashira coupling. As a result of coupling electron

deficient (hetero)aryl halides (or α,β-unsaturated β-halo carbonyl compounds) **17** and aryl propargyl alcohols **18** a new access to 1,3-di(hetero)aryl propenones **19**, *i.e.* chalcones, was developed (Scheme 9).[24]



Scheme 8. Three-component synthesis of oxazoles **16**.

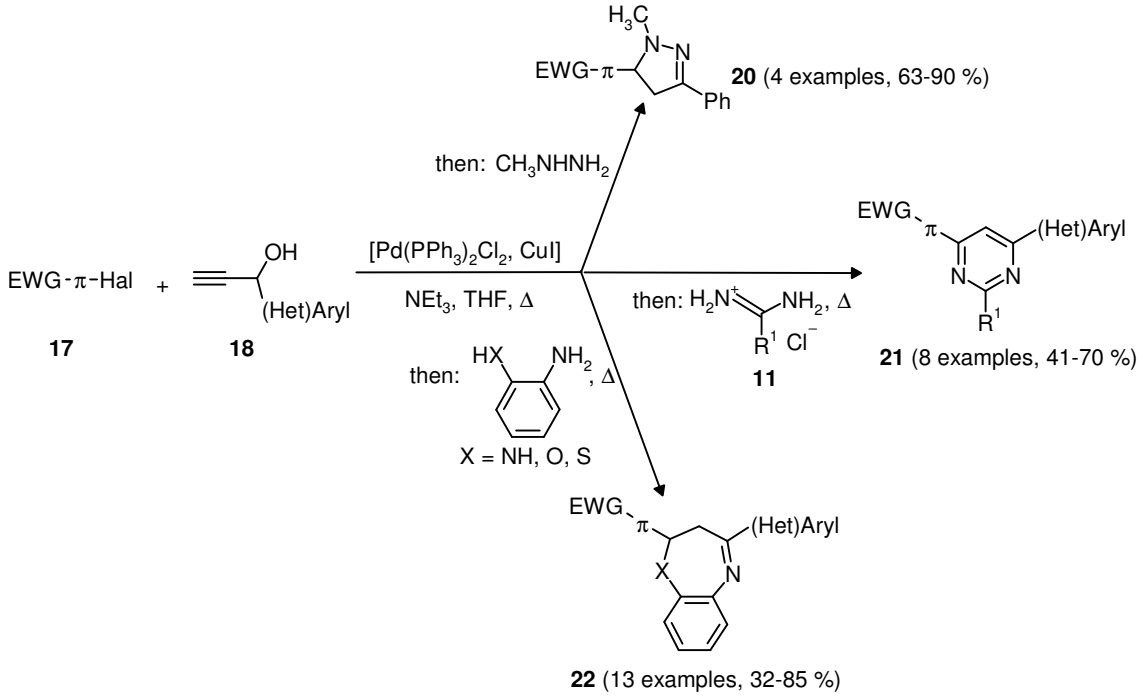


Scheme 9. Chalcones **19** by coupling-isomerization reaction (CIR).

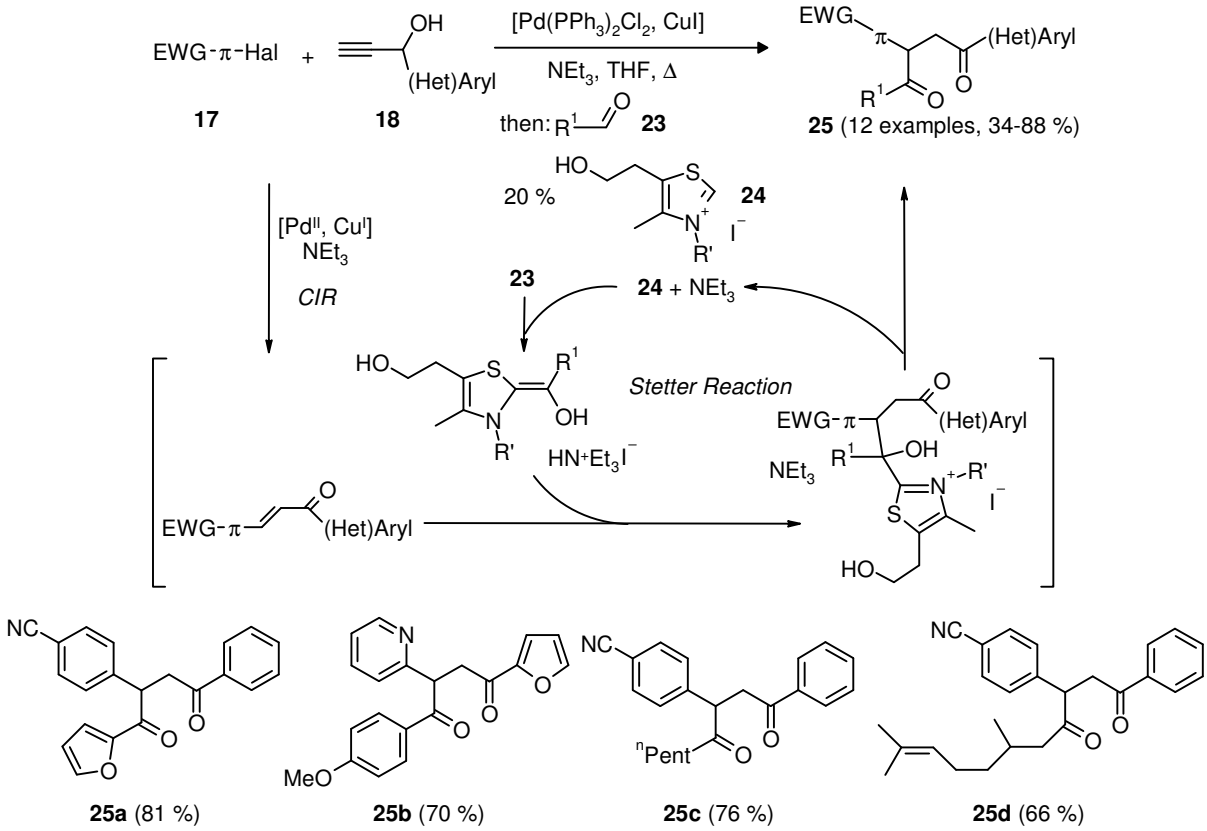
In the sense of a coupling-isomerization reaction (CIR) a slow base catalyzed isomerization transforms the initial coupling product, *i.e.* a propargyl alcohol, into the chalcone **19**. The scope for acceptor substituents on the halide **17** is fairly broad and even organometallic complexes like **19c** can be synthesized by this sequence.

Mild reaction conditions for the generation of a Michael system in a weakly basic medium has opened an entry to novel consecutive multi-component syntheses of pharmaceutically relevant heterocycles in a one-pot fashion. Thus, standard heterocycle syntheses of pyrazoles **20**,[24] pyrimidines **21**,[25] and benzohetero-

azepines **22**[26] can be readily established and give rise to the formation of these heterocycles in moderate to good yields (Scheme 10).



Scheme 10. Three-component synthesis of pyrazoles **20**, pyrimidines **21**, and benzoheteroazepines **22** by CIR-cyclocondensation.

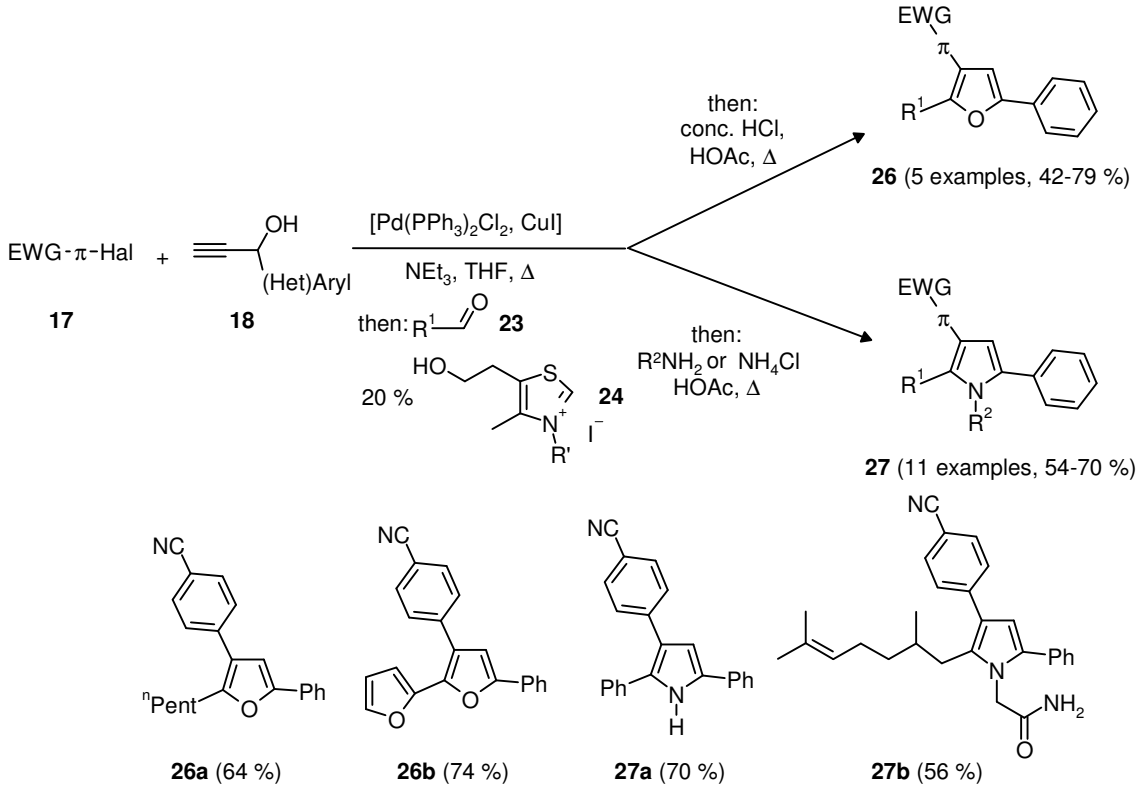


Scheme 11. Three-component synthesis of 1,4-diketones **25** by CIR-Stetter reaction.

Interestingly, the conditions of CIR are fully compatible with the organocatalytic Stetter reaction. Therefore, in a sequence of transition metal, base and organocatalysis, upon CIR of **17** and **18** with

subsequent addition of aliphatic or aromatic aldehydes **23** and catalytic amounts of thiazolium salt **24** the 1,4-diketones **25** are obtained in moderate to excellent yields (Scheme 11).[27]

This straightforward three-component approach to 1,4-diketones readily expands to a CIR-Stetter-Paal-Knorr synthesis of furans **26** and pyrroles **27** in the sense of a consecutive three-component or four-component reaction in a one-pot fashion (Scheme 12).[27]



Scheme 12. Four-component synthesis of pyrroles **26** and furans **27** by CIR-cyclocondensation.

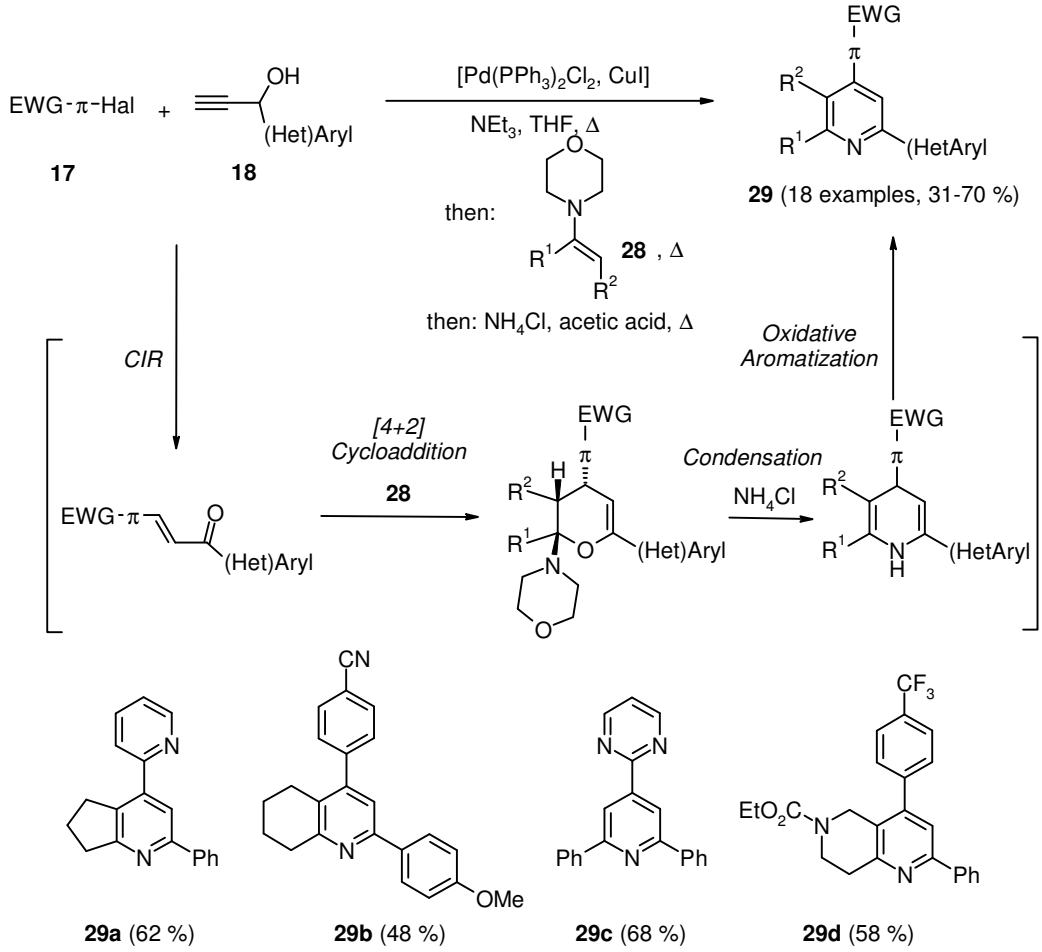
Interestingly, besides the diversity oriented synthetic aspect all these novel furans and pyrroles exhibit a strong blue fluorescence with considerable Stokes shifts.

Additionally, besides Michael additions the mild reaction conditions of CIR are also compatible with cycloadditions. Chalcones can be considered as heterodienes and by Diels-Alder reaction with inverse electron demand they are applicable in heterocycle synthesis. Therefore, after CIR (hetero)cyclic and acyclic morpholino enamines **28** are added and, finally, after adding ammonium chloride in the presence of acetic acid annelated (dihydropyrindines, tetrahydroquinolines, naphthyridines) and substituted pyridines **29** are formed in moderate to good yields (Scheme 13).[28]

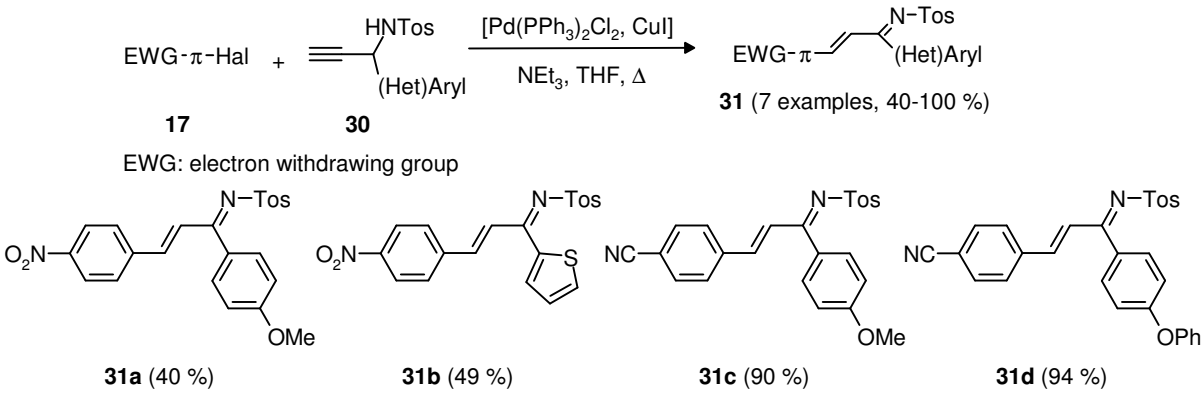
One the other hand the pyridyl nitrogen can also be introduced by a Diels-Alder reaction of an enimine and a dienophile. In analogy to the chalcone formation by CIR, the use of *N*-tosyl propargyl amines **30** leads to the formation of *N*-tosyl enimines **31** in moderate to excellent yields (Scheme 14).[29]

Likewise, this new enimine synthesis can be applied in a consecutive CIR-cycloaddition-aromatization sequence with diethyl ketene acetal furnishing 2-ethoxy pyridines in moderate yields.[29] Furthermore, upon reaction of electron poor (hetero)aryl halides **17**, terminal propargyl *N*-tosyl amines **30**, and highly reactive cyclic *N*,*S*-ketene acetals **32** annelated 2-aminopyridines **33** such as the pyrrolo[2,3-*b*]pyridine **34**, the 1,8-naphthyridine **35**, and the pyrido[2,3-*b*]azepine **36** can be synthesized in moderate to good yields

(Scheme 15).[30] These heterocycles are highly fluorescent and, *e.g.* the fluorescence of **36** is highly p*H* sensitive in a small p*H* range.



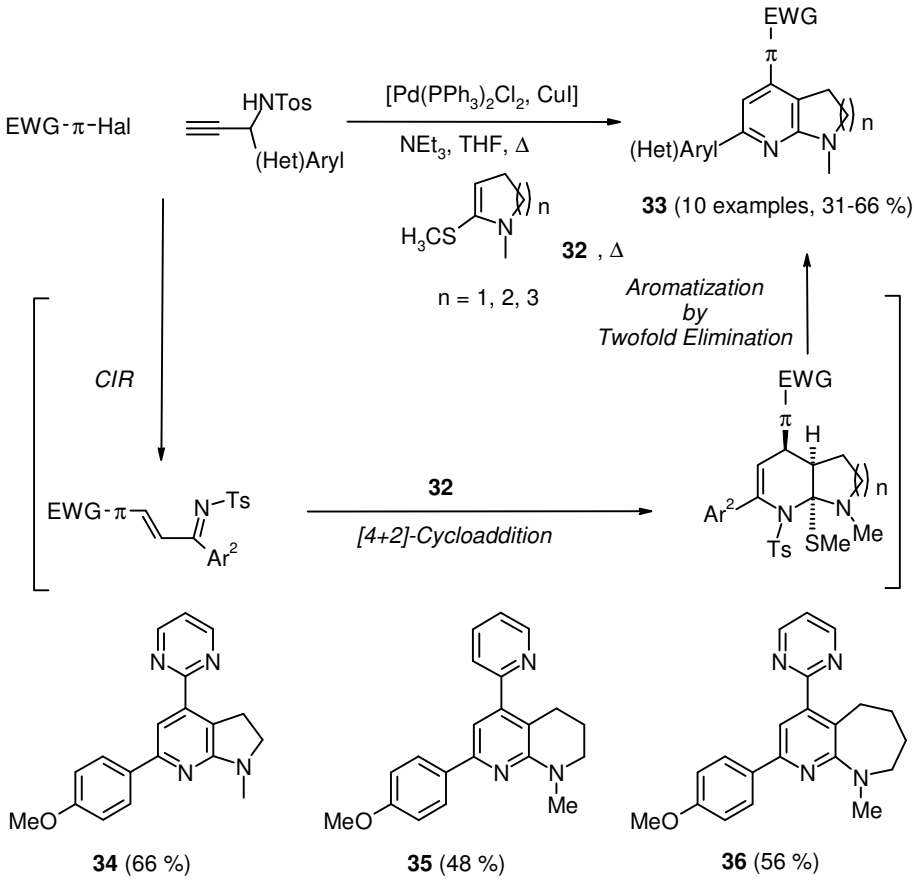
Scheme 13. Four-component synthesis of pyridines **29** by CIR-cyclocondensation.



Scheme 14. Enimines **31** by coupling-isomerization reaction (CIR).

4. Conclusion and outlook

Palladium catalyzed generation of alkynones and chalcones by palladium is an entry to sequential and consecutive transformations towards heterocycles by consecutive coupling-cyclocondensation or coupling-isomerization-cyclocondensation sequences. Advantageously, not only the compatibility of similar reaction conditions but also the tunable reaction design allows the combination of several organic and organometallic elementary reactions to new diversity oriented syntheses. Future plans will address sequentially catalyzed processes and hetero domino reactions for the rapid construction of complex molecular frameworks.



Scheme 15. Three-component synthesis of annelated pyridines **33** by CIR-cycloaddition.

Acknowledgments

The work summarized in this account was continuously supported by the Deutsche Forschungsgemeinschaft, the MORPHOCHEM AG, the Fonds der Chemischen Industrie, and the Dr.-Otto-Röhm Gedächtnisstiftung. The dedication, the intellectual input, and the skill of Alexei S. Karpov, Roland U. Braun, Markus Ansorge, Eugen Merkul, Nasser A. M. Yehia, Oana G. Schramm, and Daniel Aktah, who actually carried out the research in the laboratories in Munich and in Heidelberg, is gratefully acknowledged.

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COVALENT C=N BOND HYDRATION IN HETEROAROMATIC COMPOUNDS: CHEMICAL AND BIOLOGICAL ASPECTS

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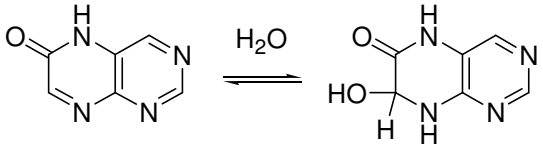
Abstract. *The recent literature describing the covalent addition reaction of water across carbon-nitrogen double bonds in heteroaromatic ring systems is reviewed. Special attention is given to the biological and biochemical importance of covalent hydration in understanding enzyme mechanisms and in the design of enzyme inhibitors. In particular, the enzymes adenosine deaminase, adenosine monophosphate deaminase, cytidine deaminase and cytosine deaminase are discussed.*

Contents

1. Introduction

The process whereby a water molecule adds reversibly across a carbon-nitrogen double bond in a heteroaromatic ring system to give a tetrahedral hemiaminal is generally referred to as "covalent hydration." The phenomenon was first reported by Albert in 1952 following investigations into the structure and chemistry of 6-hydroxypteridine (**1**).[1] Brown and Mason were later able to show that the hydration occurred across the 7,8-positions and that compound **1** existed mainly as 6,7-dihydroxy-7,8-dihydropteridine (**2**) in aqueous solution (Scheme 1).[2] Subsequently, it has become apparent that covalent hydration of heteroaromatic ring systems (and of acyclic carbon-nitrogen and carbon-oxygen double bonds) is a relatively common occurrence.[3-5] When Albert and Armarego wrote their seminal 1965 review on covalent hydration in nitrogen containing heteroaromatic compounds, the subject was of more theoretical than practical

interest.[3] However, since that time it has become apparent that covalent hydrates can be important reaction intermediates even when present in low concentrations, undetectable by normal means. For example, they are believed to be intermediates in the oxidation reactions catalysed by xanthine oxidase[6] and in the hydrolysis reactions performed by the nucleoside deaminases.[7] In addition, it has become clear that highly potent transition state type enzyme inhibitors can be synthesised by incorporating heteroaromatic rings capable of undergoing covalent hydration into the inhibitor structures.[7] The resulting compounds show a wide range of biological activities which are of interest within both the pharmaceutical and agrochemical industries.

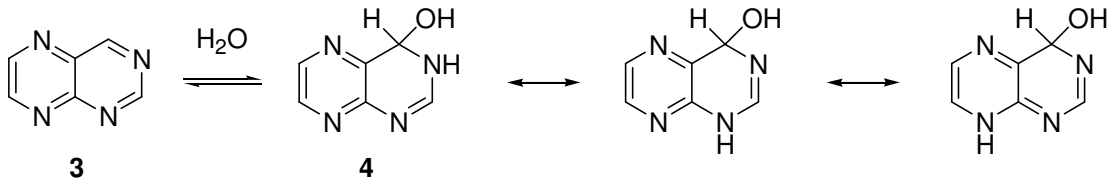


Scheme 1

This article will concentrate on literature published since Alberts last 1976 review and will pay special attention to biological and biochemical aspects of covalent hydration not covered in previous reviews.[3-5] The review will focus on the covalent hydration of neutral heterocycles or their protonated cations. The related topic of heterocyclic pseudobases, which are formed when hydroxide anion adds covalently to *N*-alkylated cations, will not be covered.[8]

2. Covalent hydration of nitrogen containing heteroaromatic rings

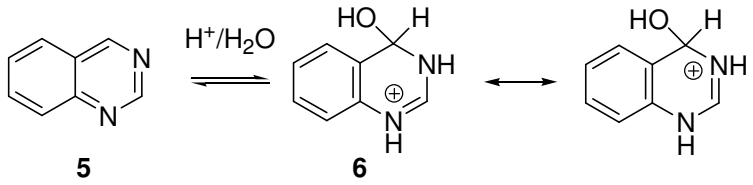
In order for water to add to a heteroaromatic ring and thereby perturb the inherent aromaticity of the system, certain structural features are necessary. The presence of electron-withdrawing centres powerful enough to deplete the π-electron current and allow isolation of a polarized C=N bond from the normal Kekulé type conjugation are an essential requirement. This role can be undertaken by introducing substituents such as a nitro or trifluoromethyl group, or by increasing the number of nitrogen or oxygen atoms within the ring system. Albert estimated that each C=N bond in a heterocyclic ring system had the same electron-withdrawing force as a nitro substituent.[3] By increasing the number of electronegative ring heteroatoms or by introducing electron withdrawing groups at suitable positions, the aromatic character of a heteroaromatic ring can be weakened to the extent that water addition becomes an exothermic process. In as much as the hydration process disrupts the aromatic ring resonance, stable hydrates always contain other possibilities for resonance stabilization in order to at least partially offset this effect. Typical resonance substructures include amidines, guanidines, ureas, aminopyridines or aminopyrazines.[3] Both amidine- and aminopyrazine-type resonance stabilizations, for example, are possible for pteridine (**3**), which exists to the extent of 22% as the hydrate **4** in aqueous solution (Scheme 2).[9] This resonance stabilization also explains, at least in part, why hydrated species such as the hemiaminal **4** do not undergo ring opening. The maximum resonance stabilization of the hydrate **4** is only achievable when the amidine functionality is co-planar to the pyrazine ring, a situation which would be more difficult to maintain in the ring opened form. Finally, it is often the case that the covalent hydration of heterocycles is greatly facilitated under acidic conditions. This is because a cationic heteroaromatic ring system is overall more electron-deficient and a protonated C=N bond is more polarised and electrophilic than the corresponding neutral species.



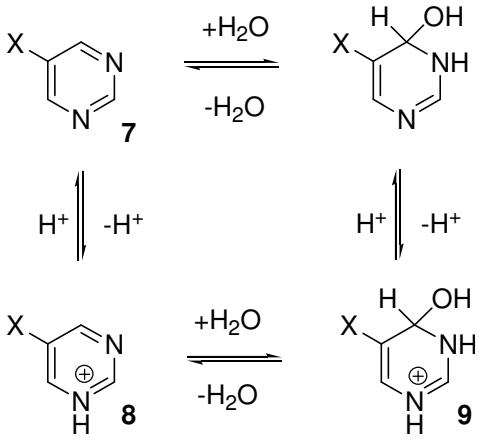
Scheme 2

2.1. Pyrimidines

The covalent hydrate of the bicyclic heteroaromatic quinazoline (**5**) is well known and has been thoroughly investigated.[4] Quinazoline exists predominantly as the resonance stabilized covalent hydrate **6** in aqueous acidic solution (Scheme 3). In contrast to this, it was formally believed that monocyclic nitrogen containing heterocycles such as pyrimidines did not undergo detectable covalent hydration due to the unfavourable loss of aromatic resonance stabilization caused by hydrate formation.[3] However, several examples of covalent hydration in simple pyrimidines have subsequently been reported.[4b,10] For example, studies on the covalent hydration of pyrimidines bearing a strong electron withdrawing group at the 5-position have shown that under acidic conditions 3,4-hydrated cations are formed (Scheme 4).[11]



Scheme 3



Scheme 4

The hydrates **9** have a sufficient lifetime to be studied but are prone to undergo ring cleavage reactions. When the 5-substituent on the pyrimidine **7** was electron donating (*e.g.* X = Me, OMe, SEt), then non-hydrated cations **8** were formed in aqueous acidic solution. However, when the pyrimidine bore a strong electron withdrawing 5-substituent (X = CN, CO_2R, SO_2R, SOMe, NO_2), then the hydrated form of the cation was preferred (Figure 1). Evidence supporting the formation of the hydrates of type **9** was provided by the upfield shifts seen for the ring hydrogen atoms in the ^{1}H-NMR spectra measured in DCl/D_2O. Efforts to obtain ^{13}C-NMR spectra of the covalently hydrated cations were frustrated by the poor stability of the cations in acidic solution. In the time needed to accumulate sufficient scans, decomposition was unfortunately already well advanced.[11]

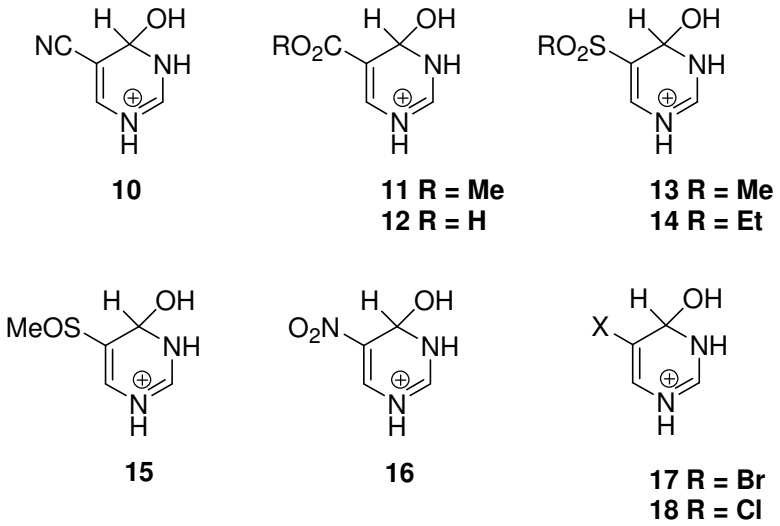


Figure 1

The electron withdrawing 5-substituent on the pyrimidine **7** increases the polarization of the C=N bonds in the pyrimidine ring and facilitates the attack of the weak water nucleophile under acidic conditions to give the hydrated products **10–16** in an approximately 9:1 ratio of hydrate to non-hydrate. Monocyclic ring systems do not have the co-planar resonance stabilization associated with fused bicyclic heteroaromatic systems and are subsequently more prone to undergo ring cleavage following covalent hydration. Interestingly, 1,3,5-triazine, which can perhaps be regarded as an extreme example of a pyrimidine containing an electron withdrawing 5-substituent, is rapidly destroyed in cold water.[12]

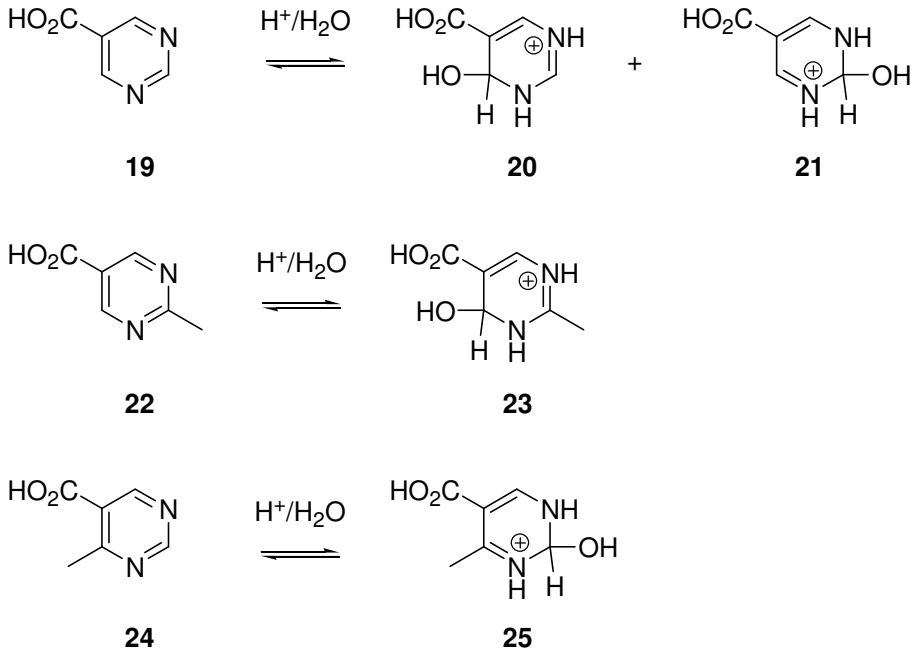
Table 1. Covalent hydration of pyrimidines.

Solvent	**Ratio 8/9**		
	X = Br	**X = CN**	**X = Cl**
D_2O	100/0	100/0	100/0
0.1M DCl/D_2O	95/5	82/18	-
1.0M DCl/D_2O	70/30	7/93	-
2.0M DCl/D_2O	59/41	3/97	60/40
4.0M DCl/D_2O	57/43	0/100	-
6.0M DCl/D_2O	73/27	0/100	-
9.0M DCl/D_2O	86/14	0/100	-

Subsequently, it was found that weaker electron withdrawing groups (*e.g.* X = Br) could also facilitate hydration of the pyrimidine **7** (Scheme 4).[13,14] The ratio of anhydrous to hydrated compound was found to be dependent on acid concentration and could be measured using ^{1}H-NMR spectroscopy (Table 1). For the bromopyrimidine **7** (X = Br, Scheme 4), no covalent hydration was observed in D_2O alone, however, in 0.1M DCl/D_2O an equilibrium mixture was observed containing 5% of the hydrated cation **17** (Figure 1). The equilibrium was found to be reversible and on neutralization of the medium, the spectrum reverted to that recorded in D_2O alone. The degree of hydration of the bromopyrimidine **7** (X = Br) reached a maximum of 43% in 4M DCl/D_2O and decreased at higher acid concentrations. Similar results were observed during

studies on the covalent hydration of quinazoline **5** and in that case the reduced hydrate formation at high acid concentrations was attributed to the decreased amount of free water in the medium.[4] Similarly, with the cyanopyrimidine **7** (X = CN, Scheme 4), no covalent hydration was observed in D_2O alone, however, with increasing acid strength, the effect of the cyano group on the electrophilicity of the 4-position became more apparent, reaching 100% in 4M DCl/D_2O. In this case, the amount of hydrate **10** (Figure 1) present did not reduce with increasing acid strength, perhaps because of the greater resonance stabilization achievable with the cyano group. Also with the chloropyrimidine **7** (X = Cl) no covalent hydrate was detected in D_2O alone, however, 40% of the hydrate **18** (Figure 1) was observed in 2M DCl/D_2O.

In a further study on the reactivity of these pyrimidines towards water, Kress synthesised and studied the hydration of pyrimidine-5-carboxylic acid (**19**) and a number of its methyl substituted derivatives by ^{1}H-NMR in dilute DCl/D_2O (Scheme 5).[15] It was observed that the acid **19** underwent hydration at both the 2 and the 4 positions to give a mixture of hydrates. The ^{1}H-NMR spectrum of compound **19** dissolved in 2M DCl/D_2O showed the presence of two new species, corresponding to the covalent hydrates **20** and **21** and the ratio of **19**:**20**:**21** was found to be approximately 1:6:3. The 2- and 4-monomethyl pyrimidine-5-carboxylic acids, **22** and **24**, each have a methyl 'blocking group' at one of the hydration positions and were found to form almost exclusively the 4- and 2-hydrated cations **23** and **25**, respectively. No observable hydration could be detected upon the concurrent introduction of methyl 'blocking groups' at positions 2 and 4 and interestingly, this was also the case for the 4,6-dimethyl compound, although here the results cannot be completely attributed to steric hindrance and must be partially electronic in nature.[15]

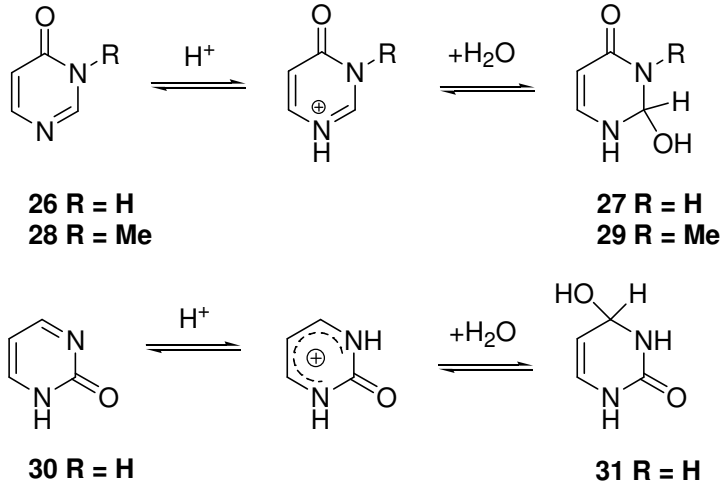


Scheme 5

2.2. Pyrimidinones

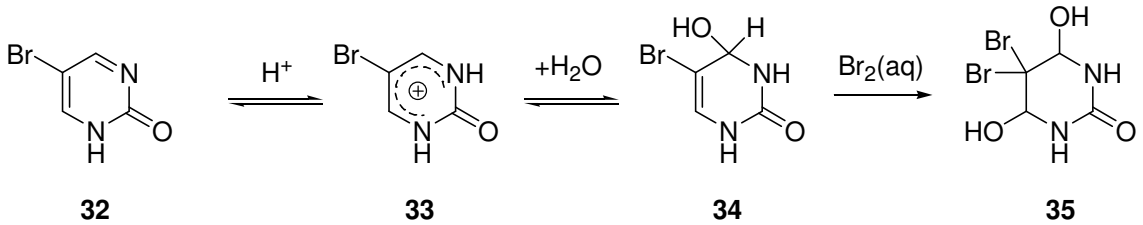
The covalent hydration of pyrimidinones is of special interest due to their important role in biological processes (*e.g.* cytidine deaminase)[7] and because of the role hydration plays in the reactivity of certain pyrimidinones.[16] For example, the bromination of pyrimidinones in acidic aqueous solution is thought to involve a multistep addition-elimination sequence involving covalent hydrates.[17,18] Despite their importance, hydrated pyrimidinones are present only in very low concentrations, as illustrated by compounds **26** and **28**

which exist only to the extent of 0.0001% as their covalent hydrates **27** and **29** even under acidic conditions (Scheme 6).[18] Nonetheless, the hydrates are believed to play a key role in the reaction of these molecules with molecular bromine at low pH.[18] In comparison the equilibrium for hydrate formation is more favourable for the 2-(1*H*)-pyrimidinone **30** which exists to the extent as 0.05% as the hydrate **31** under acidic conditions (Scheme 6).[17]



Scheme 6

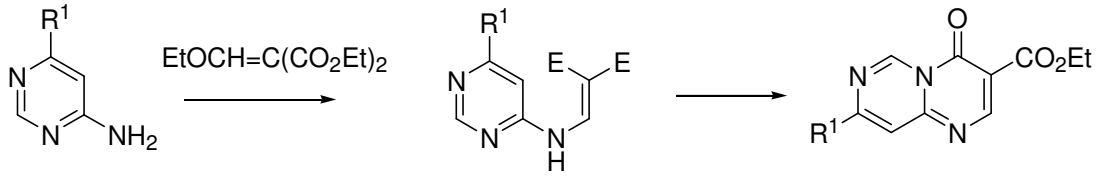
The introduction of electron withdrawing groups further shifts the equilibrium in favour of hydrate formation and the bromopyrimidinone **32** is calculated to exist to the extent of 5% as the hydrate **34**.[19] Although still present in relatively low amounts, the 100 fold increase in hydrate formation in going from the unsubstituted pyrimidinone **30** to the bromo derivative **32** is noteworthy and is of importance with regards to cytidine and cytosine deaminase inhibitors (Sections 3.2. and 3.3.). The covalent hydrate **34** could be detected using UV spectroscopy but attempts to observe it *via* NMR were thwarted by its low solubility in water and even in 50% aqueous DMSO. A study of the kinetics for the bromination of the pyrimidinone **32** suggested that the hydrate **34** was an intermediate in the bromination reaction to give the dibromide **35** (Scheme 7).[16,19]



Scheme 7

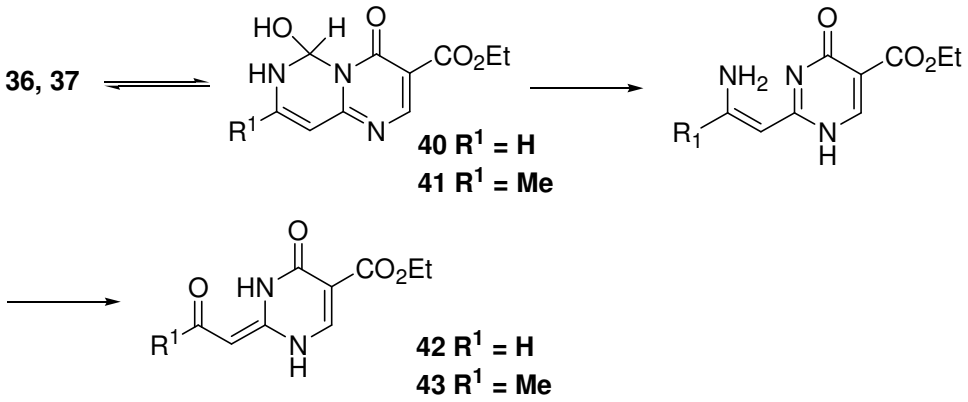
2.3. Pyrimidopyrimidines

Pyrimidopyrimidines have proven to be interesting substrates for the study of covalent hydration due to the relative ease with which their physical properties can be fine-tuned through the introduction of different substituents. The 4-oxopyrimido[1,6-*a*]pyrimidine-3-carboxylates **36–39** were readily prepared by condensation of the corresponding 4-aminopyridines with diethylethoxymethylenemalonate, followed by heating with Dowtherm A at 255 °C (Scheme 8).[20] It was found that compounds **36** and **37** were stable under anhydrous conditions but that in the presence of moist air or solvents they readily formed the covalent hydrates, **40** and **41**, respectively (Scheme 9).



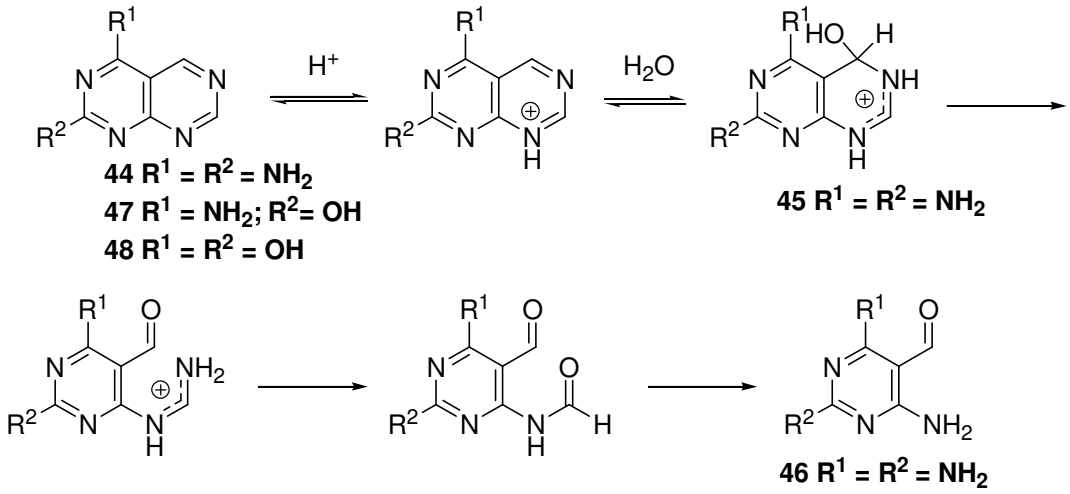
Scheme 8

The ease with which **36** and **37** form covalent hydrates under neutral conditions is due to the combined electron withdrawing effects of the ring nitrogens, 3-ethoxycarbonyl and 4-oxo groups which cause an increase in the positive character of the carbon at position 6. In contrast, compounds **38** and **39** did not form hydrates when exposed to water. A possible explanation is that the strong electron releasing capabilities of the 8-substituents in **38** and **39** are able to donate electrons into the 4-carbonyl group. This will have the effect of increasing the aromatic nature of the ring system, presumably to the extent that covalent hydration is no longer favourable. The hydrates **40** and **41** were characterized by MS and ^{1}H-NMR and further confirmation was provided by chemical transformation.[20] Thus, hydrolysis of **40** and **41** with aqueous NaOH caused ring opening to an eneamine, which upon treatment with aqueous HCl afforded compounds **42** and **43** (Scheme 9). Treatment of **40** and **41** directly with HCl also gave compounds **42** and **43**.



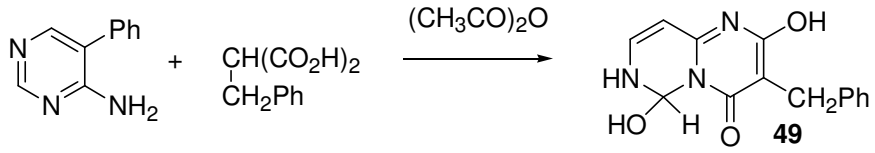
Scheme 9

The covalent hydration of the pyrimido[4,5-*d*]pyrimidines **44**, **47** and **48**, possessing simple amino and hydroxy substituents on one ring, has been reported by Delia.[21] Upon dissolving the diamino compound **44** in 0.5M DCl/D_2O, signals corresponding to the mono-cation together with weaker signals consistent with the hydrated mono-cation **45** were observed in the ^{1}H-NMR spectrum. Monitoring the ratio of **44/45** using ^{1}H-NMR spectroscopy indicated that the hydrated monocation **45** underwent slow ring opening and hydrolysis, eventually affording the aniline **46** (Scheme 10). Covalent hydration of **47** was also observed but at higher acid concentrations, while the data obtained for **48** did not indicate any covalent hydration even under strongly acidic conditions.[21] These results can be explained in terms of the lower basicity, the consequently lower degree of protonation and hence lower level of C=N bond electrophilicity of the heteroaromatic compound **48**, relative to **44** and **47**.



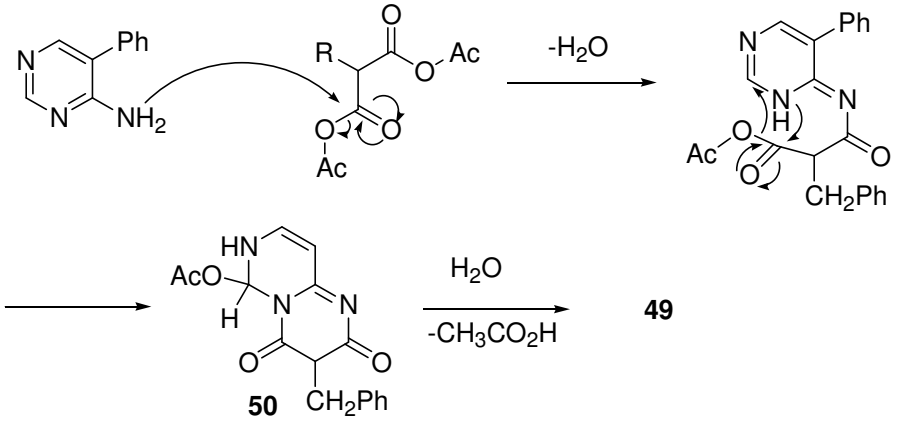
Scheme 10

The reaction of 4-amino-5-phenylpyrimidine[22] with benzylmalonic acid in refluxing acetic anhydride gave the condensation product **49**, which was found to be completely hydrated across the C6-N7 bond (Scheme 11).[23]



Scheme 11

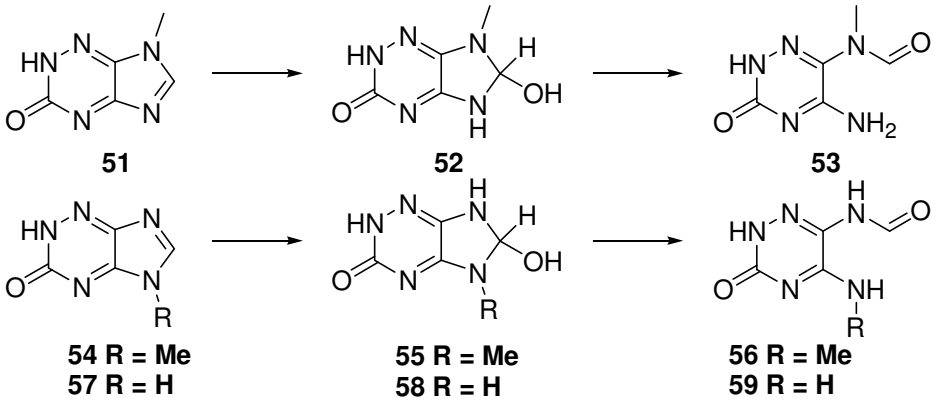
The hydrate **49** could not be dehydrated under various acidic or basic conditions and even attempts to achieve dehydration by sublimation under high vacuum failed. It was suggested that the formation of the hydrate **49** may have arisen from initial condensation of the pyrimidine and activated malonic acid derivative, followed by intramolecular migration of an acetoxy group to afford intermediate **50**, which hydrolysed to give **49** during work up (Scheme 12).[23]



Scheme 12

2.4. Imidazotriazines

The 6-azapurine **51** has been shown to undergo covalent hydration across the azomethine bond located in the imidazole portion of the ring system.[24] In the presence of water, compound **51** was found to hydrate across the N5-C6 azomethine bond to form the hydrate **52** which in turn rapidly ring-opened to furnish the formamide **53** (Scheme 13).[25]

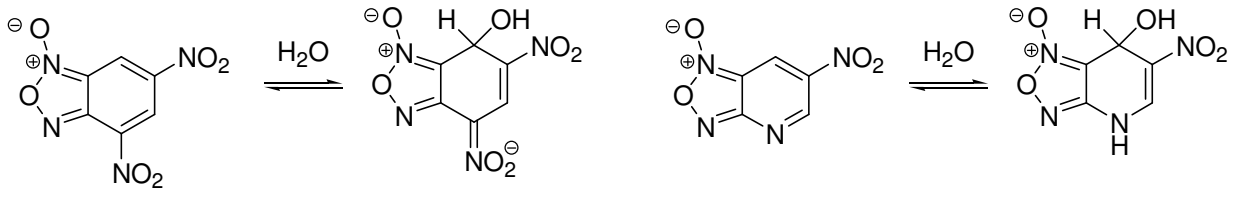


Scheme 13

The intermediacy of the σ-adduct **52** and the rapid ring cleavage to **53**, was verified by adding one drop of D_2O to a solution of **51** in DMSO-d_6 and following the reaction by ^{1}H-NMR spectroscopy. The covalent hydrate **52** formed immediately and quantitative ring opening to **53** was complete within 15 minutes. The hydration of the azapurines **54** and **57** did not proceed as readily as seen for compound **51**. However, recrystallisation of **54** or **57** from hot water afforded the formamides **56** and **59** directly (Scheme 13).[24] The ring opened compound **56** could be converted back to the azapurine **54** by rapidly heating a DMSO solution to boiling. It was concluded that **54** and **57** hydrated in a similar fashion to **51** to furnish the covalent hydrates **55** and **58**, respectively, which immediately underwent ring opening to yield **56** and **59**. Unfortunately, the hydrates **55** and **58** eluded direct detection by ^{1}H-NMR spectroscopy. The covalent hydrates **52**, **55** and **58** possess no resonance stabilization in the hydrated ring, whereas in the ring opened compounds **53**, **56** and **59** the formyl carbonyl group is conjugated with the triazine ring. This difference in resonance stabilization may explain the facile ring opening reactions seen upon hydration of these 6-azapurines.

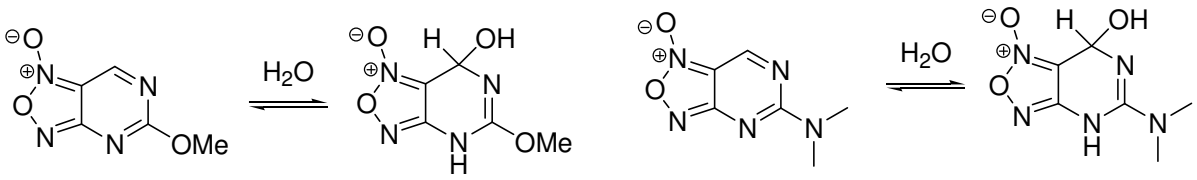
2.5. Nitrobenzofuroxans

During the past two decades there has been considerable interest in studies of nitrobenzofuroxans, a class of electron-deficient aromatic compounds that react readily with even weak nucleophiles to form σ-bonded complexes.[26] The term "super electrophiles" has been coined to describe the unusually high reactivity of these systems.[27] These ring systems are of particular interest because they have enabled the effect of aza-substitution in the aromatic ring on nucleophilic aromatic substitution processes to be evaluated.[26] The 4,6-dinitrobenzofuroxan **60** (DNBF) shows a very high susceptibility to undergo covalent hydration in neutral aqueous solution, undergoing essentially complete conversion to give the stable hydrate **61** (Scheme 14).[26d] The 6-nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine 1-oxide (**62**), in which the 4-nitro group has been replaced by a ring nitrogen, also forms a remarkably stable covalent hydrate, **63**, in aqueous solution (Scheme 14).[28]



Scheme 14

Terrier and co-workers estimated that the overall activating effect of introducing a nitrogen atom into the electron deficient aromatic system was comparable and perhaps even greater than that of the nitro substituent,[28] thus confirming the estimations made by Albert in his 1965 review.[3] In the pyrimidinofuroxans **64**[29] and **66**,[30] both nitro groups in DNBF (**60**) have been replaced by ring nitrogen atoms. These molecules readily undergo covalent C=N hydration to give covalent hydrates **65** and **67** (Scheme 15), despite the presence of the electron-donating groups at the 5-position. The high stability of the covalent hydrate **67** was illustrated by Tennant and co-workers who found that merely stirring the pyrimidinofuroxan **66** in aqueous dioxane at room temperature resulted in the formation of covalent hydrate **67**, which could be isolated in high yield.[30]



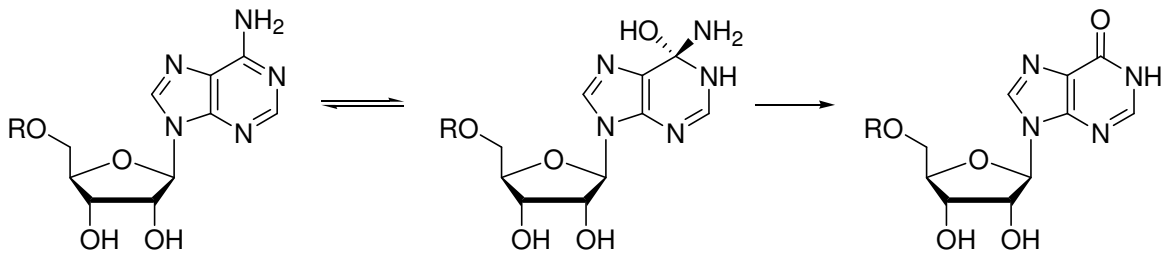
64 **65** **66** **67**

Scheme 15

3. Biological aspects of covalent hydration

3.1. Adenosine deaminase and adenosine monophosphate deaminase

The enzyme adenosine deaminase (ADA) (EC 3.5.4.4) catalyses the hydrolytic deamination of adenosine (**68**) to inosine (**70**), probably *via* the tetrahedral high energy intermediate **69** (Scheme 16). The related protein, adenosine monophosphate deaminase (AMPDA) (EC 3.5.4.6) converts adenosine 5'-monophosphate (**71**) into inosine 5'-monophosphate (**73**), *via* the phosphorylated intermediate **72**. In man, ADA plays an important role in purine metabolism and a deficiency causes a form of severe combined immunodeficiency disease,[31] whereas AMPDA does not appear to be essential.[32] In contrast, plants do not seem to contain ADA and inhibition of AMPDA results in a strong herbicidal effect.[33] Inhibitors of ADA are of interest as potential fungicides[34] and in cancer and viral chemotherapy.[35] Inhibitors of AMPDA have potential for use in the treatment of ischemia[36] and as herbicides.[33] The mechanism of the two enzymes is thought to be very similar and both utilize a zinc cofactor to bind a hydroxyl group which attacks at the C-6 position of the substrate to give the intermediates **69** or **72**. A comparison of the amino acid sequences of ADA and AMPDA indicates that the zinc and aglycone binding pockets of both enzymes are highly conserved.[37] In agreement with these observations, nucleoside-based inhibitors of ADA are, as a general rule, also inhibitors of AMPDA following 5'-monophosphorylation to give the corresponding nucleotides.[38]



68 R = H
71 R = PO_3^{2-}

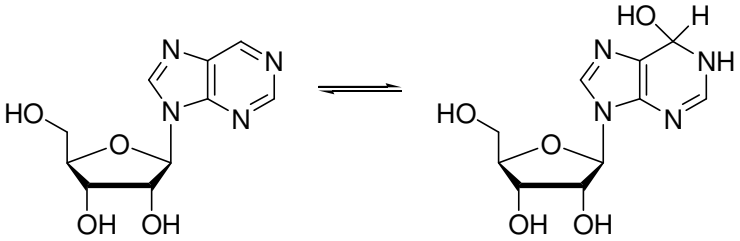
69 R = H
72 R = PO_3^{2-}

70 R = H
73 R = PO_3^{2-}

Scheme 16

3.1.1. Pteridines and purines

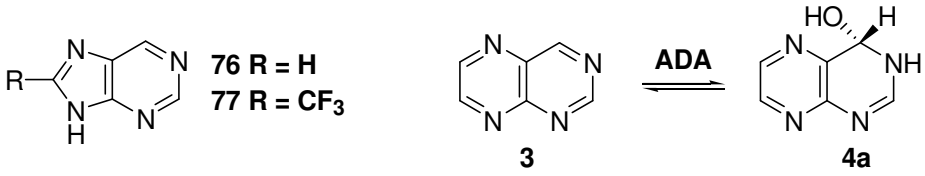
The natural product nebularine (**74**), isolated from the fungus *Agaricus nebularis*, was first reported in 1946[39] but it was not until seven years later that the 9-ß-*D*-ribofuranosylpurine structure was finally confirmed by synthesis.[40] Subsequently, Wolfenden and co-workers showed that nebularine was an inhibitor of mammalian and fungal ADA (K_i 37 and 9.3 µM, respectively) (Table 2).[41] Furthermore, they suggested the covalent addition of water to the C-6 position of nebularine to give the hydrate **75** may be important for ADA inhibition (Scheme 17).



74 **75**

Scheme 17

If formed, the hydrate **75** would be a mimic of the high energy tetrahedral intermediate **69** which is unable to undergo the normal forward reaction. In addition, it was shown that non-ribosyl fused heterocycles were capable of inhibiting ADA and that the potency of this inhibition correlated with the ease with which the compounds were able to form covalent hydrates. Thus, while purine (**76**) was a poor inhibitor, 8-trifluoromethylpurine (**77**) bound to the fungal enzyme 15 times more strongly (K_i 170 µM). This is consistent with the expected increased propensity of **77** to undergo covalent hydration due to the electron withdrawing effect of the CF_3 substituent (Scheme 18).



3 **4a**

Scheme 18

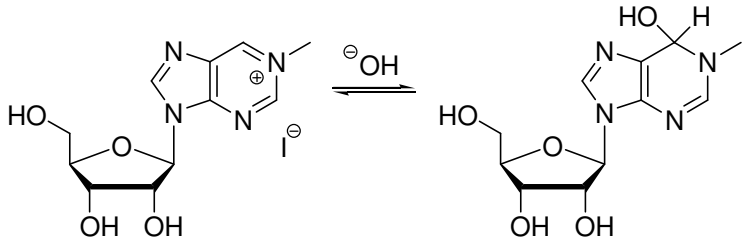
Most interesting was the observation that pteridine (**3**), which forms a stable covalent hydrate in aqueous solution (Scheme 2), was a slightly more potent ADA inhibitor (K_i 23µM) than nebularine itself, despite the fact that it lacks the entire ribose moiety. In subsequent studies, Wolfenden and Evans showed that ADA actually catalysed the covalent addition of water to pteridine to give the covalent hydrate **4**.[42] Thus, exposure of pteridine (**3**) to ADA in aqueous media resulted in the rapid production of optically active (-)-pteridine hydrate (**4a**) (Scheme 18).[43] The fact that pteridine (**3**) is a better inhibitor of ADA than purine (**76**) was ascribed to the considerably more stable covalent hydrate formed by the former. In neutral aqueous solution, pteridine exists to the extent of 22% as the 3,4-monohydrate **4** (Scheme 2),[9] whereas the covalent hydration of purines could not be detected at all under similar conditions.[44]

In order to better understand how nebularine (**74**) actually bound to ADA, Kurz and Frieden studied the ^{13}C NMR spectra of [2-^{13}C] and [6-^{13}C] labelled nebularines in the presence of ADA.[45] Upon binding to

ADA, the C-6 resonance showed a large up field shift (-73 ppm), which was interpreted as evidence for a change from sp^2 to sp^3 hybridization. Treatment of nebularine (**74**) with methyl iodide yielded the iodide salt of 1-methylpurinium riboside (**78**), which readily hydrated under basic conditions to give the adduct **79** (Scheme 19).[46] Wolfenden and co-workers showed that the ^{13}C NMR and UV spectra of ADA bound nebularine were strikingly similar to those of the covalent hydrate **79**, strongly suggesting that nebularine is bound by ADA as the 1,6-covalent hydrate **75**.[46]

Table 2. Inhibitors of *Aspergillus oryzase* ADA.[41]

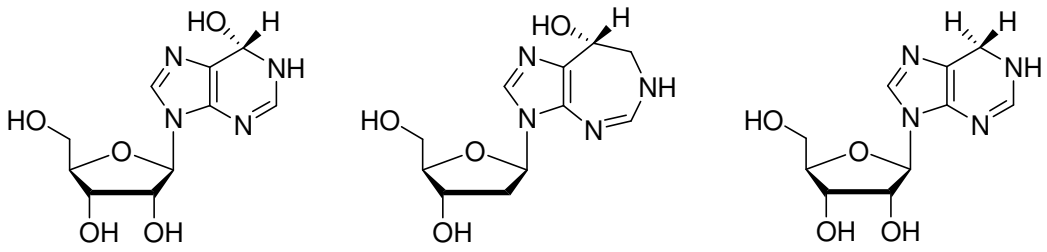
Structure	K_i (μM)
74	37
76	2600
77	170
3	23



78 **79**

Scheme 19

Subsequently, X-ray crystallographic structure determination confirmed the presence of the hydrated ligand **75** in the active site of ADA.[47,48] It is believed that ADA initially accepts nebularine as a substrate mimic and then catalyses the covalent addition of water to the C-6 position to give the true inhibitory species. The crystal structure showed that a single enantiomer of the hydrate **75** was bound within ADA, namely the 6*S*-isomer **75a** (Figure 2). The hydroxyl group was coordinated with the zinc cofactor which, it is believed, aids attack by water at the C-6 position of adenosine in the normal enzyme reaction. The stereochemistry at the C-6 position of ADA bound nebularine hydrate **75a** is the same as that found at the C-8 position of pentostatin (**80**) (Figure 2), which is the most potent transition state type inhibitor of ADA known to date (K_i 2.5 x 10^{-12} M, calf intestinal enzyme).[38]



75a **80** **81**

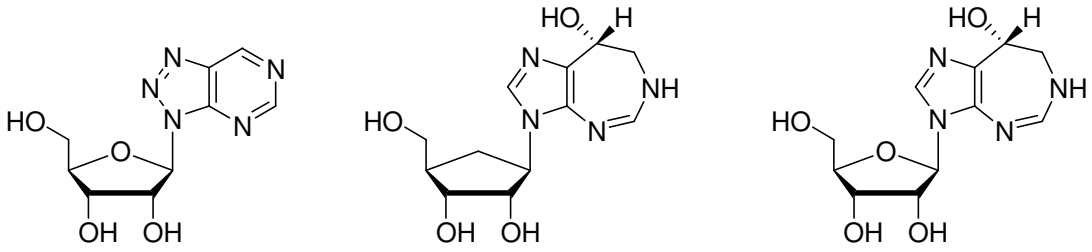
Figure 2

The X-ray crystal structure of ADA containing pentostatin bound at the active site has also been determined and shows that compounds **75a** and **80** bind to ADA in a very similar way.[48] However, the

inhibition constant for nebularine is much higher (K_i 4 x 10^{-6} M, calf intestine enzyme)[38] than that of pentostatin, due to the work done by the enzyme in stabilising the hydrate **75a**. The equilibrium constant for the hydration of **74** to **75** in dilute aqueous solution has been estimated to be 1.1 x 10^{-7} (*i.e.* 1 molecule of **75** to every 10^7 molecules of **74**).[46] By taking this unfavourable equilibrium into account, Wolfenden and co-workers estimated the true K_i value of 6*S*-hydroxy-1,6-dihydropurine ribonucleoside (**75a**) to be around 10^{-13} M.[46] The 1,6-dihydropurine derivative **81** (Figure 2) was found to bind 10^8-fold less tightly than compound **75a** which illustrates the importance of the 6-hydroxyl group in **75a** to inhibitor binding.[49] The above results suggest that nebularine analogues showing increased propensity towards addition of water across the 1,6-double bond should be stronger inhibitors of ADA than the parent compound.

3.1.2. Azapurines and pyrazolopyrimidines

The increased propensity for covalent hydration of 8-azapurines compared to purines was first reported in 1966.[50] Based upon this result and the arguments detailed in the previous section, Shewach and coworkers synthesised 8-azapurine ribonucleoside (**82**) (Figure 3) and tested it as a potential inhibitor of calf spleen ADA.[51] It was found that azapurine **82** (K_i 4 x 10^{-8} M) bound 400 times more strongly to ADA than nebularine (K_i 1.6 x 10^{-5} M). Subsequent calculations showed that the equilibrium constant for hydration of the 8-azapurine analogue **82** was 1.8 x 10^{-2}, indicating that this compound hydrated 1.6 x 10^5 times more easily than nebularine.[52] It was proposed that the large difference could be attributed to the large relative loss in resonance energy incurred by purine compared to 8-azapurine during the hydration reaction and that the difference played a major role in the enhanced ADA inhibition potency observed for compound **82**.[52]



82 **83 R = H** **84 R = PO_3^{2-}** **85 R = H** **86 R = PO_3^{2-}**

Figure 3

Carbocyclic coformycin (**83**) (Figure 3) is a naturally occurring nucleoside which exhibits strong herbicidal activity.[53] It has been shown that the primary herbicidal mode of action of compound **83** is due to inhibition of AMPDA, following *in planta* phosphorylation of the 5'-hydroxyl group to give the inhibitor **84** (IC_{50} 2 x 10^{-8} M, rabbit muscle and pea enzymes).[33] Herbicidal activity has also been reported for coformycin (**85**) itself,[54] however, even though the 5'-phosphate derivative **86** is a more potent AMPDA inhibitor (K_i 5.5 x 10^{-11} M, rabbit muscle enzyme) than **84**,[38] the latter is a much stronger herbicide.[33,53] It is believed that increased stability of the carbocyclic compound **84**, over the ribonucleoside **85**, towards metabolic degradation by nucleosidases and phosphorylases is responsible for the difference in biological activity. The 5'-phosphate derivative of nebularine **87** is a good inhibitor of AMPDA (K_i 6.5 x 10^{-6}, rabbit muscle enzyme)[38] but nebularine shows no herbicidal activity, possibly due to a rapid enzymatic cleavage of the labile glycosyl bond. In an effort to improve *in vivo* stability, the carbocyclic analogue **88** and the

C-nucleoside **89** have been synthesized and tested for inhibition of ADA.[55] Carbocyclic nebularine (**88**) did not inhibit ADA, possibly because the covalent hydrate has been significantly destabilised by the removal of the election withdrawing oxygen in the ribose mimic. However, deaminoformycin (**89**) was a good ADA inhibitor (IC_{50} 5 x 10^{-6} M, calf intestinal enzyme) which under the same test conditions bound 18 times more strongly than nebularine (**74**; IC_{50} 9 x 10^{-5} M).[55] The corresponding 5'-phosphate **90** was a good inhibitor of AMPDA (IC_{50} 1 x 10^{-7} M, pea enzyme) (Figure 4).

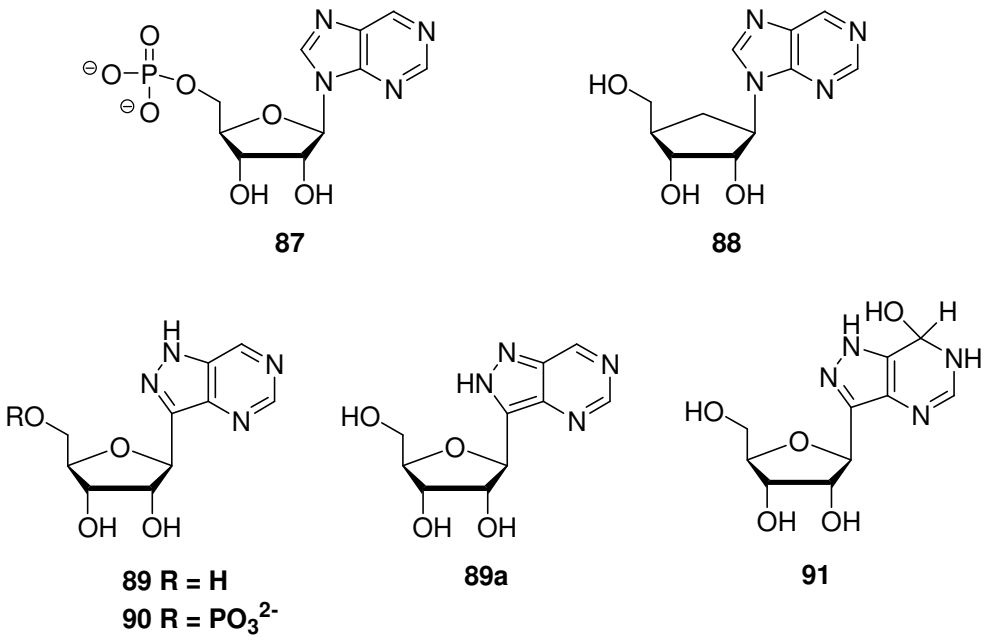


Figure 4

In an attempt to try and explain the improved binding to ADA of deaminoformycin (**89**) (Figure 4), compared to nebularine (**74**), the enthalpies for covalent hydration have been calculated and compared.[56] Hydration of the less stable N(2)H tautomer **89a** was predicted to be 3.8 kcal mol^{-1} more favourable than hydration of the N(1)H tautomer **89** and 5.4 kcal mol^{-1} more favourable than hydration of nebularine (**74**) (Table 3). In addition, the corresponding covalent hydrates of **89** and **89a** were modelled into the active site of ADA and their binding energy, relative to the known ligand **75a**, was calculated. An overall relative ADA binding affinity could then be estimated by adding together the enthalpy for covalent hydration and the relative binding energy. This showed that the binding of the covalent hydrate of tautomer **89a** should be 6.7 kcal mol^{-1} and 3.8 kcal mol^{-1} more favourable than binding of the covalent hydrates of **89** or **74**, respectively. These data suggest that the N(2)H tautomer **89a** is responsible for the observed enhancement in ADA inhibition, even though deaminoformycin normally exists almost extensively as the N(1)H tautomer **89**.[57] The observation that the hydrate of deaminoformycin, **91**, is formed under acidic conditions,[58] whereas no detectable hydration of the purine cation could be detected under similar conditions,[44] provides some experimental support for the above arguments.

3.1.3. Imidazotriazines and triazolotriazines

If the proposed reasoning for the enhanced binding of deaminoformycin (**89**) to ADA is correct (Section 3.1.2.), then nucleosides containing non-tautomeric aglycone heterocycles with electronic properties similar to those of tautomer **89a** should be more potent inhibitors of ADA than deaminoformycin (**89**). To

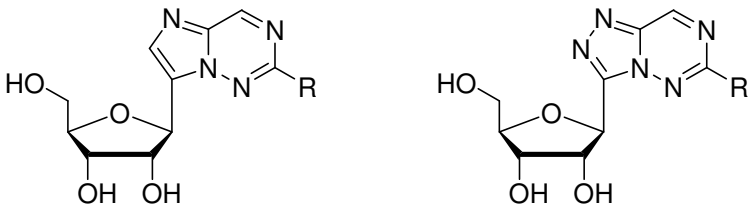
test this proposal, the enthalpy of hydration and the relative binding energy of the corresponding hydrate to ADA were calculated for several heterocyclic systems including the imidazotriazine **92** and the triazolotriazine **93** (Figure 5).[56] The calculations predicted that these two compounds would react exothermically with water to give stable covalent hydrates (Table 3).

Table 3. Covalent aglycone hydration and ADA inhibition.[56]

Inhibitor/ (Hydrate)[a]	Calculated ΔH(hydration), kcal mol^{-1}	% covalent hydration in D_2O	Calculated BE of hydrate[b] kcal mol^{-1}	Measured IC_{50}(ADA) µM
74/(75a)	7.1	0	0	90
89/(91)	5.5	0	4.5	5
89a	1.7		1.6	
92	-1.6		-1.9	
93	-4.3		6.7	
94	2.0	0	29.9	40
95/(104)	-1.7	45	72.0	180
105/(106)	-2.1	90	6.2	0.05

[a] For cases where the hydrate is referred to in the text its number is included in brackets.
[b] Calculated binding energy (BE) relative to compound **75a**.

After taking the relative binding energy to ADA into account, the overall affinity of the covalent hydrates derived from **92** and **93** was predicted to be 10.6 and 4.7 kcal mol^{-1}, respectively, more favourable than for the hydrate **75a** (Table 3). Unfortunately, the target molecules **92** and **93** proved difficult to synthesise and instead the related 6-substituted analogues **94** and **95** were prepared to test the predictive power of the calculations (Figure 5).[59,60]

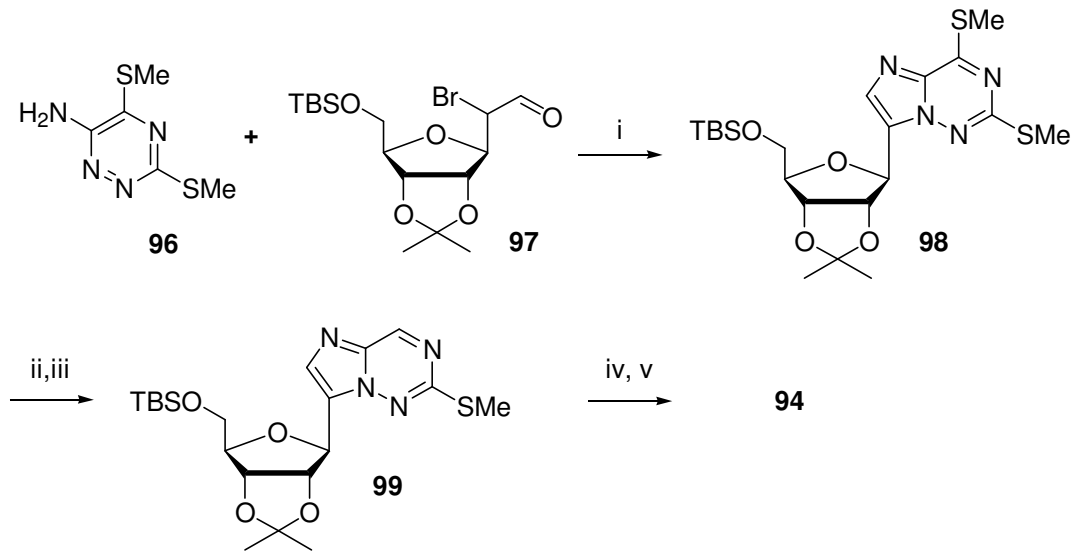


92 R = H
94 R = SMe

93 R = H
95 R = NMe_2

Figure 5

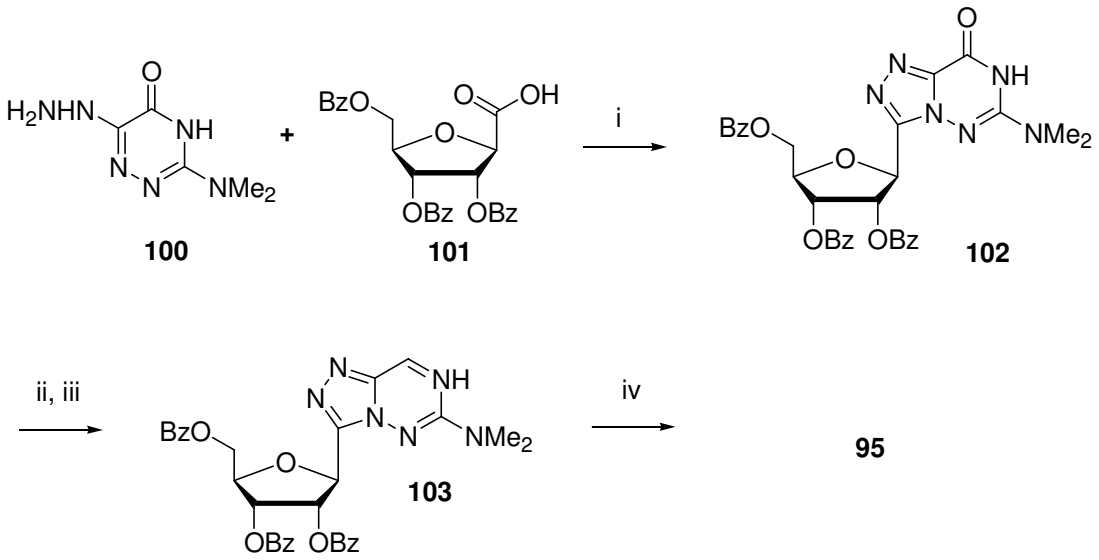
The imidazotriazine ring system of the target molecule **94** was constructed by condensation of the aminotriazine **96** with the bromoaldehyde **97** to give the intermediate **98** (Scheme 20).[59] The 8-methyl-sulfanyl group was removed in a two step procedure involving initial displacement by hydrazine, followed by oxidative cleavage with mercuric oxide to yield the protected target molecule **99**. Finally, removal of the ribose protecting groups in a two step procedure yielded the free ribosyl derivative **94** in five steps and 21% overall yield from **96** (Scheme 20).



(i) $PhCH_3$, HMPA, 100 °C, 24 h (62%); (ii) $N_2H_4.H_2O$, EtOH, reflux, 1 h (87%); (iii) HgO, EtOH, reflux, 2 h (72%); (iv) TBAF, THF, rt, 30 min (90%); (v) 60-80% AcOH, rt, 18 h (60%).

Scheme 20

The triazolotriazine ring system of target molecule **95** was synthesized in a single step by condensation of the hydrazine **100** and the protected allonic acid **101** to give the intermediate **102** (Scheme 21).[60] The C-8 carbonyl group of compound **102** was removed by initial conversion to the chloride using phosphorus trichloride oxide, followed by hydrogenolysis to yield the protected target molecule **103**. Removal of the benzoyl protecting groups from the ribose moiety then gave the target molecule **95** in four steps and 34% overall yield from **100** (Scheme 21).

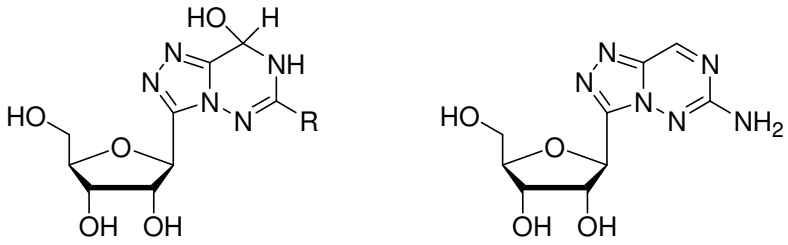


(i) DCC, *N*-hydroxysuccinimide, DMF, reflux, 24 h, (65%); (ii) $POCl_3$, $PhNMe_2$, reflux, 40 min (60%); (iii) H_2, Pd/C, MgO, EtOAc, rt, 4 days, (96%); (iv) NaOMe, MeOH, rt, 2 h, (90%).

Scheme 21

The calculated enthalpy for hydration of the imidazotriazine **94** was similar to that found for the deaminoformycin tautomer **89a**, while that for the triazolotriazine **95** was more negative and indeed exothermic (Table 3). In close agreement with these calculations, compound **95** was found to exist to the extent of 45% as the covalent hydrate **104** in aqueous solution (Figure 6).[60] Molecular modelling calculations

indicated that the presence of the 6-substituent in compounds **94** and **95** would have a deleterious effect on the binding affinity to ADA, to the extent that the 6-dimethylamino compound **95** would not be expected to bind at all (Table 3).[56] In the event, however, both **94** and **95** did inhibit ADA (IC_{50} 4 x 10^{-5} M and 1.8 x 10^{-4} M, respectively), probably because the 6-substituent is able to displace at least one of the two ordered water molecules bound within this region of the enzyme and which had been left in place for the binding energy calculations.



104 R = NMe_2
106 R = NH_2

105

Figure 6

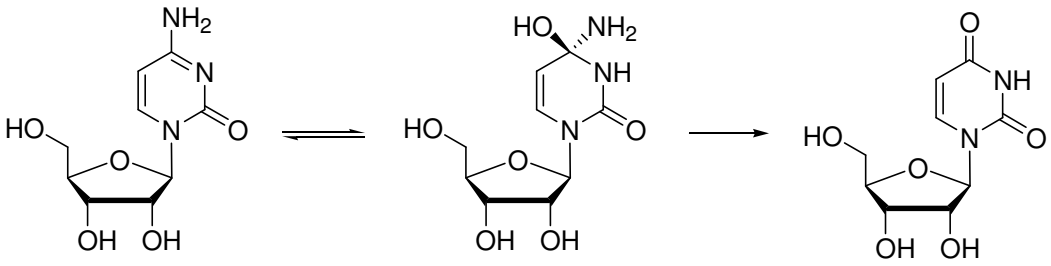
In order to try and improve the binding to ADA, Bojack and coworkers went on to synthesize the 6-aminotriazolotriazine **105** (Figure 6).[56] Molecular modelling studies showed that the 6-amino group was small enough to fit easily within the ADA substrate binding pocket even in the presence of the two bound water molecules. Calculations indicated that this compound should form a stable covalent hydrate **106** which was predicted to bind by 3.0 kcal mol^{-1} more strongly to ADA than the ligand **75a** (Table 3). Upon synthesis, the 6-amino compound **105** was found to exist to the extent of 90% as the covalent hydrate **106** in aqueous solution, an observation which is consistent with the calculated exothermic enthalpy for hydration (Table 3). This compound was a good inhibitor of ADA (IC_{50} 5 x 10^{-8} M, calf intestinal mucosa enzyme), binding 100 times more strongly than deaminoformycin (**75**). The mixture of **105** and **106** is an equipotent ADA inhibitor to the azapurine **82** but has the important advantage that it is not susceptible to degradation by nucleosidases and phosphorylases. Subsequent quantum mechanical and molecular mechanical calculations have confirmed that the overall binding strength of molecules like **105** to ADA is determined both by covalent hydrate stability and intrinsic enzyme binding energy.[61]

3.2. Cytidine deaminase

The enzyme cytidine deaminase (CDA) (EC 3.5.4.5) catalyses the hydrolytic deamination of cytidine (**107**) to uridine (**109**), very likely *via* the tetrahedral high energy intermediate **108** (Scheme 22). The catalytic site contains a tetrahedrally coordinated zinc ion, bound to two cysteines, a histidine and a hydroxyl group which attacks at the C-4 position of cytidine to give the intermediate **108**.[62] The enzyme is present in micro-organisms, plants and in mammalian tissues where it plays a role in regulating the availability of nucleic acid precursors and their anti-metabolites.[63] Inhibitors of CDA have potentially important therapeutic uses as anti-tumour agents, both alone and in combination with other anti-leukemic nucleosides which might otherwise be deaminated by CDA.[64]

It has been estimated that CDA accelerates the rate of hydrolytic deamination of cytidine to uridine by about eleven orders of magnitude.[65] In order to achieve this large rate acceleration, the enzyme must bind the

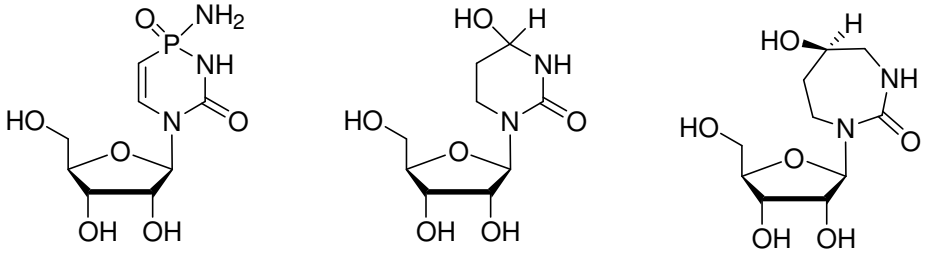
unstable high energy intermediate **108**, and the transition states leading to and from it, extremely tightly in order to achieve an effective stabilization. Consequently, chemically stable mimics of the intermediate **108**, or of the transition states, have the potential to be very potent inhibitors.[66]



107 **108** **109**

Scheme 22

Several transition state type inhibitors of CDA have been reported, including the phosphapyrimidine nucleoside **110**,[67] 3,4,5,6-tetrahydrouridine (THU) (**111**)[63] and the 1,3-diazepin-2-one (**112**)[68] (Figure 7). The strongest inhibitor of CDA reported so far is the phosphapyrimidine **110** (K_i 9 x 10^{-10} M, *E. coli* enzyme),[67] in which the tetrahedral C-4 carbon of the intermediate **108** has been replaced by a tetrahedral phosphorus atom bearing oxygen and amino substituents. Although **110** is a powerful inhibitor, not able to undergo the normal enzyme reaction, it is hydrolytically unstable in aqueous solution and is, therefore, of limited use. THU (**111**), lacks the C-4 amino substituent present in **108** and **110** but is still a strong inhibitor (K_i 2.4 x 10^{-7} M, *E. coli,* 2.2 x 10^{-7} M, mouse kidney enzyme).[63,68] Although THU binds 250 times less strongly than the inhibitor **110** it has the advantage that it is more chemically stable. The 1,3-diazepin-2-one (**112**), which contains a seven membered diazepine ring similar to that found in the ADA inhibitor coformycin (**85**), is also a good inhibitor of CDA (K_i 2 x 10^{-8} M, mouse kidney enzyme)[68] and is the most chemically stable of the inhibitors shown in Figure 7.

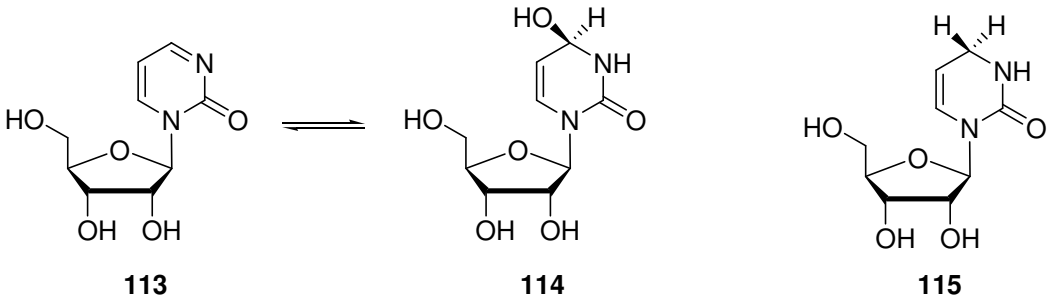


110 **111** **112**

Figure 7

The ribonucleoside zebularine **113** (Scheme 23), which is the pyrimidine counterpart of the naturally occurring ADA inhibitor nebularine (**74**), is a good inhibitor of CDA (K_i 3.6 x 10^{-7} M*, E. coli*, 2.0 x 10^{-6} M, mouse kidney enzyme).[69,70] Analogously to nebularine with ADA, zebularine binds to CDA as the covalent hydrate **114** even though the hydrate is not detectable in neutral aqueous solutions.[62] It is believed that zebularine binds to CDA in the non-hydrated form and that the enzyme actually catalyses the covalent hydration to give the inhibitory species **114**. The covalent hydrate **114** is a transition state type inhibitor, similar to THU, in which the C-4 hydroxyl group plays a key role in binding. Replacement of the hydroxyl group in structure **114** with a hydrogen gives the 3,4-dihydropyrimidin-2-one ribonucleoside **115** which is an

approximately ten-fold weaker inhibitor of CDA (K_i 3.0 x 10^{-5} M, *E. coli* enzyme).[69] As was the case with nebularine and ADA, a simple comparison of the K_i values tends to underestimate the contribution made by the hydroxyl group in binding to CDA because a substantial amount of the potential binding energy is consumed in stabilizing the unstable hydrate **114**. The equilibrium constant for the covalent hydration of **113** to **114** in dilute aqueous solution is about 4.7 x 10^{-6}, meaning that the true K_i value for the hydrate **114** can be estimated, as the product of this constant and the observed K_i for zebularine, to be around 10^{-12} M. This means that the covalent hydrate **114** actually binds seven orders of magnitude more strongly to CDA than the riboside **115**, which corresponds to about 10 kcal mol^{-1} in free energy.[69] As for nebularine and ADA, X-ray crystallography has confirmed that zebularine (**113**) binds to CDA as the covalent hydrate **114**.[62] The bound hydrate exists exclusively as the 4*R* isomer and the hydroxyl group was shown to be directly coordinated to the zinc cofactor present at the active site.



113 **114** **115**

Scheme 23

Inhibitors such as **110**, **111**, **112** and **113** all seek to take advantage of the extra enzyme binding interactions available to high energy intermediates such as **108** or the related transition states. However, the active site conformation of the ground state enzyme is such that it can rapidly bind the substrate but cannot readily accommodate a molecule that resembles the high energy transition state conformation. The binding of transition state type inhibitors, such as **110**, **111** and **112**, proceeds *via* an initially weak enzyme interaction, followed by a slow conformational change of the enzyme to give extremely tight binding complexes. This is seen in the slow onset of inhibition of such inhibitors, as exemplified by the phosphapyrimidine **110** which has a k_{on} value of 8300 M^{-1} s^{-1}.[67] In contrast, ground state type inhibitors such as zebularine (**113**), which resemble the substrate or product, are able to bind rapidly to the enzyme. Once within the active site, zebularine undergoes a slower enzymatic transformation to give the transition state type inhibitor **114**.[69] Even though zebularine (**113**) is a less potent inhibitor of CDA than the transition state type analogues **110**–**112**, its favourable binding kinetics and overall higher stability mean that it is one of the most biologically interesting CDA inhibitors.[64]

The introduction of an electron withdrawing group into the pyrimidinone ring of zebularine (**113**), should lead to an increased propensity to undergo covalent hydration across the N3-C4 bond and thereby give stronger inhibitors. In agreement with this, the bromo, chloro and fluoro derivatives of zebularine, **116**–**118**, are more powerful inhibitors of mammalian CDA than zebularine itself (Table 4) (Figure 8).[69]

The 5-fluoro compound **118** (K_i 2 x 10^{-7} M, mouse kidney enzyme) is a ten-fold better inhibitor of mouse CDA value than zebularine, inhibiting as strongly as THU, an inhibitor which already possesses the hydroxyl group required for high enzyme affinity.[69] For the mouse enzyme, the inhibition levels correlate with the electronegativity of the substituent at the 5-position and the most electronegative element fluorine

affords the highest affinity inhibitor (Table 4). In the case of the yeast enzyme, the fluoro compound **118** is still the most potent inhibitor but the bromo and chloro compounds **116** and **117** are weaker inhibitors than zebularine (**113**). This is presumably because the yeast enzyme has far stricter steric restraints within the active site than does mouse CDA. The crystal structure of CDA from *E. coli* complexed with **118** has been solved and confirms that it is the covalent hydrate **119** which is bound, as the 4*R*-isomer, at the active site (Figure 8).[71]

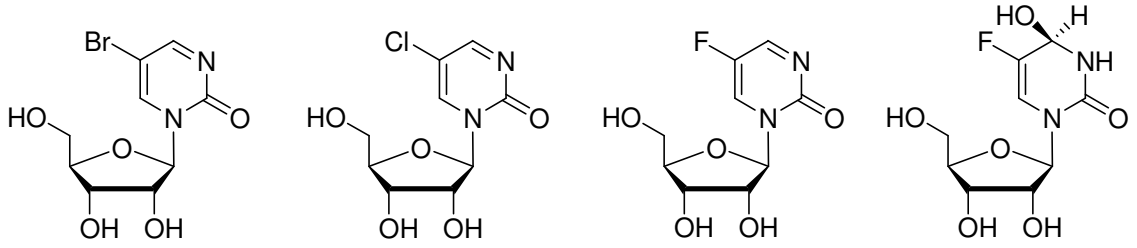
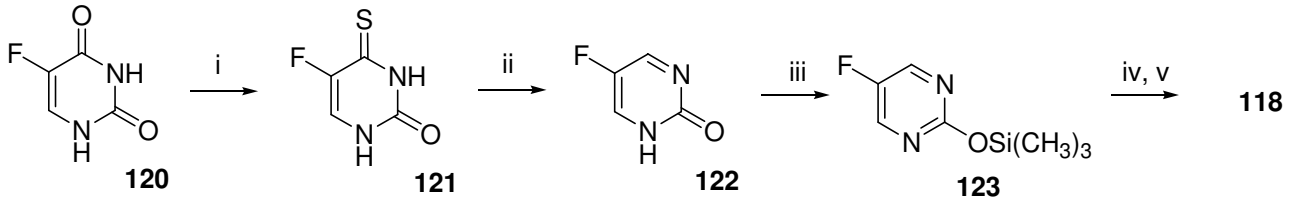


Figure 8

Table 4. Inhibitors of CDA[69]

Compound	K_i (M) mouse enzyme	K_i (M) yeast enzyme
111	2.2×10^{-7}	5×10^{-8}
113	2×10^{-6}	3×10^{-6}
116	7×10^{-7}	$>5 \times 10^{-5}$
117	3×10^{-7}	2×10^{-5}
118	2×10^{-7}	1×10^{-7}

The synthesis of 5-fluorozebularine (**118**) starts from commercially available 5-flourouracil (**120**). Treatment with phosphorus pentoxide gave the thioamide **121** which was desulfurized with Raney nickel to give the pyrimidinone **122** in 55% overall yield.[72] *In situ* silylation of **122** to afford the silyl ether **123**, followed by a tin chloride catalyzed condensation with acetyl 2,3,5-tri-*O*-benzoylribofuranoside and deprotection then afforded the target compound **118** in 15% yield (over three steps) (Scheme 24).[73]

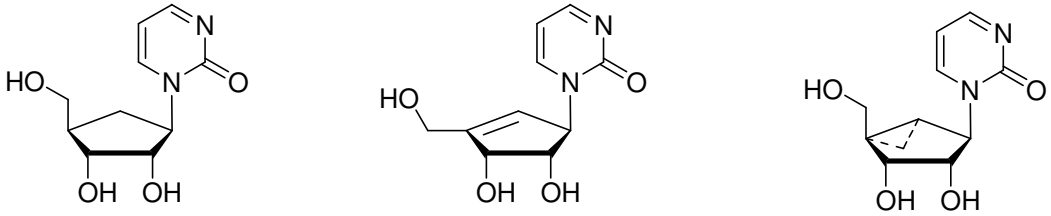


(i) P_2S_5, dioxane, reflux, 3 h (91%); (ii) Raney nickel, H_2O/NH_4OH, 1 h, (60%); (iii) MeCN, BSTFA 3 h; (iv) DCE, $SnCl_4$, 18 h, rt (26%); (v) $MeOH/NH_3$, 8 ºC, 16 h, (57%).

Scheme 24

Marquey and co-workers have investigated the synthesis of carbocyclic analogues of zebularine in an attempt to increase metabolic stability and hence activity.[74] The cyclopentyl analogue **124**, the cyclopentenyl

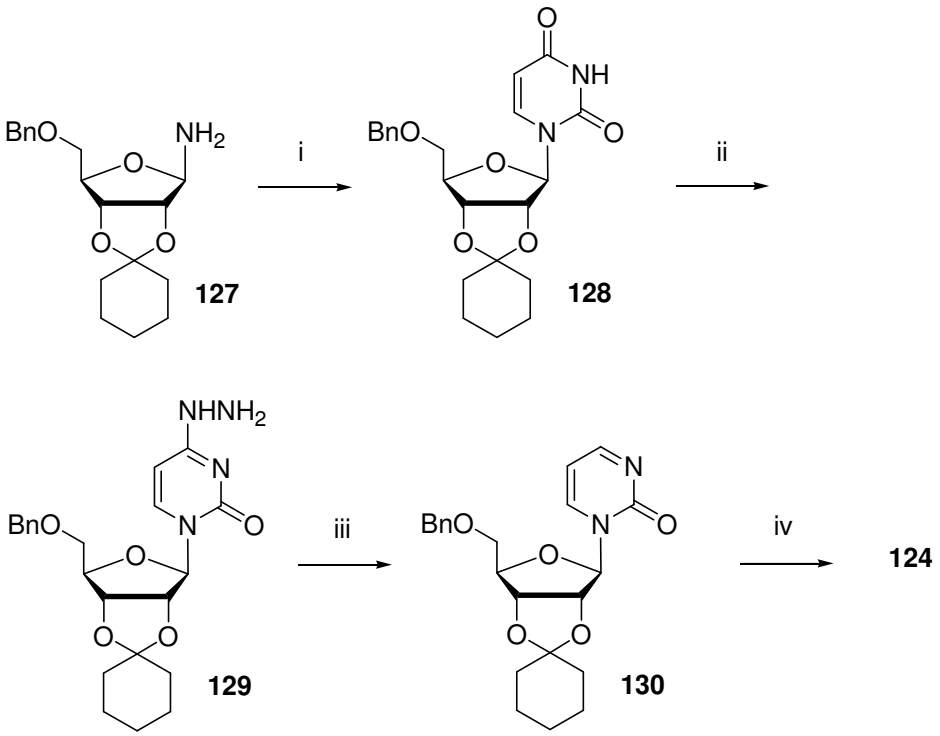
derivative **125** and a rigid bicyclo[3.1.0]hexanyl compound **126** were all prepared and tested for activity against CDA (Figure 9).



124 **125** **126**

Figure 9

The target compound **124**, which contains the cyclopentyl moiety found in carbocyclic coformycin (**83**), was prepared as outlined in Scheme 25. Treatment of amine **127** with 3-ethoxypropenyl isocyanate, followed by base catalyzed cyclization of the intermediate acrolyl urea, afforded the pyrimidinone **128**. This compound was treated with 2,4,5-triisopropyl sulfonylchloride to yield an activated sulfonate ester, which was displaced with hydrazine to afford intermediate **129**. Finally, oxidation of the hydrazine group with AgO gave the protected carbocyclic zebularine **130**, which was deprotected to give the optically active target molecule **124** in 19% yield from **128**.



(i) (a) 3-Ethoxypropenyl isocyanate, PhH, 30 min; (b) DMF, NH_4OH/NH_3 (conc.) 110 ºC 4 h (60%); (ii)(a) DCM, Et_3N, 1,2,4-triisopropylbenzenesulphonyl chloride, DMAP, 20 h, rt; (b) Dioxane, hydrazine 1 h, rt; (iii) Ag_2O, Et_3N, (iv) NaOMe, MeOH (19% from **128**).

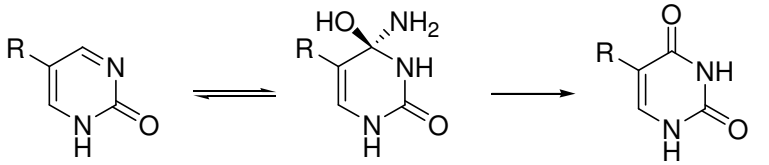
Scheme 25

The carbocyclic analogue **124** was a modest inhibitor of human CDA (K_i 3.8 x 10^{-5} M), although 16-fold less potent than zebularine. It was argued that the exchange of the ribose CO4´oxygen for the less electronegative carbon had reduced the capacity of the pyrimidinone ring to form the covalent hydrate, which is considered crucial for effective binding to CDA. Unfortunately, analogues **125** and **126** showed no

inhibition of CDA, presumably because the changes to the ribose moiety could not be accommodated within the CDA active site.

3.3. Cytosine deaminase

The enzyme cytosine deaminase (EC 3.5.4.1) catalyzes the hydrolytic deamination of cytosine (**131**) to give uracil (**133**) and of 5-methylcytosine (**134**) to give thymine (**136**), very likely *via* the tetrahedral high energy intermediates **132** and **135**, respectively (Scheme 26).



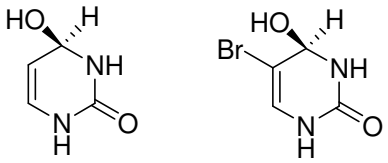
131 R = H
134 R = Me

132 R = H
135 R = Me

133 R = H
136 R = Me

Scheme 26

The enzyme plays an important role in pyrimidine salvage and is of interest in gene therapy based antitumor treatments.[7] Based upon the knowledge that 4-unsubstituted 2-pyrimidinone ribosides are good inhibitors of cytidine deaminase, Kornblatt and Tee tested the aglycones 2-(1*H*)-pyrimidinone **30** (Scheme 6) and 5-bromopyrimidinone **32** (Scheme 7) as potential inhibitors of cytosine deaminase.[75] Compounds **30** and **32** were both good inhibitors of the yeast enzyme at pH 6.4, exhibiting K_i values of 4.9 x 10^{-6} M and 2.6 x 10^{-7} M, respectively. Analogously to cytidine deaminase, it was proposed that the covalent hydrates **31a** and **34a** were the actual inhibitory species (Figure 10). That the bromide **32** is a stronger inhibitor than **30**, is consistent with the observation that this more electron deficient ring system forms the more stable hydrate (see Section 2.2.).[17,19] The level of cytosine deaminase inhibition shown by compound **32** dropped 9-fold when measured at pH 8.4 (K_i 2.4 x 10^{-6} M), probably as a result of the much reduced stability of the hydrate **34** under basic conditions.[75] More recently, the X-ray crystal structure of cytosine deaminase with the covalent hydrate **31a** bound at the active site has been determined for the *E. coli*[76] and yeast enzymes.[77] The yeast enzyme contained a zinc cofactor binding to the 4*R*-hydroxyl group of the hydrate **31a**, whereas in the *E. coli* enzyme an iron cofactor, bound to four histidines, an aspartate and the inhibitor hydroxyl group, was present.



31a **34a**

Figure 10

4. Conclusion

In the final section of their 1965 review, Albert and Armarego wrote, "It seems reasonable to predict that many aspects of covalent hydration will interest the biologist and help him in his work."[3] Their prediction has certainly turned out to be correct in the area of nucleoside and nucleotide deaminases which

have been the subject of extensive studies over the past 35 years. Four enzymes in particular, adenosine deaminase, AMP deaminase, cytidine deaminase and cytosine deaminase, have featured in these investigations. The ability of certain heteroaromatic compounds to undergo covalent hydration has been a key theme throughout much of the research undertaken in this area. Initial studies focussed on understanding the enzyme mechanisms and the results from this work have led to the design of improved inhibitors with interesting biological properties.

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CYCLODEXTRINS: HETEROCYCLIC MOLECULES ABLE TO PERFORM CHIRAL RECOGNITION (PART II)

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In memory of Professor Carlo Dell'Erba

Abstract. *The present paper collects the most significant advances appeared since late 1998 up to June 2005 in the field of applications of natural and modified cyclodextrins as chiral selectors, with particular regard for pharmaceuticals and natural products.*

Contents

1. Introduction

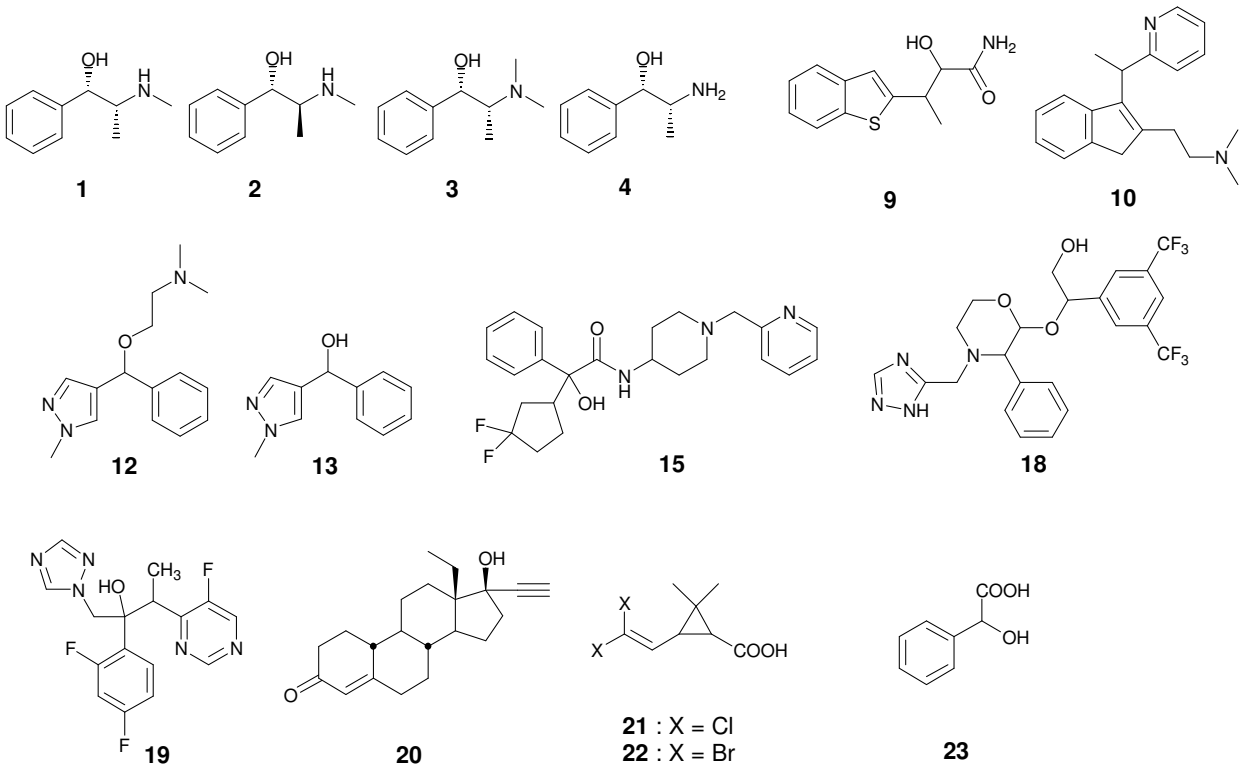
The present paper completes our recent review[1] on chiral recognition by natural and chemically modified cyclodextrins, already appeared on these volumes. It is aimed to collect the most recent literature advances (namely from late 1998 to June 2005) concerning enantiorecognition of pharmaceuticals and natural products, as well as most interesting applications of enantiorecognition properties of cyclodextrins in enantioseparation technologies, analysis and stereocontrolled processes.

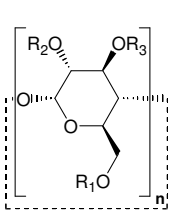
2. Recognition properties of cyclodextrins towards pharmaceuticals and natural products

Enantiodiscrimination of pharmaceuticals and naturally occurring products is an important issue in drug analysis and technologies. Therefore by far most of the papers dealing with the interaction of bioactive products with cyclodextrin systems are devoted to analytical applications rather than to the host-guest interaction *per se*.

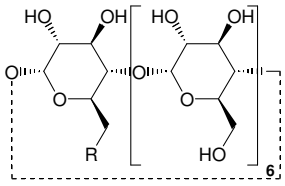
Interaction of ephedrine **1** and pseudoephedrine **2** (Scheme 1) with native αCD and βCD had been examined since 1995 by Rekharsky;[2] significant discrimination of the enantiomers of **2** at pH=6.9 by βCD was found, but the datum was not deeply discussed. Holzgrabe[3] also examined the behaviour of **1**, **2**, *N*-methylephedrine **3** and norephedrine **4** with heptakis-(2,3-*O*-diacetyl)-βCD **5**, heptakis-(6-*O*-acetyl)-βCD **6**, heptakis-(2-*N,N*-dimethyl-carbamoyl)-β-CD **7** and heptakis-(2,3-*O*-diacetyl-6-*O*-sulfo)-βCD **8**, by CE, UV and NMR. The latter host, in particular, was proven to be very effective in performing chiral discrimination; UV and NMR studies confirmed the occurrence of 1:1 host-guest complexes, with similar binding modes.

Therefore, eventual selection was once more attributed to the interaction of the secondary host rim with the aliphatic guest chain bearing the stereogenic centres. No thermodynamic data were reported.





	n	R_1	R_2	R_3
αCD	6	H	H	H
βCD	7	H	H	H
γCD	8	H	H	H
5	7	H	Ac	Ac
6	7	Ac	H	H
7	7	H	$CONMe_2$	H
8	7	SO_3H	Ac	Ac
11	7	Me	Me	Me
14	7	H	Me	Me
16	8	SO_3H	H	H
17	8	SO_3H	Ac	Ac



R	
24	$-NHCH_2CH_2NH_2$
25	$-NHCH_2CH_2OH$
26	$-NHCH(CH_3)CH_2OH$
27	$-NHCH_2CH(CH_3)OH$
28	$-NHCH_2CH_2CH_2OH$
29	$-N(CH_2CH_2OH)_2$
30	$-N(CH_2CH(CH_3)OH)_2$

Scheme 1

Cotta Ramusino examined the interaction of the 5-lipoxygenase inhibitor Zileuton **9** with βCD and γCD.[4] Binding constants were evaluated by both UV-vis and CD experiments; the two techniques afforded significantly different results for βCD. Data showed that the latter one is the most effective ligand but not the best selector, whereas selectivities near 2 are found with γCD. The affinity of Dimethindene **10** towards βCD and permethyl-βCD **11** was examined by Blaschke using NMR, CE and mass spectrometry (ESI-MS);[5] the native cyclodextrin was found a much better ligand, but a worse selector, probably due to the deeper penetration of the indene moiety of the guest into the host cavity. ESI-MS experiments account also for the formation of small amount of a 2:1 complex between βCD and the guest. Redondo performed a NMR study[6] on the interaction of Cizolirtine **12** and of its carbinol precursor **13** with native αCD, βCD and γCD and with heptakis-(2,3-*O*-dimethyl)-βCD **14**. Induced shifts and ROESY data suggest the inclusion of the phenyl group of the guest into the host cavity, and that βCD performs "the best enantiodiscrimination", but

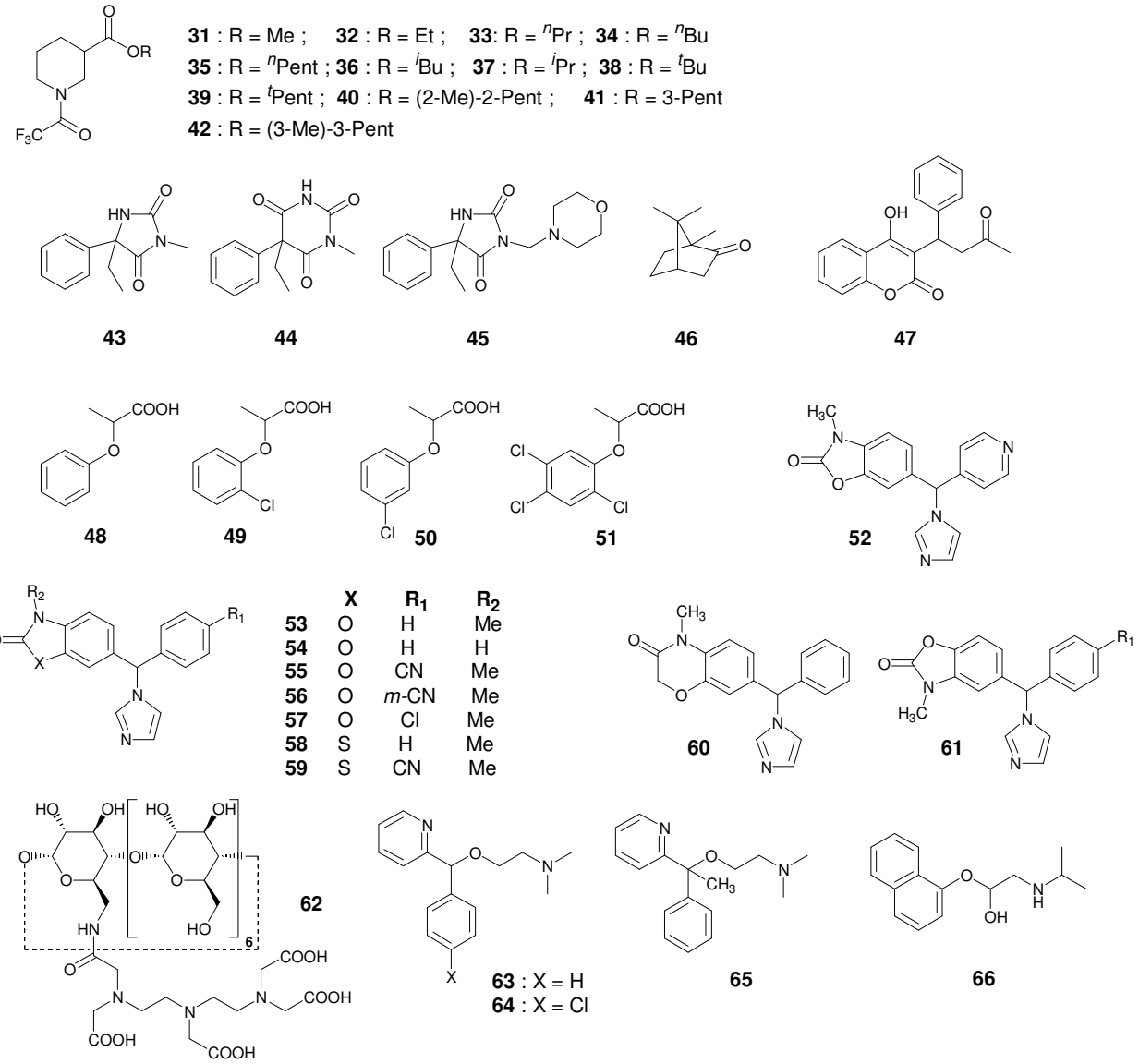
unfortunately the entire discussion is merely qualitative. Zhou reported[7] a curious peak inversion for the separation of the enantiomers of 2-*N*-(1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl)-2-(3,3-difluoro-cyclopentyl)-2-hydroxy-2-phenyl-acetamide **15** in CE experiments using either octakis-(6-*O*-sulfo)-γCD **16** or octakis-(2,3-di-*O*-acetyl-6-*O*-sulfo)-γCD **17** as selectors. NMR and IR studies account for the occurrence of 1:1 complexes, but suggest the occurrence of different interaction modes between the guest and the two different hosts: the phenyl group of the guest seems able to deeply penetrate into the cavity of the former host, whereas with the latter host the interaction seems limited to the wider rim. The same author thoroughly investigated the interaction between native γCD and compound **18**,[8] by means of CE, RPLC, ESI-MS, CD and NMR (^{1}H, ^{13}C, ^{19}F). Chiral recognition was therefore attributed to the simultaneous inclusion of the aromatic rings of the guest, and the concomitant interaction of the triazolo, morpholino and hydroxyl groups with the primary host rim. The behaviour of the four diastereoisomers of the antifungal agent Voriconazole **19** towards several cyclodextrins (αCD, βCD, γCD, commercial carboxymethyl-, hydroxypropyl, hydroxyethyl and sulfobutyl-βCD) was studied by Owens.[9] No CE enantioseparation was found for one of the two different diasteromeric couples with any auxiliary cyclodextrin used. NMR experiments surprisingly showed that these isomers are not able to form any inclusion complex, while for the other couple enantioselective interaction occurred through inclusion of the difluorophenyl group. Tárkányi[10] reported a nice study on the HPLC and CE separation of Norgestrel **20** enantiomers by means of native αCD, βCD and γCD, in correlation with NMR results. In particular, the association constants with γCD in water methanol mixtures (measured by both NMR and RP-HPLC) show fair selectivities, depending on conditions (α values up to 1.3). Association constants for Permethrinic **21**, Deltamethrinic **22** and mandelic **23** acids with a series of mono-(6-amino)-βCD derivatives **24**-**30** were obtained by means of electrophoresis studies by Iványi.[11] Data show that the presence of a mono-(hydroxyalkyl)-amino pendant group on the host structure improves its selection abilities; however the same effect is decreased for hosts bearing a bis-(hydroxyalkyl)-amino pendant group, probably due to steric hindrances. Observed selectivity α values range up to 2.14.

A good example of a systematic thermodynamic study has been very recently provided by McGachy, who examined the gas-chromatographic separation of some *N*-trifluoroacetyl-nipecotic acid esters **31**-**42** (Scheme 2) in presence of permethylated βCD.[12] Differences in behaviour were found between linear chain and branched chain derivatives. In particular, the latter ones usually presented: *i*) a reverted order of elution for the two enantiomers; *ii*) a weaker interaction with the stationary phase (for molecules having the same molecular weight); *iii*) more negative $\Delta_{R,S}\Delta H°$ values. Linear chain derivatives present also a significant enthalpy-entropy compensation. Simulated annealing computational models show also that the guest are included within the host with the trifluoroacetyl group directed towards the primary host rim. Therefore, everything considered, differences in behaviour among the various guests were tentatively explained in terms of the occurrence of slightly different interaction modes between the ester alkyl chain and the secondary host rim. The thermodynamic parameters relevant to the HPLC enantiodiscrimination of Mephenytoin **43**, Methylphenobarbital **44**, Morsuximide **45** and camphor **46** by αCD, βCD, permethyl αCD and βCD have been reported by Bielejewska.[13]

Vidal-Majar examined the thermodynamics of chromatographic separation for Warfarin **47** enantiomers[14] on an epichloridrine-βCD polymer RP-HPLC column, using water-methanol mixtures as eluents. Enantioseparation resulted function of the methanol content of the eluent; however the non-linear dependence of the thermodynamic parameters on the eluent composition accounts for a complex interaction

mechanism. A similar behaviour has been observed also by Guillaume,[15] on studying the RP-HPLC enantioseparation of four 2-phenoxy-propionic **48**-**51** acid herbicides on a Nautilus® column in the presence of hydroxypropyl-βCD as mobile phase additive. In this case the occurrence of peak inversion on changing the temperature was observed. Therefore, data suggested a change in the retention mechanism on changing the operational conditions. Within a study on capillary zone electrophoresis of some *N*-imidazole derivatives aromatase inibitors,[16] Vaccher evaluated the binding constants of compounds **52**-**61** towards αCD, βCD, γCD and their commercially avaliable hydroxypropyl derivatives (as mixtures of variously substituted compounds!). Actual CE peak resolution and, consequenly, fair enantioselectivities (α values up to 1.5 ca.) were found only for βCD and the hydroxypropyl derivatized αCD and βCD.

Finally, some lanthanide complexes of derivatized cyclodextrins (**62**, as well as commercially avaliable sulfated and carboxymethylated βCD) have been recently used as successful supramolecular chiral shift reagents by Wenzel[17-19] towards a series of aromatic derivatives of pharmaceutical interest, including in particular doxylamine **63**, carbinoxamine **64**, pheniramine **65**, propanolol **66** and some relevant derivatives.



Scheme 2

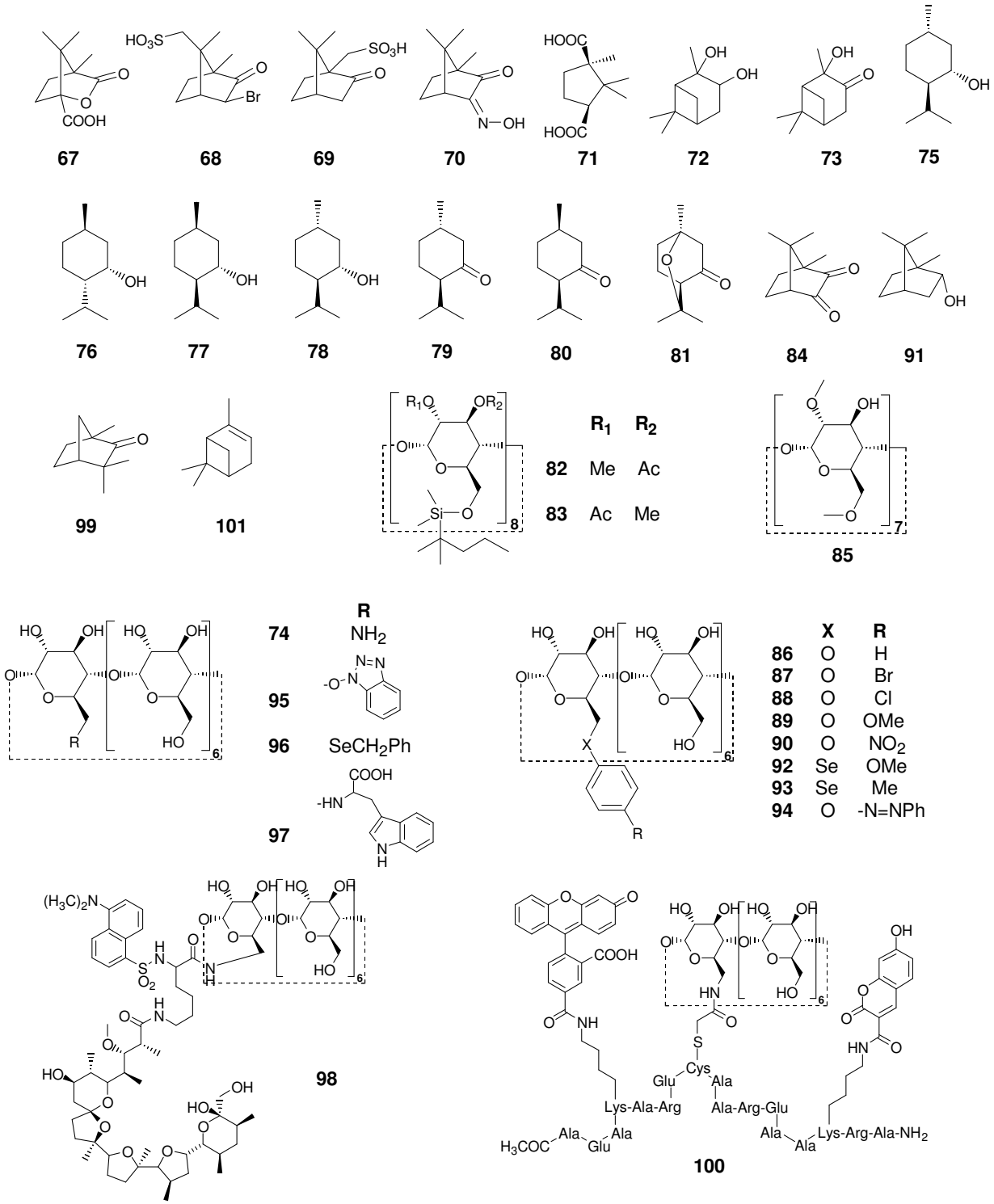
Among natural products, camphor, its related molecules and in general monoterpenes have played an important role in the investigations on the microscopic features of chiral selection properties of

cyclodextrins. Probably this is due to easy avaliability of both enantiomers of these molecules, as well as to their minor structural complexity. Camphor **46** easily forms 2:1 complexes with αCD,[20] where chiral discrimination can be evidenced not only by NMR signal splitting, but also by differentiation of the longitudinal and transverse relaxation rates.[21] Schmidtchen recently undertaken a careful examination of the thermodynamics of chiral recognition for camphor isomers,[22] showing that solvent restructuring effects (rather than specific host-guest interaction) account for the major fraction of the binding enthalpy. βCD and its derivatives form with camphor the usual 1:1 complexes. As already cited,[1] thermodynamic data for discrimination of camphanic acid **67**, 3-bromo-8-camphorsulfonic acid **68**, 10-camphorsulfonic **69**, camphorquinone-3-oxime **70**, camphoric acid **71**, pinanediol **72** and 2-hydroxy-3-pinanone **73** (Scheme 3) with βCD and cationic 6-amino-6-deoxy-βCD **74** have been reported by Rekharsky and Inoue.[23,24] A thermodynamic study relevant to the GC separation of menthol **75**, *neo*-menthol **76**, *i*-menthol **77**, *neo-i*-menthol **78**, menthone **79**, *i*-menthone **80** and 3-oxo-1,8-cineole **81** in presence of octakis-(2-*O*-methyl-3-*O*-acetyl-6-*O*-(*t*-hexyl-dimethyl)silyl)-γCD **82** and octakis-(2-*O*-acetyl-3-*O*-methyl-6-*O*-(*t*-hexyl-dimethyl)-silyl)-γCD **83** has been carried out by Bicchi.[25] Data suggest in this case that the presence of the 3-OH group and the relative *trans* configuration the substituents in the positions 3 and 4 are important factors for achieving chiral selection.

Bortolus performed a detailed investigation on the chiral discrimination of camphorquinone **84** with native cyclodextrins and heptakis-(2,6-*O*-dimethyl)-βCD **85**,[26] combining spectroscopic (UV-vis, CD, luminescence and transient triplet-triplet absorption) and computational methods. Also in this case, a 2:1 complex was found with αCD with good selection for the *R*-(-)-isomer (α=2), whereas 1:1 complexes were formed with the other host, with inversion of selection (α values up to 1.5 in favour of the *S*-(+) isomer). A recent study[27] by Liu shows good enantiomeric differentiation in presence of some mono-6-*O*-(*p*-X-phenyl)-βCDs **86**-**90** (up to α=4) for camphor, whereas worse results are found with the same hosts for borneol **91**. Fair to good results (up to α=2) were found by the same author for borneol **91** and menthol **75** with mono-(6-*p*-methoxyphenylseleno)-(6-deoxy)-βCD **92**, mono-(6-*p*-tolylseleno)-(6-deoxy)-βCD **93**,[28] mono-(6-*p*-phenylazophenyl)-(6-deoxy)-βCD **94**,[29] mono-(6-*O*-(1-benzotriazole))-βCD **95** and mono-(6-benzylseleno)-(6-deoxy)-βCD **96**,[30] and a 6-*S*-triptophan-derivatized βCD **97**.[31] An interesting result was obtained also by Ueno,[32] who synthesized a very intriguing βCD derivative **98**, bearing both a fluorophoric (dansyl) and a monensine pendant group able to bind an alkaline cation; significant enantiomeric recognition for camphor and fenchone **99** isomers can be observed with this particular host in the presence of Na^+ (α up to 1.8). A particular dansylglycine-modified βCD was designed by the same author for immobilization on a cellulose membrane.[33] The immobilized host is able to perform good discrimination of borneol enantiomers. By contrast, no significant recognition (in view of the experimental indeterminations) was achieved for camphor, borneol and menthol with another peculiar hybrid peptide-βCD-fluoresceine-coumarine **100** system designed by Mihara for fluorescence resonance energy transfer.[34]

A reversed-phase liquid chromatography study has been carried out by Bielejewska to clarify the complexation process among αCD with camphor and α-pinene **101**, occurring in aqueous phase in the presence of aliphatic alcohols as secondary modifiers.[35] In particular, the stepwise apparent stability constants for the formation of the 1:1 and 1:2 camphor-αCD complexes have been reported and examined for different solvent compositions. Data indicate very good enantiodiscrimination (α values around 1.9, nearly irrespective on solvent composition), which is substantially due to the 1:2 complexation step.

Thermodynamic data also show that the enthalpy of complexation is much more negative than the enthalpy of transfer of the solute to the stationary phase. Similar results were found by the same author by GLC techniques.[36]



Scheme 3

3. Cyclodextrins as selectors in bulk-scale enantioseparation

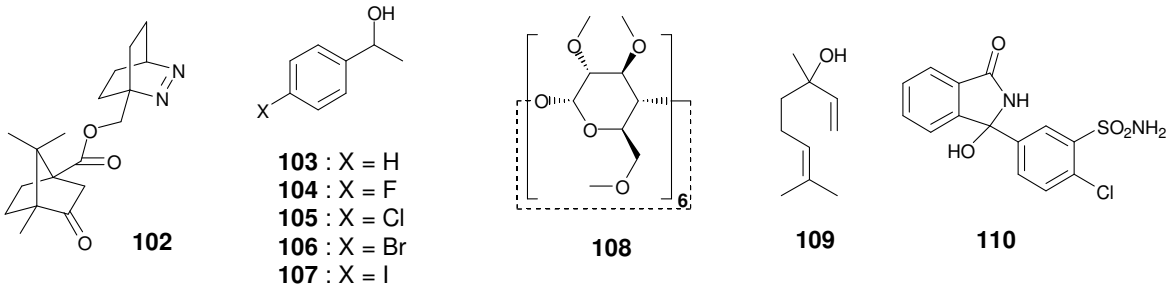
The need to provide enantiopure drugs or flavours makes separation of enantiomers, or at least enantiomeric enrichment, a main industrial goal. Cyclodextrins can be used as additives in bulk separations technologies[37] in two different ways. The first one is co-precipitation, which can be exploited when the host-guest complex is intrinsically less soluble than the free components: as a consequence, the selective

complexation in solution affords a precipitate enantiomerically enriched. The second way is the use as complexing additive in membrane separation technologies; here a cyclodextrin acts as selective transporter. In both cases, the main drawback is due to the fact that, depending on the particular substrate, native cyclodextrins usually are not enough effective as discriminating agents, whereas chemically modified cyclodextrins afford much better results, but are much more expensive to encourage their widespread industrial use.

Nau[38] reported a 30% enantioenrichment for the precipitation of the camphanic ester of 1-hydroxy-methyl-2,3-diazabicyclo[2.2.2]oct-2-ene **102** (Scheme 4) in the presence of βCD. The guest molecule is encapsulated within a 2:1 complex; under these condition the differential solubility of the diasteromeric complexes is not a strictly morphological fact, but is rather a consequence of their different thermodynamic stability. An interesting case of co-precipitation chiral resolution of alcohols **103**-**107** is illustrated in three recent papers by Petit.[39-41] Dissolution in water at 40 °C of permethyl-βCD **11** and 1-(*p*-X-phenyl)-ethanol (X = H, F, Cl, Br, I), in proper amounts, affords after a 3 hours equilibration a precipitate enantioenriched to a some extent (from 6% e.e. for the *p*-Br derivative to 27% e.e. for the *p*-F derivative). However, collection and analysis of precipitates at different times shows a dramatic decrease of enantioseparation, which passes for instance from 70% e.e. to 6% e.e. in the case of the *p*-Br compound. Moreover, careful collection of solids at different times during slow precipitation experiments, allowed to obtain crystals having both different morphology and enantiomeric composition. In particular, the case of the *p*-Br derivative **106** was thoroughly investigated.[40] Slow precipitation experiments allowed first to collect acicular crystals having a 80% e.e. in favour of the *S* enantiomer, and subsequently prismatic crystals having a 40% e.e. in favour of the *R* enantiomer. X-Ray investigation showed the cyclodextrin molecules positioned differently in the two different solids. Furthermore, the guest molecules always formed a hydrogen bond with one of the methoxy groups of the host secondary rim; however, in the *S*-enriched solid the guest was positioned with the phenyl group pointing out of the host cavity, whereas in the *R*-enriched one the phenyl group was as usual embedded into the cavity. Further experiments[41] showed that unsubstituted 1-phenyl-ethanol **103** can be effectively enantioenriched by co-precipitation with permethyl-αCD **108** (up to >97% e.e. after 7 subsequent crystallizations). However X-ray analysis shows that the solids of the diasteromeric complexes are isomorphous, therefore enantioenrichment is due only to their different solubility. It is worth noting that the author explains the best results afforded by permethylated cyclodextrins with respect to native cyclodextrins, considering that the former ones are conformationally less rigid, due to the lack of any intramolecular hydrogen bond network. Thus, the permethylated host is more prone to apt itself onto the guest structure, so that the consequent "induced fit" actually provides enantioselectivity. This effect is somehow amplified owing to the particular interactions establishing in the solid phase. This explanation is in striking contrast with the ideas discussed in our previous review[1] (section 2.3.), which however are referred to the behaviour occurring in solution.

Few recent examples are reported about the use of cyclodextrins in membrane separation technologies. Enantiomeric enrichment up to 14% has been obtained by Moulin for linalool **109**[42] using a pervaporation technique on two different hydrophobic dense membranes; in this case βCD, dissolved in the aqueous medium, was used as selective complexing agent for the substrate. An attempt to exploit an electrodialysis system for the enantioseparation of Trp is due to van der Ent.[43] Also in this case, αCD was chosen as bulk solution complexing agent. The results reported suggest that a high number of equilibrium stages is needed

in order to achieve >99% separations. Finally, a recent example of an aqueous liquid membrane containing βCD as selector has been reported by Breytenbach.[44] Enantioenrichment up to α=1.42 has been achieved for Chlortalidone **110**, depending on operational conditions.



102

103 : X = H
104 : X = F
105 : X = Cl
106 : X = Br
107 : X = I

108 **109** **110**

Scheme 4

4. Cyclodextrins as selectors in analysis (GC, HPLC, electrophoresis)

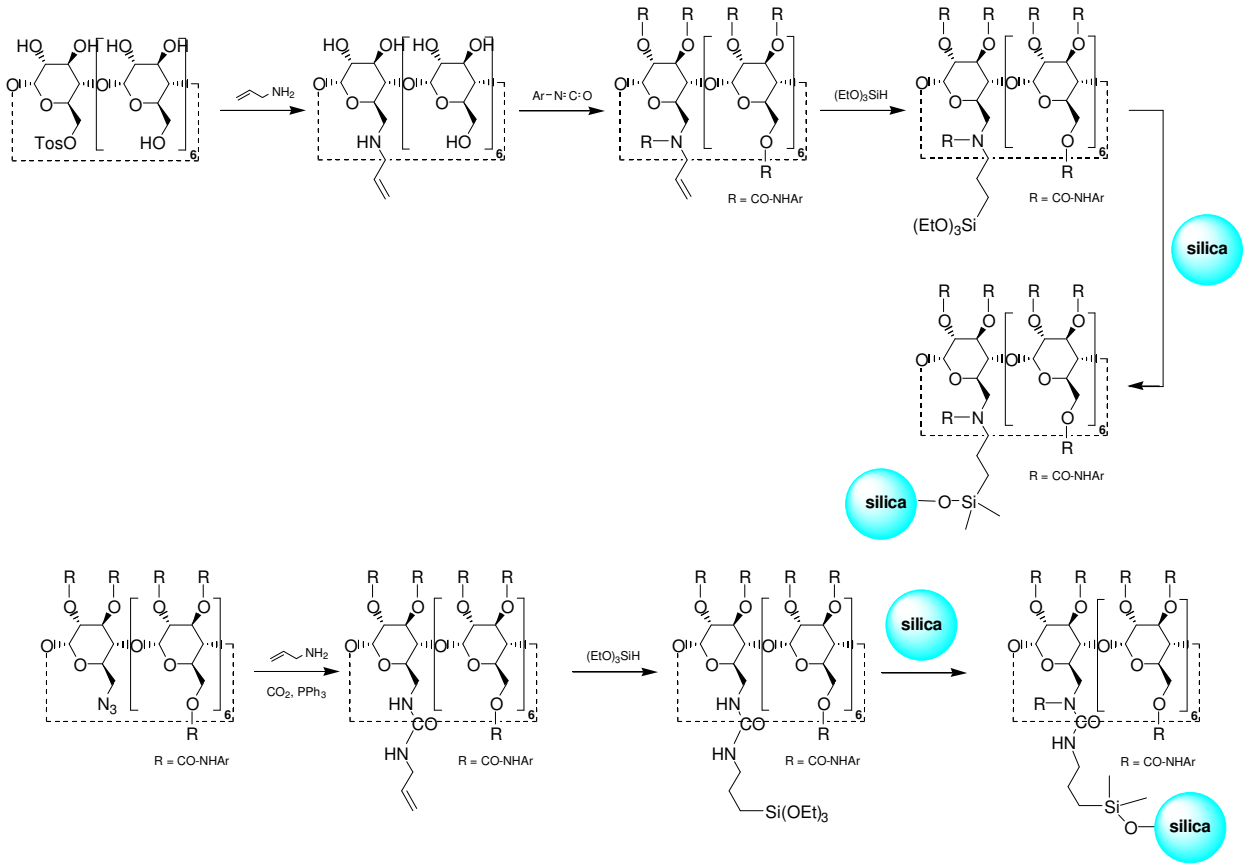
Microanalysis is undoubtedly the main application field for cyclodextrins.[45] Chromatographic (HPLC, RP-HPLC, GSC, GLC) and, in particular, electrophoresis techniques have widely and profitably exploited both natural and modified cyclodextrins as chiral selectors. Virtually, indeed, any enantiomeric pair can be adequately resolved with a sensible choice of the experimental conditions in the presence of the suitable cyclodextrin as selector. This statement easily explains why so many works are carried out and published on these topics. In fact, hundreds of papers deal with or at least cite examples of analytical microseparations. Collecting records about all of them would be a titanic effort, and matter-of-factly a pointless exercise, which absolutely exceeds the purposes of the present paper. A great number of recent reviews substantially cover almost the entire subject. Some of them report on uses of cyclodextrins within a more general picture of recent advances in chromatographic techniques,[46] both LC[47] (including supercritical fluid chromatography[47,48]) and GC,[49-51] as well as electrochromatographic or electrophoretic methodologies[52-64] (the latter ones also in non-aqueous systems[65-66]). Another group of reviews deals with uses of cyclodextrins in some particular application field, namely GC analysis of essential oils,[67,68] or electrophoresis analysis of aminoacids,[69,70] or drugs, pharmaceuticals and biomedicals[71-76] (in particular antibiotics[77] and nonsteroidal anti-inflammatories[78]). Reviewing of all these subjects is continuously updated, thus readers specifically interested in this particular area are adviced to refer to original periodicals and publications.

Anyway, it is well known that, within any separation technique, the fundamental point is the repartition of the analyte (a chiral one, for the aims of the present discussion) between a mobile and a stationary phase. Cyclodextrins can in principle be used as enantioselective additives (or even as pure components) for both. This situation is commonly encountered in LC techniques, where either eluents containing dissolved natural (aqueous systems) or modified (both aqueous and non-aqueous systems) cyclodextrins, or stationary phases bearing chemically bound cyclodextrins have been extensively used. Recent cases of profitable use of cyclodextrins in both the mobile and the stationary phases at the same time have been occasionally reported.[13] For GC applications, cyclodextrins obviously concern only the stationary phase, either pure or in mixture with a suitable inert component. It is worth noting that, on the grounds of recent studies on the enantioseparation of polychlorinated compounds by means of permethyl-βCD, high purity of the selector has been demonstrated to be an important factor in order to achieve the best results.[79] The same statement have been proven true also for CE by Holzgrabe,[80] on examining the selection properties of single-isomer or

randomly poly-methylated β-cyclodextrins. A similar comparison between single-isomer and randomly acetylated β-cyclodextrins has been carried out by Chankvetadze[81] studying drug CE separations. In general, it should be kept in mind that use of a cyclodextrin as selector additive does not strictly require the availability of a pure and expensive single-isomer species; on the contrary, commercially low-cost (relatively!) available products are usually isomer mixtures.[82] Within electrophoretic techniques, cyclodextrins are more frequently used as chiral additives for the mobile phase, in particular those modified with charged groups (sulfated cyclodextrins[64,83] are the most frequent); recent examples of uses of dual-selector systems[83-86] (a charged cyclodextrin coupled with a neutral one) or even a ternary selector system[87] are reported. Cyclodextrin-based stationary phases are quite common too. Plenty of commercial products for laboratory applications is now easily available.

The theoretical principles, the relevant mathematical treatment, and the thermodynamic implications of these applications have been thoroughly investigated and exhaustively discussed in recent publications.[10,13,35,36,54,85,88-94] In particular, comparisons between liquid chromatography and electrophoresis performances have been in some cases carried on.[88,91,95,96] So, for the aims of the present paper, in this section we will rather focus mostly on the recent advances concerning the synthesis of new cyclodextrin derivatives designed for use as selectors in analytical applications.

Mono-(6-amino)-(6-deoxy)-per-phenylcarbamoylated-β-cyclodextrin silica bound stationary phases for HPLC were obtained by Ng[97,98] by two different synthetic strategies (Scheme 5) and used for the enantioseparation of several drugs, including some β-blockers and dihydropirimidine derivatives.

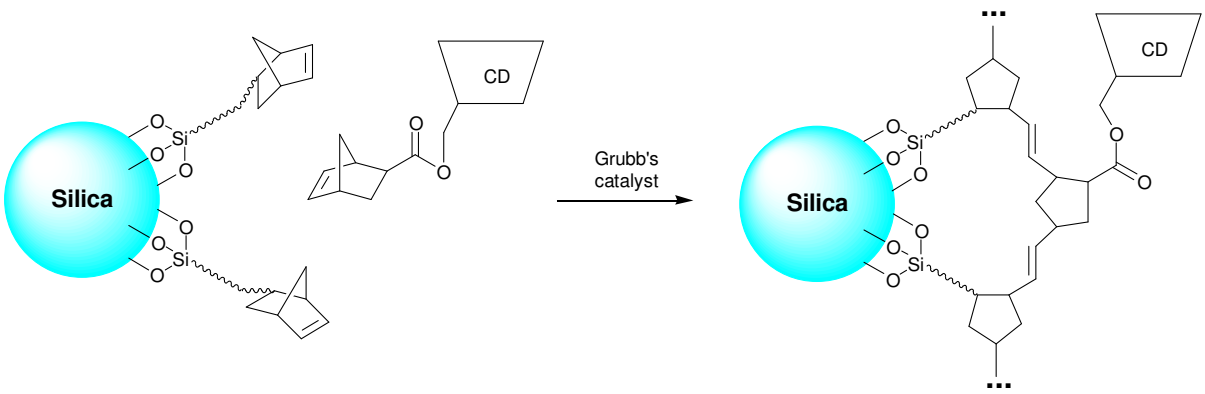


Scheme 5

In a similar way, the same author also obtained and exploited a mono-(6-amino)-(6-deoxy)-per-ethylated-β-cyclodextrin silica bound derivative[99] (effective for some flavanones), as well as a series of

mono-(6-amino)-(6-deoxy)-per-arylcarbamoylated-β-cyclodextrin derivatives[100] (all successfully tested on some pharmaceuticals). A heptakis-(6-amino)-(6-deoxy)-(2,3-di-*O*-phenylcarbamoylated)-β-cyclodextrin derivative[101] linked to amino-functionalized silica was prepared and tested by the same author too. Similarly, König[102,103] anchored on silica different β-cyclodextrin derivatives (heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin, permethyl-β-cyclodextrin, heptakis-(6-*O*-(*t*-butyl-dimethyl)silyl-2,3-di-*O*-methyl)-β-cyclodextrin) and tested them as HPLC stationary phases for enantioseparation of barbiturates, profens and other drugs. Partly hydroxy-propylated β-cyclodextrin already attached to silica gel was further derivatized by H. K. Lee as per-naphtylcarbamate[104,105] by means of a suitable liquid-solid phase reaction.

A similar procedure allowed also to obtain a diaza-18-crown-6-capped β-cyclodextrin derivative.[105] Using a ring-opening metathesis strategy (Scheme 6), Buchmeiser grafted onto a norborn-2-ene derivatized silica a series of different norborn-2-ene derivatized β-cyclodextrins;[106] materials obtained were tested for the enantioseparation of some β-blockers and derivatized aminoacids. Carboxymethyl-β-cyclodextrin coated zirconia was prepared and exploited by Park[107] for RPLC enantioseparation of *N*-2,4-dinitrophenyl-aminoacids.

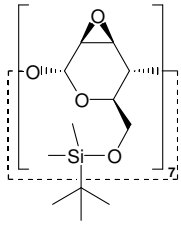


Scheme 6

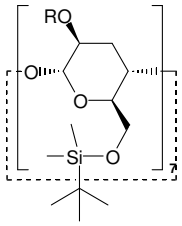
Several per-derivatized cyclodextrins designed for GC applications have been recently synthesized too. The most intriguing from a synthetic point of view are probably the heptakis-(*manno*-2,3-anhydro-6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **111**, the heptakis-(*manno*-3-deoxy-6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **112**, the heptakis-(*manno*-2-*O*-methyl-3-deoxy-6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **113** and the heptakis-(*manno*-2-*O*-benzyl-3-deoxy-6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **114** (Scheme 7) due to Kelly,[108] tested on 39 non-polar racemic analytes. Mono-(6-*O*-oct-(7-en)yl)-permethyl-γCD **115**, mono-(2-*O*-oct-(7-en)yl)-permethyl-γCD **116** and mono-(3-*O*-oct-(7-en)yl)-permethyl-γCD **117** were unambiguously prepared by Combret and Schurig[109] and anchored on a hydridomethyl-dimethyl-siloxane copolymer, showing better performances on menthyl derivatives enantioseparation than commercial Chiralsil-Dex.

Synthesis and selection performances of octakis-(2-*O*-methyl-3-*O*-acetyl-6-*O*-(*t*-hexyl-dimethyl)silyl)-γCD **82** and octakis-(2-*O*-acetyl-3-*O*-methyl-6-*O*-(*t*-hexyl-dimethyl)silyl)-γCD **83** have already been cited.[25,110] Noticeably, useful tuning of the cyclodextrin selectivity have been achieved by König[111] simply by exchanging one methyl group for an acetyl group on heptakis-(2,3-di-*O*-methyl-6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **118**. A new design octakis-(2,3-di-*O*-methoxymethyl-6-*O*-(*t*-butyl-dimethyl)silyl)-γCD **119** has been synthesized by Engel[112] and tested over 125 enantiomeric pairs from several different classes of compounds. Shi[113] prepared three new heptakis-(2,3-di-*O*-pentyl)-(6-*O*-acyl)-βCDs and tested them on 15 various

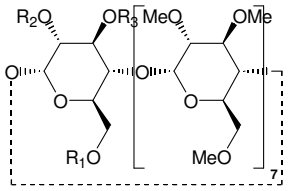
enantiomeric pairs. Best performances were achieved with the valeryl derivative. Finally, Liang exploited an easy sol-gel technique[114] to obtain a fused silica capillary GC column coated with peralkylated β-cyclodextrins. Columns obtained showed excellent properties, in terms of thermal stability (up to 300 °C), high number of theoretical plates and excellent reproducibility.



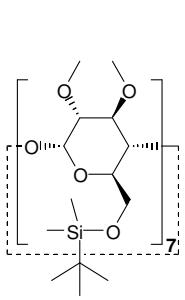
111



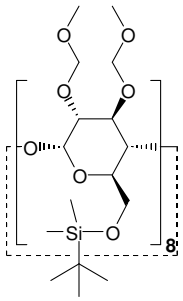
112 : R = H
113 : R = Me
114 : R = $PhCH_2$



	R_1	R_2	R_3
115	$(CH_2)_6CH=CH_2$	Me	Me
116	Me	$(CH_2)_6CH=CH_2$	Me
117	Me	Me	$(CH_2)_6CH=CH_2$



118



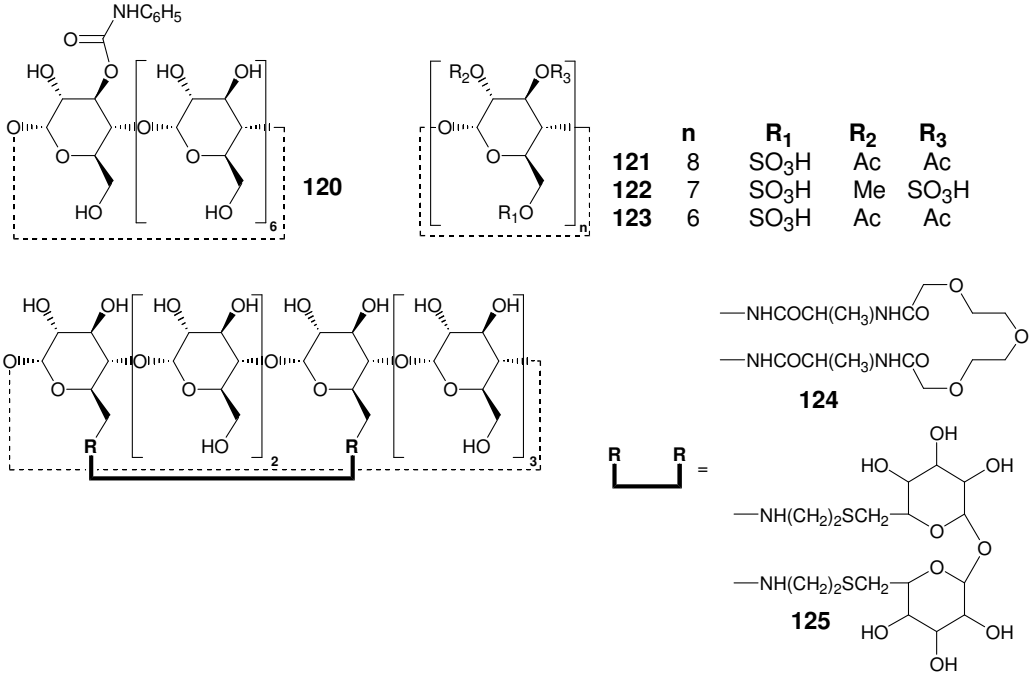
119

Scheme 7

Applications of cyclodextrins in electrochromatographic and electrophoretic methodologies deserve a more articulated discussion, upon the consideration that these have been by far the most extensively exploited and documented in recent literature. Indeed, the amount of papers available is simply immense. Nevertheless, it is undoubtedly a fertile field of research and innovation. In fact, the most interesting aspect is the continuous search for new application methodologies. For instance, Capillary Zone Electrophoresis on-line coupled with Isotactophoresis has been explored as an effective approach to the separation of aminoacid derivatives.[115] Sulfated cyclodextrins have been used as selectors of choice for ultra-fast microchip separation of aminoacid derivatives[116] or aminoindane.[117] Very recently the first application of cyclodextrins to a microemulsion electrokinetic chromatography has been reported by Foley.[118] Ethyl acetate-sodium dodecylsulfate and dodecoxycarbonylvaline microemulsions were paired with either hydroxypropyl-βCD (neutral) or sulfated-βCD (anionic) and used for the resolution of nine chiral drugs; excellent performances and dramatic improvements of enantioseparations were achieved by a suitable adjustment of operational conditions. Cyclodextrins have been profitably exploited for micellar electrokinetic chromatography too, as witnessed, for instance, in a recent example by Warner.[119]

Both neutral and charged new cyclodextrins have been recently synthesized for use as solution selectors in CE techniques. Li[120] prepared mono-(3-*O*-phenylcarbamoyl)-βCD **120** (Scheme 8) and tested it for the separation of eight different chiral drugs. Highly water soluble 2-*O*-acetonyl-2-*O*-hydroxypropyl (as a mixture of all possible isomers!) was obtained by Zhu[121] and successfully tested for the separation of 22 chiral drugs, in comparison with other commonly non-charged β-cyclodextrins of common use. Three single-isomer sulfated cyclodextrins, namely octakis-(2,3-di-*O*-acetyl-6-*O*-sulfo)-γCD,[122,123] **121** heptakis-(2-*O*-

methyl-3,6-di-*O*-sulfo)-βCD,[124,125] **122** and hexakis-(2,3-di-*O*-acetyl-6-*O*-sulfo)-αCD[126] **123** were synthesized, fully characterized and tested by Vigh. Two very intriguing - from the synthetic viewpoint - bridge-capped derivatives have been recently introduced too: the first one is the (6^A,6^D-*N,N'*-3,6,9-trioxa-undecanoyl-(*S,S*)-bis-alanyl)-(6^A,6^D-dideoxy)-βCD **124** prepared by Marchelli;[127] the second one is the "hemispherodextrin" **125** synthesized by Cucinotta[128] and tested as effective for the separation of some phenoxypropionic acid derivatives.

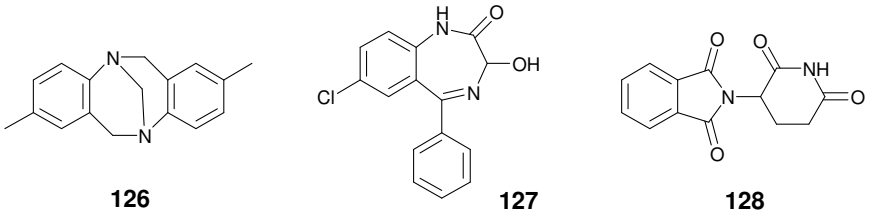


Scheme 8

On passing to stationary phases, cyclodextrin-modified monolith microcolumns for capillary electrochromatography have been object of interest. Wistuba[129] coated with Chiralsil-Dex a capillary column previously prepared by sol-gel technique; subsequent thermal immobilization of the Chiralsil-Dex component gave rise to high-stability chiral monolith. Differently, Chen[130] used a sol-gel technique to directly prepare silica monoliths charged with non-modified βCD or γCD. The same approach was exploited by Zeng[131] to prepare a silica monolith containing per-(2,6-di-*O*-butyl)-βCD. Sol-gel technique was also used by Koide[132] to prepare a negatively charged sulfo-polyacrilamide gel bearing chemically bound allyl-carbamoyl-βCD. Modified silica particles for electrochromatography applications were prepared by Lee. Non-derivatized βCD was anchored to silica and converted in its per-bromoacetyl derivative;[133] the obtained product was further modified by attachment of crown-ethers[134] or cyclam derivatives.[135] Finally, a suitable stationary phase for Electrochemically Modulated Liquid Chromatography was prepared by Porter[136] through electrosorption of βCD on porous graphite.

As a concluding remark, it is worth mentioning the utilization of cyclodextrins as selectors in Dynamic Chromatography methods, used for the determination of enantiomerization energy barriers.[137,138] By means of computer-aided analysis of chromatographic peaks form, it is possible to go back to activation parameters for enantiomer interconversion of suitable chiral molecules. In particular, Schurig exploited for this purpose both Stopped-flow multidimensional GC[137] and electrochromatographic[139] techniques, in order to study the interconversion of Tröger's base **126** (Scheme 9) enantiomers. A Chiralsil-β-Dex (permethylated βCD chemically bound to polydimethoxysilane) was employed as selector in the former case, whereas

hydroxypropyl-βCD was used as mobile phase additive in the latter one. The same author also exploited a dynamic HPLC technique to study the enantiomer interconversion of Oxazepam **127**,[140] using a Nucleosil-β-PM^{TM} column (permethylated βCD bound to silica). Moreover, heptakis-(2,3-di-*O*-methyl-6-*O*-(*t*-butyl-dimethyl)silyl)-βCD **118** dissolved in PSO86 was used for a GC investigation on Thalidomide **128**.[141] Gasparrini recently used in a similar way high-resolution GC to study the enantiomerization of some α-nitroketones.[142]



126 **127** **128**

Scheme 9

5. Cyclodextrins as auxiliaries in stereocontrolled reactions

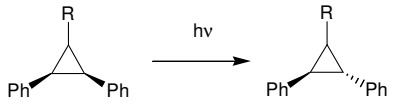
This final section concerns chiral recognition *lato sensu*; as a matter of fact, the point here is not properly selection, but rather induction of chirality. The idea is that a flexible achiral guest may be selectively forced into a chiral conformation upon complexation with the cyclodextrin host. As a consequence, induction of enantioselectivity may be achieved if the included guest undergoes a chemical reaction. In this case, the additive cyclodextrin simply acts as a confined chiral reaction environment or microreactor. It is worth noting that the water solubility of cyclodextrins (natural or suitably modified ones) allows the occurrence in aqueous medium of reactions otherwise performed only in non-polar solvents. However, the host itself may directly partecipate in the reaction, if it is modified by attachment of a suitable reactive group. In fact, in this case the cyclodextrin acts as a sort of enzyme mimick. Examples of both roles have been recently reported.

The main application field of cyclodextrins as chiral reaction microenvironment has been by far constituted by photoinduced cyclizations. Three recent examples have been provided by Ramamurthi. The author studied the photocyclization of 2-alkyloxy-tropolones in the presence of αCD, βCD or γCD to the corresponding 1-alkoxy-bicyclo[3.2.0]-3,6-dien-2-ones (Scheme 10).[143]

Scheme 10

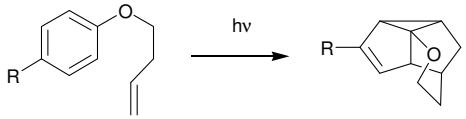
Fair enantiomeric excesses (e.e. up to 33%) upon irradiation of the complexes isolated in the solid phase were observed, whereas very poor e.e.s were obtained in aqueous solutions. Better results were gained on irradiation of the complexes of *N*-methyl-pyridone and *N*-ethyl-pyridone with βCD to the corresponding 2-*N*-alkyl-2-azabicyclo[2.2.0]-hex-5-en-3-ones.[144] In this case an e.e. up to 59% was observed irradiating the solid phase complexes obtained either by co-precipitation of the reagents or by mere mechanical mixing. However, inversion of enantioselection was observed on irradiation of the co-precipitated complex previously subjected to vacuum drying (e.e. 26%); this indicates that co-crystallized water may have an important role in the reaction course. Again, no e.e. was observed for the reaction in solution. Furthermore,

enantiomeric or diasteromeric excesses up to 30% were observed on irradiation of some *cis*-1,2-diphenyl-cyclopropanes complexed in the solid phase with βCD to afford the corresponding *trans* derivatives (Scheme 11).[145]



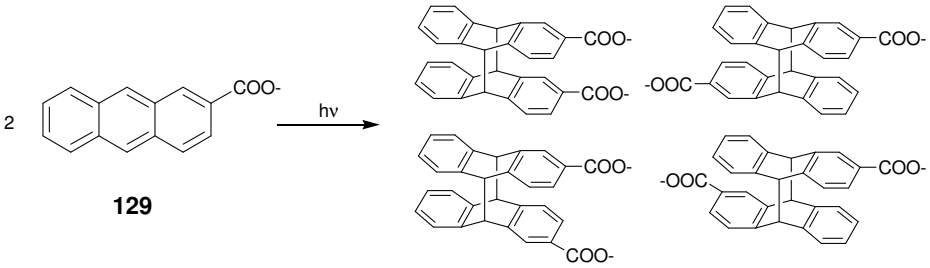
Scheme 11

Van der Eycken investigated the occurrence of the intramolecular meta-photocycloaddition of some 4-aryloxy-1-butenes (Scheme 12) in the presence of βCD;[146] unfortunately, e.e. values for the obtained polycyclic products are low (up to 17%).



Scheme 12

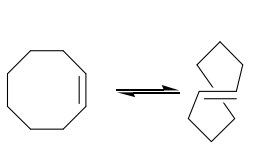
Inoue reported the photocyclodimerization of 2-anthracene-carboxylate **129** in the presence of γCD (Scheme 13).[147] In this case the host is large enough to accommodate two guest molecules in different arrangements. Four different photodimers are then formed upon irradiation, two of which are chiral. Fair e.e. are found for one of them (up to 41%, depending on temperature).



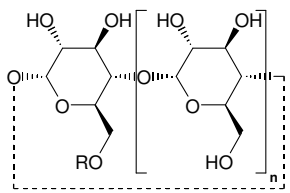
129

Scheme 13

The same author recently reported the enantiodifferentiating *Z*-*E* photoisomerization of cyclooctene **130** in the presence of mono-6-*O*-modified cyclodextrins **131**-**136** (Scheme 14) bearing a sensitizing group.[148,149] Irradiation of cyclooctene in the presence of mono-(6-*O*-benzoyl)-βCD or mono-(6-*O*-(carbomethoxy)-benzoyl)-βCD (*o*-, *m*- and *p*- isomers) resulted in a higher *E*/*Z* ratio and a fair e.e. for the *E* isomer (up to 24%). Mono-(6-*O*-benzoyl)-αCD or -γCD were scarcely effective, owing to non-ideal dimensional fit. Noticeably, e.e. values unexpectedly showed little variations with temperature, but rather depended on the degree of host occupacy.



130(*Z*) **130(*E*)**



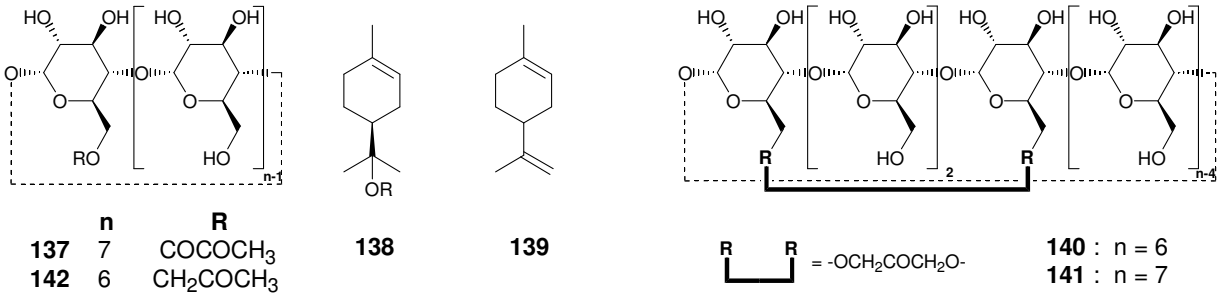
	n	R
131	6	CO-C_6H_5
132	7	CO-C_6H_5
133	7	CO-C_6H_4-*o*-COOMe
134	7	CO-C_6H_4-*m*-COOMe
135	7	CO-C_6H_4-*p*-COOMe
136	8	CO-C_6H_5

Scheme 14

Variations in e.e. values were found on changing the solvent composition. In particular, a progressive inversion of enantioselectivity was observed on irradiation of *Z*-cyclooctene in the presence of mono-(6-*O*-

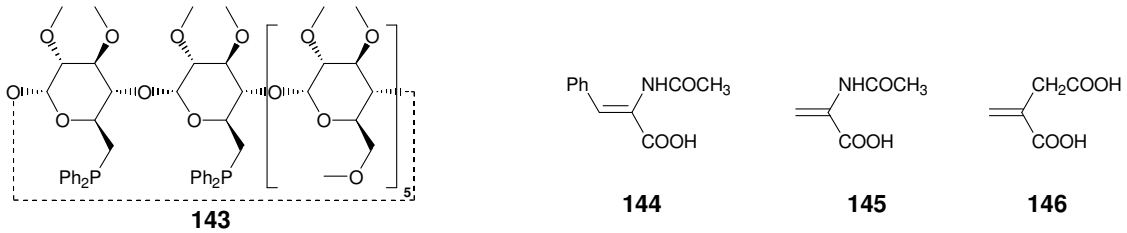
(2-methoxy)-benzoyl)-βCD on passing from aqueous to methanol solution.[149]

The latter examples introduce us in the use of derivatized cyclodextrins bearing reactive groups. Two interesting examples concern cyclodextrins designed to perform epoxidation reactions. Wong[150] synthesized and used mono-(6-*O*-pyruvoyl)-βCD **137** (Scheme 15) to catalyze the epoxidation with $KHSO_5$ (Oxone) - *via* the corresponding dioxyrane intermediate - of (*S*)-α-terpineole derivatives **138**, limonenes **139** (actually, in the case of these terpenes, it should be correct to speak of *cis-trans* diastereoselectivity) and styrenes. Noticeably, *cis*/*trans* epoxide ratio for the oxidation of terpineoles decreased from 2.5:1 to 1:1.2 on increasing the steric bulkiness of the terpene, as a function of the different penetration into the host cavity. An interesting 4.1:1 diasteromeric ratio for (*R*)-limonene was also found, while e.e. values up to 40% were found for styrenes. Bols[151] synthesized the bridged (6^A,6^D-*O*-(prop-2-one-1,3-dienyl))-αCD **140**, (6^A,6^D-di-*O*-(prop-2-one-1,3-dienyl))-βCD **141** and mono-(6-*O*-prop-(2-one)-yl)-αCD **142** to serve as epoxidation catalysts towards some styrenes, but result were generally poor.



Scheme 15

Finally, Jia[152] designed and synthesized the cyclodextrin-diphosphine ligand bis-(6^A,6^B-diphenylphosphino)-bis-(6^A,6^B-dideoxy)-per-(2,3,6-*O*-methyl)-βCD **143** (Scheme 16), and used it to prepare the corresponding dichloroplatinum and 1,5-cyclooctadienyl-rhodium complexes. The Rh complex was in turn used as asymmetric hydrogenation catalysts towards α-acetamido-cynnamic acid **144**, α-acetamido-acrylic acid **145** and itaconic acid **146** acids and their methylesters. Very satisfactory results were obtained, with e.e. values ranging from 51% to 92%, as a function of the substrate and of the solvent medium.



Scheme 16

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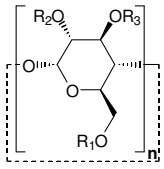
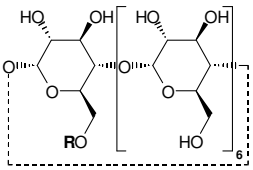
Appendix : Most recent thermodynamic data pertaining chiral discrimination by cyclodextrins (Cyclodextrin structures have been re-numbered according to the following scheme, in order to achieve a clearer and more recognizable data tabulation.)

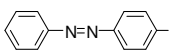
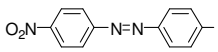
i) Native cyclodextrins



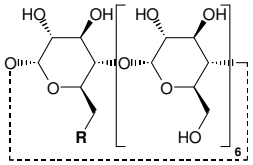
1α : n = 6
1β : n = 7
1γ : n = 8

ii) Mono-functionalized β-cyclodextrins

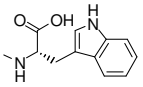
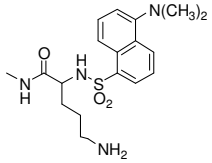


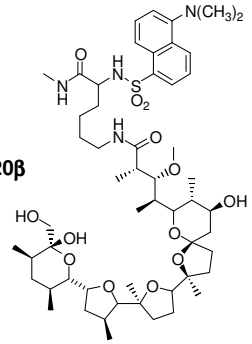
	R		R
2β	C_6H_5	**7β**	
3β	*p*-CHO-C_6H_4	**8β**	
4β	*p*-Br-C_6H_4		
5β	*p*-Cl-C_6H_4	**9β**	
6β	*p*-NO_2-C_6H_4	**10β**	*p*-HO-C_6H_4-CO

iii) Mono-(6-deoxy)-functionalized β-cyclodextrins

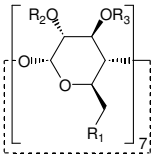


	R
11β	-NH_2
12β	-$NH(CH_2)_2OH$
13β	-$NHCH_2CH(CH_3)OH$
14β	-$NHCH(CH_3)CH_2OH$
15β	-$NH(CH_2)_3OH$

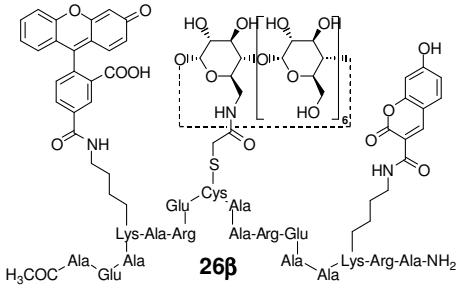
	R
16β	
17β	
18β	
19β	

	R
20β	
21β	*p*-Me-C_6H_5Se-
22β	*p*-MeO-C_6H_5Se-
23β	$C_6H_5CH_2Se$-

iv) Per-functionalized β-cyclodextrins



	R_1	R_2	R_3
24β	OMe	Me	H
25β	OMe	Me	Me



26β

Host (charge)	Guest (charge)	Log *K*	$\Delta H°$ (kJ mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	notes	method	ref.
1α	(+)-Camphor	0.95 ± 0.09			cplx 1:1	NMR	20
1α	(+)-Camphor	5.82 ± 0.01			cplx 2:1	NMR	20
1α	(+)-Camphor	5.79	-69.73	-36.69	cplx 2:1	cal.	22
1α	(+)-Camphor	6.21	-67.38	-31.93	cplx 2:1. D_2O	cal.	22
1α	(-)-Camphor	0.93 ± 0.12			cplx 1:1	NMR	20
1α	(-)-Camphor	5.56 ± 0.04			cplx 2:1	NMR	20
1α	(-)-Camphor	5.50	-68.39	-37	cplx 2:1	cal.	22
1α	(-)-Camphor	5.86	-63.21	-29.79	cplx 2:1. D_2O	cal.	22
1α	(+)-Camphorquinone	4.15 ± 0.05				CD	26
1α	(-)-Camphorquinone	3.86 ± 0.04				CD	26
1β	(+)-Borneol	4.27 ± 0.01	-20.86 ± 0.54	3.52 ± 0.55	pH 7.2	cal.	27
1β	(-)-Borneol	4.30 ± 0.01	-23.16 ± 0.07	1.34 ± 0.16	pH 7.2	cal.	27
1β	*(R)*-3-Bromo-8-Camphorsulphonic acid (-1)	3.58 ± 0.01	-30.1 ± 0.3	-9.7 ± 0.3	pH 6.9	cal.	23
1β	*(S)*-3-Bromo-8-Camphorsulphonic acid (-1)	3.56 ± 0.01	-29.6 ± 0.3	-9.3 ± 0.3	pH 6.9	cal.	23
1β	*(R)*-3-Bromo-2-methyl-1-propanol	2.15 ± 0.01	-9.3 ± 0.2	3.0 ± 0.2	pH 6.9	cal.	23
1β	*(S)*-3-Bromo-2-methyl-1-propanol	2.15 ± 0.01	-10.1 ± 0.2	2.2 ± 0.2	pH 6.9	cal.	23
1β	*(R)*-Camphanic acid (-1)	2.25 ± 0.01	-17.8 ± 0.2	-5.0 ± 0.2	pH 6.9	cal.	23
1β	*(S)*-Camphanic acid (-1)	2.32 ± 0.01	-17.8 ± 0.2	-4.5 ± 0.2	pH 6.9	cal.	23
1β	(+)-Camphor	3.92 ± 0.01	-13.82 ± 0.55	8.54 ± 0.62	pH 7.2	cal.	27
1β	(-)-Camphor	3.70 ± 0.01	-23.84 ± 0.6	-2.74 ± 0.58	pH 7.2	cal.	27
1β	*(1R,3S)*-Camphoric Acid (-2)	1.28 ± 0.02	-15.5 ± 0.6	-8.2 ± 0.6	pH 6.9	cal.	23
1β	*(1S,3R)*-Camphoric Acid (-2)	1.38 ± 0.02	-8.3 ± 0.4	-0.4 ± 0.4	pH 6.9	cal.	23
1β	*(R)*-Camphorquinone	2.51 ± 0.02				CD	26
1β	*(S)*-Camphorquinone	2.71 ± 0.05				CD	26
1β	*(R)*-Camphorquinone-3-oxime	3.42 ± 0.01	-27.1 ± 0.2	-7.6 ± 0.2	pH 6.9	cal.	23
1β	*(R)*-Camphorquinone-3-oxime	3.39 ± 0.01	-27 ± 0.2	-7.7 ± 0.2	pH 4.8	cal.	23
1β	*(S)*-Camphorquinone-3-oxime	3.39 ± 0.01	-27.2 ± 0.2	-7.9 ± 0.2	pH 6.9	cal.	23
1β	*(S)*-Camphorquinone-3-oxime	3.37 ± 0.01	-27.1 ± 0.2	-7.9 ± 0.2	pH 4.8	cal.	23
1β	*(R)*-10-Camphorsulphonic acid (-1)	2.75 ± 0.01	-20.7 ± 0.2	-5.0 ± 0.2	pH 6.9	cal.	23
1β	*(S)*-10-Camphorsulphonic acid (-1)	2.69 ± 0.01	-19.5 ± 0.2	-4.2 ± 0.2	pH 6.9	cal.	23
1β	*(R)*-Deltamethrinic acid (-1)	3.07 ± 0.06			pH 6.0	CE	11
1β	*(S)*-Deltamethrinic acid (-1)	3.12 ± 0.06			pH 6.0	CE	11
1β	*(R)*-2,3-Diazabicyclo-[2,2,2]oc 2-ene camphanate	3.08 ± 0.07			D_2O	NMR	38
1β	*(R)*-2,3-Diazabicyclo-[2,2,2]oc 2-ene camphanate 2	5.19			D_2O, cplx 2:1	NMR	38
1β	*(S)*-2,3-Diazabicyclo-[2,2,2]oc 2-ene camphanate	3.20 ± 0.05			D_2O	NMR	38
1β	*(S)*-2,3-Diazabicyclo-[2,2,2]oc 2-ene camphanate 2	5.52			D_2O, cplx 2:1	NMR	38
1β	*(R)*-Dimethindene	2.66				CE	5
1β	*(S)*-Dimethindene	2.70				CE	5
1β	*(1R,2R,5R)*-2-Hydroxy-3-pinanone	3.37 ± 0.02	-19.5 ± 0.2	-0.2 ± 0.2	pH 6.9	cal.	23

Host (charge)	Guest (charge)	Log *K*	$\Delta H°$ (kJ mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	notes	method	ref.
1β	*(1S,2S,5S)*-2-Hydroxy-3-pinanone	3.36 ± 0.01	-20.0 ± 0.2	-0.8 ± 0.2	pH 6.9	cal.	23
1β	*(R)*-Mandelic acid (-1)	1.32 ± 0.67			pH 6.0	CE	11
1β	*(S)*-Mandelic acid (-1)	1.30 ± 0.65			pH 6.0	CE	11
1β	*(R)*-Permethrinic acid (-1)	2.60 ± 0.07			pH 6.0	CE	11
1β	*(S)*-Permethrinic acid (-1)	2.70 ± 0.06			pH 6.0	CE	11
1β	*(1R,2R,3S,5R)*-Pinanediol	3.81 ± 0.01	-20.4 ± 0.2	1.3 ± 0.2	pH 6.9	cal.	23
1β	(*1S,2S,3R,5S*)-Pinanediol	3.80 ± 0.01	-20.3 ± 0.2	1.4 ± 0.2	pH 6.9	cal.	23
1β	*(R)*-Propranolol (+1)	2.06 ± 0.04	-21.2 ± 0.5	-9.4 ± 0.6	pH 4.8	cal.	23
1β	*(S)*-Propranolol (+1)	2.07 ± 0.04	-20.3 ± 0.5	-8.5 ± 0.6	pH 4.8	cal.	23
1β	(+)-Zileuton	3.77 ± 0.05				UV	4
1β	(+)-Zileuton	3.71 ± 0.02				CD	4
1β	(-)-Zileuton	3.75 ± 0.02				UV	4
1β	(-)-Zileuton	3.65 ± 0.02				CD	4
2β	(+)-Borneol	4.55 ± 0.01	-19.29 ± 0.01	6.61 ± 0.01	pH 7.2	cal.	27
2β	(-)-Borneol	4.51 ± 0.01	-18.96 ± 0.02	6.78 ± 0.04	pH 7.2	cal.	27
2β	(+)-Camphor	4.14 ± 0.01	-12.64 ± 0.07	10.97 ± 0.06	pH 7.2	cal.	27
2β	(-)-Camphor	3.76 ± 0.01	-14.24 ± 0.59	7.24 ± 0.65	pH 7.2	cal.	27
3β	(+)-Borneol	4.62 ± 0.01	-20.24 ± 0.24	6.10 ± 0.32	pH 7.2	cal.	27
3β	(-)-Borneol	4.66 ± 0.01	-22.58 ± 0.11	4.01 ± 0.13	pH 7.2	cal.	27
3β	(+)-Camphor	4.09 ± 0.02	-13.18 ± 0.38	10.17 ± 0.28	pH 7.2	cal.	27
3β	(-)-Camphor	3.94 ± 0.04	-17.97 ± 0.55	4.54 ± 0.32	pH 7.2	cal.	27
4β	(+)-Borneol	4.94 ± 0.02	-23.97 ± 0.01	4.22 ± 0.13	pH 7.2	cal.	27
4β	(-)-Borneol	4.97 ± 0.01	-22.09 ± 0.06	6.26 ± 0.15	pH 7.2	cal.	27
4β	(+)-Camphor	4.36 ± 0.01	-13.85 ± 0.16	11.07 ± 0.18	pH 7.2	cal.	27
4β	(-)-Camphor	4.06 ± 0.01	-12.37 ± 0.58	10.81 ± 0.6	pH 7.2	cal.	27
5β	(+)-Borneol	5.13 ± 0.01	-18.92 ± 0.4	10.33 ± 0.44	pH 7.2	cal.	27
5β	(-)-Borneol	4.95 ± 0.01	-22.53 ± 0.01	5.73 ± 0.02	pH 7.2	cal.	27
5β	(+)-Camphor	4.70 ± 0.01	-10.94 ± 0.26	15.86 ± 0.3	pH 7.2	cal.	27
5β	(-)-Camphor	4.09 ± 0.02	-14.15 ± 0.38	9.21 ± 0.27	pH 7.2	cal.	27
6β	(+)-Borneol	5.03 ± 0.01	-16.91 ± 0.37	11.8 ± 0.38	pH 7.2	cal.	27
6β	(-)-Borneol	4.70 ± 0.03	-23 ± 0.75	3.77 ± 0.48	pH 7.2	cal.	27
6β	(+)-Camphor	4.53 ± 0.01	-10.44 ± 0.01	15.41 ± 0.01	pH 7.2	cal.	27
6β	(-)-Camphor	4.03 ± 0.03	-15.43 ± 0.65	7.55 ± 0.84	pH 7.2	cal.	27
7β	(+)-Borneol	3.18			pH 7.2 10% DMSO	UV	29
7β	(-)-Borneol	3.38			pH 7.2 10% DMSO	UV	29
7β	(+)-Menthol	3.46			pH 7.2 10% DMSO	UV	29
7β	(-)-Menthol	3.42			pH 7.2 10% DMSO	UV	29
8β	(+)-Borneol	2.89			pH 7.2 10% DMSO	UV	29
8β	(-)-Borneol	3.20			pH 7.2 10% DMSO	UV	29
8β	(+)-Menthol	3.37			pH 7.2 10%DMSO	UV	29
8β	(-)-Menthol	3.30			pH 7.2 10% DMSO	UV	29
9β	(+)-Borneol	4.58				CD	30
9β	(-)-Borneol	4.65				CD	30
9β	(+)-Menthol	3.70				CD	30
9β	(-)-Menthol	3.55				CD	30

Host (charge)	Guest (charge)	Log *K*	Δ*H*° (kJ mol^{-1})	TΔ*S*° (kJ mol^{-1})	notes	method	ref.
10β	(+)-Borneol	4.92 ± 0.01	-24.25 ± 0.11	3.84 ± 0.20	pH 7.2	cal.	27
10β	(-)-Borneol	4.96 ± 0.01	-22.43 ± 0.07	5.91 ± 0.07	pH 7.2	cal.	27
10β	(+)-Camphor	4.27 ± 0.02	-13.50 ± 0.08	10.87 ± 0.05	pH 7.2	cal.	27
10β	(-)-Camphor	4.16 ± 0.01	-15.91 ± 0.21	7.86 ± 0.26	pH 7.2	cal.	27
11β (+1)	*(R)*-Camphanic acid (-1)	2.24 ± 0.01	-16.5 ± 0.15	-3.7 ± 0.2	pH 6.9	cal.	24
11β (+1)	*(S)*-Camphanic acid (-1)	2.31 ± 0.01	-16.4 ± 0.15	-3.2 ± 0.2	pH 6.9	cal.	24
11β (+1)	*(R)*-10-Camphorsulphonic acid (-1)	2.89 ± 0.01	-23.8 ± 0.3	-7.3 ± 0.3	pH 6.9	cal.	24
11β (+1)	*(S)*-10-Camphorsulphonic acid (-1)	2.92 ± 0.01	-24.6 ± 0.3	-7.9 ± 0.3	pH 6.9	cal.	24
11β (+1)	*(R)*-Deltamethrinic acid (-1)	3.15 ± 0.04			pH 6.0	CE	11
11β (+1)	*(S)*-Deltamethrinic acid (-1)	3.32 ± 0.04			pH 6.0	CE	11
11β (+1)	*(R)*-Mandelic acid (-1)	1.72 ± 0.21			pH 6.0	CE	11
11β (+1)	*(S)*-Mandelic acid (-1)	1.62 ± 0.24			pH 6.0	CE	11
11β (+1)	*(R)*-Permethrinic acid	2.69 ± 0.02			pH 6.0	CE	11
11β (+1)	*(S)*-Permethrinic acid	2.82 ± 0.02			pH 6.0	CE	11
12β	*(R)*-Deltamethrinic acid (-1)	3.34 ± 0.02			pH 6.0	CE	11
12β	*(S)*-Deltamethrinic acid (-1)	3.62 ± 0.02			pH 6.0	CE	11
12β	*(R)*-Mandelic acid (-1)	1.90 ± 0.10			pH 6.0	CE	11
12β	*(S)*-Mandelic acid (-1)	1.76 ± 0.12			pH 6.0	CE	11
12β	*(R)*-Permethrinic acid (-1)	2.88 ± 0.01			pH 6.0	CE	11
12β	*(S)*-Permethrinic acid (-1)	3.10 ± 0.01			pH 6.0	CE	11
13β	*(R)*-Deltamethrinic acid (-1)	3.37 ± 0.01			pH 6.0	CE	11
13β	*(S)*-Deltamethrinic acid (-1)	3.62 ± 0.02			pH 6.0	CE	11
13β	*(R)*-Mandelic acid (-1)	1.76 ± 0.10			pH 6.0	CE	11
13β	*(S)*-Mandelic acid (-1)	1.61 ± 0.13			pH 6.0	CE	11
13β	*(R)*-Permethrinic acid (-1)	2.93 ± 0.02			pH 6.0	CE	11
13β	*(S)*-Permethrinic acid (-1)	3.11 ± 0.01			pH 6.0	CE	11
14β	*(R)*-Deltamethrinic acid (-1)	3.22 ± 0.02			pH 6.0	CE	11
14β	*(S)*-Deltamethrinic acid (-1)	3.55 ± 0.02			pH 6.0	CE	11
14β	*(R)*-Mandelic acid (-1)	1.59 ± 0.13			pH 6.0	CE	11
14β	*(S)*-Mandelic acid (-1)	1.49 ± 0.14			pH 6.0	CE	11
14β	*(R)*-Permethrinic acid (-1)	2.81 ± 0.01			pH 6.0	CE	11
14β	*(S)*-Permethrinic acid (-1)	3.04 ± 0.02			pH 6.0	CE	11
15β	*(R)*-Deltamethrinic acid (-1)	3.22 ± 0.02			pH 6.0	CE	11
15β	*(S)*-Deltamethrinic acid (-1)	3.55 ± 0.02			pH 6.0	CE	11
15β	*(R)*-Mandelic acid (-1)	1.81 ± 0.07			pH 6.0	CE	11
15β	*(S)*-Mandelic acid (-1)	1.65 ± 0.10			pH 6.0	CE	11
15β	*(R)*-Permethrinic acid (-1)	2.82 ± 0.01			pH 6.0	CE	11
15β	*(S)*-Permethrinic acid (-1)	3.05 ± 0.02			pH 6.0	CE	11
16β	*(R)*-Deltamethrinic acid (-1)	3.19 ± 0.02			pH 6.0	CE	11
16β	*(S)*-Deltamethrinic acid (-1)	3.31 ± 0.02			pH 6.0	CE	11
16β	*(R)*-Mandelic acid (-1)	1.82 ± 0.12			pH 6.0	CE	11
16β	*(S)*-Mandelic acid (-1)	1.75 ± 0.13			pH 6.0	CE	11
16β	*(R)*-Permethrinic acid (-1)	2.76 ± 0.02			pH 6.0	CE	11
16β	*(S)*-Permethrinic acid (-1)	2.85 ± 0.02			pH 6.0	CE	11
17β	*(R)*-Deltamethrinic acid (-1)	3.24 ± 0.02			pH 6.0	CE	11
17β	*(S)*-Deltamethrinic acid (-1)	3.29 ± 0.02			pH 6.0	CE	11
17β	*(R)*-Permethrinic acid (-1)	2.89 ± 0.03			pH 6.0	CE	11
17β	*(S)*-Permethrinic acid (-1)	2.92 ± 0.03			pH 6.0	CE	11
18β	(+)-Borneol	3.29 ± 0.01			pH 7.2	fluor.	31
18β	(-)-Borneol	3.38 ± 0.01			pH 7.2	fluor.	31
18β	(+)-Menthol	2.63 ± 0.01			pH 7.2	fluor.	31

Host (charge)	Guest (charge)	Log *K*	$\Delta H°$ (kJ mol^{-1})	$T\Delta S°$ (kJ mol^{-1})	notes	method	ref.
18β	(-)-Menthol	2.91 ± 0.01			pH 7.2	fluor.	31
19β	*(R)*-Camphor	3.85 ± 0.01				fluor.	32
19β	*(S)*-Camphor	3.75 ± 0.01				fluor.	32
19β	*(R)*-Fenchone	3.69 ± 0.01				fluor.	32
19β	*(S)*-Fenchone	3.60 ± 0.01				fluor.	32
20β	*(R)*-Camphor	3.80 ± 0.01				fluor.	32
20β	*(S)*-Camphor	3.82 ± 0.01				fluor.	32
20β	*(R)*-Fenchone	3.76 ± 0.01				fluor.	32
20β	*(S)*-Fenchone	3.73 ± 0.01				fluor.	32
20β.Na^+	*(R)*-Camphor	3.86 ± 0.00				fluor.	32
20β.Na^+	*(S)*-Camphor	4.12 ± 0.00				fluor.	32
20β.Na^+	*(R)*-Fenchone	4.02 ± 0.00				fluor.	32
20β.Na^+	*(S)*-Fenchone	3.89 ± 0.00				fluor.	32
21β	(+)-Borneol	4.16 ± 0.01			pH 7.2	CD	28
21β	(-)-Borneol	4.39 ± 0.01			pH 7.2	CD	28
21β	(+)-Menthol	3.39 ± 0.01			pH 7.2	CD	28
21β	(-)-Menthol	2.97 ± 0.01			pH 7.2	CD	28
22β	(+)-Borneol	3.64 ± 0.01			pH 7.2	CD	28
22β	(-)-Borneol	3.82 ± 0.01			pH 7.2	CD	28
22β	(+)-Menthol	3.09 ± 0.01			pH 7.2	CD	28
22β	(-)-Menthol	3.27 ± 0.01			pH 7.2	CD	28
23β	(+)-Borneol	3.76 ± 0.01				CD	30
23β	(-)-Borneol	3.64 ± 0.01				CD	30
23β	(+)-Menthol	2.95 ± 0.01				CD	30
23β	(-)-Menthol	2.92 ± 0.01				CD	30
24β	(+)-Camphorquinone	2.64 ± 0.02				CD	26
24β	(-)-Camphorquinone	2.80 ± 0.03				CD	26
25β	*(R)*-Dimethindene	1.23 ± 0.01				CE	5
25β	*(S)*-Dimethindene	1.89 ± 0.01				CE	5
26β	(+)-Borneol	3.45 ± 0.05			pH 7.4	fluor.	34
26β	(-)-Borneol	3.51 ± 0.04			pH 7.4	fluor.	34
26β	(+)-Camphor	3.71 ± 0.07			pH 7.4	fluor.	34
26β	(-)-Camphor	3.59 ± 0.06			pH 7.4	fluor.	34
26β	(+)-Menthol	3.51 ± 0.09			pH 7.4	fluor.	34
26β	(-)-Menthol	3.53 ± 0.09			pH 7.4	fluor.	34
1γ	(+)-Camphorquinone	2.63 ± 0.02				CD	26
1γ	(-)-Camphorquinone	2.66 ± 0.03				CD	26
1γ	*(R)*-Norgestrel	3.77			H_2O/MeOH 3:1	HPLC	10
1γ	*(R)*-Norgestrel	2.73			H_2O/MeOH 1:1	HPLC	10
1γ	*(R)*-Norgestrel	3.76 ± 0.01			H_2O/MeOH 3:1	NMR	10
1γ	*(R)*-Norgestrel	2.67 ± 0.01			H_2O/MeOH 1:1	NMR	10
1γ	*(S)*-Norgestrel	3.65			H_2O/MeOH 3:1	HPLC	10
1γ	*(S)*-Norgestrel	2.67			H_2O/MeOH 1:1	HPLC	10
1γ	*(S)*-Norgestrel	3.65 ± 0.01			H_2O/MeOH 3:1	NMR	10
1γ	*(S)*-Norgestrel	2.61 ± 0.01			H_2O/MeOH 1:1	NMR	10
1γ	(+)-Zileuton	3.23 ± 0.05				UV	4
1γ	(+)-Zileuton	3.20 ± 0.08				CD	4
1γ	(-)-Zileuton	2.97 ± 0.06				UV	4
1γ	(-)-Zileuton	2.86 ± 0.13				CD	4

FROM ACYLSILANES TO FLUORINATED HETEROCYCLES

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Abstract. *Synthesis of a variety of heterocycles (imidazolidines, oxazolidines, benzodiazepines, benzothiazepines, quinolines, pyrazoles, pyrimidines) bearing both a fluorine atom and a perfluoroalkyl chain in vicinal positions is reported. These heterocycles were obtained from the addition of bis(nucleophiles) to hemifluorinated enones as fluorinated building-blocks. These key fluorinated intermediates were synthesized in a one-step sequence by reaction of perfluoroorganometallic reagents with acylsilanes, in a domino reaction which can also lead to perfluoroalkyl(trialkylsilyl)carbinols, perfluoroenol silyl ethers and 2-hydroperfluoroalkylketones which are all synthetic equivalents of hemifluorinated enones in these heterocycle syntheses. Some syntheses, especially in the pyrazole series, have been carried out in a one-pot process from the acylsilanes. This strategy was also applied in the carbohydrate series towards polyfluorinated heterocycles branched on carbohydrate moieties. Polyfluorinated homo-C-nucleosides analogues were prepared from suitably designed carbohydrate-derived acylsilanes.*

Contents

1. Introduction

1.1. Organofluorine compounds: general properties and interest

Fluorine, because of its unique electronic character and its small size, quite often imparts specific beneficial properties to organic molecules.[1] The substitution of fluorine for hydrogen atoms can greatly alter the physical, chemical and biochemical properties of compounds due to its electronegativity, low polarisability, bond strength and electron density distribution.[2] Therefore, fluorinated organic molecules, in particular trifluoromethyl(perfluoroalkyl)-substituted ones,[3] represent an interesting class of compounds involved in a wide variety of applications: pharmaceuticals and agrochemicals,[4] materials and liquid crystals.[5] Long chain substituted compounds have also gained an increasing interest in the field of fluorous chemistry.[6]

1.2. Fluorinated heterocycles

Considering the importance of the heterocycles and especially azoles in medicinal chemistry, the development of synthetic methods for fluorinated heterocycles has become an interesting research area. Besides the direct fluorination or perfluoroalkylation reactions,[7] a general and convenient alternative is the strategy based on heterocyclization of fluorinated building-blocks.[8]

Trifluoromethylated imidazolidines and oxazolidines were obtained by heterocyclization of 3-trifluoroacetyl lactams with ethylene diamine and 2-aminoethanol without opening of the lactam structure.[9] Polyfluoro-2-alkynoic acids readily underwent an intermolecular-intramolecular Michael addition reaction with a variety of bifunctional azanucleophiles to give the corresponding 2-(polyfluoroalkyl) imidazolidines and oxazolidines.[10] The formation of polyfluorinated *N,N'*-unsubstituted imidazolidines was also carried out by reactions of heteroaromatic β-amino-β-(polyfluoroalkyl)vinyl ketones with ethylenediamine.[11]

Perfluoroalkylated 1,4-diazepines have been prepared by direct condensation of perfluoroalkyl-1,3-dicarbonyl compounds with ethylene diamine[12] or *o*-phenylene diamine.[13] α-Perfluoroalkylidene ketones were also used as 1,3-bis(electrophilic) intermediates for synthesizing this type of heterocycles.[14]

Various methods were proposed for the synthesis of perfluoroalkylated pyrimidines. Beside classical reactions of amidines or guanidines on perfluoroalkyl 1,3-dicarbonyl systems[15] or on the corresponding β-enaminone,[16] some particular approaches were reported. The synthesis of 2,6-disubstituted-4-trifluoromethyl pyrimidines was performed by treatment of α,β-unsaturated trifluoromethylketones with amidines followed by a tandem dehydration-oxidation sequence.[17] α-Perfluoroalkylidene ketones proved to be versatile building-blocks, possibly prepared *in situ*, to yield 4-perfluoroalkyl pyrimidines by direct condensation or *via* the reaction of the corresponding enaminoimine with an orthoester.[18] The synthesis of 5-fluoro-4-perfluoroalkyl pyrimidines was performed by treatment of perfluoroalkenyl phosphates with amidinium salts.[19]

4-Fluoropyrazoles have generally been prepared by reaction of hydrazines with fluoromalonaldehyde[20] or its bis(dialkyl acetals),[21] with β-fluorovinamidinium salts,[22] with 2,3,3-trifluoro-1-propenyl *p*-toluenesulfonates,[23] or by irradiation of diazo derivatives.[24] The synthesis of 4-fluoro-3-perfluoroalkylpyrazoles has been reported starting from *N*-phenylsydnone and an excess of perfluoropropadiene,[25] from *F*-1-alkenyl phosphates[19] or from 2-fluoro-1,3-diketones and hydrazines.[26]

The synthesis of trifluoromethyl heterocycles has been proposed from this laboratory: using perfluoroketenedithioacetals as simple starting fluorinated building-blocks, a variety of trifluoromethyl

heterocycles have been synthesized in a few steps.[27] We have recently reviewed this chemistry.[28]

Other fluorinated heterocyclic compounds such as oxadiazoles or triazoles[29] or quinolines[30] have also been reported recently.

2. From acylsilanes to polyfluorinated heterocycles

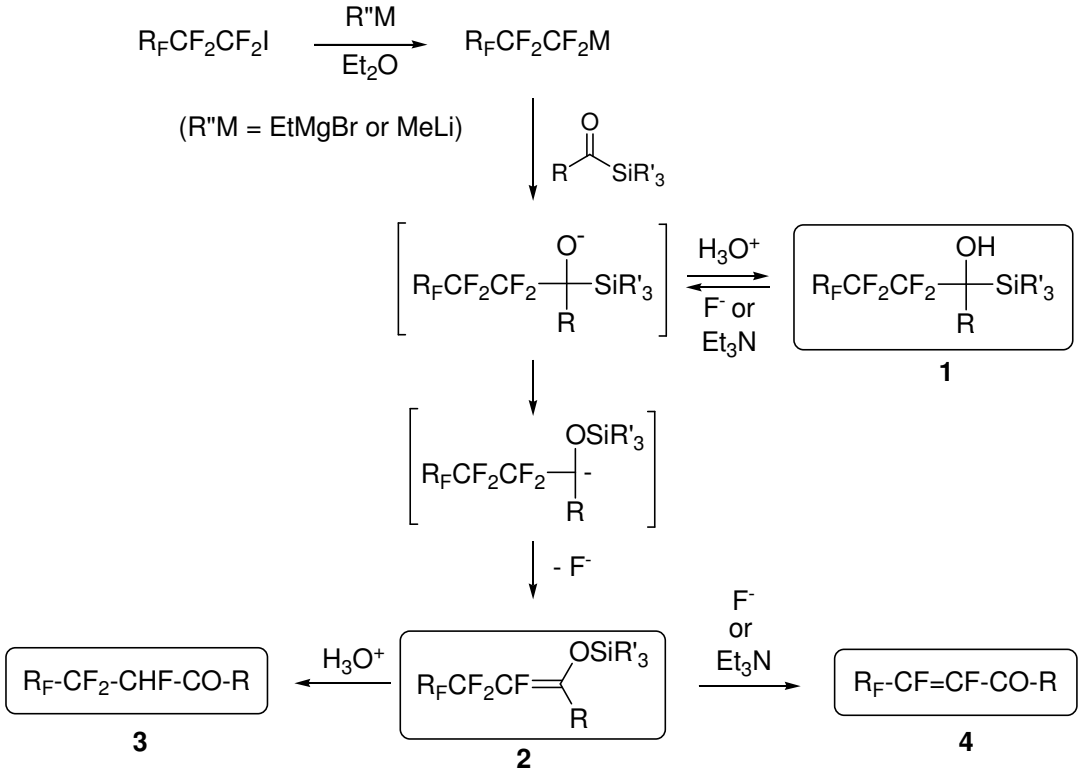
Several years ago we decided to undertake investigations in the field of "mixed organofluorine-organosilicon chemistry". The initial idea was to take profit of the high reciprocal affinity of fluorine and silicon (ΔH_{Si-F} ~ 600 kJ.mol^{-1}), combined with the high affinity of silicon for oxygen (ΔH_{Si-O} ~ 500 kJ.mol^{-1}), to develop new reactions and new applications. Owing to their properties and to the literature background, acylsilanes and perfluoroorganometallic reagents were considered as the good candidates. Indeed, this research led to a variety of interesting results. Among them, a general methodology for the synthesis of vicinal fluoro, perfluoroalkyl substituted heterocycles was found. This review is an account of these investigations. Before going straight to this point, it seems necessary to present the reactivity aspects, namely how reaction of perfluoroorganometallic reagents with acylsilanes leads to the key polyfluorinated building-blocks which react with various bis(nucleophiles) towards the corresponding heterocycles.

2.1. Acylsilanes and their reaction with perfluoroorganometallic reagents

Acylsilanes (silylketones) are useful intermediates in synthetic organic chemistry, which exhibit some specific properties beside the usual ones of carbonyl derivatives.[31] These compounds have been exploited for numerous applications in the synthesis of a wide range of polyfunctionalized molecules.

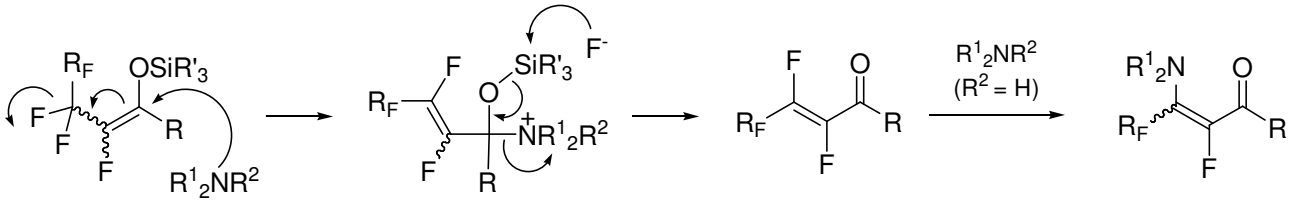
The main difference between acylsilanes and classical carbonyl compounds lies in the reaction with nucleophiles. In accordance with the high oxophilicity of silicon, the alkoxide adduct rearranges easily by migration of silicon from carbon to oxygen. Such a migration was first discovered on studying silyl carbinols, the reduced form of acylsilanes, by A. G. Brook who left his name to this rearrangement.[32] Reich's group used later this property to propose a regiospecific preparation of enol silyl ethers, by combining this Brook rearrangement with the β-elimination of a nucleofugal group borne either by the nucleophilic reagent or by the acylsilane substrate.[33]

We reasoned that the addition of a perfluoroalkyl nucleophile[34] on an acylsilane should undergo an interesting domino process (Scheme 1): the rearrangement of the adduct would give an *O*-silyl carbanion which would β-eliminate a fluoride ion and lead to the corresponding enol silyl ether; owing to the high fluorophilicity of silicon, the fluoride activation of the silicon group should induce further transformation. Beyond the expected results, this chemistry proved to be very versatile.[35] Depending on the experimental conditions, the intermediate alkoxide can be trapped (R_FMgBr, hydrolysis at low temperature) to give the tertiary perfluoroalkyl trialkylsilyl carbinol **1**.[36] The reaction can be stopped at the enol silyl ether **2** stage, which can be isolated in high yield in the case of *tert*-butyl(dimethyl)silyl (TBDMS) derivatives, or easily converted (TMS derivatives) into the corresponding 2-hydroperfluoroalkyl ketone **3** by acid hydrolysis.[37] Conversion of **2** into the hemifluorinated enone **4** takes place slowly under the expected fluoride activation, but is effectively activated on addition of triethylamine to the reaction mixture.[38] Interestingly, the cascade reaction leading to **4** can also be induced from the carbinol **1**, as depicted in Scheme 1, and even the trapping of the *O*-silyl carbanion precursor of **2** was achieved by treatment of the carbinol by ammonia under suitable conditions.[39]



Scheme 1

The enone **4** reacts easily with primary and secondary amines in an addition-elimination sequence leading to the corresponding enaminone and/or iminone. The versatility of this chemistry resides in the possibility to perform this transformation in a one-pot process from either the enol silyl ether **2** (Scheme 2),[37] the 2-hydroperfluoroalkylketone **3**, or the carbinol **1**,[39] and even from the starting acylsilane, the amine being added once the β-elimination of fluoride has taken place. Indeed, due to the strong electron withdrawing character of the perfluoroalkyl group, even weakly basic amines operate both in the basic activation of **1** or **3** and the nucleophilic activation of **2** or **4**, so that all these compounds are synthetic equivalents.

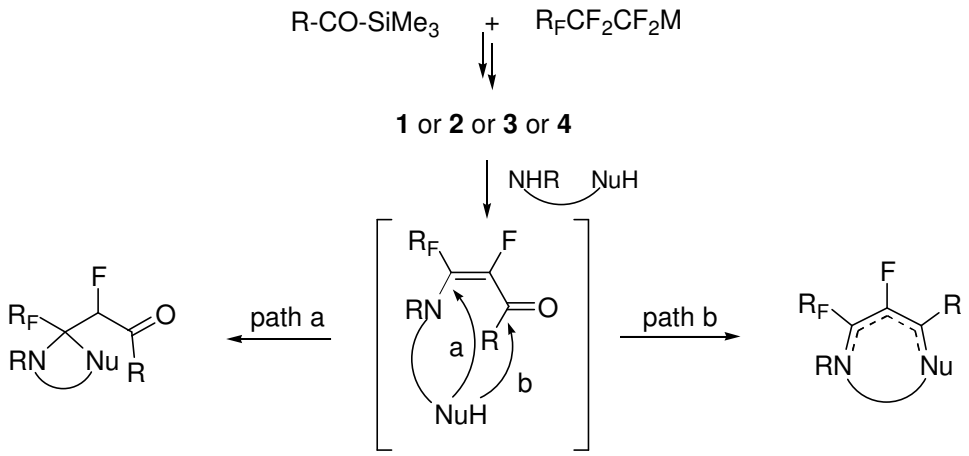


Scheme 2

2.2. Application to the synthesis of polyfluorinated heterocycles: the typical reaction scheme

The fluorine substitution makes the remaining carbonyl group and the β-carbon of enaminones/iminones good electrophilic centers, so that hemifluorinated enones **4** are intermediate of choice for applications in the synthesis of fluorinated heterocyclic compounds. Under reaction with bis(nucleophilic) amines, an intramolecular Michael addition (path a) or a cyclocondensation reaction (path b) follows the first addition-elimination sequence (Scheme 3), and leads to a variety of heterocyclic compounds the structure of which depends on the bis(nucleophile). As for simple amines, the domino process can start from **1**-**4** as well, and even one-pot transformation was performed from acylsilanes. We

describe below the various applications we have developed, based on aliphatic and aromatic acylsilanes, and also on carbohydrate-derived acylsilanes.

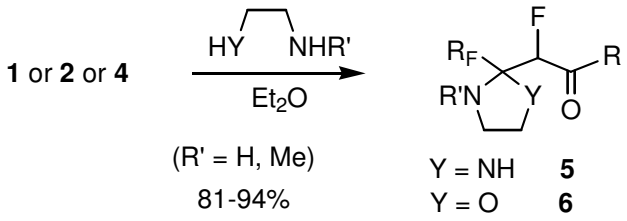


Scheme 3

3. Synthesis of fluorinated heterocycles

3.1. Synthesis of polyfluorinated imidazolidines and oxazolidines

Reaction of alcohols **1** or silyl enol ethers **2** or enones **4** with 1,2-diaminoethane or *N*-methyl-1,2-diaminoethane yielded smoothly the imidazolidines **5** as the only products.[40]



Scheme 4

Table 1. Preparation of imidazolidines **5** and oxazolidines **6**.

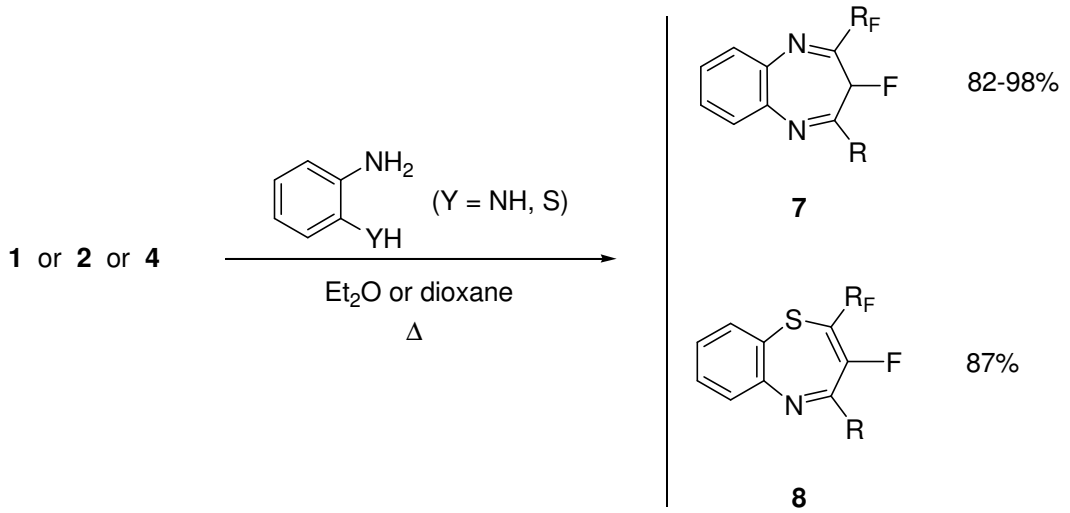
Entry	Starting compound	R	R_F	Y	R'	Yield (%)	(dr)[a]
1	**1**	Ph	C_4F_9	NH	H	**5a** 88	
2	**4**	Ph	C_4F_9	NH	H	**5a** 92	
3	**1**	Ph	C_4F_9	NH	Me	**5b** 92	
4	**4**	Ph	C_4F_9	NH	Me	**5b** 88	(75:25)
5	**2**	*n*-C_5H_{11}	C_4F_9	NH	H	**5c** 94	
6	**1**	Ph	C_4F_9	O	H	**6a** 91	(62:38)
7	**1**	Ph	C_4F_9	O	Me	**6b** 92	(72:28)
8	**2**	*n*-C_5H_{11}	C_4F_9	O	Me	**6c** 85	(91:9)

[a] dr = diastereomer ratio

In any case, no traces of diazepine were detected. Similarly, treatment of **1**, **2** or **4** with ethanolamines specifically gave the corresponding oxazolidines **6**. Results are summarized in Scheme 4 and Table 1.

3.2. Synthesis of polyfluorinated benzodiazepines and benzothiazepines

The chemoselectivity of the cyclisation was reversed with *o*-phenylene diamine which exclusively gave the benzodiazepines **7**.[40] The formation of a five-membered ring was hindered by the rigidity of this diamine and the cyclocondensation was favored. A unique tautomer with a diimine structure was obtained. Under the same reaction conditions, condensation of the enones **4** with 2-aminothiophenol provided the corresponding benzothiazepines **8** in good yields (Scheme 5, Table 2).



Scheme 5

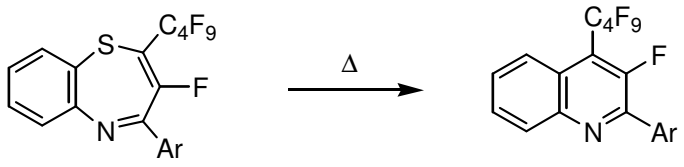
Table 2. Preparation of benzodiazepines **7** and benzothiazepines **8**.

Entry	Starting compound	R	R_F	Y	Yield (%)
1	**1**	Ph	C_4F_9	NH	**7a** 92
2	**1**	*p*-Cl-Ph	C_4F_9	NH	**7b** 98
3	**1**	*p*-F-Ph	C_4F_9	NH	**7c** 82
4	**1**	*p*-MeO-Ph	C_4F_9	NH	**7d** 82
5	**2**	*n*-C_5H_{11}	C_4F_9	NH	**7e** 91
6	**4**	*p*-F-Ph	C_4F_9	S	**8** 87

The structure of the benzothiazepine was confirmed by NMR studies. ^{1}H NMR monitoring of the reaction showed the disappearance of the SH group before the NH_2 group in the first step. Concomitant disappearance of the fluorine atom in the β-position was confirmed by ^{19}F NMR monitoring. These observations indicate a prior attack of the more nucleophilic sulfur atom on the β-carbon atom. In contrast to

reported results about an analogous reaction of β-chloro trifluoromethyl enones,[41] our reaction works in neutral medium and is chemospecific and regiospecific following path b.

Literature results showed that similar fluorinated benzothiazepine structures are quite unstable and, under basic conditions or heating, can be transformed into quinolines by elimination of the sulfur atom.[41a] In our hands, the benzothiazepine **8** proved to be stable, but effective extrusion of sulfur atom took place under heating at 120 °C, giving the corresponding quinoline **9** (Scheme 6).[40b] We have to mention that such a transformation closely depends on the structure of the thiazepine, since degradation was observed in carbohydrate series (*vide infra*).

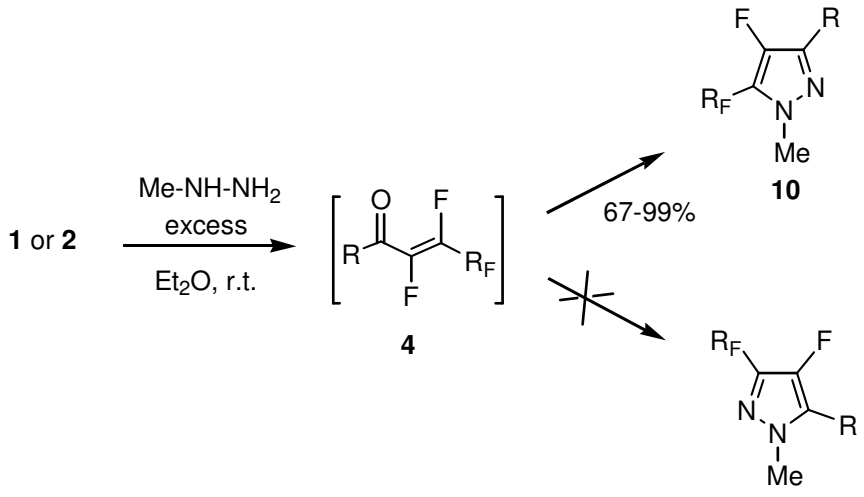


8 **9**

Scheme 6

3.3. Synthesis of polyfluorinated pyrazoles

Pyrazoles **10** were obtained under very mild and simple conditions, by mixing **1**, **2** or **4** with methylhydrazine in ether (Scheme 7, Table 3). An excess of hydrazine was required to neutralize the hydrogen fluoride generated through the substitution. In aromatic series, the reaction of alcohol **1** (R = Ar) and enone **4** (R = Ar) gave high yields of pyrazoles **10**, as a single regioisomer.[42] With aliphatic derivative **2** (R = *n*-C_5H_{11}), heterocyclization was quite efficient but the yield of **10e** was lower (Table 3). Interestingly, a one-pot procedure from an aliphatic acylsilane was also successfully performed by direct addition of methylhydrazine to the reaction mixture and provided the corresponding pyrazole **10f** in good overall yield (69%) (entry 10). The enoxysilane reacts first with the hydrazine nitrogen moiety giving the enone **4** by a S_N' substitution followed by the displacement of the amine by fluoride attack on the silicon atom. Then a Michael addition-elimination on the β-carbon by the nucleophilic function of hydrazine gives an intermediate which is able to cyclize into 4-fluoro-5-perfluoroalkylpyrazoles **10** (Scheme 7).

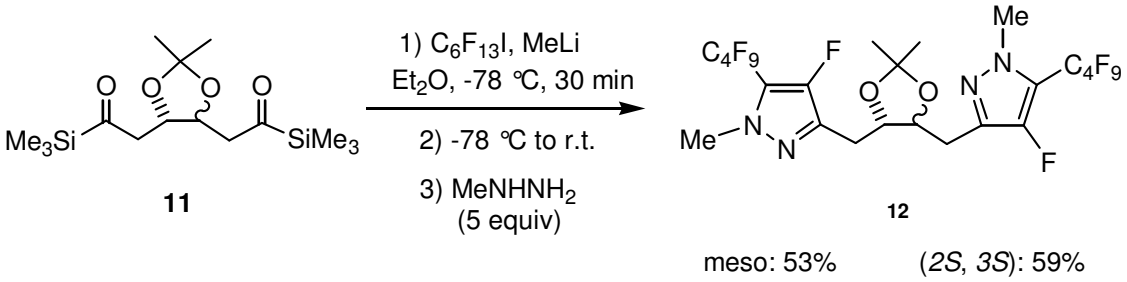


Scheme 7

Table 3. Preparation of pyrazoles **10**.

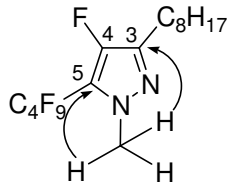
Entry	Starting compound	R	R_F	Yield (%)
1	**1**	Ph	C_4F_9	**10a** 95
2	**1**	*p*-Cl-Ph	C_4F_9	**10b** 99
3	**1**	*p*-F-Ph	C_4F_9	**10c** 74
4	**1**	*p*-MeO-Ph	C_4F_9	**10d** 98
5	**4**	Ph	C_4F_9	**10a** 95
6	**4**	*p*-Cl-Ph	C_4F_9	**10b** 94
7	**4**	*p*-F-Ph	C_4F_9	**10c** 89
8	**4**	*p*-MeO-Ph	C_4F_9	**10d** 97
9	**4**	*n*-C_5H_{11}	C_4F_9	**10e** 67
10	**Acylsilane**	*n*-C_8H_{17}	C_4F_9	**10f** 69

The one-pot reaction was also successfully applied to functionalized bis(acylsilanes) **11**.[43] Bis(pyrazole) derivatives **12** were obtained as single regioisomers, in good overall yields (53%, 59%), in *meso* and chiral series (Scheme 8).[42]



Scheme 8

Although the heterocyclization of non-symmetrical bis(electrophiles) **4** with methylhydrazine could give two regioisomers, the 5- and 3-perfluoroalkylpyrazoles, only one regioisomer was observed, even in the crude mixture. Ishihara's group has already reported the synthesis of similar pyrazoles from fluorinated enol phosphates with hydrazines.[19] The authors claimed the formation of 3-perfluoroalkylpyrazoles, but no information was given about the determination of this regiochemistry. To elucidate the structure of pyrazoles, we recorded ^{1}H-^{1}H (COSY) and ^{1}H-^{13}C NMR spectra (HMQC, HMBC) for one member of each series. Then using ^{19}F, ^{1}H and ^{13}C NMR data, we ascribed reasonably the regiochemistry of all pyrazoles. In HMBC spectrum (Figure 1), pyrazole **10f** (Table 3, entry 10) exhibited a strong correlation ($^3J_{C5,MeN}$) between C-5 and Me-N signals and a very weak one ($^4J_{C3,MeN}$) between C-3 and Me-N signals.

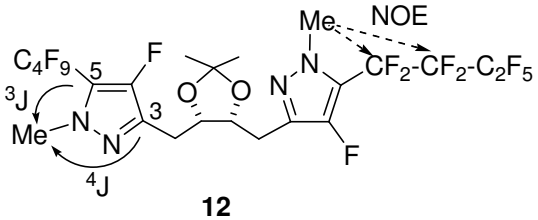


10f

Selected HMBC correlations for compound **10**.

Figure 1

To confirm the regiochemistry, we performed three types of NMR experiments on pyrazole **12**. First, using HMBC spectra, we confirmed the presence of a strong correlation ($^3J_{C5,MeN}$) between C5 and Me-N signals and a weak one ($^4J_{C3,MeN}$) between C3 and Me-N signals (Figure 2). Then, we recorded ^{1}H-^{19}F NOE spectra. Irradiation of the N-Me protons at δ = 3.89 ppm induced NOE on the adjacent fluorines (Fα and Fβ) in ^{19}F NMR spectra, indicating a close relationship between the N-Me and CF_2 groups (Figure 2). We were unable to observe any interaction between Me-N and the α-methylene groups, which constitutes a supplementary argument in favour of the 5-perfluoroalkyl isomer.

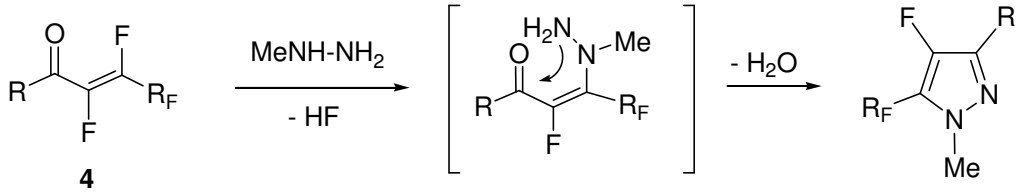


12

Selected HMBC correlations and ^{1}H-^{19}F NOE for compound **12**.

Figure 2

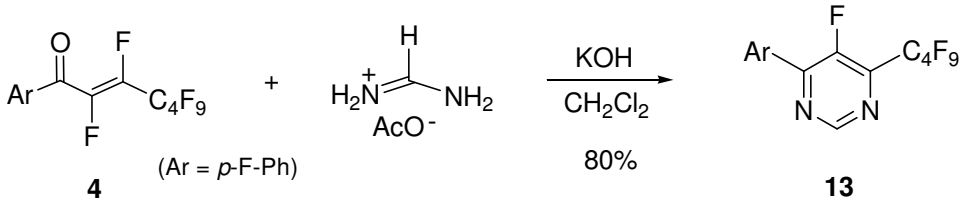
This regiochemistry is that expected if the more nucleophilic nitrogen of methylhydrazine attacks the β-carbon of **4** before cyclodehydration to lead to the pyrazole (Scheme 9). This reaction sequence is in accordance with the high reactivity of enone **4** with amines.



Scheme 9

3.4. Synthesis of polyfluorinated pyrimidines

Pyrimidines are conventionally synthesized *via* a [3+3] fragment approach of amidines and substrates containing 1,3-dielectrophilic centers. In our hands, pyrimidines **13** were obtained under mild basic conditions from hemifluorinated enone **4** and various amidinium salts.[40b]



4 (Ar = *p*-F-Ph) **13**

Scheme 10

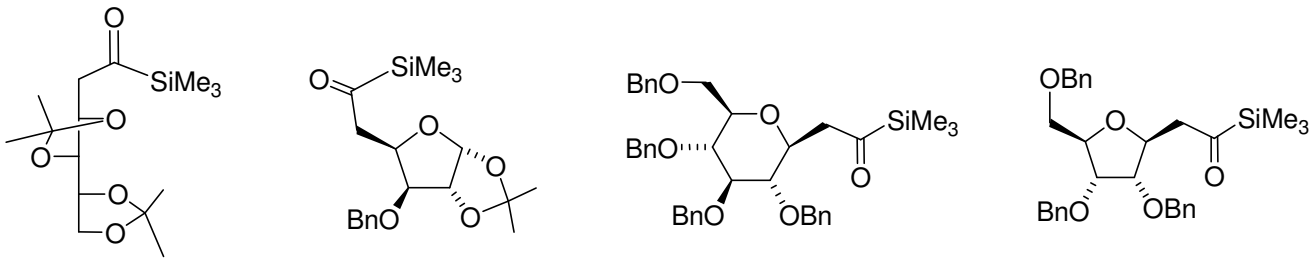
Apart from the example depicted in Scheme 10, most syntheses in this heterocycle class were performed in carbohydrate series (*vide infra*). Different conditions were tried to release the amidine from its salt. A suspension of potassium hydroxide in methylene chloride gave the best yields.

4. Applications in carbohydrate series

4.1. Synthesis of carbohydrate-derived acylsilanes

Some years ago, we reported a new general strategy for the synthesis of functionalized acylsilanes including carbohydrate-derived acylsilanes. Ring opening of an epoxide[44] or a cyclic sulfate,[45] or substitution of a suitable leaving group,[46] by 2-lithio-2-trimethylsilyl-1,3-dithiane (2-LTD) was the key reaction in these syntheses, leading to the intermediate dithioacetal then converted by oxidative hydrolysis. Compounds **14** and **15** (Figure 3) are representative carbohydrate-derived acylsilanes prepared by this way.

Homo-*C*-nucleosides are a growing class of nucleosides which are structurally composed of a sugar residue and an aglycon linked to the anomeric carbon *via* a methylene bridge.[47] In order to synthesize fluorinated homo-*C*-nucleoside analogues, we have performed the synthesis of new compounds **16** and **17** where the acylsilane function is linked to the anomeric carbon atom *via* a methylene group (Figure 3).[48] The strategy was based on 1-C-formylglycosides as key intermediates in the D-glucopyranose and D-ribofuranose series. Different routes were reported in the literature towards these compounds starting from the corresponding sugar lactones.[49] Then, two different pathways were developed to convert the aldehydes into the targeted acylsilanes **16-17**.[48]



14 **15** **16** **17**

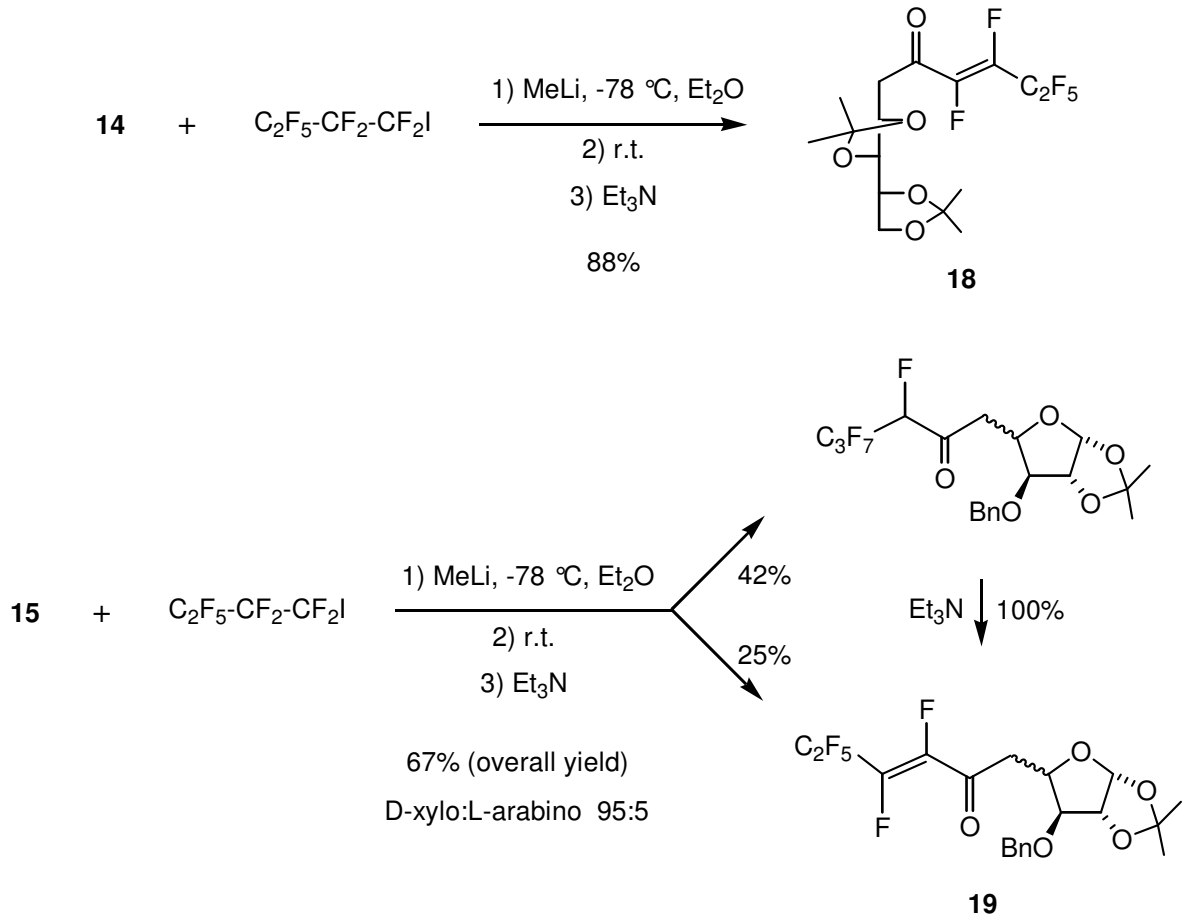
Figure 3

4.2. Carbohydrate-based polyfluorinated heterocycles

According to the previously described processes, reaction of the carbohydrate-derived acylsilanes **14-15** with perfluoroorganolithium reagents afforded the hemifluorinated enones **18-19** in good yields.[40b]

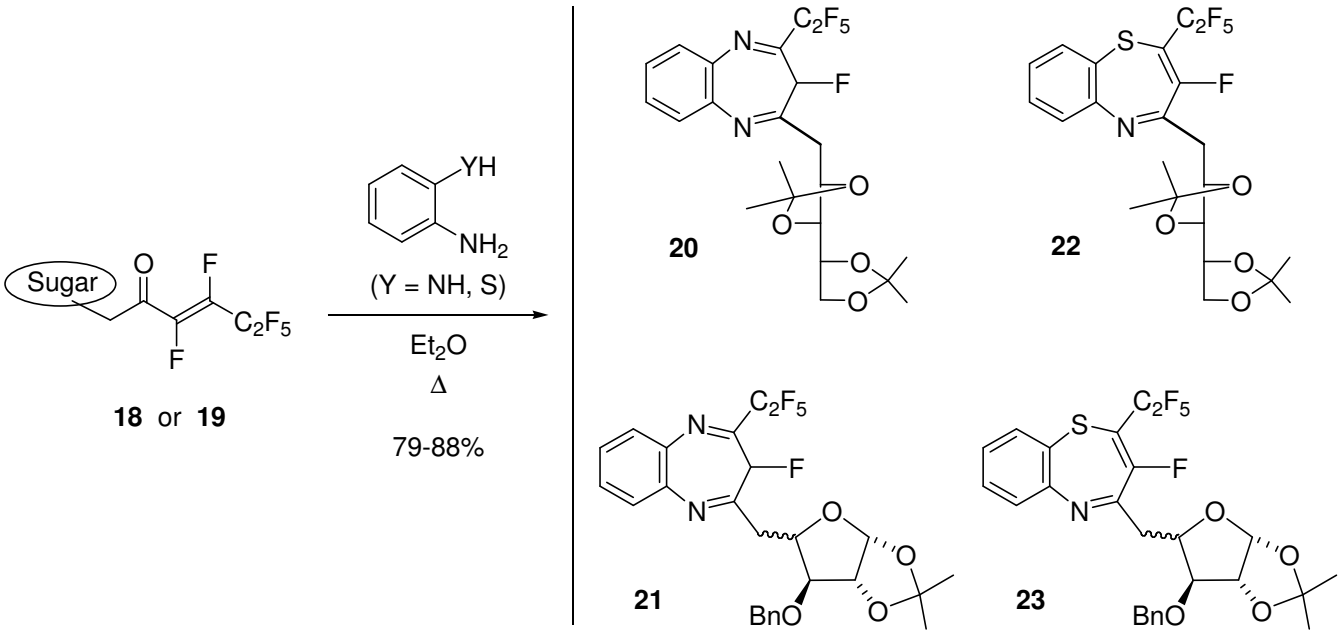
From xylitol derivative **14**, a small amount (12%) of the hydroperfluoroketone, as a 50:50 mixture of diastereomers resulting from the hydrolysis of the remaining enol silyl ether, was also obtained and separated by silica gel flash chromatography (Scheme 11). For the D-xylofuranose derivative **15**, a partial epimerization at C-4 was observed under the basic conditions of the reaction. A mixture of the expected enone and the corresponding hydroperfluoroalkyl ketone was obtained in the same 95:5 ratio (major D-*xylo*). The latter was easily and quantitatively converted into the enone **19** (same 95:5 epimeric ratio) by treatment with triethylamine in dichloromethane at room temperature (Scheme 11).

Carbohydrate-derived polyfluorinated benzodiazepines **20-21** were synthesized by treatment of the enones **18-19** with an excess of *o*-phenylenediamine in diethyl ether or dioxane at reflux.[40b] A 50:50 mixture of the two diastereomers was obtained for each compound (Scheme 12).



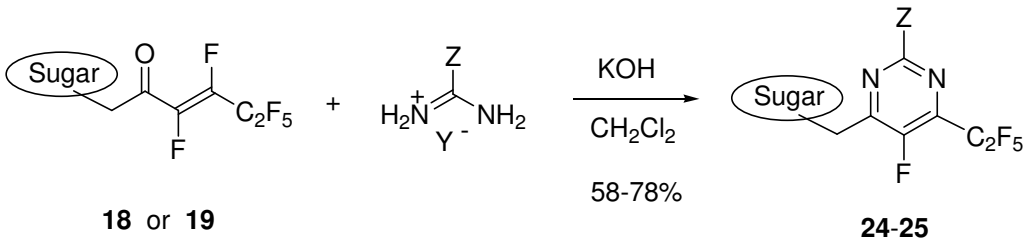
Scheme 11

A similar treatment with 2-aminothiophenol gave benzothiazepines **22-23**. Compound **23** was obtained as an epimeric mixture (D-*xylo*/L-*arabino* = 85:15) indicating a further C-4 epimerization during the formation of the heterocycle (Scheme 12). These benzothiazepines decomposed on heating at 120 °C, the conditions required for sulfur extrusion and formation of quinolines from aryl substituted analogues (*vide supra*).



Scheme 12

A range of polyfluorinated pyrimidines attached to carbohydrate moieties **24-25** were prepared by reactions of enones **18** and **19** with various amidines (Scheme 13, Table 4).[40b] In the D-xylofuranose series, the first experiments were carried out with the mixture of the two epimers D-xylo/L-arabino to give the corresponding pyrimidines in good yields, with a modified ratio of the two epimers (D-xylo/L-arabino 88:12 vs 94:6). To confirm that a further epimerisation took place during the heterocycle formation process, the same reaction was carried out from pure D-xylo epimer of the enone **19** and *O*-methyl isourea. The expected pyrimidine and its L-arabino epimer were obtained in a 88:12 ratio.



18 or **19** **24-25**

Scheme 13

Table 4. Preparation of carbohydrate-derived pyrimidines **24-25**.

Entry	Starting compound	Z	Y	Yield (%)
1	**18**	H	AcO	**24a** 58
2	**18**	Me	Cl	**24b** 64
3	**18**	OMe	0.5 SO_4^{2-}	**24c** 78
4	**18**	NH_2	Cl	**24d** 66
5	**19**	H	AcO	**25a** 65 [a]
6	**19**	Me	Cl	**25b** 74 [a]
7	**19**	OMe	0.5 SO_4^{2-}	**25c** 75 [a]
8	**19**	NH_2	Cl	**25d** 66 [a]

[a] Yields given for the mixture of the two epimers D-*xylo*/L-*arabino*

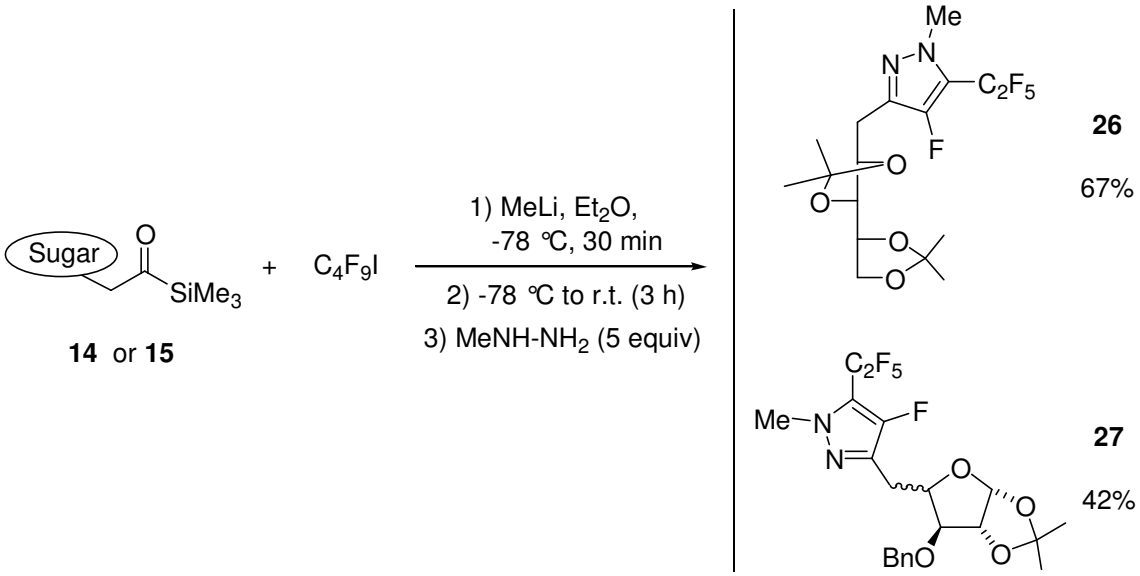
Carbohydrate-derived pyrazoles **26-27** were prepared by a one-pot methodology from acylsilanes **14** and **15**, respectively, in acceptable overall yields (42-67%) for such a multi-step process (Scheme 14).[42] They were also obtained in a two-step sequence with isolation of the intermediate enone with quite similar overall yields.

4.3. Fluorinated homo-*C*-nucleoside analogues

Treatment of an ethereal solution of the pyranosic acylsilane **16** and perfluorobutyl iodide with methyllithium at low temperature then at room temperature led to the corresponding hemifluorinated enone

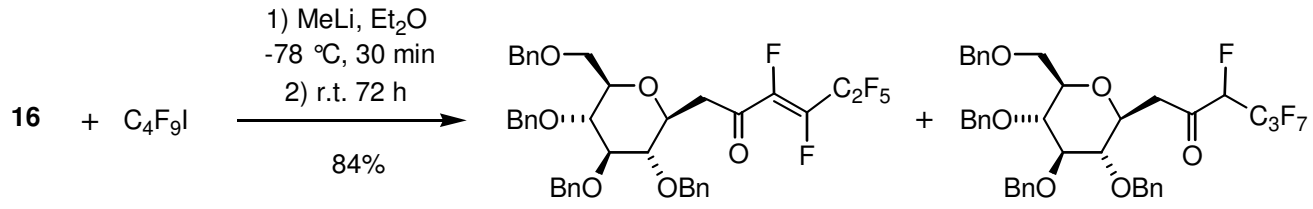
28 (β anomer exclusively) and the α-hydroperfluorobutyl ketone **29** as an inseparable 75:25 mixture (yield = 84%) (Scheme 15).[48]

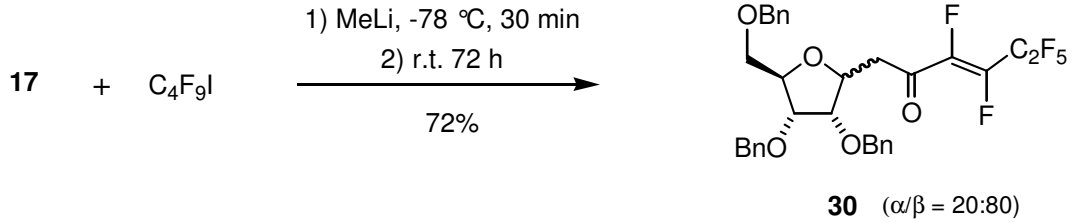
The ketone **29** results from a work-up before completion of the conversion of the enol silyl ether into the corresponding enone. Such a mixture is not problematic owing to the easy dehydrofluorination of **29** in the reaction conditions. Hence, the subsequent reactions leading to heterocycles were performed on the mixture. When submitted to the same reaction conditions, the D-ribofuranosic acylsilane **17** was quantitatively converted into the expected enone **30**, but some epimerization took place at the anomeric carbon, as already observed in a similar "furanose" situation (Scheme 15). This epimerization probably occurred *via* a retro-Michael type process. The two epimeric enones were obtained in a 80:20 ratio, the major one having the β-configuration according to a coupling constant $^{3}J_{3',4'}$ similar to those reported in literature.[50]



14 or 15

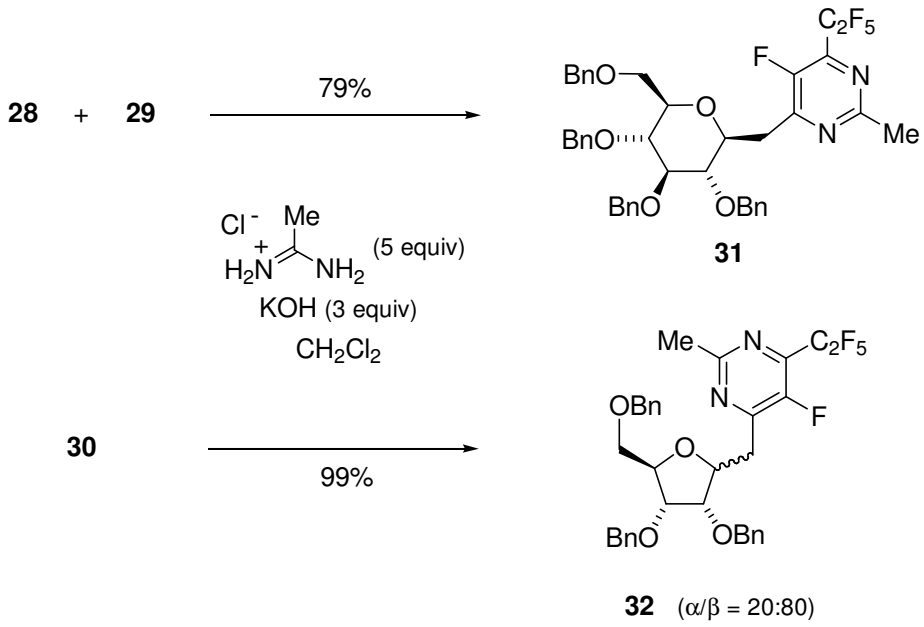
Scheme 14





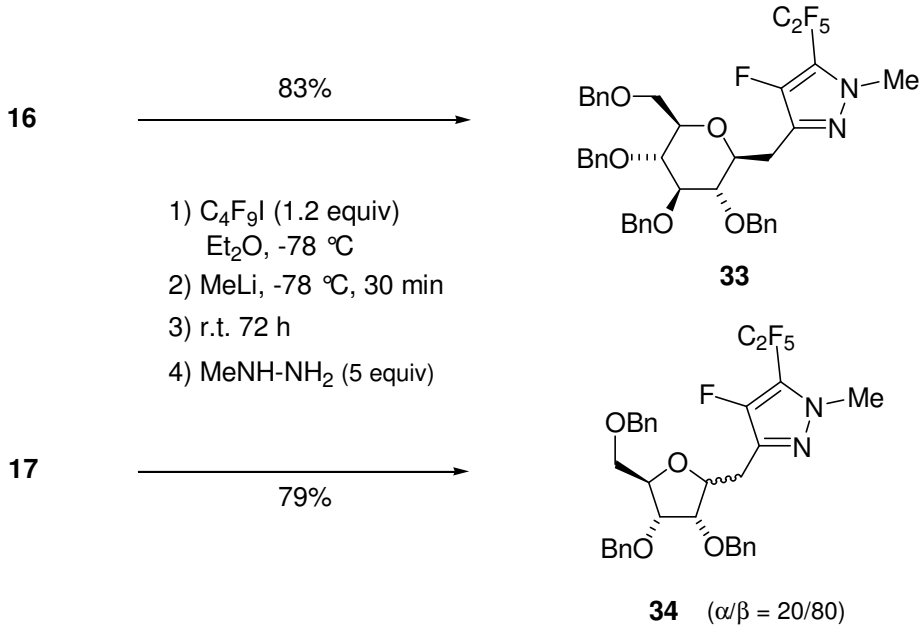
Scheme 15

Pyrimidines (from acetamidine) and pyrazoles (from methylhydrazine) derivatives were chosen to exemplify the preparation of polyfluorinated homo-*C*-nucleosides. The mixture (enone **28** + ketone **29**) and the enone **30** (mixture of epimers) were reacted with acetamidine (released from its hydrochloride) to give excellent yields of the pyrimidine derivatives **31** and **32** respectively (Scheme 16).[48] The D-ribofuranose derived pyrimidine **32** was an inseparable mixture of anomers in a ratio (β/α = 80:20) corresponding to the starting mixture.



Scheme 16

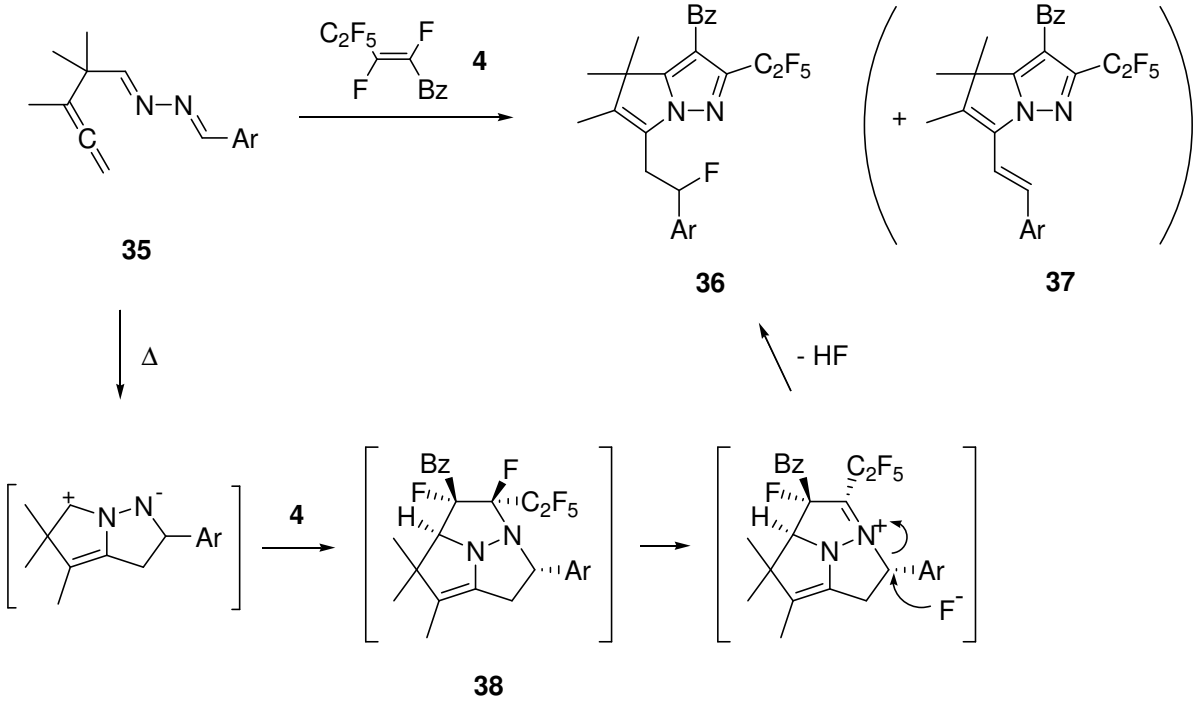
The pyrazole derivatives **33** and **34**, each as a single regioisomer, were prepared conveniently in high overall yield by simply adding methylhydrazine to the crude mixture from the reaction of acylsilanes **16** and **17**, respectively (Scheme 17).[48] Compound **34** was obtained as an inseparable anomeric mixture (β/α = 80/20) comparable to the corresponding enone mixture.



Scheme 17

5. Miscellaneous

The previous sections were devoted to the synthesis of heterocycles from hemifluorinated enones via condensation processes. These hemifluorinated enones also proved to be excellent dienophiles in Diels-Alder reaction,51 and dipolarophiles in a combined intra-intermolecular cycloaddition reaction with allenyl azines.52 Thus, enone 4 reacted with allenyl azine 35 to give the fused pyrrolopyrazole 36. Depending on the para-substituent on the aryl moiety, a minor amount of the dehydrofluorination product 37 may be formed (Scheme 18). This transformation proceeds via the tricyclic intermediate 38 which undergoes an interesting rearrangement involving the fluoride migration to lead to the bicyclic heterocycle 36.52



Scheme 18

6. Conclusion

The combination of the properties of organosilicon (acylsilanes) and organofluorine compounds (perfluoroorganometallic reagents) proved to be very fruitful, giving rise to a multistep domino transformation which can be stopped at different stages. The compounds obtained are interesting building-blocks for the elaboration of vicinal fluoro, perfluoroalkyl heterocycles of various structures.

Two main features have to be emphasized from the reactivity point of view. The fluoride elimination subsequent to a Brook rearrangement is the key sequence of this chemistry. The intermediate perfluoroenol silyl ether has an unusual behavior compared to non-fluorinated analogues: the latter act generally as enolate equivalents, therefore nucleophilic species; the fluorinated enol silyl ethers studied here react as electrophiles with amines or the amino function of bis(nucleophiles) to be converted, *via* the corresponding hemifluorinated enones, to a variety of heterocycles.

From the preparative point of view, most of syntheses reported led to the heterocycles in high or good yields, even for reactions performed in a one-pot manner from the starting acylsilanes. All compounds synthesized bear a pentafluoroethyl or a nonafluorobutyl substituent, because we got our starting materials from a company which produced only even carbon-number perfluoroalkyl iodides. The access to trifluoromethyl analogues would be as easy starting from heptafluoropropyl iodide in the initial step.

Acknowledgments

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CARBOXYMETHYL TRI-*O*-ACETYL-α-D-GLUCOPYRANOSIDE 2-*O*-LACTONE: A SYNTHON FOR THE PREPARATION OF NEOGLUCOCONJUGATES

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Abstract. *Carboxymethyl tri-O-acetyl-α-D-glucopyranoside 2-O-lactone (CMGL), the bicyclic lactone obtained in two steps from isomaltulose by an oxidation-acetylation sequence, is a convenient synthon for connecting a glucosyl moiety with other constructs. Its synthesis and its reactivity with regards to various nucleophilic species are described and the different types of glucoconjugates which have been prepared by this method, as well as other sources of carboxymethyl glycosides, are reviewed.*

Contents

1. Introduction

Being involved in the use of carbohydrates as organic raw materials,[1] we have studied the reactivity of isomaltulose (6-α-D-glucopyranosyl-D-fructofuranose, **1**) and found that its oxidation conveniently provided

carboxymethyl tri-O-acetyl-α-D-glucopyranoside (CMG, **2**).[2] Also, its 2-O-lactone (CMGL, **3**) proved to easily open by reaction with nucleophilic species leading to neoglucoconjugates as depicted in Figure 1. Such molecular constructs involving a carbohydrate moiety are interesting chemical systems, most often because of their biological significance. Indeed, various types of glycoconjugates appear to be essential species in many biological phenomena and have attracted considerable attention in terms of drug-discovery.[3] Other applications lie in the high polarity of a glucidic moiety which brings improved water solubility to the whole molecule with eventual self association properties.

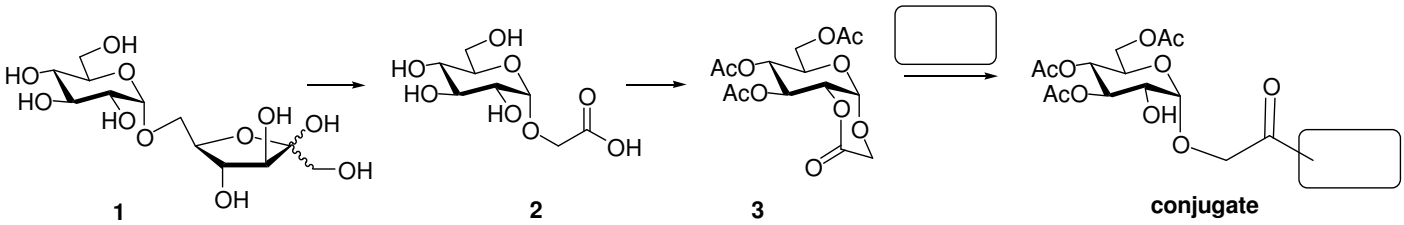


Figure 1

Among synthons designed for glycoconjugate synthesis, carboxymethyl glycosides have been used efficiently either as carbohydrate provider in the preparation of glycoconjugates analogues or as carbohydrates scaffolds able to serve as a polyfunctional and structurally constrained backbone. In the same idea, we have demonstrated that carboxymethyl glycoside lactones could be used as an activated analogues of carboxymethyl glycoside able to deliver a carbohydrate moiety under extremely mild conditions. In this first section, we will detail the synthesis and the uses of carboxymethyl glycoside lactones from isomaltulose and review some other studies of the literature in which carboxymethyl glycosides have been used as synthons as well as the main methods for their preparation.

1.1. Synthesis of carboxymethyl glucoside and its lactone from isomaltulose

Isomaltulose (**1**) and trehalulose (**5**), 6-α-D-glucopyranosyl-D-fructofuranose and 1-α-D-glucopyranosyl-D-fructopyranose respectively, are obtained in one step from sucrose (**4**) by bioconversion (Figure 2).[4] The chemistry of these available carbohydrates has been recently reviewed.[5]

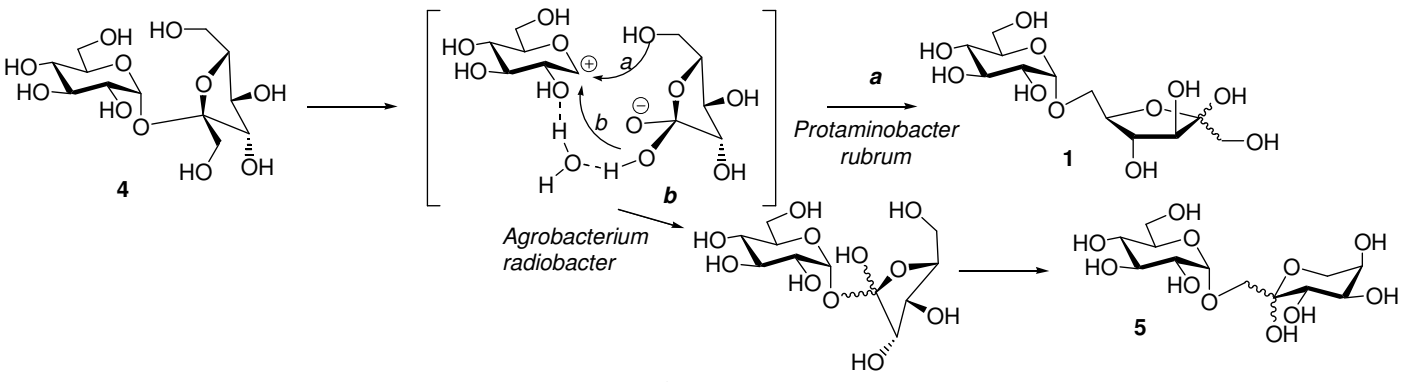
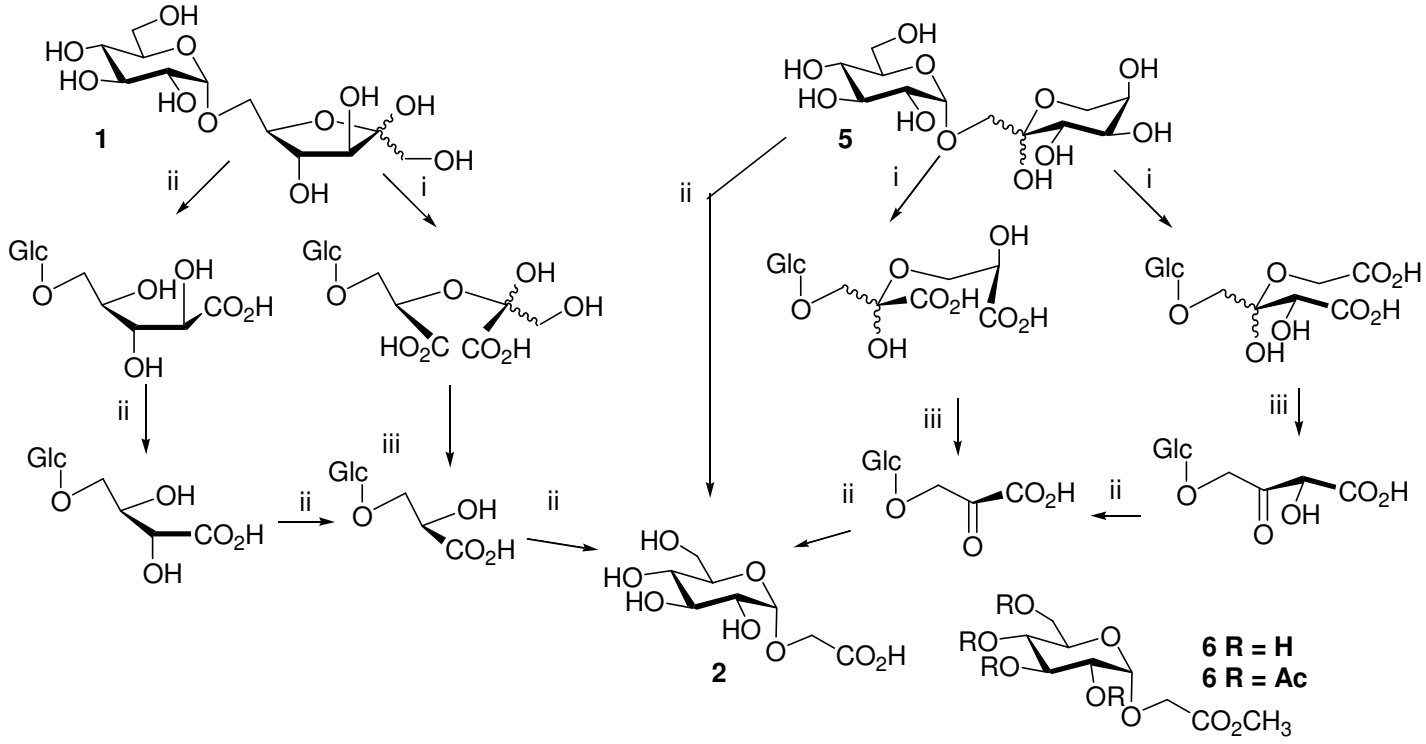


Figure 2

Upon oxidation by air under basic conditions, isomaltulose is known to provide glucosyl-α-D-arabinonates or more carboxylated derivatives under platinum-catalysed oxidation conditions.[6] Such compounds might be interesting as potential cation sequestering agents.[7]

We focused our efforts on the use of aqueous hydrogen peroxide, because it is easy to handle, easily available and generates no by-products. The efficiency and the outcome of the oxidation of carbohydrates by hydrogen peroxide depends on the occurrence of hemiacetalic centres, the basic or acidic conditions and the presence of additives such as metal salts.[8] Some of these reactions are degradative oxidation-decarboxylation sequences since the first oxidation products are themselves oxidisable, and so on, leading to short acids as final products. What we found is that under acidic conditions, the hydrogen peroxide oxidation of isomaltulose led to α-CMG (**2**). The reaction was also studied in the presence of sodium tungstate, known to promote the oxidative cleavage of glycols *via* peroxotungstate species when used in combination with hydrogen peroxide.[9] Applied to starch and maltodextrins, erythronic acid-terminated oligoglucosides were obtained.[10] α-CMG can also be obtained from isomalt, the hydrogenation product of isomaltulose, and in this case, the presence of tungstate salts proved to be indispensable.[11] A typical procedure is to treat isomaltulose with excess hydrogen peroxide in acidic conditions (pH 2) at 90 °C. The reaction can also be performed under basic conditions, but the formation of α-CMG is much slower. The possible routes towards CMG from these disaccharidic substrates are depicted in Figure 3. It is related to the work by Isbel and Frush who studied the base catalysed oxidation of other disaccharides with hydrogen peroxide leading to mixtures of oxidised products, among which carboxymethyl β-D-glucopyranoside was identified when cellobiose was used as starting material.[12] The product **2**, which can be obtained at the 5-10 g scale in *ca.* 35% yield, was identified and characterised as its methyl ester **6** and the corresponding tetraacetyl derivative **7**.



i: glycolic cleavage ; ii: oxydation-decarboxylation; iii: hydrolysis

Figure 3

We also found that the direct treatment of α–CMG under acetylation conditions led to a new product which was identified as the triacetyl lactone **3** (α-CMGL, Figure 4). ^{1}H and ^{13}C one- and two-dimensional NMR spectroscopic analyses were consistent with the presence of the α-carboxymethyl linkage, and HMBC C-H correlations were observed between H-7ab and C-1 and between H-7ab and C=O. The most likely hypothesis for the formation of this lactone is an intermediate mixed anhydride formed first, followed by the

cyclisation by reaction with OH-2. The formation of such a glucoside lactone had never been described, although it was suggested as an intermediate in the case of a β-lactoside.[13] A comparable structure has been described among intermediates towards the synthesis of a lipid-A analog in a recent patent.[14] Likewise, a phostone was observed during the acetylation step of a phosphono-*C*-glycoside.[15] The diverse side products observed after acetylation are also a way to have a clearer view of the outcome of the oxidation step. Notably, another lactone (**8**) arising from incomplete oxidation was formed when the reaction is not carefully maintained at 90 °C and glucose pentaacetate (**9**) can be present when the pH is not well controlled. Also, acetylated carboxymethyl glucosides arising from the opening of the lactone were observed, either with four acetyl groups (**10**) formed during the acetylation step or with OH-2 still unprotected (**11**), thus formed during the purification procedure.

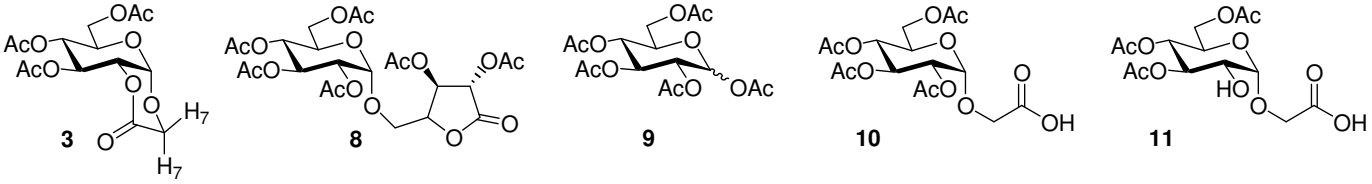


Figure 4

The ability of lactone **3** to open up in the presence of a nucleophilic species was first observed when traces of ethyl ester **31** (*vide infra*, Figure 11) were identified during a recrystallization in ethanol. This led us to investigate in a more general way whether lactone **3** could be used as a synthon for connecting a carbohydrate moiety to other systems, as detailed in the following sections. Indeed, opening of carbohydrate lactones is a popular way for such connective strategies, which can be considered as an alternative to glycosylation. It has been used for the synthesis of a variety of conjugates such as amphiphilic derivatives,[16] carbohydrate terminated dendrimers[17] and hybrid polymers.[18] Only uronic acid lactones or more complex bicyclic structures based on carbohydrates have been used in similar strategies, with the purpose of preparing either surfactants or glycopeptide analogs.[19,20]

1.2. Alternative accesses to carboxymethyl glucosides

Carboxymethyl glycosides can be prepared by different routes. The most simple one is the direct Fischer glycosylation of glycolic acid by glucose in the presence of hydrochloric acid, described by Petersson *et al.*, leading to an 70:30 α/β mixture of the glycosides in a 6 % yield (Figure 5, path a).[21] The method described in section 1.1., which leads exclusively to the α anomer, constitutes path b.[2]

A major alternative involves intermediate allyl glycosides, obtained either *via* Fischer or Koenigs-Knorr type glycosylations, which can be oxidized either by the $RuCl_3$-$NaIO_4$ method,[22-26] developed by Sharpless and co-workers,[27] by bishydroxylation followed by glycolic cleavage,[28-30] or by ozonolysis (path c).[31,32] Following Fischer and Helferich early report who described ethoxycarbonylmethyl β-D-glucopyranoside and its subsequent saponification to the carboxylic function in 1911,[33] glycolic acid esters were directly used (path d) in glycosylations involving activated glycosyl donor instead of allyl alcohol (glycosyl bromide,[34-37] fluoride,[38] trichloroacetimidate[13,31,39]). The anomeric configuration of the carboxymethyl glycoside relies therefore on the classical parameters which control the selectivity of the glycosylation step. The more stable tetrabenzylated carboxymethyl glycoside can be obtained by acid catalysed reaction with glycolic acid ethyl ester.[29] An example using the silver (I) salt of glycolic acid has

been described.[40] Also, the bisdimethylacetal of glycolylaldehyde has been used, with a subsequent oxidation step by $NaClO_2$.[41] Finally, let us mention that the carboxymethylation of alcohols or amines using α-halogenoacetic acid derivatives is a very common reaction, widely used in polysaccharide chemistry for example. Typical conditions are sodium chloroacetate in basic solution, or bromoacetonitrile in acetonitrile in the presence of NaH, followed by transformation of the nitrile group to a carboxylic acid.[42] Some esters (*t*-butyl, benzyl) of bromoacetic acid are also often used, but there has been only rare mention of their use for anomeric alkylation (path a).[43]

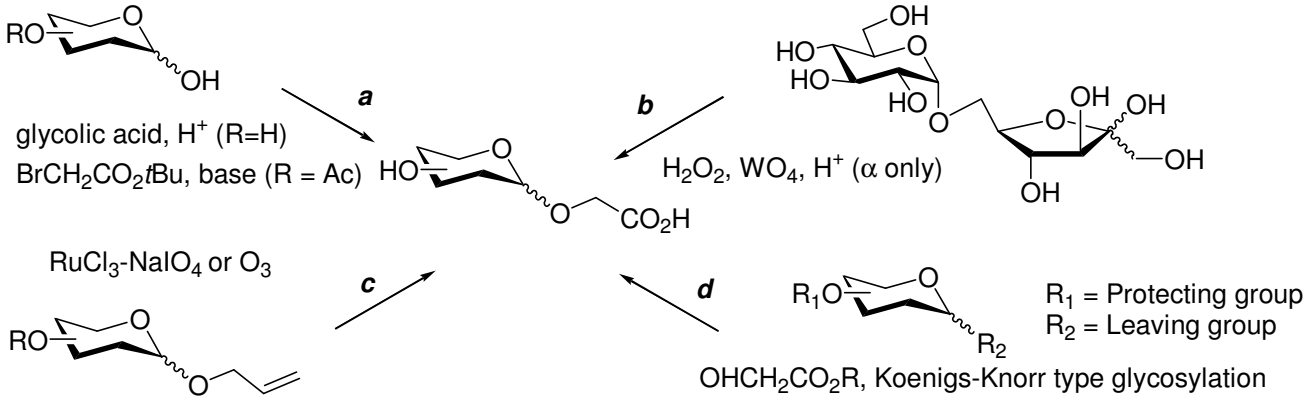
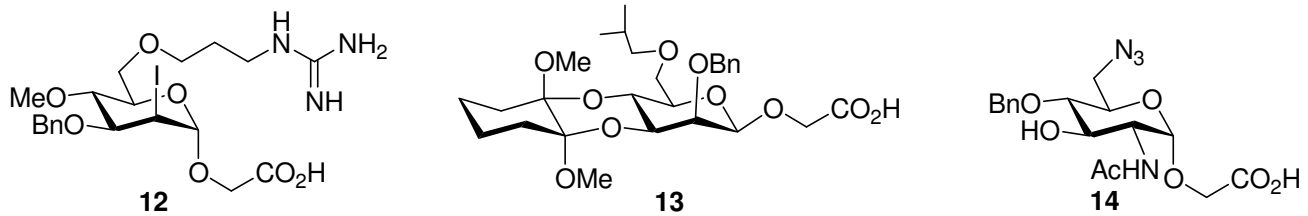


Figure 5

1.3. Uses of carboxymethyl glycosides

Carboxymethyl glycosides have been used in different syntheses of peptidomimetics constructed on carbohydrate scaffolds (Figure 6). For example, Nicolaou and co-workers designed non-peptide mimetics **12** of cRGD*F*V pentapeptide, a potent angiogenesis inhibitor.[38] In the field of cell adhesion inhibition, related with inflammatory processes, Kessler and co-workers have prepared a series of peptidomimetic integrin antagonists constructed on a carboxymethyl mannoside backbone **13**.[41] A multifunctionalised scaffold (**14**) was prepared by Ghosh and co-workers for the construction of broad screening libraries, based on a *N*-acetyl glucosamine carboxymethyl glycoside, also bearing an azido residue at C-6.[22]



12 **13** **14**

Figure 6

Glycodendrimers have stimulated considerable interest in the recent years.[44] Glycoconjugate libraries (including compound **15**) were prepared by Lockhoff with carboxymethyl glycosides serving as the carboxylic acid partner in four components Ugi reactions (Figure 7).[31] This reaction was also used by Ziegler and co-workers for the preparation of neoglycoproteins (**16**),[34] and by Westermann and Dörner, and Li and co-workers for the synthesis of glycoclusters **17** and **18**, designed for RNA and lectin binding properties.[23,24] Virta and co-workers have connected carboxymethyl glycosides to cyclopeptidic scaffolds, leading thus to diverse di and trivalent glycoclusters (including compound **19**) using a solid support methodology.[25] Other types of amphiphilic glycopeptidic clusters (**20**) were prepared by Grandjean and co-workers.[45]

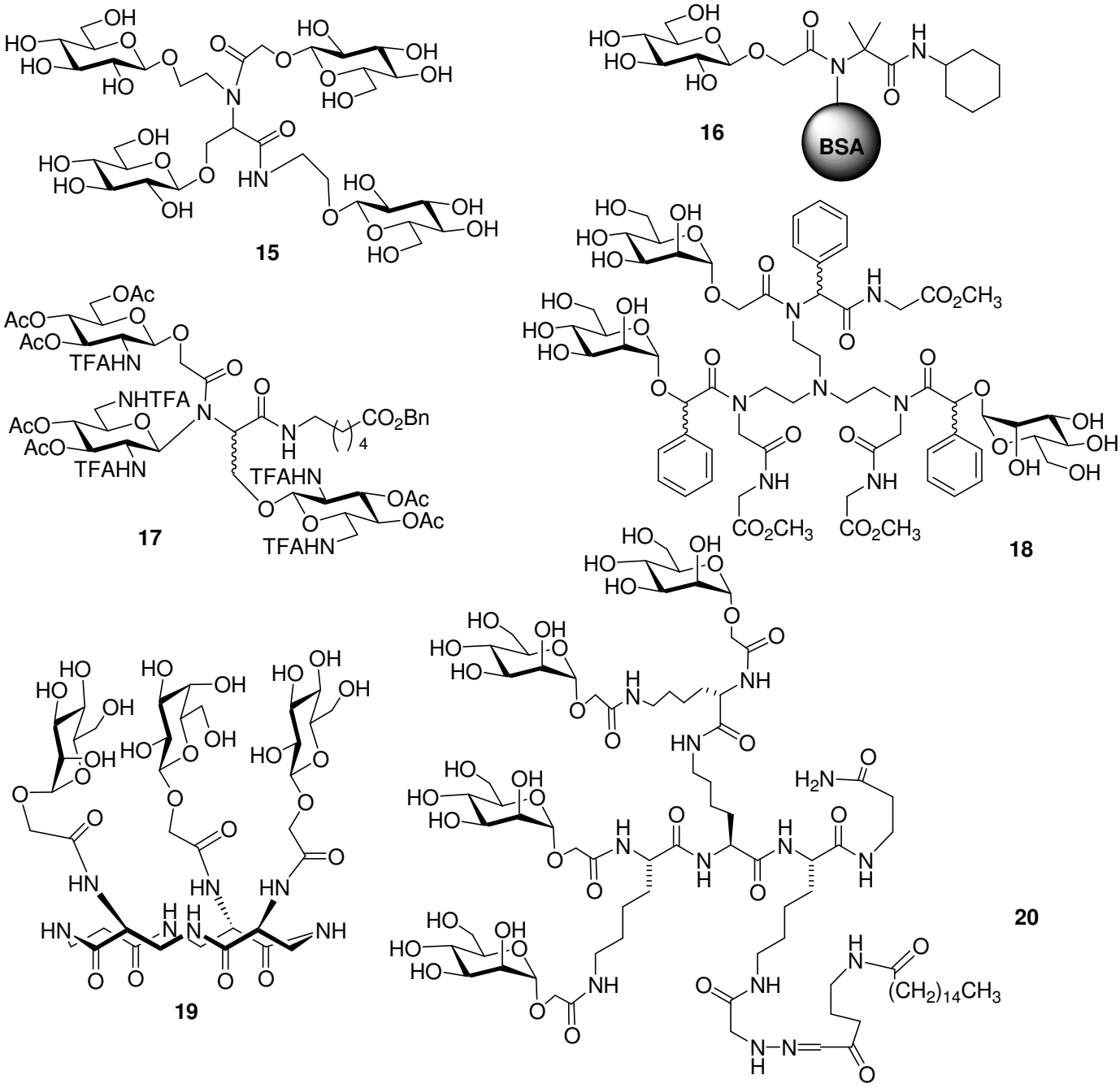
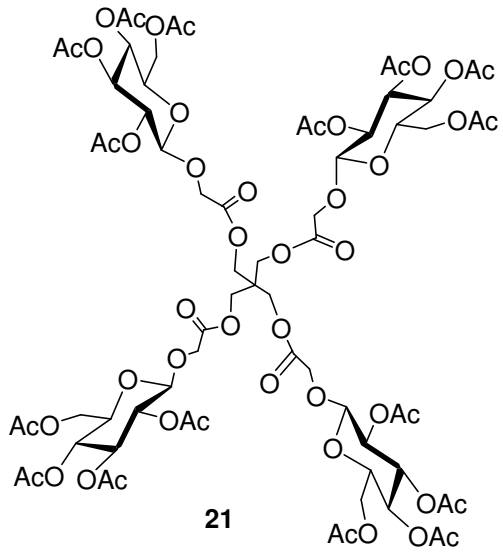


Figure 7

A tetrameric glucose based cluster (**21**) was prepared by Binder and Schmid on pentaerythritol as central polyol (Figure 8).[28] Using a carboxymethyl lactoside, Toyokuni *et al.* synthesized multivalent lactosyl clusters (**22**) designed as potential tumour metastasis inhibitors.[13] Here again, carboxymethyl glycosides are useful synthons for the connection of the external carbohydrate function to the internal multivalent core. For example, Kitaoka and co-workers prepared PAMAM dendrimers decorated with cellobiose (**23**), designed for studying the accessibility of cyclodextrin phosphorylase.[35] Multivalent systems such as **24**, involving specific disaccharides were prepared by Khan, Pieters and co-workers for the study of their properties as E-Coli antiadhesion agents.[39]

The carboxymethyl residue at the anomeric position has been also used in other types of conjugates. In a solid-phase approach to galactose based trisaccharide epitopes involved in hyperacute rejection in xenotransplantation, Elofsson, Kihlberg and co-workers used a carboxymethyl linkage for the connection of the first carbohydrate with the resin (**25**) (Figure 9).[26]



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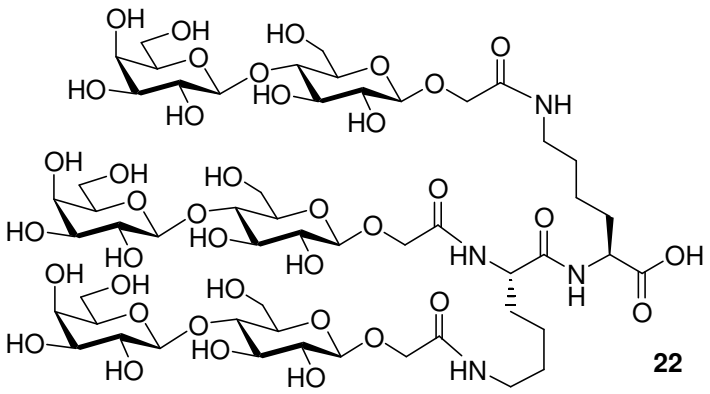

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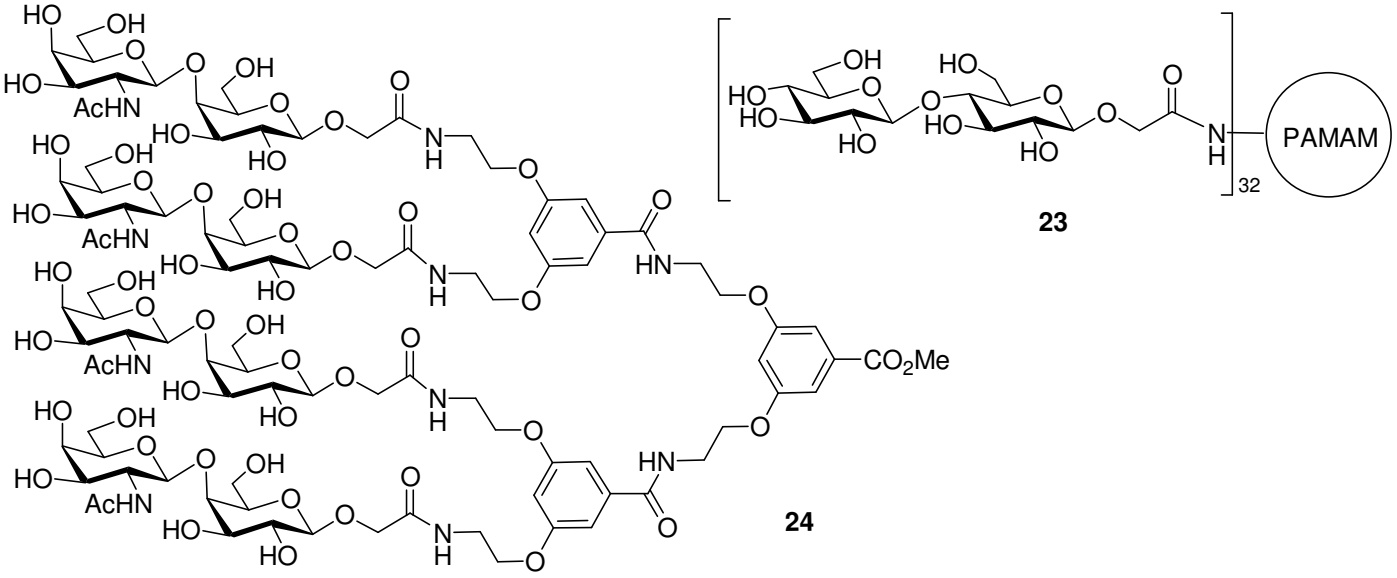

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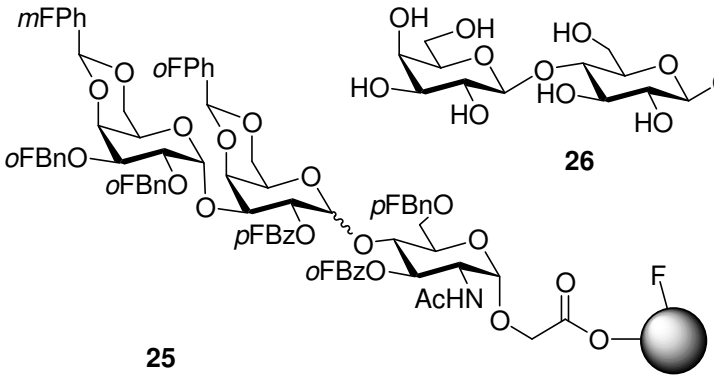
Figure 8



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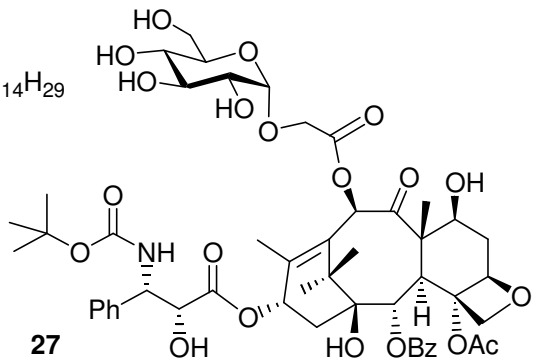


27

Figure 9

Basu and Santacroce prepared disaccharidic fatty amides (including compound **26**) linked at the anomeric position *via* amide formation from the corresponding carboxymethyl glycosides. The carbohydrate-carbohydrate interactions of these synthetic glycolipids with natural gangliosides and sphingolipids were investigated in the context of a study of the activity of cell surface glycolipids as mediators in cell adhesion.[32] A carboxymethyl glycoside moiety was used by Mandai and co-workers as a water-solubility

promoter for anticancer taxoids, *i.e.* CMG-docetaxel (**27**).[29] This approach was also shown to provide prolonged duration of action of some peptide drugs.[46]

Let us mention two last examples of the use of carboxymethyl residues. The strategy was mentioned for the preparation of complex phosphine oxides (**28**) designed for metal coordination properties as well as water solubility[47] and carboxymethyl glycosides were used by Stoodley and co-workers as starting material towards highly oxygenated dienes (**29**) used in asymmetric hetero-Diels-Alder reactions (Figure 10).[48]

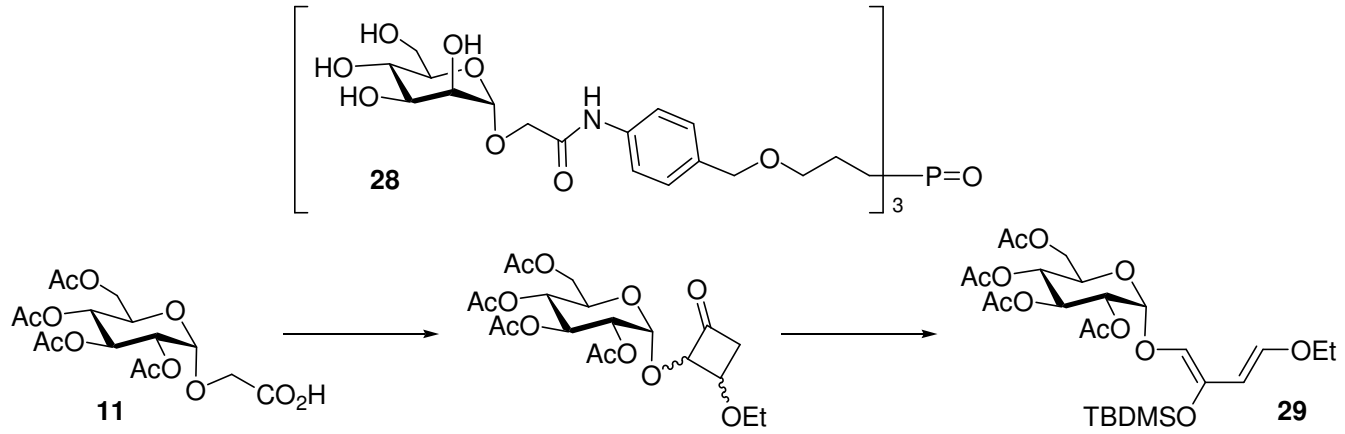


Figure 10

Finally, the properties of carboxymethyl glycoside itself were investigated among other glycosides, in the context of cation complexation studies by Van Bekkum and co-workers,[36] and for the rate of the glycosidic bond hydrolysis by Timell.[37]

2. Reactions of carboxymethyl glucoside lactone with alcohols

Alcohols react with α-CMGL (**3**) to provide the corresponding glycosyloxyacetylated compounds which have unsubstituted OH-2.[49] (Figure 11, Table 1)

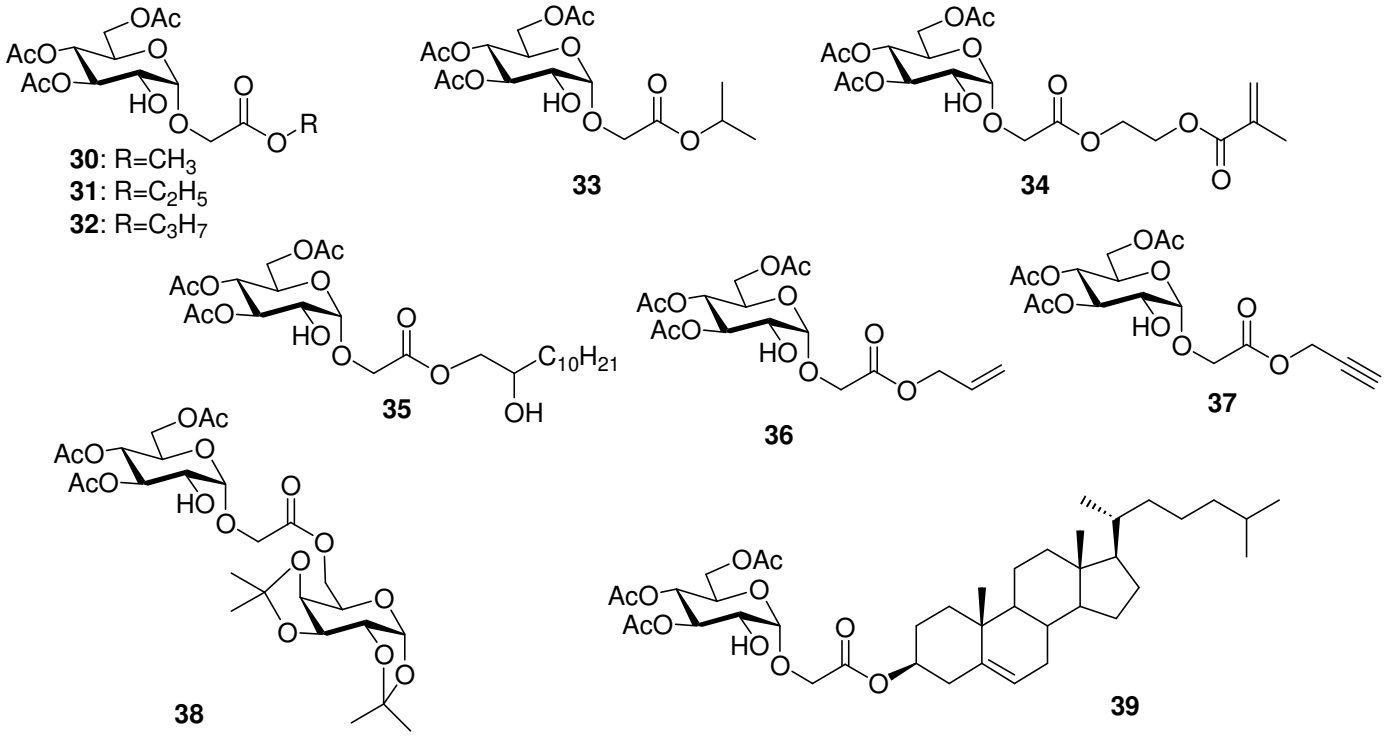


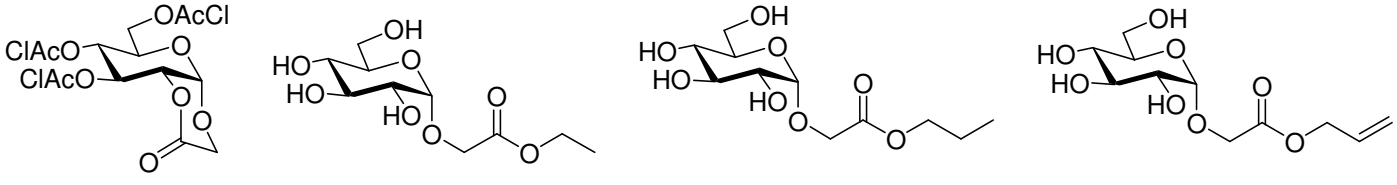
Figure 11

Table 1. Reaction of CMGL **3** with alcohols.

Alcohol	Catalyst	Equivalents	Reaction time (h)	Temperature	Obtained adducts	Yields (%)
EtOH	no	/	168	RT	**31**	26
EtOH	DMAP	0.1	38	RT	**31**	50
EtOH	DMAP	2.0	48	RT	**31**	50
EtOH	NEt_3	1.0	34	RT	**31**	45
EtOH	$AlCl_3$	0.1	36	RT	**31**	42
EtOH	$AlCl_3$	1.0	7	RT	**31**	34
EtOH	$Sc(CF_3SO_3)_3$	0.1	26	RT	**31**	48
EtOH	$Yb(CF_3SO_3)_3$	0.1	27	RT	**31**	51
EtOH	$La(CF_3SO_3)_3$	0.1	30	RT	**31**	52
EtOH	APTS	0.1	24	RT	**31**	50
MeOH	DMAP	2.0	2	RT	**30**	68
MeOH	$Yb(CF_3SO_3)_3$	0.1	288	RT	**30**	52
iPrOH	DMAP	0.5	12	RT	**33**	55
Propan-1-ol	$La(CF_3SO_3)_3$	0.1	168	40	**32**	57
Allyl alcohol	DMAP	0.5	120	RT	**36**	88
Dodecane-1,2-diol	DMAP	0.5	120	RT	**35**	46
1,2:3,4-di-O-isopropylidene-D-galactopyranose	DMAP	1.0	48	40	**38**	45
Cholesterol	$La(CF_3SO_3)_3$	1.0	120	RT	**39**	42

The reaction proceeds with either base, acid or lanthanide salts catalysis, using either alcohol as solvent (or mixed with CH_2Cl_2) or with stoichiometric amount in CH_2Cl_2. A series of alcohols were used, including simple aliphatic alcohols, glycol, cholesterol, and a protected carbohydrate having only one OH available, 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose. Methanol led to the fully deacetylated product.

When the chloroacteyl analog **40** of the lactone is used, concomitant ester deprotection is observed. Therefore, the chloroacetyl lactone is a more convenient starting material for providing the deprotected conjugates (Figure 12, Table 2).



40 **41** **42** **43**

Figure 12

Table 2. Reaction of chloroacetyl lactone **40** with alcohols.

Alcohol	Catalyst	Equvalents	Reaction time (h)	Temperature	Obtained adducts	Yields (%)
EtOH	DMAP	2	5	RT	**41**	60
Propan-1-ol	DMAP	5	5	RT	**42**	40
Allyl alcohol	DMAP	5	3	RT	**43**	57

3. Reactions of carboxymethyl glucoside lactone with amines

The main applications of CMGL as a carbohydrate connecting synthon were obtained when amines were used as the nucleophilic species for opening the lactone. Enhanced nucleophilicity of amines compared to alcohols makes the reaction general and easy to perform, even under very mild conditions. The high stability of the amide function which is thus created permits easy further elaboration of the adducts (functionalisation, deprotection). The reaction was applied to the synthesis of various types of conjugates such as glycoaminoacid hybrids,[49] pseudo disaccharides,[50] glycosylated porphyrins[51] and glycosteroids.[52]

3.1. Glycoaminoacid hybrids

Glycopeptides are an important class of biomolecules, involved in many physiological and pathological processes. Therefore various strategies have been established for the synthesis of their analogs and mimetics.[22,38,41,53,54] We thus investigated the potential of CMGL in similar strategies and examined its opening by variously protected aminoacids (Figure 13).[49] Glycine methyl ester was first used as a simple model to give the amide **44**.

The case of aspartic acid dimethyl ester permitted to verify that no loss of configurational integrity at the amino acid chiral center occurred during the reaction (**45**). Indeed, from either L- or the D- amino acids, two diasteroisomers are formed and NMR spectroscopy clearly shows that both compounds are different and pure. Lysine methyl ester, which possesses an amino group on the side chain, gave the *N,N'*-bis(glycosyl) diacetamide **50**, with small amounts of the monoamide **49**. This latter compound has still the side chain amino group available for incorporation into a peptide sequence. The alternative lysine monoamide could be prepared from benzyloxycarbonyl *N*-protected lysine methyl ester.

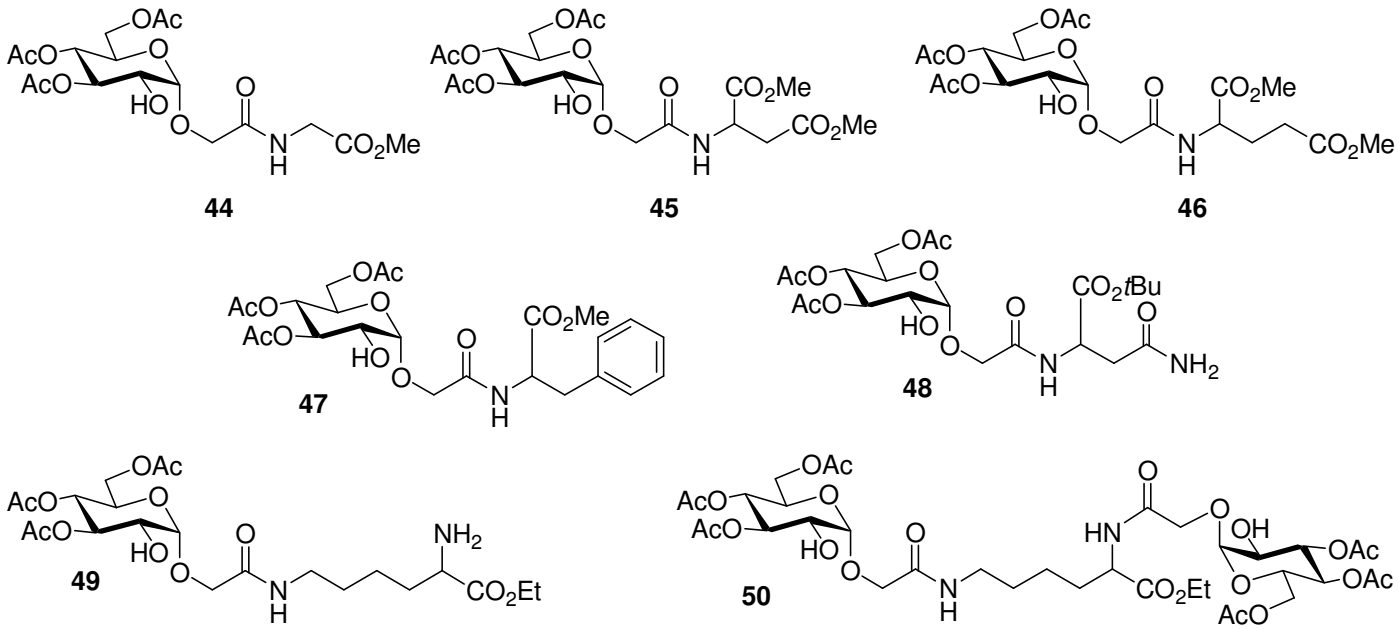


Figure 13

Removal of acetyl groups proceeded without loss of chirality at the α-amino acid centres using hydrazine in either methanol or methanol-dichloromethane, known to respect amino acid chirality[55] or acetyl chloride in methanol. This method proved to be more general because methyl ester protecting groups are not compatible with the hydrazine/methanol method. Again in this case, NMR spectroscopy clearly indicated that the chirality at the AA-center was not affected (Figure 14), unlike in the case of the NaOMe-MeOH

reaction which led to 1:1 mixtures of epimers, although this latter method was reported to allow *O*-acyl group deprotection of a disaccharidic hexapeptide.[56]

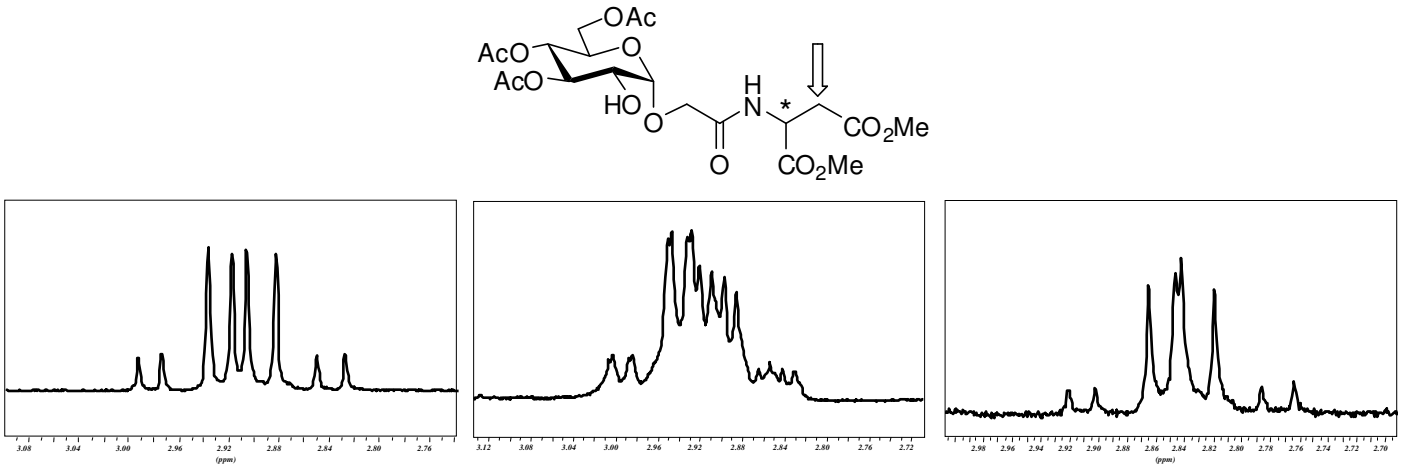


Figure 14. NMR evidence for the configurational integrity at the AA centre as observed at the CH_2-AB system of CMG-(L or D)-ASP: (left) deprotection with AcCl-MeOH of **45** and of its (D)-ASP-analog (right); mixture obtained by deprotection of **45**with MeONa-MeOH.

3.2. Pseudodisaccharides

Oligosacharides play key roles in many biological processes. Among analogues, amide-linked saccharidic structures have attracted some interest.[54,57]

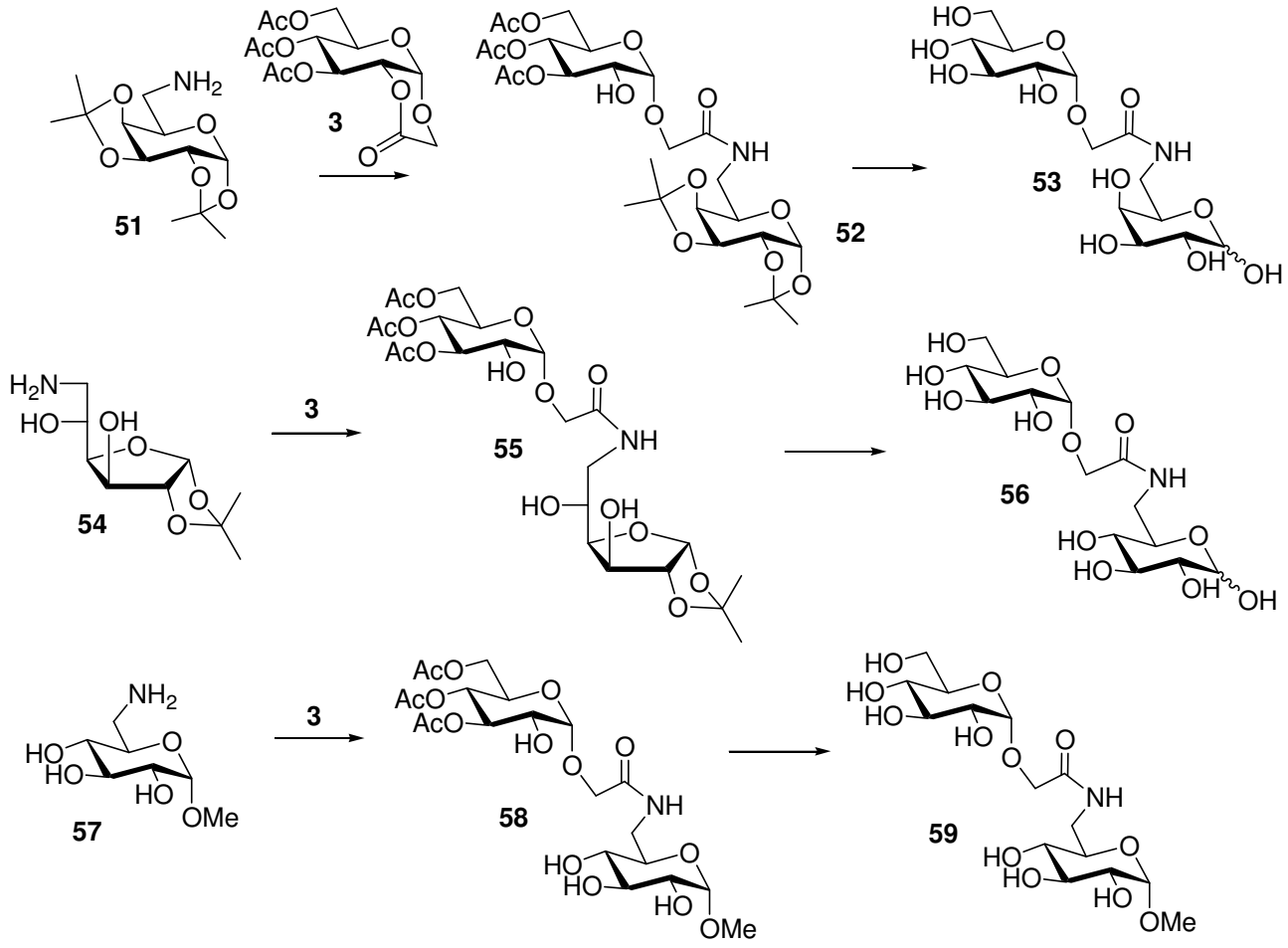


Figure 15

Sugar amino acids (SAAs) chemistry has provided compounds such as antiviral activity against HIV and inhibitors of sialyl Lewis x-dependant cell adhesion and other peptidomimetics which are interesting because of restricted conformational behavior.[58]

New amide-linked pseudodisaccharides (**53**, **56**, **59**) have been synthesised by reaction of aminodeoxy sugars with α-CMGL (Figure 15).[50] Taking into account the length (four-atom) of the inter-glycosidic linkage, these compounds are equivalent to trisaccharide mimetics. Similar examples have been described in the literature, such as linear or cyclic oligosaccharides with a four-carbon rigid connection, and a competitive inhibitor of the hydrolysis of *p*-nitrophenyl α-maltotriose by porcine alpha-amylase having a six-atom acyclic spacer between two glucose residues.[59]

Unlike the case of alcohols, the reaction with aminodeoxy sugars does not require the presence of base. This has also the advantage of limiting the formation of the undesired *N*-acetylation of the starting aminosugar arising from competitive intermolecular O-to-N acetyl exchange. Best conditions proved to be THF with a slight excess of CMGL or DMF for some aminosugars with unprotected OH groups. Deprotection of the obtained amide-linked pseudodisaccharide **58** was performed using Zemplén conditions or, in the case of compounds **52** and **55** having isopropylidene and acetyl groups, using a 0.5 M HCl solution at 50 °C (proving the satisfactory stability of the α-carboxymethyl linkage under acidic conditions).

The amide-linked sugar/nucleoside adduct **61** which could mimic the glucosyltransferases substrate (UDP-Glc) was obtained by the same strategy (Figure 16) from 5'-deoxy-5'-azidouridine (**60**).[60]

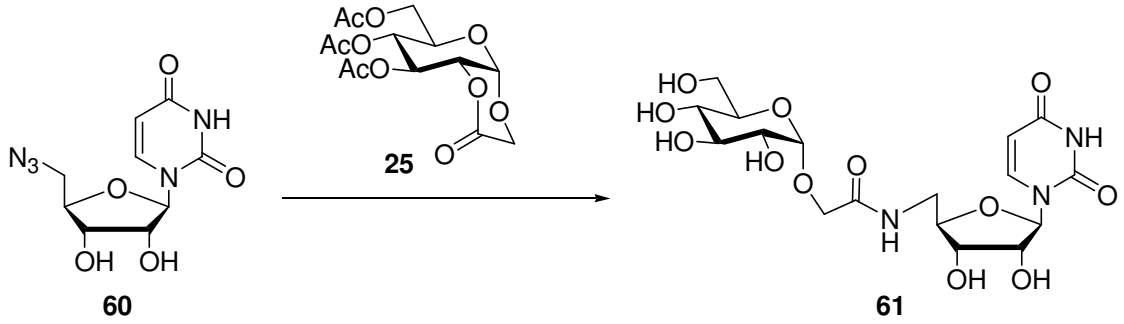


Figure 16

3.3. Glycosylated porphyrins

Porphyrins bearing glycosylated groups have potential interest as photosensitizers for cancer photochemotherapy.[61] The sugar moieties have been shown to modulate the amphiphilicity of the photosensitizers and specific membrane interactions,[62] and in some cases to increase their plasmatic life time.[63] The presence of carbohydrates on porphyrins is also known to allow cancer cell surface targeting throught specific binding to membrane receptors.[64] Use of synthetic carbohydrates as carriers in directed drug delivery could thus be an interesting approach in cancer cell targeting.

New glucosylated porphyrins **62** and **63**, having an α-D linkage, have thus been prepared by reaction of CMGL (Figure 17) with aminopropylated monohydroxyphenyltritolylporphyrins.[51,65] The decay of fluorescence observed for these porphyrins in H_2O/THF (8/2) compared to THF suggests the formation of aggregates.[66] The *in vitro* photocytotoxicity of the new porphyrins was evaluated using a K562 chronic leukaemia cell line and compared to that of Photofrin®. The *ortho* porphyrin **62** is much more active than *para* porphyrin **63**, although less active than Photofrin® at the same ponderal concentration. It induces probably early necrotic death more than secondary necrosis that could be attributed to the induction of

apoptosis. However, the photoactivity of the glycosylated porphyrin was clearly improved compared to the non glycosylated one.

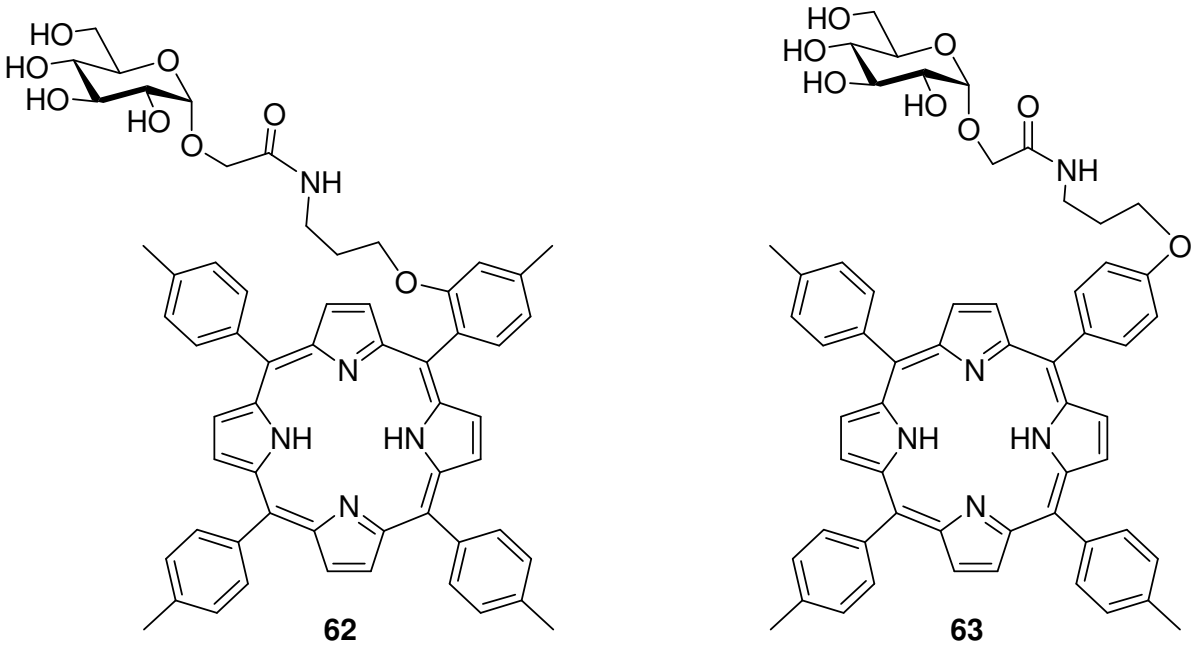


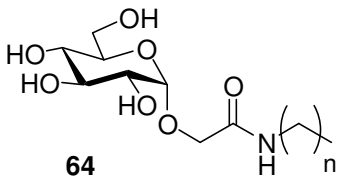
Figure 17

3.4. Neoglycolipids

Glycolipids have important properties in terms of biological or physicochemical viewpoints, these two aspects being sometimes correlated. For example, glycolipids are involved in complex mechanisms that are thought to involve membrane sub-domains, containing liquid-ordered phases, termed lipid rafts.[67]

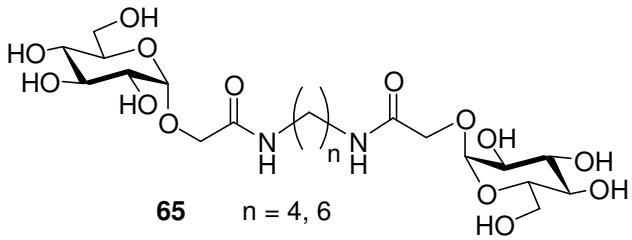
Being interested in the synthesis and study of the surface activity and thermotropic liquid-crystalline behaviour of a variety of synthetic glycolipids, notably arising from simple and available sugars,[1a,68] we also developed the CMGL strategy towards such materials.[49,52]

A series of aliphatic amines (C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}) were condensed with CMGL in THF. The resulting amides **64** were deacetylated in methanol using catalytic amounts of sodium methanolate in good yields (Figure 18). Some symmetrical diamines were also prepared and new bolaform carbohydrate based amides **65** were thus obtained. In terms of thermotropic properties, it was shown that the minimum chain length is of 10 carbon atoms, the C_{10}, C_{12}, C_{14}, and C_{16} exhibiting all lamellar phases. The stability of the amide linkage, as well as that of the α-glucosidic bond, allowed full cycles of heating up and down for the DSC analysis experiments, unlike other glycolipids such as sucrose esters or hydroxyalkylethers we had previously studied.



64
n = 5, 7, 9, 11, 13, 15

phase transitions for **64** (°C)
n = 5 : 63 iso
n = 7 : 74 iso
n = 9 : 81 smectic A* 94 iso
n = 11 : 89 smectic A* 122 iso
n = 13 : 92 smectic A* 178 iso
n = 15 : 100 smectic A* 192 iso

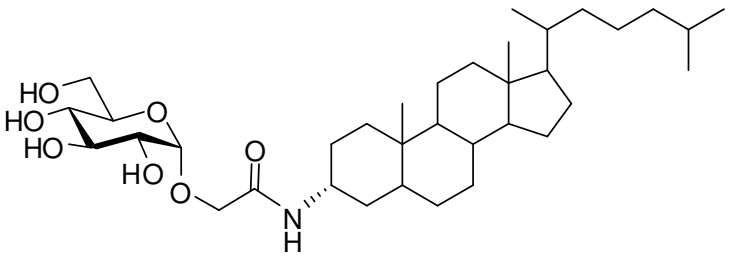


65 n = 4, 6

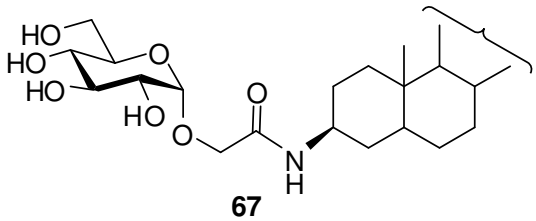
Figure 18

Four different amino steroids were also coupled onto CMGL. The 3-aminocholesterols (α and β) were obtained by reduction of 3-azido-5-cholestene prepared itself by reaction of HN_3 with cholesterol or epicholesterol under Mitsunobu conditions. The saturated equivalent systems were prepared from cholestanol and involving the same Mitsunobu reaction conditions to establish the stereochemistry at C-3 of the steroid followed by reduction of the azido group (Figure 19).[69] Reaction with CMGL was performed in anhydrous THF leading to the steroidal amides in very good yields. The typical proton NMR patterns for the CMG conjugates were observed, notably H-2, H-3 and H-4 at 3.82, 5.28 and 5.04 ppm respectively. Final amphiphilic glycosteroids **66-69** were obtained by deprotection of acetyl groups performed under Zemplén conditions.

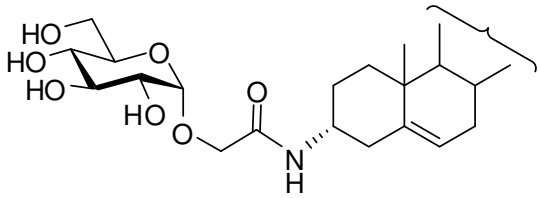
Only the saturated steroid amides **66** and **67** exhibited some liquid crystalline behaviour, in a very limited temperature range (181-230 dec and 202-230dec). This is often the case for steroidal glycolipids having direct connection or short spacer (1-4 atoms) between the carbohydrate moiety and the steroid backbone.[70] Furthermore, the relatively high melting points of these compounds increase their tendency to decompose at elevated temperatures through caramelization. The 3-β-cholestane amide **67** exhibits a wider temperature range of the liquid crystal phase with a lower melting point compared to the α one. The unsaturated analogues **68** and **69**, less flexible, did not exhibit any liquid crystalline phase as they decompose at lower temperatures.



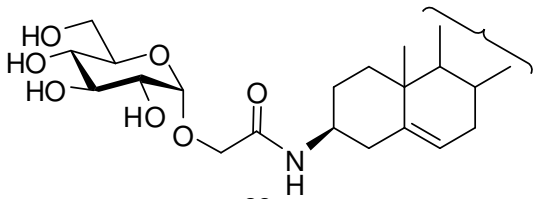
66



67



68



69

Figure 19

3.5. Miscellaneous

Other various other amines were used in the CMGL opening reaction. Notably, some amines with polymerisable residues provide amides such as the methacrylate **70** or allyl and propargyl amides **71** and **72** (Figure 20).[49] Also, some multivalent species were obtained such as the triamide **73**[71] and an octa amide on a PAMAM backbone (**74**) was identified by mass spectrometry. Likewise, a resin bearing free amino functions was shown to react with CMGL and could be used for example to eliminate excess CMGL from the reaction mixture providing **75** which could be easily removed by filtration. Finally the reaction with monoamino-β-cyclodextrin led to the corresponding amide **76**.[72]

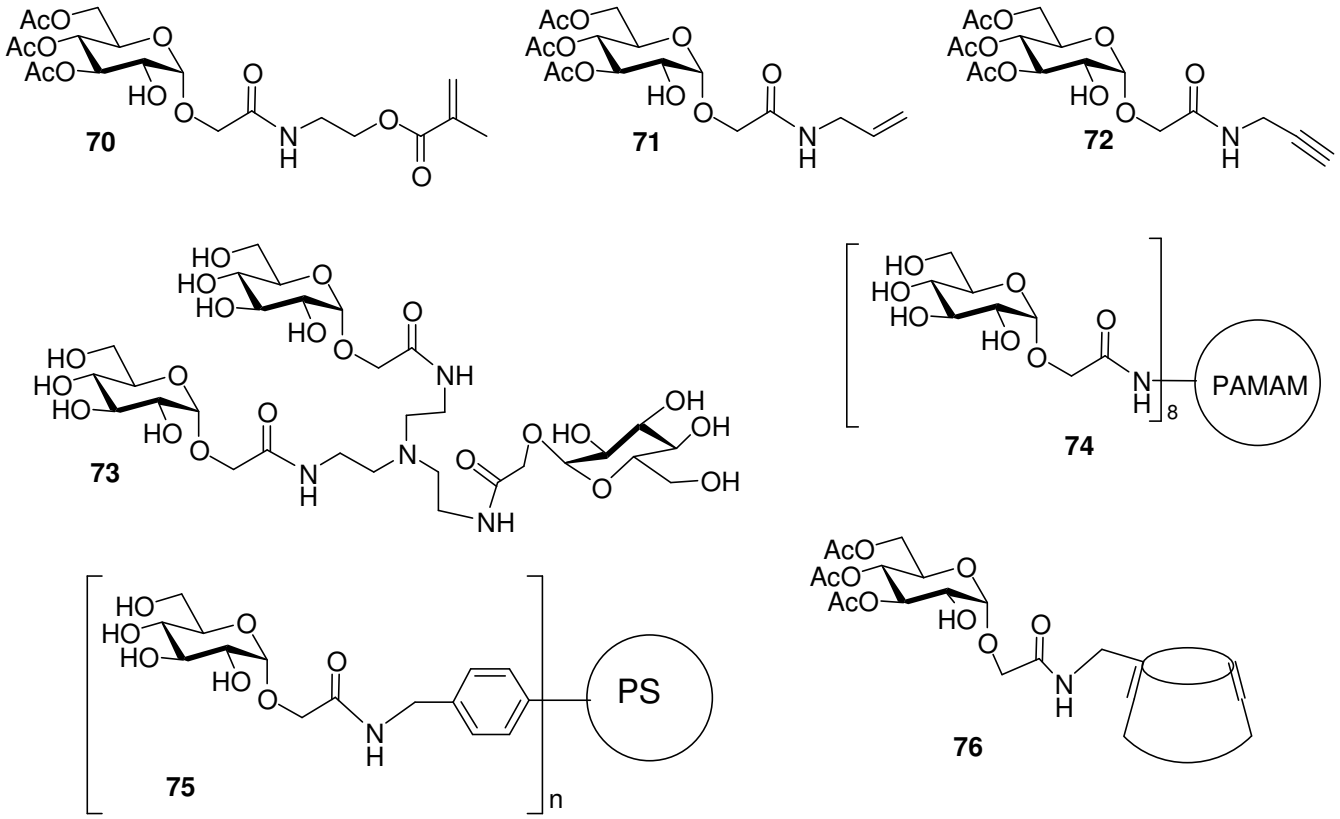


Figure 20

4. Reactions of carboxymethyl glucoside lactone with vinyl magnesium bromide

A short exploration of the reaction with vinyl magnesium bromide proved that CMGL can also be used for carbon-carbon bond connections with the carbohydrate moiety. However, yields remained rather low because of the lack of stability of the ester groups, even when the more stable tripivaloylated lactone was used. Actually, the best was to directly remove all esters in order to simplify the mixture of products, allowing the identification of the bis-vinyl alcohol **77** (Figure 21).[73]

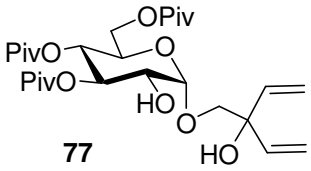


Figure 21

5. Structural variations on CMG-adducts

A major interest of the CMGL approach is to provide an isolated OH group at position 2 after the opening step (Figure 22). The selective further transformation of this function can therefore provide 1,2-disubstituted compounds in a very straightforward manner. An example is the reaction of amide **78** with dihydropyran under acidic catalysis which yield the acetal **79**, from which the acetyl groups could be exchanged to benzyl ethers to yield **80**.[74] Another example is the oxidation of the ester **32** under Swern conditions which give the non-isolable corresponding 2-keto derivative, which undergo immediate elimination of one acetic acid molecule leading to the enone **81**.[75] Further studies taking advantage of this selective functionalisation are currently ongoing in our laboratory.

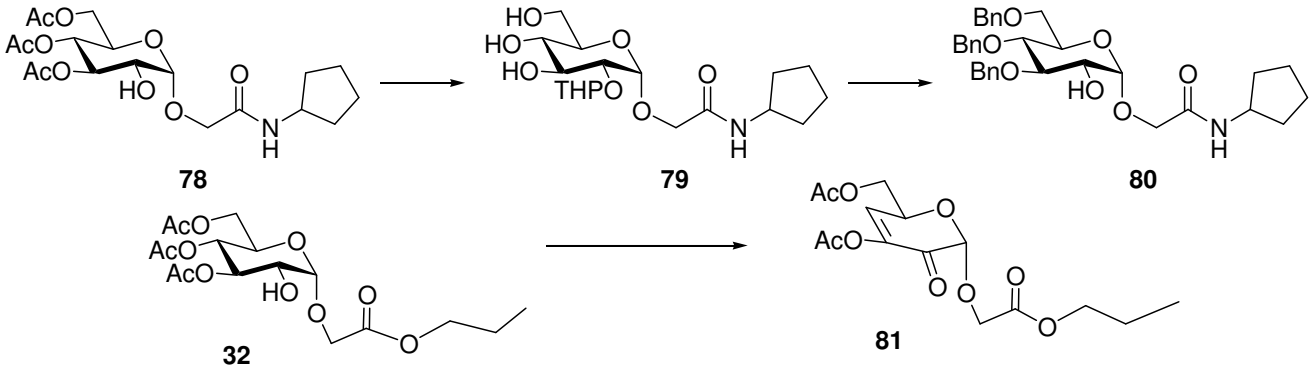


Figure 22

6. Conclusions and perspectives

Carboxymethyl α-D-glucopyranoside and its acetylated 2-*O*-lactone (CMGL) are easily prepared from the very available isomaltulose. The opening of CMGL by nucleophilic species, which occurs under very mild conditions, provides glucosyloxyacetylated compounds which can be seen as analogs of glucoconjugates. In particular, a wide variety of amides have been obtained with examples among pseudo disaccharides, gluco-aminoacids and neoglucolipids. More work is currently in progress in our laboratory to extend the scope of this strategy toward conjugates constructed on other carbohydrates, mono- or oligosaccharides. With this aim, new ways to prepare similar lactones are studied and the results will be reported soon.

Acknowledgments

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N,N-DIPROTECTED DEHYDROAMINO ACID DERIVATIVES: VERSATILE SUBSTRATES FOR THE SYNTHESIS OF NOVEL AMINO ACIDS

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Abstract. *Non-proteinogenic amino acids are an important class of organic compounds that can have intrinsic biological activity or can be found in peptides with antiviral, antitumor, anti-inflammatory or immunosuppressive activities. This type of compounds is also important in drug development, in the elucidation of biochemical pathways and in conformational studies. Therefore, research towards efficient methods that allow the synthesis of these compounds constitutes an important area of peptide chemistry. In our laboratories we have developed a new and high yielding method for the synthesis of N,N-diprotected dehydroamino acid derivatives using tert-butyl pyrocarbonate and 4-dimethylaminopyridine. These compounds were used as substrates in several types of reactions, allowing the synthesis of a variety of new amino acid derivatives. Some of these new compounds are heterocyclic systems or contain heterocyclic moieties such as pyrazole, indole, or imidazole. Thus, several nitrogen heterocycles were reacted with N,N-diprotected dehydroalanine to give new β-substituted alanines and dehydroalanines. Furanic amino acids were obtained treating the methyl ester of N-(4-toluenesulfonyl), N-(tert-butoxycarbonyl) dehydroalanine with carbon nucleophiles of the β-dicarbonyl type having at least one methyl group attached to one of the carbonyl groups. Treatment of these furanic amino acids with trifluoracetic acid afforded pyrrole derivatives in good to high yields. A N,N-diprotected 1,4-dihydropyrazine was obtained reacting the methyl ester of N-(4-toluenesulfonyl), N-(tert-butoxycarbonyl)dehydroalanine with 4-dimethylaminopyridine and an excess of potassium carbonate. Tetrahydropyrazines were synthesized by reaction of this 1,4-dihydropyrazine derivative with nucleophiles or by electrochemical reduction. Cleavage of the N-protecting groups from the 1,4-dihydropyrazine gave a disubstituted pyrazine. This review covers the synthesis of N,N-diprotected dehydroamino acids and their application as precursors for the synthesis of new compounds.*

Contents

1. Introduction

Non-proteinogenic amino acids can be found in biologically active peptides of several sources such as marine sponges and tunicates, fungi, bacteria and lower animal forms. The biological activities of these compounds include antimicrobial, antiviral, insecticidal, antitumor, anti-inflammatory or immunosuppressive actions. These types of compounds are also used as drugs or as lead compounds in drug discovery and are useful in the elucidation of biochemical pathways. Non-proteinogenic amino acids when inserted into peptides affect their conformations and biological activities. These include, among others, β-amino acids, α,α-disubstituted amino acids, α,β-dehydroamino acids and β-substituted amino acids. Several approaches are available for the synthesis of these compounds namely, amination of α-halo-acids, Strecker synthesis, multicomponent Ugi or Petasis reactions and addition reactions to dehydroamino acids.

Dehydroamino acids can be found in several yeasts and bacteria, in which they contribute with a catalytic role in the active sites of some enzymes, as well as in a variety of peptide antibiotics of bacterial origin that include the lantibiotics (nisin, epidermin, subtilin, gallidermin).[1] Since they affect both chemical reactivity and conformation, dehydroamino acids have been introduced into peptides for structure-function relationship studies and have also been used as linkers in solid phase peptide synthesis.[2] Another important application for dehydroamino acid derivatives is their use as substrates for the synthesis of new amino acids.[3] Owing to the wide variety of biological activities and uses found among the known compounds and also to the economical importance of many of them, α,β-dehydroamino acids are promising synthons for exploration of new compounds with new biological properties and applications. A key step to progress in this area is the production of α,β-dehydroamino acid derivatives suitable for incorporation into peptide sequences or, otherwise, a method for dehydration of appropriate peptidic precursors.

β-Substituted, α,α-disubstituted amino acids and α-aminoglycines can have biological activity, can be used in the synthesis of peptides more stable towards proteolytic degradation and also for introducing chemical diversity into bioactive peptides. Thus, several β-substituted alanines exhibit important biological activities: β-(pyrazol-1-yl)alanine has hypoglycaemic properties;[3] quisqualic acid possesses neuroexcitatory activity;[4] *S*-substituted cysteines have cytotoxic activity.[5] The β,β-dimethoxyalanine derivatives have been used in a variety of synthetic transformations namely, the synthesis of ifetroban, a cardiovascular drug and of several capreomycins and tuberactinomycins.[6] Pyrazines can be obtained from dehydroamino acids and are found in the luminescent chromophores of certain marine organisms, in cephalostatins which are powerful anticancer agents, and in foods as potent flavour components.[7] Pyrazinamide is one of the front agents against *M. Tuberculosis*.[8] 1,4-Dihydropyrazines are found in certain redox active biological molecules like flavin coenzymes and in certain marine luciferins.[9] These compounds are also interesting electron-donors in conducting charge transfer complexes. Certain dihydropyrazines such as 2,3-dihydro-5,6-dimethylpyrazine show DNA strand-breaking activity in plasmid[10] and tetrahydropyrazines have been used in the synthesis of a HIV protease inhibitor.[11] α-Aminoglycines are used in the synthesis of retro-inverso-peptides more stable towards proteolytic degradation.[12]

2. Synthesis of α,β-dehydroamino acid derivatives

2.1. Introduction

The main biosynthetic route to α,β-dehydroamino acid derivatives has been described as β-elimination reactions from precursors containing serine, cystein and threonine residues to give the corresponding dehydroalanine (ΔAla) and dehydroaminobutyric acid (ΔAbu) derivatives.[2a] Other possible biosynthetic routes to dehydroamino acid derivatives are the dehydration of *N*-hydroxyamino acids obtained by *N*-hydroxylation of amino acids or peptides and of α-hydroxyamino acids obtained by condensation of α-keto acids and amides or by direct oxidation of amino acids.[2a]

The chemical synthesis of α,β-dehydroamino acids and their derivatives has been attempted through several methods. Those that follow the biosynthetic routes involving elimination reactions of β-hydroxyamino acids, β-mercaptoamino acids and *N*-hydroxyamino acids are the most important. However, other methods can be used, namely, condensation reactions of α-ketoacids with amides or nitriles,[13] Hofmann degradation of α,β-diaminopropionyl residues,[14] reduction of α-azidoacrilates and α-azidocarboxilates[2c] and hydrolysis of unsaturated oxazolinones.[15]

2.2. Elimination reactions

Elimination reactions using β-substituted or α-amine substituted amino acids as starting materials have been the most widely used approach to the chemical synthesis of dehydroamino acid derivatives. For the synthesis of dehydroalanines and dehydroaminobutyric acids, serine and threonine have been the main substrates and several reactants have been used to promote elimination reactions. Thus, triphenylphosphine with diethylazodicarboxylate were used to dehydrate the methyl esters of *N*-acylserine and threonine, however, the yields were moderate (55%-69%) and led to a 1:1 mixture of *Z* and *E*-isomers in the case of the dehydroaminobutyric acid derivatives.[16] Higher yields could be obtained when the methyl esters of *N*-benzyloxycarbonylserine and threonine were treated with disuccinimido carbonate and triethylamine in acetonitrile.[17] The yields in dehydroalanine and dehydroaminobutyric acid derivatives were 90% and 70%, respectively, and in the case of the latter, the reaction was stereoselective towards the *Z*-isomer. Reaction of *N*-benzyloxycarbonylserine and threonine esters with diethyl chlorophosphate in the presence of sodium hydride in THF gave the corresponding *N*-benzyloxycarbonyldehydroamino acid esters in good yields.[18] This method is also stereoselective towards the *Z*-isomer of the dehydroaminobutyric derivative. Goodall and Parson used several haloacetyl chlorides and triethylamine to react with serine and threonine derivatives giving dehydroamino acids in yields from 39% to 89%, however the reaction was not stereoselective with the threonine derivatives.[19]

Dehydroalanine derivatives have also been obtained from cysteine. *N*-Acylcysteine derivatives suffer β-elimination reactions when treated with silver oxide (I), silver carbonate (I), mercury oxide (I) and ferric salts.[2a] Synthesis of *N*-(4-chlorobenzyloxycarbonyl) dehydroalanine has also been carried out by treatment of *N*-(4-chlorobenzyloxycarbonyl) cysteine with DCC.[20]

The elimination of *O*-arylsulfonate derivatives of β-hydroxyamino acids in the presence of a base has been used for the preparation of dehydroamino acids and dehydropeptides.[2a] Several side reactions occur, namely, formation of oxazolinones, aziridines and hydantoines, thus reducing the yield in the wanted products.

β-Halogenated amino acid derivatives have been used as precursors of dehydroamino acids, however in most cases the elimination reactions occur in drastic conditions.[2a]

Selective synthesis of *Z* and *E*-dehydroaminobutyric acid from L- and L-*allo*-threonine, respectively was carried out *via* the formation of a selenoether followed by oxidative elimination by treatment with hydrogen peroxide.[21]

N-Substituted amino acids can also suffer elimination to yield dehydroamino acid derivatives. Thus, *N*-chloroamino acids obtained by treatment of *C*-protected amino acids with *tert*-butylhypochlorite, eliminate hydrogen chloride in the presence of base giving rise to the corresponding enamine.[2c]

Treating *N*-hydroxyamino acids with triethylamine in dry benzene at room temperature for 24 hours gave dehydroamino acid derivatives.[22] The replacement of triethylamine for DBU significantly reduces the reaction time to approximately 1 hour.[23] Alkyl esters of *N*-acyl, *N*-hydroxyamino acids and *N*-acyl, *O*-acylhydroxyamino acids by treatment with triethylamine eliminate water and acid, respectively giving dehydroamino acids.[2c] Alkyl esteres of *N*-acyl, *N*-hydroxyamino acids can also be converted to dehydroamino acids by treatment with 4-toluenesulfonyl chloride and triethylamine.

Some of the above methods are usually low yielding, multistep processes requiring tedious purifications to remove side products. In the case of dehydroaminobutyric acid derivatives the work-up procedures can be complicated by the formation of two stereoisomers. Thus, there is still a need for developing simple and efficient approaches to these compounds.

2.3. Synthesis of *N,N*-diprotected dehydroamino acids

Our initial strategy for the synthesis of α,β-dehydroamino acids was based on Berkowitz and Pederson's method for simultaneous amine and carboxyl protection of amino acids with benzyl chloroformate in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine.[24] We found that under these conditions, serine undergoes elimination; the only product isolated being the corresponding fully protected dehydroalanine derivative (Z-ΔAla-OBzl, Table 1, **10**) in a yield of 51%.[25] Applying the same procedure to several amino acids protected either at their *N*-terminus with *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Z), 4-nitrobenzyloxycarbonyl [Z(NO_2)] and 4-toluenesulfonyl (Tos) (Table 1, **2**-**5**) or at both the *N*- and the *C*-terminus (Table 1, **6**), the yields in dehydroamino acid derivatives were within the range of 56-76% (Table 1, **11**-**13**).

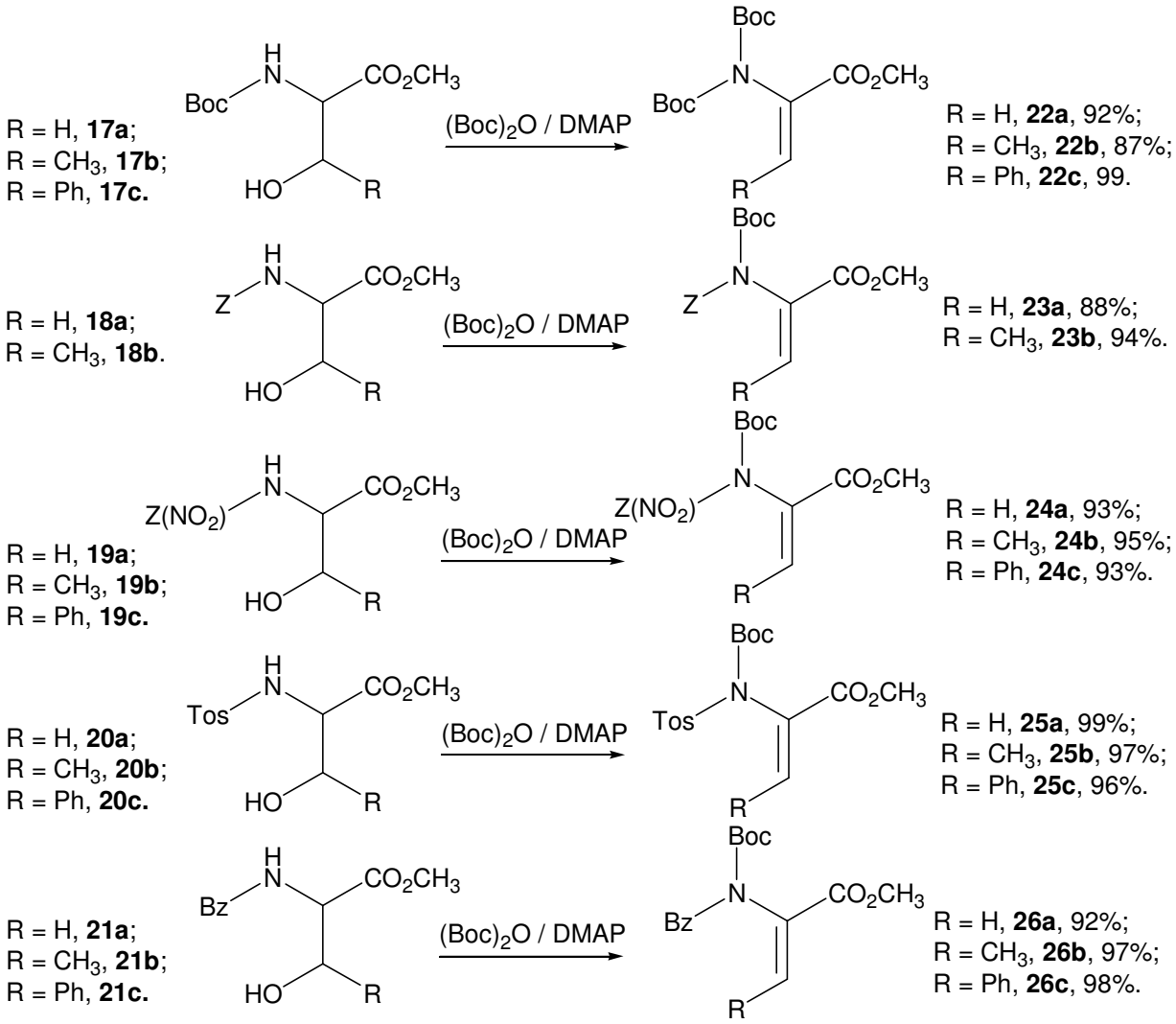
Table 1. Results obtained in the synthesis of dehydroalanine derivatives.[25]

Reagent	**Product**	**Yield / %**
H-Ser-OH, **1**	Z-ΔAla-OBzl, **10**	51
Boc-Ser-OH, **2**	Boc-ΔAla-OBzl, **11**	58
Z-Ser-OH, **3**	Z-ΔAla-OBzl, **10**	56
Z(NO_2)-Ser-OH, **4**	Z(NO_2)-ΔAla-OBzl, **12**	74
Tos-Ser-OH, **5**	Tos-ΔAla-OBzl, **13**	76
Tos-Ser-OBzl, **6**	Tos-ΔAla-OBzl, **13**	68
Z-Gly-Ser-OMe, **7**	Z-Gly-ΔAla-OMe, **14**	54
Z-Ala-Ser-OMe, **8**	Z-Ala-ΔAla-OMe, **15**	61
Z-Phe-Ser-OMe, **9**	Z-Phe-ΔAla-OMe, **16**	57

The method could also be applied to the dehydration of serine containing dipeptides (Table 1, **7**-**9**). With a threonine derivative, although all the starting material was consumed, we failed to obtain any pure product and NMR spectroscopy of the reaction mixture was consistent with the presence of two isomers of dehydroaminobutyric acid.

Nugent has patented a method for dehydration of *N*-acyl, β-hydroxyamino acid esters by treatment with an excess of acetic anhydride in the presence of pyridine.[26] In this reaction an acetyl group was introduced at the amide function to give the *N*-acetyl, *N*-acyldehydroamino acid esters. The second acyl group bonded to the nitrogen atom helps formation of the new double bond and the reported yields were approximately 60%. However, the product thus obtained is of limited value, once the acetyl group cannot be easily removed.[2b]

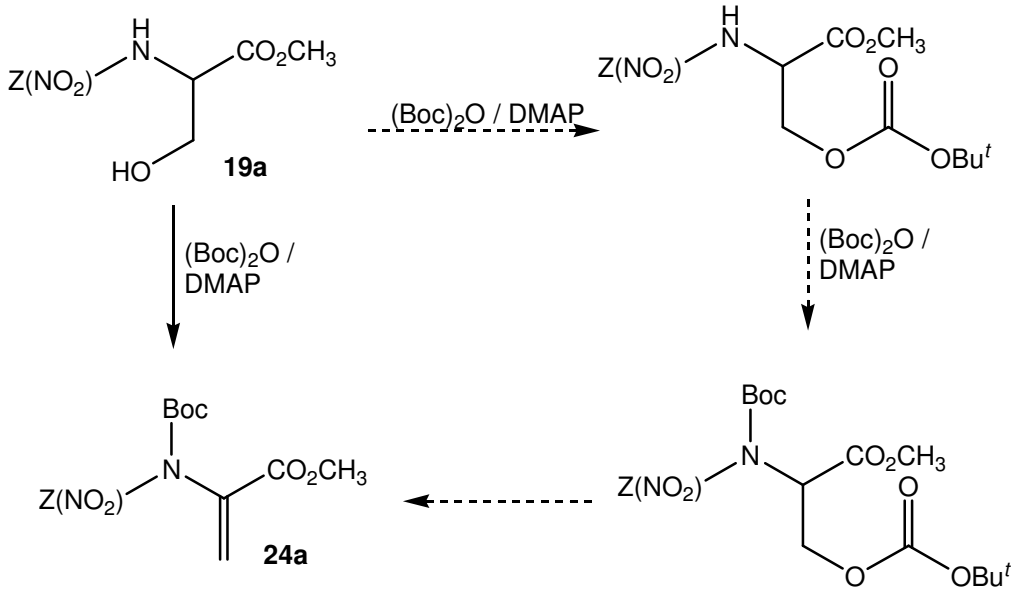
In view of these results, we considered introducing a more bulky second group at the nitrogen atom of the *N,C*-diprotected β-hydroxyamino acids in order to facilitate β-elimination and thus improve the reaction yields. The *tert*-butoxycarbonyl group is easily introduced by reaction of the previously *N*-protected amino acid with *tert*-butyl pyrocarbonate [$(Boc)_2O$] in the presence of DMAP as catalyst, according to Ragnarsson's method for *tert*-butoxylation of amides.[27] The reaction of β-hydroxyamino acids with *tert*-butyl pyrocarbonate in the presence of DMAP resembles significantly the method we had taken advantage of previously to prepare Z-ΔAla-OBzl (**10**).



Scheme 1

The use of two equivalents of $(Boc)_2O$ would thus suit both tasks, *i.e.* further acylation and dehydration. Thus serine, threonine or β-hydroxyphenylalanine methyl esters protected with one of the following groups: *tert*-butoxycarbonyl (Scheme 1, **17a**-**c**), benzyloxycarbonyl (Scheme 1, **18a**, **b**), 4-nitrobenzyloxycarbonyl (Scheme 1, **19a**-**c**), 4-toluenesulfonyl (Scheme 1, **20a**-**c**) and benzoyl (Scheme 1, **21a**-**c**) were reacted in dry acetonitrile with *tert*-butyl pyrocarbonate in the presence of DMAP as catalyst. In these conditions the only products isolated were the corresponding ΔAla [Scheme 1, **(22**-**26)a**], ΔAbu [Scheme 1, **(22**-**26)b**] or dehydrophenylalanine (ΔPhe) [Scheme 1, **22c**, **(24**-**26)c**] derivatives.[28]

The increased bulkiness created at the nitrogen atom assisted elimination during the dehydration step, giving as the only product isolated the corresponding dehydrated diacylamino acid ester in almost quantitative yields. By sampling the reaction mixture throughout the preparation of compound $Z(NO_2)$-ΔAla(*N*-Boc)-OMe (**24a**), it was found that the reaction proceeds with formation of a *tert*-butylcarbonate, which undergoes *β*-elimination to the final product after a *tert*-butoxycarbonyl group is bound to the amine function (Scheme 2).



Scheme 2

In an attempt to use a *N*-trityl serine derivative (Trt-Ser-OMe) as substrate for β-elimination, the only product obtained was Trt-Ser(*O*-Boc)-OMe. In this case, the steric hindrance of the trityl group prevented further reaction at the nitrogen atom. The absence of dehydration suggests that a second acyl group is essential as a driving force for elimination.

With both threonine and β-hydroxyphenylalanine derivatives (threo type) the reaction was stereoselective, giving only the *Z*-isomer. This selectivity seems again to result from the bulkiness of the groups bound to the nitrogen atom, which would force and thus facilitate a *trans* E_2-elimination. This is in agreement with results obtained by Srinivasan *et al.* who have reported that base induced *β*-elimination of *N*-acyl-DL-Thr(*O*-Tos)-OMe (threo type) proceeds *via* a *trans* E_2-elimination to give the *Z*-isomer.[29]

DMAP catalysed esterifications with dicarbonates have been described by Takeda *et al.*.[30] With the aim of simplifying our procedure by saving one of the two otherwise required protection steps, *N*-Boc serine and threonine derivatives having a free carboxyl function were reacted with 3 eq. of *tert*-butyl pyrocarbonate in the presence of DMAP. As expected, both dehydration and esterification occurred to give the *tert*-butyl

ester of the *N,N*-bis(*tert*-butoxycarbonyl) dehydroamino acid. However, the reactions were more sluggish and the yields slightly lower when compared to those of dehydration of the corresponding methyl or benzyl esters. We have also investigated the direct dehydration of the methyl ester of serine. The reaction of this amino acid derivative with 3 eq. of *tert*-butyl pyrocarbonate allowed the preparation of the *N,N*-bis(*tert*-butoxycarbonyl) dehydroalanine methyl ester in 82% yield.

The applicability of our methodology to the dehydration of peptides containing β-hydroxyamino acids was also investigated.[28b,31] Thus, dipeptides containing serine, threonine or β-hydroxyphenylanine in either the amine or the carboxyl terminus (Table 2, **27**-**36**) were reacted under the previously described conditions. In these reactions, 3 eq. of *tert*-butyl pyrocarbonate were used, *i.e.* 2 eq. for acylation of both amide nitrogen atoms and a third equivalent to generate the carbonate at the β-carbon atom. The yields in dehydrodipeptides (Table 2, **37**-**46**) were high and again, peptides containing threonine and β-hydroxy-phenylanine gave only one of the two possible geometric isomers. In the case of a dipeptide containing both threonine and serine (**35**) and of another containing two residues of threonine (**36**), simultaneous dehydration of both amino acid residues was achieved (**45** and **46**, respectively).

Table 2. Results obtained in the synthesis of dehydropeptide derivatives.[28b,31]

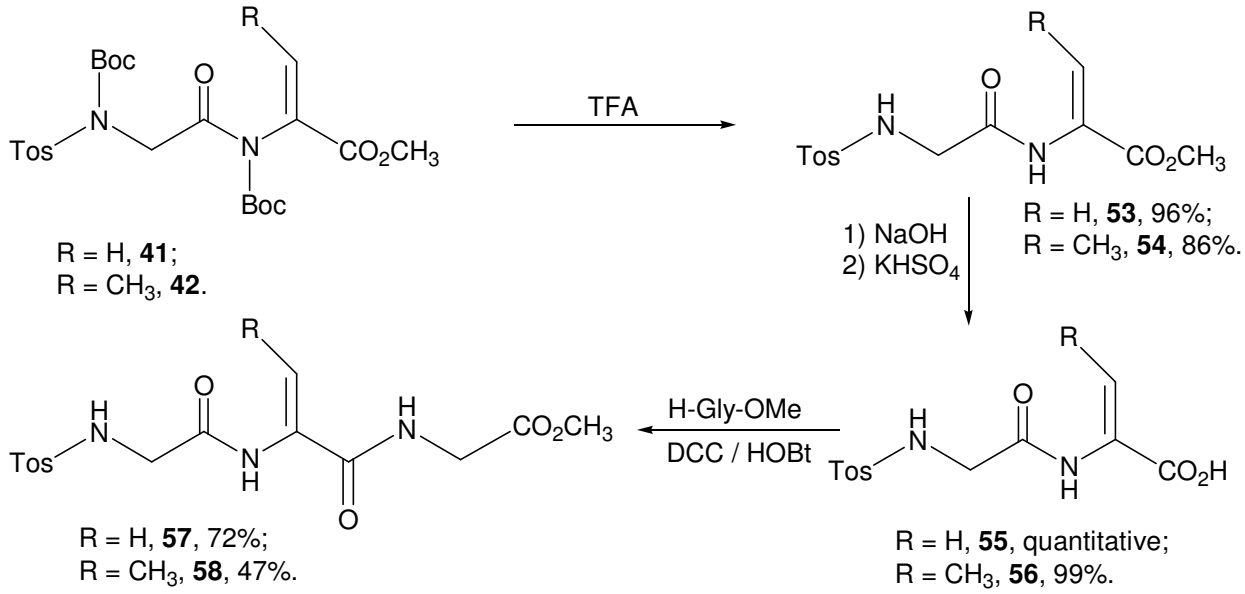
Reagent	Product	Yield / %
Z(NO_2)-Ser-Phe-OEt, **27**	Z(NO_2)-ΔAla(*N*-Boc)-Phe(*N*-Boc)-OEt, **37**	93
Boc-Ala-Ser-OMe, **28**	Boc-Ala(*N*-Boc)-ΔAla(*N*-Boc)-OMe, **38**	91
Z-Thr-Gly-OMe, **29**	Z-*Z*-ΔAbu(*N*-Boc)-Gly(*N*-Boc)-OMe, **39**	81
Boc-Ala-Thr-OMe, **30**	Boc-Ala(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **40**	84
Tos-Gly-Ser-OMe, **31**	Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe, **41**	96
Tos-Gly-Thr-OMe, **32**	Tos-Gly(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **42**	91
Boc-Gly-Thr-OMe, **33**	Boc-Gly(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **43**	82
Tos-Gly-Phe(β-OH)-OMe, **34**	Tos-Gly(*N*-Boc)-*Z*-ΔPhe(*N*-Boc)-OMe, **44**	96
Boc-Thr-Ser-OMe, **35**	Boc-*Z*-ΔAbu(*N*-Boc)-ΔAla(*N*-Boc)-OMe, **45**	83
Boc-Thr-Thr-OMe, **36**	Boc-*Z*-ΔAbu(*N*-Boc)-*Z*-ΔAbu(*N*-Boc)-OMe, **46**	74

All of the protecting groups used were intended to allow the investigation of their cleavage from dehydroamino acids using mild reaction procedures. One such method is electrolysis[32] which offers a clean, non-polluting alternative to the classical methods of reduction. Thus, both Z(NO_2) and Tos were selectively removed from compounds **24a**,**b** and **25a**,**b**, by electrolysis at controlled potential to give the methyl ester of the respective *N*-(*tert*-butoxycarbonyl)dehydroamino acid (**49**, **50**) in yields ranging from 73% to 88% (Table 3). However, when electrochemical equipment is not available selective cleavage can still be achieved by reduction with an appropriate metal.[33] Thus, the Z(NO_2) group was cleaved from compounds **24a** and **b** by selective reduction with mercury activated aluminum to give the methyl ester of the respective *N*-(*tert*-butoxycarbonyl)dehydroamino acid in high yields (**49**, **50**). Selective cleavage of the Boc group with trifluoroacetic acid (TFA) gave *N*-protected, *C*-protected dehydroamino acid derivatives (**47**, **48**). Saponification of the methyl esters allowed the preparation free carboxyl dehydroamino acid derivatives (**51**, **52**).

Table 3. Results obtained in selective cleavage of protecting groups from *N,N*-diprotected dehydroamino acid derivatives.[28b,31]

Reagent	Deprotecting method	Product	Yield / %
Z(NO_2)-ΔAla(*N*-Boc)-OMe, **24a**	e^-	Boc-ΔAla-OMe, **49**	88
Z(NO_2)-*Z*-ΔAbu(*N*-Boc)-OMe, **24b**	e^-	Boc-*Z*-ΔAbu-OMe, **50**	88
Tos-ΔAla(*N*-Boc)-OMe, **25a**	e^-	Boc-ΔAla-OMe, **49**	73
Tos-*Z*-ΔAbu(*N*-Boc)-OMe, **25b**	e^-	Boc-*Z*-ΔAbu-OMe, **50**	78
Z(NO_2)-ΔAla(*N*-Boc)-OMe, **24a**	Al/Hg	Boc-ΔAla-OMe, **49**	87
Z(NO_2)-*Z*-ΔAbu(*N*-Boc)-OMe, **24b**	Al/Hg	Boc-*Z*-ΔAbu-OMe, **50**	95
Z(NO_2)-*Z*-ΔAbu(*N*-Boc)-OMe, **24b**	TFA	Z(NO_2)-*Z*-ΔAbu-OMe, **47**	85
Z-*Z*-ΔAbu(*N*-Boc)-OMe, **23b**	TFA	Z-*Z*-ΔAbu-OMe, **48**	87
Z(NO_2)-*Z*-ΔAbu-OMe, **47**	NaOH	Z(NO_2)-*Z*-ΔAbu-OH, **51**	78
Z-*Z*-ΔAbu-OMe, **48**	NaOH	Z-*Z*-ΔAbu-OH, **52**	77

The *C*-deprotected dehydroamino acid derivatives could be coupled with *C*-protected amino acids to give *N,C*-diprotected dehydrodipeptides. Saponification of *N,C*-diprotected dehydrodipeptides and subsequent coupling with a *C*-protected amino acid derivative gave *N,C*-diprotected dehydrotripeptides (Scheme 3, **57**, **58**).[31]



Scheme 3

3. *N,N*-Diprotected dehydroamino acids as precursors of novel amino acid derivatives

3.1. Introduction

Non-natural amino acids can show pharmacological activities and can also be used to reduce the rates of degradation of several pharmaceuticals in living organisms. Dehydroamino acid derivatives are versatile synthetic precursors since they can be readily transformed into various natural and non-natural amino acids due to the presence of a double bond.

Although Michael addition is one of the most powerful and widely used synthetic tools, there are only a few reports on Michael addition of nucleophiles to dehydroamino acids. The limited use of these

compounds in Michael addition can be assigned mainly to the fact that dehydroamino acids are only fairly reactive Michael acceptors.

Zahn has reported a 96.5% yield in the synthesis of a β-substituted alanine by the addition of N^{α}-acetyl-L-lysin to the ethyl ester of *N*-acetyldehydroalanine in the presence of sodium hydroxide.[34] Morin and Labia prepare a α,β-diaminopropionic acid derivative in a 55% yield by reacting a dehydroalanine with an excess of benzylamine in methanol.[35] The preparation of cysteine derivatives by sulfenylation using P_4S_{10} in benzene at reflux of *N*-formyldehydroamino acid esters was described by Hruby *et al.*.[36] Moore *et al.* reported the synthesis of a β,β-dialkylcysteine derivative in 80% yield by a Michael addition of 4-methylbenzylmercaptan to a dehydroamino acid unit using a catalytic amount of sodium hydride in toluene.[37] Michael additions of nitrogen nucleophiles to dehydroalanine derivatives using $FeCl_3$ as catalyst have been reported, giving various β-substituted alanine derivatives in yields varying within the range of 13-98%.[38] A orthogonally protected lanthionine derivative was prepared *via* Michael addition of a fully protected cysteine to a dehydroalanine derivative using cesium carbonate as base in acetonitrile (80% yield).[39]

Addition reactions using as substrate the methyl ester of *N*-acetyldehydroalanine and as nucleophiles pyrazole and 1,2,4-triazole in the presence of an inorganic base gave the corresponding β-substituted alanine in 54% and 78% yield, respectively.[40] In order to circumvent difficulties met in attempted solution synthesis, namely difficult purification of the products due to similarity of their solubility to that of the corresponding starting materials, a solid phase strategy was used. Thus, *N*-acetyldehydroalanine was anchored to a Wang resin and reacted with nucleophiles in the presence of potassium carbonate under forcing conditions (6 to 15 eq. of nucleophile were used in 2-day reactions at temperatures within the range 50-60 °C).[40] *N*-Acetyl, β-substituted alanine salts were prepared in good yields by treatment of methyl 2-acetamidoacrylate with several nitrogen heterocycles in the presence of an inorganic base at 60 ºC.[41]

Naidu *et al*. found that the rate of Michael addition of thiols and amines to dehydroalanine amides was greatly accelerated in water. The authors used this method to prepare several β-substituted alanines in good to high yields.[42]

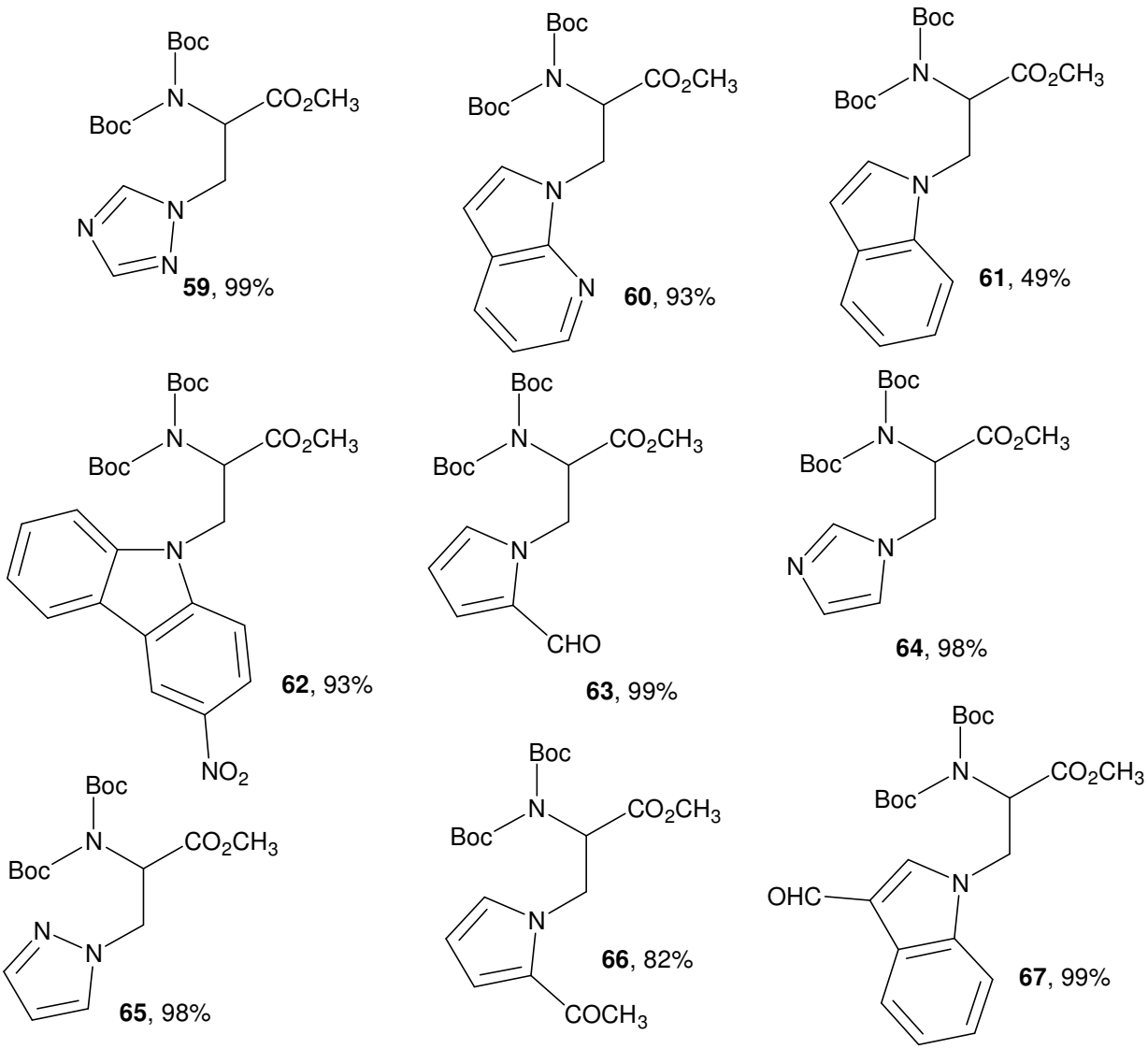
The enantioselective rhodium-catalysed conjugate addition of aryl boronic acids to dehydroalanine derivatives was successfully carried out in the presence of C_2-symmetric aryl diphosphite ligands.[43] This type of reaction can be performed in water with low catalyst loading.[44] Darses and Genet prepared several β-substituted alanines by reacting the methyl ester of *N*-acetyldehydroalanine with potassium trifluoro(organo)borates which are highly stable and easily prepared in the presence of rhodium complexes.[45] The same authors introduced enantioselectivity to this reaction using BINAP as a chiral ligand and guaiacol as a proton donor. The preparation of β-substituted alanines from dehydroalanines and trifluoro(organo)borates was accomplished with enantioselectivities of up to 90%.[46]

Chen *et al.* reported the synthesis of β-benzylsulfanyl-β-trifluoromethyl-α-amino acid esters with moderate to good diastereoselectivies from *Z*-β-substituted-β-trifluoromethyl-α,β-dehydroamino acid esters *via* a Michael addition in the presence of Et_3N and LiBr which acted as a bifunctional catalyst.[47]

3.2. Synthesis of β-substituted amino acids

The high yielding synthesis of *N*,*N*-disubstituted dehydroamino acids developed by us made these compounds available in large amounts and ready for further applications.[28a-b] It was possible to use these

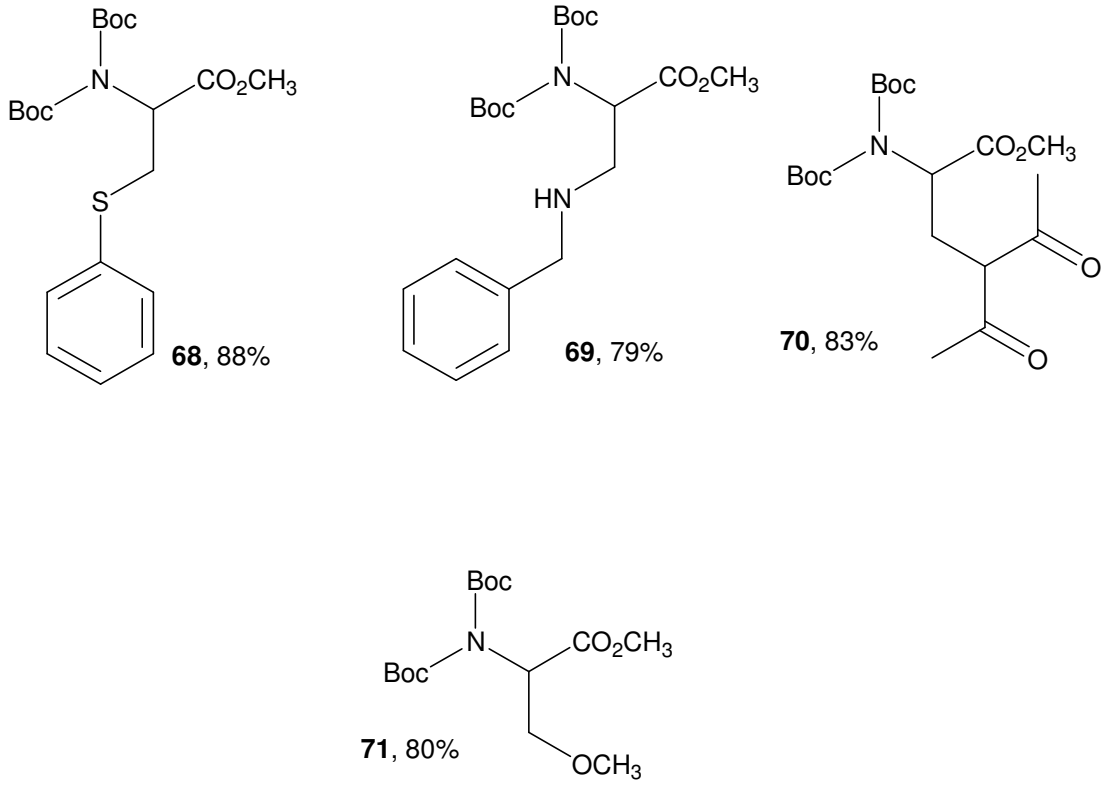
compounds successfully as substrates in Michael addition reactions, since the presence of two substituents at the nitrogen atom greatly increases the reactivity of the β-carbon atom of the dehydroamino acids towards nucleophilic attack. This allowed the use of one equivalent of nucleophile which simplifies the work-up procedures. Thus, using as substrate the methyl ester of *N*,*N*-bis(*tert*-butoxycarbonyl)dehydroalanine (**22a**) and as nucleophiles nitrogen heterocycles we were able to prepare β-heterocyclic alanines (Scheme 4, **59**-**67**).



Scheme 4

It was possible to observe a correlation between the reaction yields and the chemical shift of the nitrogen protons of the heterocycles. Some of the compounds obtained are analogues of tryptophan and histidine. Using as nucleophiles thiols, amines, carbon nucleophiles of the β-dicarbonyl type and oxygen nucleophiles we were able to prepare several other β-substituted alanines in good to high yields (Scheme 5, **68**-**71**).[48] This reaction was also investigated with several dehydroalanine derivatives having unsymmetrical double substitution at their nitrogen atom. In many cases, specially with the 4-nitrobenzoyl group, a large amount of the methyl ester of *N*-*tert*-butoxycarbonyl dehydroalanine (**49**) was detected in the reaction mixture. This may result from competitive nucleophilic cleavage of the substituents at the nitrogen atom of the dehydroalanine derivative in a manner similar to that described by Ragnarsson *et al.*.[49] Cleavage of the protecting groups was carried out. Thus, the Boc groups were easily removed from the *N*,*N*-diprotected,

β-substituted alanine methyl esters (Table 4, **59**, **60**, **72**) by treatment with TFA, the benzoyl group was removed using 2-(diethylamino)-ethylamine (DEAEA) (**73**) or *N,N,N',N'*-tetramethylguanidine (TMG) (**74**) while 4-nitrobenzyloxycarbonyl and 4-nitrobenzoyl were cleaved by reduction with mercury activated aluminum (**75** and **76**, respectively).[48] Saponification of the *N,N*-bis(*tert*-butoxycarbonyl) amino acid methyl esters (**59**, **60**, **65**, **67**) gave the corresponding *N,N*-bis(*tert*-butoxycarbonyl) amino acids (Table 4, **82**-**85**).[48]

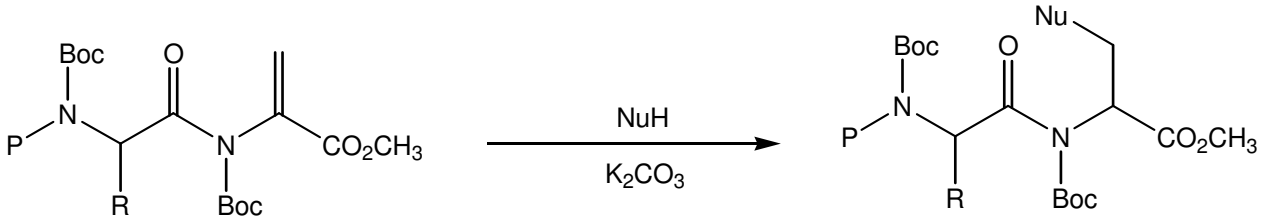


Scheme 5

Table 4. Yields in the selective cleavage of heterocyclic β-substituted alanine derivatives.[48]

Substrate	Deprotection reactant	Product	Yield %
Boc-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **59**	**TFA**	H-Ala[β-(1,2,4-triazol-1-yl)]-OMe.2TFA, **77**	80
Boc-Ala[*N*-Boc, β-(7-azaindol-1-yl)]-OMe, **60**	**TFA**	H-Ala[β-(7-azaindol-1-yl)]-OMe .TFA, **78**	85
Boc-Ala[*N*-Boc, β-(carbazol-9-yl)]-OMe, **72**	**TFA**	H-Ala[β-(carbazol-9-yl)]-OMe .TFA, **79**	91
Bz-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **73**	**DEAEA**	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe, **80**	78
Bz-Ala[*N*-Boc, β-(7-azaindol-1-yl)]-OMe, **74**	**TMG**	Boc-Ala[β-(7-azaindol-1-yl)]-OMe, **81**	74
Z(NO_2)-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **75**	**Al/Hg**	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe, **80**	86
Bz(NO_2)-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **76**	**Al/Hg**	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe, **80**	58
Boc-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OMe, **59**	**NaOH**	Boc-Ala[*N*-Boc, β-(1,2,4-triazol-1-yl)]-OH, **82**	86
Boc-Ala[*N*-Boc ,β-(7-azaindol-1-yl)]-OMe, **60**	**NaOH**	Boc-Ala[*N*-Boc, β-(7-azaindol-1-yl)]-OH, **83**	94
Boc-Ala[*N*-Boc, β-(pyrazol-1-yl)]-OMe, **65**	**NaOH**	Boc-Ala[*N*-Boc, β-(pyrazol-1-yl)]-OH, **84**	91
Boc-Ala[*N*-Boc, β-(3-formylindol-1-yl)]-OMe, **67**	**NaOH**	Boc-Ala[*N*-Boc, β-(3-formylindol-1-yl)]-OH, **85**	89

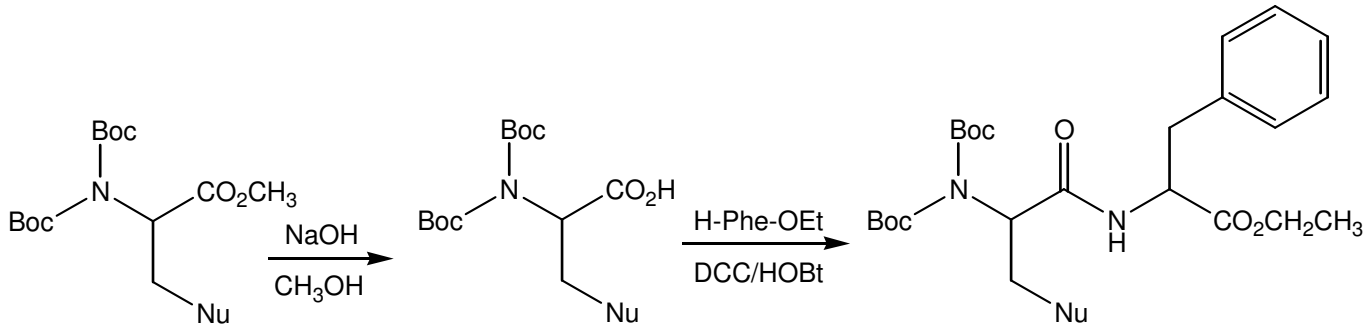
Using as substrates dehydrodipeptides containing dehydroalanine residues, it was possible to obtain several dipeptides containing β-substituted alanines in good to high yields (Scheme 6, **86**-**91**).[48]



P = Tos, R = H, Nu = 1,2,4-triazole, **86**, 76%;
P = Boc, R = CH_3, Nu = 1,2,4-triazole, **87**, 98%;
P = Tos, R = H, Nu = 7-azaindole, **88**, 90%;
P = Tos, R = H, Nu = thiophenol, **89**, 87%;
P = Tos, R = H, Nu = benzylamine, **90**, 53%;
P = Tos, R = H, Nu = 1,3-cyclohexadione, **91**, 60%.

Scheme 6

The synthesis of dipeptides containing β-heterocyclic alanines was also accomplished by cleavage of the methyl ester followed by coupling with an amino acid ester (Scheme 7, **92**, **93**).[31]



Nu = 7-azaindol-1-yl, **60**, 94%;
Nu = pyrazol-1-yl, **65**, 91%.

Nu = 7-azaindol-1-yl, **83**, 94%;
Nu = pyrazol-1-yl, **84**, 91%.

Nu = 7-azaindol-1-yl, **92**, 86%;
Nu = pyrazol-1-yl, **93**, 80%.

Scheme 7

The *N*,*N*-diprotected dehydroaminobutyric acid derivatives, due to the β-substitution, are poorer Michael acceptors when compared with dehydroalanine. It was found that these compounds only react with the stronger nucleophiles such as imidazole and 1,2,4-triazole giving in considerably lower yields the corresponding β-triazol-1-yl and β-imidazol-1-yl aminobutyric acid derivatives as 1:1 diastereomeric mixtures. The dehydrophenylalanine derivatives showed an even lower reactivity and no addition product were obtained using Boc-ΔPhe(*N*-Boc)-OMe (**22c**) and Bz-ΔPhe(*N*-Boc)-OMe (**26c**) as substrates.[48]

The possibility of activating *N*-acyldehydroalanines by electrochemical reduction at an appropriate potential and thus converting them into nucleophiles which could attack other molecules of *N,N*-diacyldehydroalanines was investigated. Thus, the activation potentials of several *N*-acyl- and *N,N*-diacyldehydroamino acid derivatives were determined by cyclic voltammetry and compared with those for the respective β-hydroxyamino acid derivatives (Table 5).[50]

Table 5. Peak potentials obtained by cyclic voltammetry of amino acid and dehydroamino acid derivatives.[50]

	-*Ep* (V *vs* S.C.E.)[a]				
P	**Z(NO_2)**	**Bz**	**Tos**	**Z**	**Boc**
Compound					
P-Thr-OMe	1.14	2.36	2.50	2.82	[b]
P-Ser-OMe	1.04	2.42	2.48	2.86	[b]
P-Phe(β-OH)-OMe	1.08	2.38	2.53		[b]
P-ΔAbu-OMe	0.97	2.21	2.18	2.34	2.46
P-ΔAla-OMe	1.10	1.91	1.90	2.29	2.12
P-ΔPhe-OMe	1.12	1.87	1.65		1.84
P-ΔAbu(*N*-Boc)-OMe	1.02	2.02	2.12	2.19	2.36
P-ΔAla(*N*-Boc)-OMe	1.04	1.84	1.88	2.04	2.01
P-ΔPhe(*N*-Boc)-OMe	1.02	1.80	1.74		1.84

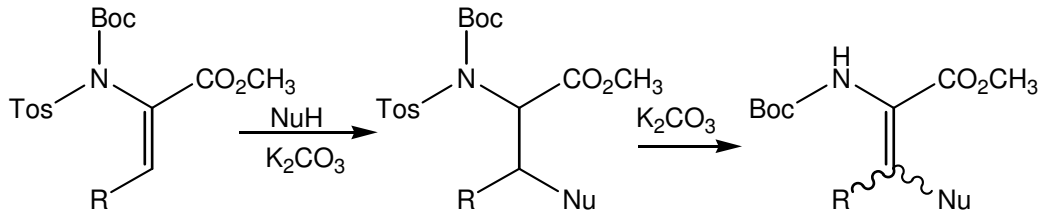
[a] Cathode: vitreous carbon. Solvent: dimethylformamide. Supporting electrolyte: Bu_4NBF_4 0.1 mol dm^{-3}. Substrate conc.: ≈0.005 mol dm^{-3}.
[b] No reduction peak was detected.

The peak potentials found with all the Z(NO_2) amino acid derivatives investigated fell within a fairly narrow range (0.15 V); the reduction potential of this group is not affected by the neighbourhood of either a *tert*-butoxycarbonyl group or a double bond. However, this was not the case of both benzoyl and 4-toluenesulfonyl dehydroamino acid derivatives, which exhibit reduction potentials shifted to significantly less negative values than those of the corresponding β-hydroxyamino acid compounds. We assign this behaviour to stabilisation of the radical anion by conjugation of the aromatic ring of these two groups with the α,β-double bond and with the Boc carbonyl group. This effect is enhanced in the dehydrophenylalanine series by further conjugation with the amino acid β-phenyl ring and markedly weakened in the dehydroaminobutyric acid series, certainly due to the electron donating effect of the β-methyl group. All cyclic voltammograms were consistent with irreversible processes occurring after formation of the radical anions, and previous results obtained in electrolyses of Z(NO_2) and Tos in *N,N*-diacyl-dehydroalanine and dehydroaminobutyric acid derivatives showed that these two protecting groups undergo cleavage at the peak potentials listed in Table 5.[28b] However, cyclic voltammograms for dehydroamino acids mono and diacylated with Boc showed peak potentials between –1.84 and –2.46 V *v*s S.C.E. Since this group is stable to electrochemical reduction,[51] the irreversible voltammograms found for these compounds could not be related to cleavage of Boc. In addition, once the aromatic ring of Z is not conjugated with the rest of the molecule, potential shifts of 0.63 V or more would be related to the α,β-double bond in conjugation with at least two carbonyl groups, and not to the protecting group.

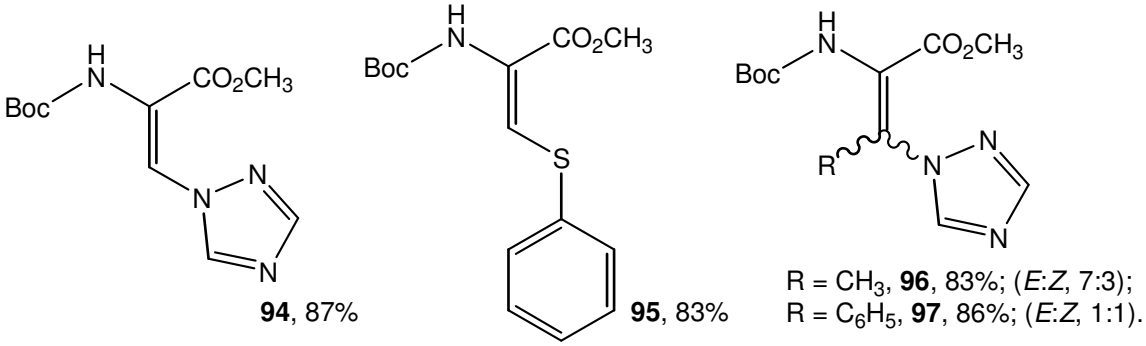
Controlled potential electrolysis of Boc-ΔAla(*N*-Boc)-OMe (**22a**) and Z-ΔAla(*N*-Boc)-OMe (**23a**) at the peak potentials indicated in Table 5 were carried out. With both substrates, a 2,5-diaminoadipic acid derivative was isolated as diastereomeric mixtures in yields of 85% and 78%, respectively.[50] We believe that the reaction proceeds *via* formation of a carbanion at the β-carbon atom, which acts as a nucleophile and adds to a molecule of the starting material. This is supported by the fact that no such reaction occurred with Boc-ΔAla-OMe (**49**) and Boc-ΔPhe(*N*-Boc)-OMe (**22c**), which are known not to be sufficiently strong electrophiles to undergo nucleophilic attack.

3.3. Synthesis of β-substituted dehydroamino acids

When *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroamino acids (**25a**-**c**) were reacted with nitrogen heterocycles and thiols the corresponding Michael addition products were obtained. However, these underwent elimination of 4-toluenesulfinic acid giving the corresponding β-substituted dehydroamino acid derivatives in good to high yields (Scheme 8, **94**-**97**). In the case of dehydroalanines the reaction is stereoselective for the *E*-isomer. With the dehydroaminobutyric acid and dehydrophenylalanine derivatives mixtures of the *E* and *Z*-isomers were obtained (Scheme 8).[48c,52]



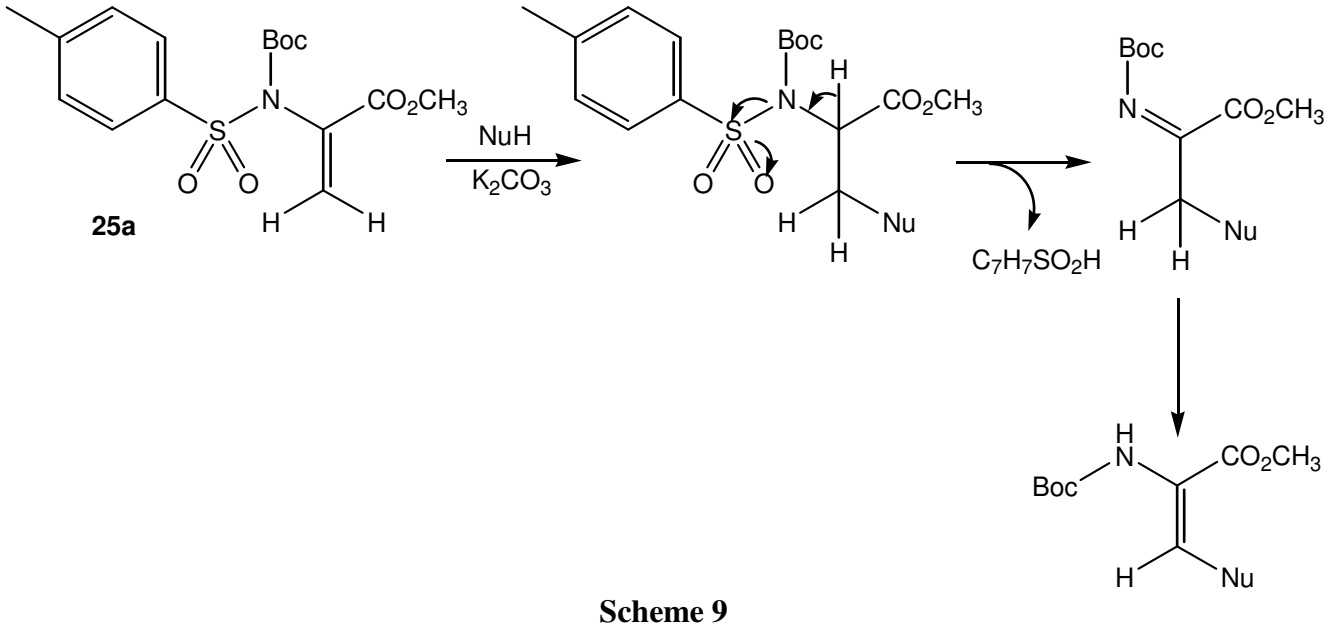
R = H, **25a**; CH_3, **25b**; C_6H_5, **25c**.
NuH = nitrogen heterocycles and thiols.



R = CH_3, **96**, 83%; (*E*:*Z*, 7:3);
R = C_6H_5, **97**, 86%; (*E*:*Z*, 1:1).

Scheme 8

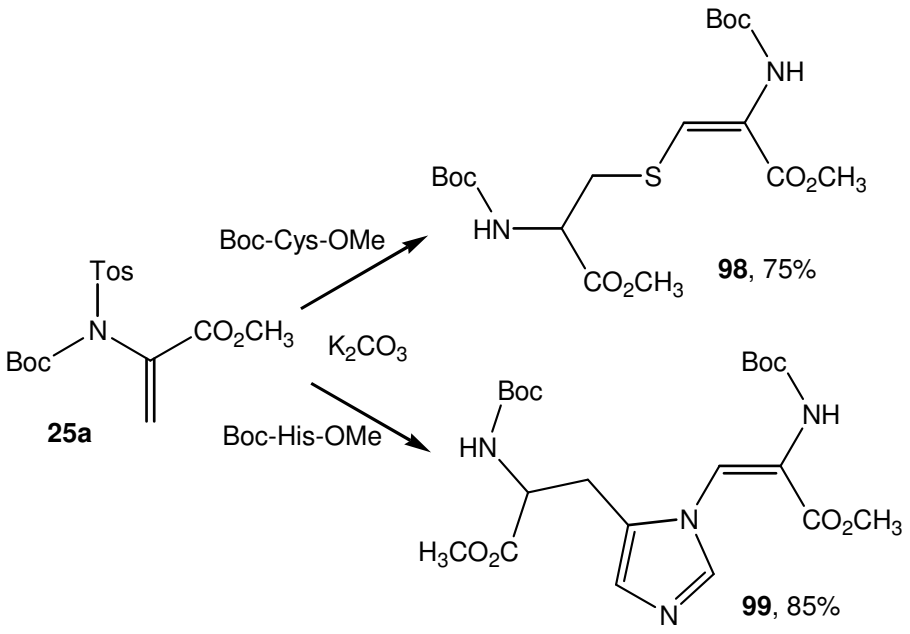
We propose a mechanism for this reaction that involves the elimination from the addition products of the 4-toluenesulfonyl group followed by regeneration of the α,β-double bond (Scheme 9).[48c]



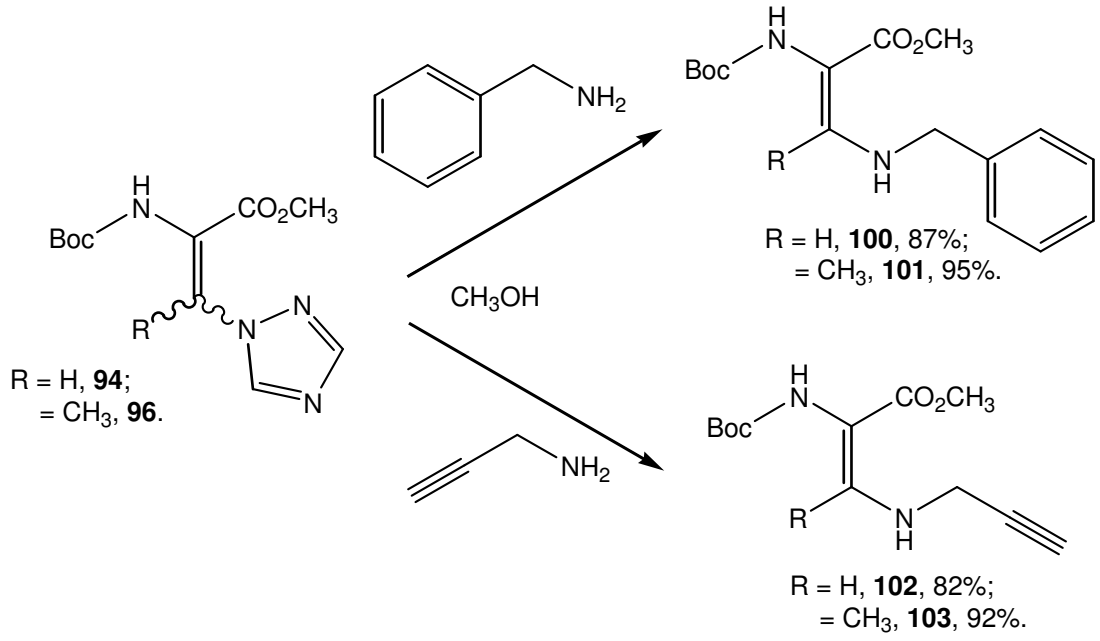
Scheme 9

Using amines as nucleophiles the only products obtained were the corresponding β-substituted alanines. Carbon nucleophiles of the β-dicarbonyl type, such as, diethyl malonate or 1,3-cyclohexadione react with the methyl ester of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine (**25a**) to give β-substituted alanines. Thus, the mechanism proposed in Scheme 9 does not explain why this reaction only occurs with nitrogen heterocycles and thiols and, up until now, the reason for this is not yet clear to us. With carbon nucleophiles having at least one methyl group attached to one of the carbonyl groups, a different reactivity is observed and described later in this review.

The reactivity of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine (**25a**) towards nitrogen heterocycles and thiols was used to synthesize in high yields cross-linked amino acids namely, histidino-α,β-dehydroalanine and dehydrolanthionine derivatives (**98** and **99**, respectively) using as nucleophiles *N*,*C*-diprotected derivatives of histidine and cysteine, respectively (Scheme 10).[53]



Scheme 10

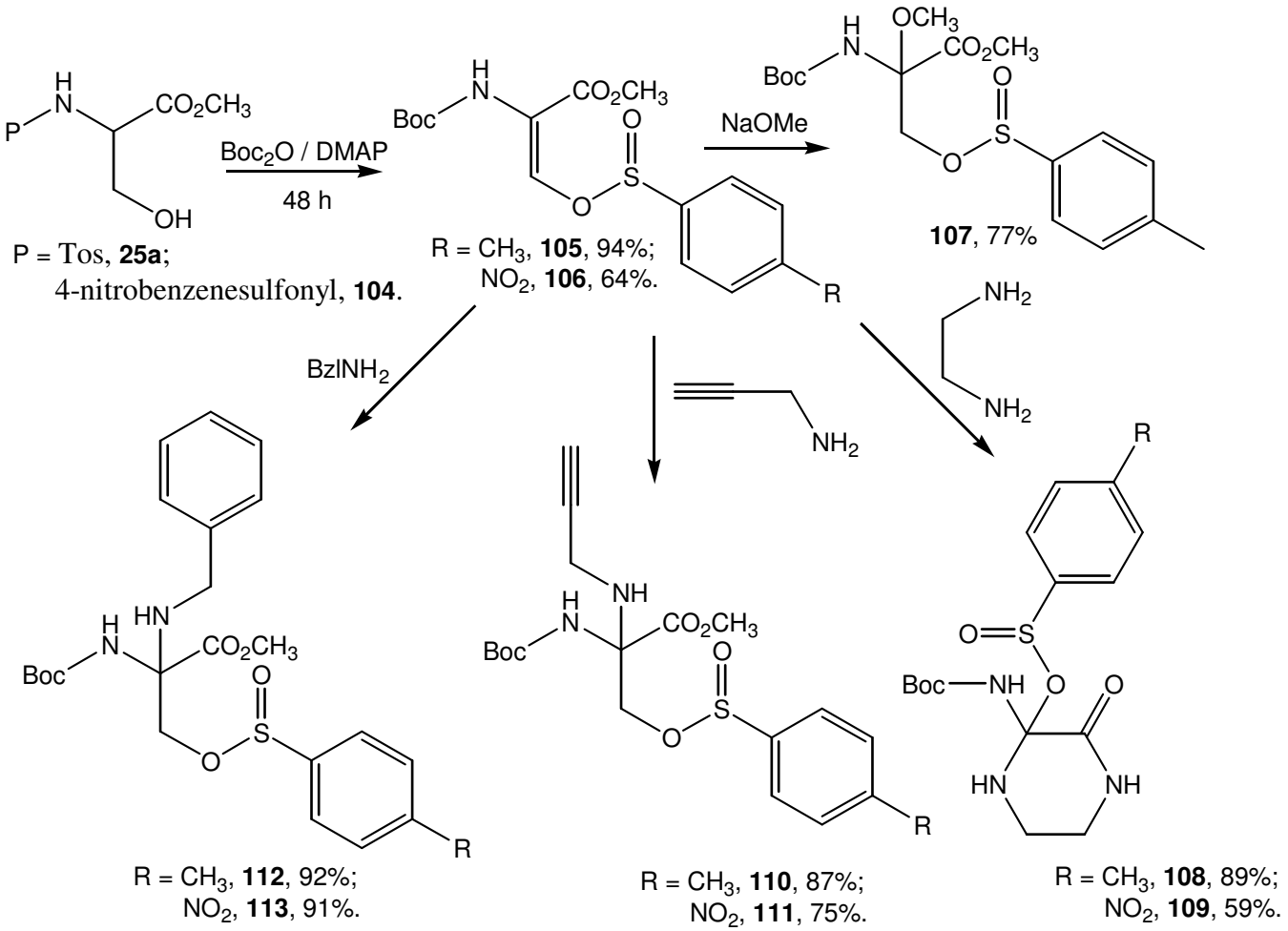


Scheme 11

As referred above, the reaction of compound **25a** with primary amines affords β-substituted alanines. However, the preparation of β-aminodehydroalanines could be carried out by reacting a β-heterocyclic dehydroalanine namely the methyl ester of *N*-(*tert*-butoxycarbonyl), β-(1,2,4-triazol-1-yl)dehydroalanine (**94**) with amines in methanol (Scheme 11, **100** and **102**).[53,54] The same reaction was applied to the dehydroaminobutyric acid derivative (**96**) thus allowing the synthesis of β-aminodehydroaminobutyric acid derivatives (Scheme 11, **101** and **103**). The β-(1,2,4-triazol-1-yl)dehydrophenylalanine (**97**) does not react with amines, possibly due to stabilization of the substrate through conjugation with the aromatic ring.

3.4. Synthesis of α,α-disubstituted amino acids

The methyl esters of *N*-(4-toluenesulfonyl) or *N*-(4-nitrobenzenesulfonyl), *N*-(*tert*-butoxy-carbonyl)dehydroalanine (Scheme 12, **25a** and **104**, respectively) in the presence of base undergo a rearrangement to give the *E*-isomer of *O*-(4-toluenesulfinyl) or *O*-(4-nitrobenzenesulfinyl) dehydroserine derivatives (**105** and **106**, respectively).[53,54] When these compounds were treated with amines and oxygen nucleophiles, addition to the α-carbon occurs to give the corresponding α-substituted, *O*-(arenesulfinyl)serine (Scheme 12, **107**-**113**).

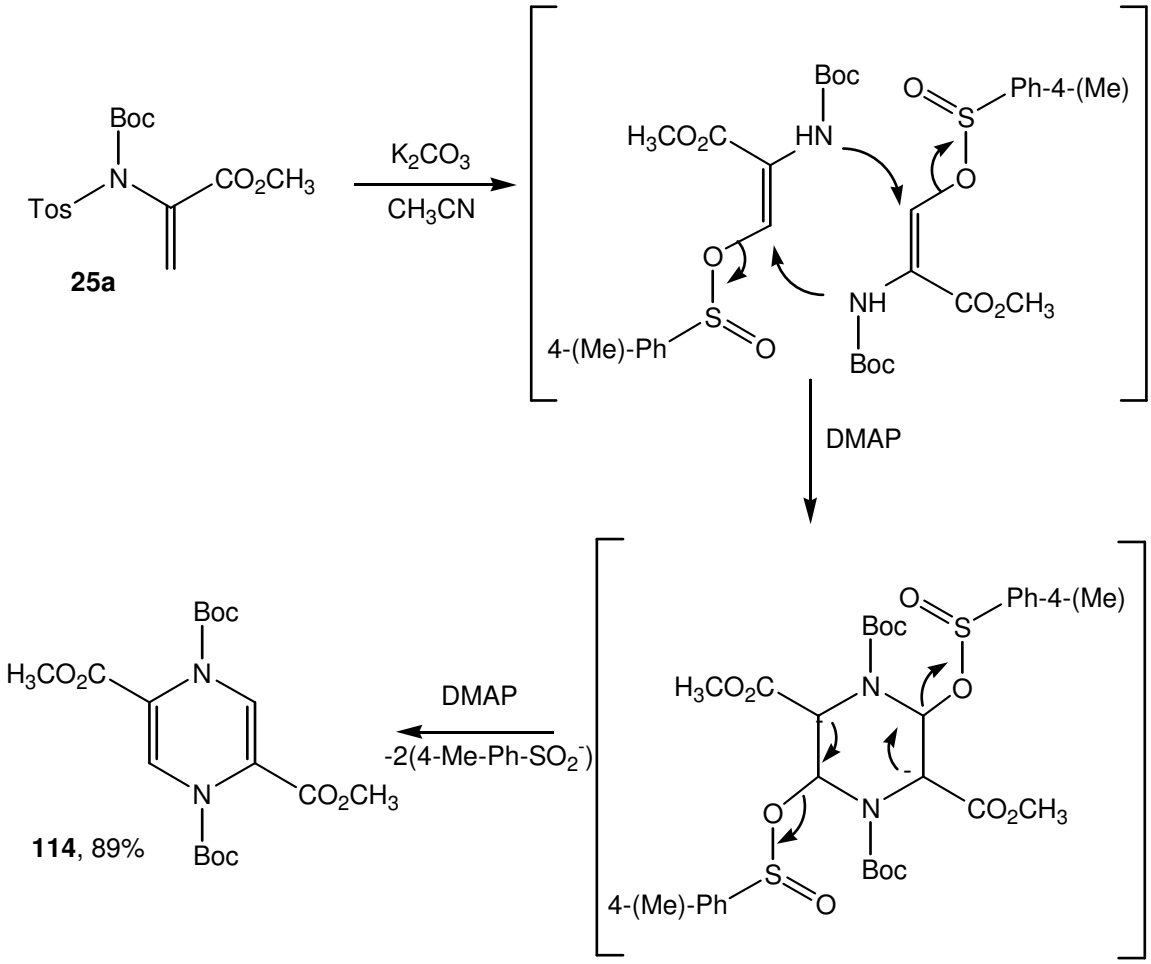


Scheme 12

The strong electron withdrawing effect of the sulfinyl group increases the electrophilic character of the α-carbon atom, when compared with the β-carbon atom, making the former more susceptible to nucleophilic attack. The reaction with 1,2-ethylenediamine gave a piperazine derivative resulting from addition to α-

carbon atom followed by an intramolecular aminolysis (**108**, **109**). However, it was found that the reaction of the *O*-(4-toluenesulfinyl)dehydroserine (**105**) with nitrogen heterocycles and thiols gives by substitution of the *O*-toluenesulfinyl group the corresponding β-substituted dehydroalanines. The same reactivity was observed for the methyl ester of *N*-(4-nitrobenzenesulfonyl), *N*-(*tert*-butoxycarbonyl) dehydroalanine (**106**).[53,54]

A 1,4-dihydropyrazine derivative (Scheme 13, **114**) was obtained reacting the methyl ester of *N*-*tert*-butoxycarbonyl, *O*-(4-toluenesulfinyl)dehydroserine (**105**) with DMAP and potassium carbonate in acetonitrile according to Scheme 13.[55] The presence of electron-withdrawing substitutents on the *N,N*-bis(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine (**114**) has a stabilizing effect which allowed the preparation and isolation of this compound.

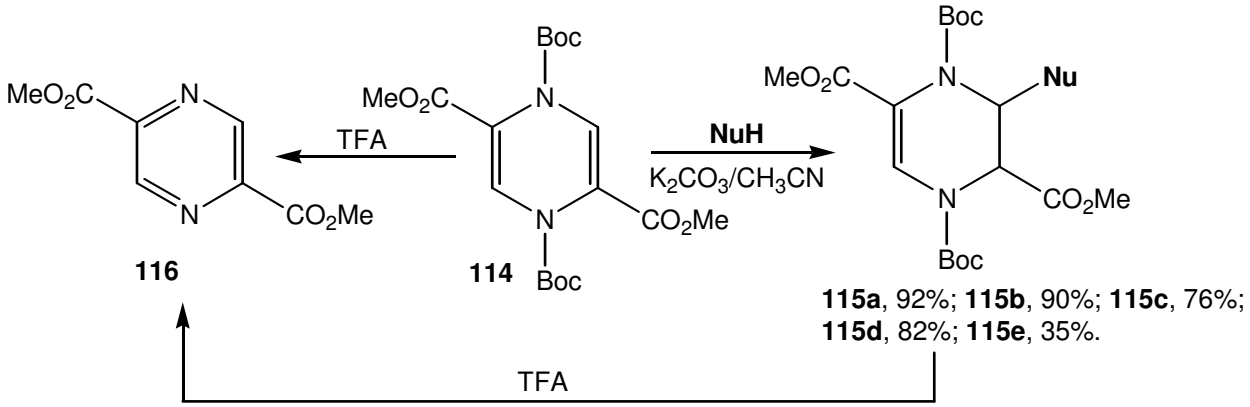


Scheme 13

Using this dihydropyrazine derivative as substrate it was possible to obtain tetrahydropyrazines and a pyrazine. Thus, the reaction of compound **114** with nucleophiles gave 3-substituted, *N,N*-bis(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazines (Scheme 14, **115a**-**e**). The removal of the *tert*-butoxycarbonyl groups with TFA from **114** gave the pyrazine derivative **116** in a 71% yield.[55]

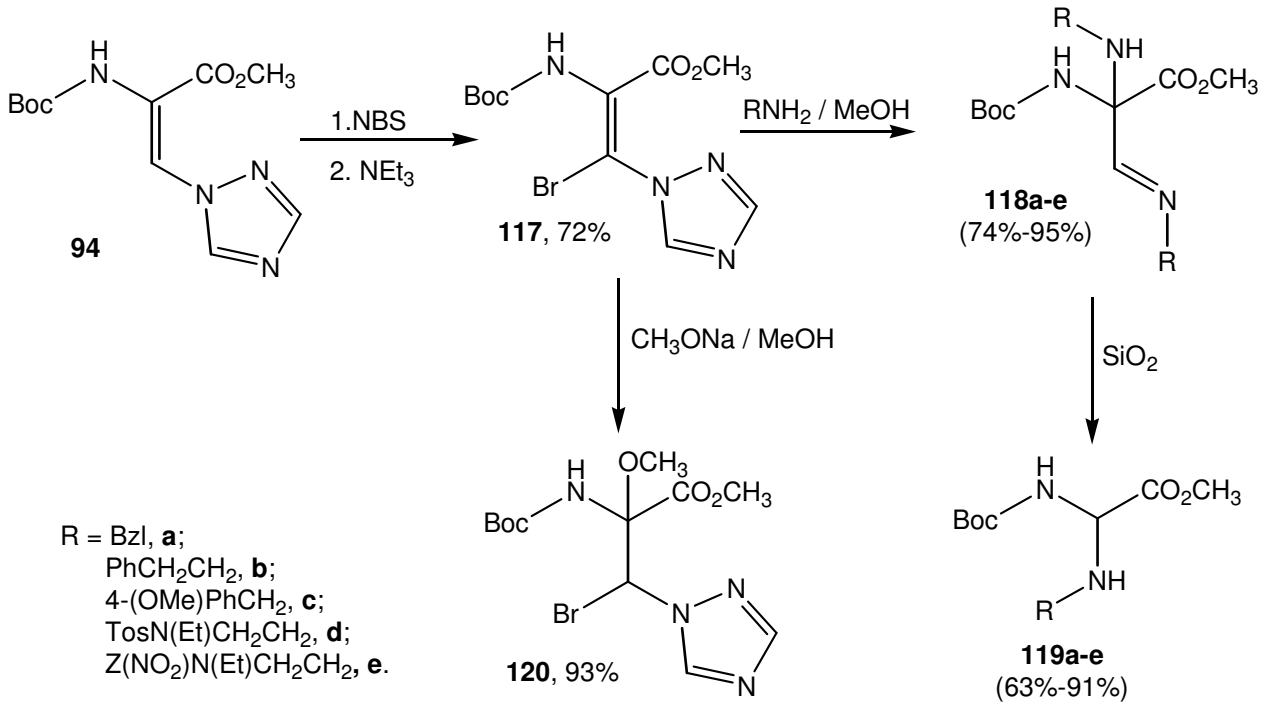
A β-heterocyclic dehydroalanine derivative namely the methyl ester of *N*-(*tert*-butoxycarbonyl), *Z*-β-bromo-β-(1,2,4-triazol-1-yl)dehydroalanine (Scheme 15, **117**) reacts with amines in methanol to give, after α-addition, β-substitution and β-elimination, α-alkylamino-β-alkyliminoalanines in high yields (**118a**-**e**).[56]

Compound **117** was prepared from a β-(1,2,4-triazol-1-yl)dehydroalanine derivative (**94**) by reaction with *N*-bromosuccinimide (NBS), followed by treatment with Et_3N. The α-alkylamino-β-alkyliminoalanines were easily converted into α-aminoglycines in good to high yields by treatment with silica in dichloromethane (Scheme 15, **119a**-**e**). This reaction may involve the addition of water to the imine carbon atom and elimination of an amide. The β-bromo-β-(1,2,4-triazol-1-yl)dehydroalanine (**117**) reacts with oxygen nucleophiles to give α,α-disubstituted amino acids (**120**). The α-addition in this case is due to the electronwithdrawing effect of the groups attached to the β-carbon atom.[56]



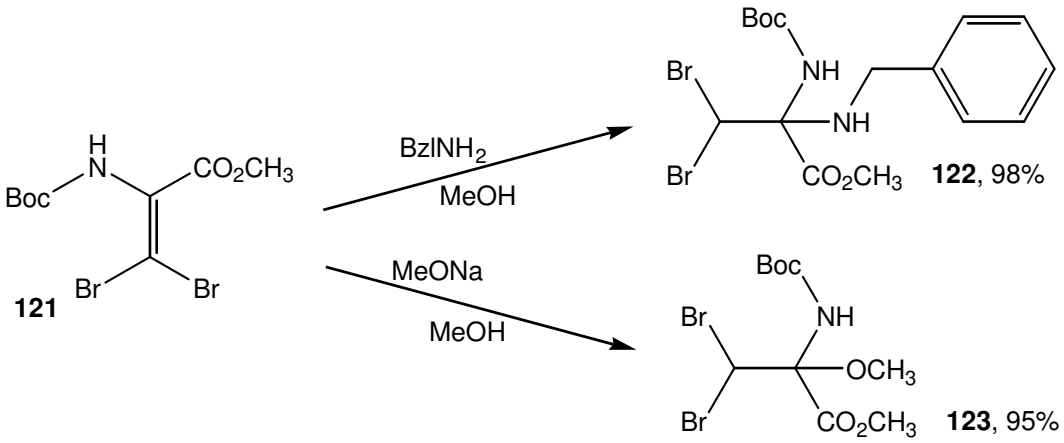
NuH: 1,2,4-triazole, **a**; 3-formylindole, **b**; 4-bromothiophenol, **c**; benzylamine, **d**; sodium methoxide, **e**.

Scheme 14



Scheme 15

α-Addition was also observed when a β,β-dibromodehydroalanine derivative (Scheme 16, **121**) was treated with primary amines and methoxyde in methanol (**122** and **123**, respectively).[56]

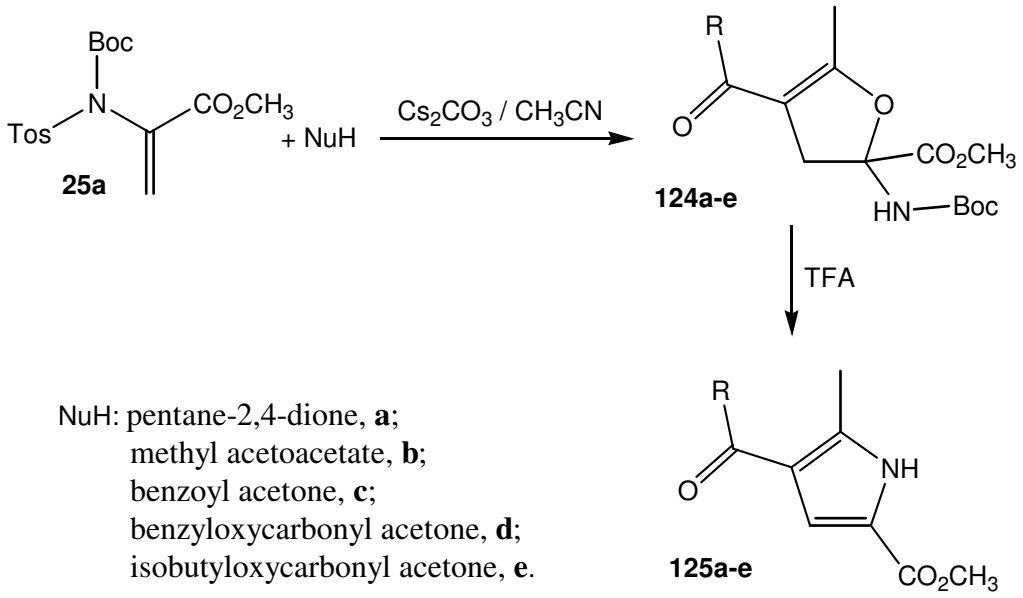


Scheme 16

3.5. Synthesis of dihydrofurans and pyrroles

Cyclic amino acids of the furan type were synthesized in good yields from a dehydroalanine derivative and carbon nucleophiles. These amino acids were converted into pyrroles with TFA.

The methyl ester of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine (**25a**) reacts with carbon nucleophiles with at least one methyl group bonded to one of the carbonyl groups to give the corresponding addition products. These undergo spontaneous elimination of the 4-toluenesulfonyl group followed by cyclization to afford dihydrofurans in good yields (Scheme 17, Table 6, **124a**-**e**).[53,57] These compounds resulted from a rearrangement of the detosylated β-substituted alanines *via* enolization with attack of the enolic oxygen atom on the amino acid α-carbon atom.

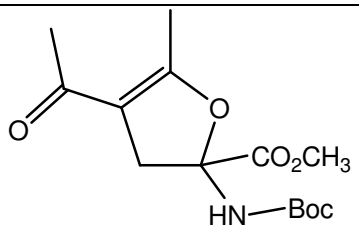
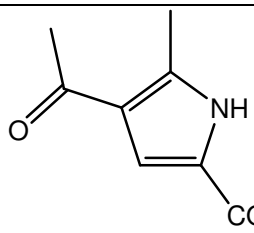
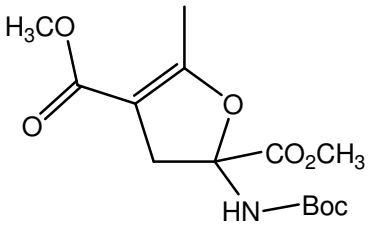
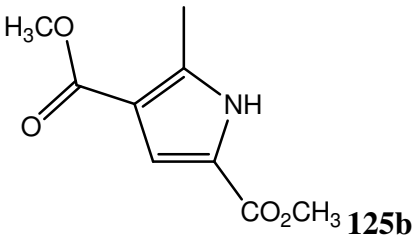
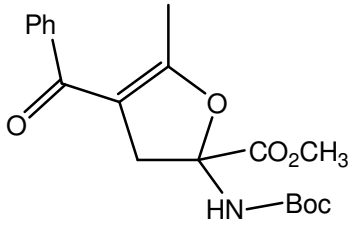
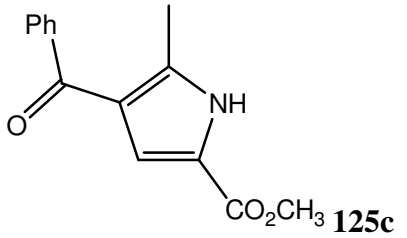
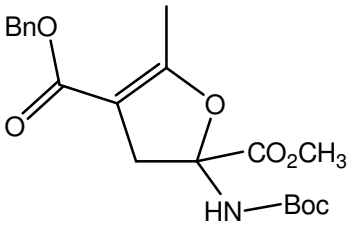
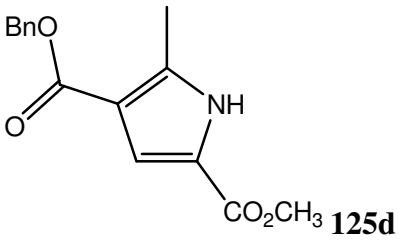
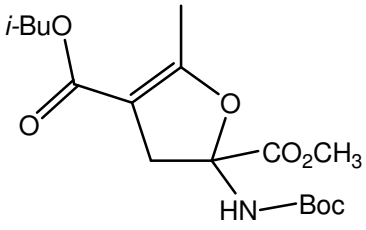
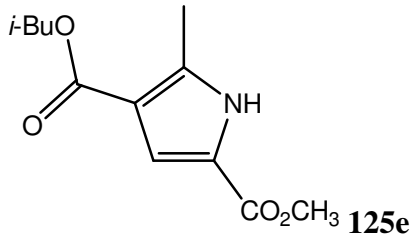


NuH: pentane-2,4-dione, **a**;
methyl acetoacetate, **b**;
benzoyl acetone, **c**;
benzyloxycarbonyl acetone, **d**;
isobutyloxycarbonyl acetone, **e**.

Scheme 17

Cleavage of the *tert*-butoxycarbonyl group from the furanic amino acids with trifluoroacetic acid resulted in a new rearrangement to give the corresponding pyrrole derivatives (Scheme 17, Table 6, **125a**-**e**). This reaction seems to proceed *via* ring opening and subsequent attack of the nitrogen atom of the amine function on the enolic carbon atom.

Table 6. Results obtained in the synthesis of furanic amino acids and pyrroles.[53,57]

Dihydrofurans	Yields / %	Pyrroles	Yields / %
 **124a**	88	 **125a**	92
 **124b**	86	 **125b**	90
 **124c**	80	 **125c**	77
 **124d**	78	 **125d**	79
 **124e**	82	 **125e**	88

4. Conclusions

An efficient and practical method for the synthesis of *N,N*-diacyldehydroamino acids from β-hydroxyamino acids with *tert*-butyl pyrocarbonate and 4-dimethylaminopyridine was developed in our laboratories. The method can be applied to various β-hydroxyamino acids with several *N*- and *C*- protecting groups and also to the synthesis of dehydrodipeptides.

The *N,N*-diprotected dehydroamino acids were versatile synthons allowing the preparation of a large variety of non-proteinogenic amino acids. Thus, *N,N*-diacyldehydroamino acid derivatives were used as substrates in Michael addition reactions allowing the synthesis of β-substituted amino acids. Using as nucleophiles nitrogen heterocycles it was possible to prepare new β-heterocyclic amino acids namely indolylalanines, 1,2,4-triazolylamino acids, pyrazolylamino acids and histidylamino acids. Some of these compounds are analogues of the amino acids histidine and tryptophan others, such as pyrazolylalanine are

known to have biological activity (hypoglicaemic proprieties) or can be used in structure-activity relationship studies or as fluorescent markers (7-azaindolylalanine). When one of the protecting groups was a 4-toluenesulfonyl group and the nucleophiles were nitrogen heterocycles or thiols it was possible to synthesize the corresponding β-substituted dehydroamino acid derivatives. Piperazine derivatives were prepared in good yields by treatment of *O*-(arenesulfinyl)dehydroserines with 1,2-ethylenediamine. A 1,4-dihydropyrazine was obtained reacting the methyl ester of *N*-(4-toluenesulfonyl), *N*-(*tert*-butoxycarbonyl)dehydroalanine with DMAP and potassium carbonate. This compound gave tetrahydropyazines by treatment with nucleophiles, and with TFA gave the corresponding pyrazine. Furanic amino acids can be prepared from *N,N*-diprotected dehydroamino acids and were easily converted into pyrroles with TFA.

This work shows that *N,N*-diprotected dehydroamino acid derivatives constitute excellent substrates for the synthesis of a wide range of heterocyclic amino acids and amino acids containing heterocyclic moieties.

Acknowledgments

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PYRAZOLO[4,3-e][1,2,4]TRIAZOLO[1,5-c]PYRIMIDINES AND LINKED HETEROCYCLES AS TEMPLATE FOR THE ADENOSINE RECEPTOR ANTAGONISM: MEDICINAL CHEMISTRY APPROACH AND SAR CONSIDERATIONS

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Abstract. *The organic and medicinal chemistry approach on the synthesis of pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines and related compounds have permitted to complete the SAR evaluation on this class of molecules. Planning several structural modifications, efforts made by our research group allowed the discovery of a variety of selective antagonists for the human A_{2A} and A_3 receptors, and in particular, chemical adaptations introduced at the N^7-, N^8-, N^5-, C^9-, C^2-positions of the pyrazolo-triazolo-pyrimidine core revealed new potent and selective pharmacological candidates. Modifications at the N^7-pyrazole nitrogen performed by the introduction of different alkyl or arylalkyl chains, led to the discovery of very potent and selective A_{2A} receptor antagonists. Otherwise different functionalisations at the N^5-position together with modulation of the pattern of substitution on the N^8-pyrazole nitrogen revealed new A_3 antagonists suitable to represent new tools for the pharmacological investigations. Other modifications performed to the tricyclic nucleus, such as the introduction at the C^9-position of short thioalkyl, aminoalkyl and (cyclo)alkylamino radicals and the replacement of the 2-(2-furyl)[1,2,4]triazole molecular fragment with substituted 2-thioxotriazole, dioxotriazine, oxotriazine moieties led to a diminished receptor affinity and/or selectivity but allowed us to really understand which structural modifications introduced on the pyrazolo-triazolo-pyrimidine structure played an important role on ligand-receptor interaction.*

Contents

1. Introduction

Adenosine is a purine nucleoside, presents in the extracellular space of all mammalian tissues where it plays a key role in protein, nucleic acid and energy metabolism.[1] Adenosine is formed intracellularly from degradation of AMP through 5'-nucleotidase and it is maintained at low concentration mainly by its conversion to AMP by the adenosine kinase and its degradation to inosine by adenosine deaminase.[2-5] The extracellular level of adenosine depends upon ATP breakdown and synthesis and is greatly increased under metabolical stressful conditions. To date four adenosine receptor subtypes (ARs), A_1, A_{2A}, A_{2B} and A_3, are cloned and characterized in several species including the human.[3]

ARs are made of 7 transmembrane α-helices (7TM) of approximately 25 residues in length which are connected by intra- and extracellular loops. The helices are placed in a lipidic environment, while the loop regions are surrounded by an aqueous medium.

The adenosine receptors subtypes can also be distinguished according to the concentration of physiological agonist adenosine required for the receptor stimulation.[1] Thus, the long-know subtypes A_1 and A_{2A} are "high affinity" adenosine receptors, which are activated at concentrations of *ca.* 10^{-8} – 10^{-7} M, while the A_{2B}- and A_3-AR are "low affinity" adenosine receptors, with adenosine activating only in the micromolar concentration range (*ca.* 10^{-6} – 10^{-5} M).[3]

Adenosine concentration in cells can vary within a wide range, rising under hypoxic conditions from 10^{-7} to 10^{-5} molar, *e.g.* during ischemia. High affinity AR subtypes appear to be constitutively stimulated, while low affinity receptors will only be activated under pathological conditions. The A_1 and A_3 receptors cause the inhibition of the adenylate cyclase whereas the A_{2A} and A_{2B} receptors determine its activation.[2] They belong to the Rhodopsin-like family of G protein-coupled receptors (GPCRs), and are encoded by distinct genes. Their expression is widespread such that adenosine practically controls the function of every organ and tissue. However, receptor subtype distribution and density vary greatly.

In the last years several experiments have provided insights into the physiology and pathophysiology of these four subtypes.[3] These studies contributed to confirm their important pharmacological role in the treatment of a variety of conditions such as asthma, neurodegenerative disorders, psychosis and anxiety, chronic inflammatory diseases and many other physiopathological states that are believed to be associated with changes in adenosine levels.[6-19]

1.1. Adenosine receptor antagonists: non-xanthine derivatives

In the last two decades, different classes of compounds have been synthesized and tested for their antagonistic properties at the four adenosine receptor subtypes. These compounds can be divided mainly into two groups: xanthine and non-xanthine derivatives, but only the second ones will be described.

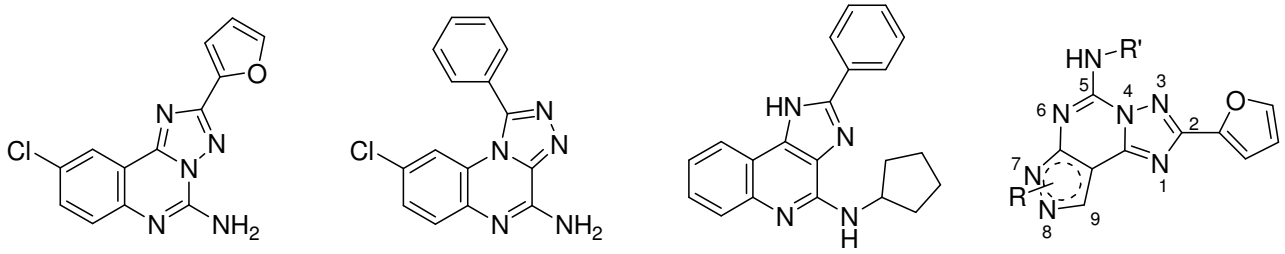


Figure 1. Non-xanthine derivatives as adenosine receptor antagonists.

A great number of structures of non-xanthine adenosine antagonists have been identified. Unlike xanthines, the structure-activity relationships for these novel classes of antagonists are not well defined, nor have they been optimized to achieve maximal adenosine receptor binding affinity or subtype selectivity. Of particular interest are four classes of related heterocycles which include the triazoloquinazolines **1**,[20] triazoloquinoxalines 2,[21] imidazoquinolines **3**[22] and the pyrazolo-triazolo-pyrimidine derivatives **4** as prototypical template for A_{2A} and A_3 adenosine antagonism (Figure 1).

The first non-xanthine adenosine receptor antagonist identified was the triazoloquinazoline **CGS 15943** (5-amino-9-chloro-2-(fur-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline) (Figure 2). This compound is a non-selective antagonist with a K_i-value in the low nanomolar range for the A_1 and A_{2A} receptors and an approximately ten-fold lower potency at the A_{2B} and A_3 subtypes. Modifications at this molecule led to the development of an A_3 selective compound named **MRS 1220** (9-chloro-2-(2-furyl)-5-[(phenylacetyl)amino][1,2,4]-triazolo[1,5-c]quinazoline) with a subnanomolar affinity.[23,24]

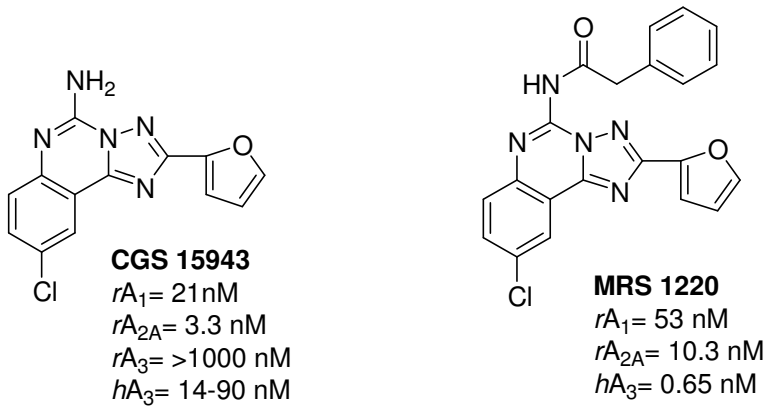
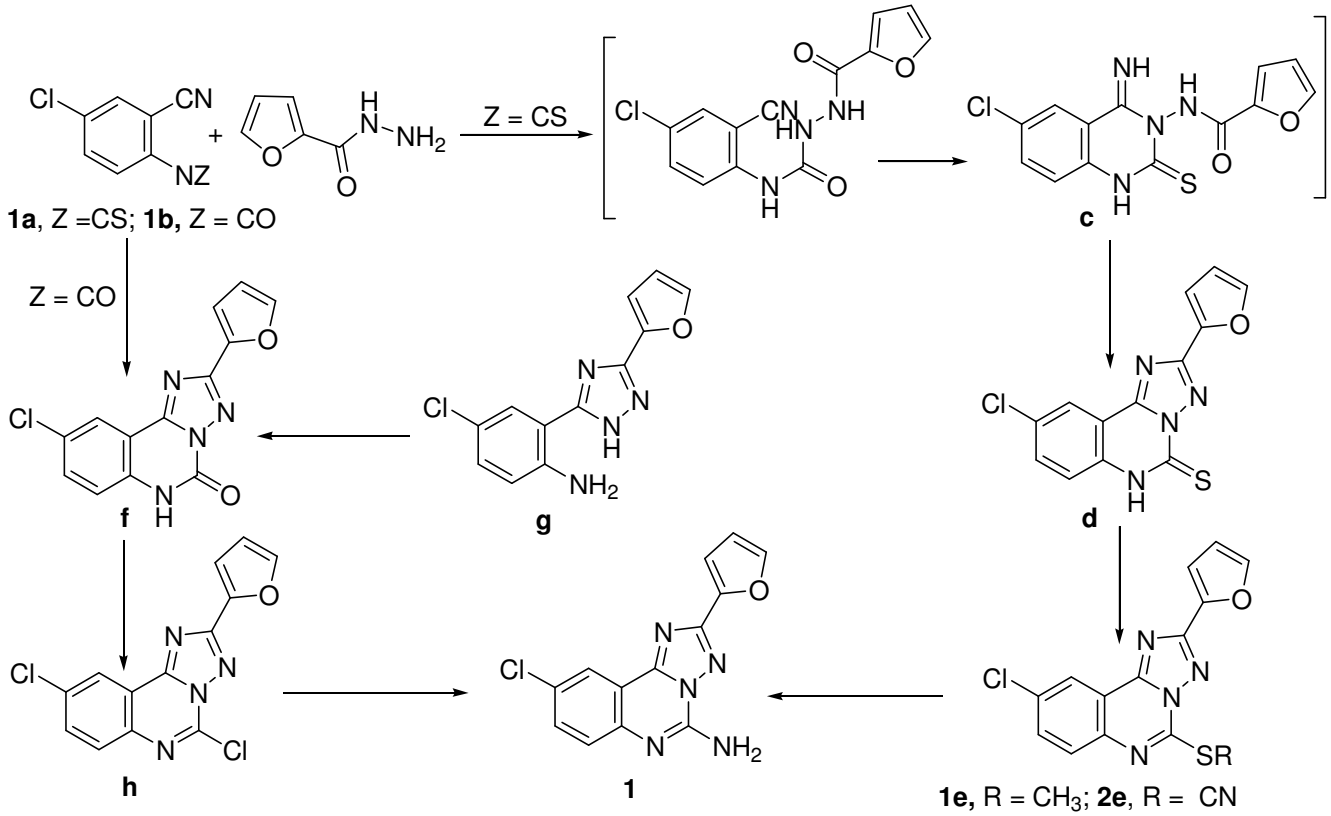


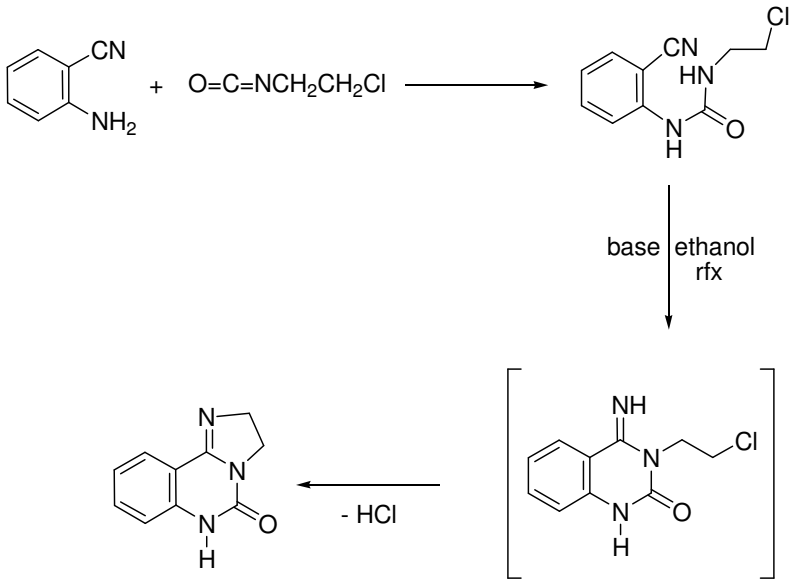
Figure 2. Adenosine receptor antagonists displaying a non-xanthinic structure.



Scheme 1. Brief illustration of the synthesis of triazoloquinazolines.

The family of 5-amino-2-substituted-[1,2,4]triazolo[1,5-c]quinazolines were prepared by two different procedures.[25] The first method involved displacement of a favorable leaving group from the 5-position of the heterocycle, either the 5-methylmercapto moiety, the 5-isothiocyanato group, or the 5-chlorosubstituent by an amine. A second method, the ring closure of a 5-(*o*-aminophenyl)-3-substituted-1*H*-1,2,4-triazole with cyanogen bromide or cyanamide produced only 5-amino (or 5-imino-5,6-dihydro) compounds. All of these methods used to prepare the lead compound **1** and congeners are illustrated in Scheme 1.

Treatment of the isothiocyanate **1a** (prepared from 5-chloroanthranilonitrile and thiophosgene) with 2-furoic acid hydrazide preferably in a polar, nonhydroxylic solvent such as dimethylacetamide or *N*-methyl-2-pyrrolidinone at temperatures above 100 °C led to the tricyclic thiono compound **d** in one step. This double cyclization is reminiscent of the work of Papadopoulus,[26] who found that anthranilonitrile reacted smoothly with 2-chloroethyl isocyanate to form a urea, which, on warming with an alcohol under basic conditions, produced 2,6-dihydroimidazo[1,2-c]quinazolin-5(3*H*)-one in excellent yield (Scheme 2).[26]



Scheme 2. Brief illustration of the synthesis of dihydroimidazo-quinazolinones.

The formation of intermediate **c** in this synthesis seems likely, but the efforts to isolate and purify this compound resulted in its cyclization. Similarly, the *o*-isocyanatobenzonitrile **1b** reacts with a hydrazide under similar conditions to produce a 5-oxo compound such as **f** (Scheme 1). This tricyclic urea was first prepared by reaction of the triazole **g** with the phosgene equivalent trichloromethyl chloroformate. Since the double cyclization occurs so readily, it seems likely that no Dimroth-type rearrangement[27] occurs, which could lead to the isomeric [1,2,4]triazolo[4,3-c]quinazoline ring system.

The anion of **d** was converted to either the methylthio compound **1e** or the isothiocyanato derivative **2e**. The alkylthio intermediate was converted to the target compound with ammonia/ ammonium hydroxide mixture in a sealed vessel or with an amine in a hydroxylic solvent under pressure to produce an *N*-alkylated target. The isothiocyanato group was readily displaced by ammonia bubbled through a solution in 1,3-dimethyl-2imidazolidone at room temperature. Alternatively, **f** was converted by phosphoryl chloride/ phosphorous pentachloride in pyridine to the 5,9-dichloro compound **h** and thence to the target compound by ammonia treatment.[27]

2. Pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine template as adenosine receptor antagonist

The tricyclic pyrazolo-triazolo-pyrimidine nucleus was widely studied in the last years by our research group at finding a potent and selective antagonist for the A_{2A} or A_3 adenosine receptor subtypes.[28-31] The structural elements on which we could work were the substitution pattern at the N^7-, N^8- and N^5- positions in order to modulate the affinity of the synthesized molecules versus the A_{2A} or A_3 receptor subtypes.

It should be stressed that some structural elements are fundamental for the receptor affinity of the compounds such as the furan ring at the 2-position of the tricyclic core, necessary for the receptor anchorage, the free amino group at the 5 position, crucial to maintain of the A_{2A} affinity and the functionalization of this amino group into urea or amide for molecules planned as A_3 antagonists.[32,33] Also the position of the radical of the pyrazolo nitrogen determined the receptor affinity: N^7-substituted molecules preferably bind to the A_{2A} adenosine subtype, while the N^8-derivatives showed the best values of affinity versus the A_3 receptor subtype.[33]

2.1. A_{2A} Adenosine receptor antagonists: chemical approach

The first potent but poor selective antagonist for the A_{2A} adenosine receptor subtype was the compound named **8FB-PTP** (8-(4-fluorobenzyl)-2-(2-furyl)-8*H*-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine) (Figure 3),[34] which represented the first example of adenosine antagonist displaying the pyrazolo-triazolo-pyrimidine core. Some structural features of this compound highlighted the essential requirements for the A_{2A} affinity, *i.e.* the furyl moiety and the free amino group at the 5 position. Starting from these observations, we focused our interest on the pattern of substitution on the pyrazolo moiety, preserving unmodified the others structural elements. Several alkyl, aryl, phenylalkyl substituents have been introduced both at the N^7- and N^8- position. The biological data derived from the obtained molecules indicated that the best substituents were phenylalkyl chains, in which the length of the alkyl chain was optimised in two or three carbon atoms (**SCH 58261** and **SCH63390**) (Figure 3).[35] It was also noted that the N^7-derivatives were more selective for the A_{2A} receptor than the corresponding N^8-isomers.

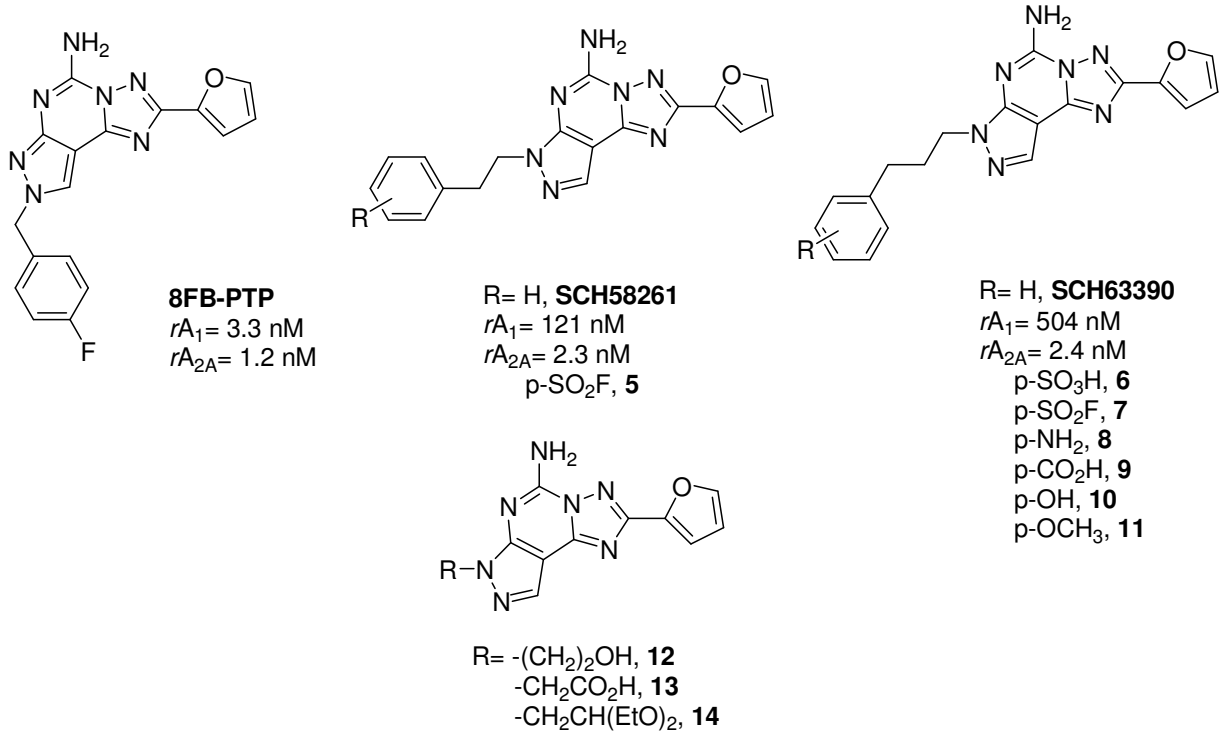
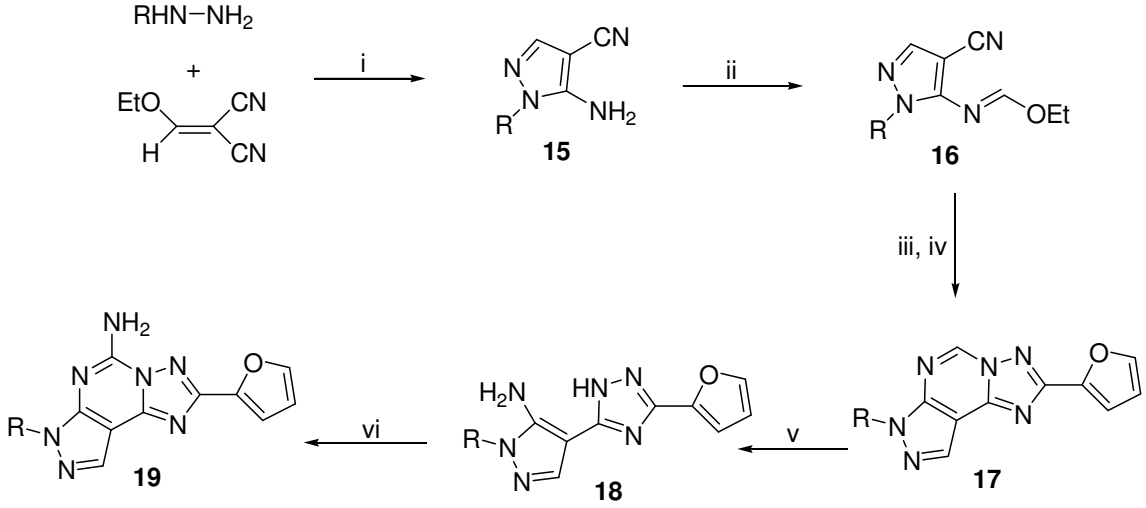


Figure 3. Potent and selective A_{2A} adenosine receptor antagonists.

The synthesis of the lead compound **SCH58261** and congeners was reached according to a well-known synthetic procedure reported by Gatta *et al.*[34] for the synthesis of the pyrazolo-triazolo-pyrimidine nucleus (Scheme 3). Following this strategy, the first step of reaction involved the transformation of the substituted pyrazolo **15** into the corresponding imidate **16** through refluxing in triethyl orthoformate.[34,36]

To avoid tedious separation processes, only the N^1- or N^2-substituted pyrazoles could be obtained by reacting the appropriate alkylhydrazine (N^1, Scheme 3) or protected alkylhydrazine (N^2, Scheme 6) with ethoxymethylene malononitrile.[37]

The intermediate **16** was cyclized into the tricyclic core **17** first, by reaction with 2-furohydrazide and then, by a thermally induced cyclization in the presence of diphenylether. Treatment of the tricycle **17** with a refluxing solution of 10% HCl induced the pyrimidine ring-opening to give the 4-(1*H*-1,2,4-triazol-5-yl)pyrazol-3-amine **18** in a good yield. The subsequent reaction of this intermediate with an excess of cyanamide in 1-methyl-2-pyrrolidone at 140 °C furnished the N^5-amino derivatives of general formula **19** that could be functionalised at the N^5-position by acylation or nucleophilic addition to achieve molecules planned for the A_3 adenosine receptor subtype.



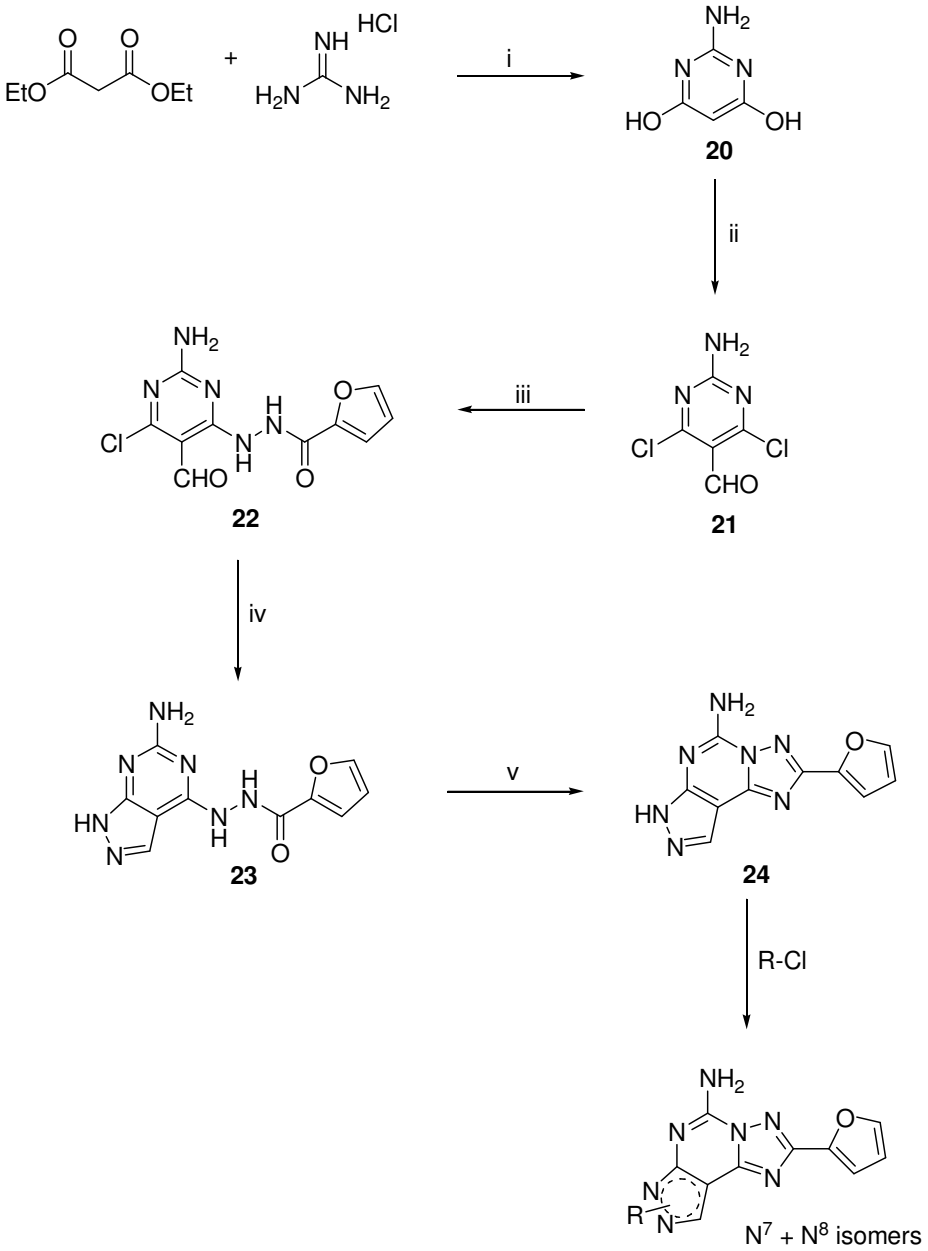
Reagents and conditions: (i) EtOH, rfx; (ii) $HC(OEt)_3$; (iii) 2-furohydrazide, 2-methoxyethanol; (iv) diphenylether, 260 °C; (v) 10% HCl; (vi) NH_2CN, *p*-TsOH. R= (substituted)-phenylalkyl chains.

Scheme 3

To obtain water-soluble derivatives, modifications on the phenyl ring of the radical connected to N^7-pyrazole nitrogen have been performed, introducing mainly at the *para* position hydrophilic moieties, such as hydroxyl group or other oxygenated functions (Figure 3).[38] Among the new derivatives achieved, N^7-(4-hydroxyphenyl)propyl derivative **10** and N^7-(4-methoxyphenyl)propyl derivative **11** showed a very interesting activity versus the A_{2A} receptor (K_i= 0.94 and 5.3 nM respectively). In spite of the great results obtained in terms of affinity and selectivity, compounds **10** and **11** did not show an interesting increase of the water solubility measured through the evaluation of their *Rm* values, being quite similar to former parent compounds SCH 58261 and SCH 63390.

Based upon the speculation of the presence of a pocket endowed with particular characteristics in the receptor binding site, several other compounds bearing chiefly phenylpropyl chains on the N^7- of the pyrazole endowed with substituents at the para position of the aromatic ring able to form hydrogen bonds, have been reported. Among these it should be retained information of the sulfonic (**6**,**7**), carboxylic (**9**) and amino (**8**) derivatives with the aim to employ these functionalities for the preparation of salts or prodrugs.[39]

The chemical approach for the synthesis of the water-soluble derivatives was dual: (i) application of the synthetic steps depicted in Scheme 3, or (ii) following an alternative route based on the alkylation of a common tricyclic intermediate 5-amino-2-(furan-2-yl)-7*H*-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine **24** (Scheme 4). This chemical unit suitable for alkylation, was obtained in the past by a tedious de-*tert*-butylation procedure, performed by the treatment of 5-amino-7-*tert*-butyl-2-(fur-2-yl)-7*H*-pyrazolo[4,3-e] [1,2,4]triazolo[1,5-c]pyrimidine with 99% formic acid for 48 hours.[40]

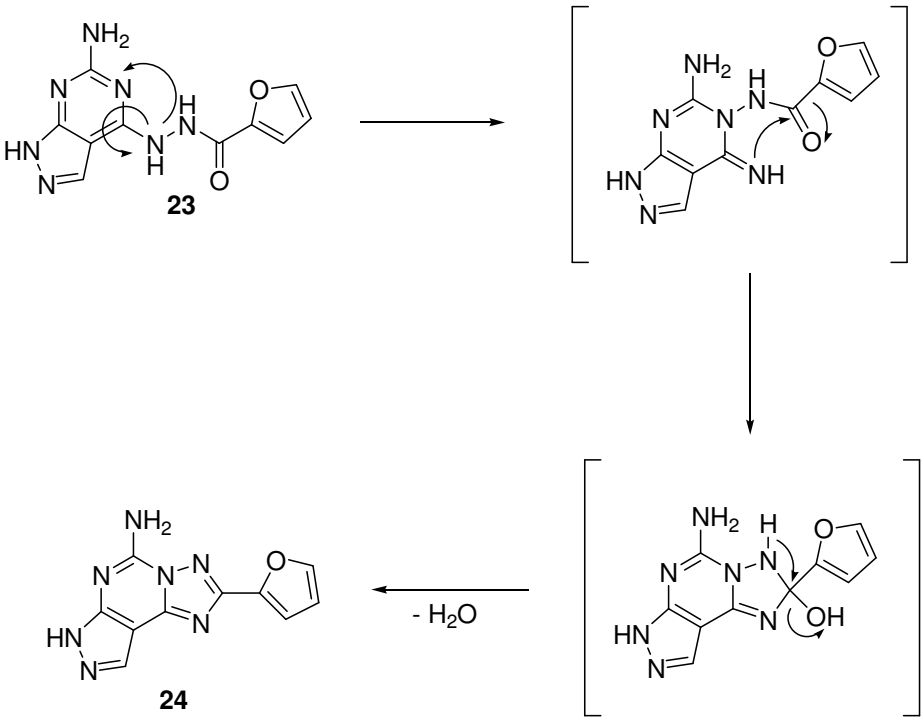


Reagents and conditions: (i) EtONa, EtOH abs.; (ii) $POCl_3$, DMF, reflux; (iii) 2-furohydrazide, THF; (iv) hydrazine hydrate, 2-methoxyethanol; (v) HMDS, BSA, DMF.

Scheme 4

Recently reported by the Schering Corporation and subsequently applied by our research group, the chemical route (ii) permitted to obtain a large amount of the tricyclic key intermediate **24**[47] in a very short time as illustrated in Scheme 4.[41] The condensation of diethylmalonate with guanidine hydrochloride in basic conditions gave the 2-aminopyrimidin-4,6-diol **20**. The transformation into compound **21** was achieved in a very good yield by treatment with $POCl_3$ and DMF (Vilsmeier reaction)[42] at refluxing temperature. This

latter intermediate was then reacted with furan-2-carboxylic acid hydrazide to furnish the intermediate **22** which was then cyclized into **23** by treatment with hydrazine in 2-methoxyethanol. Treatment of **23** with DMF, HMDS and BSA at 220 °C (Dimroth-type rearrangement, Scheme **4a**) induced the formation of the key compound **24** in acceptable yield.

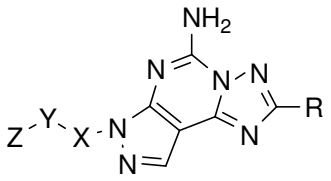


Scheme 4a. Proposed mechanism for the Dimroth-type rearrangement.

Taking advantage of this new chemical route, we reported new tricyclic structures displaying substituents on the N^7-pyrazole nitrogen able to improve the water solubility and, at the same time, to maintain the affinity and selectivity for the human A_{2A} adenosine receptor subtype.[37] The substituents selected for the pyrazole nitrogen were oxyalkyl functions such as β-hydroxyethyl, acetic, and diethyloxyethyl chains. The derivatives **12-14** (Figure 3) were obtained by direct alkylation of the key intermediate **24** with alkylating agents[37] like 2-bromoacetic acid *t*-butylester (**13**), chloroacetaldehyde diethyl acetale (**14**), and 2-iodioethanol (**12**). Compound **13** was obtained by the treatment of *t*-butyl ester with trifluoro acetic acid. Also the diethyloxy group of compound **14** furnished a versatile functionality with the possibility of transform the diacetal to the corresponding aldehyde which can be coupled with amines or other kind of nucleophiles to obtain derivatives with enhanced water solubility. The two isomers (N^7- and N^8-) obtained from the direct alkylation of **24** were easily separated by flash chromatography. Contrary, derivatives **5-7** were obtained directly by the reaction of SCH 58261 or SCH 63390 with chlorosulfonic or fluorosulfonic acid and the final hydrolysis with 10% HCl afforded the corresponding SO_3H functionality.

The Schering Corporation also reported an enlarged series of pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines as new A_{2A} receptor antagonists,[41,43,44] describing several innovative substitutions on the N^7-pyrazole nitrogen. The general formula disclosed was **I** (Figure 4), where X was characterized by alkylene or $C(O)CH_2$ groups, Y was represented by O, S, thiomethyl or alkylamino chains and Z (together with Y) was correspond to substituted piperidinyl or substituted phenyl amines.

The substituent R in the 2-position of the tricycles reported was represented by furyl, thienyl, oxazolyl or pyridyl moieties.

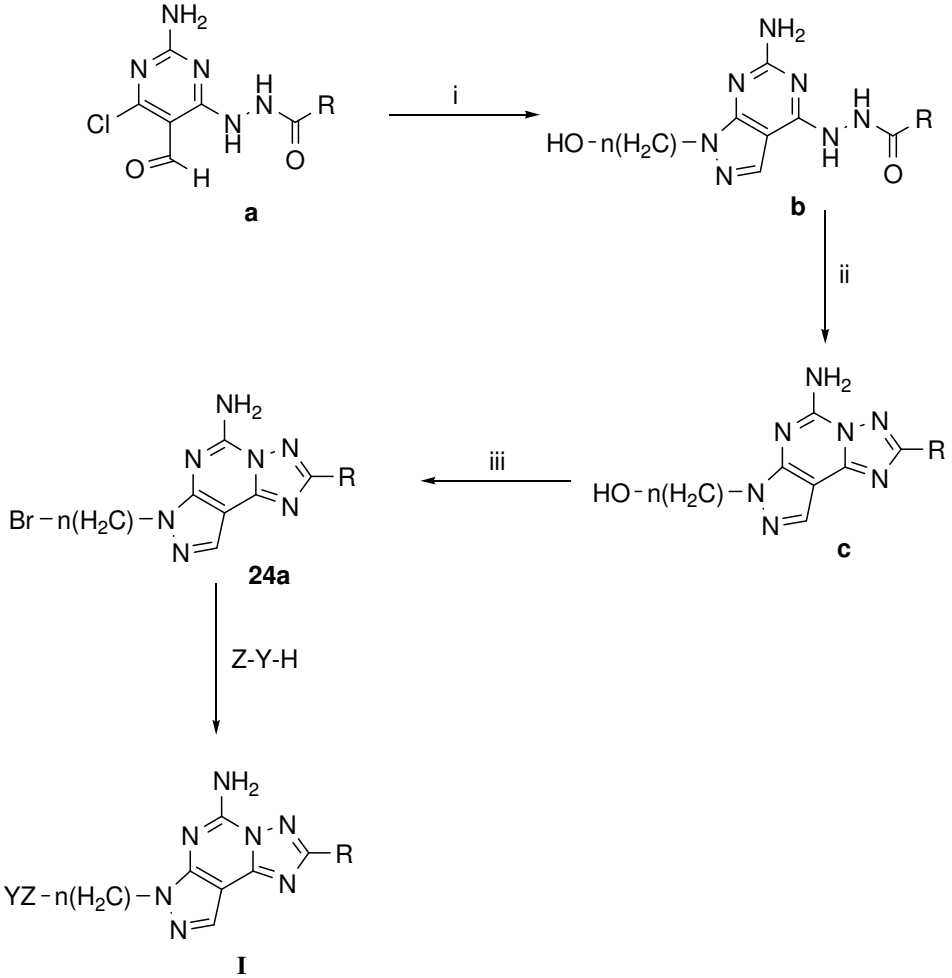


I

Figure 4. Tricyclic A_{2A} antagonists synthesized using Dimroth-type rearrangement.

Results of the binding assay on the molecules of this invention showed A_{2A} K_i values from 0.3 to 57 nM and the selectivity versus the A_1 adenosine receptor subtype ranging from about 100 to 2000 nM.

The compounds of general formula **I** were prepared by direct alkylation of **24** or by nucleophilic reaction between **24a** and selected amines (Z-Y-H) as reported in the Scheme 5. The 2-substituted 7-(ω-bromoalkyl)-7*H*-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amines **24a** were obtained by treating the chloride **a** with ω-hydrazinoalkan-1-ols to furnish **b**. These derivatives were then converted into **c** by dehydrative rearrangement and then transformed into **24a** by treatment with PBr_3. [43,44]



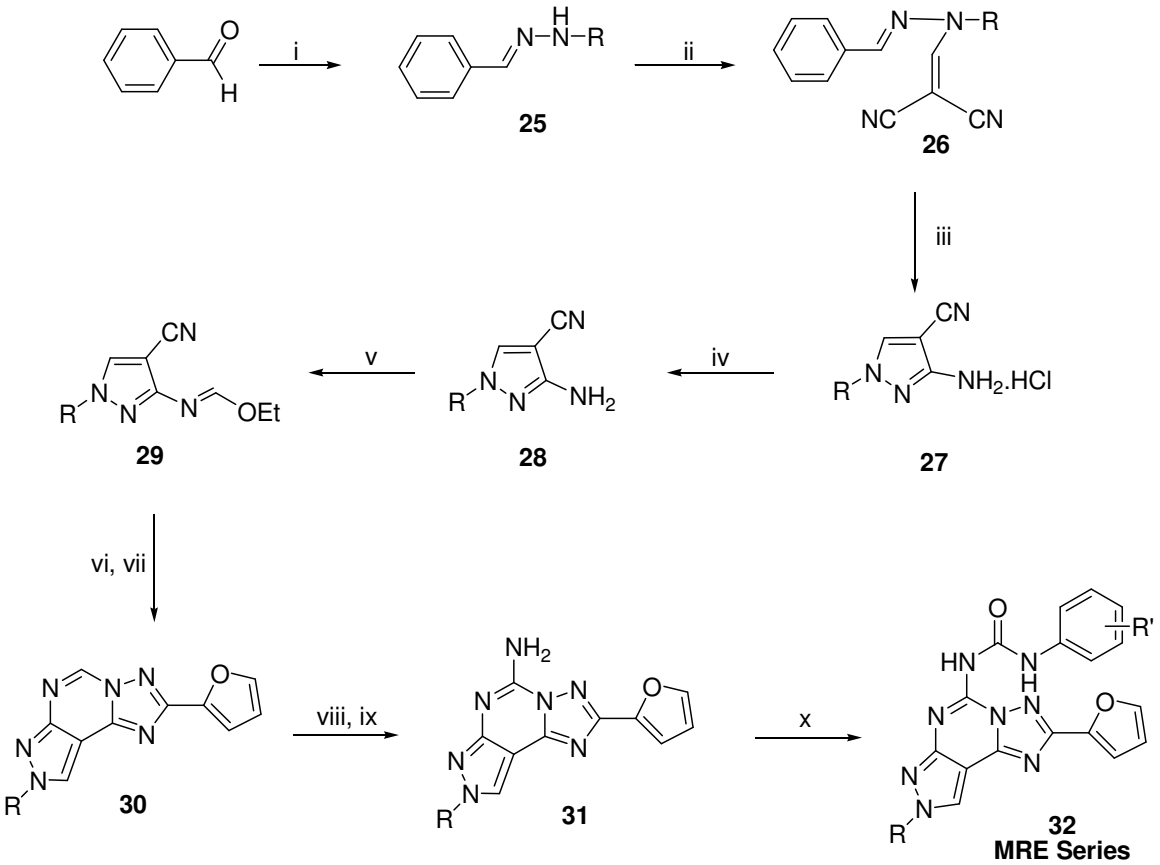
Reagents: (i) ω-hydrazinoalkan-1-ols; (ii) HMDS, BSA, DMF; (iii) PBr_3.

Scheme 5

2.2. Pyrazolo-triazolo-pyrimidines as A_3 adenosine receptor antagonists

Different classes of compounds have been reported to be selective A_3 receptor antagonists (eight classes with non-xanthine structure, including dihydropyridine and pyridine analogs, flavonoid, isoquinoline and triazoloquinazoline derivatives, triazolonaphthiridine and thiazolopyrimidine analogs).[45-52] The best results in terms of A_3-antagonism were obtained by our research group with the synthesis of 5-*N*-(substituted phenylcarbamoyl)amino-8-substituted-2-(2-furyl)pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines, where the best substitution on the phenyl ring of the phenyl carbamoyl moiety was a methoxy at the para position or a chlorine atom at the meta position (**MRE series**, compounds of general structure **32**, Scheme 6).[30,31,53,54]

This chemical approach was based on the design of new structural hybrids between the N^8-substituted pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines and the phenylcarbamoyl chain displayed in a series of N^6-(substituted phenylcarbamoyl)adenosine-5'-uronamides, previously reported as potent and selective A_3 adenosine agonists.[40,54-56] The biological data of the combined compounds **32** clearly indicated that the selectivity at the A_3 adenosine receptor subtype was accomplished by the introduction of phenylcarbamoyl residues at the N^5-position of the pyrazolo-triazolo-pirimidine nucleus. The SAR studies on these compounds revealed that the A_3 affinity was modulated by the introduction of different radicals on the N^8-pyrazole nitrogen.[56] In particular the increase of the steric hindrance determined a diminished affinity. The best value of hA_3 affinity was displayed by derivatives which combines the N^8-unsubstitution (or small alkyl radicals) and the N^5-(4-methoxyphenyl)carbamoyl chain.



Reagents and conditions: (i) substituted-hydrazine, abs. EtOH; (ii) ethoxymethylene malononitrile, benzene; (iii) conc. HCl; (iv) NH_3; (v) $HC(OEt)_3$, rfx; (vi) 2-furoic acid hydrazide, 2-methoxyethanol; (vii) Ph_2O, 260 °C; (viii) aq. HCl 10%; (ix) NH_2CN, pTsOH; (x) substituted-phenylisocyanate, TEA.
R= CH_3, C_2H_5, n-C_3H_7, $Ph(CH_2)_2$, $Ph(CH_2)_3$; R'= 4-OCH_3, 3-Cl, 4-Br, 4-CF_3, 2-Cl.

Scheme 6

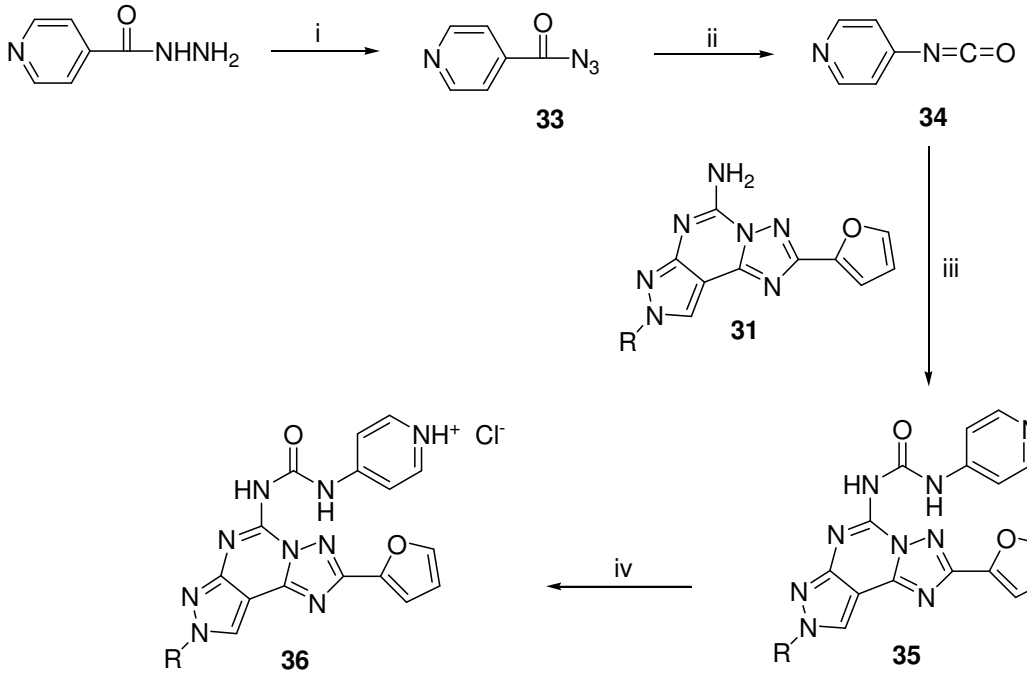
As depicted in Scheme 6, a regio-specific procedure allowed only the preparation of the tricyclic N^8-isomers. The reaction between benzaldehyde and *N*-substituted-hydrazine, commercially available, gave the corresponding hydrazone **25**. Subsequent reaction with ethoxymethylene malononitrile and hydrolysis with 37% HCl provided the N^2-substituted pyrazoles of general structure **27** in good yield. The free amino group of **28** was transformed into the imidate **29** by refluxing in $HC(OEt)_3$. The tricyclic amine **31** was achieved using the synthetic steps already employed for the synthesis of the tricyclic compounds and reported in the synthetic Scheme 3.[30,37,56] The urea derivatives were easly obtained by treatment of **31** with substituted-phenyl isocyanate to afford the analogs of general structure **32**.

The chemical developments proceeded with the optimization of substituents on the phenyl moiety of the arylcarbamoyl radical.[54] The introduction of halogens or methyl groups on the aromatic ring was not well tolerated inducing a decrease on the receptor affinity from 2 to 5 fold with respect to the unsubstituted parent compounds.

The next medicinal chemistry approach was the isosteric replacement of the arylcarbamoyl with a phenylacetic chain even if this modification led to a reduction on the receptor affinity. This fact justifies the hypothesis that the NH group of the urea was better tolerated than the methylene group of the amide function of the phenylacetic analogues.[54]

2.3. Water soluble A_3 adenosine receptor antagonists

An important goal reached by our research group was the synthesis of the first water-soluble hA_3 antagonist (compound **36**, R=CH_3, Scheme 7). This compound (along with its analogs) represents an ideal candidate for the pharmacological and clinical investigations of the human A_3 adenosine receptor subtype in which the isosteric replacement of the phenyl with a 4-pyridyl moiety provided higher water solubility avoiding the steric hindrance of para substituents (K_i hA_3 from 0.01 nM to 2 nM).[57,58] For the synthesis of **36** the Curtius rearrangement[59] permitted the transformation of the commercially available isonicotinohydrazide into the corresponding isocyanate **34**.



Reagents and conditions: (i) $NaNO_2$, aq. 10% HCl; (ii), benzene, reflux; (iii) THF, reflux; (iv) HCl/methanol, 0 °C.
R= CH_3, $(CH_2)_2OH$, $(CH_2)_3OH$.

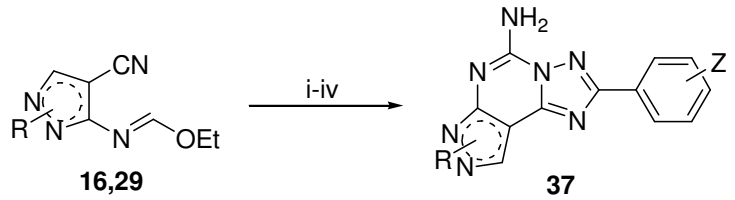
Scheme 7

This one, highly unstable, was at once allowed to react with the tricyclic amine **31** in THF at reflux to furnish **35**. This latter compound was transformed into the corresponding hydrochloride **36** by the treatment with a satured solution of hydrochloric acid in methanol (Scheme 7).

3. Modifications introduced to the pyrazolo-triazolo-pyrimidine nucleus

3.1. Modification at the 2-position

The furanyl group at the 2-position of the tricyclic core was shown to be important for the receptor binding of the pyrazolo-triazolo-pyrimidine derivatives. Substitution of this heterocycle with other heterocyclic rings such as thiophene or tetrahydrofuranyl, led to a severe loss of affinity.[25] Our research group reported the introduction of a phenyl or an aromatic ring functionalized at the *para* position with groups endowed with electron negative centers able to interact with the adenosine receptors (*e.g.* halogens, free hydroxyl group; compounds of general formula **37**, Scheme 8).[56,60] The ortho position of the aromatic ring was also functionalized with an ethoxy group in an attempt to mimic the oxygen of the furane. The structure-activity relationship study was evaluated based on the lead compound **SCH58261** to appreciate the change in receptor affinity and selectivity. The synthesis of this innovative derivatives was performed as previously reported in the synthetic Scheme 3, except for the phenyl hydrazide utilized (Scheme 8).

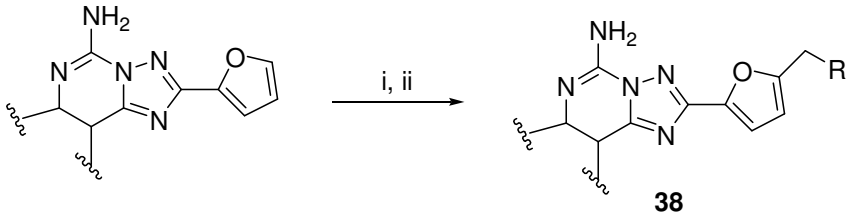


16,29 **37**

Reagents and conditions: (i) (substituted)-phenyl hydrazide, 2-methoxyethanol; (ii) Diphenylether, 260 °C; (iii) 10% HCl; (iv) NH_2CN, *p*-TsOH.
R= 2-phenyl ethyl, methyl; Z= H, 4-OH, 4-Cl, 2-OEt.

Scheme 8

The principal difficulty in evaluating the adenosine tricyclic antagonists were their very lipophilic nature. Starting from these observations we reported the introduction of additional chemical modifications at the 5'-position of the furanyl ring.[56,60] The aim of this modification was to improve the water solubility of the new compounds obtained and to further evaluate the change in terms of affinity and selectivity of the final molecules (compounds of general formula **38**, Scheme 9). The amines used for this type of reaction were morpholine and *N*-methylpiperazine. Treatment with hydrochloric acid solution to form the corresponding salt was effected to increase the water solubility and to make pharmacological testing easier.



38

Reagents and conditions: (i) 36% aq. formaldehyde, glacial acetic acid; (ii) Morpholine, *N*-CH_3-piperazine
R= Morpholine, *N*-CH_3-piperazine.

Scheme 9

The purpose of this research effort was to better understand what structural modifications introduced on the tricyclic antagonist core played an important role on ligand-receptor interaction. In this way, we notice

what position of the heterocyclic structure is not allowed to be modified and, on the contrary, what position is susceptible of modifications or functionalizations, to develop new drugs which targeting A_{2A} and A_3 adenosine receptor subtypes. For the modifications at the 5' position of the furan the Mannich reaction was applied, as depicted in Scheme 9: the appropriate tricyclic derivatives were reacted with *N*-methyl-piperazine or morpholine and 36% aqueous formaldehyde in glacial acetic acid at reflux for 12-18 hours to give the target compounds **38** in 20-30% yield.[56,60]

Unfortunately, the final compounds of general formula **37** and **38** resulted completely inactive versus all the adenosine receptor subtypes.

3.2. Modifications at the 9-position

The 9-position of the pyrazolo-triazolo-pyrimidine scaffold was also investigate by the introduction of various substitutens. To evaluate the change in affinity and selectivity versus A_{2A} and A_3 adenosine receptor subtypes, all the other structural requirements necessary for antagonism and present in the lead compounds SCH 58261 and MRE series – *e.g.* planar structure, alkyl or arylalkyl substituents on the pyrazole ring, free exocyclic amino group for A_{2A} -antagonists, transformation of the free amino group into an amide or urea function for A_3-antagonists- were maintained. The compounds synthesized were pyrazolo-triazolo-pyrimidines N^8-substituted principally with small alkyl groups. The substituents introduced at the 9-position were examined for their parameters of steric hindrance and hydrophilic/lipophilic balance as cycloalkyl, alkyl or amine functions bound to the tricyclic core by thioether or amine functions.[56,60]

The amino group at the 5 position was reacted with isocyanates or acyl chlorides to obtain ureidic or amidic compounds respectively, which were tested to the human A_{2A} and A_3 adenosine receptor subtypes.

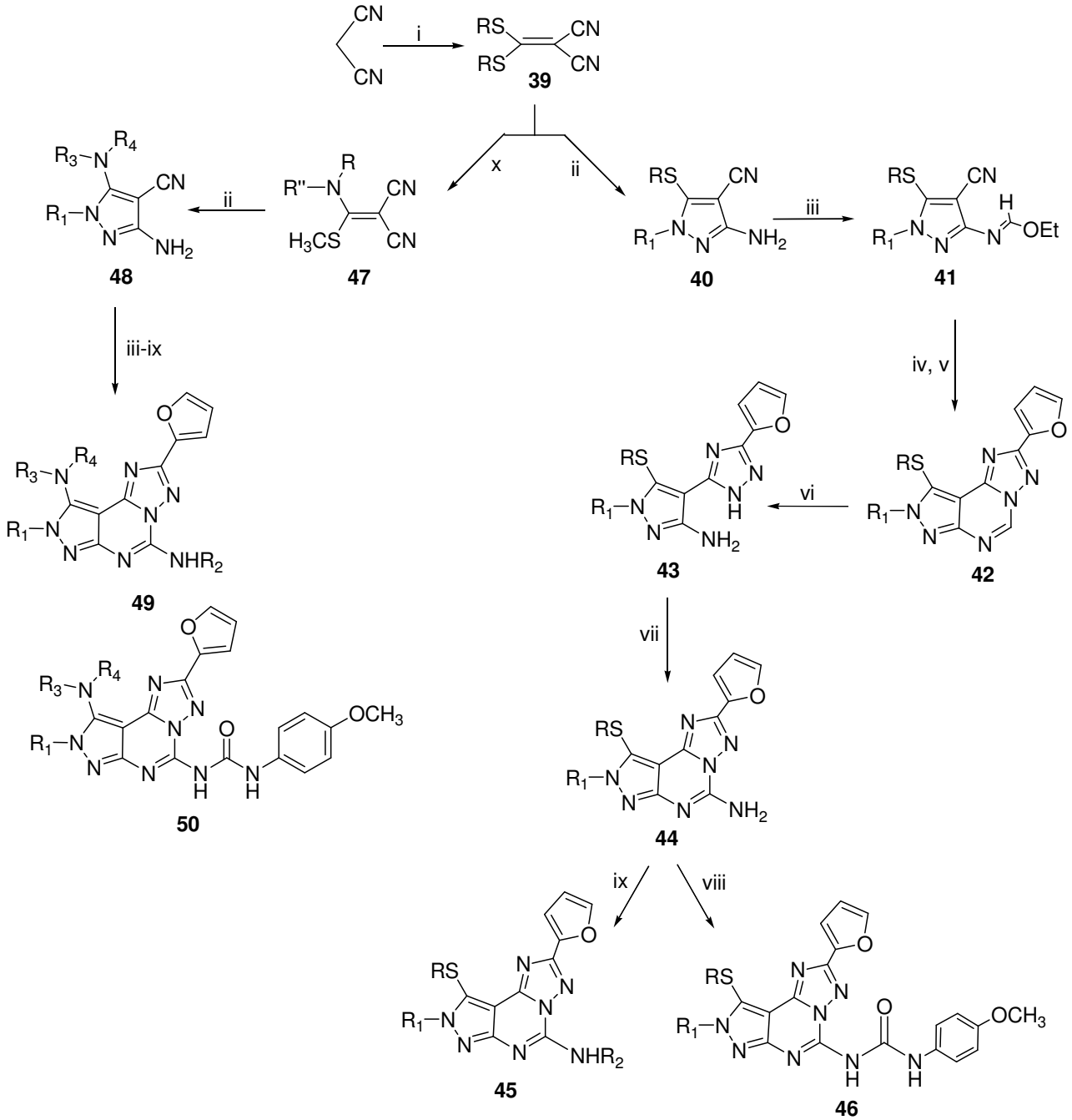
The synthesis of the C^9-substituted tricycles is depicted in Scheme 10: using malononitrile as starting material which reacting with carbon disulfide and alkyl-iodide (indicated as RI in the synthetic scheme) provided the [bis(alkylsulfanyl)methylene]malononitrile **39** in a good yield.[61,62] The next reaction with substituted-hydrazines in ethanol gave the corresponding 3-amino-1-(substituted)-5-(alkyl-sulfanyl)-1*H*-pyrazole-4-carbonitrile **40** which was finally converted into the final compounds of general structure **44** using the well-know procedure for the synthesis of the pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives.[34]

To introduce the (cyclo)alkylamino functions the intermediate **39** was treated with the appropriate amine in refluxing ethanol to afford the mono-substituted methylene malononitrile derivative **47**.

To evaluate the A_3 receptor affinity, the free amino group at the 5 position was converted into urea or amide by treatment with the corresponding isocyanates or acyl chlorides (compounds **45**, **46**, **49**, **50**). Some of these compounds were transformed into the corresponding salts observing a little increase in the binding affinity of the hydrochloric derivatives with respect to the free bases.[60]

A SAR evaluation on this class of antagonists revealed that the introduction of a substituent at the 9-position led to a loss of selectivity that is present in the lead compounds SCH and in the MRE series, but the receptor affinity was maintained in the nanomolar range. In general the methylthio group at the 9-position was the best tolerated. A methyl group at 8-position was better tolerated than a phenylpropyl substituent by A_{2A} adenosine receptor subtype. Compound of general formula **44**, displaying a free amino group at the 5-position, showed good affinity for A_{2A} adenosine receptor but, unfortunately, low selectivity. Transformation of the amino group into urea or amide functions preserved A_{2A} affinity, but the interaction

with A_3 adenosine receptor subtype decreased. In this case we can say that the presence of a substituent at 9-position didn't permit the A_3-interaction ever obtained by similar functionalization of the free amino group at the 5-position of the simpler pyrazolo-triazolo-pyrimidine structure.



Reagents and conditions: (i) CS_2, RI; (ii) substituted-hydrazines; (iii) $HC(OEt)_3$; (iv) 2-furohydrazide; (v) diphenyl ether, 260 °C; (vi) aq. 10% HCl; (vii) NH_2CN, *p*-TsOH; (viii) 4-methoxyphenyl isocyanate, TEA; (ix) acyl chlorides; (x) ethylamine, substituted-anilines, *N*-methylpiperazine.
R= CH_3, C_3H_7; R_1= CH_3, $Ph(CH_2)_3$; R_2= $COCH_2Ph$-4-isobutyl, $COCH_2Ph$-3,4-Medioxy, $COCH_2Ph$-4-OCH_3; R_3= H, R_4= C_2H_5, Ph-4-OCH_3, Ph-4-OH; R_3=R_4= *N*-CH_3-piperazine.

Scheme 10

The substitution of the methylthio group by a propylthio group at 9-position maintained the A_{2A} affinity and increased the selectivity, whereas the introduction of a phenylpropyl group at N^8-position, instead of a methyl group led to a diminished A_{2A}-interaction. Derivatives showing an ethylamino group at the 9-position, exhibited a quite good affinity for the A_{2A} adenosine receptor subtype. Functionalization of the amino group into a p-methoxyphenylurea causes a decrease of A_{2A} affinity, but a good increase in A_3

affinity (compound of general formula **46** and **50**) was observed. The introduction of hindered amino functions at 9-position, like *p*-methoxyphenylamino, *N*-methylpiperazino or *p*-hydroxyphenylamino was ineffectual for A_{2A}-interaction. Also the conversion of the amino group of these compounds into urea was negative for A_3 interaction, possibly due to an important steric impediment of the radicals introduced.[56,60]

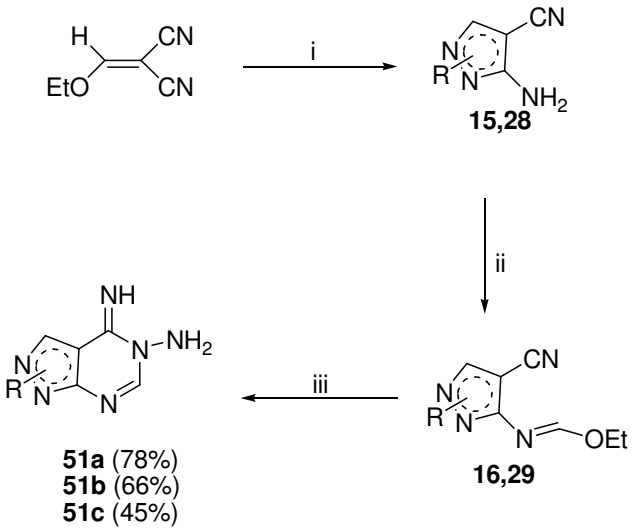
4. New heterocycles with a conserved pyrazolo[3,4-d]pyrimidine core

In order to complete the SAR profile on the tricyclic antagonist familiy, we reported the design and the synthesis of new adenosine ligands, based on the preservation of the pyrazolo[3,4-d]pyrimidine nucleus and the replacement of the 2-(2-furyl)-triazole moiety with other five, six and seven membered rings, fused to the pyrazolo[3,4-d]pyrimidine ring system and functionalized by the introduction of different radicals, such as ester, acid, amide, hydrazide, and alkyl groups.[63]

This chemical purpose started from the key intermediates **51a-c** (5-amino-4-imino-1(2)-substituted-1(2)*H*-pyrazolo[3,4-d]pyrimidines), easily obtained from the N^1- or N^2-substituted amino-cyano-pyrazoles **15** or **28** (Scheme 11). These substrates proved to be versatile items by virtue of their vicinal amino and imino functions, evaluating their reactivity in several cyclization reactions performed with the aim of obtaining new heterocycles with a conserved pyrazolo[3,4-d]pyrimidine core. The substituents selected for the pyrazole nitrogen were mainly N^1-phenyl, but 1-(2-phenylethyl) -like SCH 58261-, and 2-methyl -like the MRE series- were also chosen for comparison reasons.

In this chemical study, the principal employment of the intermediate **51a** (5-amino-4-imino-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine) is described, due to its easy preparation, high reactivity and good yield of reactions. The major limitations of compounds **51b** and **51c** were their low solubility in organic solvents employed in the clusters of reactions performed and, at the same time, the restricted yield of reactions.

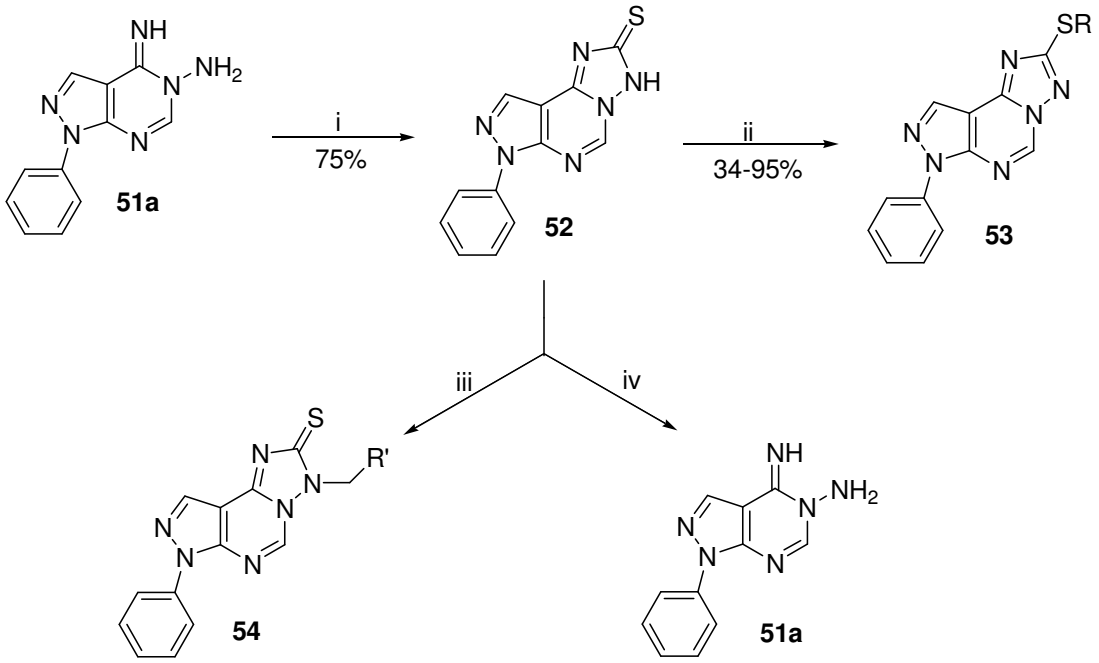
The N^1- or N^2-substituted amino-cyano-pyrazoles **15** or **28** were reacted with triethylorthoformate to give the corresponding ethoxymethylene amino derivatives **16** and **29**. These latter compounds were used as intermediates for the preparation of the key compounds **51a-c** by cyclization with hydrazine hydrate, as depicted in Scheme 11.



Reagents and conditions: (i) substituted-hydrazines; (ii) $HC(OEt)_3$; (iii) hydrazine hydrate.
R= N^1-phenyl (**a**), N^1-2-phenylethyl (**b**), N^2-methyl (**c**).

Scheme 11

When **51a** was allowed to react with CS_2, the pyrazolo-triazolo-pyrimidine-2-thione **52** was obtained. This latter compound was alkylated using several alkylating agents (RX) in refluxing ethanol in the presence of anhydrous sodium acetate to give the corresponding derivatives of general structure **53**. The Mannich bases **54** were obtained *via* the reaction of **52** with formaldehyde and the corresponding amines. In a trial to prepare the hydrazino derivative *via* the reaction of **52** with hydrazine hydrate, unexpectedly the reaction product was found to be starting compound **51a** (Scheme 12).

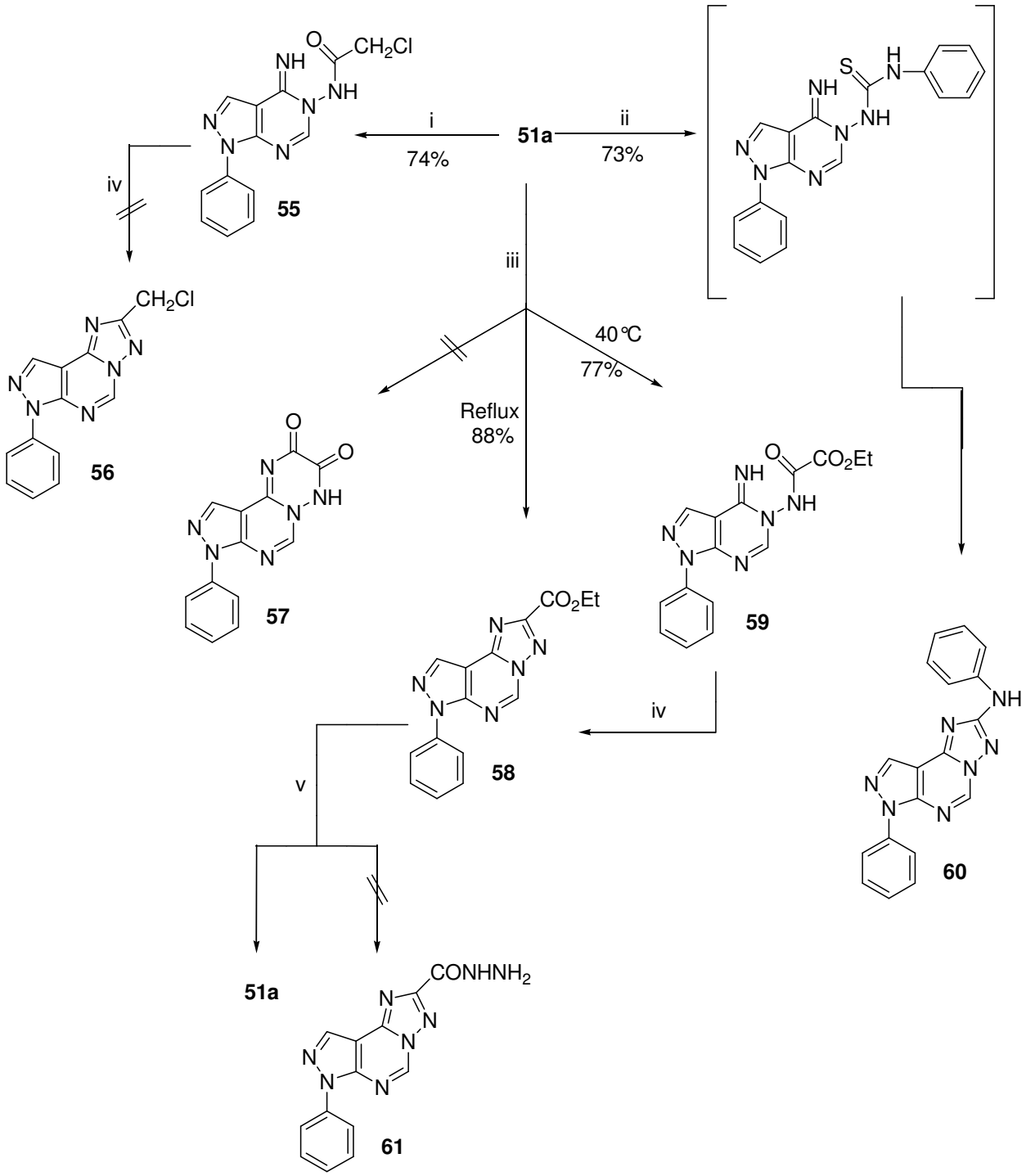


Reagents and conditions: (i) CS_2; (ii) RX, AcONa; (iii) amine, formaldehyde; (iv) hydrazine hydrate.
R= CH_2CO_2Et, 34%; CH_2CO_2H, 80%; CO_2Et, 48%; CH_2COCH_3, 42%; CH_2CONH_2, 39%; CH_2CN, 91%; CH_3, 95%; Et, 48%; $CH_2CONHC_6H_4CH_3$, 56%; $CH(CN)_2$, 37%.
R'= NC_4H_8O, $NHCH_2C_6H_5$, NHC_6H_5.

Scheme 12

As depicted in Scheme 13 the 2-phenylamino derivative **60** was obtained when **51a** was treated with phenylisothiocyanate in refluxing pyridine. Obviously this reaction proceeded *via* the thiourea intermediate with concomitant dehydrosulfurization. Also, the reaction of **51a** with chloroacetyl chloride did not afford the chloromethyl derivative **56** but resulted in the formation of chloroacetylamino derivative **55**, which could not be cyclized into **56** in boiling $POCl_3$. Interestingly, upon warming **51a** in diethyl oxalate the intermediate **59** was obtained. This upon heating in boiling $POCl_3$ gave the ester **58**. Alternatively, compound **58** could be obtained directly from **51a** by heating under reflux with diethyl oxalate and no evidence for the formation of the possible dioxotriazine derivate **57** was observed. Interestingly, hydrazinolysis of the ester **58** did not afford the expected carbohydrazide derivative **61** but resulted in ring opening of the triazole ring giving back the amino-imino compound **51a**.

In Scheme 14, reaction of **51a** with an excess of diethyl malonate gave directly the ester **64**. As was the case with compound **58**, hydrazinolysis of compound **64** did not afford the expected hydrazide derivative but also resulted in opening of the triazole ring with the formation of the aminoimino compound **51a**. The interaction of compounds **51a-c** with an equimolar ratio of ethyl chloroformate gave the corresponding triazino derivatives of general structure **62**, whereas the reaction of **51a** with an excess of same reagent gave the diethoxycarbonylamino compound **65**.

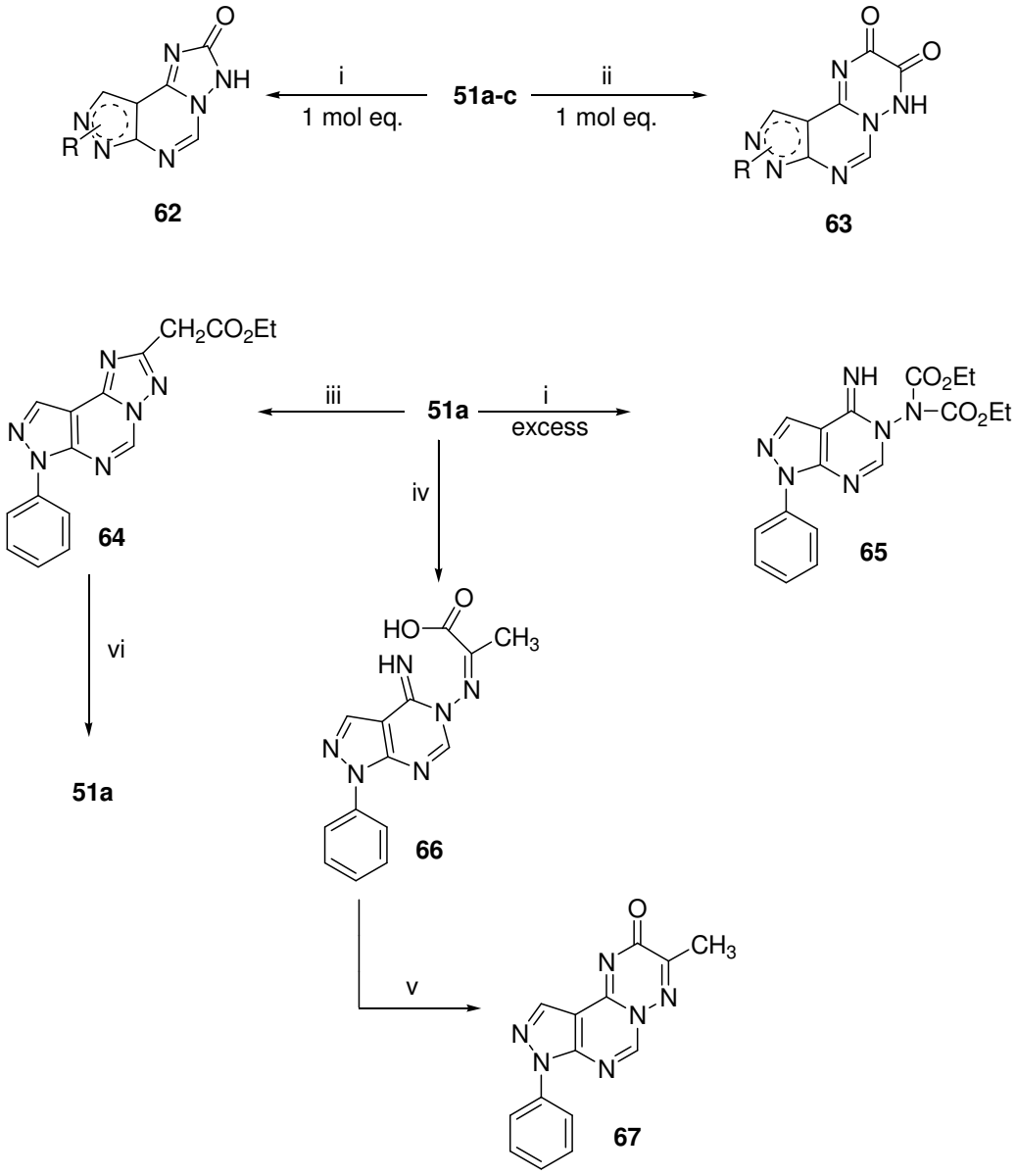


Reagents and conditions: (i) $ClCOCH_2Cl$; (ii) phenyl isothiocyanate; (iii) diethyl oxalate; (iv) $POCl_3$; (v) hydrazine hydrate.

Scheme 13

Treatment of compounds **51a-c** with oxalyl chloride in refluxing dry benzene afforded the corresponding dioxotriazine compounds **63**. However, reaction of **51a** with pyruvic acid gave the intermediate **66**, which was cyclized in boiling $POCl_3$ to give the triazinone compound **67** (Scheme 14).

In a comparative study, it was reported that the reaction of the 3-amino-4-imino-3,4-dihydrothieno[2,3-d]pyrimidine with acetylacetone gave 2-methythieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine and its reaction with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate led to the formation of the parent thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine.[64]



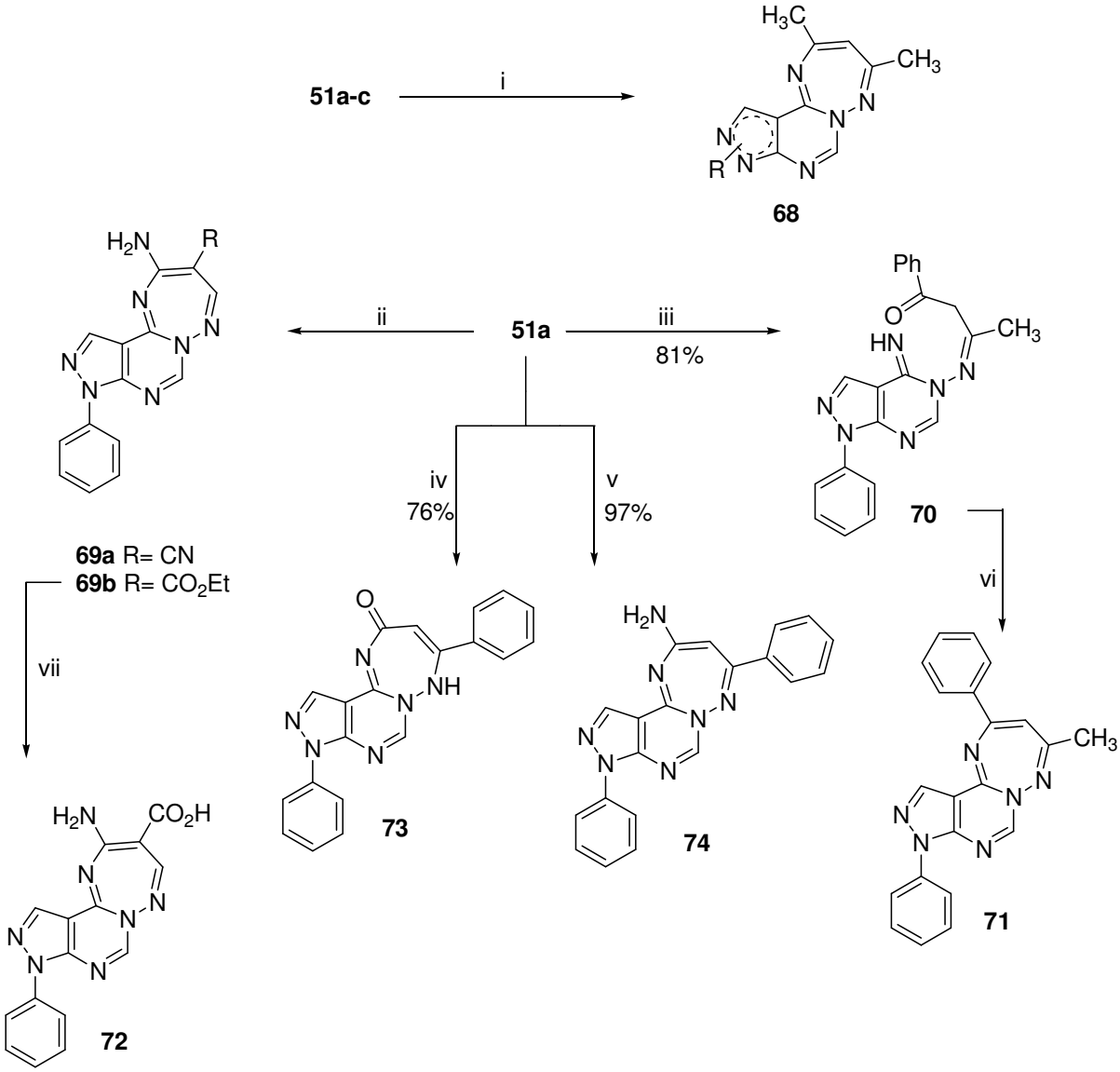
Reagents and conditions: (i) ethyl chloroformate; (ii) oxalyl chloride; (iii) diethyl malonate; (iv) pyruvic acid; (v) $POCl_3$; (vi) hydrazine hydrate.

Scheme 14

In contrast, in our hands when the aminoimino compounds **51a-c** was allowed to react with acetylacetone under the same reaction conditions reported for the reaction described above, the NMR spectrum of the products formed showed two additional methyl signals. This is in agreement with the structure of 5,7-dimethyl-1(2)-substituted-1(2)*H*-pyrazolo[3',4':4,5]pyrimido[1,6-b]triazepines **68**. It is noteworthy that when the reaction was carried out with **51a** in benzoylacetone, the product was identified as the intermediate azomethine compound **70** which could be cyclized to the corresponding triazepine **71** by heating in refluxing phosphoryl chloride (Scheme 15). The reaction between **51a** and ethyl benzoylacetate led to the formation of the triazepine **73**. On the other hand the reaction of **51a** with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyano-acetate did not afford the triazolo derivative, as would be expected from the same reaction reported for the amino-imino derivative of the thienopyrimidine,[64] however the reaction products were identified as the triazepine-aminonitrile and aminoester derivatives **69a,b**. respectively. Compound **74** was finally obtained from the reaction between **51a** and benzoylacetonitrile.

In conclusion, the amino ester **69b** could be hydrolyzed to the corresponding amino acid **72**, however the hydrazinolysis of the ester function of **69b** did not lead to the corresponding amino hydrazide derivative but gave back the amino imino derivative **51a**.

These new derivative above described proved to be completely inactive versus all the adenosine receptor subtypes but allowed us a chemical reactivity study of key starting materials crucial for the synthesis of tricyclic derivatives such as the pyrazole and pyrazolo-pyrimidine nucleus. Further, this new approach permitted the accomplishment of the SAR on the tricyclic antagonists family.[63]



Reagents and conditions: (i) acetylacetone; (ii) ethoxymethylene malononitrile or ethyl (ethoxymethylene)cyanoacetate; (iii) benzoylacetone; (iv) ethyl benzoylacetate; (v) benzoylacetonitrile; (vi) $POCl_3$; (vii) KOH.

Scheme 15

5. Conclusion

All the data herein reported indicate that great chemical, biological and structure-activity relationships results have been obtained with the pyrazolo-triazolo-pyrimidines as antagonists for the adenosine receptor subtypes, and in particular for the A_{2A} and A_3 receptors.

It should be stressed that the chemical functionalizations introduced to the tricycle core and the nature of the radical chosen for the pyrazole nitrogen, for the free exocyclic amino group and for the 2- and 9-positions, are crucial for the modulation of the affinity and selectivity of the antagonists obtained.

Basically, the biological data obtained underlined that the presence of the pyrazolo-triazolo-pyrimidine nucleus is the structural feature necessary to furnish adenosine receptor interaction and antagonism. A clear attempt of the SAR profile can be summarized as subsequently reported: (i) arylcarbamoyl moieties at the N^5-position furnished high A_3 AR-selectivity with the respect to amidic functionalities introduced at the same position; (ii) arylalkyl chains introduced at the N^7-pyrazole position confer good affinity and selectivity for the A_{2A} subtype, whereas any substitutions resulted to be ineffective in terms of affinity for all the other receptor subtypes; (iii) small substituents, like methyl or ethyl, confer good affinity for the human A_3 subtype if introduced at the N^8-pyrazole position; (iv) the radicals introduced at the C^9-position of the pyrazolo-triazolo-pyrimidine scaffold, undependably of their chemical nature, led to a decreased adenosine receptor selectivity even if the receptor interaction was preserved; (v) the furyl ring at the 2-position is indispensable for the affinity at all four adenosine receptor subtypes. No chemical modifications are allowed and the replacement of this heterocycles revealed inactive compounds.

Even if the chemical efforts conducted to replace the 2-(2-furyl)[1,2,4]-triazole moiety with other five, six and seven membered rings fused to the pyrazolo[3,4-d]pyrimidine ring structure revealed a complete series of inactive compounds, they provided new chemical approaches for the synthesis of pioneering heterocyclic systems.

Acknowledgments

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PALLADIUM-CATALYZED ONE-POT MULTIPLE BOND FORMATION IN NITROGEN-CONTAINING POLYHETEROCYCLES SYNTHESIS

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Abstract. *Cascade reactions has become a powerful tool in organic synthesis since several bonds are created in the same step allowing the formation of complex structures from simple starting materials. Such processes, in which ideally a single event triggers the conversion of a starting material to a product which then becomes a substrate for the next reaction until termination leads to a stable final product, are highly desirable not only due to their elegance, but also because of their efficiency and economy in terms of reagent consumption and purification. The discovery of cascade processes is favored in palladium-mediated reactions because they proceed through non-isolable intermediates such as catalytic organometallic species. Therefore, cascade reactions under palladium catalysis were extensively utilized in heterocyclic chemistry. This review is devoted to the contributions appeared after 2003 in the synthesis of nitrogen-containing polyheterocyclic compounds involving a palladium-catalyzed multiple bond formation in a single reaction pot.*

Contents

1. Introduction

The development of new chemical processes designed to produce elaborate heterocyclic structures in rapid, environmentally friendly way has become an important area of research in organic chemistry. The best way in order to achieve rapid syntheses is to combine multiple reaction steps in the same chemical transformation. Such sequential processes offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedure step, thus omitting the need for several workup and purification operations and allowing savings of both solvents and reagents. These processes allowing the one-step multiple bonds formation in the same pot refer in the literature to domino, tandem or cascade reactions, this last term being attributed to reactions involving the formation of more than three bonds during their course.[1] When three or more starting materials are mixed together, the cascade process is referred as a multicomponent reaction.[2]

Palladium has recently achieved a prominent role in synthesis due to the manifold and unique transformations that it is capable of mediating.[3] The wide functional group tolerance and the catalytic nature of most of these processes make palladium an ideal basis for devising unbeatable domino processes. Palladium-mediated reactions proceed through non-isolable intermediates, such as catalytic organometallic species, then contributing to the discovery of such processes.

The focus of this review is to discuss recent achievements in the design of palladium-based cascade synthesis of nitrogen-containing polyheterocycles. It is essentially concerned with cascade processes allowing the construction of the heterocyclic part. Occasionally, the addition of certain reactants, reagents or catalysts can be delayed, so as to increase efficiency. Adjustment of the reaction parameters may also be made during the course of the multiple-reaction chemical processes.

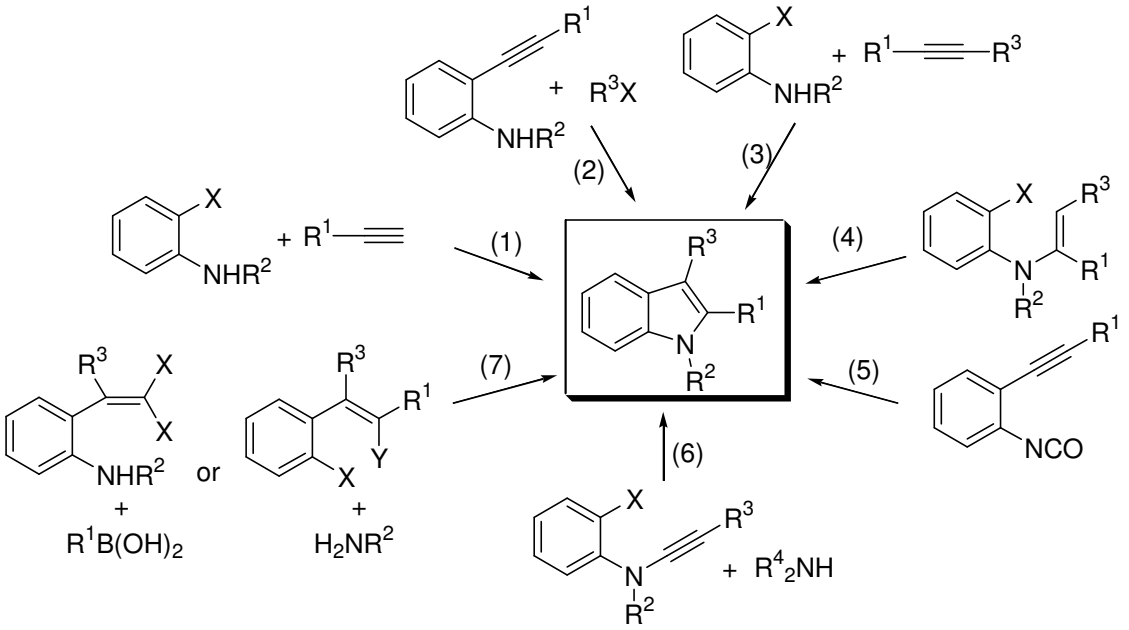
The number of publications concerning cascade reactions in heterocyclic synthesis has greatly increased during the last decade. Palladium has found a wide utility in this field because it effects an extraordinary number of very different reactions, including many carbon-carbon and carbon-nitrogen bond-forming reaction. The palladium and metal-catalyzed synthesis of heterocyclic compounds has been summarized in previous reviews, in which papers published before 2003 are extensively cited.[4] Therefore, in this review are summarized contributions published after 2003.

2. Fused five-membered heterocycles

2.1. Indoles and other annulated pyrroles

The indole ring system is probably the most ubiquitous heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents. Although many procedures have been developed for the synthesis of indoles,[5] annulation mediated by palladium catalysts is one of the most powerful tools.

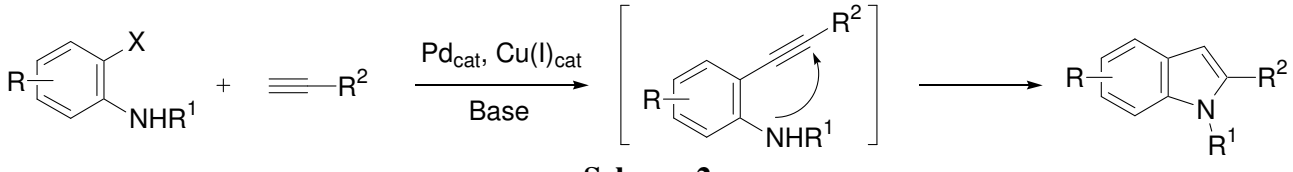
The representative procedures for the palladium-catalyzed cascade synthesis of indoles are categorized as follows (Scheme 1): (1) the Sonogashira reaction between *o*-haloanilines and terminal alkynes followed by the intramolecular amination, (2) the aminopalladation/reductive elimination domino reaction between *o*-alkynyltrifluoroacetanilides and aryl halides (Cacchi reaction), (3) the cyclization *via* the intermolecular Heck-type reaction between *o*-haloanilines and alkynes (Larock heteroannulation), (4) the cyclization *via* the intramolecular Heck reaction of *in situ* generated *N*-arylenamines, (5) the cyclization of arylalkynes bearing an isocyanato group at the *ortho* position, (6) the cyclization of *o*-halo-*N*-alkynylanilides, and (7) the cyclization *via* Buchwald-Hartwig amination reaction.



Scheme 1

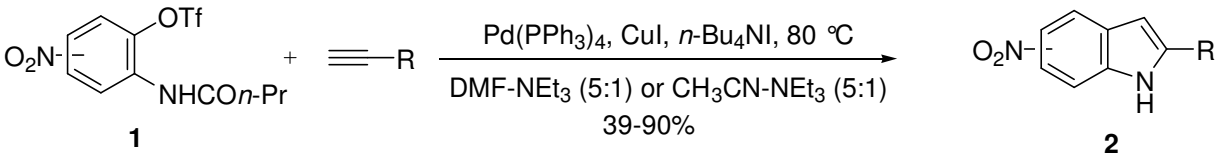
2.1.1. Sonogashira/amination domino reaction between *o*-haloanilines and terminal alkynes

The palladium-catalyzed one-pot cross-coupling and heteroannulation of *o*-haloanilines with terminal alkynes have received considerable attention as a useful method for the construction of indoles.[6] The domino process allows the formation of a C-C bond by Sonogashira reaction[7] and the formation of a C-N bond by an intramolecular amination reaction thus leading to 2-substituted indoles (Scheme 2).



Scheme 2

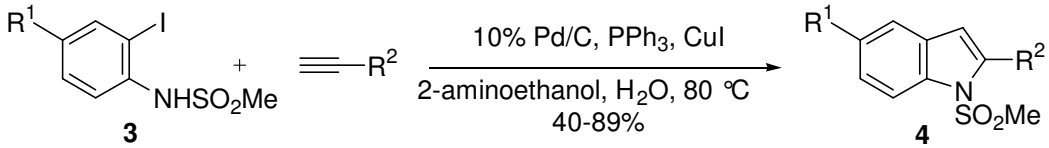
Dai and co-workers reported the preparation of 2-substituted 5-, 6- and 7-nitroindoles **2** by coupling trifloxyanilides **1** with various terminal alkynes (Scheme 3).[8] A variety of functional groups were tolerated in this reaction, and protection of the OH group was not required. Formation of C-7 nitroindole was problematic and harsher conditions were needed to achieve a complete conversion: higher temperature of 100 °C and the stronger base tetramethylguanidine (TMG). It was suggested that the *ortho*-nitro group may form a hydrogen bond with the amido moiety and interfere with the indole ring closure reaction.



1 **2**

Scheme 3

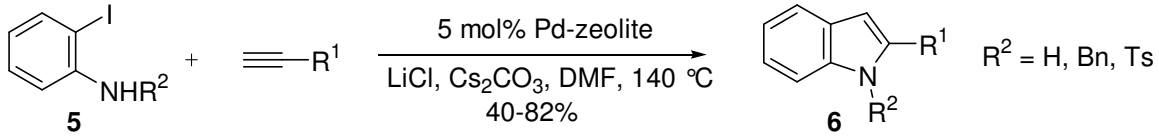
Pal and co-worker have disclosed a straightforward synthesis of 2-substituted *N*-methanesulfonyl indoles **4** starting from derivatives **3** catalyzed by Pd/C in water/2-aminoethanol (Scheme 4).[9] Good to excellent yields were obtained with a large variety of alkynes in this safe and inexpensive water-based reaction.



3 **4**

Scheme 4

Pd incorporated in NaY zeolite was proven by Hong and co-workers to be an excellent catalyst for the one-pot Sonogashira-heteroannulation reaction (Scheme 5).[10] This synthesis required 2 equiv. of the terminal alkyne, 1 equiv. of LiCl, 2 equiv. of Cs_2CO_3, 5 mol% of Pd-loaded zeolite, and DMF at 140 °C. Different protecting groups on the nitrogen of the *o*-iodoanilines **5** were tolerated in this reaction as well as various alkynes giving access to a wide range of functionalized indoles **6**. The catalyst could be recycled up to five times, although with a little loss of its catalytic activity leading to longer reaction times.



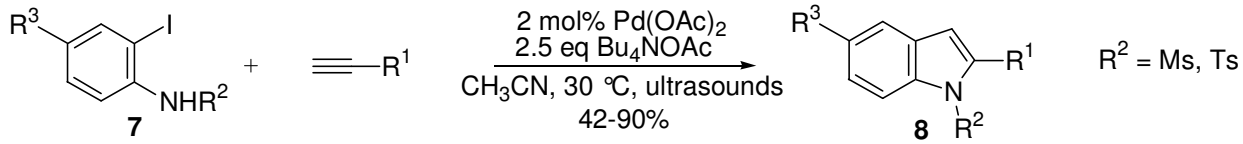
5 **6**

Scheme 5

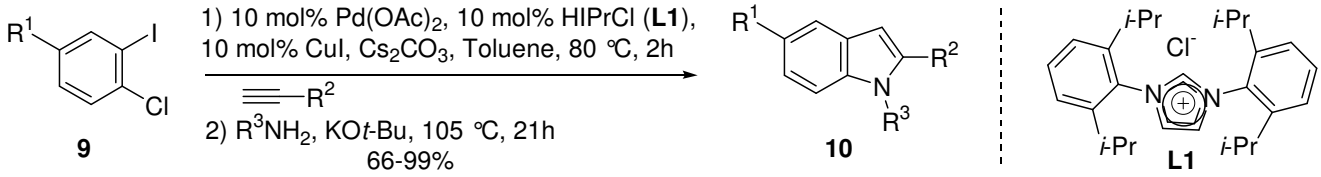
Recently, Palimkar and co-workers reported a ligand-, copper-, and amine-free one-pot synthesis of 2-substituted indoles **8** *via* the Sonogashira/cyclization sequence (Scheme 6).[11] This mild and efficient synthesis has been carried out at room temperature under ultrasound irradiation and standard stirred conditions by using $Pd(OAc)_2$ as the catalyst and Bu_4NOAc as the base in acetonitrile. Both electron-donating and electron-withdrawing substituents on the aryl ring of *o*-iodoanilides **7** were tolerated.

Ackermann has recently extended the domino process for the synthesis of 2-substituted indoles **10** starting from *o*-dihaloarenes **9** (Scheme 7).[12] This indole synthesis consisted of a selective Sonogashira

coupling of the terminal alkynes in the iodo position, a Buchwald-Hartwig amination (see Section 2.1.7.) with primary amines in the chlorine position and a heteroannulation reaction leading to the desired indoles **10**. A single catalytic system consisting of an *in situ* generated palladium carbene complex and CuI gave rise to a highly regioselective transformation and led to the indole derivatives in good yields of isolated products.

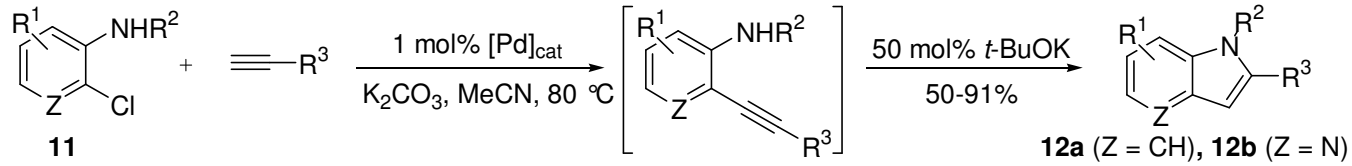


Scheme 6



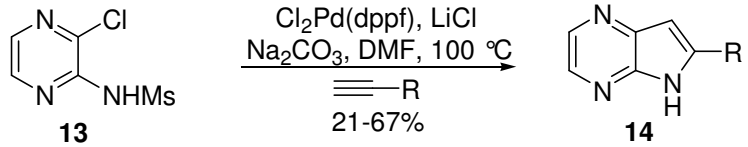
Scheme 7

Pointing out the harsh conditions of the Ackermann synthesis as well as the fact that 1-bromo-2-iodobenzenes and 1-chloro-2-iodobenzenes are normally prepared *via* Sandmeyer iodination of the corresponding *o*-haloanilines, McLaughlin and co-workers reported an efficient access to indoles and azaindoles from readily available *o*-chloroarylamines **11** (Scheme 8).[13] This novel one-pot process comprised a copper-free Sonogashira alkynylation and a base-mediated indolization reaction. Various *N*-substituted substrates were used in this reaction affording a wide range of indoles **12a** and azaindoles **12b** in good yields. An electronic effect was observed for the base-promoted indolization of the alkynylated intermediates. It was found that all pyridine-based substrates and other electron-deficient alkynylated arylamines performed satisfactorily in the indolization, regardless of the substituent on the incipient indole nitrogen atom. In contrast, more electron-rich intermediates were either sluggish or unreactive under the standard conditions.



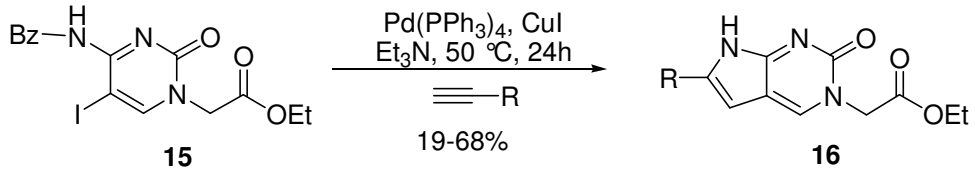
Scheme 8

The Sonogashira/annulation strategy was applied recently by Hopkins and Collar to the synthesis of pyrrolo[2,3-*b*]pyrazines **14** from readily accessible pyrazine **13** and terminal alkynes (Scheme 9).[14] This technique provided an alternative to the previously reported procedures and allowed for more structural diversity due to the greater functional group tolerance. Aryl, heteroaryl and alkyl groups could be introduced successfully at the 6-position.



Scheme 9

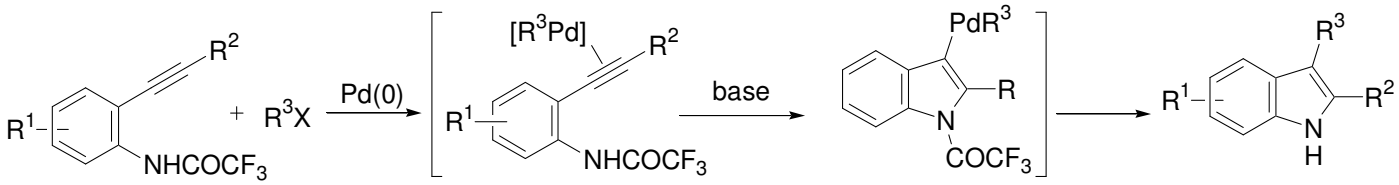
Hudson and co-workers reported the synthesis of fluorescent 7-deazapurine derivatives **16** from 5-iodocytosine **15** in a one-pot sequential Sonogashira cross-coupling and annulation with terminal alkynes (Scheme 10).[15] The spectral properties of these compounds have shown that 7-deazapurines synthesized from substituted phenylacetylenes possess greater fluorescence than those derived from alkyl substituted alkynes.



Scheme 10

2.1.2. Aminopalladation/reductive elimination domino reaction: the Cacchi reaction

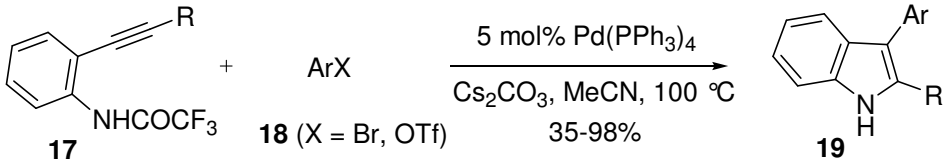
The aminopalladation/reductive elimination domino reaction of alkynes containing proximate nitrogen nucleophiles is a versatile synthetic methodology to build up 2,3-substituted indoles (Scheme 11).[16]



Scheme 11

In their initial studies,[17] Cacchi and co-workers reported that the presence of the trifluoroacetamide group was necessary for the reaction to proceed. This observation supports the notion that the acidity of the nitrogen-hydrogen bond plays a major role in this cyclization reaction. Most probably, a strong anionic nucleophile is required, in order to perform an intramolecular attack across the carbon-carbon triple bond of the (η^2-alkyne)organopalladium intermediate. Alternatively, proton removal from the amido group in the transition state, giving rise to the *trans* addition aminopalladation intermediate, might also be involved. The trifluoroacetamide group provides the additional advantage of being readily cleaved, so as to allow the formation of the indole product containing the free amino functionality.

Cacchi's group has extensively studied this reaction and some selected examples are given in this Section. They reported in 2003 that aryl bromides or triflates **18** are good coupling partners for *o*-alkynyl-trifluoroacetanilide **17** leading in good yields 2-substituted 3-arylindoles **19** (Scheme 12).[18] Several aryl and heteroaryl groups could be introduced in 3-position with moderate to excellent yields.

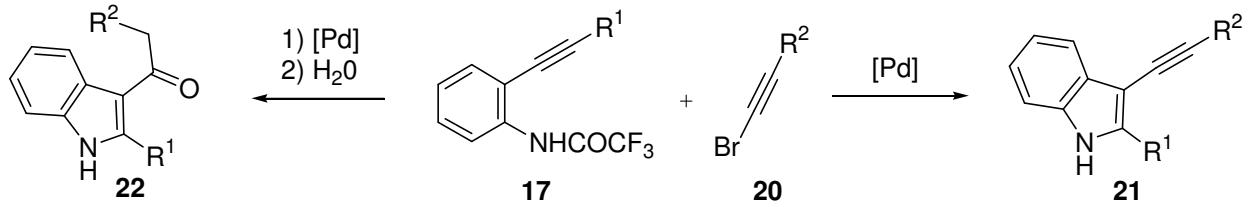


Scheme 12

The same group recently widened the scope of this indole synthesis by reacting *o*-alkynyl-trifuoroacetanilides with aryl chlorides.[19] Increasing the temperature to 120 °C and using a more active

catalyst composed by $Pd_2(dba)_3$ and XPhos (**L2**, see Scheme 24), various arylchlorides as well as 2- and 3-chloropyridines reacted smoothly giving 2,3-disubstituted indoles in moderate to excellent yields.

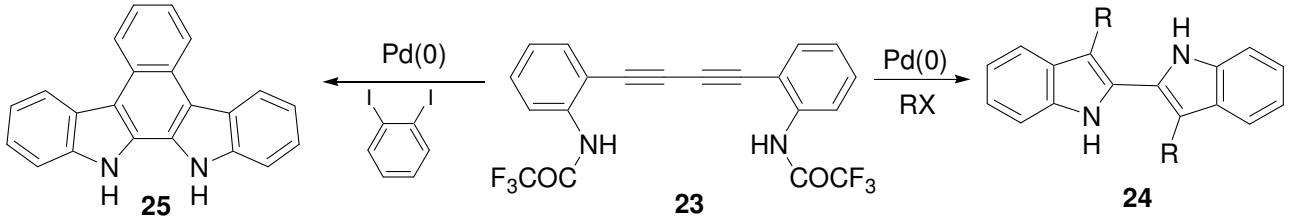
Cacchi and co-workers reported also the use of 1-bromoalkynes **20** for the preparation of 2-substituted 3-alkynylindoles **21** and 2-substituted 3-acylindoles **22** (Scheme 13).[20] The process occurred under mild conditions and tolerated many important functional groups. Acylindoles **22** could be prepared from *o*-alkynyltrifluoroacetanilides **17** and 1-bromoalkynes **20** *via* a one-pot cyclization-hydration protocol, omitting the isolation of alkynylindoles **21**. This methodology can provide a useful approach to this important class of indole derivatives and a convenient alternative to classical methods based on the acylation of indoles.



22 **17** **20** **21**

Scheme 13

Arcadi and co-workers have extended this methodology to the synthesis of biindolyl compounds **24** through a double Cacchi reaction of the diyne derivative **23** (Scheme 14).[21] Aryliodides have proven to be the best partners in this reaction avoiding non- and mono-arylated side products. A nice entry to the new benzo[*c*]indolo[2,3-*a*]carbazole **25** was described by employing 1,2-diiodobenzene as the coupling partner.



25 **23** **24**

Scheme 14

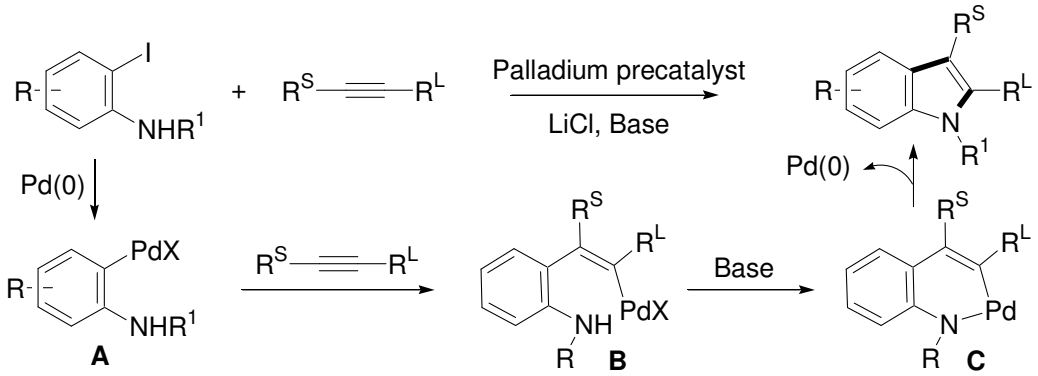
Lu and co-workers reported recently a practical one-pot, regiospecific three-component process for the synthesis of 2,3-disubstituted indoles *via* consecutive Pd-catalyzed Sonogashira coupling, amidopalladation, and reductive elimination (Scheme 15).[22] In an initial study, bromobenzene was added after the Sonogashira coupling between *o*-iodotrifluoroacetanilide **26** and phenylacetylene was complete. To further simplify the procedure, bromobenzene was added from the beginning, in a one-pot reaction, thus eliminating the need to monitor the progress of the Sonogashira coupling before proceeding to the next step. The overall reaction rate was significantly enhanced and 2,3-substituted indoles **27** were obtained in good to excellent yields from various alkynes and bromoaryl compounds.

26 **27**

Scheme 15

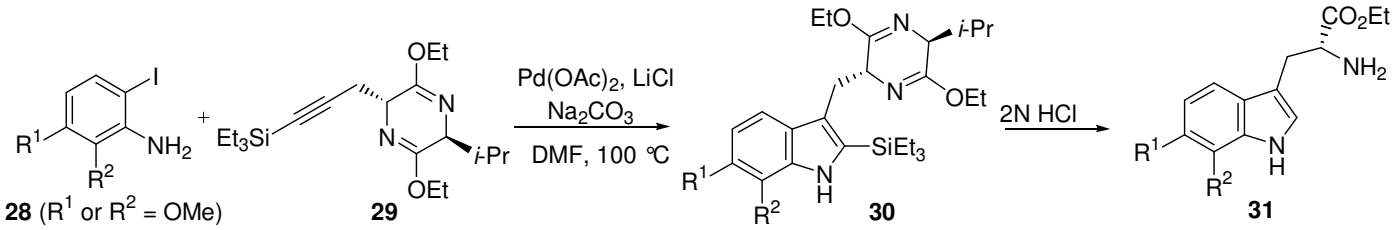
2.1.3. Intermolecular Heck-type reaction between *o*-haloanilines and alkynes: the Larock heteroannulation

The Larock heteroannulation reaction[23] was shown to work well in the presence of a catalytic amount of palladium precatalyst (more frequently $Pd(OAc)_2$) associated or not with a phosphine ligand, a base and a stoichiometric amount of a chloride source (better yields are usually obtained with LiCl) (Scheme 16). The heteroannulation reaction is regioselective and almost always gives the 2,3-disubstituted indoles, where the more sterically hindered group (R^L) of the alkyne occupies the 2-position of the indole ring while the small group (R^S) occupies the 3-position. This intermolecular reaction allows the construction of the indole ring by the successive formation of a C-C bond and a C-N bond. From a mechanistic consideration,[24] this indole synthesis proceeds *via* oxidative addition of the aryl halide to Pd(0), regioselective *syn*-insertion of the alkyne into the arylpalladium **A**, nitrogen displacement of the halide in the resulting vinylic palladium intermediate **B** to form a six-membered, heteroatom-containing palladacycle **C**, and reductive elimination to form the indole and regenerate Pd(0). This protocol can be used to generate indoles with high structural complexity since both starting materials can possess considerable functionality. Therefore, it is not surprising that this important reaction has received considerable attention since its discovery[25] but only recent examples will be highlighted in this Section.



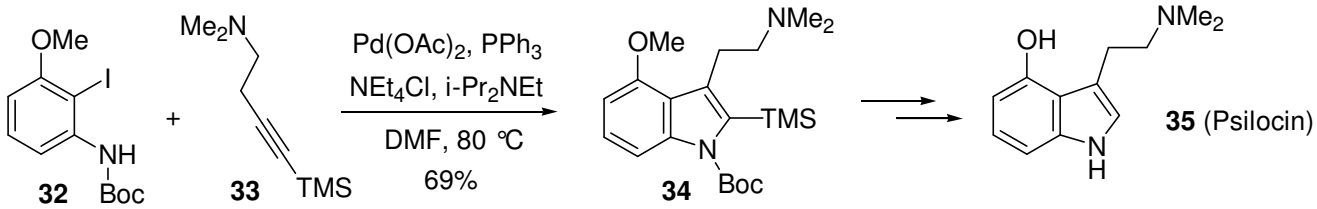
Scheme 16

In an elegant approach to optically active tryptophans, Cook and co-workers have utilized the Larock heteroannulation for the large-scale synthesis of D-tryptophans **31** (Scheme 17).[26] The key indole-forming step involved reaction between iodoanilines **28** and the propargyl-substituted chiral auxiliary **29** generating indoles **30** in good yields. Further acidic hydrolysis of **30** in order to remove the chiral auxiliary with concomitant loss of the indole-2-silyl group gave D-tryptophan ethyl esters **31**.



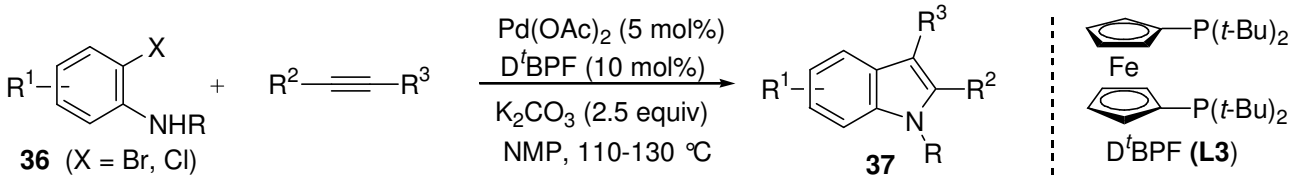
Scheme 17

In a similar fashion, Gathergood and Scammells reported the preparation of *N*,*N*-dimethyl tryptamine **34** from *N*-Boc protected *o*-iodoaniline **32** and alkyne **33**. Indole **34** was then used for the synthesis of the natural product psilocin **35** (Scheme 18).[27]



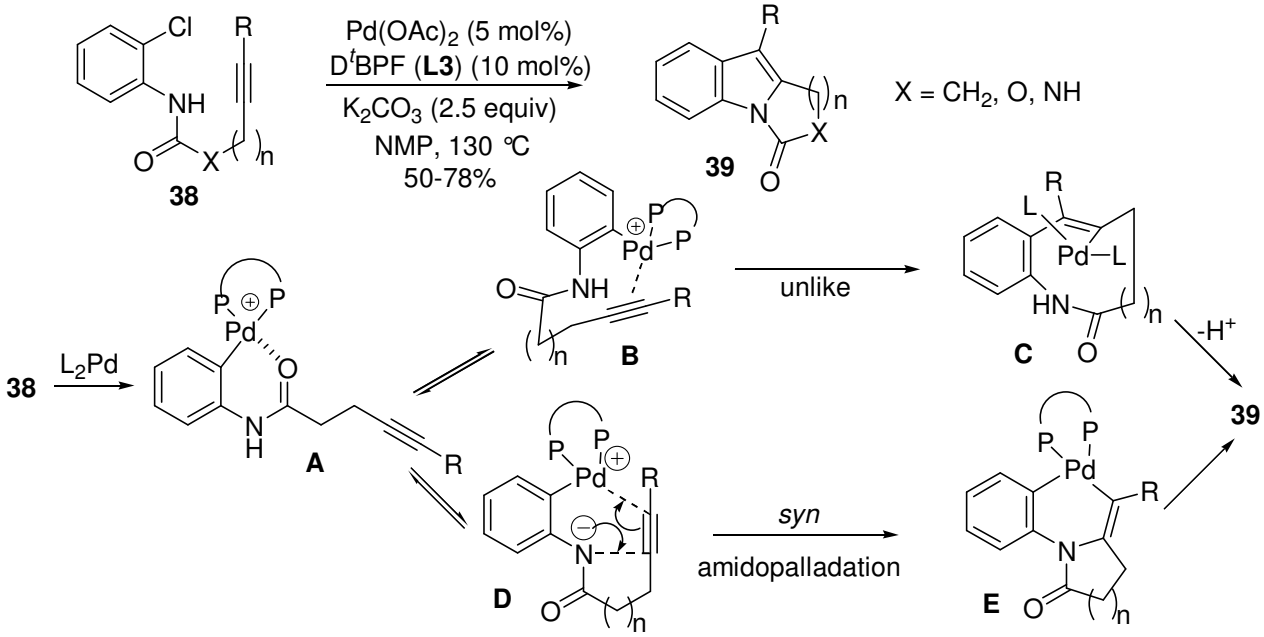
Scheme 18

Recently, Lu and co-workers reported the first Larock heteroannulation using 2-bromo- and 2-chloroanilines with internal alkynes, which greatly extended the scope and utility of this reaction which was limited to iodoaniline derivatives (Scheme 19).[28] Reaction of a variety of either 2-bromo- or 2-chloroanilines **36** with various internal alkynes in the presence of K_2CO_3 and $Pd(OAc)_2$ employing 1,1'(di-*tert*-butylphosphino)ferrocene (**L3**) as the ligand in NMP at 110-130 °C provided 2,3-disubstituted indoles **37** in yields ranging from 60 to 99% and with excellent regioselectivity.



Scheme 19

More recently, the same group reported an intramolecular version of the Larock heteroannulation. Under the same reaction conditions used previously, several polycyclic indole skeletons **39** were obtained in reasonable yields from 2-chloroanilines bearing tethered acetylenes **38** (Scheme 20).[29]



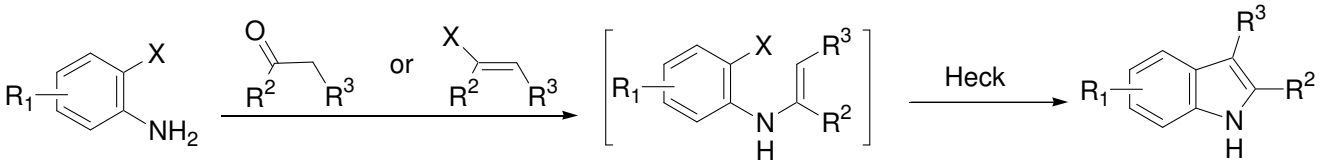
Scheme 20

It was pointed out that an unusual *syn* amidopalladation was necessary for the reaction to proceed. Indeed, the usual "*endo-dig*" carbopalladation which would afford aminopalladacycle **C** (through **B**) is unlikely with small *n* value because of the strained geometry. Therefore, this novel domino process involves, more likely, the following steps: (1) formation of the Pd-containing zwitterion **D** by standard oxidative

addition of Pd(0) to **38**, probably through **A**, (2) formation of the bicyclic palladacycle **E** by *syn* amidopalladation of the acetylene into **D**; and (3) reductive elimination of the palladacyle **E** to afford the indole ring.

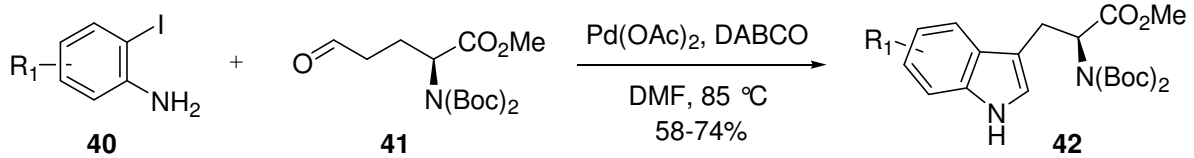
2.1.4. Cyclization *via* the intramolecular Heck reaction of *N*-arylenamines

The *N*-arylenamines necessary for the intramolecular Heck reaction[30] can be formed from *o*-halo-anilines either by condensation with carbonyl compounds (aldehydes or ketones) or by palladium-catalyzed alkenylation reaction (Scheme 21). The original idea was reported in 1997 by Chen and co-workers by reacting *o*-iodoanilines and ketones in the presence of a palladium catalyst.[31] An amine base was critical to the successful coupling and DABCO (1,4-diaza-bicyclo-[2,2,2]-octane) was found to be the base of choice producing indole derivatives in good yields.



Scheme 21

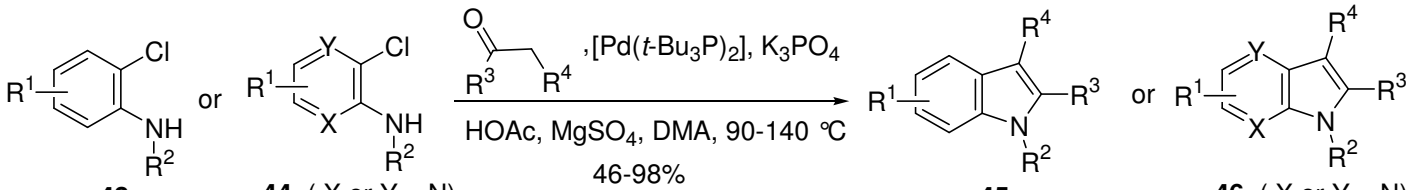
Zhu and co-workers reported that aldehydes can serve as coupling partners in this reaction and they applied this methodology to perform an efficient synthesis of tryptophans (Scheme 22).[32] Coupling of substituted *o*-iodoanilines **40** with methyl (S)-2-*N*,*N*'-di-*tert*-butoxycarbonyl-5-oxo-pentanoate **41**, derived from glutamic acid, in DMF in the presence of $Pd(OAc)_2$ and DABCO provided substituted tryptophans **42** in good to excellent yields.



40 **41** **42**

Scheme 22

Nazaré and co-workers extended the scope of the Heck annulation reaction by coupling chloroanilines **43** and chloroaminopyridines **44** with cyclic and acyclic ketones.[33] Indoles **45** and azaindoles **46** were obtained in moderate to excellent yields (Scheme 23). The optimized reaction conditions, using K_3PO_4/acetic acid and $[Pd(tBu_3)P)_2]$, are very broadly applicable and tolerate a wide variety of substitution patterns and functionalities.

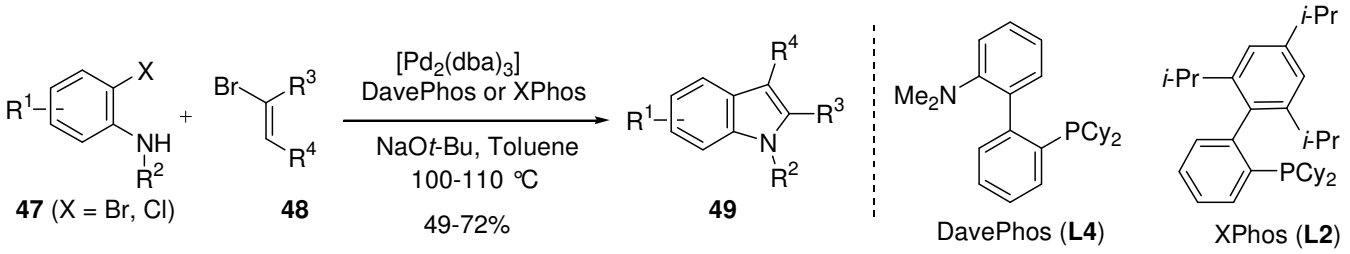


43 **44** (X or Y = N) **45** **46** (X or Y = N)

Scheme 23

Barluenga and co-workers disclosed a new palladium-catalyzed cascade reaction consisting of an alkenyl amination followed by an intramolecular Heck reaction (Scheme 24).[34] Various substituted indoles **49** were obtained in good yields from the reaction of *o*-haloanilines **47** and alkenyl bromides **48**. The reaction

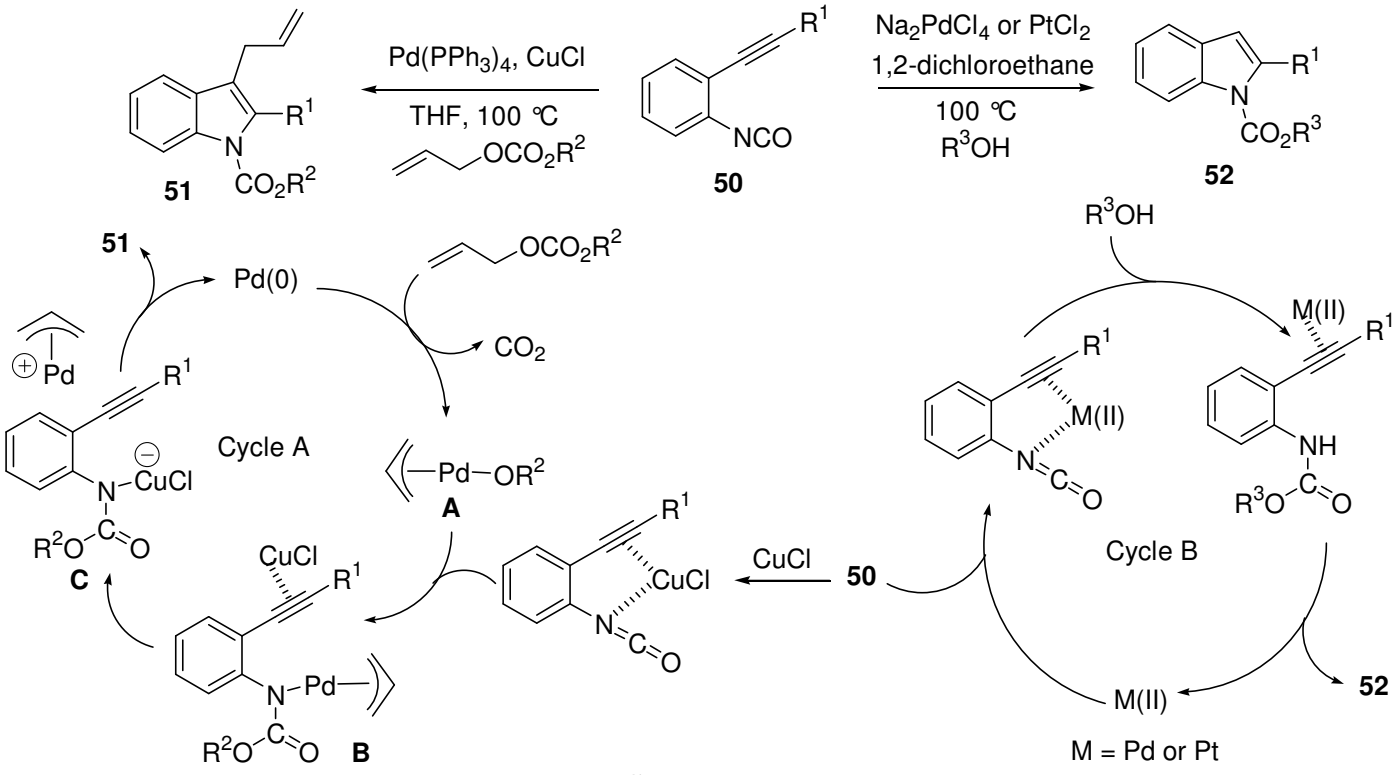
proceeded with aryl, alkyl, and functionalized substituents in both starting reagents. An extensive screening of ligands, bases, and reaction conditions revealed that the $[Pd_2(dba)_3]$/DavePhos (**L4**), NaO*t*Bu, toluene combination at 100 °C were the optimized reaction conditions to carry out the cascade process with *o*-bromoanilines while *o*-chloroanilines required XPhos **L2** as the ligand. The cyclization was also studied with *N*-substituted *o*-bromoanilines which gave rise to *N*-substituted indoles; however, in that case, indole formation occurred only with 1-substituted-2-bromoalkenes.



Scheme 24

2.1.5. Cyclization of arylalkynes bearing an isocyanato group at the *ortho* position

2-Substituted 3-allylindoles **51** were prepared by Yamamoto and co-workers *via* cyclization of *o*-(alkynyl)phenylisocyanates **50** with allyl carbonates in the presence of $Pd(PPh_3)_4$ and CuCl (Scheme 25).[35]



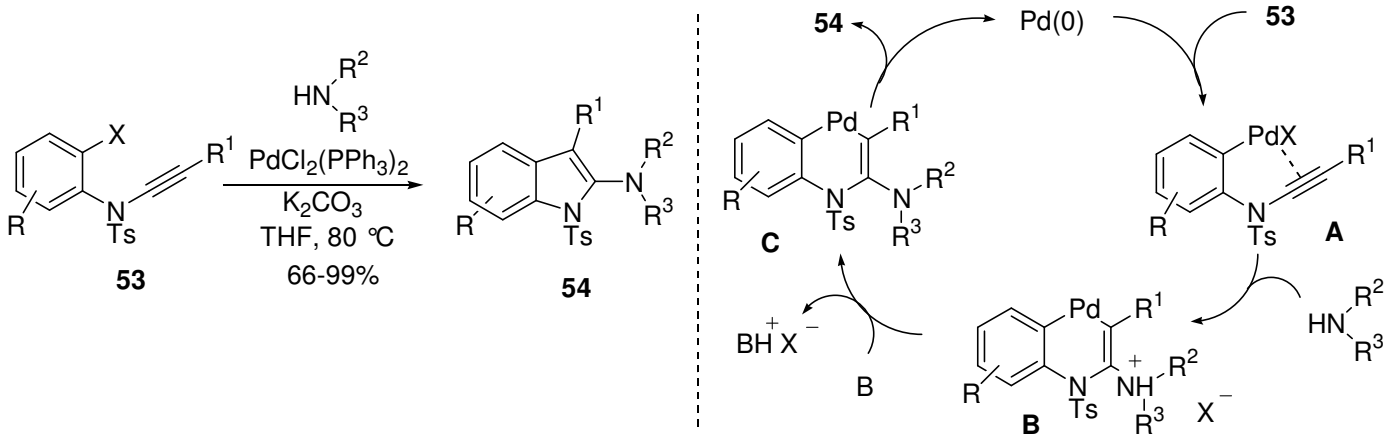
Scheme 25

CuCl gave higher yields than CuBr and was found to be far superior to other copper salts such as CuI, CuOAc, $Cu(OTf)_2.C_6H_6$ and $CuCl_2$. Longer reaction times were required when R^1 was a bulky substituent, and with a *tert*-butyl group, no allylindole was obtained. The authors noted that changing the catalyst system to Na_2PdCl_4 or $PtCl_2$ and using alcohols instead of allyl carbonates generated 2-substituted *N*-(alkoxycarbonyl)indoles **52** in good yields. For the formation of indoles **51**, a likely sequence involves the

reaction of the isocyanate group, activated by the coordination of CuCl, with the π-allylpalladium alkoxide complex **A** to give the π-allylpalladium complex **B**, a transmetallation step generating the intermediate **C**, and, most probably, a trans-aminopalladation followed by reductive elimination (Scheme 25, cycle A). Indoles **52** are formed after coordination of the metal salt to both alkynyl and isocyanate groups which facilitates the addition of the alcohol to the isocyanate, and successive aminometalation and regeneration of the catalyst (Scheme 25, cycle B).

2.1.6. Cyclization of *o*-halo-*N*-alkynylanilides

As it was shown, a variety of synthetic protocols to indole derivatives were based on the use of alkynes with acetylenic moiety *ortho* to a nitrogen functionality. A strategy has been developed by Witulsky and co-workers in which the alkyne fragment is bound to the nitrogen atom.[36] Reaction of *o*-halo-*N*-alkynylanilides **53** with primary or secondary amines gave the interesting class of 2-aminoindoles **54** (Scheme 26). In the search of optimal conditions, several additional bases such as DABCO, KOH, KO*t*-Bu, K_2CO_3, and Cs_2CO_3 were tested. K_2CO_3 and Cs_2CO_3 proved to be the most efficient ones. THF was found to be more suitable than DMF or toluene. $PdCl_2(PPh_3)_2$ as precatalyst gave higher yields than $Pd(PPh_3)_4$, very likely because of its lower phosphine content. In the proposed mechanism the Pd(0) species generated *in situ* inserts into the carbon-halogen bond of **53** to give the σ-aryl-π-alkynepalladium complex **A**. Subsequently, addition of amine to the activated carbon-carbon triple bond affords the palladacycle **B**. Deprotonation of the positively charged nitrogen atom followed by reductive elimination of the resultant intermediate **C** gives rise to the indole product **54** and regenerates the active catalyst.



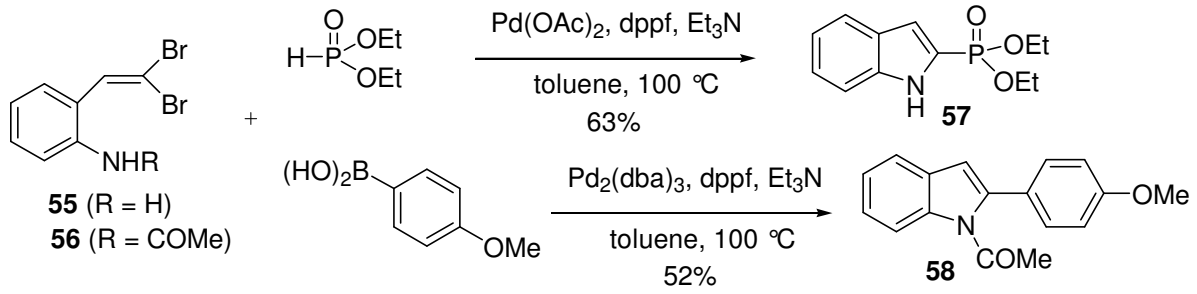
Scheme 26

2.1.7. Cyclization *via* Buchwald-Hartwig amination reaction

After the pioneering work of Buchwald[37] and Hartwig[38] groups on the palladium-catalyzed C-N bond forming reaction from aryl halides and triflates with amines, amides, and carbamates, the methodology has gained enormous popularity due to its wide substrate scope. Its utility in indole synthesis as a part of a cascade process has appeared only very recently.

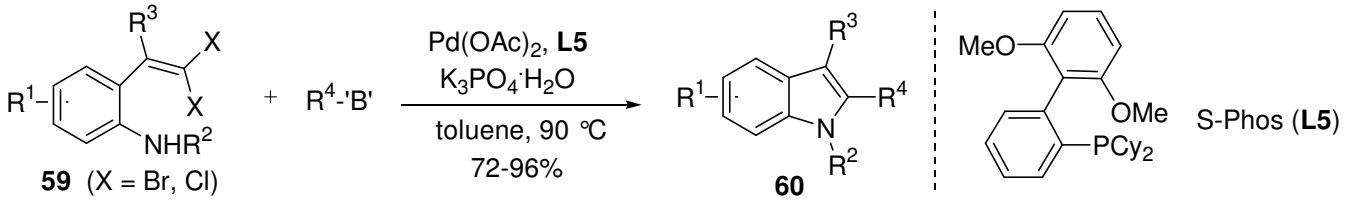
Bisseret and co-workers reported the synthesis of 2-substituted indoles **57** and **58** starting from *o*-(2,2-dibromovinyl)-phenylaniline **55** and its *N*-acyl derivative **56** (Scheme 27).[39] The indole synthesis based on the tandem Suzuki coupling/amination required the utilization of the acetanilide derivative (unsatisfactory results were obtained with the free aniline or the Boc derivative) and the presence of

$Pd_2(dba)_3$ instead of $Pd(OAc)_2$. A possible mechanism would involve first the reaction of the *trans* C-Br bond with the boronic acid and in a second step the intramolecular amination with the *cis* C-Br bond.



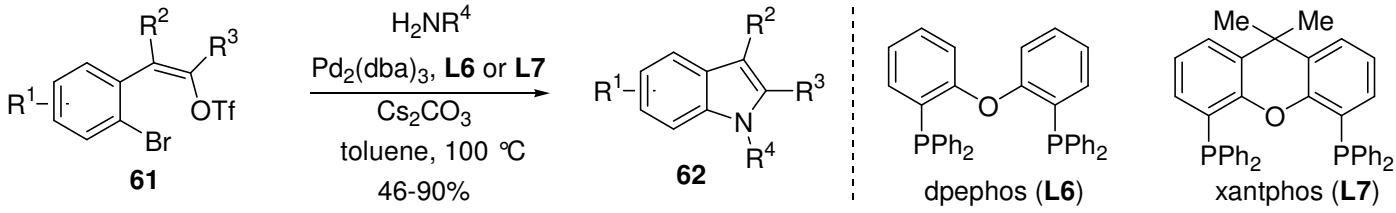
Scheme 27

Lautens and co-workers extended the scope of the tandem Suzuki/amination reaction for the synthesis of various 2-substituted and 2,3-disubstituted indoles (Schema 28).[40] Optimization studies showed that $Pd(OAc)_2$ coupled with S-Phos ligand **L5** in the presence of $K_3PO_4 \cdot H_2O$ in toluene at 90 °C were the best reaction conditions. Various commercially available aryl- and heteroarylboronic acids of different electronic and steric character were evaluated. For all cases, the expected indoles **60** were isolated in good yields. Extension to alkenyl boronic acids, alkenyl catechol boronate esters and trialkylboron reagents also gave the desired products in good yields. Various substituted *ortho-gem*-dibromo- and dichlorovinylanilines **59** reacted smoothly with phenylboronic acid under the reaction conditions. Substitution on the aniline nitrogen using *N*-benzyl-substituted secondary amine worked almost as well as the primary amine substrate. In contrast, the use of an activating acetyl or tosyl protecting group gave very low yields.



Scheme 28

Willis and co-workers reported a tandem alkenyl and aryl C-N bond formation for the rapid preparation of functionalized indoles (Scheme 29).[41] Under optimized conditions ($Pd_2(dba)_3$, dpephos **L6**, Cs_2CO_3, toluene, 100 °C) a wide variety of primary amines performed well producing the desired indoles **62** in good yields. For electron-poor nucleophiles, the use of xantphos **L7** as ligand was optimal.



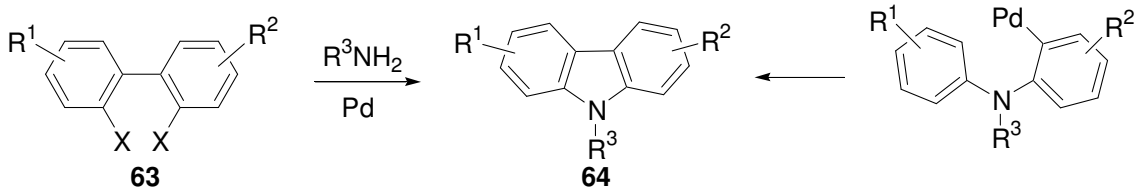
Scheme 29

Under these modified conditions carbamate, sulfonamide, and amide functionalities were all incorporated in good yields. The use of propionamide has the benefit of also allowing efficient access to the free indole NH function. Variations in the ketone and aryl halide component of the bis-activated carbon

frameworks **61** were also explored. Indole formation was effective for a variety of architectures: five-, six-, and seven-membered cyclic ketones, simple acyclic, aryl and ketal-functionalized ketones were all incorporated efficiently.

2.2. Carbazoles

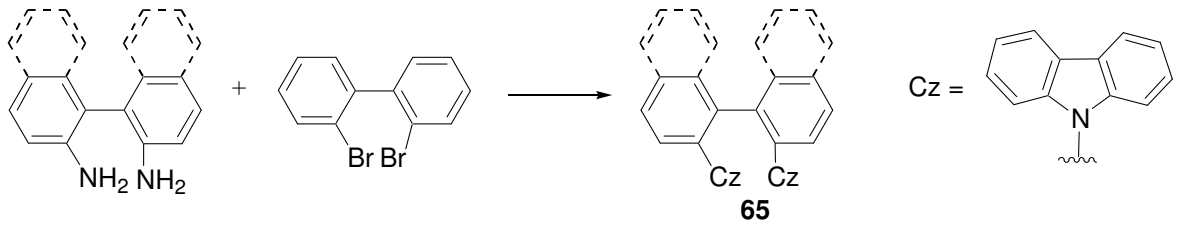
Due to the wide range of biological and physical properties of carbazoles, a number of methodologies for their construction have been reported.[42] Although palladium catalysts were used to generate the carbazole ring, syntheses based on a palladium-catalyzed cascade process are not numerous and are very recent. They are based on two main reactions for the ring closure: Buchwald-Hartwig amination of 2,2'-dihalobiphenyl with primary amines and intramolecular Heck-type reaction between two aryl groups of diarylamines (Scheme 30).



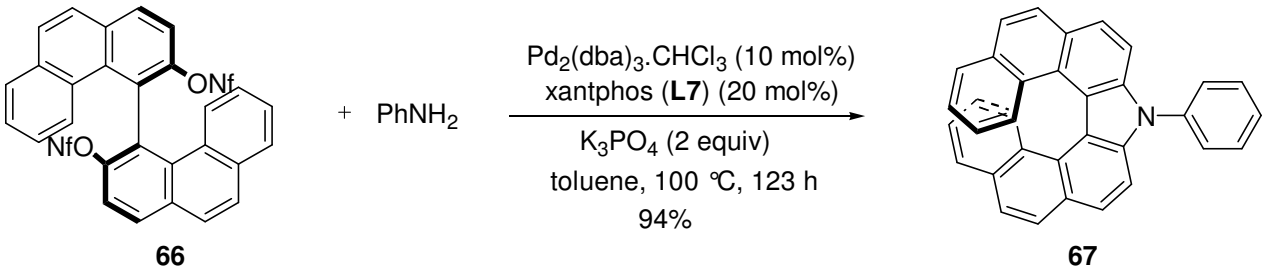
Scheme 30

2.2.1. Double Buchwald-Hartwig amination of 2,2'-dihalobiphenyl

The double *N*-arylation strategy for the synthesis of carbazoles was first reported by Nozaki and co-workers in 2003.[43] They reported the synthesis of various highly substituted carbazoles **64** by reaction of primary amines with 2,2'-dihalobiphenyl compounds **63** in the presence of $Pd_2(dba)_3$, a phosphine ligand (*t*-Bu_3P or (S)-BINAP) and NaO*t*-Bu in toluene at 80 °C (Scheme 30). This methodology was also applied to the efficient synthesis of sterically crowded 2,2'-dicarbazolyl-1,1'-biaryl compounds **65** which exhibited interesting fluorescence properties (Scheme 31).



Scheme 31

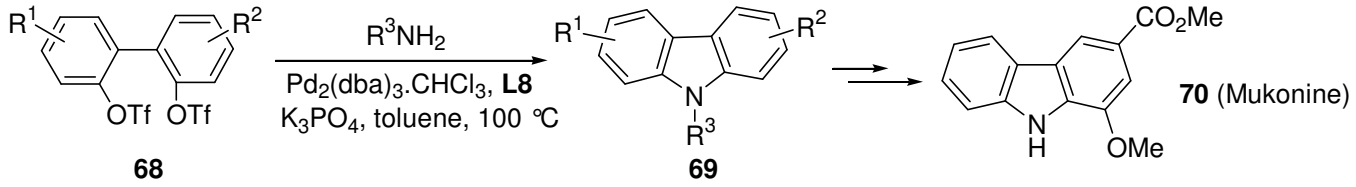


Scheme 32

Convinced by the powerful utility of the double *N*-arylation strategy for the efficient synthesis of attractive organic materials, Nozaki and co-workers reported recently the stereospecific synthesis of aza[7]helicene **67** from optically active 4,4'-biphenanthr-3,3'-ylene dinonaflate **66** (Scheme 32).[44] Compound

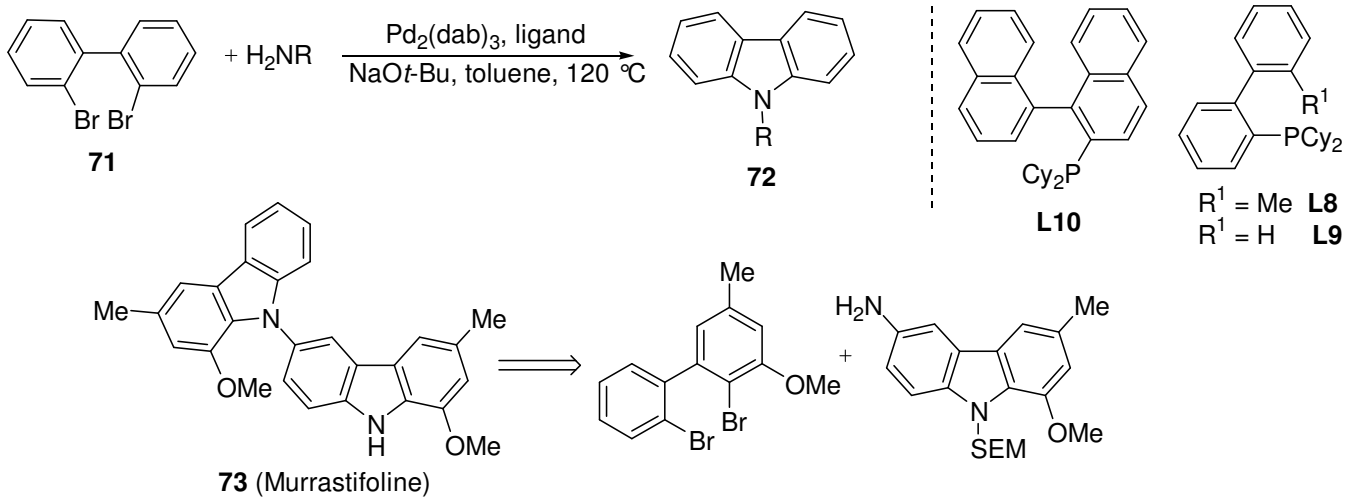
67 did not undergo racemization even under the harsh conditions used for this reaction (toluene, 100 °C for 123 h).

Nozaki and co-workers have investigated the scope of the double *N*-arylation strategy for the synthesis of multisubstituted carbazoles **69** (Scheme 33).[45] Palladium complexes supported by ligand **L8** (Scheme 34) or xantphos **L7** (Scheme 29) were found to be efficient catalysts for the reaction. These catalysts allowed the use of anilines with an electron-donating or electron-withdrawing substituent and multisubstituted ditriflates **68** as substrates. *N*-unsubstituted carbazoles could be prepared using *O*-tert-butyl carbamate which served as ammonia equivalent after deprotection. This methodology was also applied to the synthesis of mukonine carbazole alkaloid **70**.



Scheme 33

Chida and co-workers reported recently the synthesis of various *N*-substituted carbazoles **72** by reaction of primary amines and 2,2'-dibromobiphenyl **71** (Scheme 34).[46] By the choice of ligands, both aryl and aliphatic amines including *tert*-butylamine and *O*-protected glucopyranosylamine could be transformed into the corresponding carbazoles. Ligand **L9** was found to be the best ligand for arylamines while the more electron-rich and sterically bulky **L10** allowed the reaction of alkylamines. It was proposed that the electronic and steric factors of this ligand play an important role in suppressing any undesired side reactions, such as the formation of unreactive Pd bis-amine complexes and/or β-hydride elimination of the Pd-amido intermediates. For *tert*-butylamine, Xphos **L2** (Scheme 24) was needed to reach an acceptable yield of 42%. Based on this methodology, the first total synthesis of murrastifoline **73** has been accomplished.

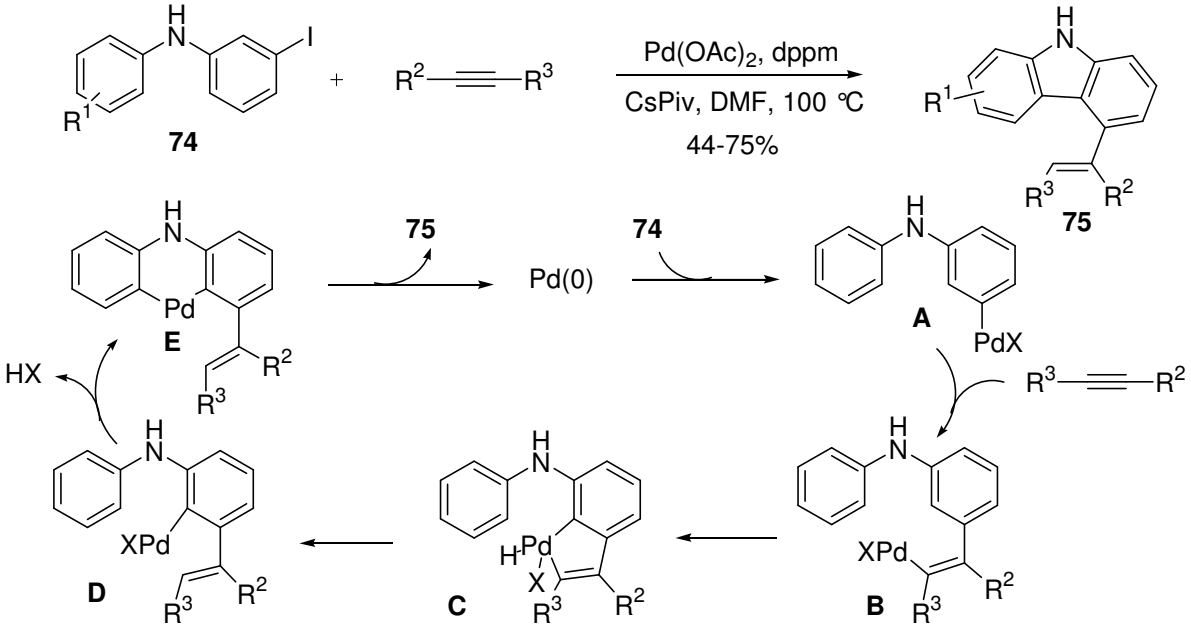


Scheme 34

2.2.2. Intramolacular Heck-type reaction of diarylamines

Larock and Zhao reported the preparation of substituted carbazoles **75** by coupling alkynes and *N*-(3-iodophenyl)anilines **74** under palladium catalysis (Scheme 35).[47] This synthesis required 5 mol% of $Pd(OAc)_2$, 5 mol% of bis(diphenylphosphino)methane (dppm), 2 equiv. of CsO_2CMe_3 (CsPiv) in DMF at

100 °C and allowed the formation of carbazoles **75** in good yields and with good regioselectivities for the alkyne insertion. A plausible mechanism for this process is proposed in Scheme 35. Intermediate **A** is first generated by oxidative addition of the aryl iodide **74** to Pd(0). Subsequent intermolecular carbopalladation would be expected to afford intermediate **B**. The resulting vinylic palladium intermediate undergoes simultaneous C-H activation and palladium migration from the vinylic position to the aryl position generating intermediate **D** through palladacycle **C**. The six-membered ring intermediate **E** is presumably generated by a second C-H activation directed by the nitrogen, and the desired products **75** are formed after reductive elimination.



Scheme 35

2.3. (Iso)indoline, (iso)indolinone and fused pyrrolidines

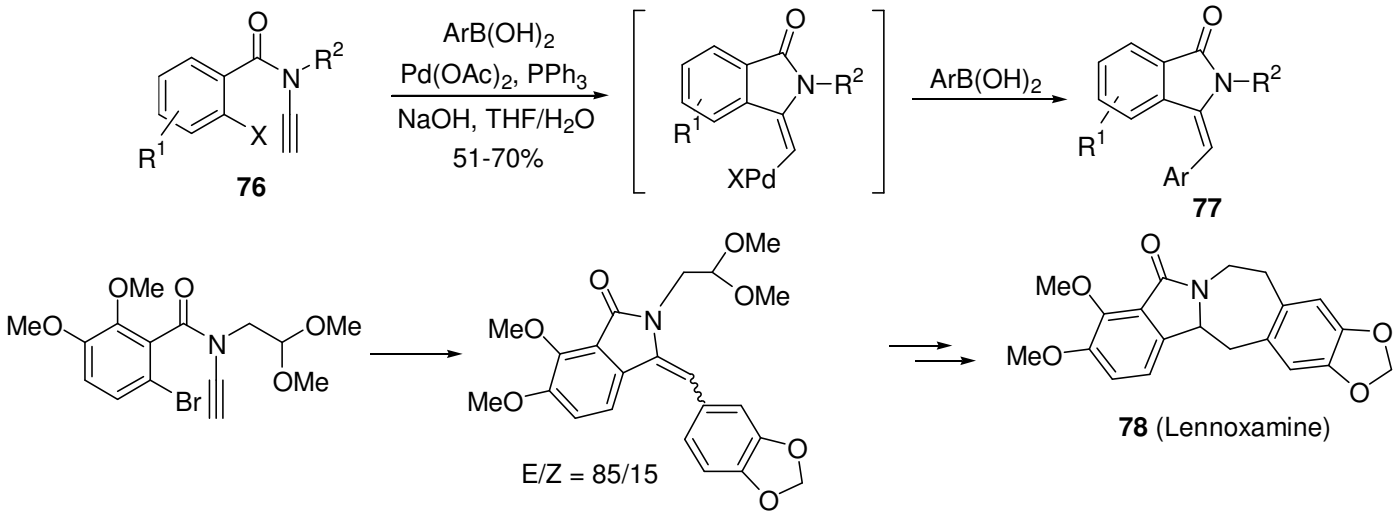
Molecules containing the hydrogenated and/or oxygenated pyrrole and indole motifs have been incorporated in a significant number of pharmaceutically relevant compounds. Therefore, several rapid syntheses have been developed to prepare these interesting pharmacophores.

2.3.1. Cyclisation *via* Heck reaction

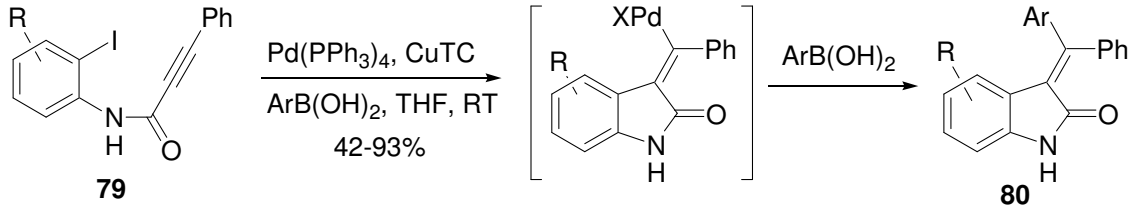
Cossy and co-workers reported the efficient regioselective synthesis of 3-(arylmethylene) isoindolinones **77** from various ynamides **76** and boronic acids by a Heck-carbocyclization/Suzuki-coupling domino reaction (Scheme 36).[48] The interest of this methodology has been highlighted by its application to the preparation of the natural product lennoxamine **78**.

An analogous strategy was utilized by Player and co-workers for the stereoselective synthesis of non symmetrical 3,3'-(diarylmethylene)indolinones **80** (Scheme 37).[49] The starting *o*-iodoanilide derivatives **79** were reacted under the base-free Suzuki coupling reaction conditions of copper-2-carboxylate (CuTC) with $Pd(PPh_3)_4$ at room temperature to furnish the desired indolinones in moderate to excellent yields.

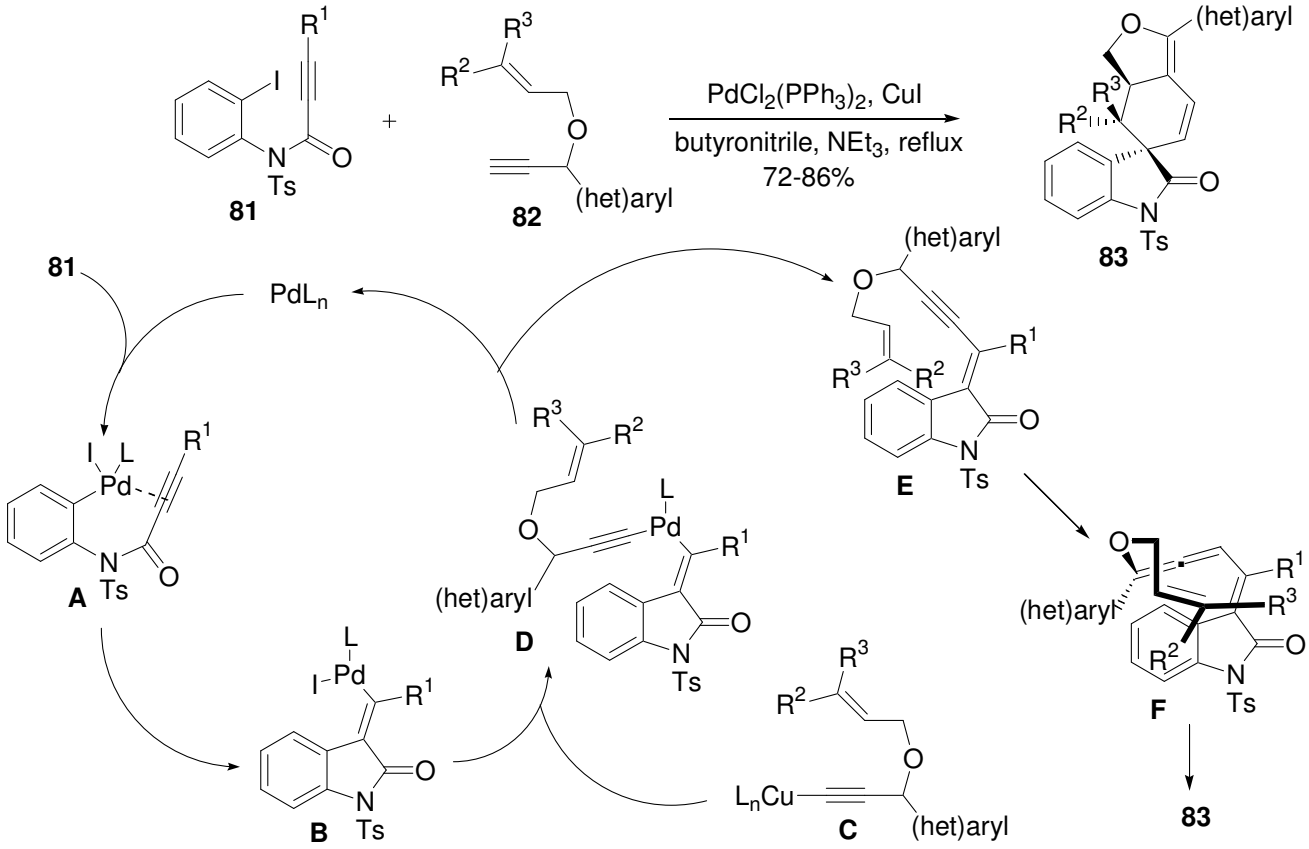
Müller and co-workers reported a cascade process consisting of intramolecular Heck-carbocyclization, Sonogashira coupling, isomerization and Diels-Alder steps for the preparation of highly complex spirocycles **83** containing the indolino skeleton (Scheme 38).[50]



Scheme 36



Scheme 37

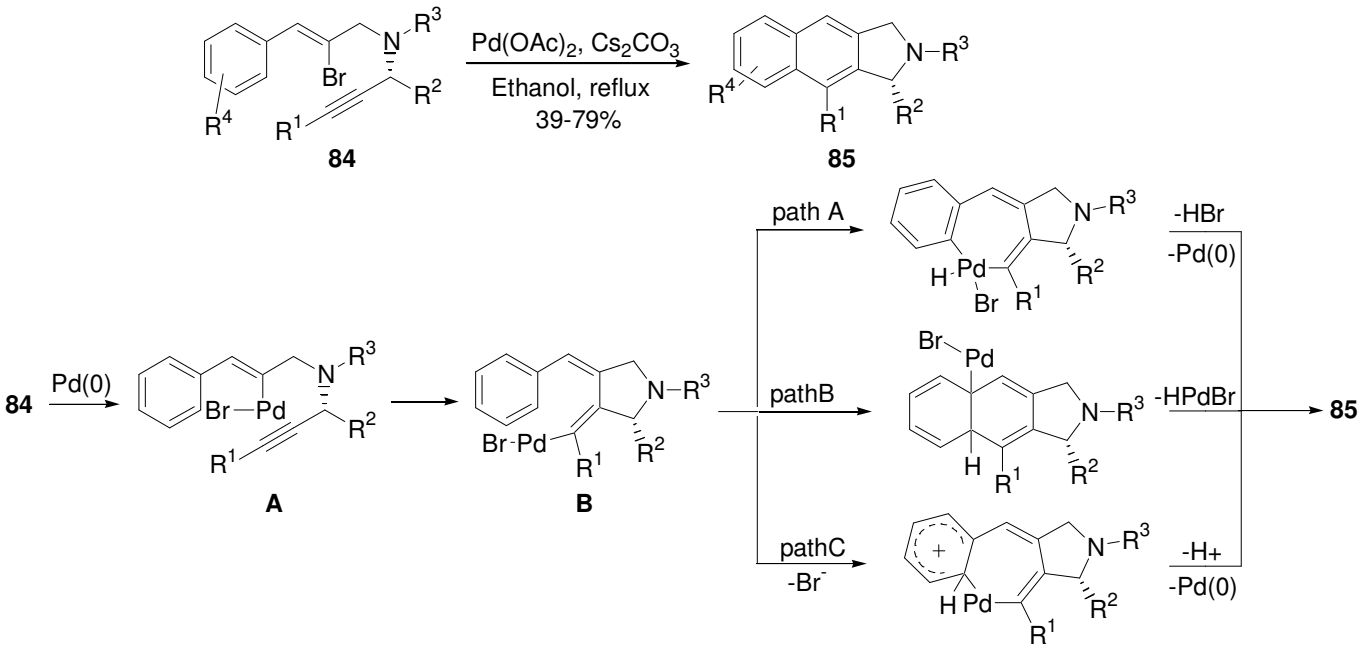


Scheme 38

Ortho-iodo amides **81** were reacted with propargyl allyl ethers **82** in the presence of $PdCl_2(PPh_3)_2$, CuI, triethylamine in butyronitrile at reflux for 3 days. Several structural modifications were allowed in both substrates; in the alkyne part of amides **81** and in the alkene part and the propargylic position of ethers **82**. A

mechanism was proposed to explain the product formation. After the oxidative addition of the aryl halide **81** to the Pd(0) species generated *in situ*, the arylpalladium halide **A** intramolecularly coordinates and inserts the tethered triple bond by means of *syn*-carbopalladation to furnish stereospecifically the cyclized vinylpalladium species **B**. Transmetallation of the copper acetylide **C** generated *in situ* gives rise to the palladium complex **D**, which readily undergoes reductive elimination and liberates the vinylpropargyl allyl ether **E**. The triethylamine-catalyzed propargyl-allene isomerization furnishes the enallene **F**, which reacts in an intramolecular [4+2] cycloaddition to conclude the sequence with the formation of spirocycle **83**.

Ohno and co-workers described a tandem cyclization of bromoenynes **84** for the synthesis of functionalized polyheterocycles **85** (Scheme 39).[51] This new reaction involving a Heck-carbocyclization followed by an aromatic C-H bond functionalization was performed in the presence of $Pd(OAc)_2$ and Cs_2CO_3 in refuxing ethanol and furnished the desired benzoisoindoles in moderate to good yield. Three different pathways were proposed for the final arylation step: intramolecular oxidative addition of an aromatic C-H bond to palladium(II) (path A); carbopalladation onto the aryl group in **B** and subsequent β-hydride elimination (path B); electrophilic attack by the palladium (II) intermediate **B** to the aromatic carbon atom followed by deprotonation and reductive elimination (path C).

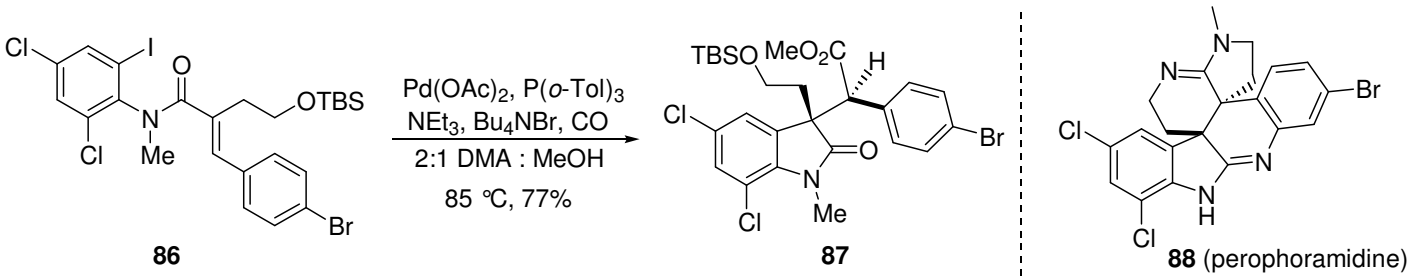


Scheme 39

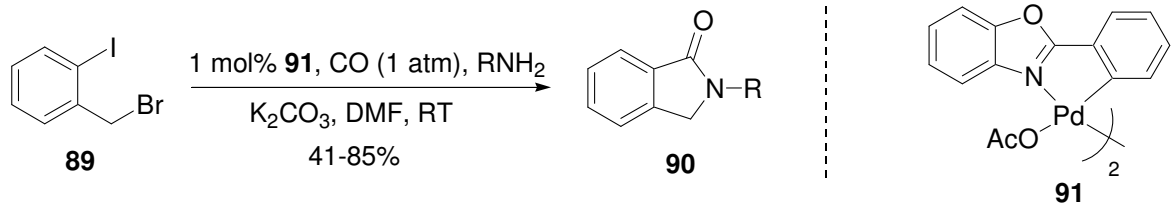
A tandem Heck/carbonylation strategy was reported by Weinreb and Artmann III in their approach to the total synthesis of the marine ascidian metabolite perophoramidine **88**.[52] The process has been effected on the iodo amide **86** in the presence of both chlorine and bromine atoms found in the natural product leading to the indolinone product **87** in good yield (Scheme 40).

2.3.2. Cyclizations involving an intramolecular amination reaction

Grigg and co-workers reported a three-component cascade process involving a nucleophilic substitution/carbonylation/amination sequence for the preparation of isoindolinones **90** (Scheme 41).[53] This room temperature reaction was catalyzed by palladium nanoparticles generated *in situ* from palladacycle **91**. Several primary amines and diamines effected the coupling with 1-bromomethyl-2-iodobenzene **89** in an atmosphere of CO in good yields.

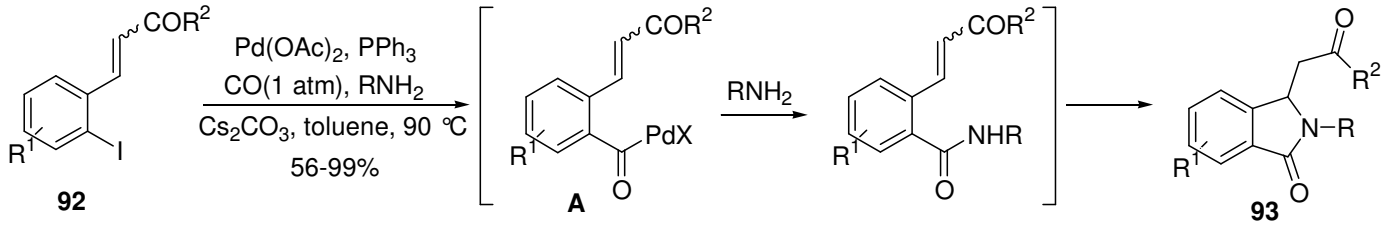


Scheme 40



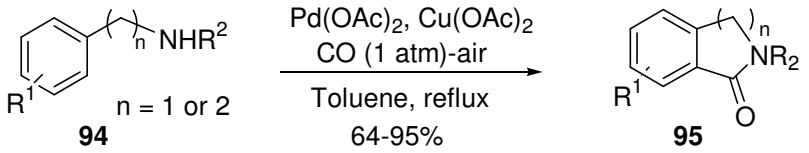
Scheme 41

By introducing a Michael acceptor instead of the bromomethyl group in substrate **89**, Grigg and co-workers described a three-component process involving a carbonylation/amination/Michael addition sequence for the synthesis of substituted isoindolinones **93** (Scheme 42).[54] The focused structures possess anxiolytic activity and are of interest as sedatives, hypnotics and muscle relaxants. The acyl palladium species **A** generated by carbonylation of the aryl iodide **92** could be intercepted by primary amines, aromatic amines, amides or sulfonamides.



Scheme 42

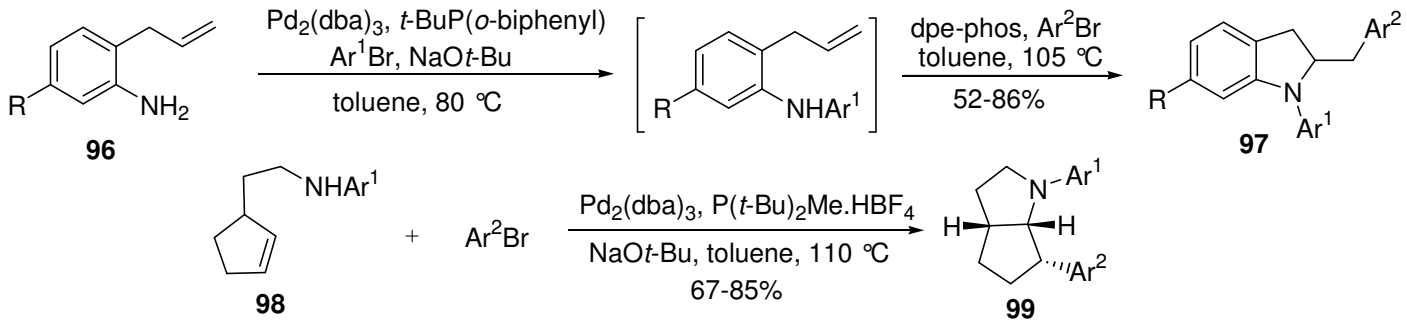
Orito and co-workers reported the Pd(II)-catalyzed direct aromatic carbonylation of secondary ω-phenylalkylamines **94** followed by an intramolecular amination to afford a variety of five- and six-membered benzolactams **95**.[55] This high yielding reaction proceeded in a phosphine-free catalytic system using $Pd(OAc)_2$ and $Cu(OAc)_2$ in an atmosphere of CO containing air (Scheme 43).



Scheme 43

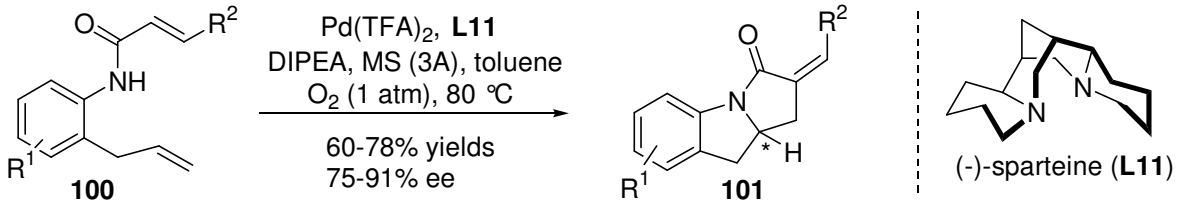
Wolfe and Lira reported a new method for the synthesis of *N*-aryl-2-benzylindoline derivatives **97** from 2-allylamines **96** *via* a *N*-arylation/alkene amination/C-arylation sequence (Scheme 44).[56] A wide range of aromatic bromides were introduced in this palladium-catalyzed transformation, and high selectivity was observed for the sequential installation of two different aryl groups. The selectivity was achieved by a ligand

modification during the course of the reaction. In a first step, the bulky, electron-rich *t*-Bu_2P(o-biphenyl) ligand was used to effect selective monoarylation of the primary amine and in a second step, bidendate dpephos ligand **L6** (Scheme 29) was added to allow intramolecular amination and C-arylation of the alkylpalladium intermediate. When cyclic alkenes **98** were used as substrates for the intramolecular amination, bicyclic arylated pyrrolidines **99** were produced in good yields with high regio- and diastereoselectivities.[57]



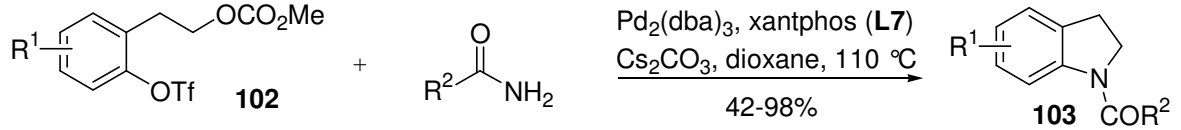
Scheme 44

Yang and co-workers described a catalytic enantioselective formation of indolines through C-N and C-C bond formation.[58] The enantioselective oxidative tandem cyclization of substrates **100** was realized using readily available (-)-sparteine **L11** as chiral ligand and molecular oxygen as a green oxidant and furnished fused indolines **101** with enantioselectivities up to 91% ee (Scheme 45).



Scheme 45

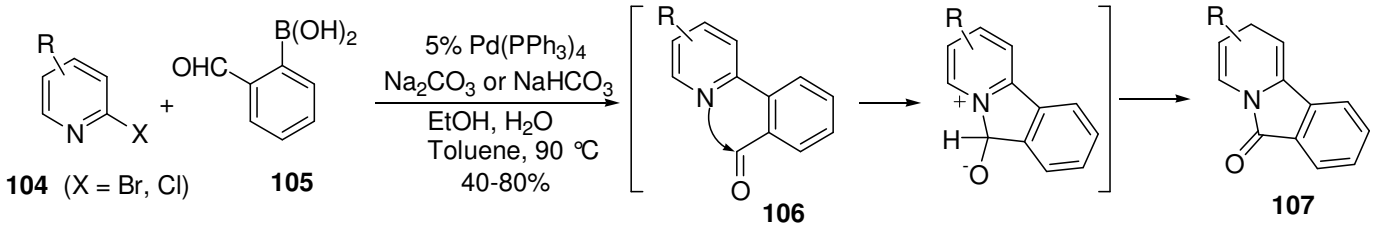
A domino amidation route to indolines **103** was developed by Kerr and Ganton from *o*-triflyl-oxyphenethyl carbonates **102** (Scheme 46).[59] In addition to the expected aryl cross-coupling, the authors observed an additional non palladium-catalyzed intramolecular amidation with net displacement of the carbonate. Moderate to excellent yields were obtained in this domino reaction which could not be extended to the synthesis of six-membered rings.



Scheme 46

Mamane and Fort reported a cascade process for the synthesis of pyrido[2,1-*a*]isoindolone **107** starting from readily available starting materials (Scheme 47).[60] The three-step cascade process was initiated by a Suzuki coupling between halopyridine **104** and boronic acid **105** to generate cross-coupled product **106** which underwent an internal attack of the aldehyde by the pyridine nitrogen followed by a hydrogen

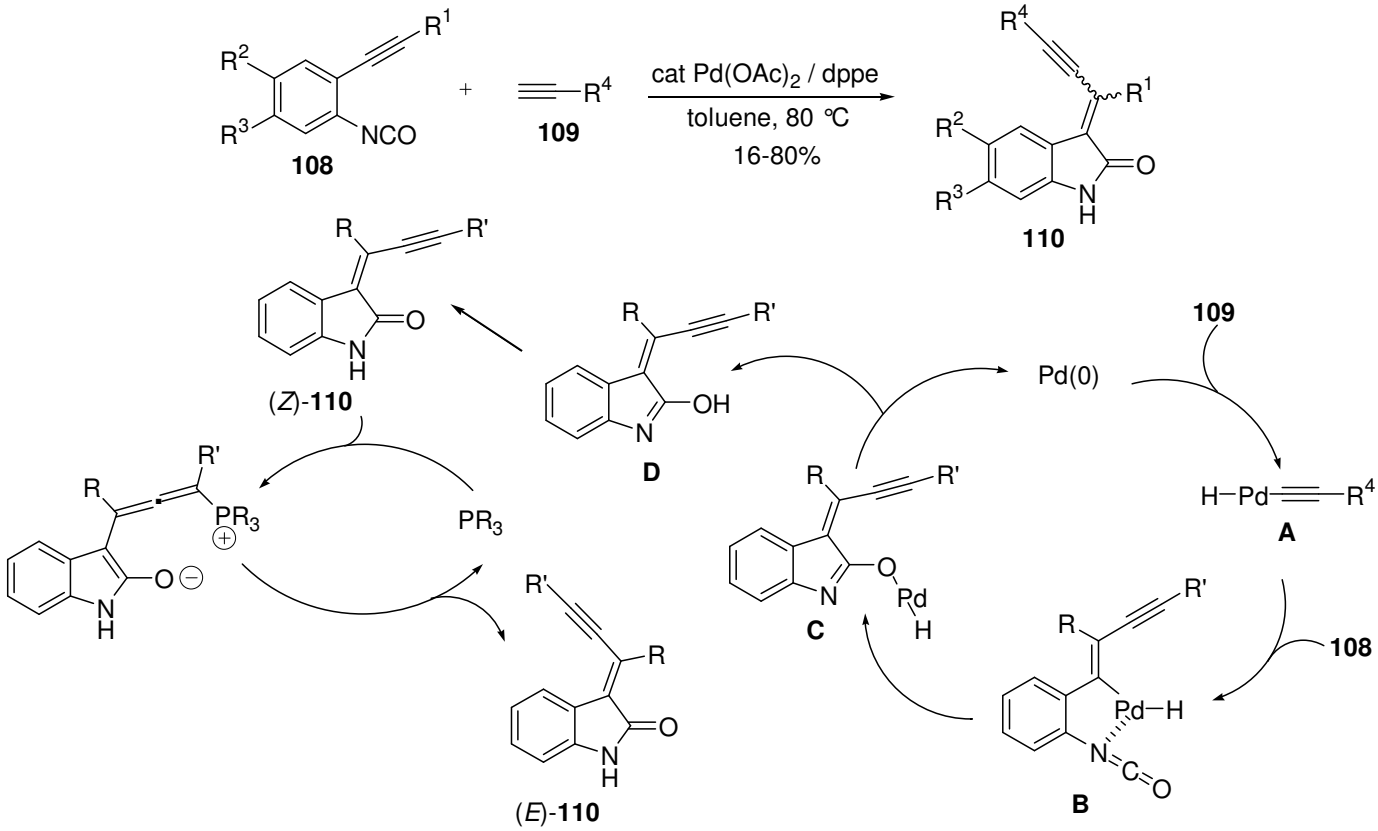
migration to form dihydropyridine and isoindolone cores. Several functional groups were tolerated in this reaction and the methodology could be applied to the coupling of 2-chloroquinoline and 1-chloro-isoquinoline.



Scheme 47

2.3.3. Cyclization of arylalkynes bearing an isocyanato group at the *ortho* position

Kamijo and co-workers described the synthesis of indolinones **110** through a coupling reaction between 2-(alkynyl)phenylisocyanates **108** and terminal alkynes **109** (Scheme 48).[61] The reaction under a catalytic amount of $Pd(OAc)_2$ and dppe produced *E*, *Z* or *E*/*Z* mixtures depending on the substitution pattern of starting materials. The following mechanism was proposed for this transformation. A Pd(0) species is generated *in situ* and oxidatively adds to the C-H bond of terminal alkyne **109** to give intermediate **A**. The vinylpalladium intermediate **B** is formed after coordination of **A** to both the alkyne and isocyanato groups of **108** and carbopalladation of the C-C triple bond.



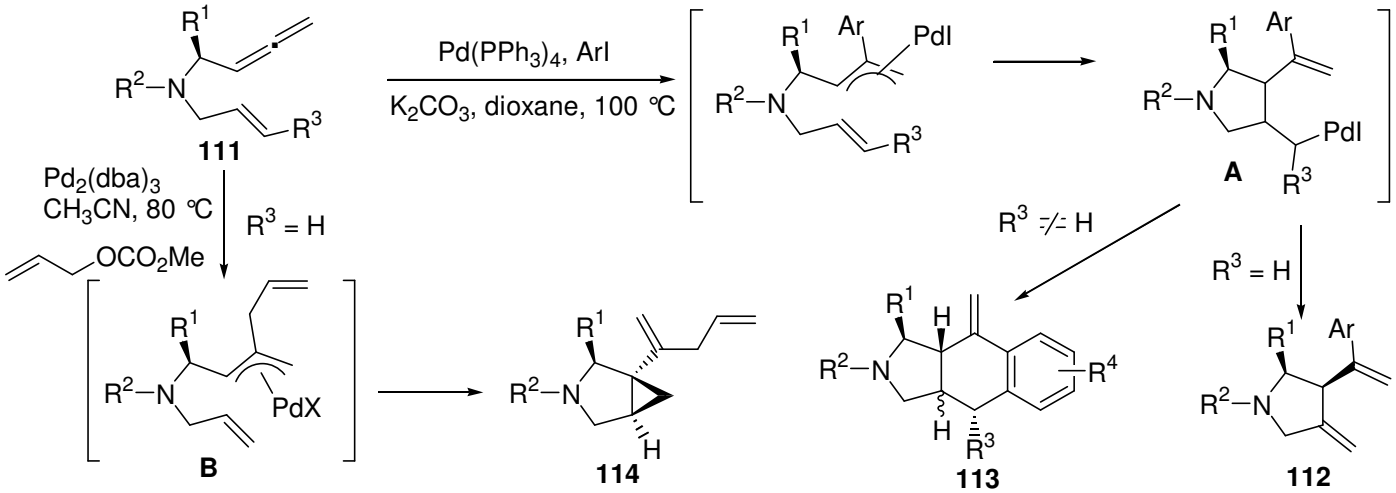
Scheme 48

Intramolecular nucleophilic attack of the vinylpalladium species on the isocyanato group would produce the cyclized oxypalladium intermediate **C**, which would be transformed into **D** after reductive elimination of the Pd(0). The intermediate **D** would isomerize to the corresponding indolinone (*Z*)-**110**.

Conversion of the *Z* isomer of **110** to its *E* isomer is catalyzed by the phosphine ligand through a reversible nucleophilic addition to the electrophilic carbon centre in the alkynyl moiety. This explains well that the exclusive or predominant formations of *Z* products were observed when the reaction was conducted with electron-rich methoxy-substituted substrates **108** or with bulky terminal alkynes **109**. The electron flow from the properly methoxy group to the enyne moiety or the steric congestion around the enyne moiety would avoid the nucleophilic approach of the phosphine.

2.3.4. Cyclizations involving allenes

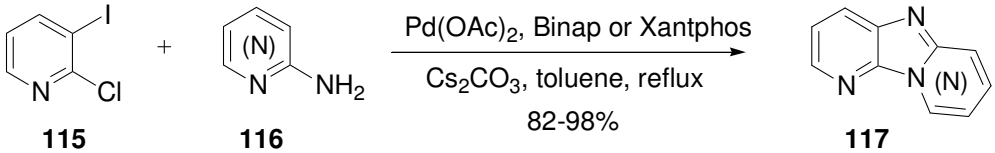
Ohno and co-workers reported the synthesis of mono- and polycyclic pyrrolidines **112**-**114** from allene-ene substrates **111** (Scheme 49).[62] The outcome of the reaction depended on the nature of the coupling partner and on the substitution of the alkene part. Aryliodides added on the central carbon of the allene to form intermediate **A** which followed two different pathways depending on the nature of R^3. With mono-substituted alkene (R^3 = H), a β-hydride elimination occurred and pyrrolidines **112** were produced. The introduction of a substituent at the olefin terminus ($R^3 \neq$ H) prevented β-hydride elimination to occur. Therefore, tricyclic products **113** could be obtained through an aromatic C-H bond activation. When allylcarbonates were used instead of aryliodides, bicyclic compounds **114** were formed *via* intermediate **B**.



Scheme 49

2.4. Other five-membered heterocyles

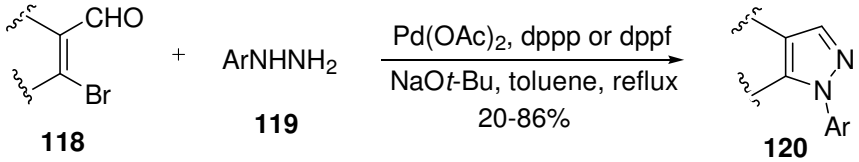
Maes and co-workers reported the one-pot inter- and intra-molecular Buchwald-Hartwig amination of 2-chloro-3-iodopyridine **115** with aminoazines and –diazines **116** for the synthesis of dipyrido[1,2-*a*:3'-2'-*d*]imidazole and its benzo- and aza-analogues **117** (Scheme 50).[63] Excellent yields were obtained by using $Pd(OAc)_2$, Binap or xantphos (**L7**) as ligand and Cs_2CO_3 in refluxing toluene.



Scheme 50

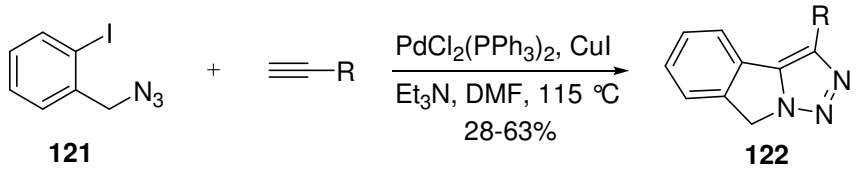
The intramolecular Buchwald-Hartwig amination was utilized by Cho and co-workers for the preparation of 1-aryl-1*H*-indazoles **120** from *o*-bromobenzaldehydes or β-bromovinyl aldehydes **118** and

hydrazines **119** (Scheme 51).[64] The one-pot condensation of the hydrazine and the aldehyde followed by the intramolecular amination was effected using $Pd(OAc)_2$ – dppp or dppf system as the catalyst and in the presence of NaO*t*-Bu in refluxing toluene. Title compounds **120** were obtained in moderate to good yields.



Scheme 51

Chowdhury and co-workers reported an expeditious synthesis of isoindoline fused with triazoles **122** from *o*-iodobenzyl azide **121** and acetylenes (Scheme 52).[65] The internal alkyne generated *in situ* under Sonogashira conditions ($PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF) at room temperature was heated to 115 °C in order to achieve the intramolecular cycloaddition with the azide group. This reaction was found to be equally applicable to both aromatic and aliphatic alkynes.



Scheme 52

3. Fused six-membered heterocycles

3.1. (Iso)quinolines, (iso)quinolones and derivatives

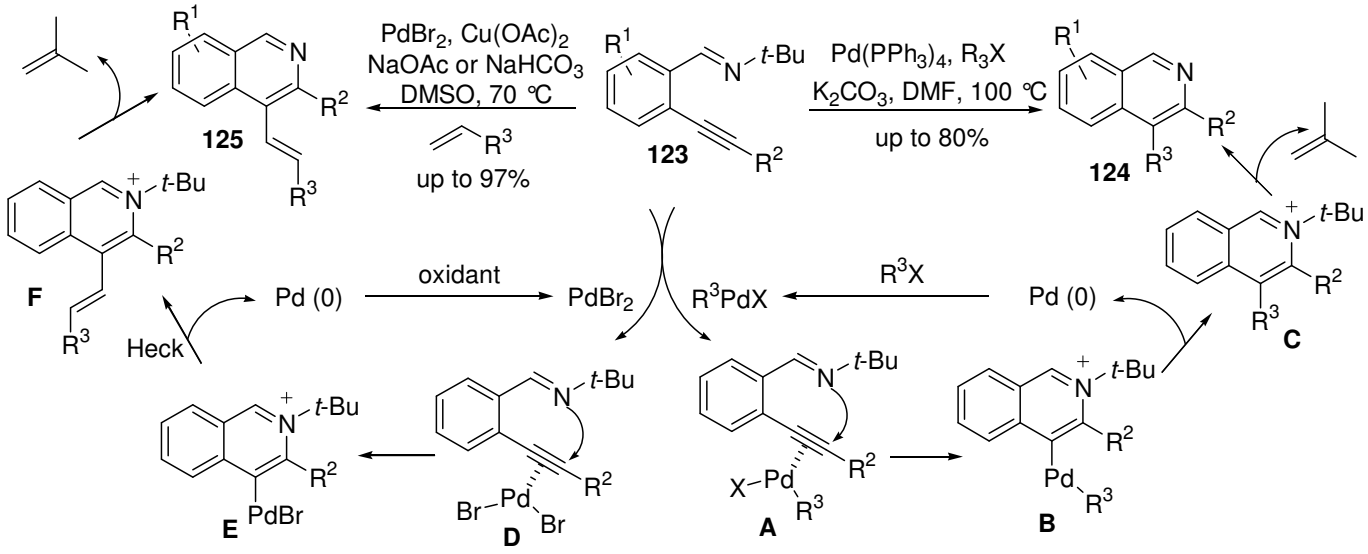
The synthesis of quinoline derivatives has received considerable attention since they are present in numerous naturally occurring alkaloids. Several cyclization strategies involving cascade sequences have been reported during the last three years.

3.1.1. Iminoannulation strategy

In two successive publications Larock and co-workers reported the cyclization of *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines **123** followed by either a cross-coupling or an olefination reaction (Scheme 53).[66] The cross-coupling reaction was effected successfully with aryl, allylic, benzylic, alkynyl halides as well as a vinylic halide giving access to a wide range of 3,4-disubstituted isoquinoline derivatives **124**. The reaction required an aryl group on the end of the acetylene to allow moderate to good yields of isolated products.

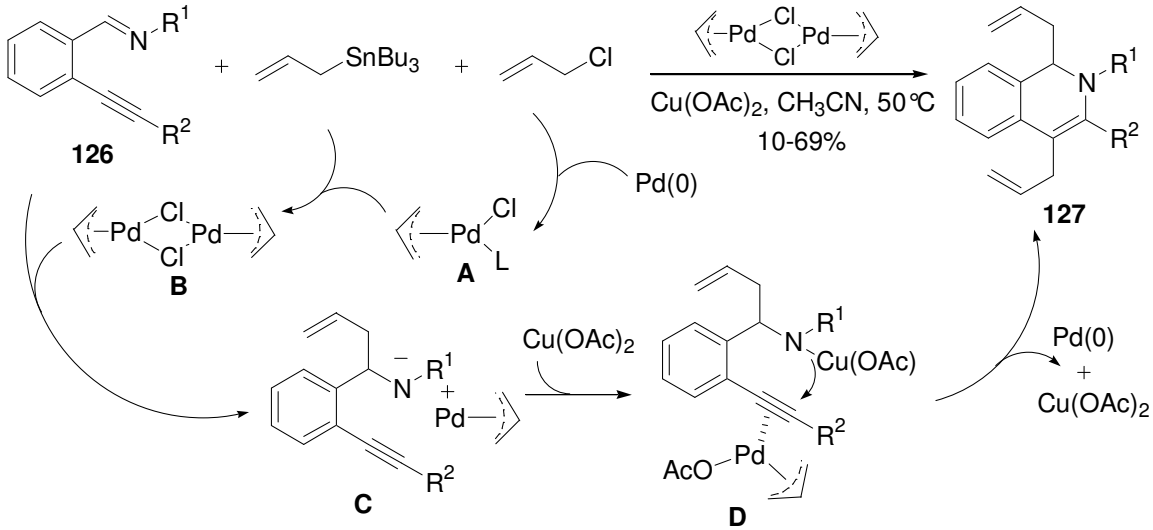
The present synthesis is believed to proceed through coordination of the alkyne by the complex resulting from oxidative addition of R^3X by Pd(0) to generate intermediate **A**, intramolecular nucleophilic attack of the nitrogen atom of the imine on the activated alkyne to give complex **B** which undergoes a reductive elimination to form intermediate **C** with simultaneous regeneration of Pd(0), and cleavage of the *tert*-butyl group from the N atom to generate 3,4-disubstituted isoquinolines **124**. For the preparation of 4-(1-alkenyl)-3-arylisoquinolines **125**, the reaction was catalyzed by a Pd(II) catalyst in the presence of $Cu(OAc)_2$ as oxidant and moderate to excellent yields were obtained in the presence of various alkenes. The possible mechanism for this transformation starts by formation of complex **D** through coordination of $PdBr_2$ to the alkyne. This intermediate undergoes intramolecular cyclization to form complex **E** which reacts with

the olefin following the Heck reaction mechanism (cis addition and β-hydrid elimination) to afford intermediate **F** and Pd(0). Further fragmentation of the *tert*-butyl group generates the desired isoquinoline compounds **125**. The Pd(0) generated can be reoxidized back to $PdBr_2$ by $Cu(OAc)_2$ present in the reaction mixture.



Scheme 53

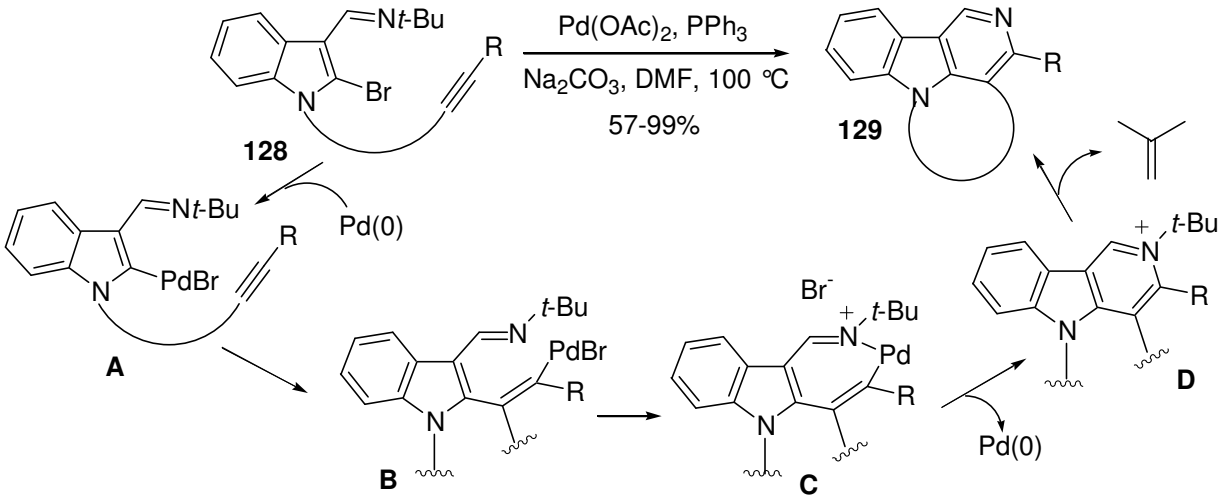
Yamamoto and co-workers reported the synthesis of 1,4-diallyl-1,2-dihydroisoquinolines **127** by the reaction of *o*-alkynylarylimines **126** with allyltributylstannane and allyl chloride in the presence of allylpalladium chloride dimer and $Cu(OAc)_2$ in acetonitrile at 50 °C.[67] A mechanistic rationale which accounts for the product formation is shown in Scheme 54. The oxidative addition of Pd(0) to allyl chloride produces the π-allylpalladium chloride complex **A**. The transmetallation between **A** and allyltributylstannane gives the bis-π-allylpalladium complex **B**, which reacts with **126** in a nucleophilic manner to give the π-allylpalladium amide **C**. $Cu(OAc)_2$ assists cleavage of the Pd-N interaction and the formation of the Pd-alkyne comlex **D**. Attack of the nitrogen atom to the alkyne followed by reductive coupling would give **127**, Pd(0) and $Cu(OAc)_2$ being regenerated.



Scheme 54

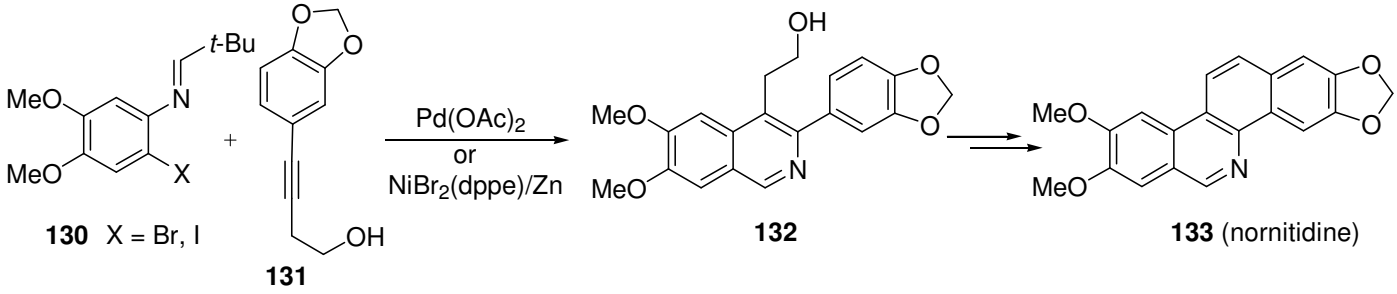
Larock and co-workers reported the efficient synthesis of several polyheterocycles **129** by the intramolecular iminoannulation of alkynes (Scheme 55).[68] Various *tert*-butylimines derivatives **128** with

tethered alkynes has been subjected to 5 mol% of $Pd(OAc)_2$, 10 mol% of PPh_3 and one equivalent of Na_2CO_3 to afford the desired compounds in good to excellent yields. The proposed mechanism involves oxidative addition of the indole bromide to Pd(0) to produce organopalladium intermediate **A**, intramolecular insertion in the tethered triple bond through an *exo-dig* addition producing the vinylic palladium intermediate **B** which reacts with the neighbouring imine substituent to form the seven-membered palladacyclic immonium salt **C**, reductive elimination to form *tert*-butylcarbolinolium salt **D** and regeneration of Pd(0), and cleavage of the *tert*-butyl group.



Scheme 55

The intermolecular version of the previous strategy was recently used by Lu and co-workers for the synthesis of nornitidine **133**, a benzo[*c*]phenanthridine alkaloid.[69] Isoquinoline **132** was obtained from readily available *tert*-butylimines **130** and alkyne **131** by using palladium or nickel catalysis (Scheme 56).



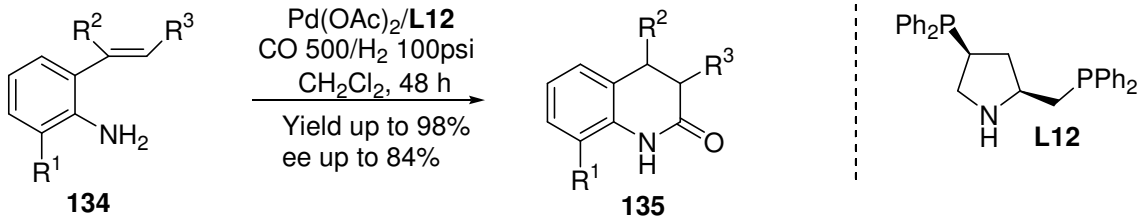
Scheme 56

3.1.2. Carbonylation/aminocyclization strategy

Halper and Dong reported the enantioselective synthesis of dihydroquinolinones **135** from *o*-vinylanilines **134** (Scheme 57).[70] A catalyst system based on $Pd(OAc)_2$/diphosphinopyrrolidine ligand **L12** was found to effect asymmetric cyclocarbonylation of *o*-vinylanilines **134** to enantiomerically enriched six-membered ring lactams in up to 98% yield and 84% ee. The enantiopurity of the lactam was further improved by recristallization to reach 99% ee in some cases.

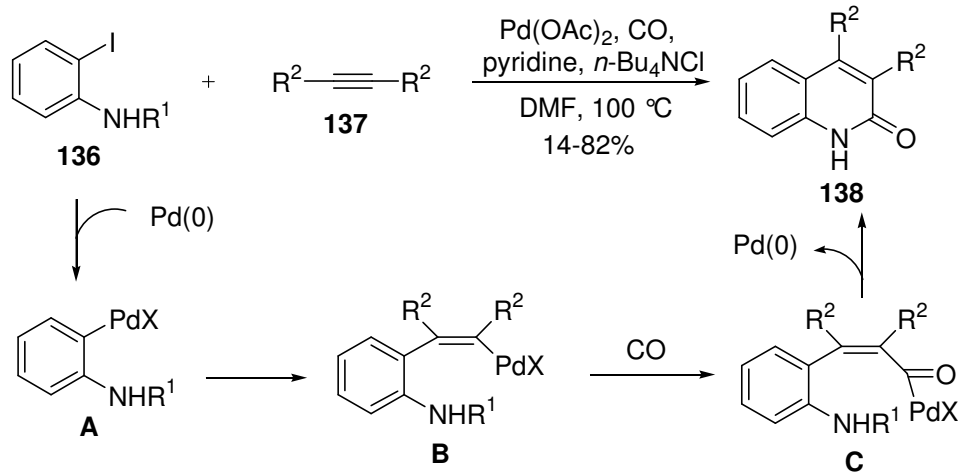
Larock and Kadnikov disclosed a new synthesis of 2-quinolinones **138** *via* carbonylative annulation of internal alkynes **136** by *N*-substituted *o*-iodoanilines **137** (Scheme 58).[71] The nature of the substituent on the nitrogen was crucial to obtaining high yields of 2-quinolinones. The best results were obtained using

alkoxycarbonyl, *p*-tosylsulfonyl, and trifluoroacetyl substituents which are lost during the reaction resulting in the formation of *N*-unsubstituted 2-quinolinones.



Scheme 57

A variety of internal alkynes, bearing alkyl, aryl, heteroaryl, hydroxyl, and alkoxyl substituents, were effective in this process. Electron-rich and electron-poor *N*-substituted *o*-iodoanilines, as well as heterocyclic analogues, could be employed as annulating agents. The mechanism shown in Scheme 58 involves oxidative addition of **136** to Pd(0) generating arylpalladium intermediate **A**, insertion of the alkyne into the arylpalladium bond of **A** to give intermediate **B**, insertion of CO to generate the acylpalladium complex **C**, and nucleophilic attack of the nitrogen on the carbonyl group of **C** leading to regeneration of Pd(0) and formation of **138** after removal of the R^1 group.

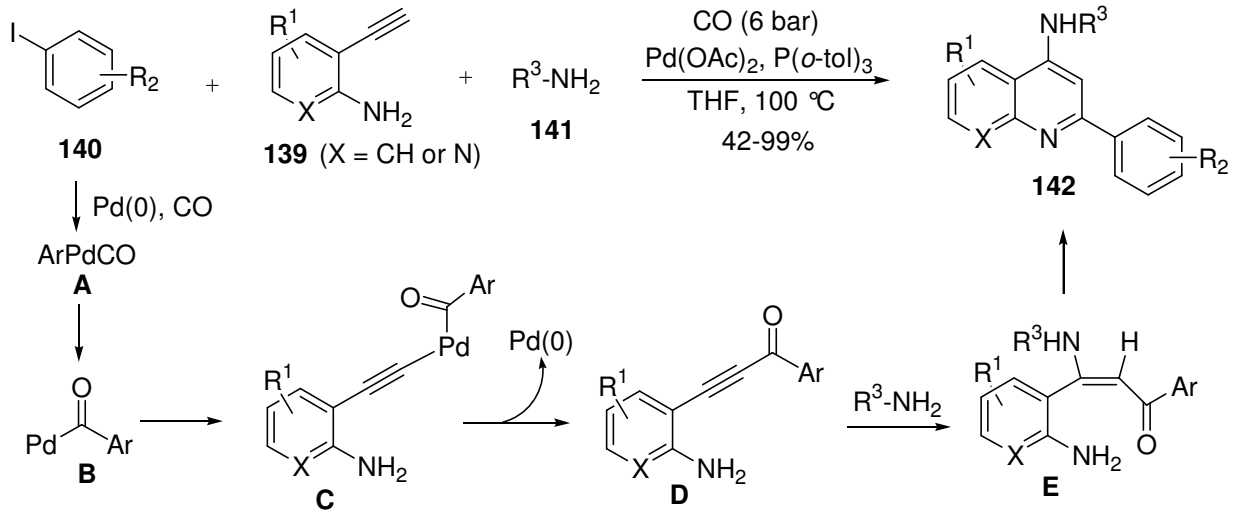


Scheme 58

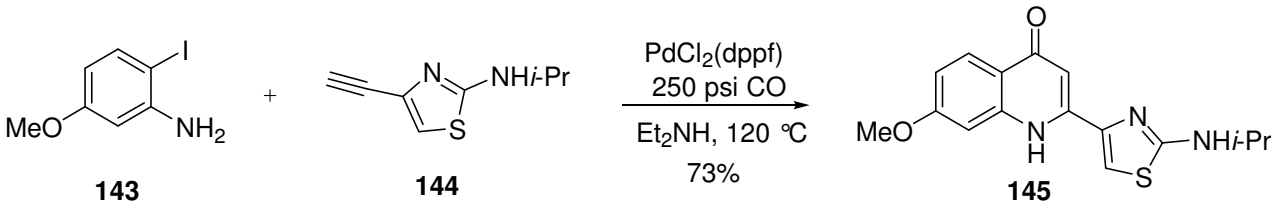
Rossi and co-workers reported a multicomponent cascade reaction leading to 2-aryl-4-amino-quinolines and naphtyridines **142** starting from carbon monoxide, 2-ethynyl-arylamines **139**, aryl iodides **140**, and primary amines **141** (Scheme 59).[72] $Pd(OAc)_2$/tri(*o*-tolyl)phosphine system was found to catalyze efficiently this transformation allowing the formation of products in good to excellent yields with various substrates. The proposed reaction mechanism is presented in Scheme 59. Oxidative addition of Pd(0) to the aryl iodide **140** followed by coordination of carbon monoxide furnished complex **A**. 1,2-Migration of the aryl group from palladium to coordinated CO generates the aroyl palladium complex **B** and subsequent addition of the incipient acetylide anion derived from 2-ethynyl-amine **139** gives rise to a σ-alkynyl-σ-acylorganopalladium complex **C**. After reductive elimination, the resulting ynone intermediate **D** is trapped by amine **141** in 1,4-addition to generate **E** which reacts intramolecularly to give the desired compounds **142** with elimination of water.

Haddad and co-workers reported the synthesis of quinolone **145** *via* carbonylative Sonogashira coupling/cyclization sequence of *o*-iodoaniline **143** and alkyne **144** (Scheme 60).[73] The quinolone **145** which

is the key substructure of a protease inhibitor was obtained with a good yield of 73% in the presence of $PdCl_2$(dppf) and CO (250 psi) in diethylamine at 120 °C.



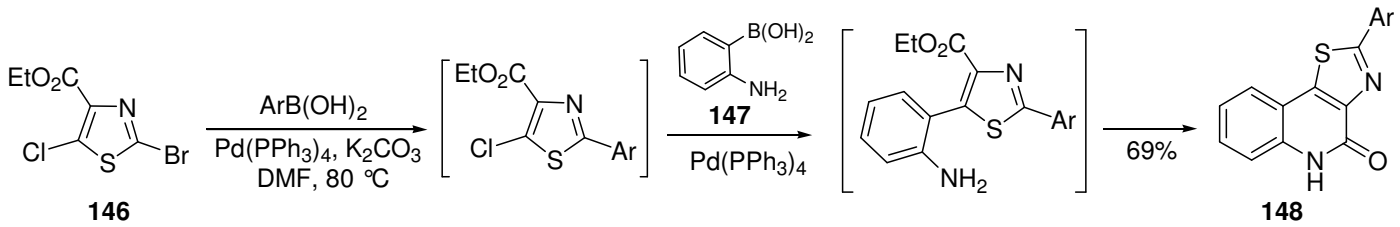
Scheme 59



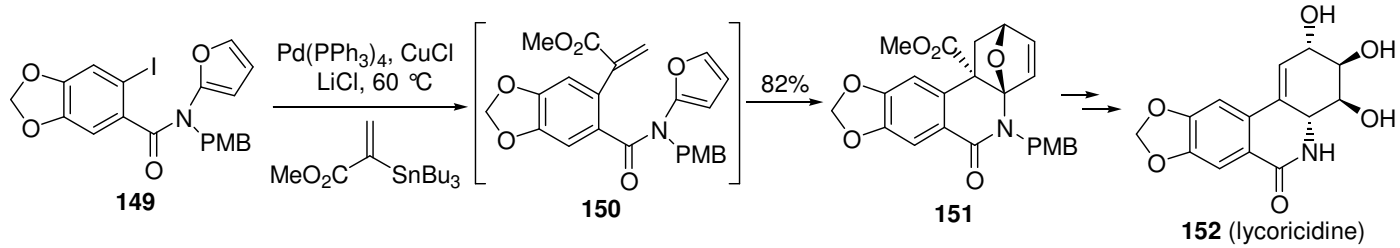
Scheme 60

3.1.3. Cross-coupling/cyclization strategy

Hodgetts and Kershaw reported the synthesis of fused quinolinone **148** from 2-bromo-5-chlorothiazole-4-carboxylate **146** using a one-pot process comprising two successive Suzuki couplings followed by an intramolecular cyclization (Scheme 61).[74] After the completion of the first cross-coupling, arylboronic **147** and more $Pd(PPh_3)_4$ were added to effect the second cross-coupling which introduced a free amino group ideally placed for an intramolecular cyclization with the ester present in the starting product.



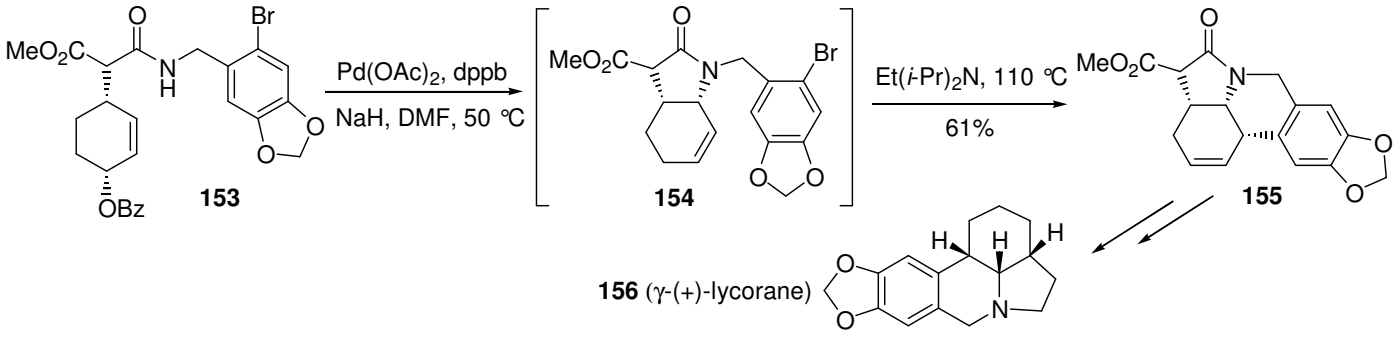
Scheme 61



Scheme 62

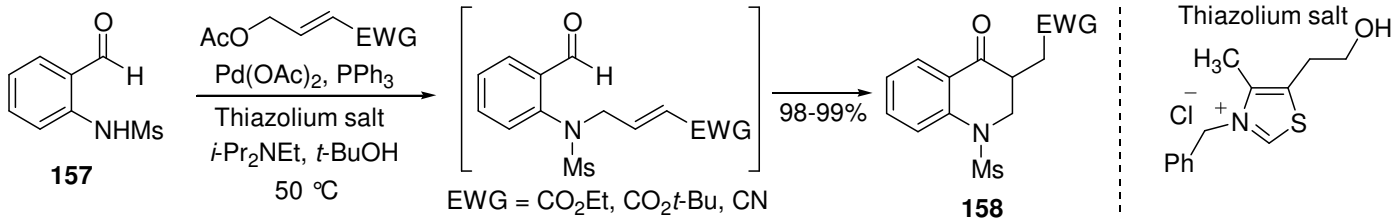
Padwa and Zhang utilized a Stille coupling/cycloaddition cascade in order to build the tricyclic core of (±)-Lycoricidine **152**.[75] Amidofuran **149** reacted with 2-tri-*n*-butylstannylacrylate using a combination CuCl/Pd(0)/LiCl in DMSO to give intermediate **150** which underwent a spontaneous [4+2] intramolecular cycloaddition between the furan group and the alkene moiety affording the quinolinone derivative **151** in 82% yield (Scheme 62).

Ojima and Chapsal reported an elegant total synthesis of enantiopure (+)-γ-lycorane **156** based on a tandem allylic alkylation/Heck coupling reaction (Scheme 63).[76] The mixture of $Pd(OAc)_2$, dppp and NaH in DMF at 50 °C allowed the enantiopure compound **153** to undergo an intramolecular allylic alkylation of the amide to furnish **154** having an aryl bromide and a double bond close together. Intermediate **154** was then treated by the addition of *i*-$PrNEt_2$ and by heating to 110 °C in order to allow the Heck reaction and to furnish the cyclized compound **155** in a good yield of 61%.



Scheme 63

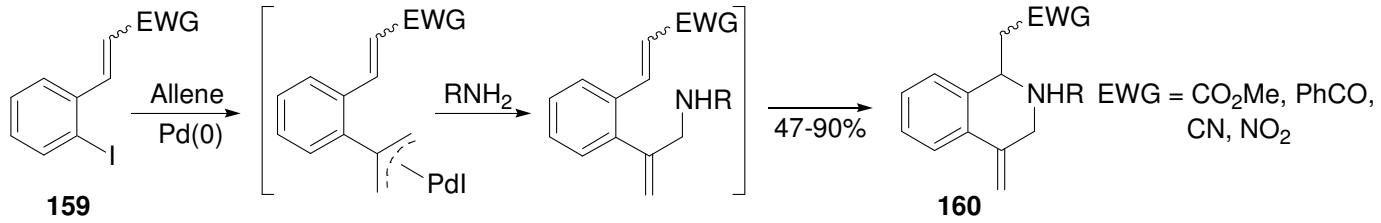
Hamada and co-workers developed an efficient method for the synthesis of 3-substituted 2,3-dihydroquinolin-4-ones **158** using a one-pot sequential multi-catalytic process: intermolecular Pd-catalyzed allylic amination between compound **157** and allylic acetates followed by a thiazolium salt-catalyzed intramolecular Stetter reaction (Scheme 64).[77] This process was successful even when both catalysts coexisted in the reaction mixture at the first stage of the reaction giving dihydroquinolinones **158** with excellent yields.



Scheme 64

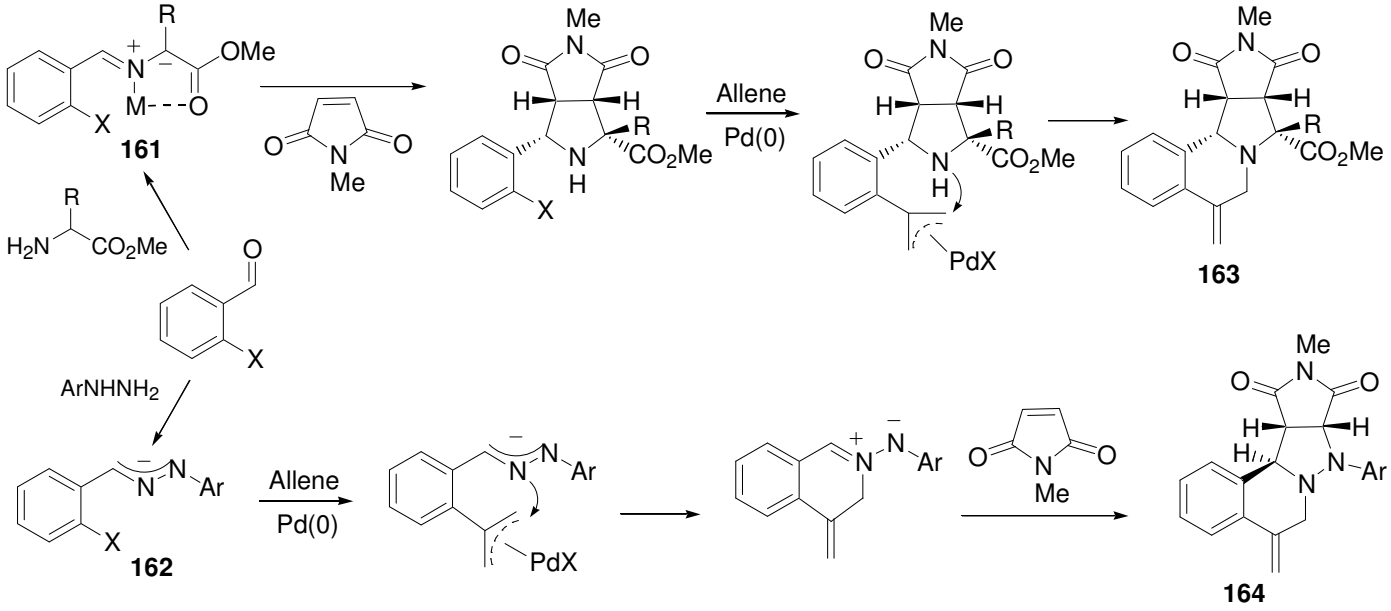
3.1.4. Cyclizations involving allenes

Grigg and co-workers reported the synthesis of dihydroisoquinoline derivatives **160** through a cascade sequence involving allenilation of an aryl iodide to generate a (π-allyl)palladium species which is intercepted by a nitrogen nucleophile followed by intramolecular Michael addition (Scheme 65).[78] A wide range of primary amines reacted with aryl iodides **159** using allene (1 bar) and in the presence of $Pd(OAc)_2$, PPh_3 and K_2CO_3 in toluene at 80 °C to furnish substituted dihydroisoquinolines **160** in good yields.



Scheme 65

Grigg and co-workers reported the four-component cascade synthesis of fused polycyclic isoquinolines **163** and **164** (Scheme 66).[79] This transformation involved 1,3-dipolar cycloaddition/allene insertion/nucleophile addition that proceeds *via* intermediate azomethine ylides and azomethine imines. Imines **161** underwent cycloaddition through an *endo* transition state prior to incorporation of the allene. The precise order of events in the case of hydrazines **162** is not clear but may involve an initial incorporation of the allene followed by trapping of the π-allylpalladium species by the ambident hydrazone and finally cycloaddition through an *exo* transition state.



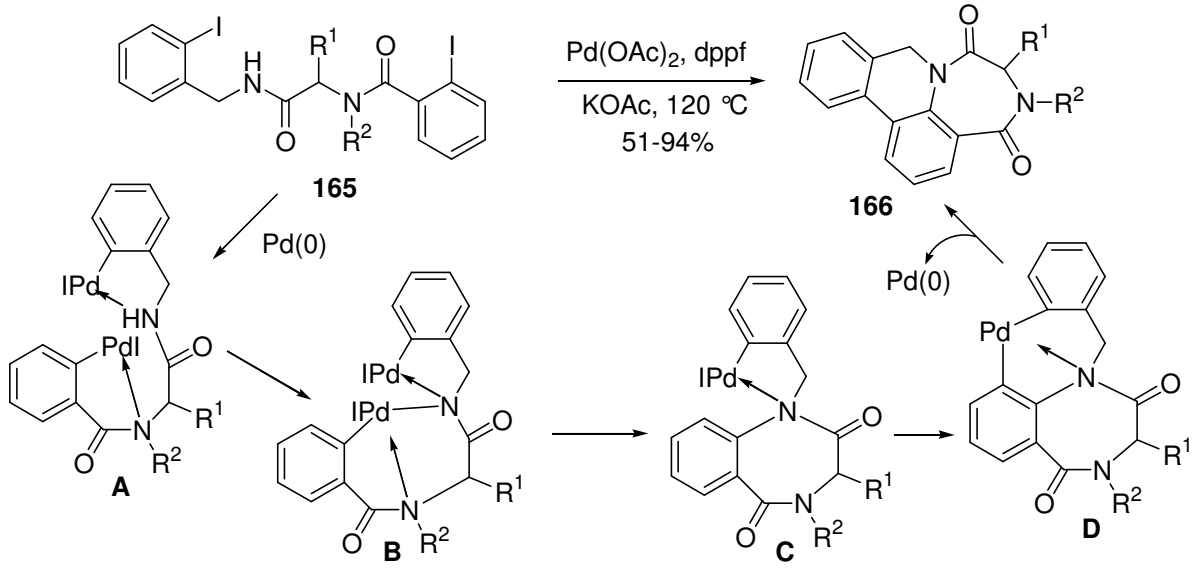
Scheme 66

3.2. Phenanthridin(on)es

Zhu and co-workers described a domino process involving intramolecular *N*-arylation of amide/C-H activation/aryl-aryl bond formation for the efficient synthesis of phenanthridine derivatives **166** (Scheme 67).[80] Reaction of linear amides **165** in the presence of $PdCl_2$(dppf) and KOAc in DMSO at 120 °C afforded the polycyclic compounds **166** in good to high yields. The first step would be a double oxidative addition of Pd(0) species generated *in situ* to the bisaryl diiodide **165** leading to intermediate **A**. The internal chelation of amide to palladium adduct **A** should entropically facilitate the formation of arylpalladium-amido complex **B**. Reductive elimination of complex **B** would provide **C** with the concurrent formation of C-N bond. The intermediate **C** undergoes an intramolecular C-H process to form palladacycle **D** followed by a second reductive elimination to give compound **166** with regeneration of the Pd(0) catalyst.

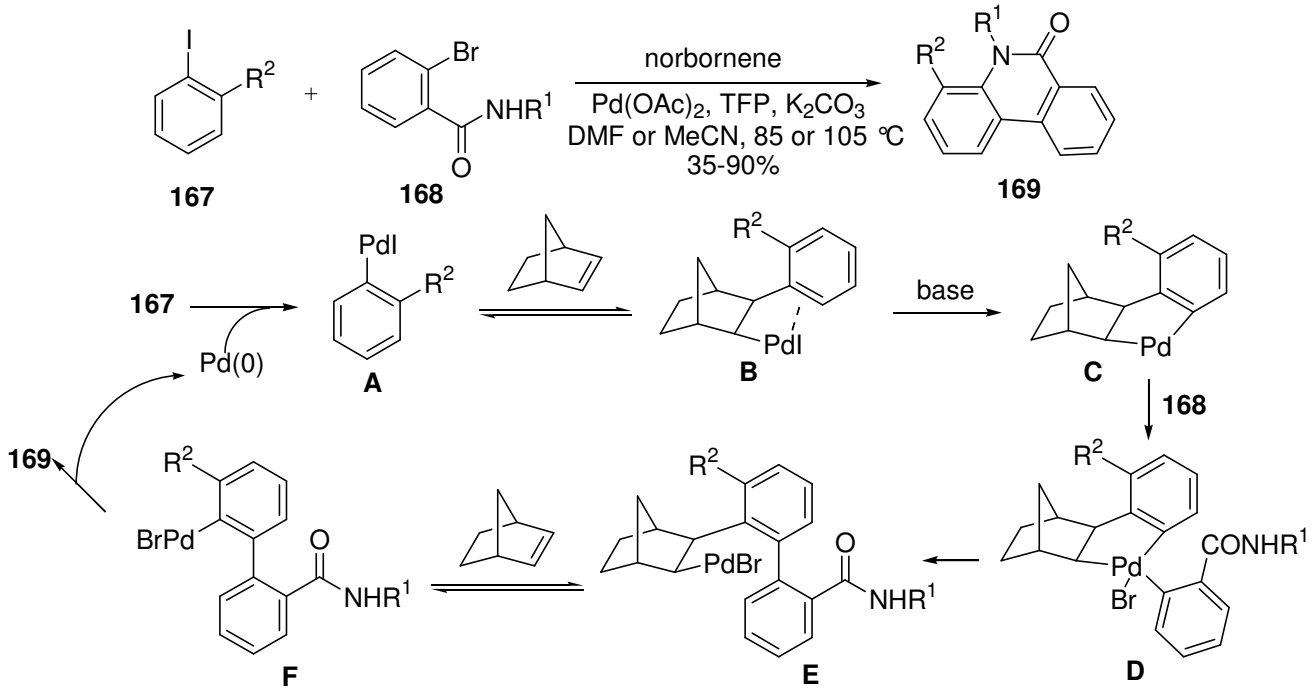
Ferraccioli and co-workers reported a nice entry to 6-phenanthridinones and their heterocyclic analogues **169** by a sequential aryl-aryl and *N*-aryl coupling between electron-rich *o*-iodoarenes **167** and

o-bromobenzamides **168** (Scheme 68).[81] $Pd(OAc)_2$/tri(2-furyl)phosphine (TFP) catalytic system in presence of norbornene allowed the formation of the desired phenanthridinone derivatives **169** in moderate to excellent yield. The reaction proceeds as follows: the *o*-iodoarene **167** adds to Pd(0) giving complex **A**.



Scheme 67

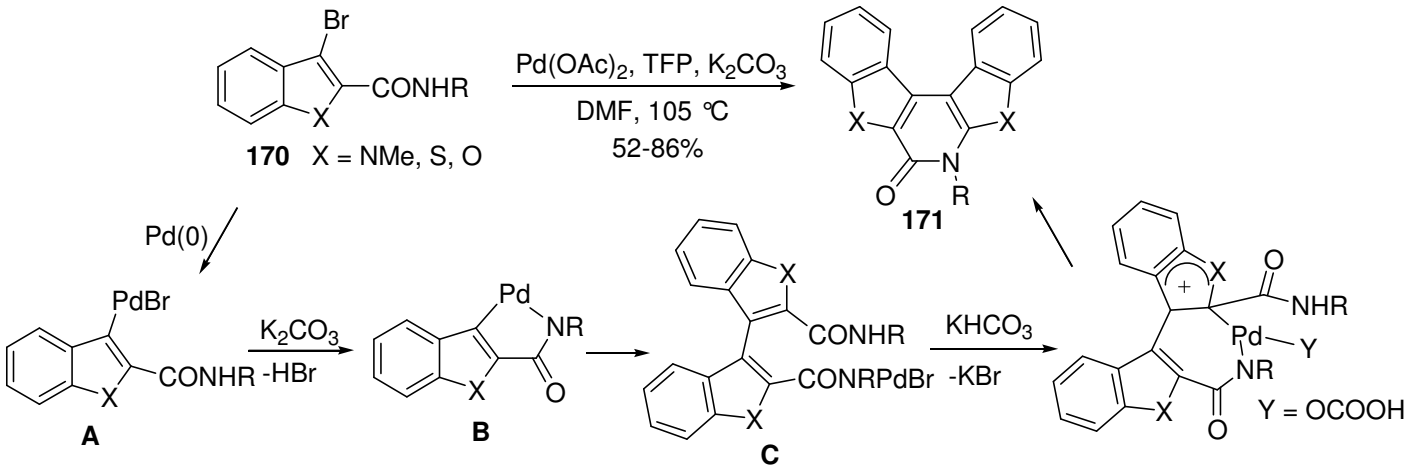
Norbornene insertion and subsequent ring closure through C-H activation leads to palladacycle **C** (through intermediate **B**). Bromoamide **168** reacts with **C** (probably through oxidative addition leading to palladium (IV) metallacycle **D**) giving complex **E**. Norbornene desinsertion, caused by the steric effect of the two ortho substituents, affords intermediate **F** in which the $CONH_2$ group is in a suitable position to afford an intramolecular amidation leading to **169** with regeneration of the palladium catalyst.



Scheme 68

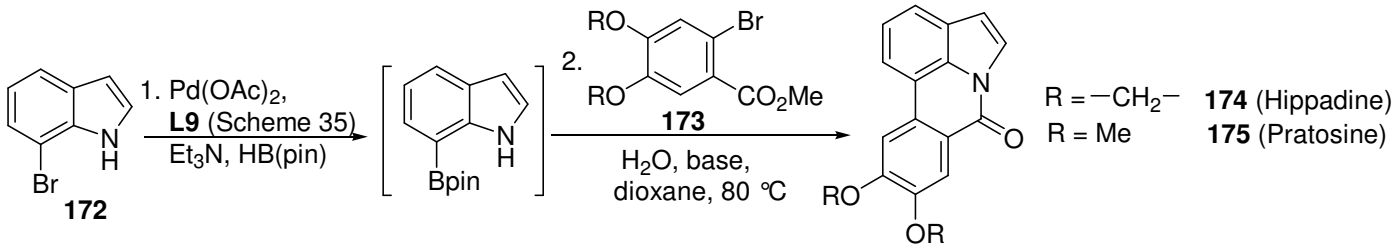
The same group reported later that in the absence of norbornene, the reaction followed a completely different pathway leading to compounds **171** by coupling of two molecules of the *o*-bromoaromatic

carboxamide (Scheme 69).[82] Electron-rich bicyclic heterocycles **170** underwent the homocoupling efficiently giving condensed pyridones **171** in good yields while monocyclic rings as benzene and thiophene gave lower yields of coupled product. A possible reaction pathway was proposed starting by the oxidative addition of Pd(0) to the bromoamide **170** to furnish complex **A** which gives rise to a five-membered palladacycle **B**. A second molecule of **170** reacts with **B** possibly through an oxidative addition process involving a Pd(IV) species leading to C-C bond formation in the new palladium complex **C**. The latter then undergoes intramolecular *ipso* aromatic substitution at the carbon bearing the CONHR group with formation of **171**, amine, and CO_2.



Scheme 69

Tonder and co-workers reported the synthesis of the pyrrolophenanthridinone alkaloids hippadine **174** and pratosine **175** by a tandem borylation/Suzuki coupling/lactamization strategy.[83] The reaction using 7-bromoindole **172** as the starting component and *o*-bromoaryl esters **173** as the second component occurred smoothly to give hippadine and pratosine in 74 and 62% yield respectively (Scheme 70). The protection of the indole nitrogen was not required which allowed the *in situ* intramolecular lactamization after the cross-coupling reaction.

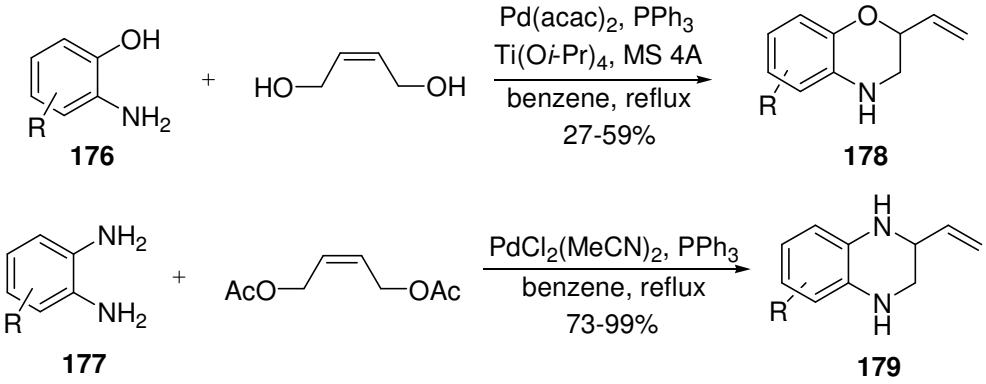


Scheme 70

3.3. Other six-membered heterocycles

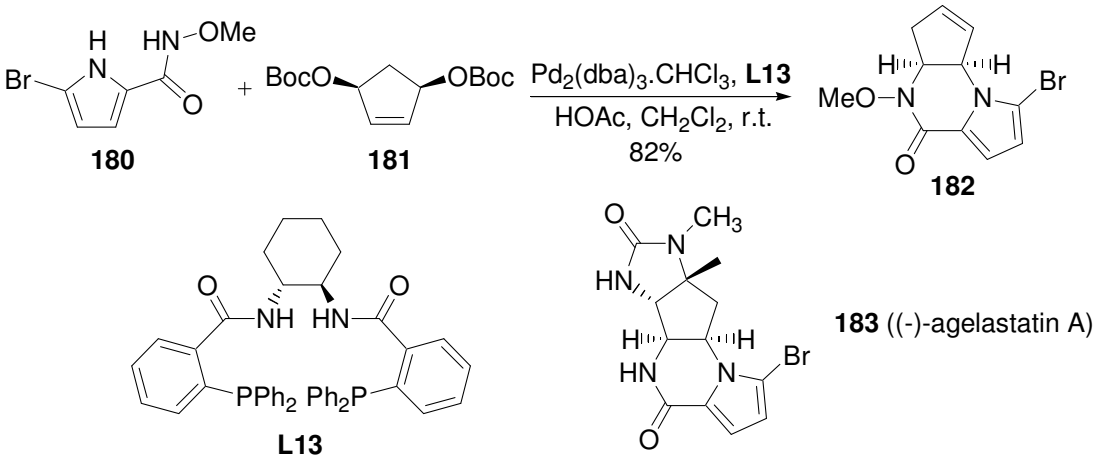
Yang and co-workers reported the tandem allylation of 2-aminophenols **176** and 1,2-phenylene-diamines **177** using 2-butene-1,4-diol and 1,4-diacetoxy-2-butene respectively (Scheme 71).[84] In the first case, the reaction was carried out in the presence of a titanium reagent in order to enhance the rate of the palladium-catalyzed allyl-OH bond cleavage which lead to a great yield improvement of benzoxazine derivatives **178**. Moreover, this reaction was regiospecific leading to **178** after successive *N*-allylation and *O*-allylation of 2-aminophenols **176**. In the second case, good to excellent yields of quinoxalines **179** were

obtained when diamines **177** were reacted with 1,4-diacetoxy-2-butene in the presence of $PdCl_2(MeCN)_2/PPh_3$ catalytic system.



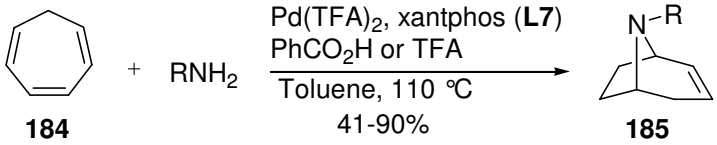
Scheme 71

An enantioselective double allylic amination strategy was utilized by Trost and Dong for the synthesis of piperazinone **182**, an important intermediate for the total synthesis of (-)agelastatin A **183** (Scheme 72).[85] *N*-Methoxyamide **180** was used as a double nucleophile in the reaction with Boc-activated cyclopentene-1,4-diol **181** in the presence of a catalytic amount of acetic acid. No reaction occurred when base was present and it was hypothesized that **180** itself could act as a good bidendate ligand for palladium thus inhibiting the reaction.



Scheme 72

Hartwig and co-workers reported recently the synthesis of tropene derivatives **185** by a sequential intermolecular and transannular intramolecular hydroamination reaction of cycloheptatriene **184** (Scheme 73).[86] Primary arylamines and alkylamines effected the double hydroamination process in moderate to good yield by using Pd(TFA)/xantphos **L7** (see Scheme 29) catalyst system.



Scheme 73

4. Conclusions

The discovery of the ability of palladium transition metal to interact with organic moieties, to connect inter- or intra-molecularly alkenes, alkynes, allenes, carbon monoxide, etc. in cascading process is certainly a breakthrough in heterocyclic synthesis. It was showed in this review that several methodologies based on cascade processes were developed during the last years. These new methodologies offer straightforward routes to a wide range of polyfunctionalized heterocyclic compounds that may not be easily obtainable by other means. It is to be expected that further combinations of fundamental Pd-catalyzed carbon-carbon and carbon-nitrogen bond-forming processes will be investigated toward this goal in the near future.

Acknowledgments

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STUDY OF THE BY-PRODUCTS OF BENZO[*f*]INDOLIZINES SYNTHESES: A QUEST TOWARDS STRUCTURAL DIVERSITY

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Abstract. *The purpose of this review is to show how the systematic study of the formation of by-products obtained during the cyclization of pyroglutamic derivatives was a guide towards easy syntheses of a diversity of chemical structures. The main parts of these by-products were isolated from Friedel-Crafts cyclization of N-arylmethylpyroglutamic acids to benzo[f]indolizines, and concerned the N-acyliminium ions chemistry. Possible mechanisms for these new reactions were postulated then utilized to synthesize a series of new potential anti-cancer agents.*

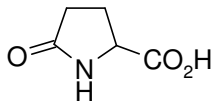
Contents

1. Introduction: some background on pyroglutamic acid

The purpose of this review is to show how the systematic study of the formation of by-products obtained during the cyclization of pyroglutamic derivatives was a guide towards easy syntheses of a diversity of chemical structures. Most of these by-products were observed from Friedel-Crafts cyclization of *N*-arylmethylpyroglutamic acids to benzo[*f*]indolizines, and concerned the *N*-acyliminium ions chemistry. Possible mechanisms for these new reactions were postulated then utilized to synthesize a series of new potential anti-cancer agents.

1.1. The forgotten aminoacid

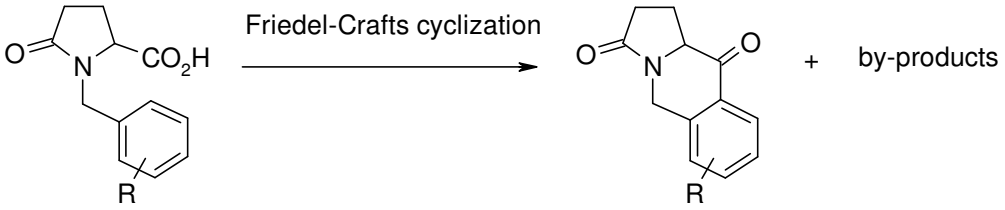
The 2-pyrrolidinone ring system is common to many molecules with great value in medicinal chemistry.[1] 2-Pyrrolidinone-5-carboxylic acid (pyroglutamic acid) (Scheme 1), which has been called "the forgotten amino acid",[2] is a biologically important member of the "chiral pool". It is found in large amounts in many plants[3] for which it works as a growth regulator.[4] It also takes part in the biology of mammals, including man.[5] It is commercially available in both configurations at low price and its utilization in organic synthesis has been reviewed several times.[6]



Pyroglutamic acid

1.2. The *N*-benzylpyroglutamic acids

N-Benzylpyroglutamic acids are easily obtained from the sodium salt[7] or the iminoether[8] of pyroglutamic esters. One of the best method utilizes *N*-trimethylsilylpyroglutamic esters,[9] and an easier way is the reductive amination of glutamic acid[10] (preferably as triethylammonium salts in methanol).[11] Many groups have studied the cyclized derivatives of *N*-arylmethylpyroglutamic acids,[7b,12] partly because the benzo[*f*]indolizine skeleton[13] of these compounds can be manipulated, leading to naphtoindolizidine[12d,14] or phenanthroindolizidine[12b,15] alkaloids. These compounds have attracted much attention because they exhibit interesting biological properties.[16]



1 **2**

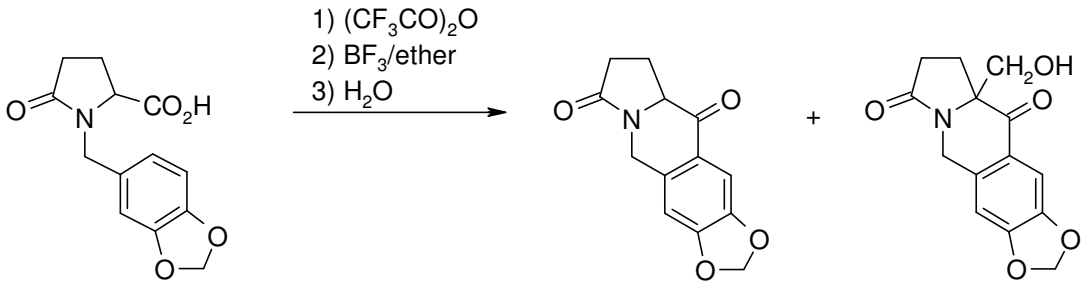
Scheme 1

The reaction described in Scheme 1 is an intramolecular Friedel-Crafts cyclization; this old and well-known formation of a ketone is one of the most utilized in synthesis. Nevertheless, the cyclization of *N*-benzylpyroglutamic acids is not a quantitative process, and many by-products can be observed by TLC.

2. Initial investigations

2.1. Is dichloromethane a solvent or a reactive?

The choice of the solvent employed for the cyclization of *N*-benzylpyroglutamic acids was found to be important for the yield and purity. Dichloroethane often gives good yields,[9e,f,12h] and dichloromethane[12c] often leads to poor purity.[9e,12a,h] Thus cyclization of acid **1a** in dichloroethane (TFAA, BF_3/ether) gave a 75% yield of ketone **2a** (Scheme 2).[17] While studying this reaction in dichloromethane, an unexpected formation of a small amount of the hydroxymethyl ketone **3** was observed after accidental extension of the heating time. After optimization of this new reaction, compound **3** was obtained in 60% yield by heating a mixture of acid **1a** and trifluoroacetic anhydride with BF_3/ether in dichloromethane for 14 hours (Scheme 2).

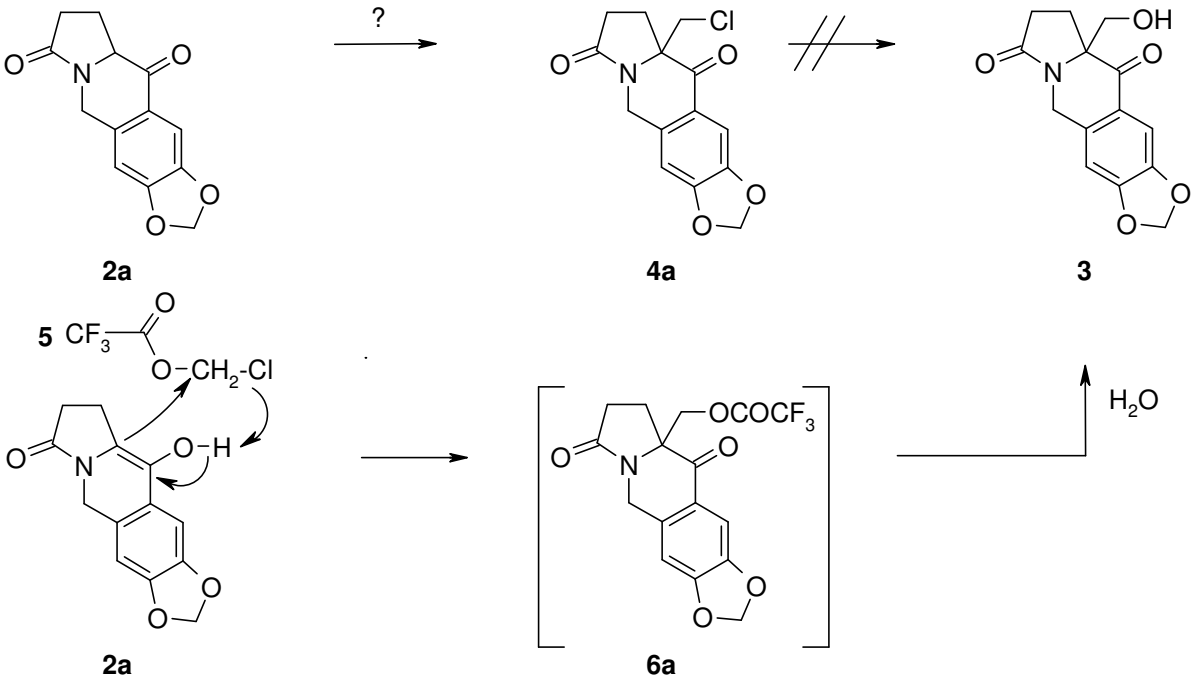


1a	**2a**	**3**
4 h, 20 °C, **CH_2Cl_2**	65%	5%
14 h, 45 °C, **CH_2Cl_2**	13%	60%
4 h, 20 °C, **$ClCH_2CH_2Cl$**	75%	0%

Scheme 2

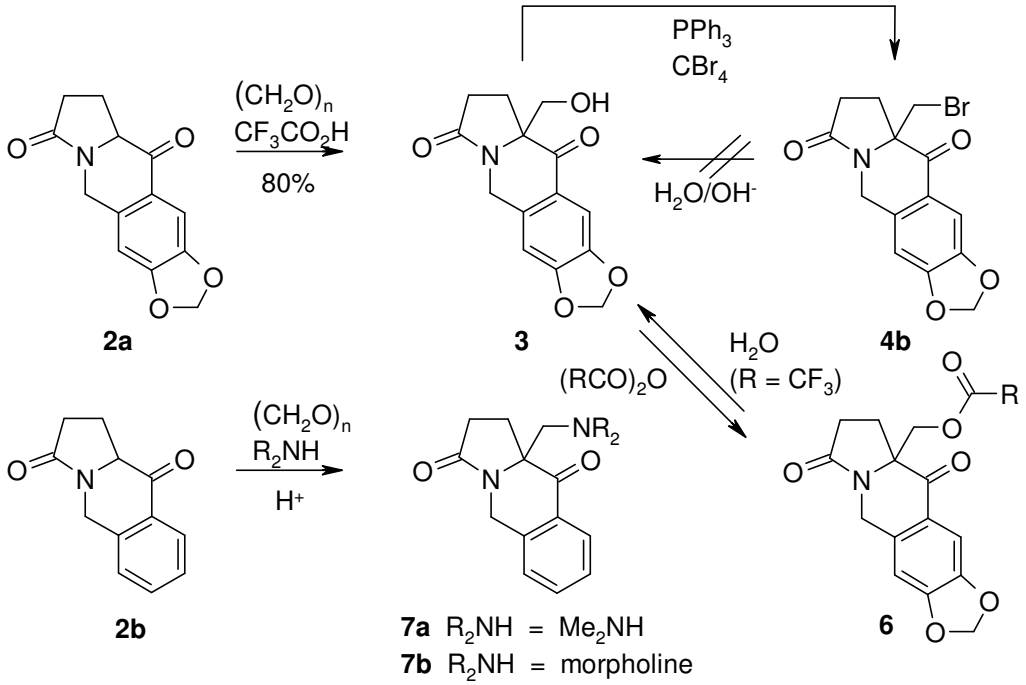
Two different mechanistic hypotheses can account for the formation of alcohol **3** (Scheme 3). In the first possibility, a boron (or acetyl) enolate could be obtained from the reaction of $BF_3.Et_2O$ with ketone **2a** in the presence of trifluoroacetic acid anhydride. Reaction of this enolate with dichloromethane could then give the chloromethyl ketone **4a** whose hydrolysis could produce the hydroxymethyl ketone **3** (Scheme 3). This reaction scheme was rejected because it requires easy hydrolysis of the chloromethyl compound **4a**, although this product and his bromo analog **4b** proved to be rather unreactive towards nucleophiles.[17] According to another possible mechanism, reaction of $BF_3.Et_2O$, trifluoroacetic acid and dichloromethane could produce a transient chloromethyl trifluoroacetate **5**. It is known that chloromethyl esters are very

reactive compounds, especially in the presence of Lewis acids.[18] Then, a classical Mannich type reaction of **5** with ketone **2a** would lead to trifluoro ester **6a** whose easy hydrolysis[17] could give the hydroxymethyl product **3**.



Scheme 3

This second mechanistic hypothesis requires an efficient Mannich type reaction of ketone **2a**. Indeed, in these series it proves to be very easy to perform such reactions. Thus, the condensation of compound **2a** with polyoxymethylene in trifluoroacetic acid and dichloroethane yields 80% of the hydroxymethyl ketone **3**; furthermore ketone **2b**[12a] reacts with polyoxymethylene and dimethylamine[19] or morpholine[17] to give good yields of aminoketones **7a,b** (Scheme 4).

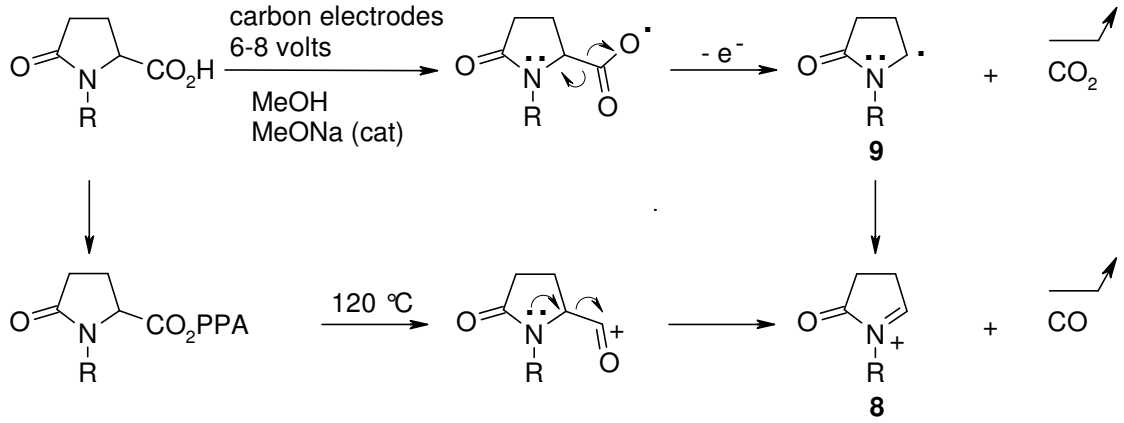


Scheme 4

These reactions were interesting not only because they explain why dichloromethane must not be used as solvent of the Friedel-Crafts reactions in these series, but also because they teach us some aspects on the reactivity of ketones **2**; this easy synthesis of 4-hydroxymethylbenzo[*f*]indolizines allowed our industrial partner to use it in parallel synthesis of many esters like **6**.[20]

2.2. *N*-Acyliminium salts from pyroglutamic acids

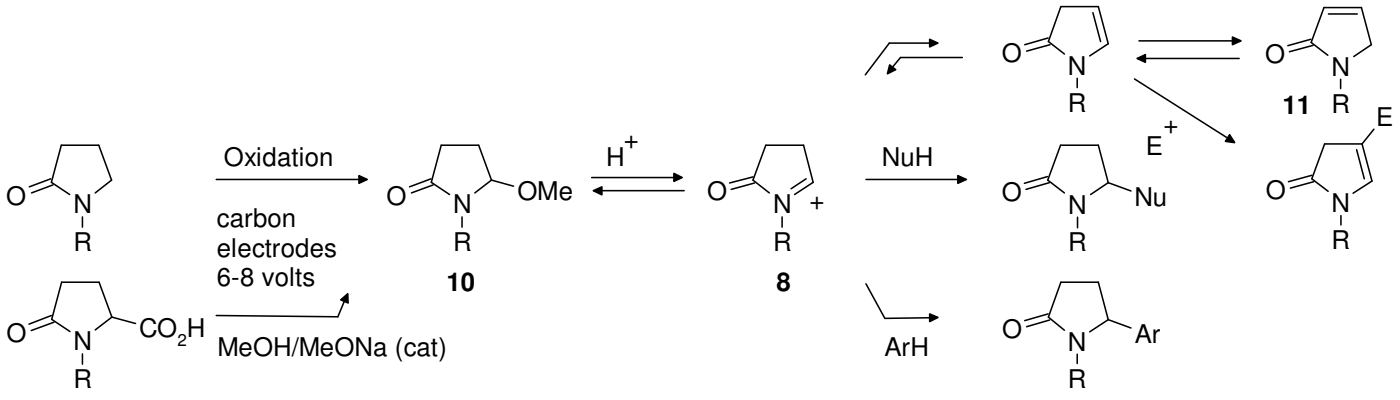
In the beginning of this work, it appeared that heating *N*-arylmethylpyroglutamic acids in PPA led to gas evolution and that ketones **2** were not obtained;[12a] sometimes the ketone was obtained in low yields.[13c] Later, carbon monoxide was identified with a Dräger tube,[21] and the mechanism of its formation was acknowledged to be the same as for the aminoacid decarbonylation leading to iminium salts.[22] In this new reaction, an *N*-acyliminium salt **8** was formed (Scheme 5). This decomposition of *N*-acylaminoacids is rather similar to the one observed by von Braun while investigating ring closure of sulfonamide glycine derivatives by $AlCl_3$-catalyzed decarbonylation of the corresponding acid chloride.[23] It was already known that pyroglutamic acid undergoes photochemical decarboxylation to give 2-pyrrolidone.[24] It can also be oxidized to succinimide by iodosobenzene,[25] and be converted to radical **9**, then to *N*-acyliminium salt **8** by anodic oxidation[26,27] or by diacetoxyiodobenzene / I_2.[28]



Scheme 5

2.3. General reactivity of *N*-acyliminium salts

As shown in Scheme 5, decarbonylation of pyroglutamic acids can lead to *N*-acyliminium salts **8**. Chemistry of these very reactive ions have recently been reviewed[29] and in Scheme 6 are recorded only few preparation and properties that we have encountered during this work.

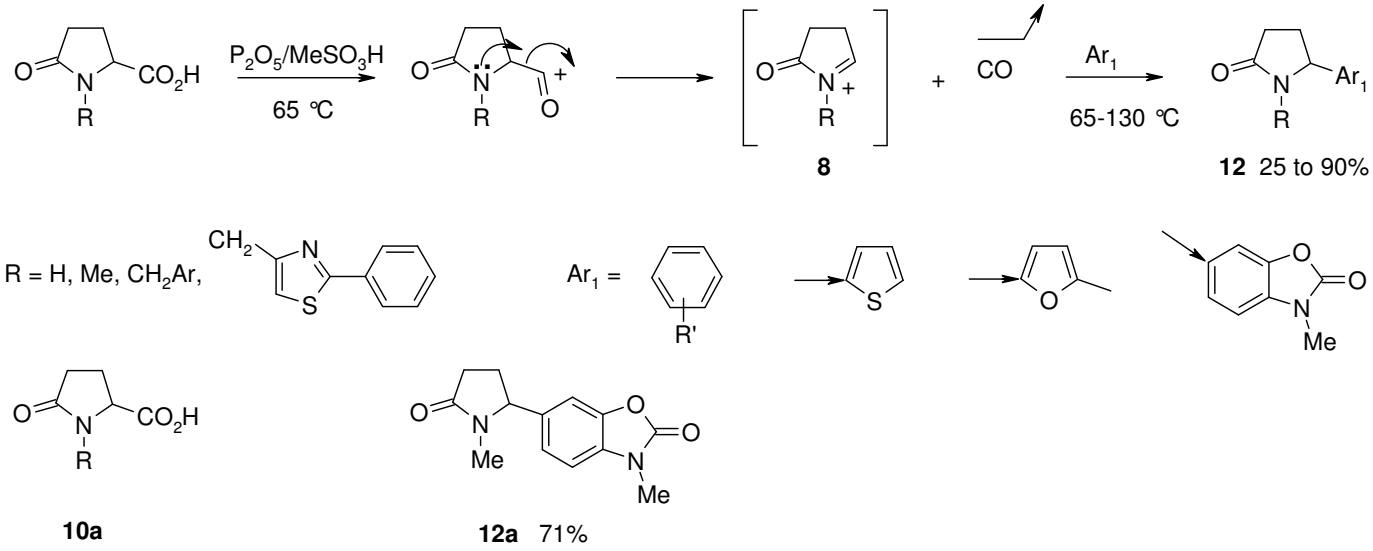


Scheme 6

The most important being that the *N*-acyliminium ion precursor **10** can result from oxidation of a lactam (either by using electrochemical method,[30] or with oxidants such as DDQ[31] or $RuO_2/NaIO_4$[32]), and that if a nucleophile is missing, **8** can evolve to give a 3(or 4)-pyrrolinone **11**.[29,33]

2.4. Synthesis of 5-arylpyrrolidinones

Many different syntheses of 5-aryl pyrrolidones **12** have already been described by not using the *N*-acyliminium ion chemistry.[34] Precursors **10** or **11** can also react with an activated aromatic (H^+ cat.)[1a,35] or with phenyl magnesium bromide[36] to give **12**. We thought that the decarbonylation of pyroglutamic acids described in Scheme 5 could lead to 5-aryl pyrrolidones **12**, and that Eaton reagent ($P_2O_5/MeSO_3H$ 1/10)[37] could interestingly replace PPA. Indeed when pyroglutamic acids and aromatic compounds were heated in that reagent, lactams **12** were obtained in moderate to good yields (Scheme 7).[21] The carbon monoxide evolution began at 60 °C, and other activating reagents such as PPA, PPE or PPSE promote this reaction as well. The decomposition of acid sensitive aromatic compounds (thiophene, 2-methylfuran) can be avoided by addition of triethylamine or by using a chloroform solution of PPE. No reaction was observed with indole, 2-methylbenzimidazole or with chlorobenzene. Interestingly, benzoxazolone **12a** was obtained in very bad yield (18%) starting from **10a**. By using the new method, **12a** was isolated in 71% yield. Recently the formation of a mixed anhydride of pyroglutamic and triflic acid was described to react in the same way.[38]



Scheme 7

Although it is not always successful, this new synthesis of 4-arylpyrrolidinones is really more interesting that the other one, mainly because it is a very short reaction pathway which does need not the preparation of an *N*-acyliminium precursor.

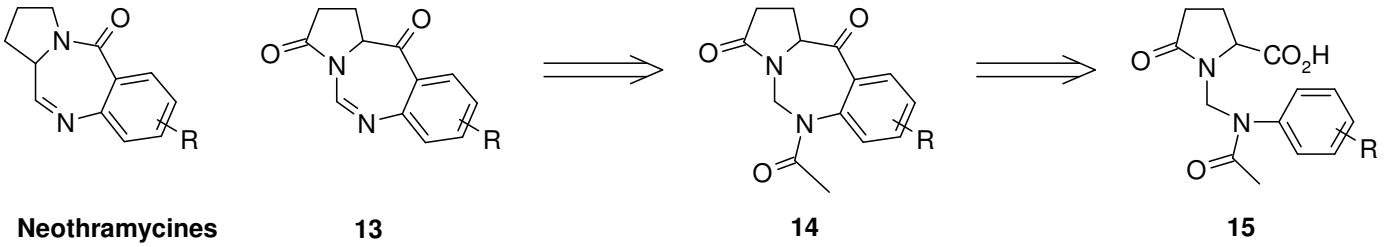
From these results it seems ascertained that the decarbonylation of pyroglutamic acids lead to *N*-acyliminium ions. It will appear in the next parts of this work that this is not true in all case.

2.5. Are the reactivities of 5-carboxy and 5-methoxypyrrolidone identical?

2.5.1. A proposal: pyroglutamic acids can lead to neothramycine-like compounds

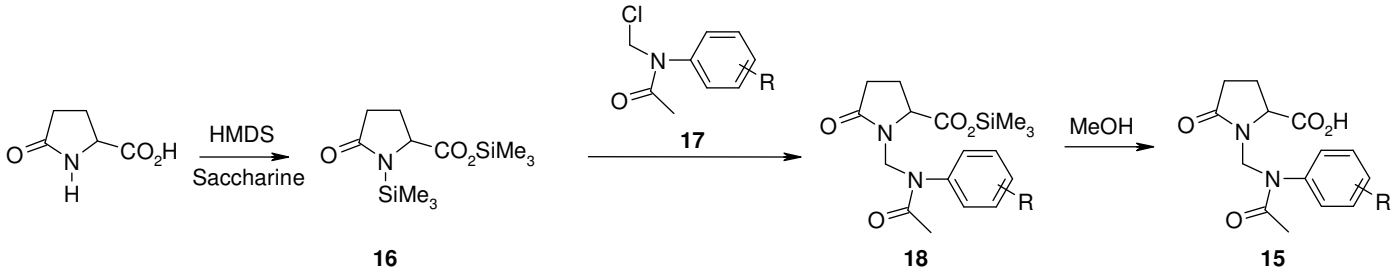
As part of a study on DNA alkylating agents, we have been interested on neothramycines. These compounds are anticancer compounds, which reversibly add a guanine NH_2 group.[39] The aim of this work was to study the reactivity of ketones **13**, whose design was based on the possibility for an amine to add the

(vinylogous) diacylamidine group of **13** similarly to the imine group of neothramycines. Precursor of lactam **13** could be the *N*-acetyl benzodiazepine **14**, obtained by Friedel-Crafts cyclization of acid **15** (Scheme 8).



Scheme 8

Treatment of pyroglutamic acid with hexamethyldisilazane (reflux 2 h, saccharine cat.) gave 90% of *N*,*O*-bis trimethylsilylpyroglutamic acid **16** whose reaction with *N*-chloromethylacetanilides **17** gives 70-96% of the methylenediamides **18**. Then solvolysis of the silyl ester **18** was easily realized by stirring in methanol (Scheme 9). The isolated yields for this step were only 50-60% because acids **15** formed hydrates which are difficult to crystallize. It is noteworthy that *N*-chloromethylacetanilides **17** are *N*-acyliminium ion precursors, easily obtained in 80-90% yield by refluxing a mixture of the acetanilide, chlorotrimethylsilane and polyoxymethylene in chloroform.[40]



R = H, 2-Cl, 2-OMe, 3-OMe, 4-OMe, 4-Me, 2,5-(OMe)$_2$

Scheme 9

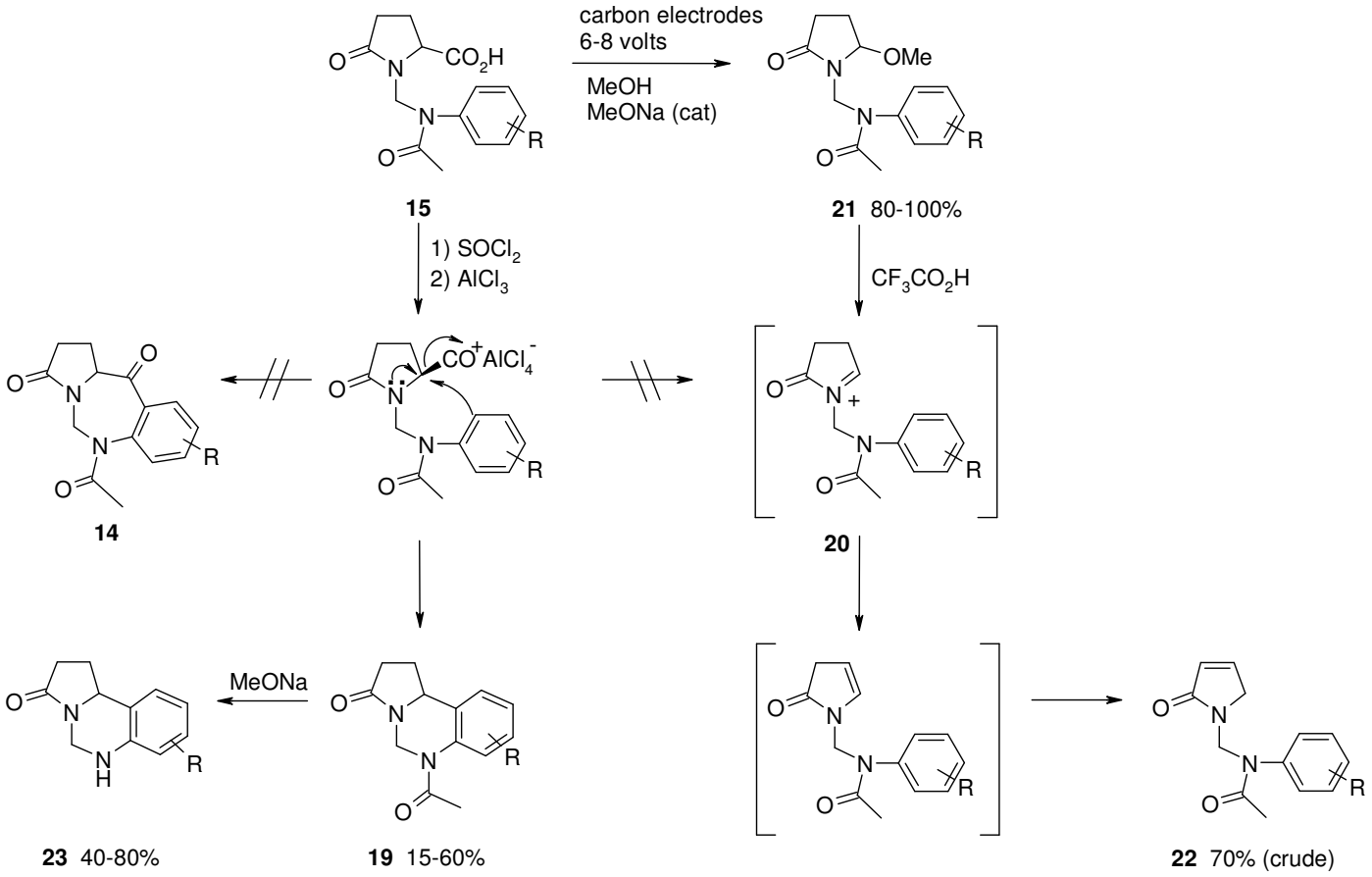
2.5.2. This is not an *N*-acyliminium salt!

Friedel-Crafts cyclization of acids **15** to benzodiazepine **14** was then attempted.[41] Benzohydropyrimidines **19** were isolated in 15-60% yield instead of ketones **14** (Scheme 9). A decarbonylation of the acid functions (Scheme 6), could give *N*-acyliminium ions **20** which could have later cyclized to **19**, but this is not the truth! Indeed, real *N*-acyliminium salts **20** were formed when the 5-methoxy lactams **21**, obtained in good yields by electrochemical oxidation of **15**, were treated with trifluoroacetic acid. These ions then evolved to 3-pyrrolinones **22** as described in Scheme 6.

It was then realized (see later) that a balance between the reactivity of the aromatic and the geometry of the molecule was responsible for this result; attack of the aromatic ortho position on the position 5 of the lactam ring, was concerted with elimination of carbon monoxide, without intervention of an *N*-acyliminium ion (Scheme 10).[12i]

Thus, the formation of analogs **13** of neothramycines would need another way of synthesis. However, to the best of our knowledge there are no compounds described in literature with the same scaffold as compounds **19**.[42] In order to study the biological properties of benzopyrimidines **19** and **23**, the solvolysis of the *N*-acetyl group of **19** was realized by stirring in MeONa/MeOH for 5 days at room temperature. In these

conditions, the lactam ring of these compounds remained unaltered, and amines **23** were obtained in good yields (Scheme 10).[41]



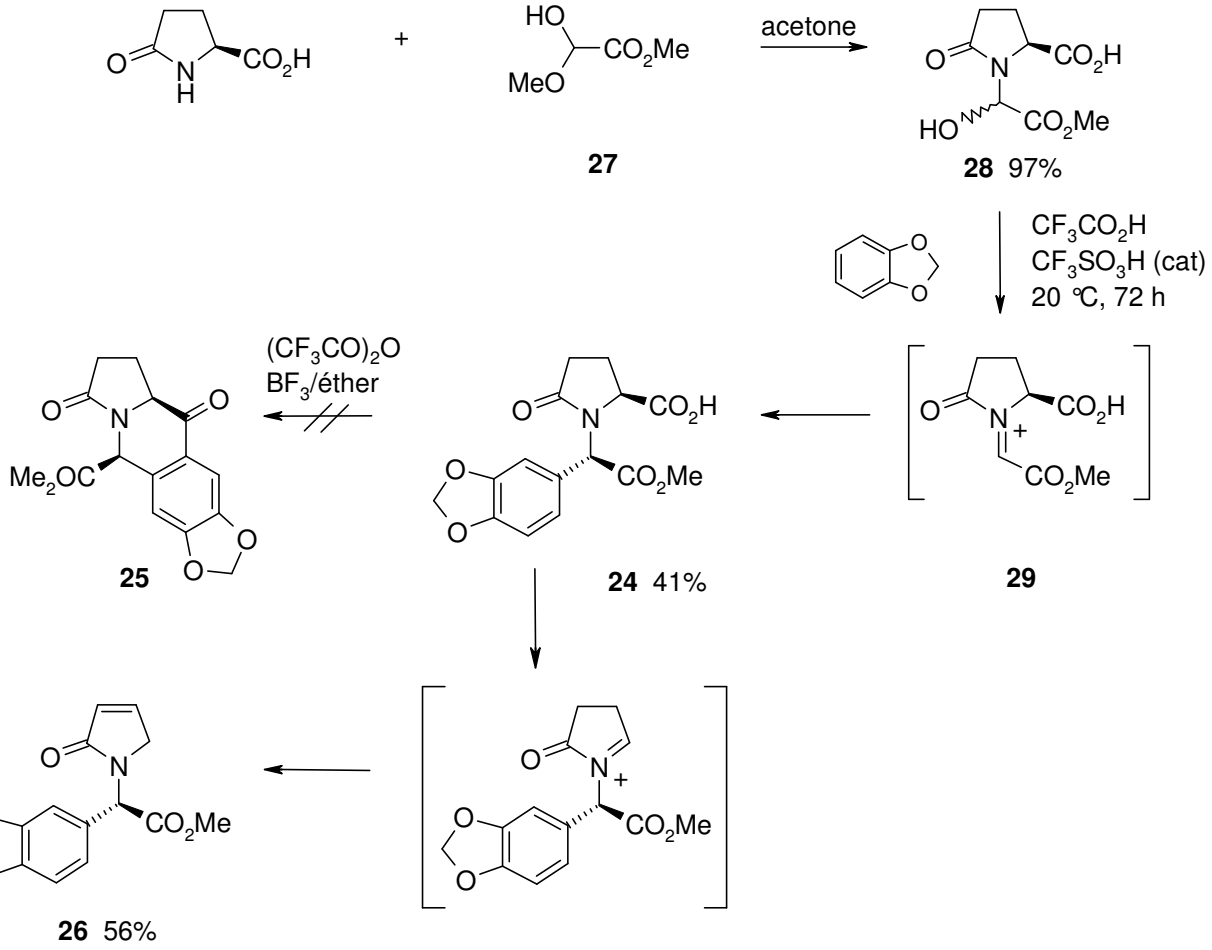
Scheme 10

2.6. Some other cases of pyroglutamic acids decarbonylation

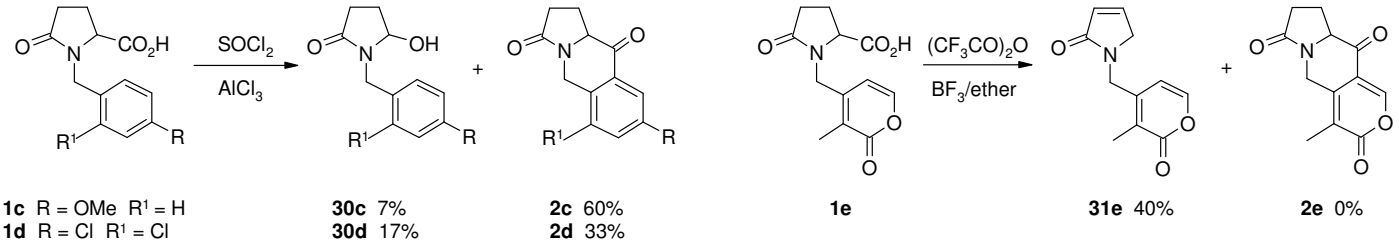
The influence of the molecule geometry on the result of a Friedel-Crafts reaction in the series of *N*-benzylpyroglutamic acids was even more obvious in the following case:[12i] in an attempt to cyclize the racemic acid **24** using TFAA and BF_3/ether, ketone **25** was not formed and only 3-pyrrolinone **26** was isolated in 56% yield.

Heterocycle **25** was obtained by a modification of a method reported by Roth:[43] condensation of D,L-pyroglutamic acid with the hemiacetal **27** of methyl glyoxylate yields lactam **28** as a 50/50 mixture of diastereoisomers. In acidic medium, *N*-acyliminium ion **29** was formed; steric interactions between the lactam carbonyl group and the ester function of compound **29** explain the formation of a single isomer of this iminium salt.[43] Approach of the benzodioxole is favored on the side opposed to the acid group, giving then acid **24**, also as a single isomer.[43] Again, steric interactions between the lactam carbonyl group and the ester function does not make it possible for the phenyl group to interact with the intermediate carboxylic acid anhydride. Decarbonylation then occurred giving pyrrolinone **26** (Scheme 11).

More pieces towards understanding the reaction of activated pyroglutamic acids were obtained from attempted cyclization of compounds **1c-e**, which led to *N*-acyliminium products **30c-d** and **31e** (Scheme 12) showing again the importance of electronic factors.



Scheme 11



Scheme 12

2.7. A first conclusion on pyroglutamic acids decarbonylation

It is thus obvious from all these results that, when an activated form of a pyroglutamic acid is formed, there is a competition between two reactions with different kinetics; generally speaking, the fastest process is the reaction of the activated form of the acid, to give an aromatic ketone. When the aromatic group is deactivated (**1d**,**e**) (Scheme 12) or must be cyclized in the meta position of an ortho/para directing group (**1c**) (Scheme 12) the cyclization rate is lower, and loss of carbon monoxide can occur. In other compounds (**24**) (Scheme 11), the aromatic nucleus is farther away from the acid carbonyl group, thus decreasing the rate of ketone formation below those of the decarbonylation step, leading to an *N*-acyliminium ion. Finally, the aromatic group can be well placed near the carbon α to the nitrogen (acid **15**, Scheme 10), and there is cyclization, with loss of carbon monoxide.

In order to have a better understanding of these reactions, a graphical representation of the first two LUMO's of some acids was realized. A LUMO or LUMO(+1) overlap was observed in case of cyclization to ketone.[12i]

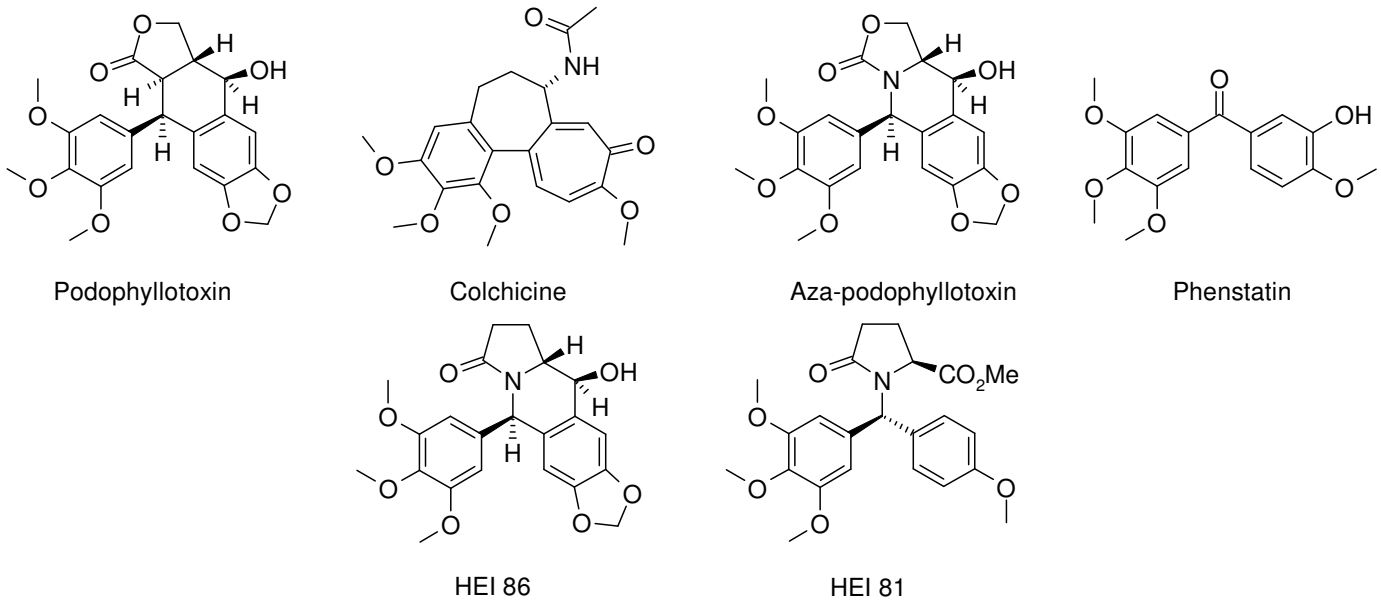
3. Some other pieces to the puzzle

Influence of the molecule geometry on the results of the Friedel-Crafts cyclization in the pyroglutamic series was further highlighted by some results of the following study on compounds acting on tubulin.

3.1. Some background on tubuline inhibitors

This study was part of a research on anti-cancer agents. Podophyllotoxin or phenstatin are spindle poison, which are effective inhibitors of cell division, interacting with tubulin at the colchicine site. These compounds are too toxic to be useful for cancer therapy. In order to obtain less toxic products many derivatives of podophyllotoxin have been synthesized. While some of its aza-analogs lack of a strong anticancer activity, some other compounds, such as aza-podophyllotoxin have been reported to display a good antitumor activity and only a low toxicity (Scheme 13).[44]

Thus, we designed other aza-analog of podophyllotoxin.[9e] From all the cyclic compounds synthesized, only the strict analog HEI 86 of podophyllotoxin inhibited significantly tubulin polymerization (IC_{50} = 5 μM), but none had interesting antitumor activity in the standard NCI test. *N*-Benzhydrylpyroglutamic esters and acids that were the starting materials for HEI 86 were also submitted to the same screening. Methyl *N*-(3,4,4',5-tetramethoxybenzhydryl) pyroglutamate (HEI 81) emerged from these tests.[9g] The middle anticancer properties of HEI 81 (IC_{50} = 0.4 μM (MCF-7 cells)) were interesting because of its atypical structure (Scheme 13).



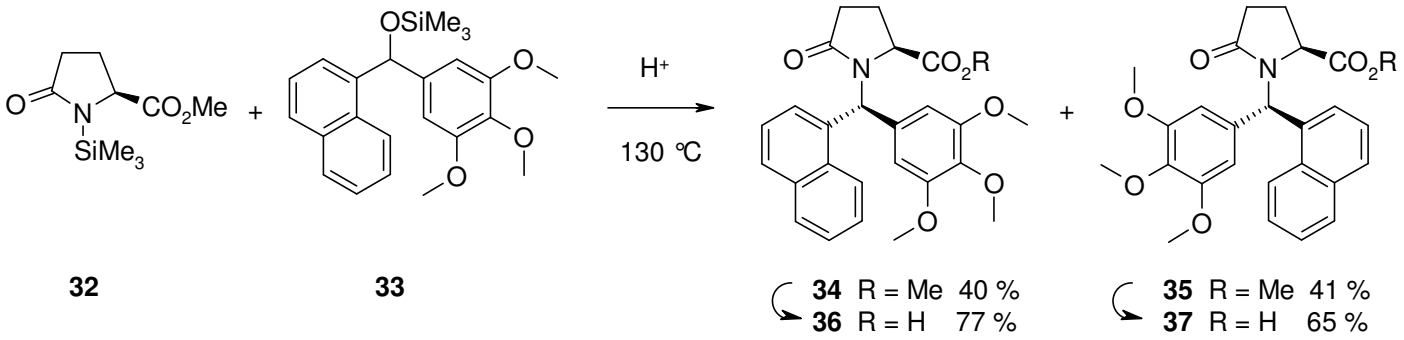
Scheme 13

3.2. Cyclization of benzhydryl derivatives

Due to the interesting biological properties of HEI 81 and HEI 86 (Scheme 13), a number of products was synthesized by using the same reaction pathway as described in Scheme 14. Condensation of racemic *N*-trimethylsilylpyroglutamic methyl[45] (**32**) or trimethylsilyl[40] ester with trimethylsilyl benzhydryl ether such as **33**[47] gave rapidly very good yields of the corresponding *N*-substituted pyroglutamic ester.[9c,d,f,g,46] In the naphtyl series, esters **34** and **35** were separated then saponified to give acids **36** and **37** which were submitted to the Friedel-Crafts reaction.[9e]

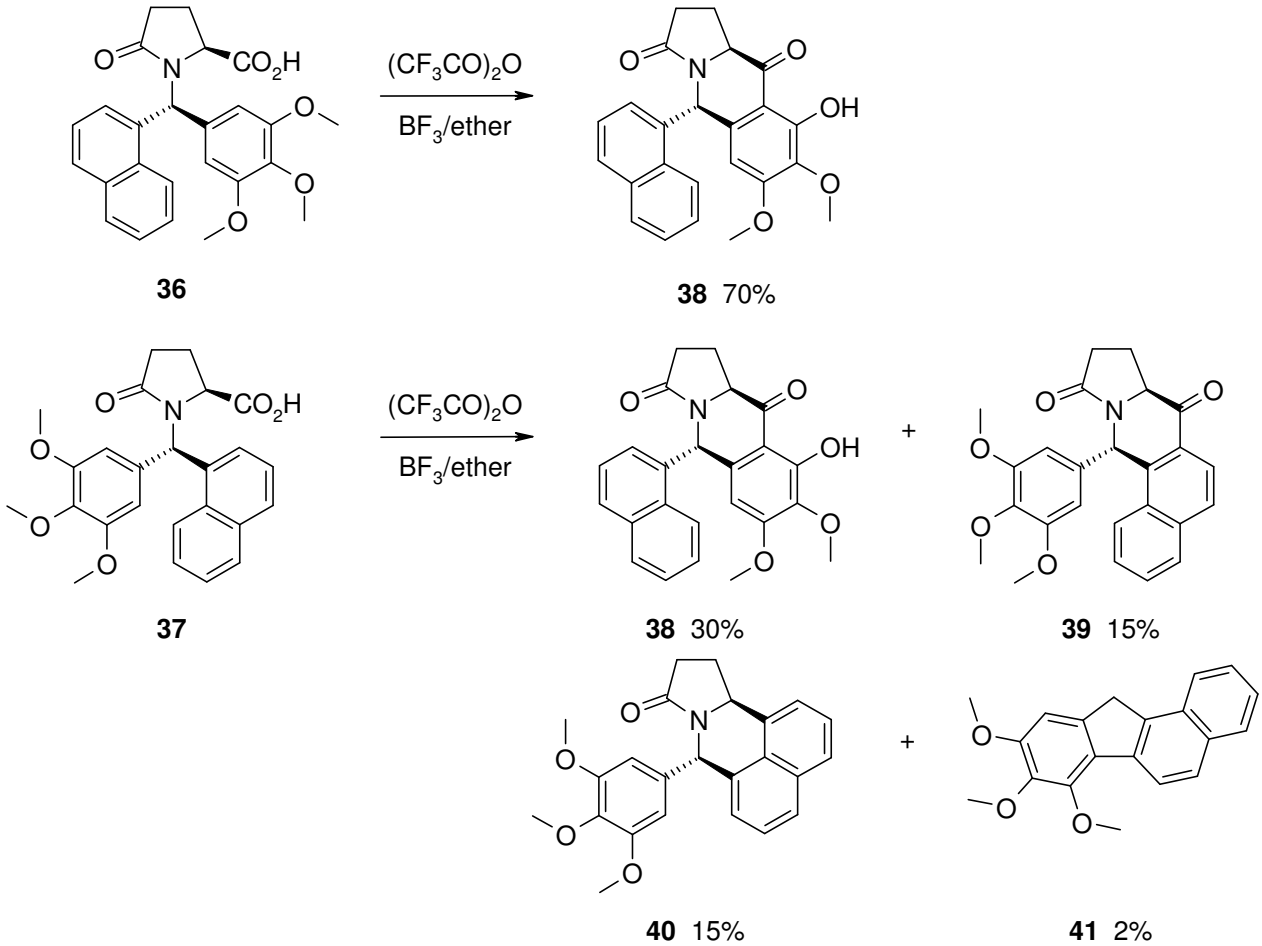
Thus, acid **36** was cyclized by using trifluoroacetic anhydride, followed by $BF_3.Et_2O$, giving ketone **38** in 70% yield. Interestingly the proximity of a ketone and a methoxy group leads to the formation of a phenol

(Scheme 15). Noteworthy, the ^{1}H NMR spectrum of the crude mixture shows only the presence of aromatic cleavage products and the absence of another cyclization compound. Acid **37** was then reacted in the same conditions as lactam **36**. A complex mixture of products was obtained, the separation of which gave the target ketone **39**, as well as ketone **38**, the aryllactam **40** and the polyaromatic product **41**. The ^{1}H NMR spectrum of the residues shows also the presence of some other aromatic compounds (Scheme 15).



32 **33**

Scheme 14



Scheme 15

3.3. X-Ray diagram of ester 35

Geometric considerations allowed again understanding these results: in the ^{1}H NMR spectrum of product **34**, the methyl ester group gives a peak at the expected value of 3.39 ppm, but for compound **35**, the same group yields a singlet at 2.45 ppm. This very strong shielding effect shows that, in deuteriochloroform,

the methyl ester group of **35** is placed above the B ring of the naphtyl substituent, while in ester **34**, this methyl group is not in the shielding cone of an aromatic ring. A X-ray study performed on ester **35** confirmed this observation (Figure 1)[48] and the results allowed to assign the stereochemistry of **36** and **37** as shown in Scheme 14.

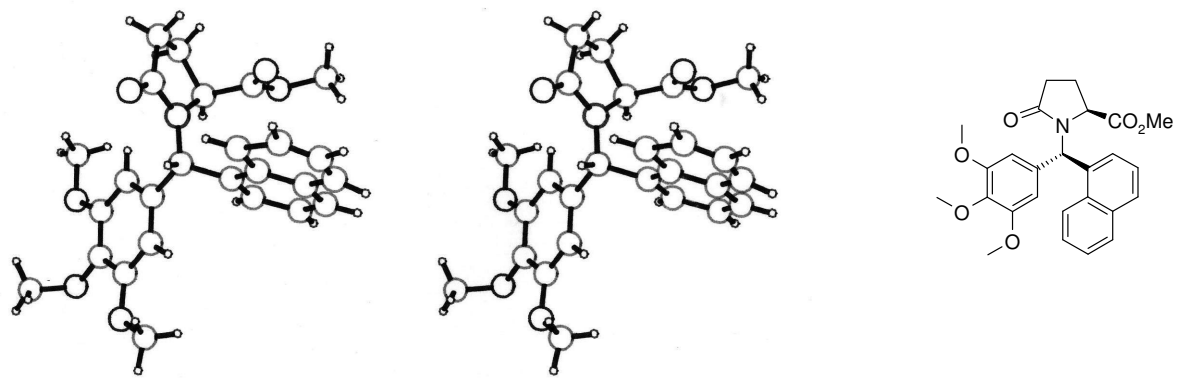
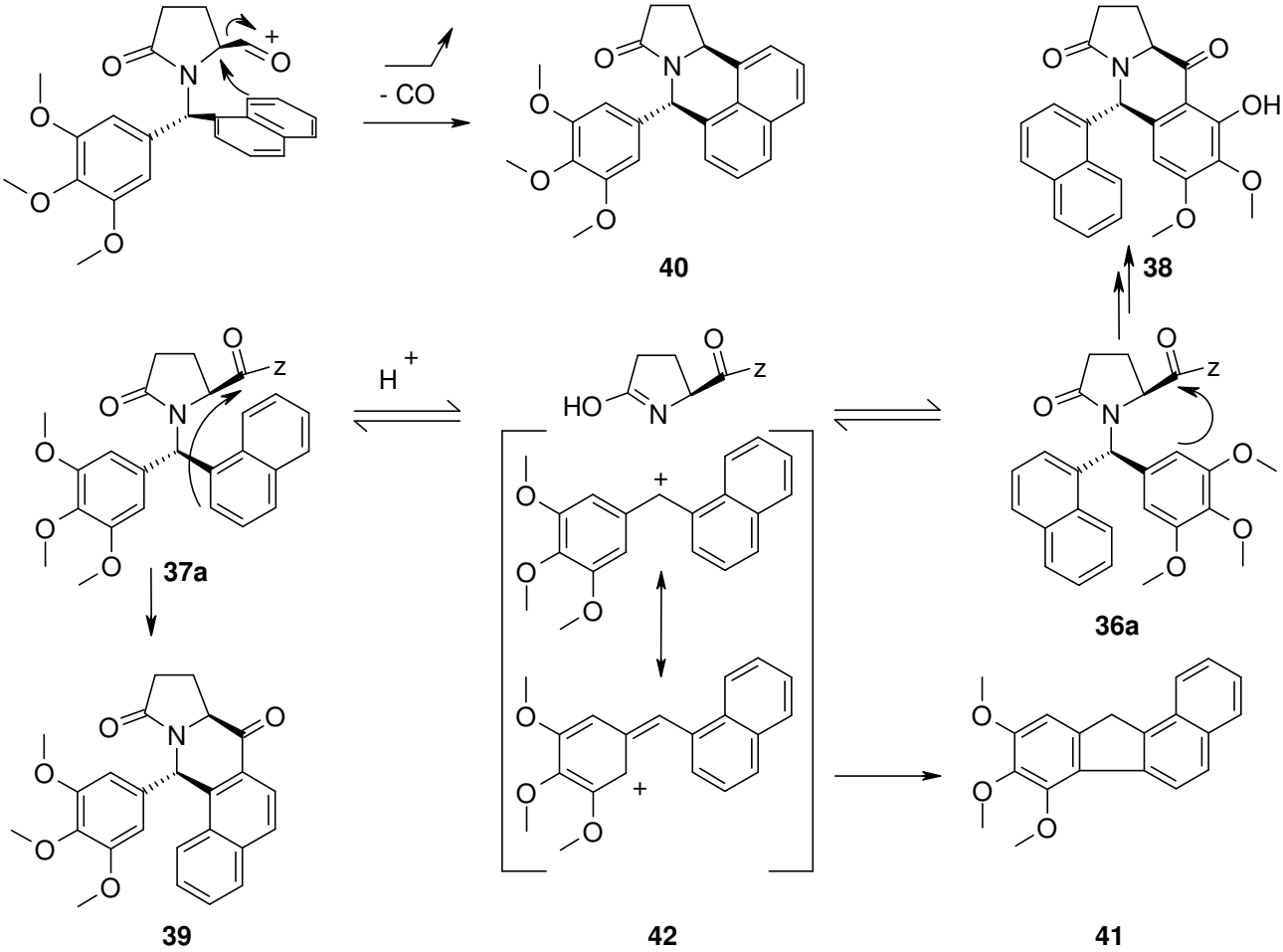


Figure 1. ORTEP Diagram of ester **35**.



Scheme 16

3.4. A proposal mechanism

Friedel-Crafts reaction of acid **37** can now be described in the following way: in its basic conformation, the proximity of the C_5 carbon of the pyrrolidinone ring with the B ring of the naphthalene

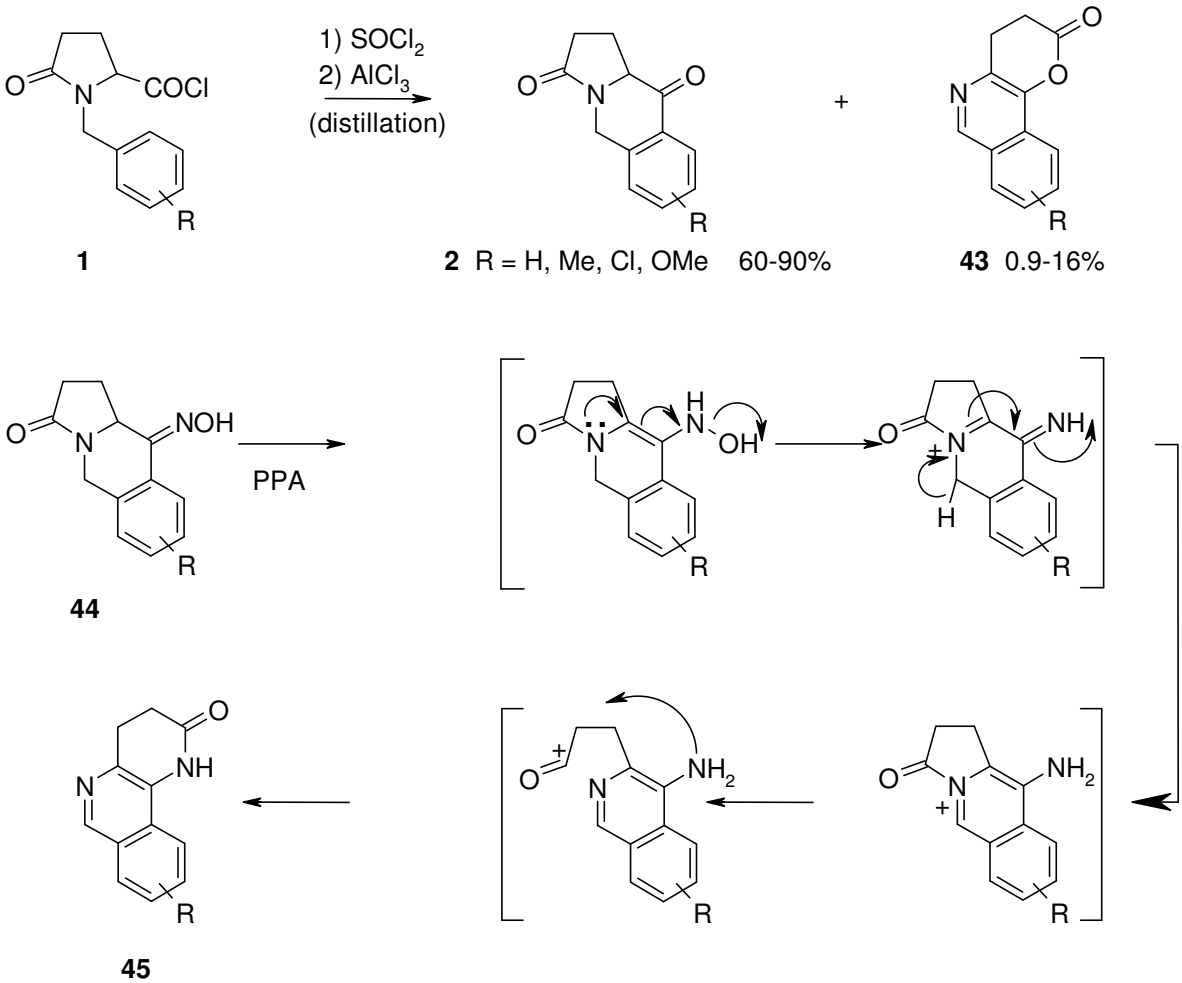
nucleus allowed the cyclization to lactam **40** and formation of carbon oxide. The "normal" ketone **39** can only be formed after a rotation of the naphtyl group (Scheme 16). These two cyclization processes being rather slow, another pathway leading to **41** has time to take place.

This formation of benzofluorene **41** is interesting because it explains why ketone **38** was obtained during the cyclization of acid **37**: breaking the benzhydryl bond of mixte anhydride **37a** could give cation **42**; recapture of the pyrrolidinone moiety would then yield the mixture of **37a** and **36a**, which cyclized to ketones **38** and **39** respectively. On the other hand, evolution of cation **42**, followed by cyclization would give the aromatic **41** (Scheme 16).

We did not try to obtain lactam **40** starting from an *N*-acyliminium precursor such as a 5-methoxypyrrolidinone but that probably can be realized. However the by-product **41** was an interesting new compound that we did not succeed to synthesize directly from the benzhydrol corresponding to **33** (Scheme 14).

4. Rearrangements in the benzo[*f*]indolizinedione series

By-products resulting from behavior of *N*-benzylpyroglutamic acids as *N*-acyliminium precursors during Friedel-Crafts reaction are not the only one. Many transformations of the ketones formed were observed, giving other by-products with interesting new structures. We will now be concerned by these compounds and by their mechanism of formation; that will be a guide towards a series of new potential anti-cancer agents.



Scheme 17

4.1. Transposition in acidic media

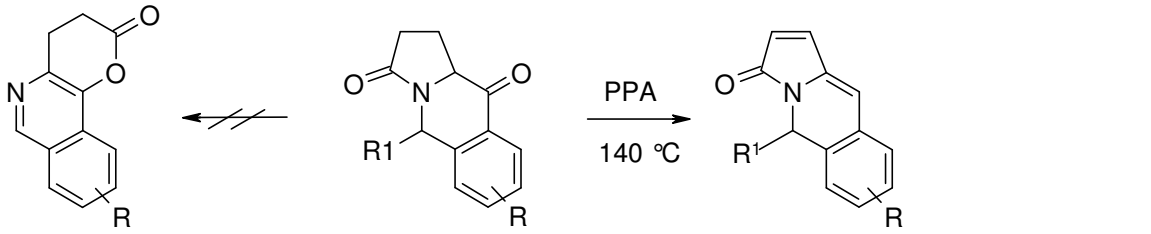
After some of the Friedel-Crafts reactions described above, the ketones formed were purified *by distillation*, and lactones **43**, or the products of their hydrolysis, were sometimes isolated in low yields (Scheme 17).[49]

The structure of lactones **43** was rather similar to that of lactam **45**, obtained by Martin from a Semmler-Wolff rearrangement of the oximes **44** derived from ketones **2** (Scheme 17).[12c,50] Structures **43** were interesting because, by using a well-selected aromatic group, they can lead to new isoquinolines, which could get dressed to give potentially intercalating agents (see later).

Lactones **43** were isolated from the acidic media of a Friedel-Crafts reaction. We thought that they could have been formed from a rearrangement of ketones **2** caused by an acid, and we checked what happens when heterocycles **2** were treated with different acids.

4.1.1. Reaction in PPA

Taking the results of Martin[12c] into account, ketones **2** were heated in hot PPA. Lactones **43** were not formed, but the dienyl lactams **46** were isolated in moderate to good yields. The low stability of *N*-methoxybenzyl lactams towards acids[51] probably explains the low yield of compound **46b** (R = *p*-OMe) (Scheme 18).[52] The mechanism of formation of these compounds will be described later. Heterocycles **46** are interesting because, although they posses a sp^3 carbon, their structures are flat (Figure 2), and also because they can be considered as well as acrylamides as enamides. That could give reactions with electrophiles and with nucleophiles, but to date we have not studied the reactivity of these new compounds.



43 **2** **46** R^1 = H, Ph; R = H, Me, Cl, Br 55-90%
R^1 = H; R = *p*-OMe 24%

Scheme 18

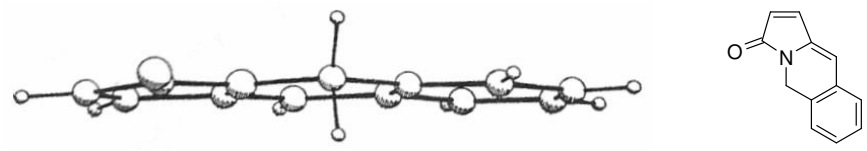
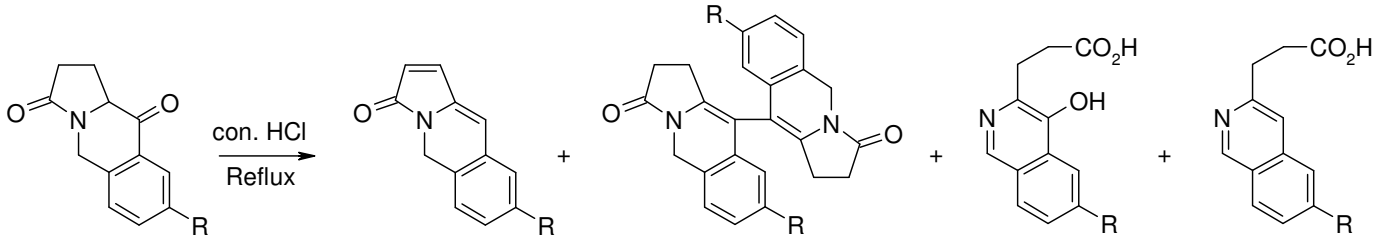


Figure 2. ORTEP Diagram of lactam **46b**.

4.1.2. Reaction in aqueous HCl

Because treatment of ketones **2** did not lead to isoquinolines, their reaction with refluxing concentrated aqueous HCl was then examined, and four main products **46-49** were isolated (Scheme 19). Whereas lactams **46** and isoquinolines **48** and **49** were easily identified from the results of previous works,[49,52] characterization of compounds **47** was more difficult. Indeed their symmetry led to a strong simplification of the NMR spectra that showed only half a molecule. X-Ray analysis of product **47f** provided the exact structure of these

dimers. This X-Ray spectrum reveals complex π-π "stacked" interactions[53] between the aromatic rings of three neighbouring molecules (Figure 3). The same pattern of products was obtained from other ketones **2**.



2

46b R = H 0.5%
46f R = Cl 3%
46g R = Br 2%

47b R = H 44%
47f R = Cl 25%
47g R = Br 69%

48b R = H 21%
48f R = Cl 31%
48g R = Br 14%

49b R = H 26%
49f R = Cl 19%
49g R = Br 9%

Scheme 19

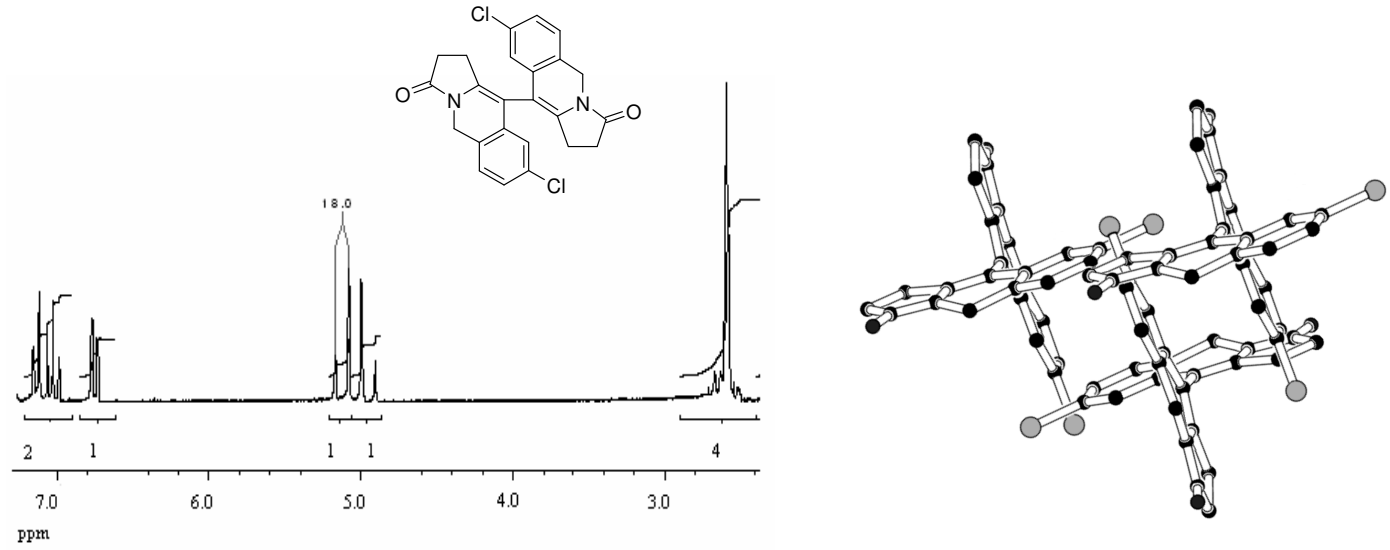
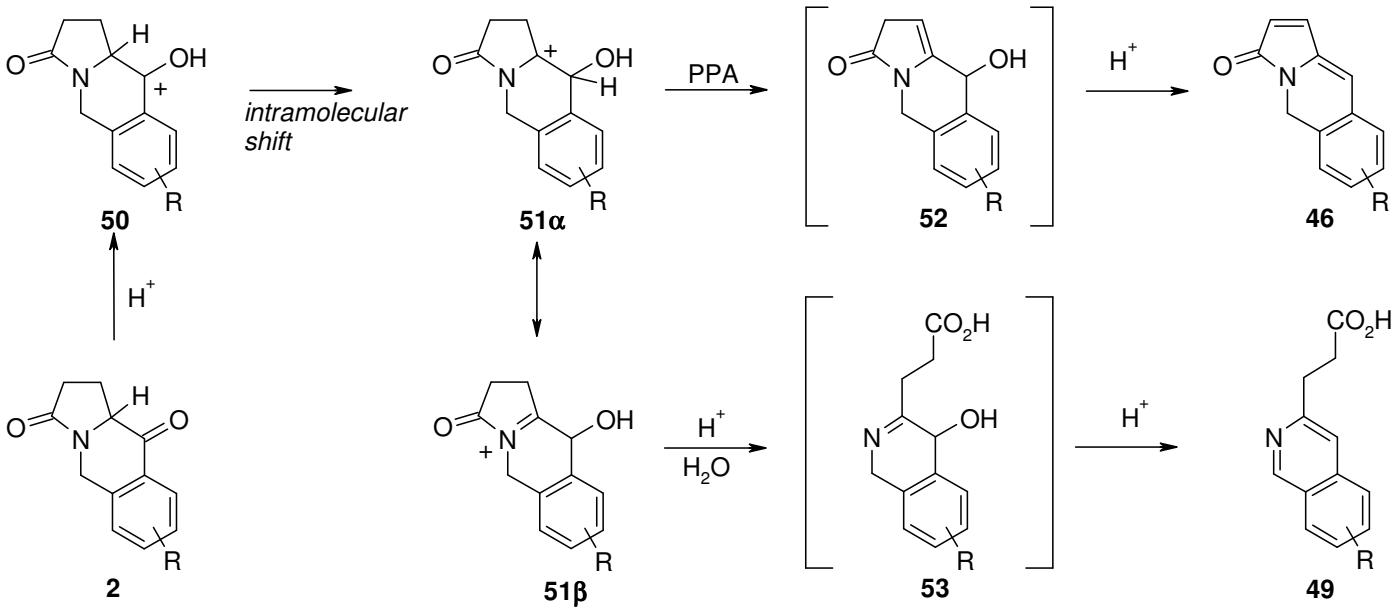


Figure 3. ^{1}H NMR spectrum, and crystal structure of **47f** showing the formation of π–π "stacked" interactions between the aromatic rings of two neighboring molecules in a unit cell comporting three dimer molecules.

It was difficult to perform a good separation between acids **48** and **49**, and the yields were low and poorly reproducible. Two syntheses, in principle identical, can lead to 50% differences in the relative yields, depending of the size of the flask, the type of condenser, the stirring speed or the exact temperature. Thus more work was performed in order to understand the formation of dimers **47** and of isoquinolines **48** and **49**, and to find conditions leading to better reproducibility, yields and separation of acids **48** and **49**.

4.1.3. Mechanisms based on pinacol transposition and *N*-acyliminium salts

The easier part of the understanding of these reactions concerns diene **46** and acid **49** (Scheme 20) for which two parallel mechanisms can account for the formation: protonation of ketones **2** leading to cation **50** was followed by a retro-pinacol reaction. This *intramolecular* hydride shift[54a] yields the *N*-acyliminium salts **51α–51β** which in anhydrous conditions (such as in PPA) evolve to enamides **52**.[54b] Then an allylic dehydration allylic gives lactams **46**. In concentrated HCl hydrolysis of the *N*-acyliminium salts **51α–51β** occurs, leading to hydroxyimines **53** which dehydrate to **49** (Scheme 20).



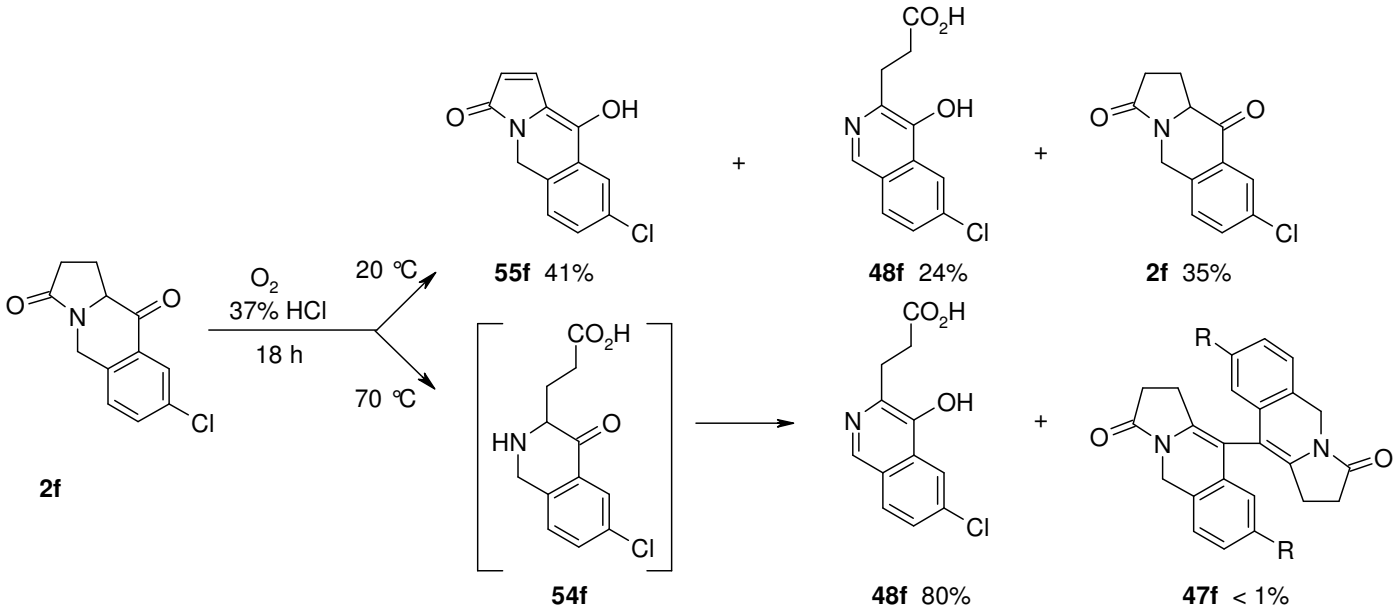
Scheme 20

A more intriguing fact was the coupling of ketones **2** leading to dimers **47** coming from a pinacol-like reaction. In the literature,[55a] only two examples of compounds of the type $(RCO\text{-}N\text{-}CH{=}CH)_2$ are described.[55b] The first one is the natural bis lactam ilicifoline, a Berberine dimer alkaloid,[55c] and the other one is a bis[oxyberberine] formed during the pyridinium chlorochromate oxidation of oxyberberine.[55d] The mechanism leading to this product cannot be extended to reactions of ketones **2** in strongly acidic conditions. We ruled out a photochemical pinacol reaction[56] because the same results were obtained in the dark. In the same way, metal promoted pinacol[57] or McMurry[58] reactions were not possible because the HCl utilized was of analytical grade, free of metal traces.

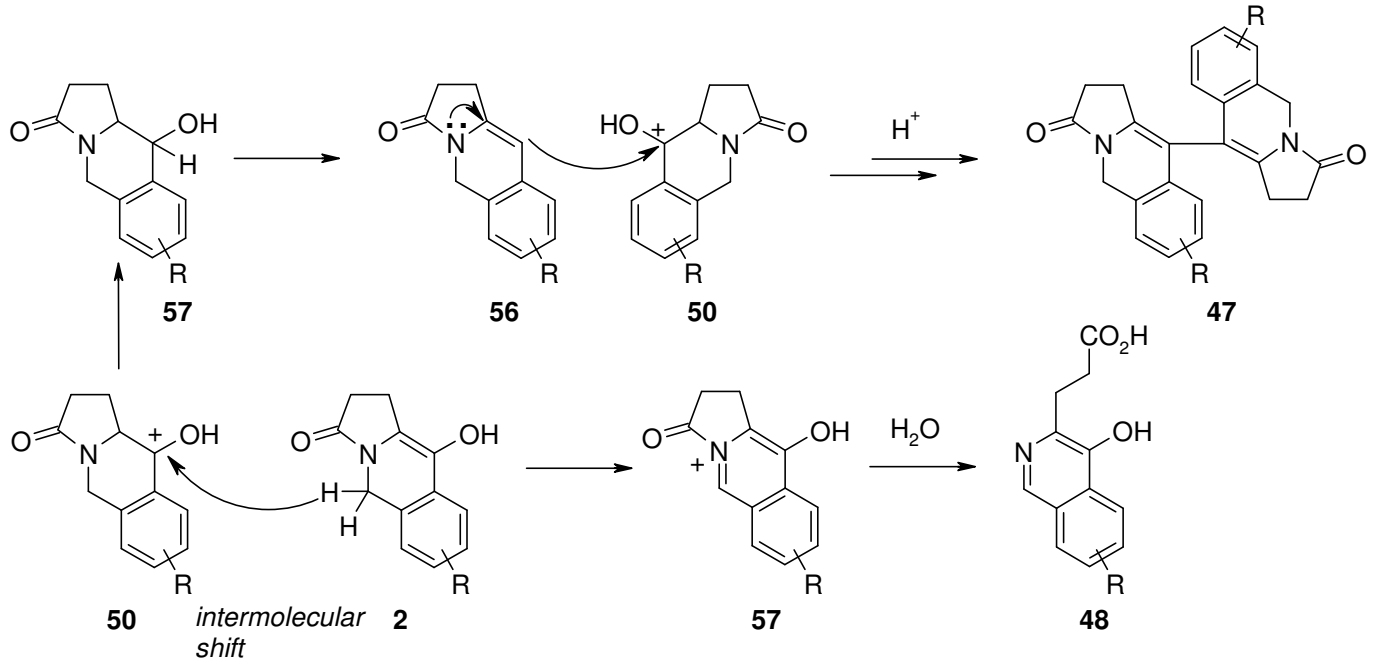
Other possibilities for dimerization of radicals were then considered. It is known that pyrrolidinones easily form radicals in the position α to the nitrogen.[59] However such a radical (or the cation-radical[60] formed after protonation of the ketone group) is expected to lead to dimers from the 10a and not from the 10 position.[61] However conditions were designed to interfere with a radical pathway. For instance 5-10% of $FeCl_2$, NBS, AIBN or hydroquinone was added to the reaction media, but the reproducibility and the yields did not change noticeably and the corresponding mechanism was ruled out.

Another possible pathway implies oxidation from atmospheric oxygen which could explain the notable influence of the flask, condenser and stirring. During the course of reactions performed at 110 °C with 37% HCl, variable amounts of compounds **54** (Scheme 21) were observed as intermediates, and it is known that this type of amino ketone readily undergoes oxidation to provide the fully aromatic products.[62] Model reactions with ketone **2f** were then realized at lower temperature, in hydrochloric or hydrobromic acid, with addition of *tert*-butyl hydroperoxide or while bubbling oxygen (Scheme 21). These reactions confirm that an oxidation process can lead to hydroxyisoquinolines **48**. Interestingly under these mild conditions, another oxidized product **55f** was also obtained (the mechanism of formation of this type of compounds will be described later). The solubility of enol **55f** is very low, thus this product can easily be separated from the isoquinoline **48f** by filtration of the reaction mixture, while CH_2Cl_2/water partition leads to nearly pure acid **48f**. The likely mechanism at 70 °C is an opening of the lactam ring yielding aminoketone **54f** whose oxidation gives isoquinoline **48f**. At 20 °C, ring opening leading to **54f** then to **48f** is slower, and oxidation

of the lactam rings gives **55f**. Application of these observations led to the design of an improved synthesis of hydroxyisoquinolines **48b** (R = H): a strong magnetic stirring of ketone **2b** in dilute HCl, at 55 °C in a large beaker open to the air, gives a 70% reproducible yield of pure hydroxyacid **48b**. Under these conditions, only a very low amount (less than 5%) of dimer **47b** was also formed.



Scheme 21



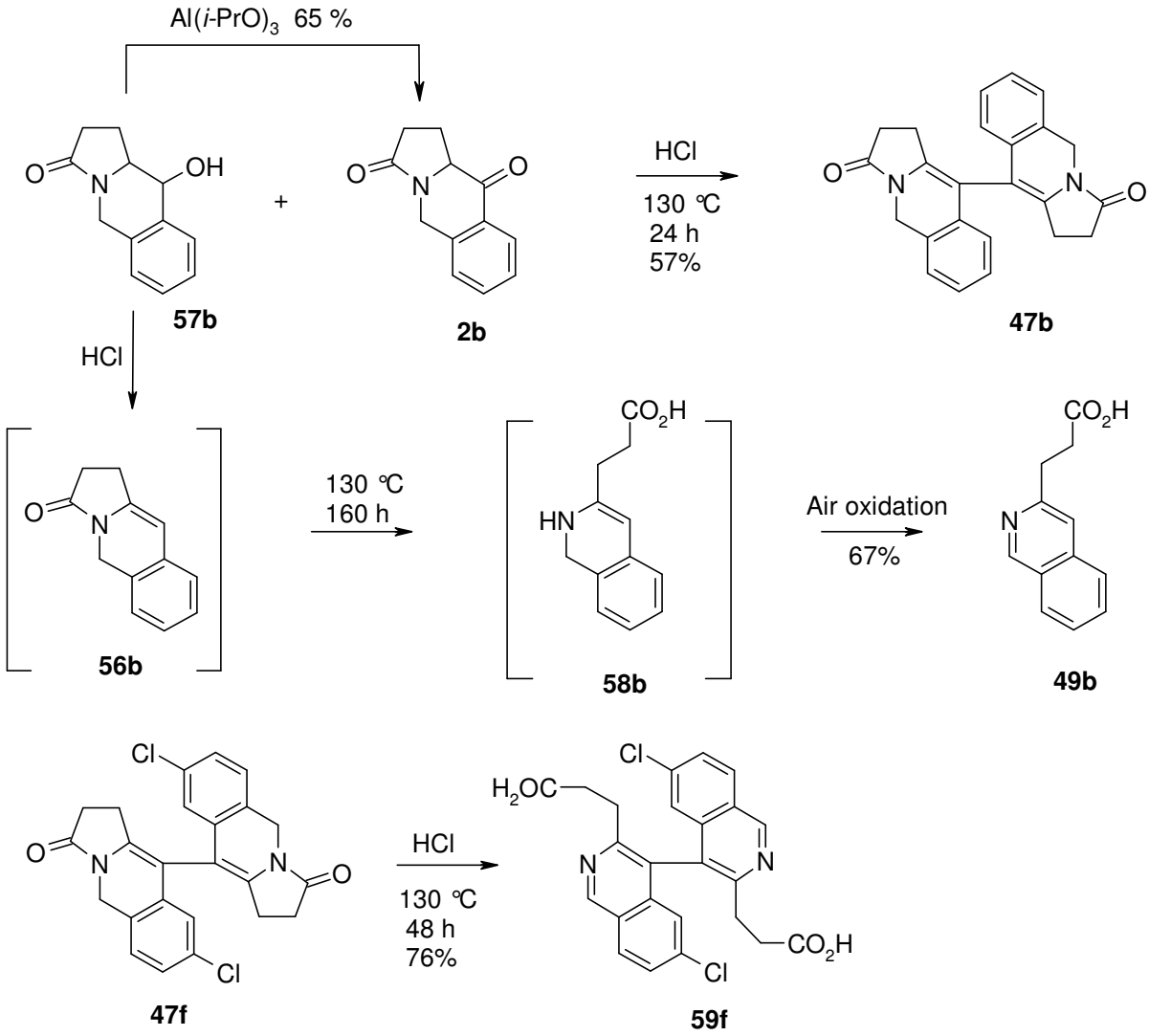
Scheme 22

During a part of this study, hydrochloric acid was replaced by hydrobromic acid. The most interesting result from these reactions of **2b** and **2h** was that in some experiments, 5% of alkene **56b** (R = H)[12a] or 12% of **56h** (R = 8-Me) were isolated (Scheme 22). Formation of enamides **56** can be explained by an *intermolecular* hydride shift between the enol form of unprotonated ketones **2** and its protonated form **50** (Scheme 22), which is a route rather similar to the *intramolecular* hydride shift leading to compounds **46**

(Scheme 20). This yield alcohols **57** then alkenes **56**. It is known that enamides react with electrophiles.[63] In the present reaction, condensation of enamide **56** with protonated ketone **50** led to the pinacol-like derivatives **47**. The driving force for the intermolecular hydride shift reaction can be the formation of aromatized isoquinolinium salts **57**, which later hydrolyze to hydroxy acids **48**.

4.1.4. Mechanistic considerations show the ways for useful syntheses

This hypothesis of alcohols **57** being key intermediates in the formation of dimers **47** was then experimentally confirmed. Heating of a mixture of 1 g of **2b** with an equimolar amount of **57b**[12a] at 130 °C for 24 h in concentrated HCl yielded 1.05 g (57%) of isolated dimer **47b**. This yield strongly exceeded the amount (0.4 g) of **47b** which could be obtained if only ketone **2b** had yielded the dimer, without intervention of enamide **56b** (other products observed by NMR were **2b**, **46b**, **48b**, **49b** and **58b**) (Scheme 23).



Scheme 23

Observation of lactam ring hydrolysis of **2** (Scheme 21) opened the question of the stability of compounds (**46,47** and **56)** formed in these reactions (Schemes 20 and 22). Thus, **57b**[12a] (as a precursor of **56b**) was heated in HCl leading rapidly to an amino acid **58b**. This was followed by oxidation of the dihydroisoquinoline **58b** which occurred slowly, leading to 67% of aromatized isoquinoline **49b** as the only compound isolated. This formation of acids **49** starting from alcohols **57** was very clean and proved to be the

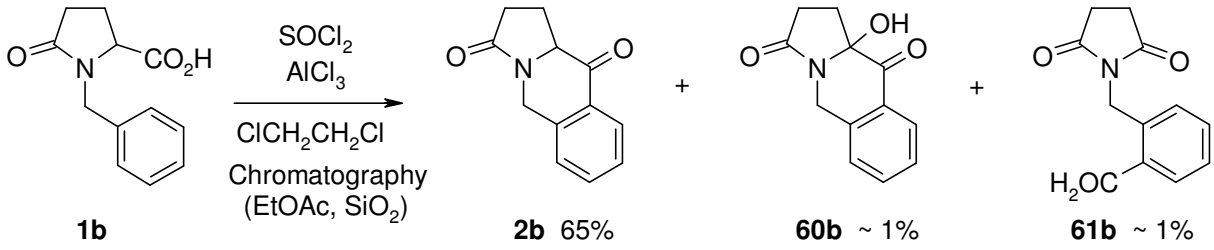
best method to obtain these compounds. The same reaction was also performed with the diene (**46b**) also leading to the same acid **49b**, but the reaction medium was less clean than starting from **57b**. In the same way, heating **47f** in HCl led to the formation of bis-isoquinoline **59f**, the exact duration of these oxidations being strongly dependent of the size of the opening to the air condenser (Scheme 23).

4.1.5. Conclusion on transpositions in acid conditions

Thus, distillation of the crude mixture obtained after Friedel-Crafts reaction of *N*-benzylpyroglutamic acids allowed isolations of by-products formed in acidic conditions from allylic dehydration, retro-pinacol, pinacol-like and enamide reactions. The understanding of these hydride transfers and oxidative processes allows the specific and easy synthesis of isoquinolines **46-49,55** and **59** (Scheme 18, 21, 23). We will see now that other purification methods furnish other unexpected compounds.

4.2. Oxidations of benzo[*f*]indolizinediones

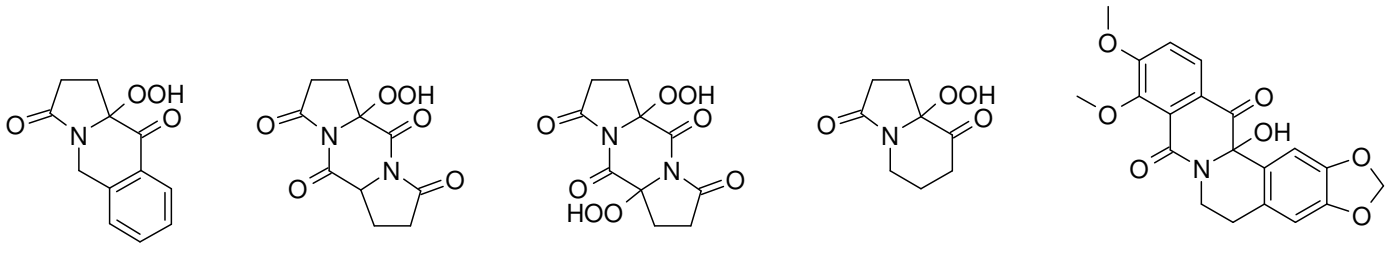
We have seen that oxidation of ketones **2** in acidic medium led to isoquinolines **48** and **55** which can be isolated by *distillation* (Scheme 21). Other oxidative processes can also operate; they were observed when purification of a crude mixture from the synthesis of **2b** was realized by using *preparative chromatography* on SiO_2. Thus, alcohol **60b** and succinimide **61b** were isolated in the minute amounts of about 1% (Scheme 24).[64] Because the carbinolamide group function of **60b** is potentially precursor of *N*-acyliminium ions and therefore could conduce to a rich chemistry, we engaged on the synthesis of this class of compounds and explored a part of his reactivity.



Scheme 24

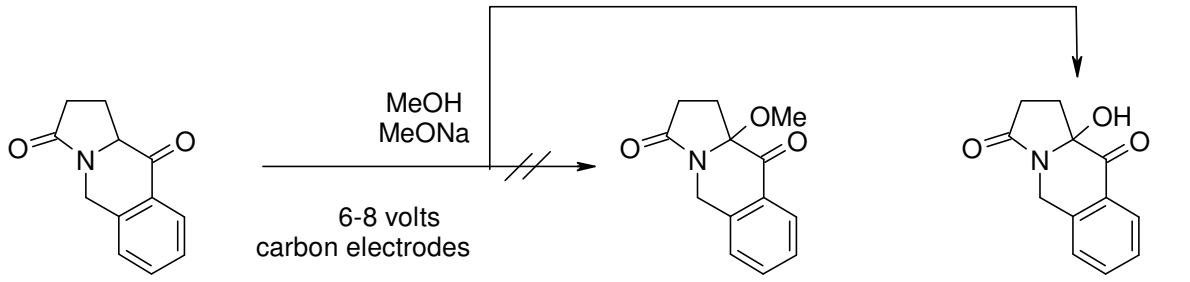
4.2.1. Oxidation of ketones in MeONa/MeOH

Alcohol **60b** was obviously formed from peroxidation of ketone **2b** with oxygen from air. Indeed we have already observed that heterocycle **2b** was rapidly degraded in the presence of oxygen, and formation of peroxide **63b** have been postulated.[12a] Oxidation of the CO-N-CH-CO group has often been described,[65] leading to compounds such as hydroperoxides **64-66**[66] or alcohols such as **67**[67] (Scheme 25).



Scheme 25

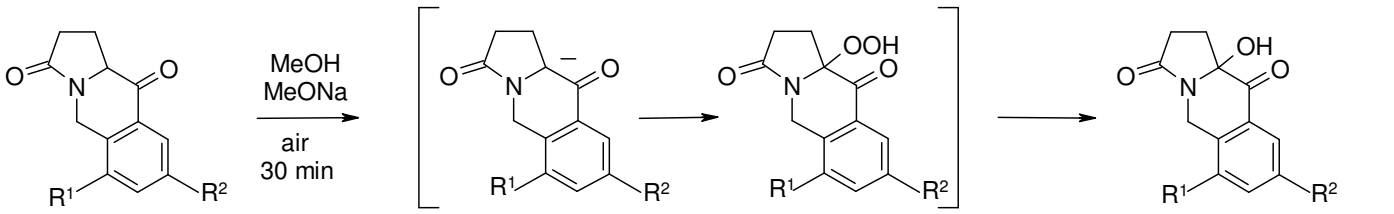
It is known that a hydroxy or a methoxy group can be introduced in the α-position of lactams by electrochemical oxidation.[68] Thus we attempted to obtain **68b** by electrolysis of lactam **2b** in a MeOH/MeONa solution. Interestingly, transformation into alcohol **60b** can be observed *before connecting the carbon electrodes to the power line* (Scheme 26).[64]



2b **68b** **60b** 5 min. 10 %

Scheme 26

Thus, ketone **2b** was spontaneously oxidized in the reaction media. It is known that electron-rich structures as enolates can react with oxygen triplet, by intermediate formation of carbon centered radicals, to yields alcohols.[69] Therefore oxidation of heterocycles **2b,2d** and **2i** was realized by stirring these ketones 30 minutes in an open to air MeONa/MeOH solution. In these conditions, alcohols **60b,d,i** were obtained in 70-75% yields (Scheme 27). Noteworthy, further reaction of products **60** with O_2 and MeONa were not observed (see later); it showed also to be important to perform purification of these alcohols by using EtOAc and not CH_2Cl_2 as the solvent during the extraction step (see later). In the same way, it was necessary to use the weakly acidic citric acid and not HCl to realize the neutralization of MeONa (see later).



2 **63**

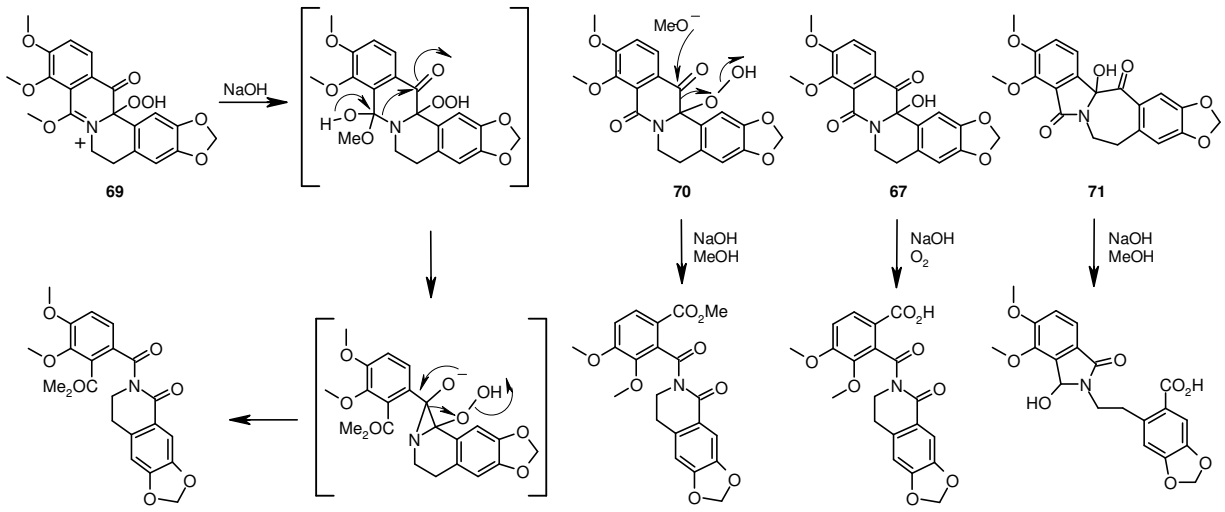
60b R^1,R^2 = H 70%
60d R^1, R^2 = Cl 75%
60i R^1 = Me, R^2 = H 75%

Scheme 27

Interestingly only one aromatic group is included in the structure of alcohols **60**. It was thought previously that complex α-ketocarbinolamides needed to be stabilized by the presence of two neighboring aromatic rings.[70]

4.2.2. Transformations of the CON-C(OR)-CO group described in literature

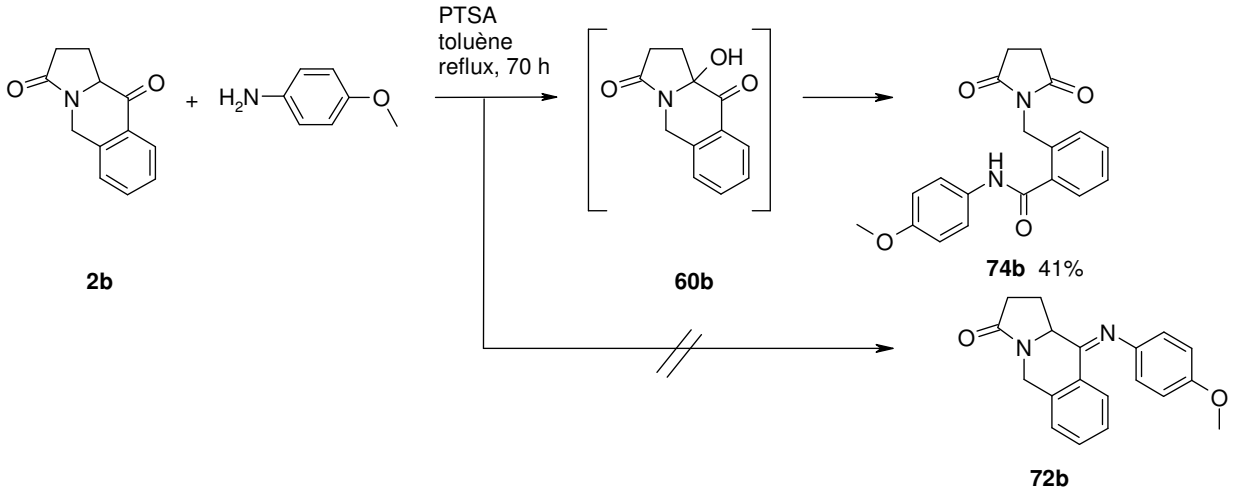
The alcohol function of compounds **60** is vicinal to a lactam and a ketone group. Literature indicates that the CON-C(OOH)-CO and CON-C(OH)-CO scaffold are rather reactive when they are exposed to sodium methoxide or sodium hydroxide; for instance, in the chemistry of berberines, the opening in these conditions of the ketone ring of hydroperoxides **69** and **70**[70] or alcohols **67**[71a] and **71**[71b] was described (Scheme 28).



Scheme 28

4.2.3. Oxidation in dichloromethane

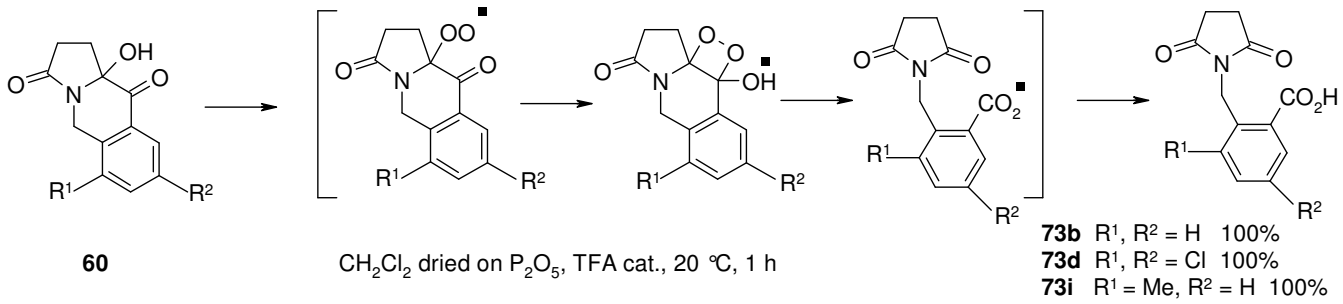
Unlike hydroxylactams **67** or **71** (Scheme 28), alcohols **60** remained unaltered in the presence of sodium methoxide in methanol and, after their formation, they can be isolated by extraction with ethyl acetate; when the extraction step was performed with dichloromethane, these compounds were slowly converted to succinimides **61**[64] (Scheme 24). The same transformation was observed when pure alcohols **60** were solubilized in CH_2Cl_2, and was accelerated by heating, even under a nitrogen atmosphere. Succinimides **61** were also rapidly obtained by stirring compounds **60** in a solution of trifluoroacetic acid in dichloromethane or by refluxing **60b** one hour with PTSA in toluene. Oxidation of **2b** to **60b** then transposition to succinimide explained also the result obtained in an attempt to synthesize imine **72b**: a mixture of ketone **2b**, PTSA and anisidine was refluxed in toluene to give amide **74b** as the only isolated product; that also focus on the low reactivity of the ketone function of heterocycles **2** towards amines (Scheme 29).[64]



Scheme 29

These results can be explained by the fact that trace amount of oxygen still remained in the solvent used.[72a] The dichloromethane utilized was dehydrated by distillation on P_2O_5, and reaction rates decreased in the presence of hydroquinone, or if the solvent was deoxygenated with nitrogen. Thus it is clear that oxygen dissolved in the solvent leads to incorporation of a new oxygen atom in the structure of the heterocycle;

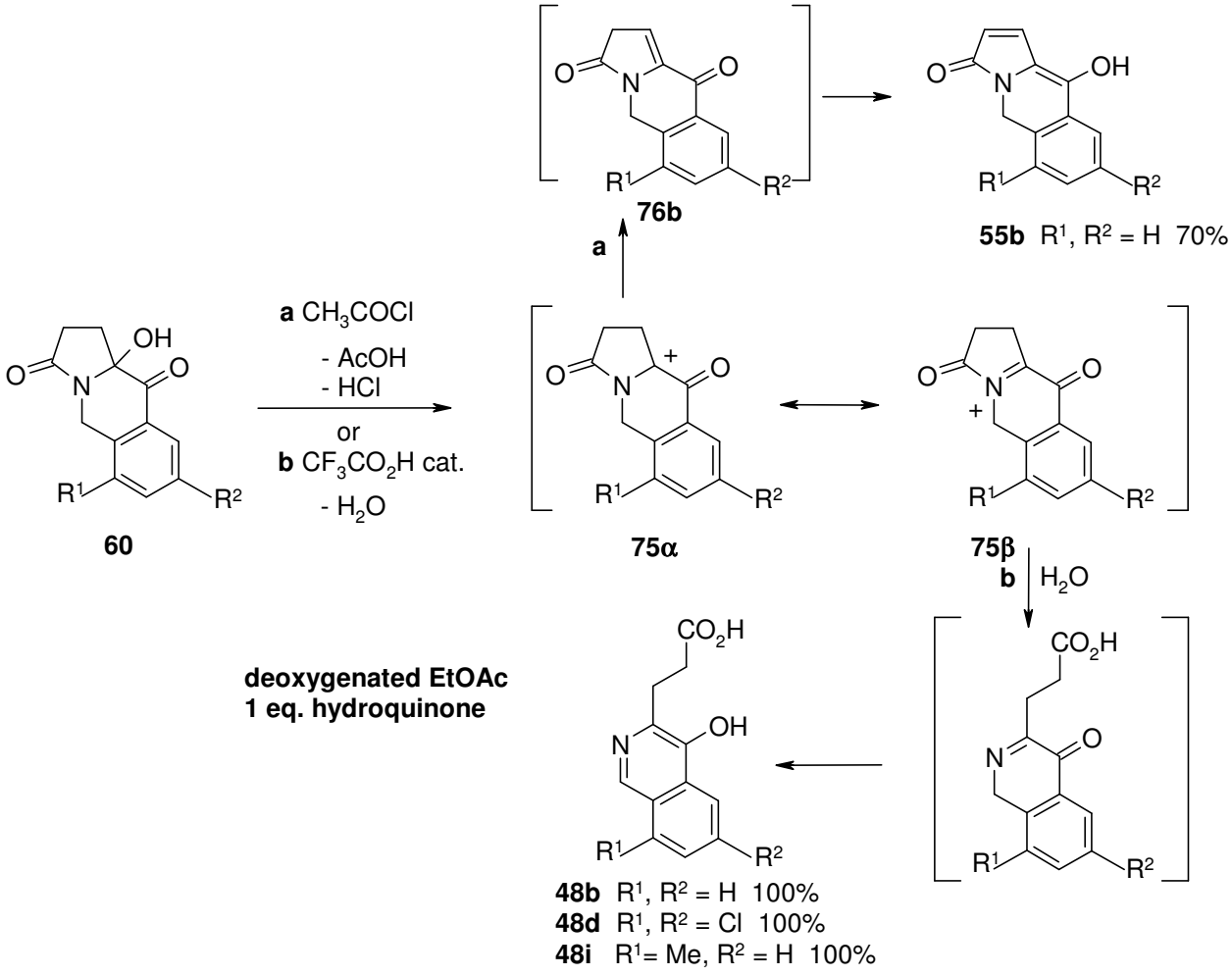
although exact mechanism of this oxidation was not studied, it is not apparent to the Bayer-Villiger reaction,[72b] and it is possible to suggest a pathway (Scheme 30) based on the results of Compostella.[72c]



Scheme 30

4.2.4. An easier synthesis of previous compounds

We have already indicated that alcohols **60** were not rapidly oxidized in ethyl acetate. In that solvent, trifluoroacetic acid did not led to succinimide **73** but to water and an *N*-acyliminium salt **75α-75β**.[29]



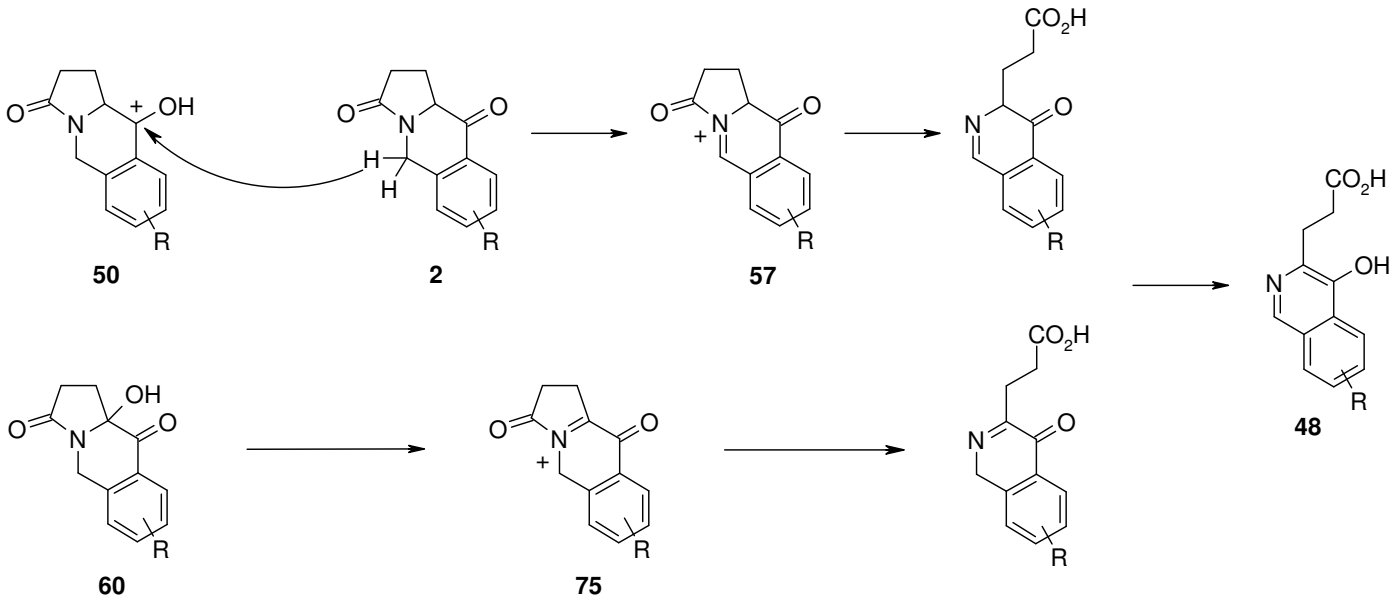
Scheme 31

The formed water acting as a nucleophile open the lactam ring, and then aromatization led to quantitative yields of hydroxyisoquinolines **48** (Scheme 31).[64] Noteworthy, formation of acids **48** was very easy when using that route (oxidation of ketones **2** in basic medium, then acidic rearrangement) and gave no by-products, whereas the method previously described (reflux of ketones **2** in HCl, Scheme 21), gave lower yields and needed a considerable purification of heterocycles **48** (Scheme 21).

In other conditions, reaction of **60b** with acetyl chloride in deoxygenated ethyl acetate gave good yield of pyrrolinone **55b**.[64] As shown in Scheme 31, acyliminium salt **75** was again an intermediate: in the absence of a good nucleophile such as water, lactam ring opening did not occur, and elimination of the proton α to the carbocation gave a 4-pyrrolinone **76b**. Migration of the double bond and enolization of the ketone group then yielded compound **55b**. We have previously described that heterocycle **55f** (R^1 = H, R^2 = Cl) can be obtained less efficiently (40%) by bubbling oxygen in a solution of ketone **2f** in hydrochloric acid at room temperature (Scheme 21).

We have already described in Scheme 20 a situation where, depending on the presence of water, *N*-acyliminium salt **51** evolved towards either dehydration or hydrolysis.

It is also fascinating to observe that two different *N*-acyliminium ions **57** (Scheme 22) and **75** (Scheme 31) issued from the same ketone **2** through an *hydride* intermolecular shift for the first and an *oxidative* process for the second, evolved to give the same final product **48** (Scheme 32).



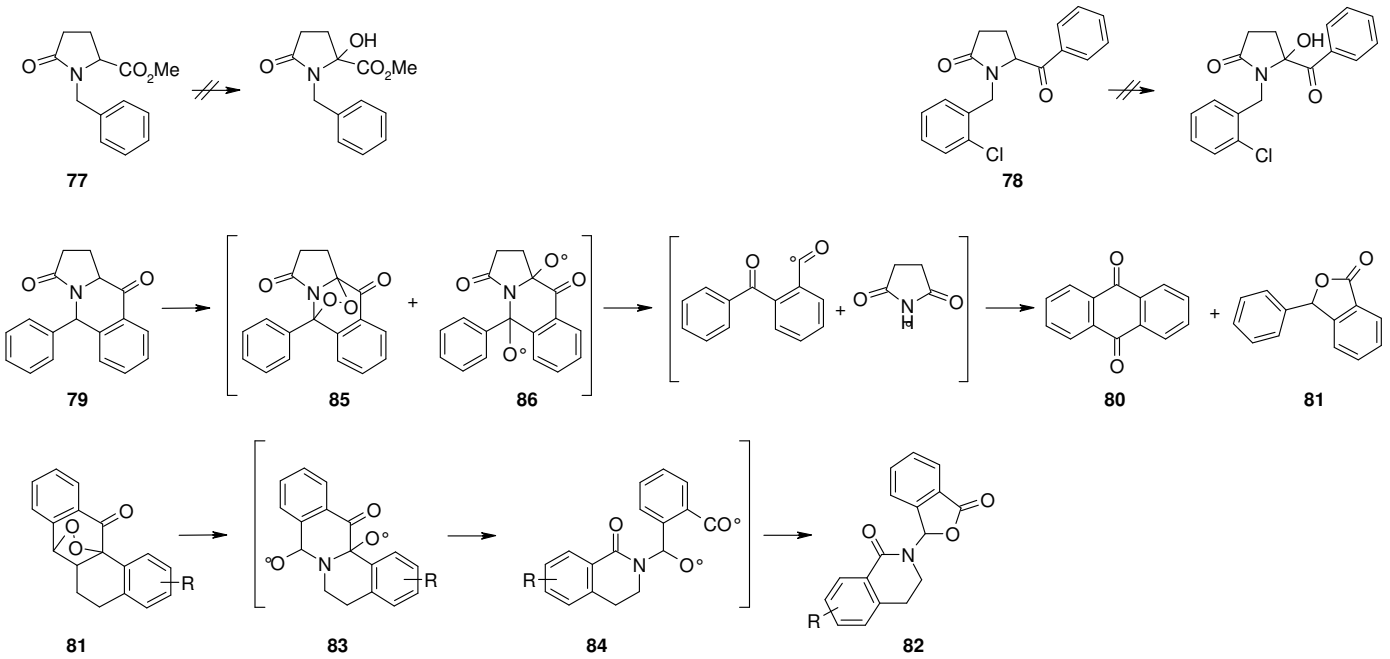
Scheme 32

4.2.5. Attempted generalization of the oxidations

As indicated previously, the oxidation of ketones **2** in basic media is the manifestation of a property common to many compounds with the CO-N-CH-CO scaffold. We attempted to generalize the same reaction to ester **77** and ketone **78**. These oxidations did not succeed. However, when a solution of ketone **79** and sodium methylate in methanol was stirred in the presence of air, anthraquinone **80** and lactone **81** were quickly formed (Scheme 33).[73]

It is known that the photo-oxygenation[74] of some protoberberine derivatives yields products such as **81**, which decomposes to **82** *via* **83** then **84**. Taking these results into account, it is postulated that formation of

an epidioxide **85** leads to intermediate **86** (Scheme 33). The breaking of the N-C(Ar)$_2$ bound in the **86** was due to the presence of two aromatic groups, and ring closure of the resulting acyl radical yielded **80** and **81**.

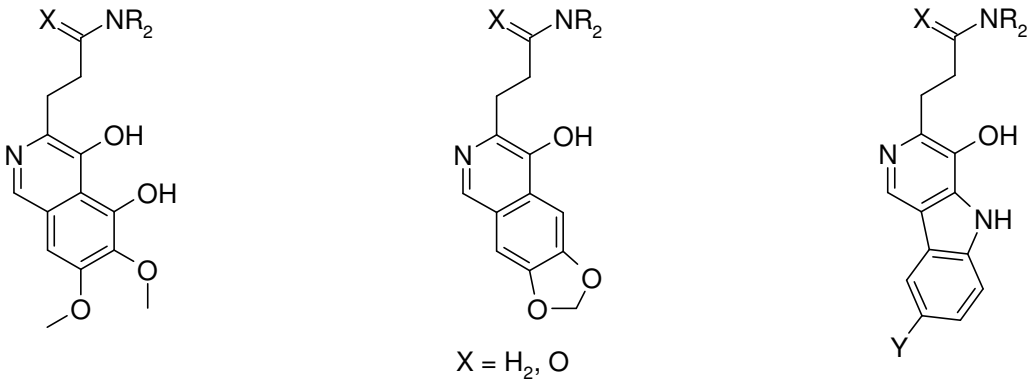


Scheme 33

An important information was thus obtained from these unexpected reactions of condensed ketones issued from pyroglutamic acids: they can easily be rearranged to hydroxyisoquinolines with an unusual propionic acid chain. That was a strong incentive to use these heterocycles in our search for biologically active compounds.

5. From by-products to potential DNA-intercalators

Topoisomerases are enzymes essential to cell replication. They alter DNA topology by passing one DNA helix through another, thus controlling the superhelical torsion. One of their most important roles is in DNA replication, and corruption of their catalytic cycle can lead to cell death. Topoisomerases are classified into four distinct subfamilies: type IA, IB, IIA and IIB. Most of topoisomerase poisons act by trapping a reversible topo I/II-drug-DNA ternary complex. Many of these inhibitors possess the composite pharmacophore of an aza polycyclic surface, often able to intercalate with DNA, and a pendant (poly)-amino chain, able to interact with minor or major DNA groove.[75]



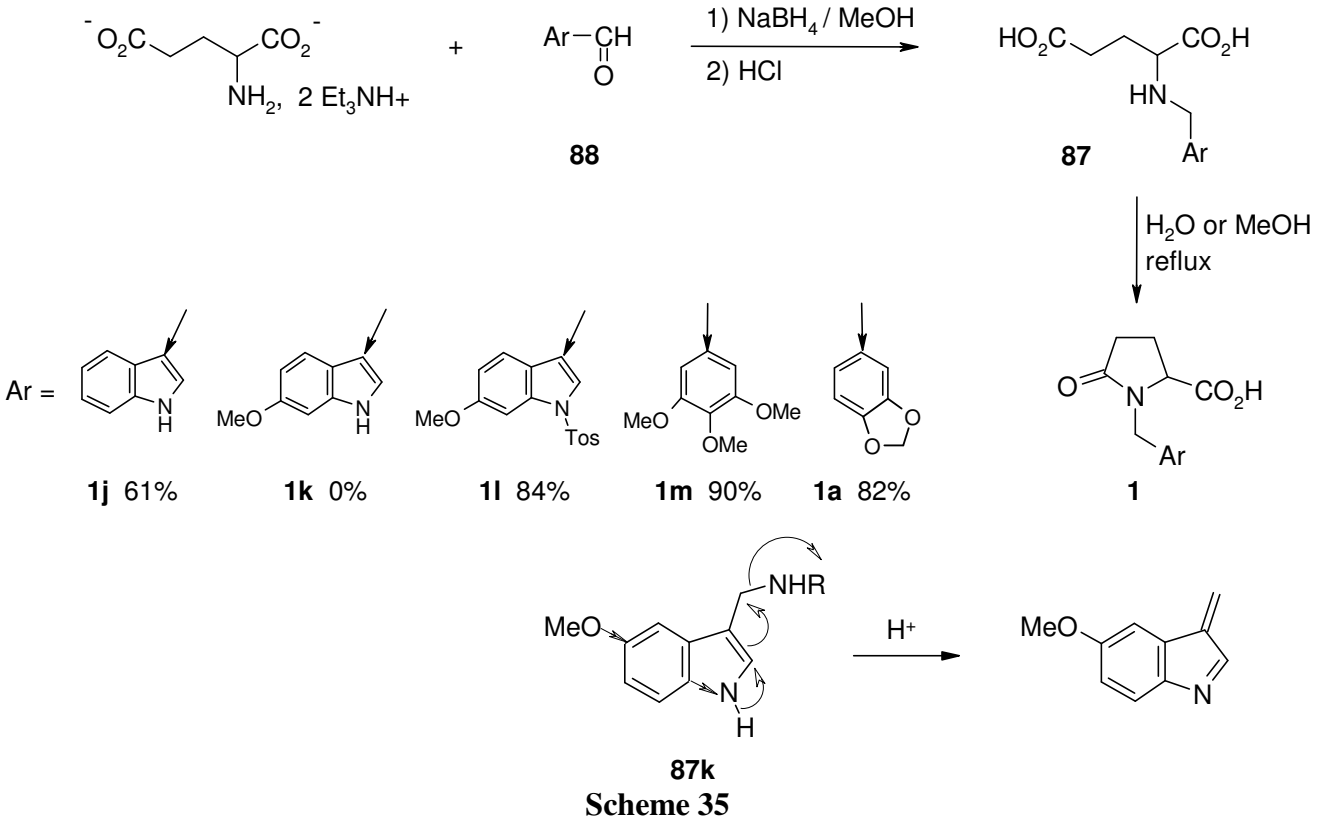
X = H_2, O
Y = H, OMe

Scheme 34

The chemical methods described earlier can be adjusted to lead to such compounds. Because of our interest for anti-cancer products, we engaged a project on potential intercalating agents based on the condensed hydroxypyridines of Scheme 34.[76]

5.1. Synthesis of the *N*-arylmethylpyroglutamic acids

The starting points of these syntheses were acids **87a,j,m** and **1a,j,m**, which were easily synthesized in good yields from the reductive alkylation ($NaBH_4$) of the triethylammonium salt of glutamic acid with aromatic aldehydes **88** (Scheme 35).[10] In the series of 5-methoxyindole heterocycle, which possess a stronger electronic density, complete degradation was observed during the acidification step leading to glutamic acid **87k** (Scheme 1).

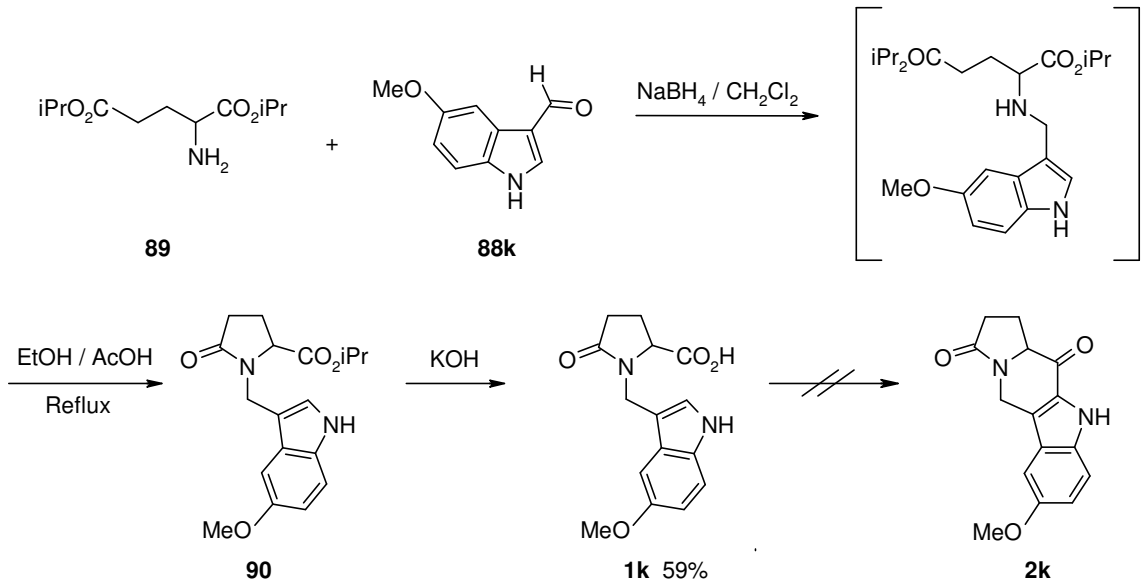


Scheme 35

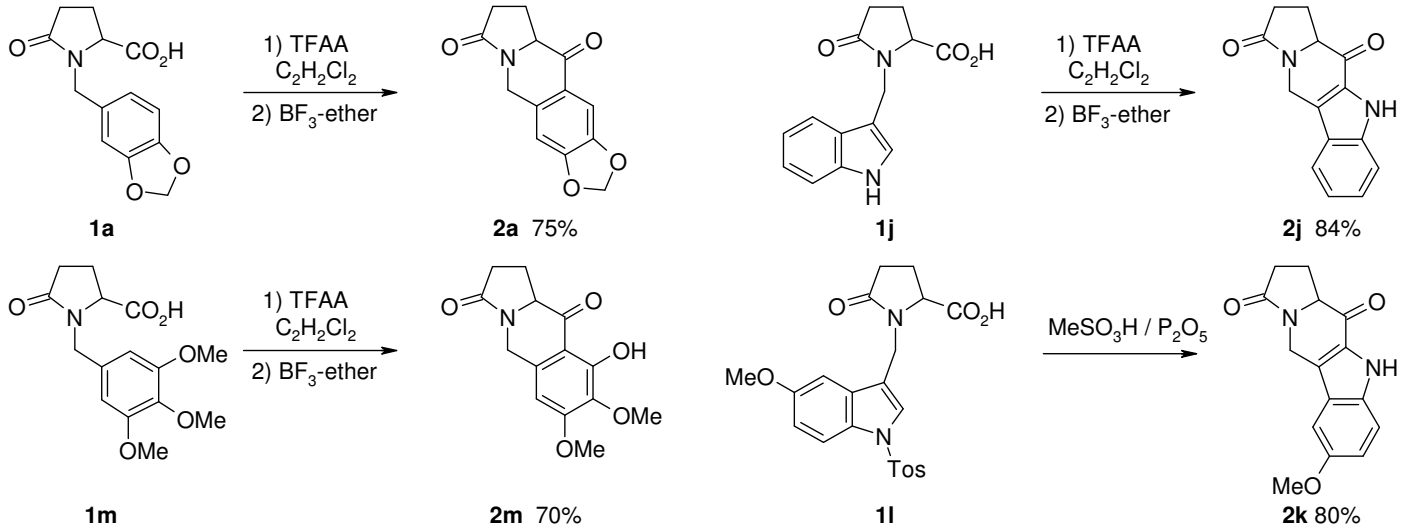
A similar decomposition of aminomethylindoles has already been described.[77] It was then necessary to use the reductive alkylation of diisopropyl glutamate **89**[12b] followed by saponification of ester **90** to obtain a cumulated yield of 59% of acid **1k** (Scheme 36). Because pyroglutamic acid **1k** also decomposed during cyclization to ketone **2k** (see later), a tosyl protection of the 5-methoxyindole nitrogen was introduced in order to lower the electronic density on this ring. Following the reaction pathway of Scheme 35, acid **1l** was then easily obtained in 84% yield from *N*-tosylindole-3-carbaldehyde **88l** (Scheme 35).[78]

5.2. Friedel-Craft cyclization of the pyroglutamic acids

Cyclization of pyroglutamic to ketones was then undertaken; the synthesis of heterocycle **2a** has already been described in § 2.1., and ketones **2j-2m** were also easily obtained in the same way by BF_3 catalyzed Friedel-Crafts cyclization of acids **1**.[12h,17] As for **2k**, heating of acid **1l** in Eaton's reagent ($MeSO_3H/P_2O_5$)[37] leads to cleavage of the tosyl group and formation of this ketone in 80% yield.



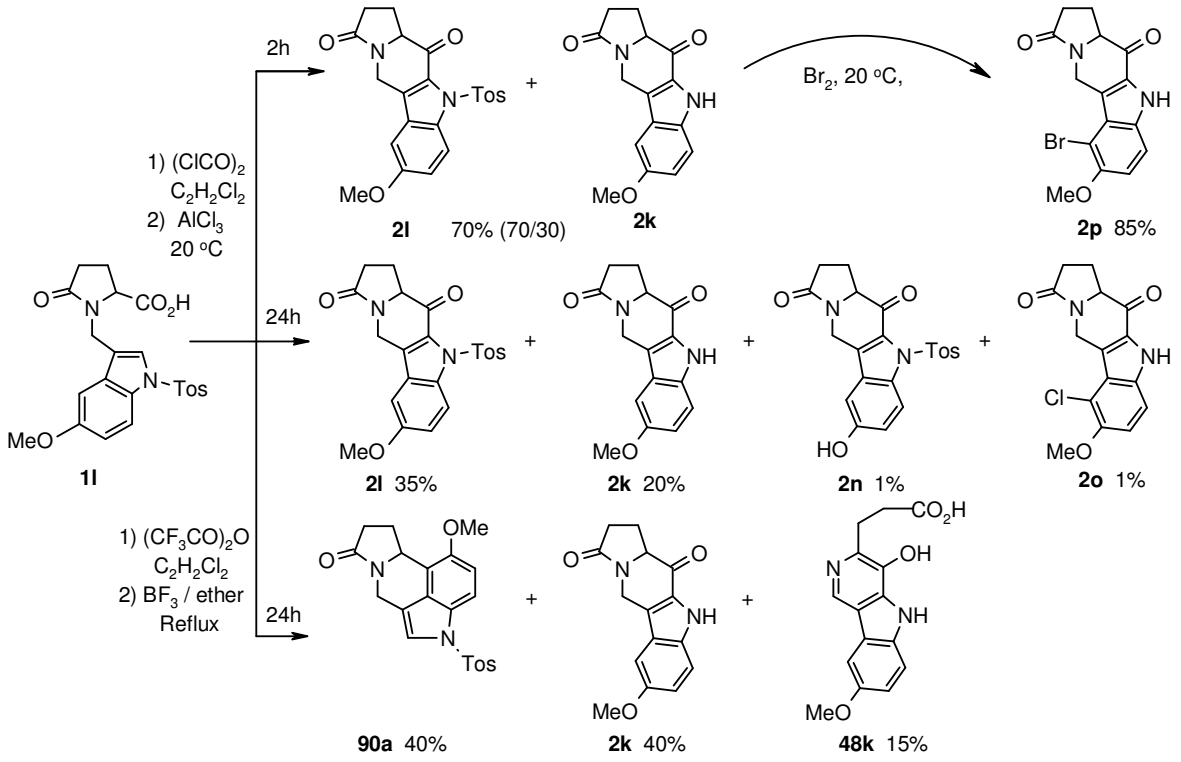
Scheme 36



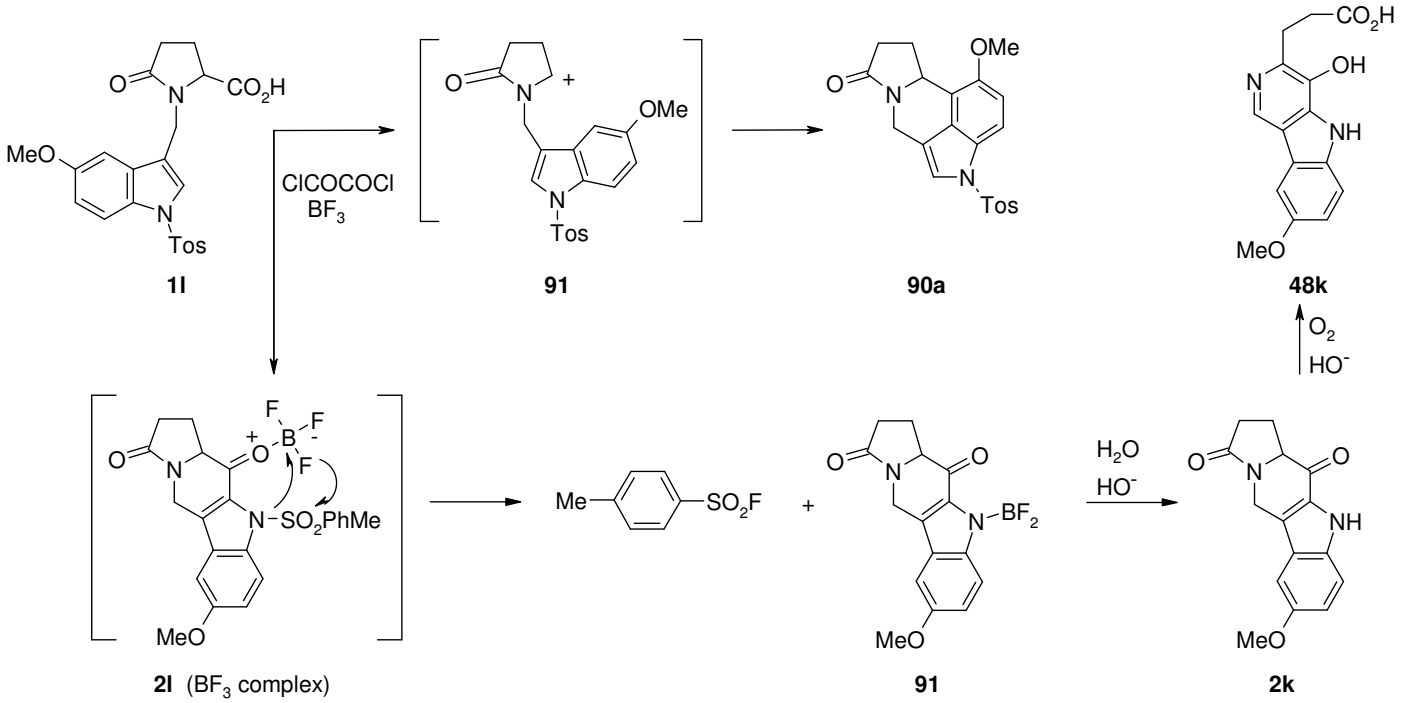
Scheme 37

Despite these good results, acid **1l** was also submitted to the Friedel-Crafts reaction in the presence of $AlCl_3$ (Scheme 38). With this catalyst, at room temperature for 2 hours, 70% of a 70/30 mixture of ketones **2l** and **2k** was obtained. A strong decomposition of the reaction mixture was observed when the reaction time was extended to 24 hours: the yields of **2l** and **2k** strongly decrease and minute amounts of ketones **2n** and **2o** were also isolated. Cleavage of aromatic methyl ethers by $AlCl_3$ is a common reaction[79] which already explained the formation of phenol **2m** from acid **1m** (Scheme 37).[17] The reactivity of indole ring of **2k** towards halogenating reagents can explain the formation of **2o** from $AlCl_3$; we checked this reactivity by submitting **2k** to bromine, and indeed bromoketone **2p** was obtained in the good yield of 85% (Scheme 38).

In another set of reactions, $BF_3.Et_2O$ was used as Lewis acid, leading to a mixture of ketone **2k** (40%), transposed acid **48k** (15%) and a novel heterocycle **90a** (40%) (Scheme 38). As demonstrated in the preceding parts, formation of acid **48k** was explained by an oxidation process, perhaps during the basic neutralization step of the reaction mixture (cf. § 4.). On the other hand, elimination of carbon monoxide from acid **1l** (cf. § 2. and 3.) lead to acyliminium salt **91** which cyclized to lactam **90a** (Scheme 39).



Scheme 38

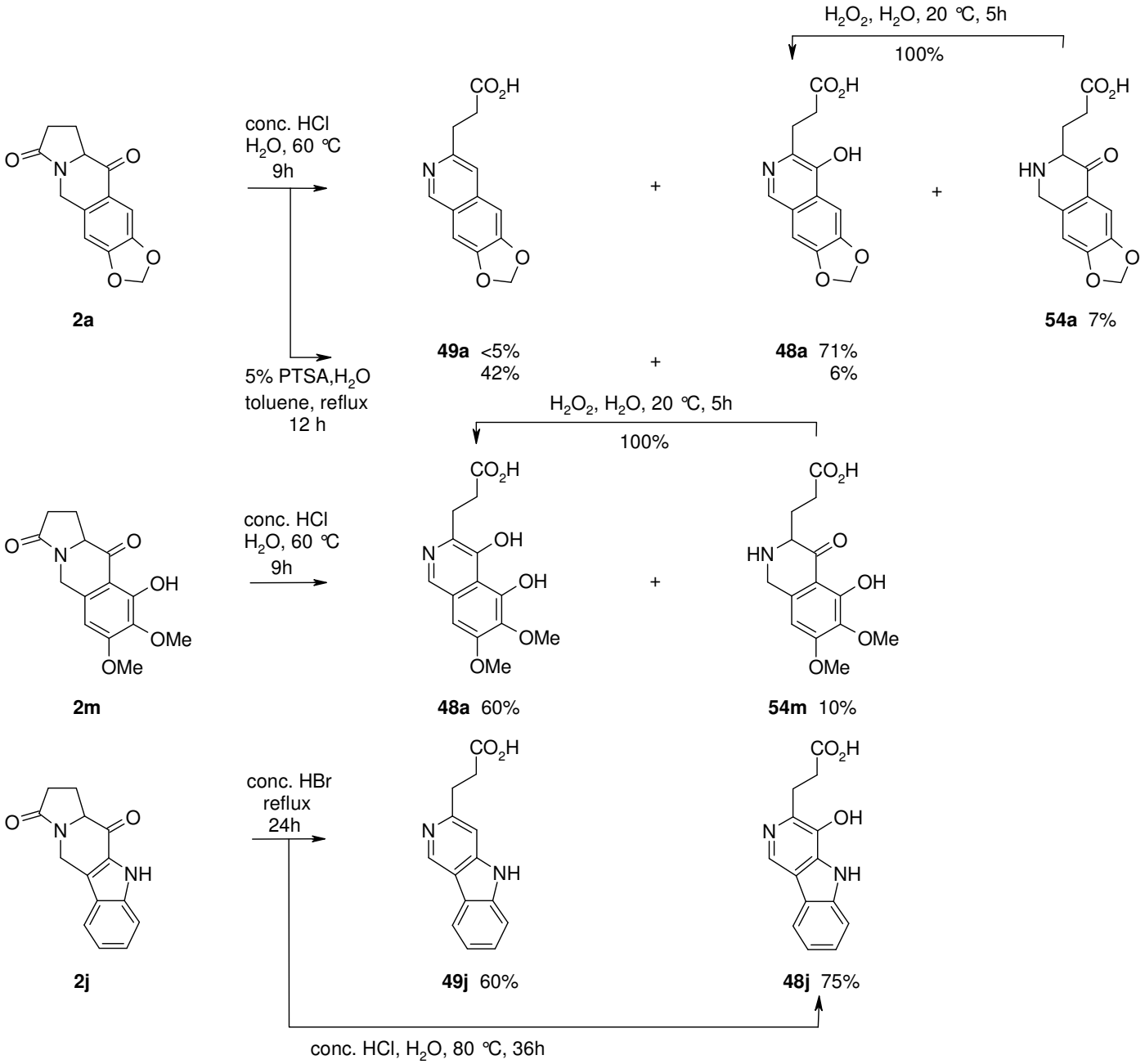


Scheme 39

As for detosylation of compound **2l** leading to ketone **2k**, a mechanism similar to the demethylation of a methoxy group near an aromatic ketone explains this reaction: complexation of the Lewis acid on the ketone group of **2l** allowed an easy attack of the halogen atom on the vicinal sulfonyl group. Salt **91** was thus obtained. It was later hydrolyzed during the final treatment (Scheme 39).

5.3. Syntheses of the hydroxyquinoline scaffolds

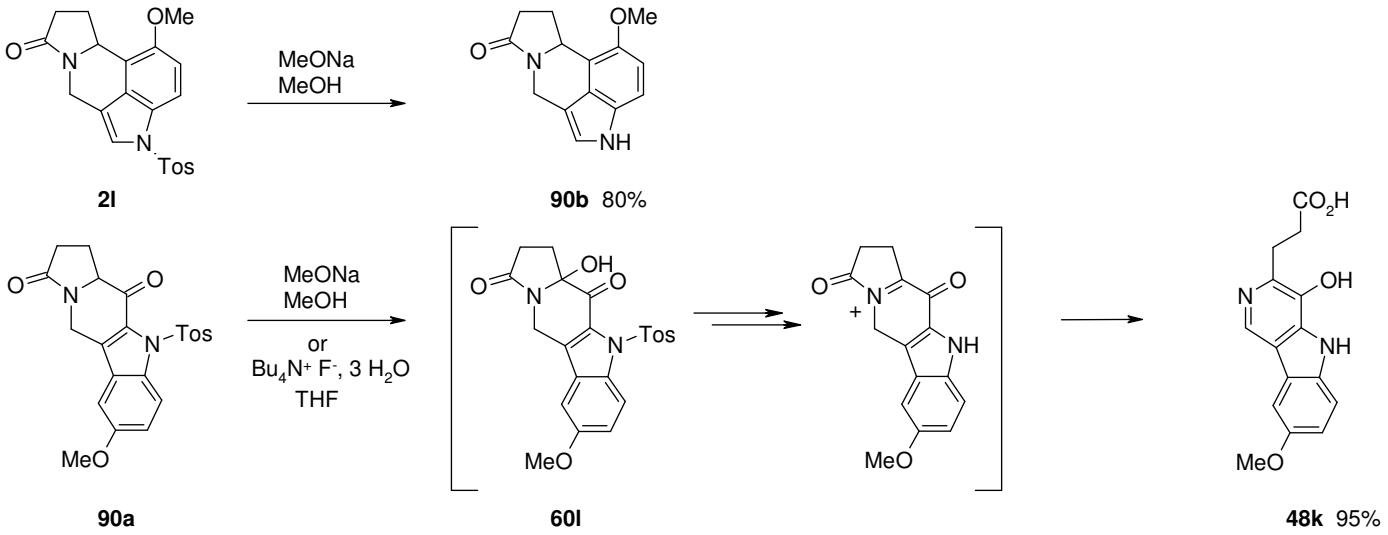
Hydroxypyridine **48k**, which was one of our objectives, was thus directly obtained from the Friedel-Crafts cyclization of acid **1l** (Scheme 38). The other starting compounds were synthesized by using the methods described in §4.1.: transposition of ketones **2a,j,m** with conc. HCl or PTSA, H_2O gave heterocycles **48a,j,m** (Scheme 40). Quinoline **49a** was observed as a by-product of the reaction of ketone **2a** and, as described previously, the small amount of amino ketones **54** formed were easily oxidized to hydroxyacids **48**. Because of the low solubility of ketone **2j** in the reaction medium, it proved to be necessary to extend the heating period to 36 hours in conc. HCl to obtain 75% yield of hydroxyacid **48j**, whereas when ketone **2j** was refluxed in conc. HBr it yielded 60% of acid **49j**.



Scheme 40

In order to remove the protecting tosyl group of compounds **90a** and **2l**, they were submitted to the action of sodium methylate in refluxing methanol. Heterocycle **90b** was thus easily obtained in 80% yield,

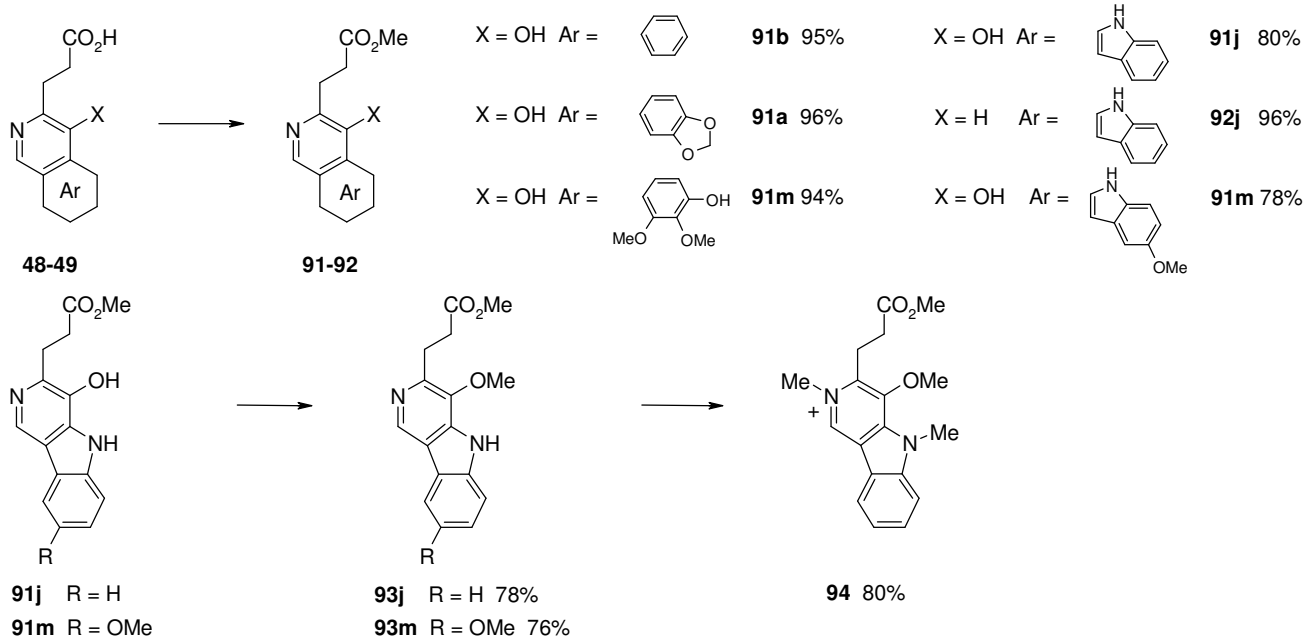
but under these conditions, ketone **2l** underwent an oxidation reaction (§ 4.2.1.) with the oxygen dissolved in MeOH: hydroxyketone **60l** thus formed was not isolated; formation of an acyliminium salt occurred during acidification of the reaction mixture, and opening of the lactam ring then yielded 95% of hydroxyacid **48k** (Scheme 40). The same reaction took place when *ter*-butylammonium fluoride in THF was used as the deprotecting agent.



Scheme 41

5.4. Activation of the acids

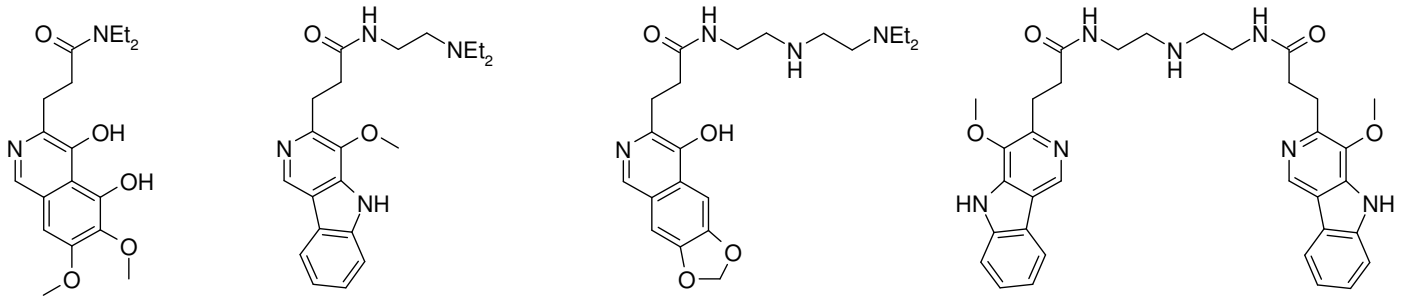
Activation of acids **48** as chlorides ($SOCl_2$/DMF) was tried on **48b** (R = H, Scheme 19). At least three by-products were observed by TLC. Thus, activation as a methyl ester was realized by using the action of chlorotrimethylsilane in methanol.[80] Ester **91b** was isolated in 95% yield, and the same method gave the methyl esters described in Scheme 42 in excellent yields (78-96%). The free hydroxy group of heterocycles **91j** and **91m** was also etherified by using dimethyl sulfate; esters **93j** and **93m** were then easily obtained in 76-78% yields; in reflux conditions, salt **94** was formed (Scheme 42).



Scheme 42

5.5. Syntheses of the amides

Synthesis of the amides, ultimate targets of this work, was realized by reacting the previous esters with amines. Since poor results where obtained by using a solvent, reactions were realized neat, at 120 °C or in reflux conditions of an excess of amine. In many cases, cooling the reaction mixture lead to crystallization of a salt between the free hydroxy group of the heterocycle and the amine utilized. Washing the product with dilute hydrochloric acid or chromatography on SiO_2 column then gave pure amides as exemplified in Scheme 43, in 60-80% yield.



Scheme 43

6. Conclusion

In this review, we have shown how the systematic study of the formation of by-products obtained during the cyclization of pyroglutamic derivatives was a guide towards easy syntheses of a diversity of chemical structures. In our laboratory, this research has culminated in the synthesis of a series of new potential anti-cancer agents. This method can be put into practice in other cases, leading again possibly to many interesting results.

Acknowledgments

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SYNTHESIS OF SULFUR-HETEROCYCLES FROM AROMATIC THIOKETONES. PART II: FIVE- AND SIX-MEMBERED AND LARGER RINGS

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Abstract. *The applications of aromatic thioketones in the synthesis of five- to eight-membered heterocycles with a variable number of sulfur atoms are summarized. The importance of aromatic thioketones as 'superdienophilic' and 'superdipolarophilic' compounds is described in the light of the recent literature. The methods for the generation of reactive sulfur-containing intermediates with their possible applications toward sulfur heterocycles are also presented.*

Contents

1. Introduction

In the first part of this review,[1] reactions of aromatic thioketones leading to three- and four-membered heterocycles which contain at least one sulfur atom and appear as stable products were summarized. Unstable S-containing species proposed as intermediates in some conversions of aromatic thioketones were not discussed in detail. The same approach will be used for the presentation of the reaction of aromatic thioketones applied for the preparation of five- to eight-membered sulfur heterocycles.

It is worth mentioning that in the case of five- and six-membered rings the most important methodologies concern [2+3] and [2+4] cycloadditions, respectively. As demonstrated by Huisgen and Sauer, thioketones in general, and aromatic thioketones especially, are versatile dipolarophiles and dienophiles.[2,3] On the other hand, aromatic thioketones can act as reactive heterodienes, in which a C,C-double bond of the aromatic ring is involved in the reaction (C=C-C=S). Moreover, aromatic thioketones can be efficiently used for the *in situ* generation of highly reactive 1,3-dipolar species, namely the S-centered 1,3-dipoles: thiocarbonyl *S*-methylides,[4] *S*-sulfides (thiosulfines),[5] and *S*-imides.[6] The analogous thiocarbonyl *S*-oxides (sulfines) are stable compounds and easily available by oxidation of aromatic thioketones.[7a] They can also serve as 1,3-dipoles in reactions with thiocarbonyl compounds.[7b-d] In some instances, intramolecular cyclizations of properly substituted thiocarbonyl *S*-ylides, *i.e.*, 1,5-dipolar electrocyclizations,[8] leading to five-membered sulfur heterocycles, are of preparative interest. The head-to-head dimerization of aromatic thiocarbonyl *S*-ylides, which leads to 1,4-dithianes, is of special interest from a mechanistic point of view.[4]

Typically, the reactions of aromatic thioketones with nucleophiles are less important compared with their oxygen analogues. On the other hand, the S-atom of aromatic thioketones interacts as a nucleophile with the strongly polarized S,Cl-bonds of SCl_2 or S_2Cl_2 initiating a cascade reaction which yields cyclic polysulfanes of different ring size.[9]

Relevant symmetrically substituted aromatic thioketones quoted in this review are thiobenzophenone and its 4,4'-disubstituted analogues **1**, 9*H*-fluorene-9-thione (**2**), 9*H*-xanthene-9-thione (**3a**, X = O), and 9*H*-thioxanthene-9-thione (**3b**, X = S). Reactions with non-symmetrical aromatic thioketones **4**-**7** are also reported and will be included in this review. In the case of thioacetophenone (**6**, R = Me), reactions are typically carried out with its trimer, which is decomposed *in situ* to generate the monomeric form.

The methods of preparation of the aromatic thioketones **1**-**7** (Figure 1) were summarized in Part I of this review.[1]

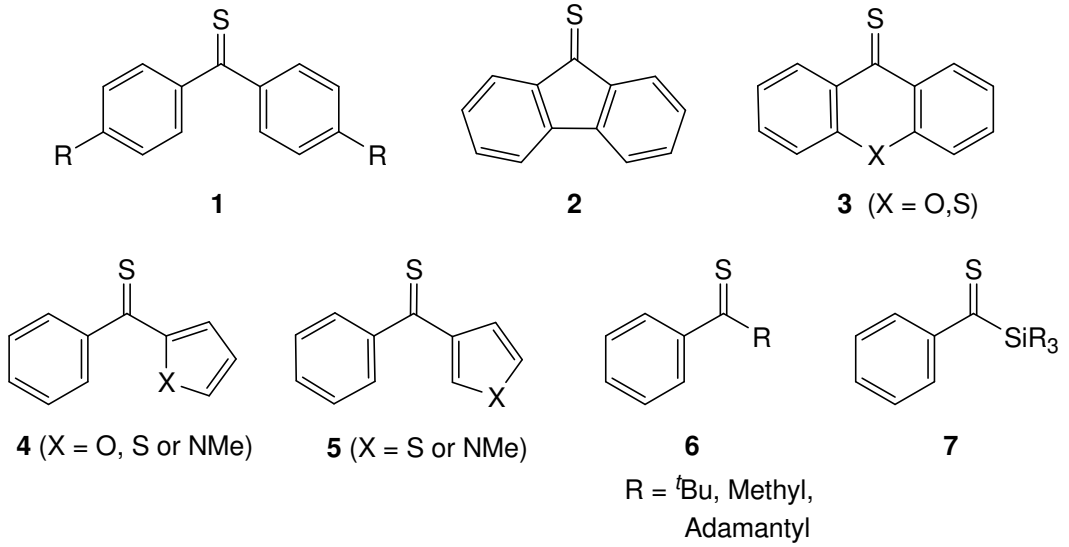
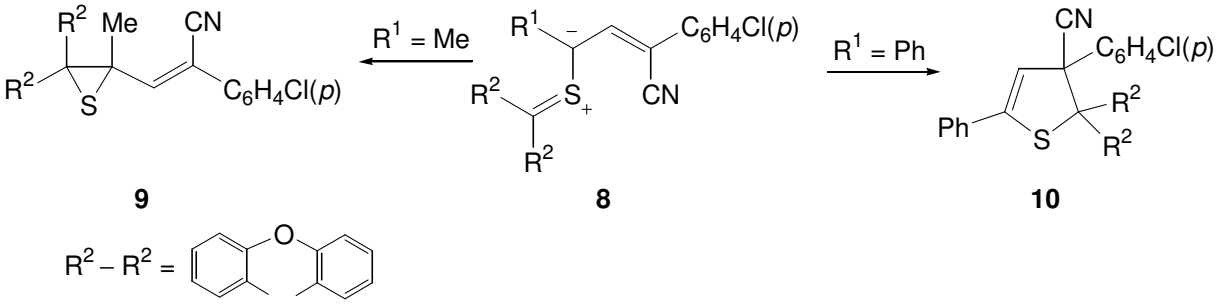


Figure 1

2. Synthesis of five-membered rings

2.1. Thiophene derivatives

The reactions of thiocarbonyl ylides, obtained by addition of carbenes or carbenoids to aromatic thioketones, which afford thiiranes *via* 1,3-dipolar electrocyclization, have been reported in Chapter 3 of Part I. In the case of vinyl substituted thiocarbonyl ylides **8**, the alternative 1,5-dipolar electrocyclization resulting in the formation of dihydrothiophene derivatives **10** competes with the formation of thiirane **9** (Scheme 1).[10]

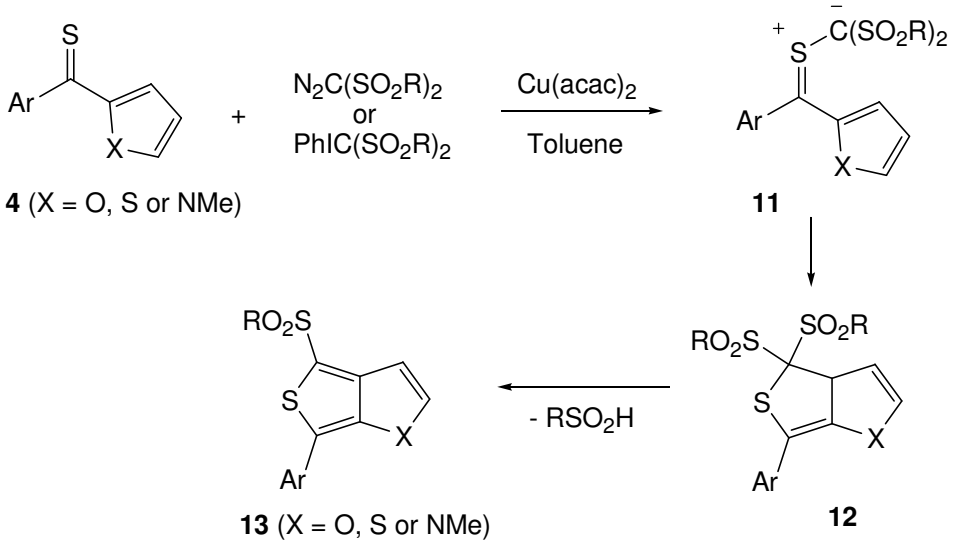


Scheme 1

Thiocarbonyl ylides generated from diarylthioketones by thermal decomposition of diazodisulfonylmethanes, or phenyliodonium disulfonylmethylides in the presence of catalytic amounts of $Cu(acac)_2$, undergo intramolecular cyclization with elimination of sulfinic acid to give benzo[*c*]thiophene derivatives.[11] In the first report of this reaction, a wrong structure of the product was proposed.[12] In the reactions of heteroaromatic thioketones **4** and **5**, the intermediate thiocarbonyl ylides **11** undergo cyclization with the heteroaromatic ring, exclusively (Scheme 2).[13] The bicyclic products **12** spontaneously eliminate sulfinic acid to give the aromatic fused products **13**.

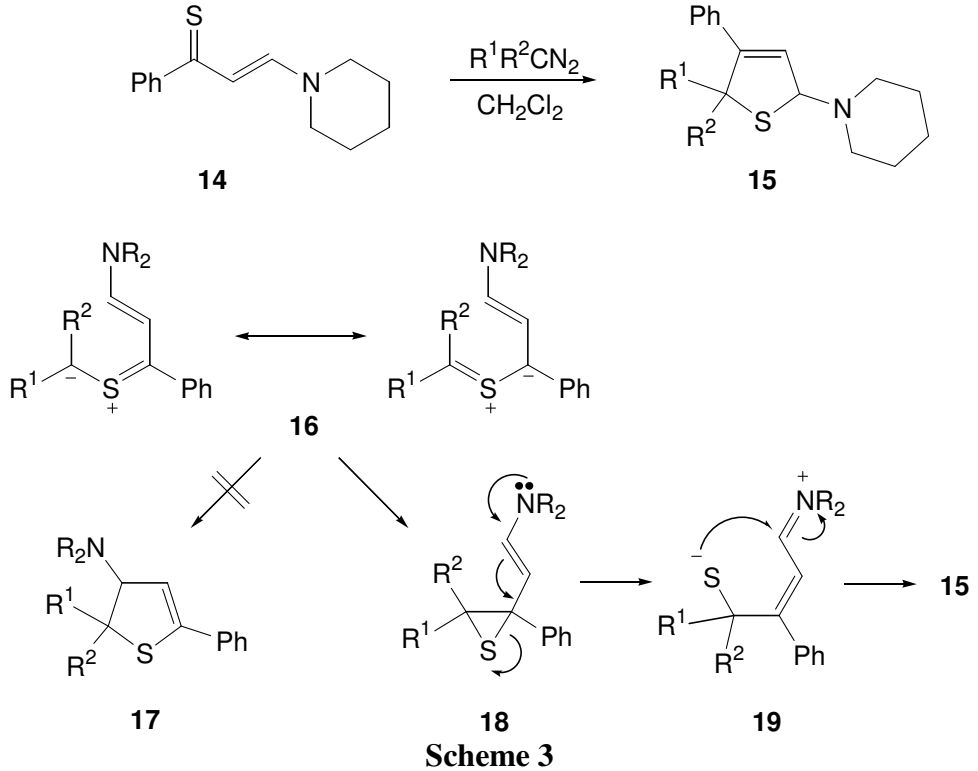
Diarylmethylidenemalonates are obtained when the diazodisulfonylmethane is replaced by dimethyl diazomalonate. In this case, the cyclization/aromatization sequence cannot take place. Therefore, the

transient thiocarbonyl ylide reacts in a known fashion to afford the corresponding thiirane, which eliminates sulfur under the reaction conditions (see Chapter 3, Part I).[1]



Scheme 2

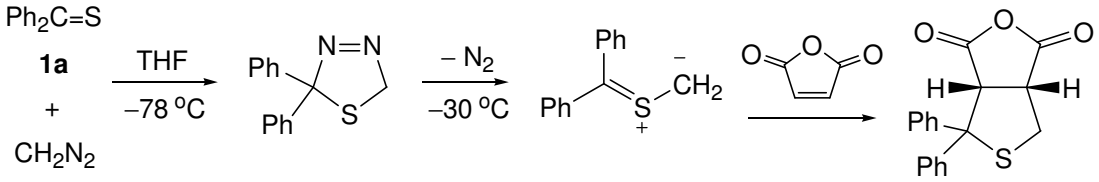
An unexpected cyclization of a vinyl-substituted thiocarbonyl ylide is observed when thioketone **14** (a vinylogous thioamide) is treated with substituted diazomethanes.[14] In all these cases, a dihydrothiophene derivative **15**, which is an isomer of the expected product of the 1,5-dipolar electrocyclization, is obtained (Scheme 3). A reasonable explanation is based on the assumption that the initially formed thiirane **18** undergoes a ring opening to give the zwitterionic thiolate **19**, which cyclizes to yield **15**. This result points out that thiocarbonyl ylide **16**, which bears an 'enamine' residue, is not able to form the five-membered product **17** *via* a direct ring closure.



Scheme 3

Thiocarbonyl ylides bearing two aromatic rings at the same C-atom, analogous to **20**, which can be generated *in situ* by [2+3] cycloaddition of aromatic thioketones with diazomethane followed by nitrogen elimination, are excellent precursors of thiophene derivatives obtained by reaction with electron-poor C=C and C≡C dipolarophiles.[4,15] For example, thiobenzophenone (**1a**) instantaneously reacts with diazomethane in THF at –78 °C to give 2,5-dihydro-2,2-diphenyl-1,3,4-thiadiazole (**21**), which slowly eliminates nitrogen at *ca.* –30 °C. The *in situ* generated thiocarbonyl methanide **20** can be trapped by tetracyanoethene (TCNE), maleic anhydride and maleimides to afford tetrahydrothiophenes, *e.g.*, **22** (Scheme 4).[16] Similarly, acetylenic dipolarophiles react with **20** to yield 2,5-dihydrothiophenes.

The exocyclic C,C-double bond of 5-benzylidene-3-phenylrhodanine intercepts efficiently the thiocarbonyl ylide **20** to give regioselectively a spirocyclic tetrahydrothiophene.[17]

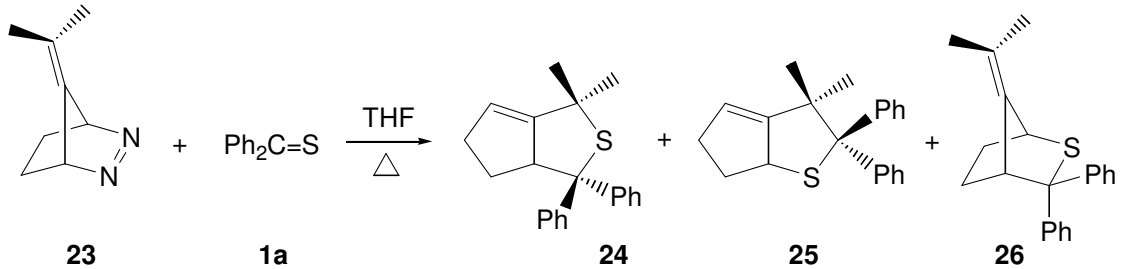


21 **20** **22**

Scheme 4

The synthetic method presented in Scheme 4 is limited to highly reactive diazo compounds, which quantitatively react with aromatic thioketones at low temperature before the decomposition of the thiadiazole. On the other hand, the thiocarbonyl ylide is captured by the 'superdipolarophile' **1a** to give a 1,3-dithiolane (see Chapter 2.2.). Thiofluorenone (**2**) is the most reactive dipolarophile and, therefore, less reactive diazo compounds, *e.g.*, diethyl diazophosphonate, can be applied for the synthesis of thiophene phosphonates.[18] An additional limitation is the reactivity of the C,C-dipolarophile: in the presence of less reactive dipolarophiles, the thiocarbonyl ylide **20** undergoes dimerization to give a 1,4-dithiane (see Chapter 3), or a 1,3-dipolar electrocyclization to afford a thiirane derivative (Chapter 3, Part I).[1]

The thermal decomposition of the azocompound **23** in the presence of thiobenzophenone (**1a**) leads to a mixture of three thiophene derivatives **24-26** which are formed through the trapping of the biradical intermediate by **1a** (Scheme 5).[19]

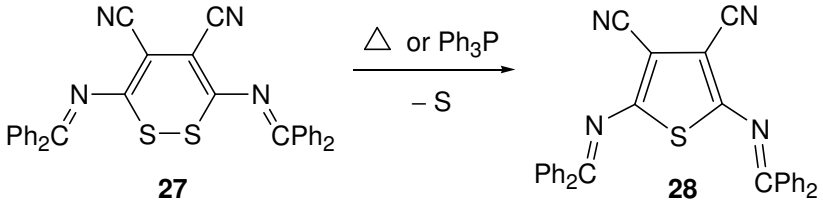


23 **1a** **24** **25** **26**

Scheme 5

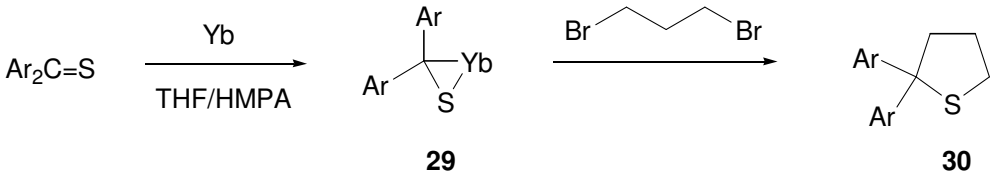
The strongly electron-deficient tetracyanoethene (TCNE) reacts in boiling benzene with thiobenzophenone (1:2 ratio) to yield the 1,2-dithiin **27** and thiophene **28** in a multistep process.[20] Thermal or phosphine-induced desulfurization of **27** quantitatively leads to **28** (Scheme 6).

Treatment of diarylthioketones with ytterbium metal in THF/HMPA at 0 °C leads to thiametallacycles **29**, which easily react with 1,3-dibromopropane to give the tetrahydrothiophene **30** in 74% yield (Scheme 7).[21]



27 **28**

Scheme 6



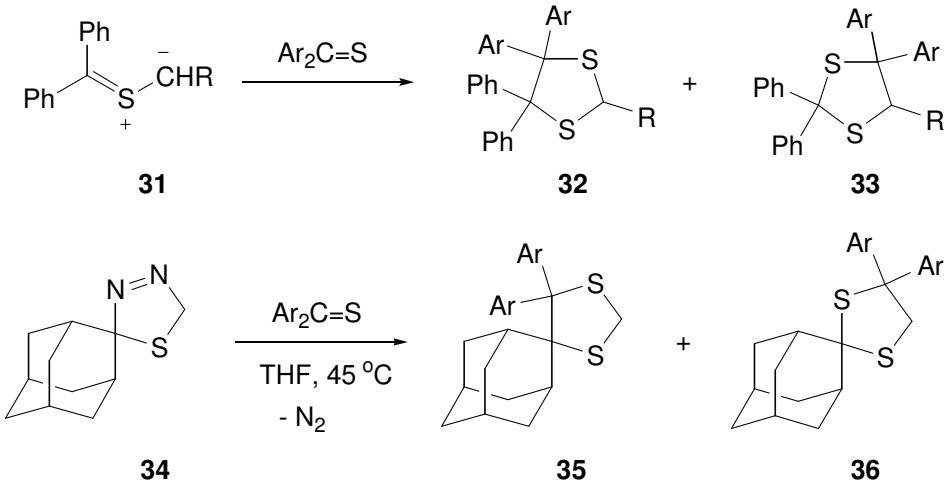
29 **30**

Scheme 7

2.2. Dithiolanes and dithioles

The *in situ* addition of reactive thiocarbonyl ylides **31**, generated from aromatic thioketones according to Scheme 4, with C=S dipolarophiles is an excellent method for the preparation of 1,3-dithiolanes **32** and/or **33** (Schönberg reaction, Scheme 8).[22-24]

The thiocarbonyl ylides derived from diazomethane (R = H) react with aromatic thioketones in a regioselective manner to give the sterically more congested product **32**.[23] The same regioselectivity is observed with phosphonylated intermediates **31** (R = $P(O)(OR')_2$).[18] However, ylides **31** bearing an ester group (R = CO_2R') react with thiobenzophenone (**1a**) to afford mixtures of the corresponding 1,3-dithiolanes **32** and **33**.[25] The thiocarbonyl ylide **31** (R = $SiMe_3$), generated from (trimethylsilyl)diazomethane and thiofluorenone (**2**), reacts with **2** to yield the 1,3-dithiolane **32**.[26] A similar result is obtained when **2** is treated with α-diazo ketones.[27]



31 **32** **33**

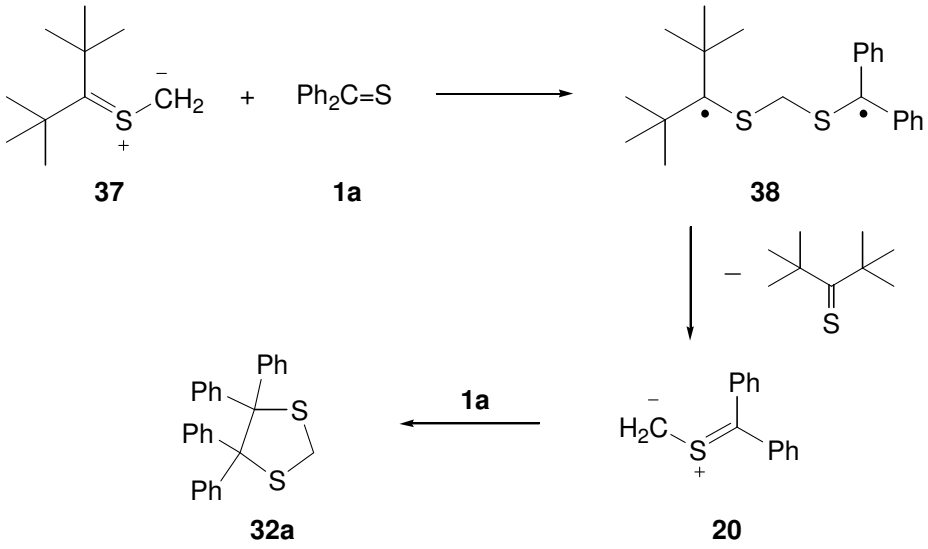
34 **35** **36**

Scheme 8

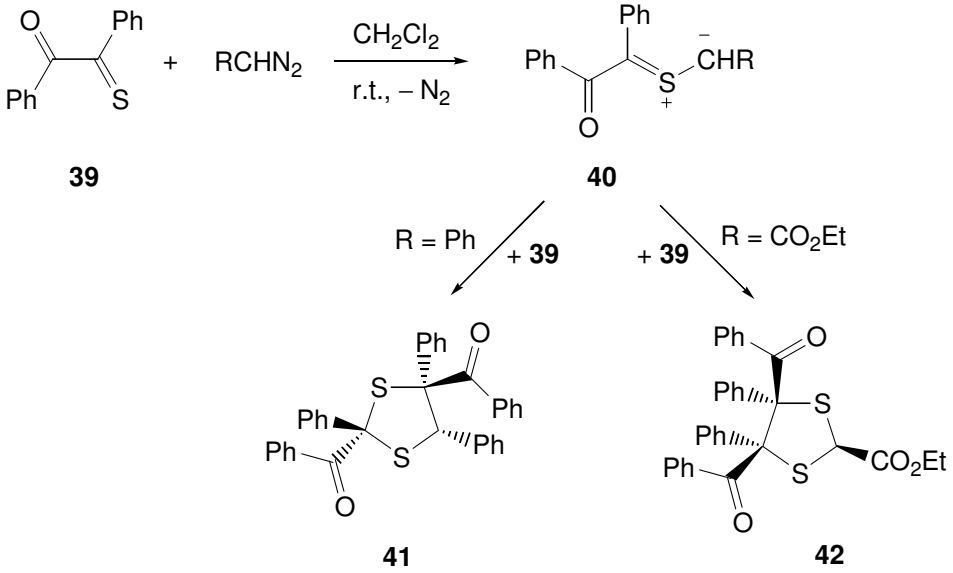
Cycloaliphatic thioketones (adamantanethione, 2,2,4,4-tetramethyl-3-thioxocyclobutanone) are also suitable dipolarophiles to intercept thiocarbonyl *S*-methanides **20** generated from aromatic thioketones such as **1a** and **2**. In these reactions, mixtures of regioisomeric 1,3-dithiolanes are formed.[23] A recent study shows that a rhodanine derivative also reacts with thiobenzophenone *S*-methanide (**20**) to afford a mixture of a tetrahydrothiophene derivative as the major product and an unstable 1,3-dithiolane as the minor one (Chapter 2.1.).[17]

The 2,5-dihydro-1,3,4-thiadiazoles derived from aliphatic thioketones, *e.g.* **34**, are stable at room temperature and eliminate nitrogen at *ca.* 45 °C to give the corresponding thiocarbonyl ylides as reactive intermediates. Decomposition in the presence of aromatic thioketones leads to a mixture of regioisomeric 1,3-dithiolanes **35** and **36** in favor of the sterically more hindered isomer (Scheme 8).[4,28,29]

The thiocarbonyl ylides of type **37** derived from very bulky aliphatic thioketones, such as di(*tert*-butyl)thioketone or 2,2,6,6-tetramethylcyclohexanethione, react with thiobenzophenone (**1a**) to give unexpectedly 4,4,5,5-tetraphenyl-1,3-dithiolanes **32** (Scheme 9).[29] Computational calculations support the assumption that the initially formed 1:1 adduct is a diradical **38**, which eliminates the sterically more congested aliphatic thioketone. The resulting thiobenzophenone ylide **20** is immediately trapped by **1a** to give compound **32a**. Similarly, ylides **37**, generated in reactions with diazoethane and 2-diazopropane, react with thiobenzophenone to yield 2-methyl and 2,2-dimethyl derivatives of **32a**.



Scheme 9



Scheme 10

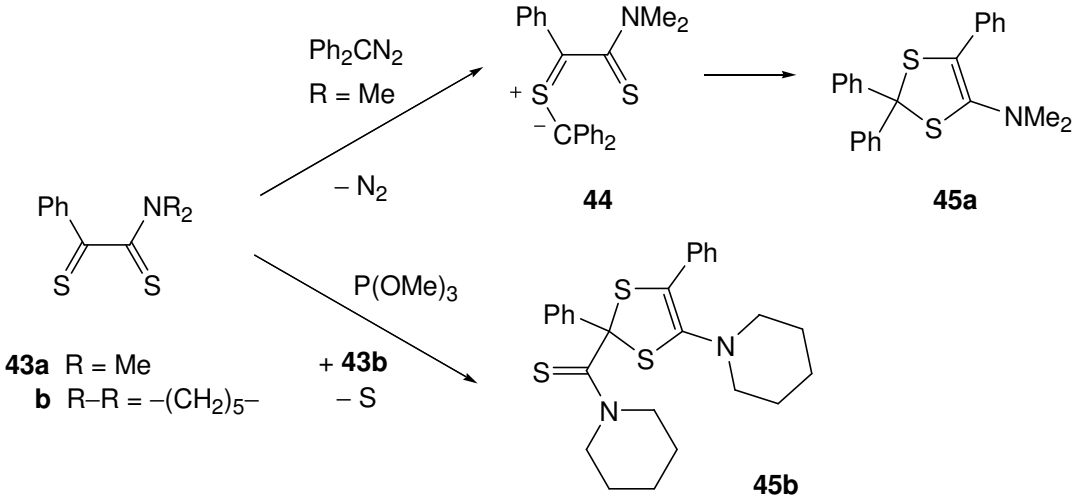
In the reactions with phosphonylated or sulfonylated dithioformates, diazomethane is used to generate the corresponding *S*-methanides, which subsequently are trapped by aromatic thioketones, mainly thiobenzophenone (**1a**) or thiofluorenone (**2**), yielding 1,3-dithiolanes in a regioselective manner.[30,31] It is

worth mentioning that the products containing a sulfonyl group easily undergo a rearrangement, which leads to a noncyclic isomer.[31]

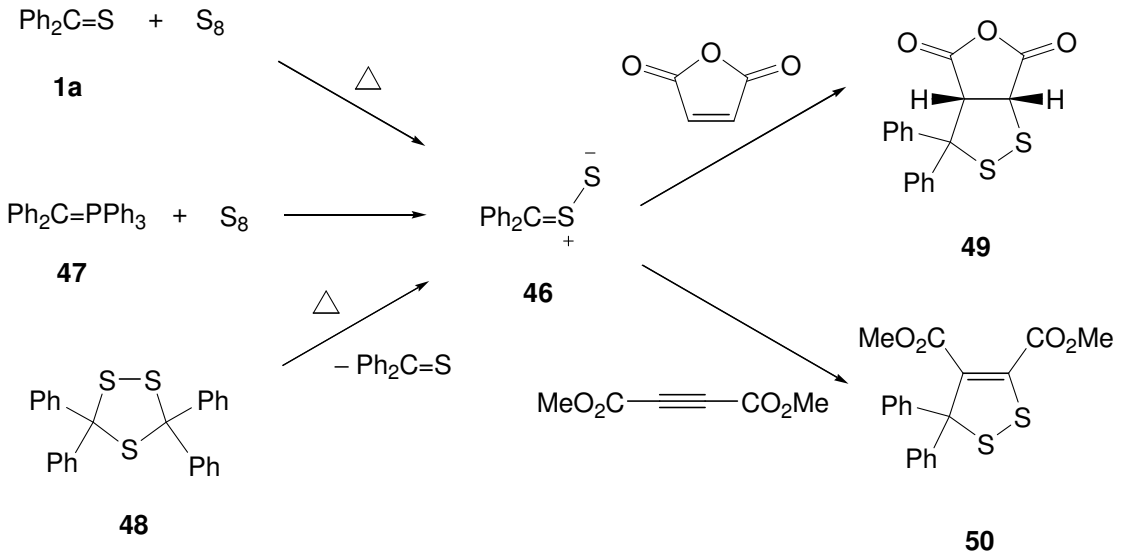
Recently, the synthesis of 1,3-dithiolanes from reactions of 1,2-diphenyl-2-thioxoethanone (**39**) and diazo compounds have been reported. Depending on the structure of the diazo reagent, different regio- and stereoisomeric products are isolated.[32] For example, thiocarbonyl ylides **40a,b**, generated from addition reactions of **39** and phenyldiazomethane or ethyl diazoacetate, respectively, undergo [2+3] cycloaddition reactions with **39** to give the respective 1,3-dithiolanes **41** and **42**, *via* regioisomeric transition states.

The formation of minor amounts of 1,3-dithiolanes is also observed when aromatic thioketones are reacted with oxiranes in the presence of BF_3.[33] It has been proposed that oxiranes are competitively converted into thiiranes,[34] which subsequently react with a second equivalent of the thioketone to give the ring-enlarged product.

The synthesis of the 1,3-dithiole derivative **45a** is achieved by reaction of the thiobenzoyl compound **43a** with diphenyldiazomethane (Scheme 11).[32a] Most likely, the thiocarbonyl ylide **44** is the key intermediate, which preferably undergoes the 1,5-dipolar electrocyclization. A similar process can be suggested for the formation of **45b**, which is obtained from **43b** upon treatment with trimethylphosphite.[32b]



Scheme 11

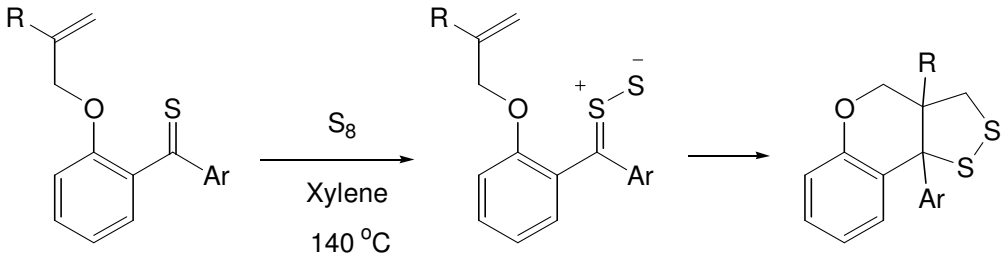


Scheme 12

Some derivatives of 1,2-dithiolanes and 1,2-dithioles are efficiently prepared by trapping of thiobenzophenone *S*-sulfide (**46**, a thiosulfine) with olefinic or acetylenic dipolarophiles, respectively (Scheme 12).

The reactive sulfine **46** can be generated *in situ* by treatment of **1a** or the phosphonium ylide **47** with elemental sulfur,[35] or by thermal cycloreversion of the thermolabile 1,2,4-trithiolane **48**.[36] For example, the interception of **46** and its 4,4'-disubstituted analogues with maleic anhydride affords **49** in up to 90% yield,[35] and with dimethyl acetylenedicarboxylate as dipolarophile, **50** is obtained in 59% yield.[36]

The intramolecular [2+3] cycloaddition of the *in situ* generated thiocarbonyl *S*-sulfide **52** is presented in Scheme 13. Numerous diarylthioketones (Ar = Ph or heteroaryl) **51** are transformed into the polycyclic products **53** in good yields.[37]



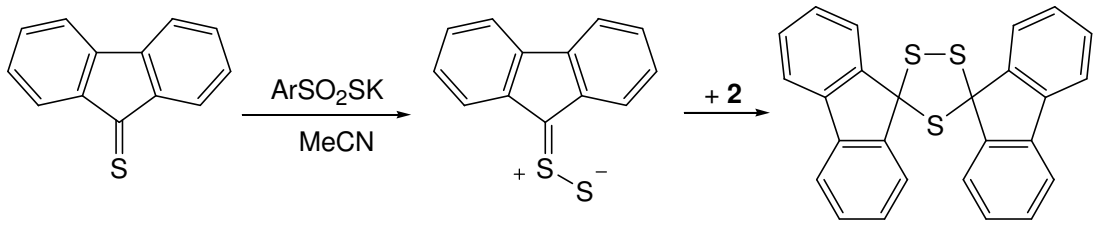
51 **52** **53**

Scheme 13

2.3. 1,2,4-Trithiolanes

Convenient methods for the preparation of tetraaryl substituted 1,2,4-trithiolanes are based on oxidative transformations of aromatic thioketones. Treatment of thiobenzophenone with tetrachloro-*ortho*-quinone at 2 °C[38] or with Chloramine T (p-$MeC_6H_4SO_2N(Cl)Na\cdot 3H_2O$) at room temperature[39] leads to 2,2,5,5-tetraphenyl-1,2,4-trithiolane (**48**) in 54 and 90% yield, respectively. A preparative useful method for the synthesis of **48** is the reaction of **1a** with primary amines at room temperature.[40]

Additional procedures, with more general importance for the preparation of 1,2,4-trithiolanes, are [2+3] cycloadditions of thiocarbonyl *S*-sulfides with thioketones. Thiofluorenone *S*-sulfide (**54**) generated from **2** by sulfur-transfer from potassium aryl thiosulfonate, is efficiently trapped by **2** to give regioselectively **55** in 95% yield (Scheme 14).[41]



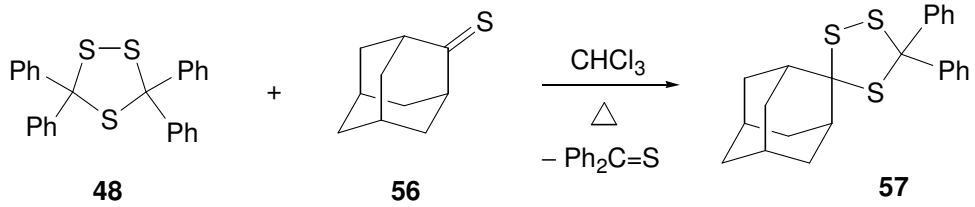
2 **54** **55**

Scheme 14

Thionation of (*tert*-butyl)(*p*-tolyl)ketone with P_4S_{10} in refluxing pyridine leads to a mixture of *cis*- and *trans*-3,5-di(*tert*-butyl)-3,5-di(*p*-tolyl)-1,2,4-trithiolane in favor of the *cis* isomer.[42] A mixture of the same isomeric trithiolanes is obtained by treatment of the corresponding thioketone with elemental sulfur in

boiling toluene.[43] A similar experiment carried out in DMF at room temperature yields the *cis*-configured product, exclusively. Another protocol based on the application of Lawesson's reagent is also available.[44]

For the synthesis of unsymmetrically substituted 1,2,4-trithiolanes, the thermal exchange of a thiocarbonyl unit in **48** is recommended. For example, heating a $CHCl_3$-solution of **48** and **56** to reflux leads to the mixed 1,2,4-trithiolane **57** (Scheme 15).[36] Similarly, an exchange of one thiocarbonyl unit occurs upon heating the *cis*-3,5-di(*tert*-butyl)-3,5-di(*p*-tolyl)-1,2,4-trithiolane in toluene in the presence of adamantanethione (**56**) to yield an unsymmetrical, thermally stable 1,2,4-trithiolane.[42]



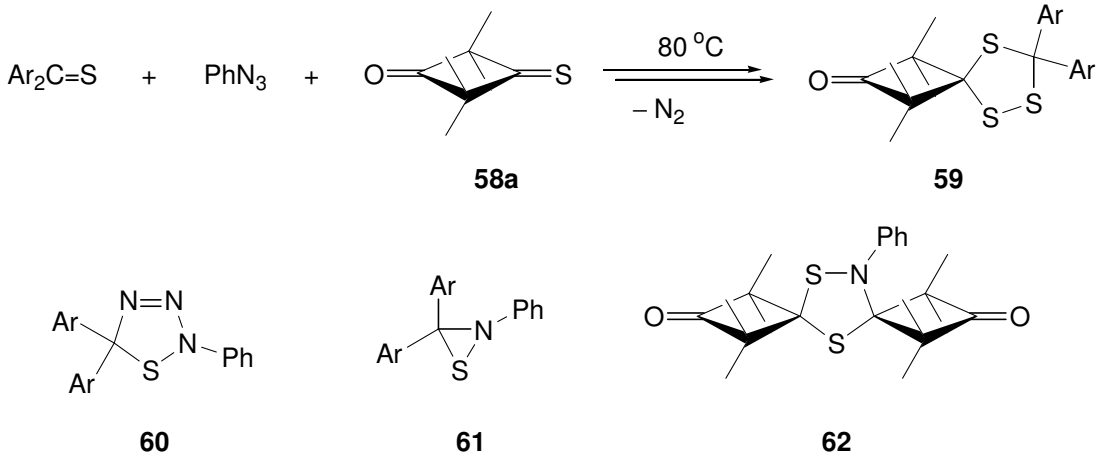
48 **56** **57**

Scheme 15

A sulfur-transfer from 2,2-diphenylthiiranes to thiobenzophenone (**1a**) occurs at room temperatur and gives rise to the dipole **46**, which is efficiently trapped by an additional equivalent of **1a** to afford **48**.[36] In a similar reaction, carried out with 9*H*-fluorene-9-thione (**2**), 1,1-diphenylethene has been detected by ^{1}H-NMR analysis as the second component of the reaction mixture.

Mixed 1,2,4-trithiolanes, *e.g.* **59**, are obtained in good yields when an aromatic thioketone is heated in an excess of phenylazide and in the presence of sterically congested thioketones. The [2+3] cycloaddition of the azide to the C=S group of the more reactive aromatic thioketone is the first step of this multistep reaction to give **60**, which is followed by elimination of nitrogen. A transient thiaziridine **61**, which transfers the sulfur atom to the thioketone leading to the thiocarbonyl *S*-sulfide **46**, is suggested. Subsequent addition of a second molecule of thioketone yields the thermally stable mixed 1,2,4-trithiolanes (Scheme 16).[45]

The reaction of phenylazide with aromatic thioketones **1** shows that only imines and elemental sulfur are formed as products of the decomposition of a thiaziridine **61**.[46] On the other hand, the cycloaliphatic thioketone **58a** reacts with phenylazide to give a thiocarbonyl *S*-imide as an intermediate, which is trapped by another molecule of thioketone to form the thermally stable 1,4,2-dithiazolidine **62**.[47]



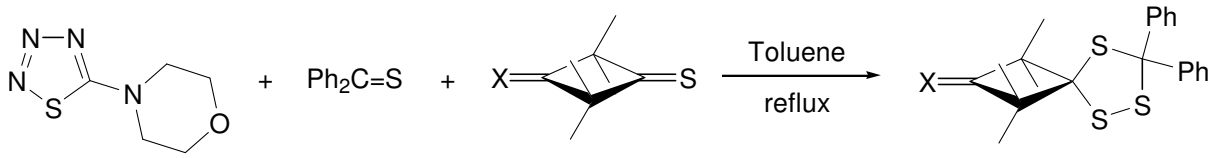
58a **59**

60 **61** **62**

Scheme 16

The isolable 5-morpholino-1,2,3,4-thiatriazole **63** decomposes in boiling toluene, extruding nitrogen and sulfur to give *N*-cyanomorpholine. When the decomposition is performed in the presence of an

equimolar mixture of **1a** and sterically crowded 2,2,4,4-tetramethylcyclobutanethiones **58**, the *in situ* formed thiocarbonyl *S*-sulfide is trapped by a thioketone to give unsymmetrically substituted 1,2,4-trithiolanes **59** (Scheme 17).[48]



63 **1a** **58a** X = O **58b** X = Cl_2 **59a** X = O **59b** X = Cl_2

Scheme 17

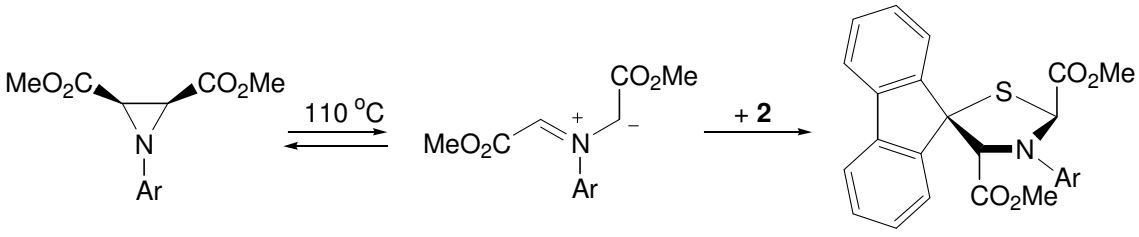
The preferred mechanism postulated for the formation of 'mixed' trithiolanes involves the [2+3] cycloaddition of **1a** with the thiocarbonyl *S*-sulfide, which is generated by sulfur transfer to the cycloaliphatic thioketone **58**.

2.4. Rings with S,N- or S,O-atoms

2.4.1. 1,3-Thiazole derivatives

The synthesis of 1,3-thiazole derivatives from aromatic thioketones is limited to [2+3] cycloadditions with azomethine ylides and nitrile ylides.

Several methods are described for the generation of azomethine ylides, *i.e.*, electrocyclic ring opening of aziridines, desilylation of iminium salts, decarboxylation of 1,3-oxazolidin-5-ones, tautomerization of aminoacid ester imines, and carbene addition to imines.[49] Almost all these methods have been applied in reactions with aromatic thioketones. A representative example of the reaction with aziridines is shown in Scheme 18. Thermally induced conrotatory ring opening of the *cis*-configured aziridine **64** affords the azomethine ylide **65**. Sequential [2+3] cycloaddition of the aromatic thioketone **2** yields the *trans*-disubstituted 1,3-thiazolidine **66**.[50]

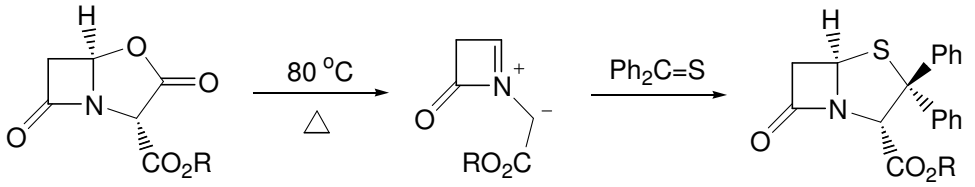


64 **65** **66**

Scheme 18

Similarly, the reaction with the *trans*-isomer of **64** yields the *cis*-isomer of **66**. A similar approach to 1,3-thiazolidines employs the decomposition of a 1,2,3-triazoline derivative in the presence of thiobenzophenone.[50a,51]

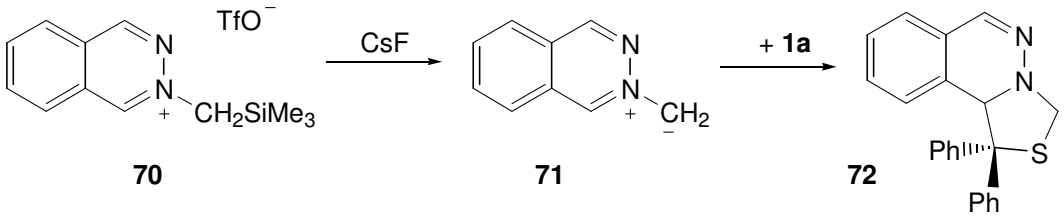
The decarboxylation approach for the generation of azomethine ylides has been used for the preparation of penam derivatives (Scheme 19).[52] The thermal decomposition of **67** in the presence of **1a** gives **69** in moderate yield. The azomethine ylide **68** is a plausible intermediate in this reaction. Similar to other [2+3] cycloadditions of unsymmetrically substituted azomethine ylides with C=S dipolarophiles, the reaction occurs with complete regioselectivity.



67 **68** **69**

Scheme 19

Several reports describe the synthesis of 1,3-thiazolidines under exploitation of the desilylation method. In these reactions, the azomethine ylides are generated by treatment of the corresponding trimethylsilyliminium salts with fluoride in the presence of an aromatic thioketone. An example of this approach is depicted in Scheme 20.[53] In this case, treatment of **70** with CsF leads to the intermediate **71**, which is trapped by **1a** in a regioselective manner.

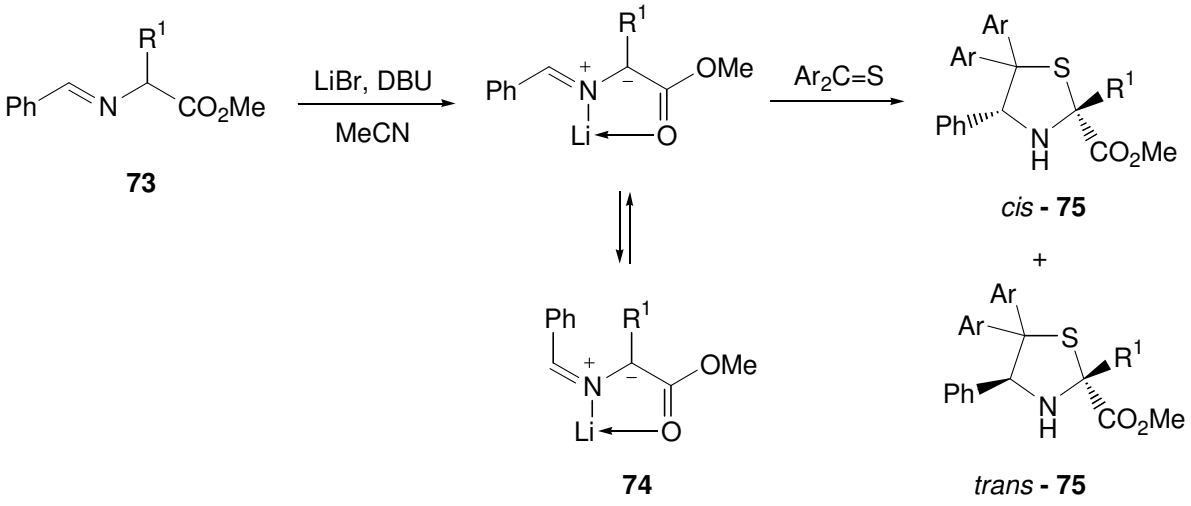


70 **71** **72**

Scheme 20

In a similar reaction, an azomethine ylide generated from benzylidene[(trimethylsilyl)methyl]amine reacts with **1a** and **2** to give mixtures of the regioisomeric *N*-unsubstituted cycloadducts.[54] Furthermore, *N*-substituted ylides without substituents at the C-atoms are generated by desilylation[55] or by dehydration of amine *N*-oxides[56] and used in [2+3] cycloadditions with aromatic thioketones.

A convenient access to 1,3-thiazolidine-2-carboxylates **75** *via* [2+3] cycloaddition of metallo-azomethine ylides **74**, generated from aminoacid ester imines **73**, with aromatic thioketones is depicted in Scheme 21.[57]



73

cis **- 75**

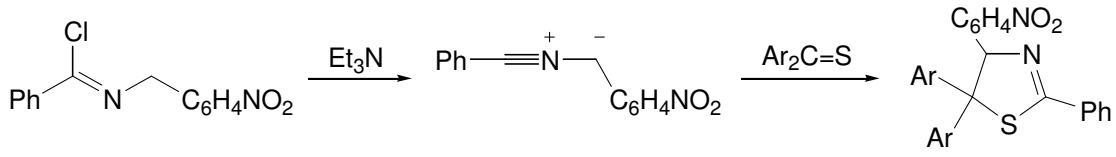
+

74

trans **- 75**

Scheme 21

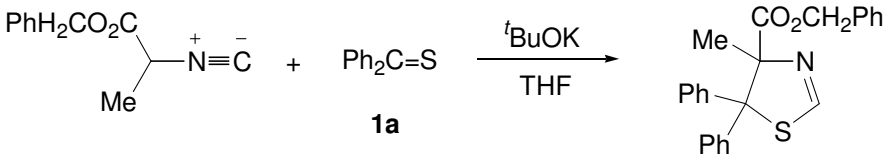
Similar to azomethine ylides, nitrile ylides **77** are employed as 1,3-dipoles in [2+3] cycloadditions with aromatic thioketones. Treatment of the benzimidoyl chloride **76** with triethylamine in benzene and in the presence of diarythioketones leads to the 4,5-dihydro-1,3-thiazole **78** in good yields (Scheme 22).[58]



76 **77** **78**

Scheme 22

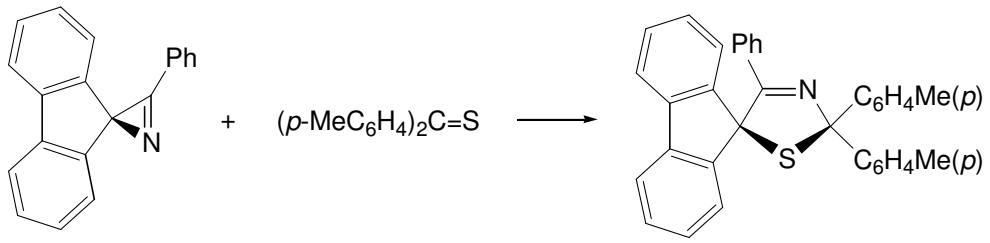
A different approach to 4,5-dihydro-1,3-thiazoles is presented in Scheme 23. Treatment of the isonitrile **79** with ^{t}BuOK in THF in the presence of **1a** gives **80** *via* a carbophilic attack of the *in situ* generated carbanion of **79** to thiobenzophenone (**1a**).[59]



79 **1a** **80**

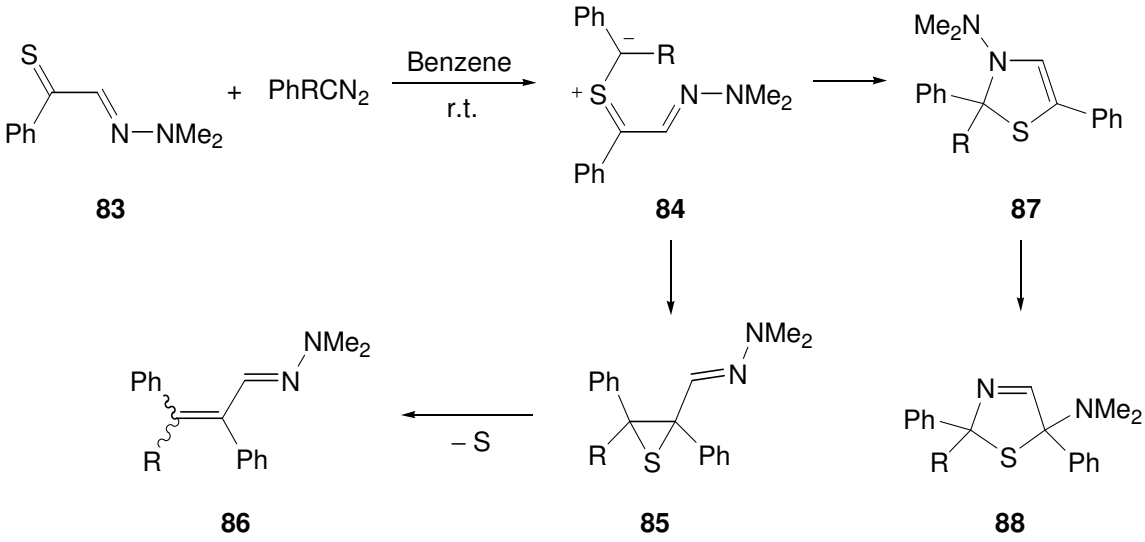
Scheme 23

The 2,5-dihydro-1,3-thiazole **82** is synthesized by a thermal reaction of the 2*H*-azirine **81** and **1b** (Scheme 24). This product is formed *via* cleavage of the azirine C,N-single bond.[60]



81 **1b** **82**

Scheme 24



83 **84** **87**

86 **85** **88**

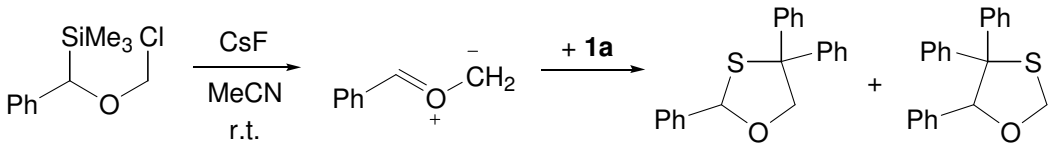
Scheme 25

The reaction of the conjugated thioketone (an α-iminothioketone) **83** with phenyl or diphenyldiazomethane leads to a mixture of the unsaturated hydrazone **86** and the 2,5-dihydro-1,3-thiazole **88** as a minor product (Scheme 25).[61] The intermediate thiocarbonyl ylide **84** undergoes competitive 1,3- and

1,5-dipolar electrocyclizations to give thiirane **85** and 2,3-dihydro-1,3-thiazole **87**, respectively. Whereas the first product spontaneously eliminates sulfur to yield **86**, the latter isomerizes *via* 1,3-migration of the Me_2N group to give **88**.

2.4.2. 1,3-Oxathiolanes and 1,3-oxathiols

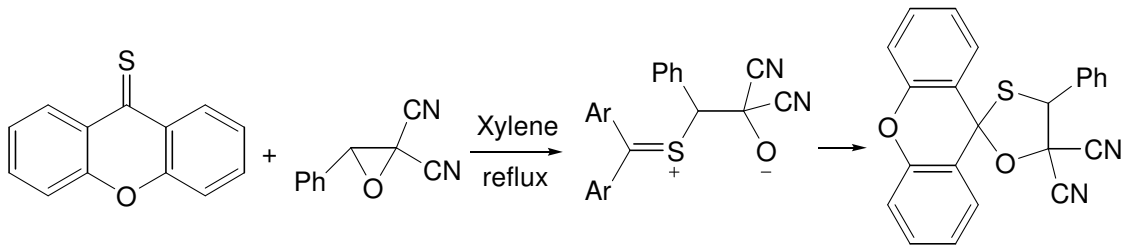
Aromatic thioketones found also application in the synthesis of 1,3-oxathiolanes as well as 1,3-oxathioles. One of the described methods is based on [2+3] cycloadditions with carbonyl ylides. The carbonyl ylide **90**, which is generated by desilylation of **89**, reacts with **1a** to give a mixture of the regioisomeric 1,3-oxathiolanes **91** and **92** (Scheme 26).[62] The alternative approach, which uses thiocarbonyl ylides derived from aromatic thioketones and ketones or aldehydes as dipolarophiles, is not known.



89 **90** **91** **92**

Scheme 26

The attempted [2+3] cycloaddition of the carbonyl ylide derived from **93** with 9*H*-xanthene-9-thione (**3a**) in boiling xylene leads to the 1,3-oxathiolane **95** (Scheme 27).[63] The expected product derived from [2+3] cycloaddition of the carbonyl ylide, which should be formed by electrocyclic ring opening of the oxirane **93**, is not found. In this case, a nucleophilic attack of **3a** most likely causes an alternative ring opening affording the zwitterion **94**, which spontaneously cyclizes to **95**. It is worth mentioning that the cycloaliphatic thioketones react with the carbonyl ylide formed from **93** to give the expected 1,3-oxathiolanes.[63]



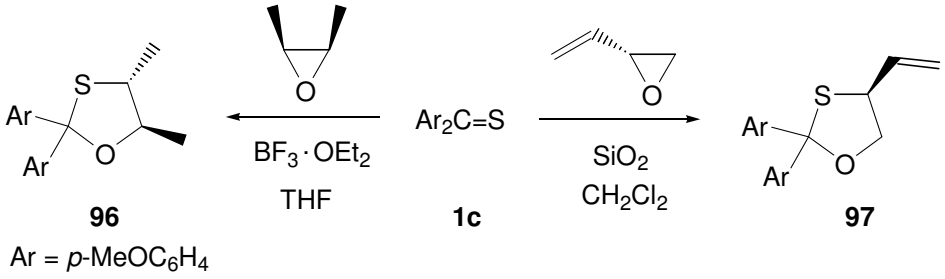
3a **93** **94** **95**

Scheme 27

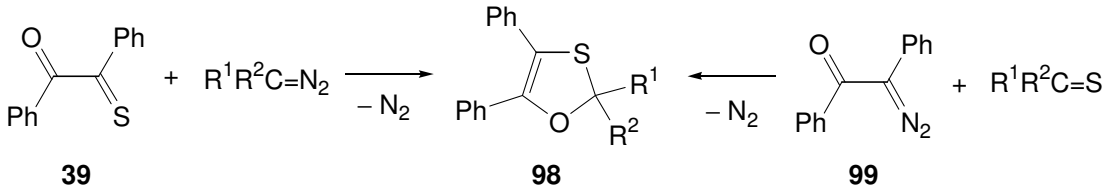
The Lewis acid catalyzed addition of aromatic thioketones with substituted oxiranes offers a convenient access to 1,3-oxathiolanes.[33,64-66] An important feature of this reaction is the regio- and stereoselectivity observed in reactions with enantiopure oxiranes. For example, the BF_3-catalyzed reaction of 4,4'-dimethoxythiobenzophenone (**1c**) with *cis*-2,3-dimethyloxirane yields the *trans*-4,5-dimethyl-2,2-diphenyl-1,3-oxathiolane **96** as a racemate, exclusively (Scheme 28).[64] The reaction of **1c** with (*R*)-2-vinyloxirane, catalyzed with SiO_2, gives regio- and stereoselectively the (*S*)-configured 4-vinyl-1,3-oxathiolane **97**.[66b]

The synthesis of 1,3-oxathioles is achieved *via* 1,5-dipolar electrocyclizations of thiocarbonyl ylides, which bear a conjugated carbonyl group. Only two methods have been reported on the preparation of thiocarbonyl ylides which use aromatic thioketones as precursors. The reactions of the α-thioxoketone **39**

with substituted diazomethanes smoothly occur to yield the corresponding 4,5-diphenyl-1,3-oxathioles **98** (Scheme 29).[32,67,68] The same product **98** with R^1, R^2 = Ph can be obtained when thiobenzophenone (**1a**) is treated with the α-diazoketone **99**.[27,69] In the latter case, the yield of **98** can be enhanced by using $LiClO_4$ as the catalyst.[27]



Scheme 28



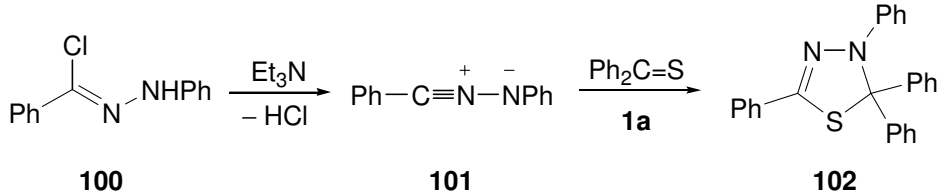
Scheme 29

However, replacement of **1a** with other aromatic thioketones leads to thiiranes or thiethanones (see Part I, Chapter 4).[1] Reactions of **1a** with other α-diazoketones, such as diazoacetophenone and α-diazocyclohexanone, are also reported to yield 1,3-oxathioles.[70,71] On the other hand, the formation of the five-membered ring heterocycles *via* 1,5-dipolar electrocyclization starting with thiobenzophenone (**1a**) is limited, and in the case of α-diazocamphor, only thiiranes are obtained.[72]

2.5. Rings with one S- and two other heteroatoms

2.5.1. Thiadiazole derivatives

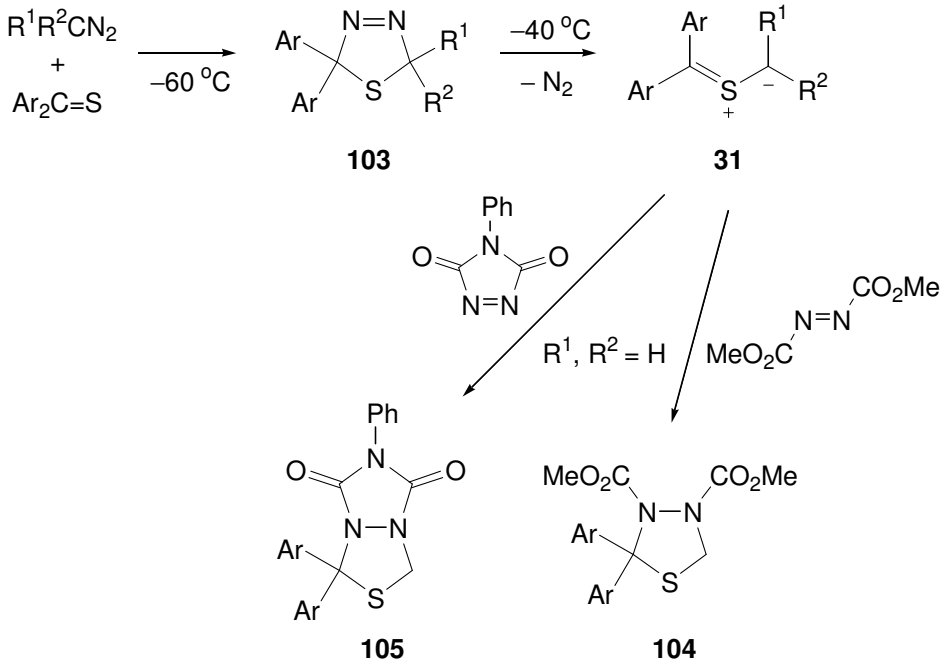
A convenient access to 1,3,4-thiadiazoles is provided by the [2+3] cycloadditions of aromatic thioketones with 1,3-dipoles, which contain two nitrogen atoms, such as nitrile imides and diazo compounds. For example, the dehydrochlorination of *N*-phenyl benzhydrazonoyl chloride (**100**) with triethylamine in the presence of thiobenzophenone (**1a**) leads to the tetraphenyl substituted 2,3-dihydro-1,3,4-thiadiazole **102** in high yield (Scheme 30).[73-75] The nitrile imide **101** appears as the reactive intermediate. Reactions with other aromatic thioketones are also described.[74]



Scheme 30

The same method is applied for the preparation of spirocyclic derivatives starting from 2-phenyl-3-(piperidin-1-yl)indene-1-thione.[76] Subsequent hydrolysis of the resulting enamine yields the corresponding indan-3-one derivative.

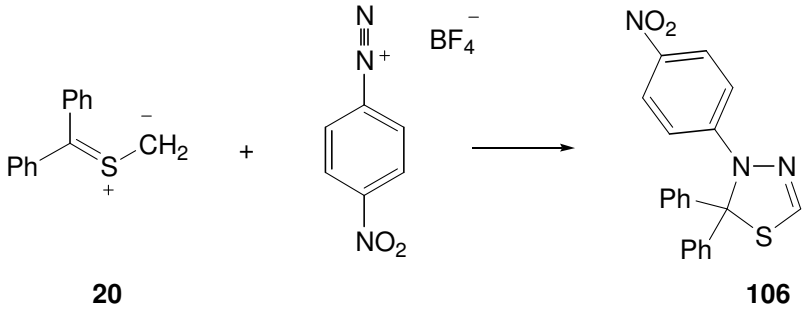
An alternative approach for the generation of a nitrile imide is based on the thermal or photochemical nitrogen elimination from 2,5-diphenyltetrazole. The reaction with **1a** in boiling xylene provides **102** in 60% yield.[77]



Scheme 31

Aromatic thioketones are very reactive reagents in [2+3] cycloadditions with diazoalkanes.[2c,4a,78] Thus, these reactions can be performed at low temperature, typically at *ca.* –60 °C. Under these conditions, 2,5-dihydro-1,3,4-thiadiazoles **103** are formed exclusively. These products cannot be isolated and eliminate nitrogen already at *ca.* –40 °C to generate the reactive thiocarbonyl ylides **31**, which can be trapped by a variety of dipolarophiles to give five-membered heterocycles (Scheme 31).[4] The analogous reactions with less reactive aliphatic thioketones, *e.g.*, adamantanethione, lead to mixtures of 2,5-dihydro-1,3,4- and 4,5-dihydro-1,2,3-thiadiazoles, which can be isolated in most cases.[79] The reactions of thiocarbonyl ylides **31** with electron deficient N=N dipolarophiles offers a convenient access to 1,3,4-thiadiazolidines, *e.g.* **104** and **105**, as shown in Scheme 31.[80]

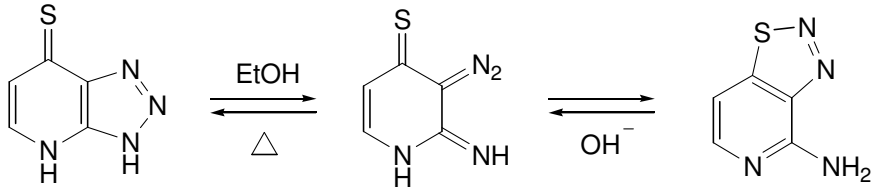
An example of the reaction of thiobenzophenone *S*-methylide (**20**) with an aromatic diazonium salt is also described (Scheme 32).[81] The initially formed cycloadduct stabilizes by deprotonation to give **106** in low yield.



Scheme 32

As mentioned above, 1,2,3-thiadiazole derivatives are not accessible *via* [2+3] cycloaddition of a diazo dipole with aromatic thioketones. However, some fused 1,2,3-thiadiazoles can be prepared in good yields *via*

a ring-opening/ring-closure sequence.[82] An example of such an isomerization, **107** → **109**, is outlined in Scheme 33. Under basic conditions, the reaction is reversed, leading to the starting material. The crucial intermediate is the diazo compound **108**.



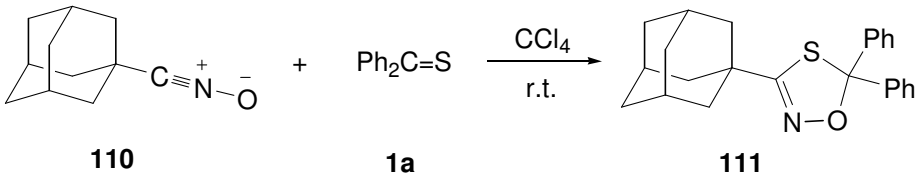
107 **108** **109**

Scheme 33

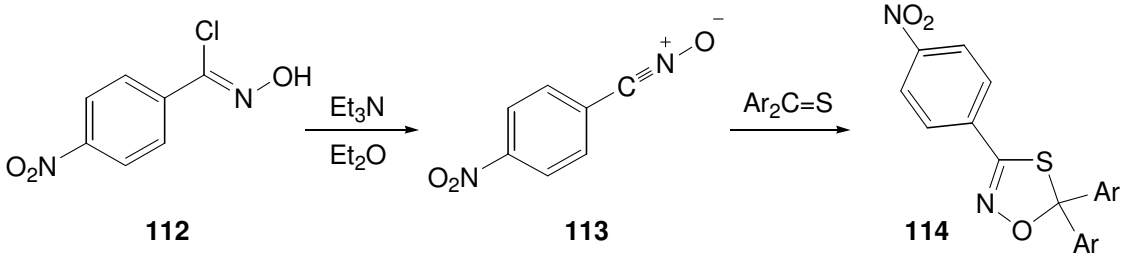
2.5.2. 1,4,2-Oxathiazole derivatives

The [2+3] cycloadditions of aromatic thioketones with nitrile oxides are well documented. The reactions occur in a regioselective manner to give the 1,4,2-oxathiazoles in good yields. Some sterically crowded nitrile oxides, *e.g.*, 2,4,6-trimethylbenzonitrile oxide (mesitylnitrile oxide), are stable compounds but in general, nitrile oxides are prepared *in situ via* dehydrochlorination of benzhydroxamoyl chlorides.[83]

Numerous aromatic thioketones, including **1a** and **2**, but also the less explored thioacetophenone (**6**, R = Me)[84] and 3-hydroxy-4-methyl-1,2-diphenylpentane-1-thione,[85] are used in reactions with nitrile oxides. Selected examples with a stable nitrile oxide **110** and with an *in situ* generated dipole **113** are presented in Scheme 34.



110 **1a** **111**



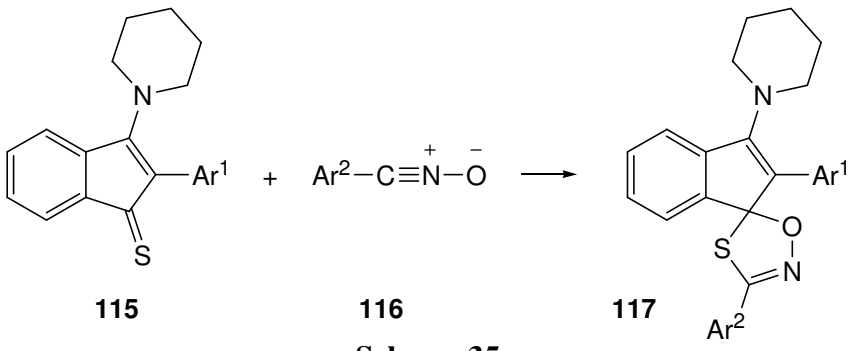
112 **113** **114**

Scheme 34

Along with **110**, mesitylnitrile oxide is widely applied for the synthesis of 3-mesityl-1,4,2-oxathiazoles of type **114**.[84,88,89] The spirocyclic 1,4,2-oxathiazole derivatives **117** are obtained from aromatic nitrile oxides **116** in reactions with 2-aryl-3-(piperidin-1-yl)indene-1-thiones **115** in high yield (Scheme 35).[76,90]

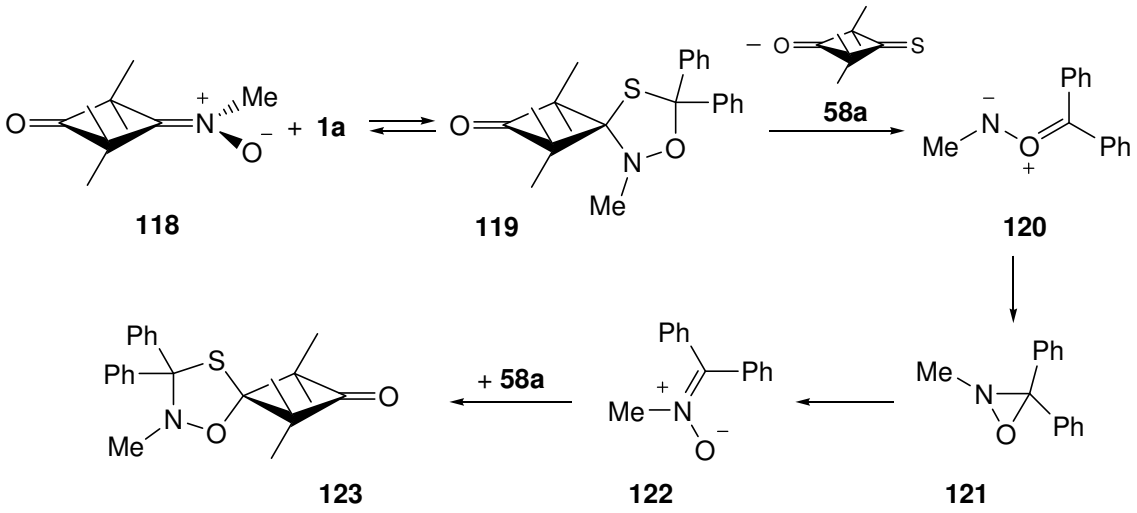
An attractive approach for the preparation of 1,4,2-oxathiazolidines is the [2+3] cycloaddition of nitrones with thiocarbonyl compounds. This method has been efficiently applied to a series of sterically crowded aliphatic thioketones.[91,92] The corresponding reactions with aromatic thioketones are scarcely reported. In the case of thiobenzophenone (**1a**), the reaction with nitrone **118** leads to the product **123**, which is an isomer of the expected cycloadduct **119**.[92c] The mechanism of this multistep conversion is presented in

Scheme 36. The initially formed 1,4,2-oxathiazolidine **119** decomposes to give the cycloaliphatic thioketone **58a** and carbonyl imide **120**. The latter rearranges *via* oxaziridine **121** to give nitrone **122**, which is trapped by **58a** to yield the final product.



115 **116** **117**

Scheme 35

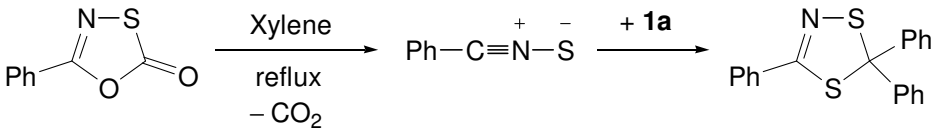


118 **119** **120** **121** **122** **123**

Scheme 36

2.5.3. 1,4,2-Dithiazole derivatives

Thermal decomposition of 2-phenyl-1,4,3-oxathiazol-5-one (**124**) is a well known method for the generation of nitrile sulfide **125**. When the reaction is carried out in boiling xylene in the presence of **1a**, the reactive intermediate **125** undergoes the [2+3] cycloaddition with **1a** to yield 1,4,2-dithiazole derivative **126** (Scheme 37).[93]



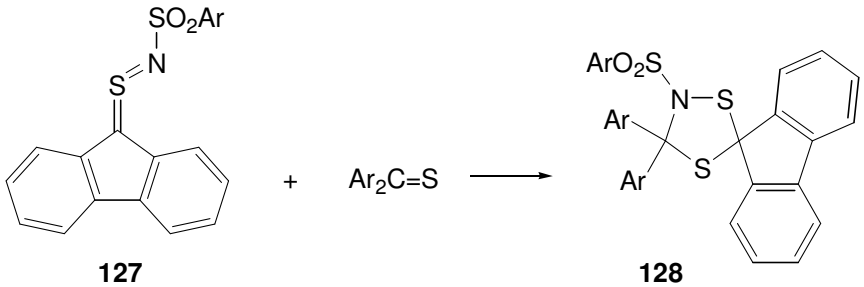
124 **125** **126**

Scheme 37

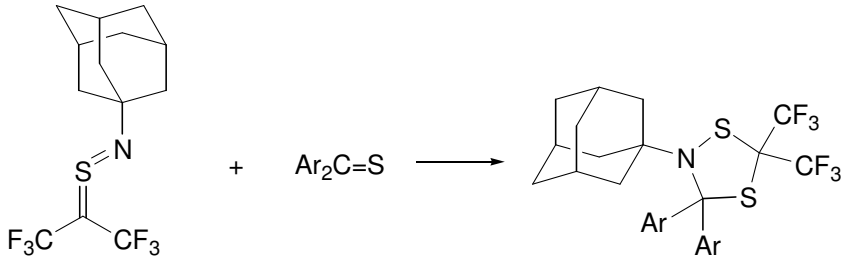
In the same report, corresponding reactions with other aryl- and methyl-substituted precursors of type **124** and (akyl)(aryl)thioketones leading to the corresponding products **126** are described.

Saturated 1,4,2-dithiazolidines are obtained in [2+3] cycloadditions of stable thiocarbonyl *S*-imides with aromatic thioketones.[94,95] For example, the *N*-tosylated thiocarbonyl *S*-imide **127** reacts with thiobenzophenone to give the heterocycle **128** regioselectively (Scheme 38). The same type of product, *i.e.*

130, was obtained when the *S*-imide **129** of hexafluorothioacetone was treated with aromatic thioketones.[95] In accordance with the reactivity scale of thioketones in reactions with thiobenzophenone *S*-methylide (**20**),[96] the fastest reaction is observed with 9*H*-fluorene-9-thione (**2**). On the other hand, 4,4'-dimethoxy-thiobenzophenone (**1c**) is the least reactive among the investigated thioketones.



127 **128**

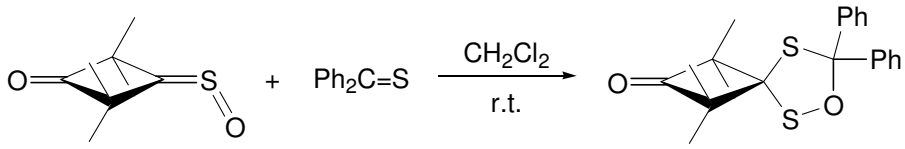


129 **130**

Scheme 38

2.5.4. 1,2,4-Oxadithiolane derivatives

Thiocarbonyl *S*-oxides (sulfines) are suitable dipolarophiles and dienophiles.[97] Only recently, 'superdipolarophilic' aromatic thioketones were shown to react with sulfines according to the [2+3] cycloaddition principles. The easily available *S*-oxide of the sterically crowded 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**131**) decolorizes the blue solution of **1a** in dichloromethane to give the cycloadduct **132** in good yield (Scheme 39).[98] Analogous reactions are performed with 4,4'-disubstituted thiobenzophenones **1** and with thiofluorenone (**2**).



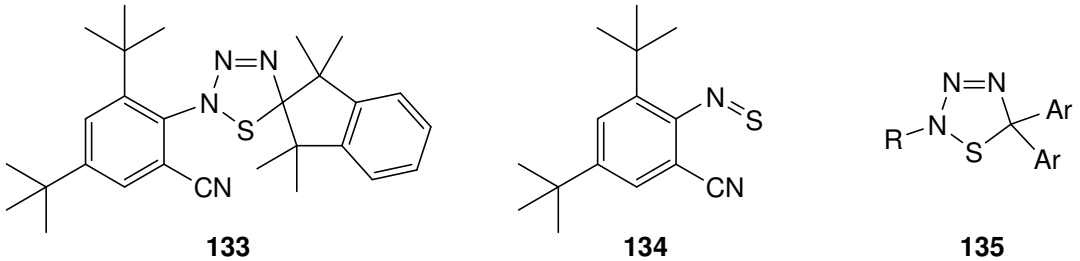
131 **1a** **132**

Scheme 39

2.5.5. 1,2,3,4-Thiatriazole derivatives

The sterically congested 1,2,3,4-thiatriazole **133**, a representative member of this class of heterocycles, is stable and isolable.[99] Similar heterocycles bearing aryl substituents at C(5) are proposed as transient intermediates derived from the reaction of thionitroso compound **134** with diaryldiazomethanes (Figure 2).

The [2+3] cycloadditions of organic azides with aromatic thioketones leading to imines, are suggested to occur *via* formation of 1,2,3,4-thiatriazoles of type **135** (Figure 2).[45,100] These heterocyles undergo 'two-fold extrusion' of both the nitrogen and sulfur atoms, affording thiaziridines as possible intermediates.



133 **134** **135**

Figure 2

3. Synthesis of six-membered rings

3.1. Thiopyrane derivatives

The formation of thiopyrane derivatives from aromatic thioketones *via* [2+4] cycloadditions reactions is well documented. The thioketones act as either diene or dienophile.

3.1.1. Aromatic thioketones as dienophiles

Substituted buta-1,3-dienes as well as cyclic 1,3-dienes react smoothly with thiobenzophenone (**1a**), 9*H*-fluorene-9-thione (**2**), and other aromatic thioketones.[3,101,102] A rate constant ratio of 1:1300 was found in the reactions of **2** and **1a** with 2,3-dimethylbuta-1,3-diene.[3] Studies on the influence of diene substituents on the reaction rates with **1a** and **2** show that cyclopentadiene is the most reactive diene. For example, the reactions of **2** with cyclopentadiene, 2,3-dimethylbuta-1,3-diene, and buta-1,3-diene in dichloromethane show a rate constant ratio of 600:10:1.[102] The same dienes have been used in the hetero-Diels-Alder reaction with silylated thioketones **7**.[103] In the case of cyclopentadiene, the *endo*-silyl cycloadduct **136** is formed, exclusively (Scheme 40).

7 (R = Me, Ph) **136**

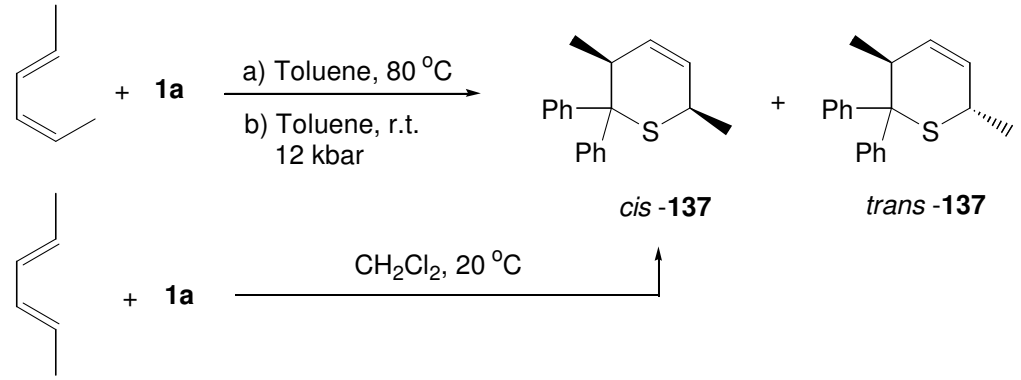
Scheme 40

Reactions of **1a** and **2** with asymmetric dienes are regioselective.[3] Thus, **1a** and 1-arylbuta-1,3-dienes afford 3-aryl-2,2-diphenyl-3,6-dihydro-2*H*-pyranes exclusively, whereas the reaction with 2-arylbuta-1,3-dienes leads to the 5-aryl isomers.

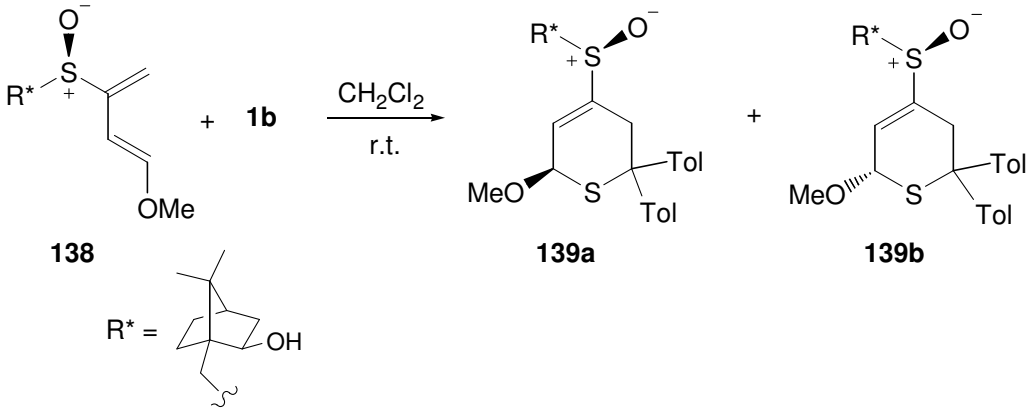
The reactions of (*E*,*E*)-hexa-2,4-diene with **1a** or **2** give the *cis*-3,6-dimethylthiopyrane derivative *cis*-**137**, stereoselectively.[102a] On the other hand, the corresponding reaction of **1a** with the less reactive (*E,Z*)-hexa-2,4-diene in toluene at 80 °C leads to a mixture of the *cis*- and *trans*-configured cycloadducts in favor of the unexpected *cis*-isomer (Scheme 41).[104] This unexpected stereochemical outcome results from a stepwise mechanism which involves a diradical intermediate. It is worth to note that the same reaction carried out at room temperature under high-pressure conditions (12 kbar) provides the same products but in lower yields, however, the *cis/trans* ratio of 4:96 indicates that the configuration of the diene is preserved in the six membered ring.

Optically active 2-sulfinyldienes are used in the reaction with **1b** and **1c** to probe the diastereoselectivity of the [2+4] cycloaddition reaction, which was rather low.[105] For example, a **139a/139b**

= 7:3 diastereomeric ratio is found in the reactions of **1b** and **138** (Scheme 42), while no selectivity is observed in the reaction with 1-[(1'-sulfinyl)vinyl]cyclohexane.

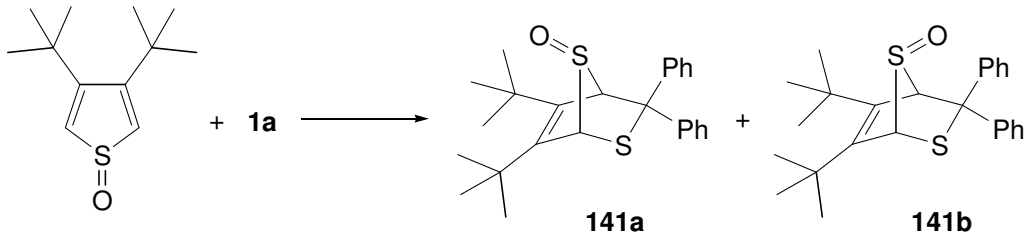


Scheme 41



Scheme 42

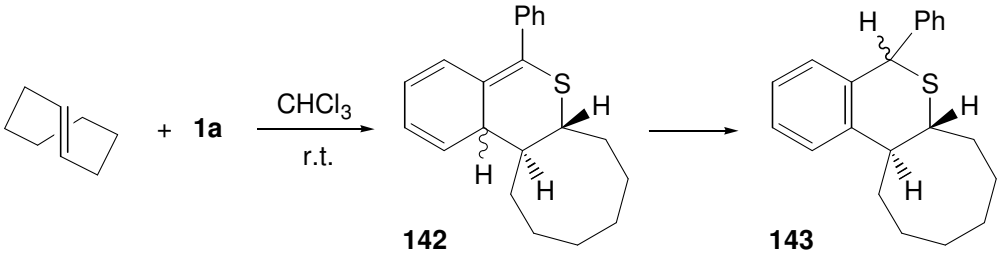
The reaction of 3,4-bis(*tert*-butyl)thiophene *S*-oxide with **1a** yields a mixture of the two stereoisomers **141a** and **141b** (Scheme 43).[106] A similar reaction of thioacetophenone (**6**, R = Me) with 3,4-dimethyl-1-phenyl-1*H*-phosphole 1-sulfide furnishes a single isomer of the corresponding bicyclic product.[107]



Scheme 43

3.1.2. Aromatic thioketones as heterodienes

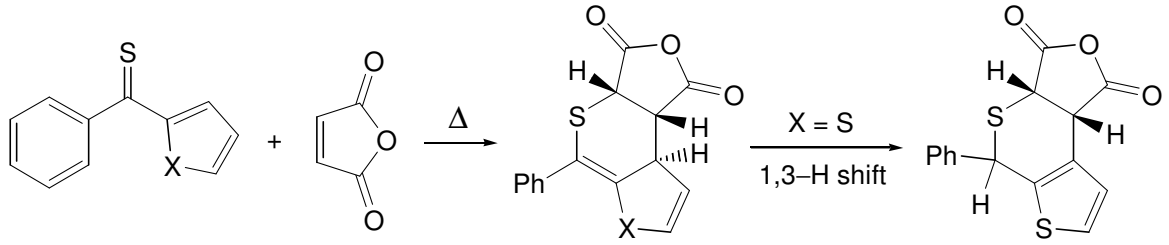
In analogy to α,β-unsaturated thioketones,[108] aromatic thioketones react with activated alkenes, such as norbornene,[109,110] maleic anhydride,[109] and (*E*)-cyclooctene[111,112] to yield 2-benzothiopyran derivatives. The reaction of (*E*)-cyclooctene with **1a** affords the transient [2+4] cycloadduct **142**, only detected by means of NMR spectroscopy. At room temperature, this compound slowly undergoes aromatization to give **143** (Scheme 44).



142 143

Scheme 44

Analogous reactions are reported for non-symmetric aromatic thioketones **4** bearing 2-furyl or 2-thienyl residues.[113] In another paper, reactions with corresponding *N*-methylpyrrol-2-yl thioketones are described.[114] Regioselective cycloaddition reactions of **4** with maleic anhydride include the C,C-double bond of the heteroaromatic ring as a part of the diene system. The more reactive 2-furyl derivative reacts in refluxing benzene to give the non-aromatic product **144** (X = O) (Scheme 45). However, the reaction with the 2-thienyl thioketone requires harsher conditions (boiling xylene) and leads to the aromatized isomer **145**. With norbornene, the non-aromatic cycloadduct of type **144** is obtained in both series.[114]

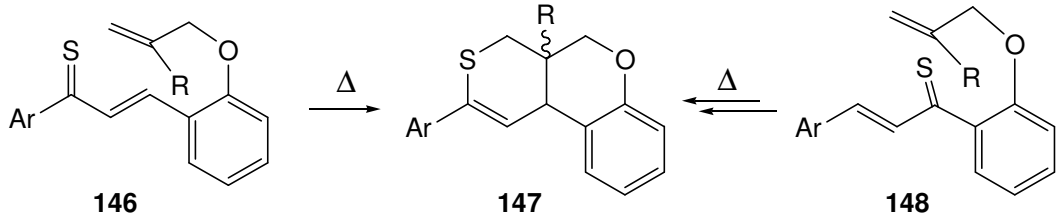


4 (X = O,S) **144** **145**

Scheme 45

The reactions of **4** with acrylonitrile occur regioselectively to yield mixtures of *cis*- and *trans*-configured cycloadducts, which subsequently isomerize to afford a single aromatized compound. Furthermore, 2-chloroacrylonitrile and styrene were used as dienophiles.[114]

An intramolecular [2+4] cycloaddition is observed with a nonactivated C,C-double bond.[115] The α,β-unsaturated aromatic thioketone **146** smoothly reacts with the allyl ether to give the polycyclic thiopyrane derivative **147** in high yield (Scheme 46). Remarkably, the isomeric thioketone **148** gives the same product along with small amounts of a seven-membered dithiepin derivative (see Chapter 4).[116] The formation of **147** from **148** is explained *via* a multistep pathway, involving the intermediate formation of **146**.



146 **147** **148**

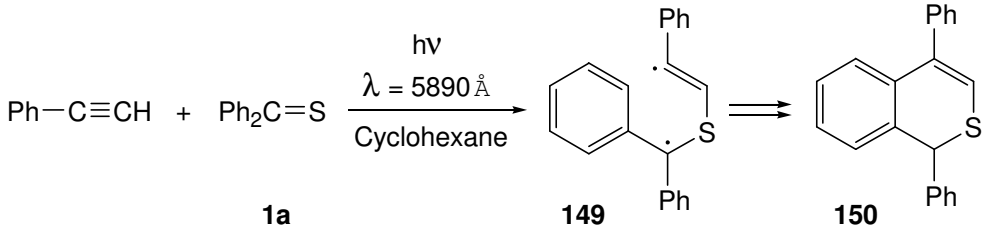
Scheme 46

The *in situ* generated 2-[(phenylthio)methylene]tetralin-1-thione acts as a reactive heterodiene in [2+4] cycloadditions with activated C=C dienophiles.[117]

Typically, photochemical reactions of aromatic thioketones with allene systems lead to thietanes *via* [2+2] cycloaddition.[1] In the case of 9*H*-xanthene-9-thione (**3a**) and (allenyl)(*tert*-butyl)ether, irradiation in

dichloromethane affords 3-[(*tert*-butoxy)methylene]-1-phenylisothiochroman as a minor product, along with two isomeric thietanes.[118]

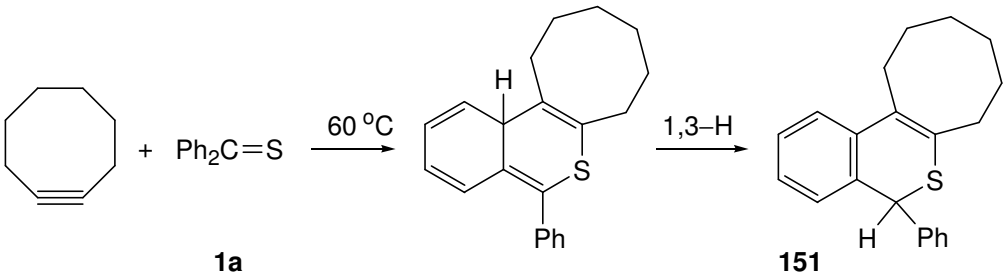
The first reported reactions of aromatic thioketones with acetylenes were carried out photochemically. Under these conditions, the intermediate diradical **149** undergoes cyclization to give benzo[*c*]thiopyrane **150** in a regioselective manner (Scheme 47).[119]



1a **149** **150**

Scheme 47

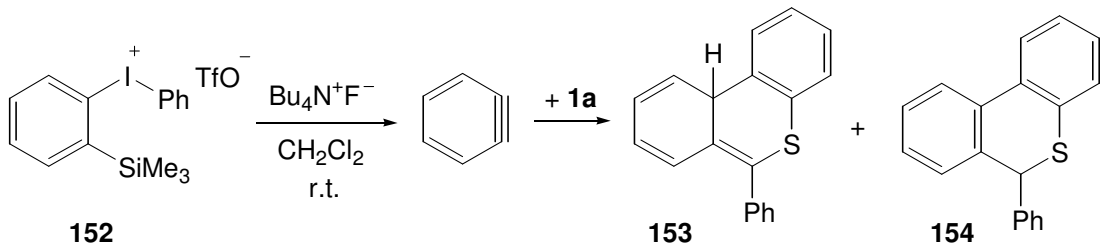
Aromatic thioketones as electron-rich heterodienes smoothly react with electron-deficient acetylenes in thermal [4+2] cycloadditions. The initially formed cycloadducts isomerize *via* 1,3-H shift to give the aromatic benzo[*c*]thiopyranes. With **1a** and methyl propiolate, the reaction proceeds regioselectively to yield methyl 1-phenylbenzo[*c*]thiopyrane 4-carboxylate.[111] The strained cyclooctyne combines with **1a** at 60 °C (10 min) to afford the expected cycloadduct **151** (Scheme 48).



1a **151**

Scheme 48

The highly strained benzyne, generated from the iodonium salt **152** by treatment with tetrabutylammonium fluoride, is trapped by thiobenzophenones **1** to yield a mixture of the initially formed [2+4] cycloadduct **153** and its aromatized isomer **154** (Scheme 49).[120]



152 **153** **154**

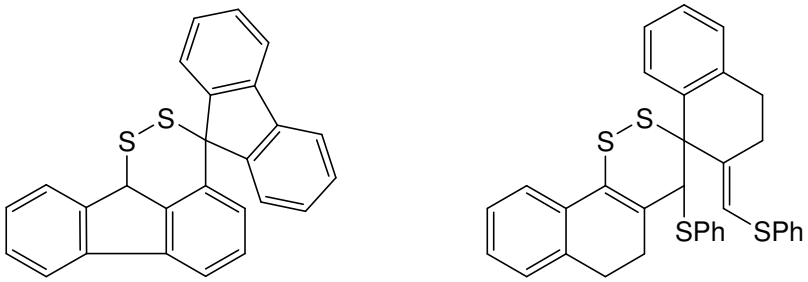
Scheme 49

Whereas the analogous reaction with thiopivalophenones carried out at room temperature affords the corresponding benzothiete ([2+2] cycloadduct) exclusively, a 3:7 mixture of benzothiete and the [2+4] cycloadduct of type **154** is formed in boiling toluene.[120]

3.2. Rings with two S-atoms

3.2.1. 1,2-Dithiine derivatives

An interesting example of an efficient formation of a 1,2-dithiine derivative is the spontaneous dimerization of 9*H*-fluorene-9-thione (**2**). The structure of this dimer was wrongly described as a 1,3-dithietane derivative,[121] but X-ray diffraction analysis revealed the polycyclic 1,2-dithiine structure **155** (Figure 3).[122]



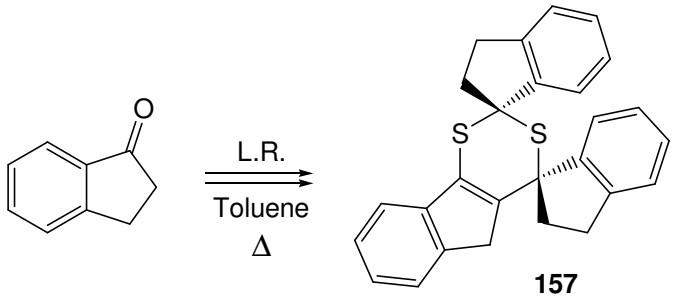
155 **156**

Figure 3

The formation of **155** can be explained by a formal hetero-Diels-Alder reaction, in which one molecule of **2** acts as the heterodiene and another one as the heterodienophile. An analogous structure, *i.e.* **156** (Figure 3), is assumed for the dimer of the previously mentioned 2-methylenetetralin-1-thione derivative.[117]

3.2.2. 1,3-Dithiine derivatives

Thionation of indan-1-one with Lawesson's reagent (L.R.) in boiling toluene unexpectedly leads to the crystalline 1,3-dithiin **157** (Scheme 50). Its structure has been established by X-ray crystallography.[123] The formation of **157** is supposed to occur *via* the intermediate bis(inden-1-yl)sulfide, which subsequently reacts with a third molecule of indane-1-thione.



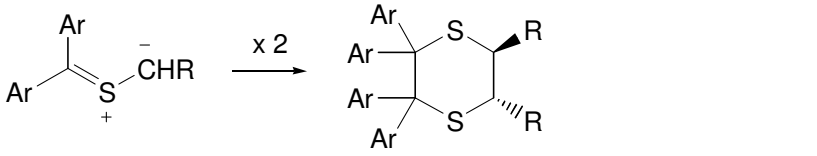
157

Scheme 50

3.2.3. 1,4-Dithiane and 1,4-dithiine derivatives

Thiocarbonyl *S*-methanides **31** (R = H), derived from aromatic thioketones, in the absence of intercepting agents undergo head-to-head dimerization to yield 1,4-dithianes as products of a 1,6-cyclization of the biradical intermediate.[23a,29] The substitution pattern of the ylide strongly influences the dimerization process, which competes with the 1,3-dipolar electrocyclization leading to thiiranes (Chapter 3, Part I).[1] Thiocarbonyl ylides **31**, bearing alkyl or aryl substituents at the 'ylide C-atom' (R = alkyl, aryl), do not undergo the dimerization.[23a,124] The same result is observed in the case of R = CO_2R'.[25a] However, the

reactive thiocarbonyl ylide **31** derived from **2** and diethyl diazomethylphosphonate at –45 °C smoothly forms the six-membered ring **158** with *trans*-configuration of the phosphonate groups (Scheme 51).[18] The same configuration is established for the product obtained from **2** and (trimethylsilyl)diazomethane.[26]

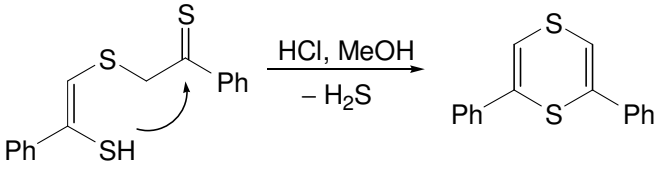


31 **158** R = H, $P(O)(OEt)_2$, $SiMe_3$

Scheme 51

An alternative approach to 1,4-dithianes **158** involves the photochemical reaction of thiobenzophenone (**1a**) with electron-rich alkenes.[125] The reaction occurs stepwise in a regioselective manner. The first step is the C,S-bond formation, leading to a biradical *via* addition of the excited thiobenzophenone (**1a**) to the alkene. This intermediate intercepts a second molecule of **1a**, and the resulting 2,5-dithiahexane-1,6-diyl cyclizes to yield the product.

The acid-catalyzed cyclization of the aromatic thioketone **159** accompanied by elimination of H_2S leading to 2,6-diphenyl-1,4-dithiine (**160**) has been recently reported (Scheme 52).[126]



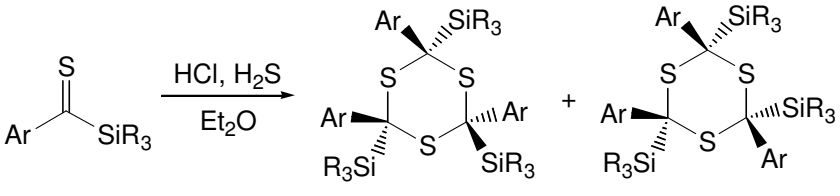
159 **160**

Scheme 52

3.3. 1,3,5-Trithianes, tetrathianes, and pentathianes

3.3.1. 1,3,5-Trithianes

The formation of a 1,3,5-trithiane by trimerization of thioacetophenone (**6**, R = Me) was proposed by Baumann and Fromm in 1891.[127] The synthesis of the parent compound and *para*-substituted derivatives by treatment of the corresponding acetophenones with H_2S/HCl in alcoholic solution is reported in subsequent papers.[128] To date, the stereochemical details of their structures are unknown. The diastereomeric trimers **162a** and **162b** of the silylated thioketones **161** are obtained by passing a H_2S and HCl stream through an etheral solution (Scheme 53). The structure of **162b** (Ar = Ph, R = Me) has been established by X-ray crystallography.[129]

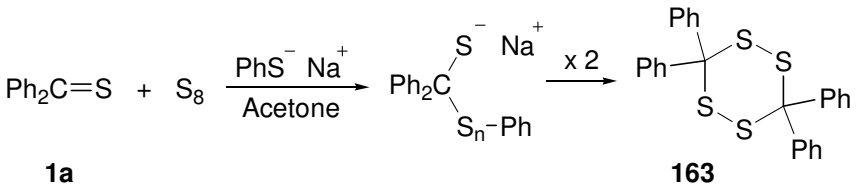


161 **162a** **162b**

Scheme 53

3.3.2. Tetrathianes

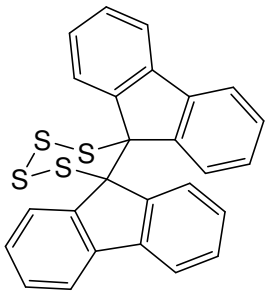
The chemistry of different tetrathianes has been reviewed by Franek.[130] Treatment of **1a** in acetone solution with elemental sulphur (S_8) in the presence of sodium thiophenolate represents an efficient method for the preparation of 3,3,6,6-tetraphenyl-1,2,4,5-tetrathiane (**163**) (Scheme 54).[131] Formally, the formation of **163** is the result of the head-to-tail dimerization of thiobenzophenone *S*-sulfide (**46**). However, a multi-step reaction initiated by the nucleophilic addition of a phenylpolysulfide anion onto **1a** is more likely. Although similar conversions of aliphatic thioketones are known, reactions with other aromatic thioketones have not been reported so far.[130,131]



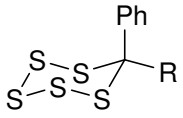
1a **163**

Scheme 54

An unprecedented example of a 1,2,3,4-tetrathiane, *i.e.* **164** (Figure 4), derived from 9*H*-fluorene-9-thione (**2**), is isolated from the reaction mixture with methyl *N*-benzylidene-phenylglycinate, after treatment with 1,6-diazabicyclo[5.4.0]undecane (DBU).[132]



164



165

R = ^{t}Bu, 1-Adamantyl

Figure 4

3.3.3. Pentathianes

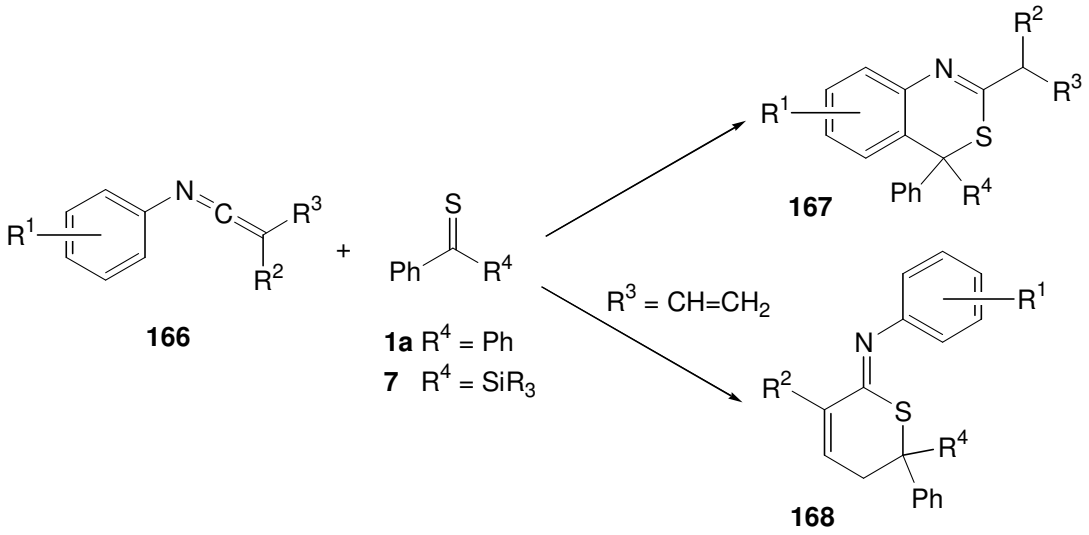
Pentathianes belong to rarely reported sulphur heterocycles. Recently, sterically crowded derivatives **165** (Figure 4) were obtained by thionation of the corresponding thioketones with S_8 at room temperature.[133] The use of 1,3-dimethylimidazolidin-2-one as the reaction solvent is of crucial importance for the preparation of **165**. An alternative approach to **165** (R = 1-adamantyl) is based on the reaction of (adamantan-1-yl)phenylketone hydrazone with S_2Cl_2. In this case, the corresponding thioketone is formed *in situ.*[134]

3.4. Rings with S,N- or S,O-atoms

3.4.1. 1,3-Thiazine derivatives

Aromatic thioketones undergo [4+2] cycloadditions with *N*-aryl ketenimines **166** in competition with the previously described [2+2] cycloaddition leading to thietanes (Chapter 4, Part I).[1] The substitution pattern of the benzene residue remarkably influences the periselectivity. While the formation of the 4*H*-3,1-

benzothiazine **167** competes with the [2+2] process in the unsubstituted system (R^1 = H), only the [2+4] cycloaddition, which leads to **167**, is observed when a *p*-tolyl residue (R^1 = 4-Me) is present (Scheme 55).[135]



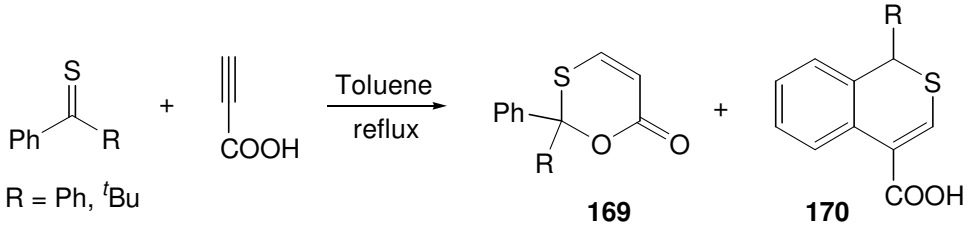
Scheme 55

In the presence of a vinyl group, ketenimine **166** (R^2 = Me, R^3 = CH=CH_2) undergoes an alternative reaction, in which the vinyl group and the C=C bond of the cumulated π-system act as a diene. In the case of the mesityl group (R^1 = 2,4,6-triMe), the reaction with **1a** affords the corresponding thiopyrane **168**, exclusively, whereas **167** and **168** are competitively formed when the benzene ring bears two methyl groups in positions 3 and 5. The nature of the aromatic thioketone also influences the course of the reaction. In contrast to **1a**, the silylated thioketones **7** (R = Me, Ph) react with the vinyl substituted **166** (R^1 = 4-Me, R^2 = Me, R^3 = CH=CH_2) to give only products **168** in good yields.[136]

A following paper reports the reactions of *in situ* generated *N*-vinyl ketenimines with 4,4'-dimethoxy-thiobenzophenone (**1c**) which yield 1,3-thiazine derivatives as sole products.[137]

3.4.2. 1,3-Oxathiin derivatives

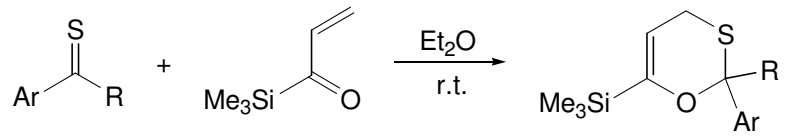
All known syntheses of 1,3-oxathiins, which base on reactions with aromatic thioketones, involve [2+4] cycloadditions. A recently described approach involves the reaction of thiobenzophenone (**1a**) and thiopivalophenone (**6**, R = ^{t}Bu), respectively, with propiolic acid.[138] In all known cases, the 1,3-oxathiin **169** is accompanied by the corresponding benzo[*c*]thiopyrane **170**, and the ratio of these products depends on the nature of the R substituent at the thioketone: thiopivalophenones afford **169** as major products (Scheme 56).



Scheme 56

The formation of **169** is the result of a hetero-Diels-Alder reaction, in which propiolic acid acts as the heterodiene. Most likely, acid catalysis is a relevant factor in this process as analogous reactions with methyl propiolates yield benzothiopyranes as sole products.[111]

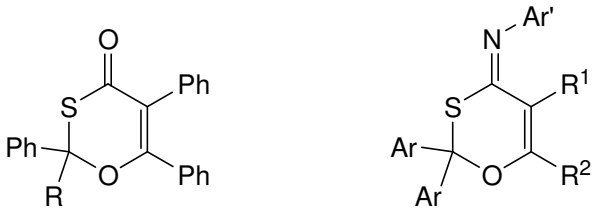
Surprisingly, the attempted reaction of **1a** with benzyne, generated by decomposition of benzenediazonium-2-carboxylate, leads to 3,1-benzoxathian-4-one instead of the expected benzo[*c*]thiopyrane[120] (see Scheme 49). An efficient synthesis of 1,3-oxathiins **171** is the hetero-Diels-Alder reaction of aromatic thioketones with (trimethylsilyl)(vinyl)ketones (Scheme 57).[139]



R = Ar, SiR_3 **171**

Scheme 57

The thermal decomposition of dibenzoyldiazomethane in the presence of aromatic thioketones **6** (R = Me, $PhCH_2$) provides 1,3-oxathiin-4-ones **172** in good yields (Figure 5).[140] The first step of the reaction sequence is the formation of dibenzoylcarbene which undergoes the Wolff rearrangement to give (benzoyl)phenylketene, which intercepts the thioketone in a [2+4] cycloaddition. A similar process allows the preparation of 1,3-oxathiin-4-imines **173** (Figure 5) from acylketenimines and aromatic thioketones.[141]



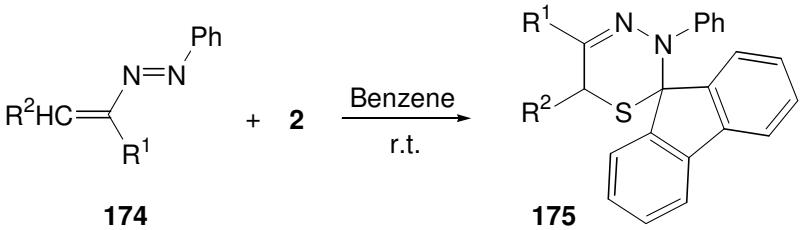
172 **173**

Figure 5

3.5. Rings with one S-atom and two other heteroatoms

3.5.1. 1,3,4- and 1,3,5-Thiadiazine derivatives

Substituted vinyldiazenes **174** react with 9*H*-fluorene-9-thione (**2**) at room temperature to give 1,3,4-thiadiazines **175** in a regioselective manner (Scheme 58).[142] The less reactive thioketones **1** fail to undergo the [2+4] cycloaddition. It is worth mentionig that the *S*-oxide of **2** in reactions with **174** gives the *S*-oxides of the isomeric 1,2,3-thiadiazines, *i.e.*, the [2+4] cycloaddition occurs with the opposite regioselectivity.

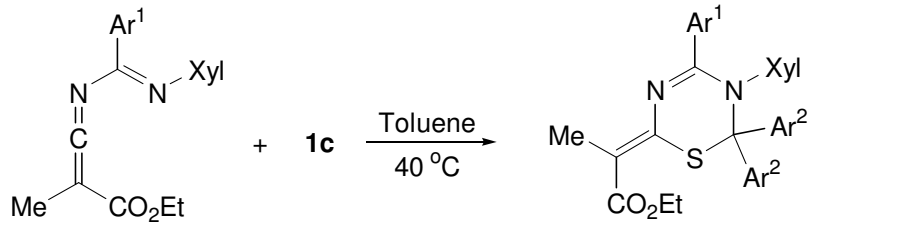


174 **175**

Scheme 58

Another approach to 1,3,4-thiadiazines is the hetero-Diels-Alder reaction of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine with thiobenzophenones (**1**).[102b] The initially formed [2+4] cycloadduct eliminates nitrogen spontaneously.

A single example of a 1,3,5-thiadiazine derivative **175** was obtained by heating a mixture of **1c** and the iminoketenimine **174** in toluene at 40 °C (Scheme 59).[143]

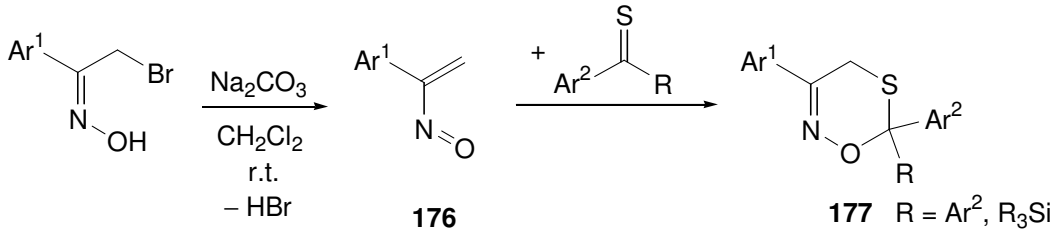


174 Ar^1 = *p*-$NO_2C_6H_4$ **175** Ar^2 = *p*-$MeOC_6H_4$

Scheme 59

3.5.2. 1,5,2- and 1,3,5-Oxathiazine derivatives

Hetero-Diels-Alder reactions were exploited for the preparation of the title compounds. Thus, *in situ* generated nitrosoalkenes **176** smoothly react with diverse aromatic thioketones to give 4*H*-1,5,2-oxathiazines **177** *via* a regioselective [2+4] cycloaddition in excellent yields (Scheme 60).[136,144] The structure of the heterocycles has been established by X-ray crystallography for the compound **177** with Ar^1 = Ph, Ar^2 = R = *p*-MeC_6H_4.

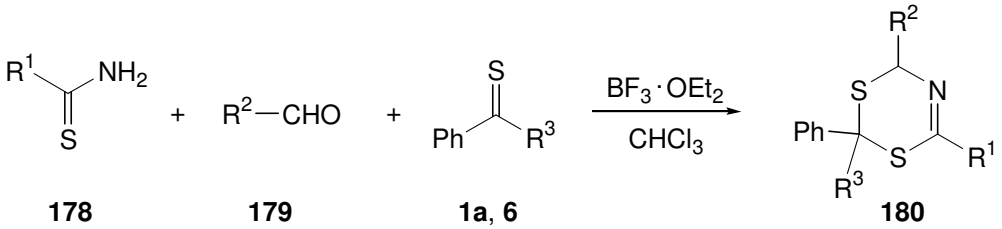


Scheme 60

In analogy to the reaction depicted in Scheme 59, the treatment of **1c** with the *N*-benzoyl analogue of **174** leads to the corresponding 4-alkylidene-4*H*-1,3,5-oxathiazine.[143] The reaction occurs spontaneously at room temperature.

3.6. Rings with two S-atoms and another heteroatom

Two methods are described for the synthesis of the 1,3,5-dithiazine ring starting from aromatic thioketones. The three-component mixture of thioamide **178**, aldehyde **179**, and thioketone **1a** or **6** (R = Me) in the presence of $BF_3{\cdot}OEt_2$ affords, after workup with aqueous Na_2CO_3, products **180** (Scheme 61).[145] Better yields are achieved by means of a two-component reaction with *N*-(hydroxymethyl)thioamides and thioketone. A possible interpretation of the reaction pathway is the [2+4] cycloaddition of an *in situ* formed *N*-methylidenethioamide with the thioketone as the dienophile.



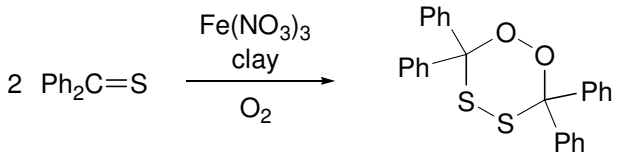
178 **179** **1a**, **6** **180**

Scheme 61

A second synthetic approach is the photochemical reaction of **1a** with an imine of benzophenone, which gives 5,6-dihydro-2,2,4,4,6,6-hexaphenyl-4*H*-1,3,5-dithiazines in low yield.[146]

3.7. Other six-membered sulfur heterocycles

Treatment of aromatic thioketones with oxidizing agents leads to the formation of 1,2,4-trithiolanes (Chapter 2.3.) or thiocarbonyl *S*-oxides (sulfines).[7] Under particular conditions (using clay-supported ferric nitrate), thiobenzophenones can be converted to benzophenones.[147] However, optimization of the reaction conditions allows the isolation of 1,2,4,5-dioxadithianes **181** (Scheme 62).[148] These products undergo slow decomposition to give benzophenones during storage.

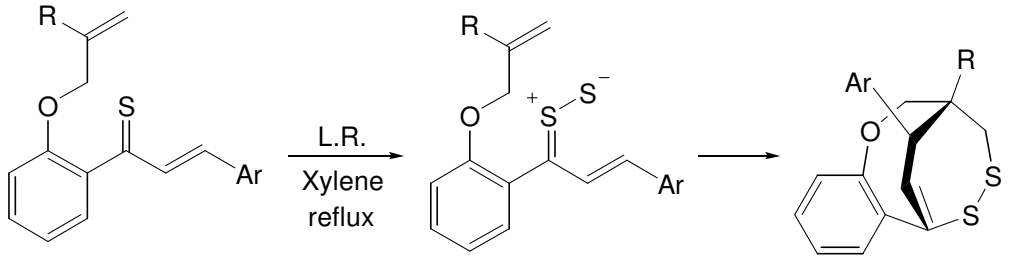


1a **181**

Scheme 62

4. Synthesis of seven- and eight-membered rings

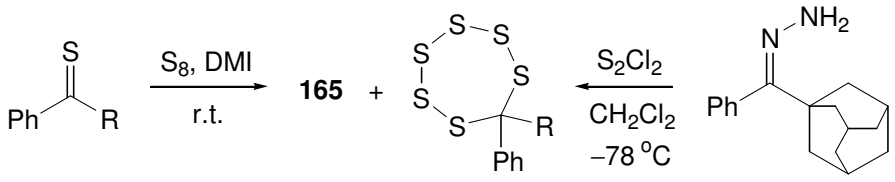
In the course of the study of the α,β-unsaturated aromatic thioketones **148**, the treatment with Lawesson's reagent in boiling xylene leads to 1,2-dithiepins **183** (Scheme 63).[116] The formation of the product is proposed to occur *via* intramolecular [2+5] cycloaddition of thiocarbonyl *S*-sulfide **182**.



148 **182** **183**

Scheme 63

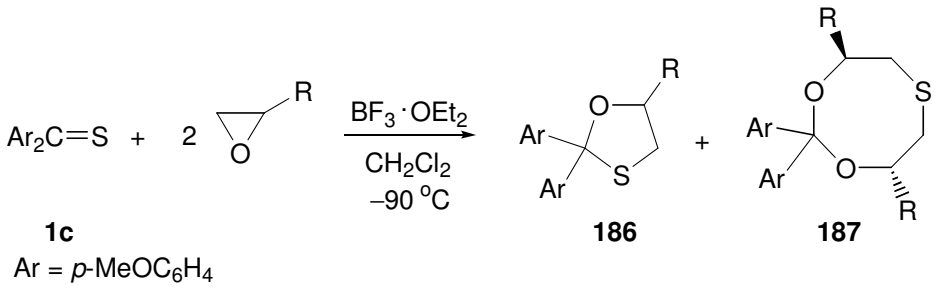
The thionation of thioketones **6** with S_8 in 1,3-dimethylimidazolidin-2-one (DMI) affords, along with pentathianes **165** (Chapter 3.3.3.), variable amounts of hexathiepanes **184** (Scheme 64).[133] The ratio **165/184** is 1:5 in the case of R = ^{t}Bu and 20:1 with R = 1-adamantyl. Small amounts of **184** (R = 1-adamantyl) are also obtained when the hydrazone **185** was treated with S_2Cl_2 at low temperature.[134]



6 R = ^{t}Bu, 1-Adamantyl **184** **185**

Scheme 64

As mentioned in Chapter 2.4.2., the Lewis-acid catalyzed reaction of oxiranes with aromatic thioketones offers a straightforward access to 1,3-oxathiolanes. In experiments, which have been carried out at low temperature, 1,3,6-dioxathiocanes are obtained in yields up to 10% (Scheme 65).[65,66a] In the case of R = Me, the ratio **186/187** is determined to be 2:1.



1c

Ar = *p*-$MeOC_6H_4$

186 **187**

Scheme 65

5. Conclusions

Aromatic thioketones are versatile dipolarophiles for the synthesis of a variety of five-membered sulfur heterocycles. They can also be employed for the *in situ* generation of reactive so-called '*S*-centered' 1,3-dipoles such as thiocarbonyl *S*-ylides, *S*-sulfides, and *S*-imides, which subsequently react with suitable dipolarophiles to provide five-membered heterocycles with a variable number of S-atoms. Furthermore, aromatic thioketones can be used in hetero-Diels-Alder chemistry either as very reactive heterodienophiles or as heterodienes. The reviewed results strongly underline that the synthesis of S-heterocycles with different ring size up to eight atoms is possible.

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ORGANOPHOSPHORUS REAGENTS AS A VERSATILE TOOL IN THE SYNTHESIS OF α-ALKYLIDENE-γ-BUTYROLACTONES AND α-ALKYLIDENE-γ-BUTYROLACTAMS

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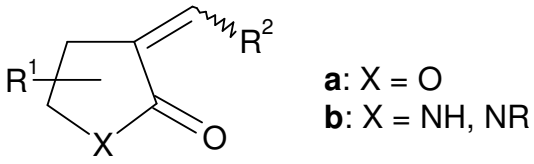
Abstract. *α-Alkylidene-γ-butyrolactones and α-alkylidene-γ-butyrolactams are a very important group of natural products and exhibit a wide spectrum of biological activities. Their occurrence in nature, biological activity and mode of action are briefly described. The majority of the review is devoted to synthetic methods leading to α-alkylidene-γ-butyrolactones and α-alkylidene-γ-butyrolactams in which organophosphorus reagents are employed. Different techniques used for the construction of alkylidene moiety via the Wittig or Horner-Wadsworth-Emmons olefination as well as different approaches to the synthesis of organophosphorus olefinating reagents of needed structure are presented.*

Contents

1. Introduction

The α-alkylidene-γ-butyrolactone (3-alkylidenedihydrofuran-2-one) **1a** and α-alkylidene-γ-butyrolactam (3-alkylidenepyrrolidin-2-one) **1b** rings (Figure 1) are integral building blocks of many natural products, mainly sesquiterpenes, which exhibit a wide spectrum of biological activities.

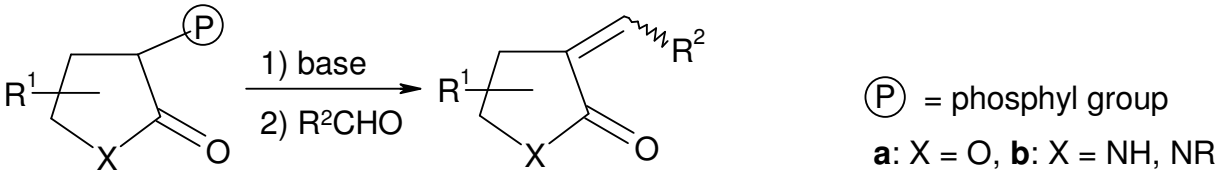


1a,b

Figure 1

Numerous methods of the synthesis of α-alkylidene-γ-butyrolactones **1a** have been corroborated so far. Several reviews are available.[1-3] However, the most recent one was published in 1986. α-Alkylidene-γ-butyrolactams **1b**, which are much less abundant in nature, haven't received that much attention so far and no review has been published describing synthetic methods leading to their preparation.

To at least partially fill the gap, in this review we focus on the synthetic methods leading to the title compounds in which organophosphorus reagents **2a,b** were employed. These reagents have recently emerged as a very convenient and versatile tool for the introduction of the alkylidene bond onto lactone or lactam ring *via* the Wittig type reaction (Scheme 1). Their limited availability however, remains a major drawback. Therefore the emphasis of this review is placed on the construction of the organophosphorus reagents of the desired structure.



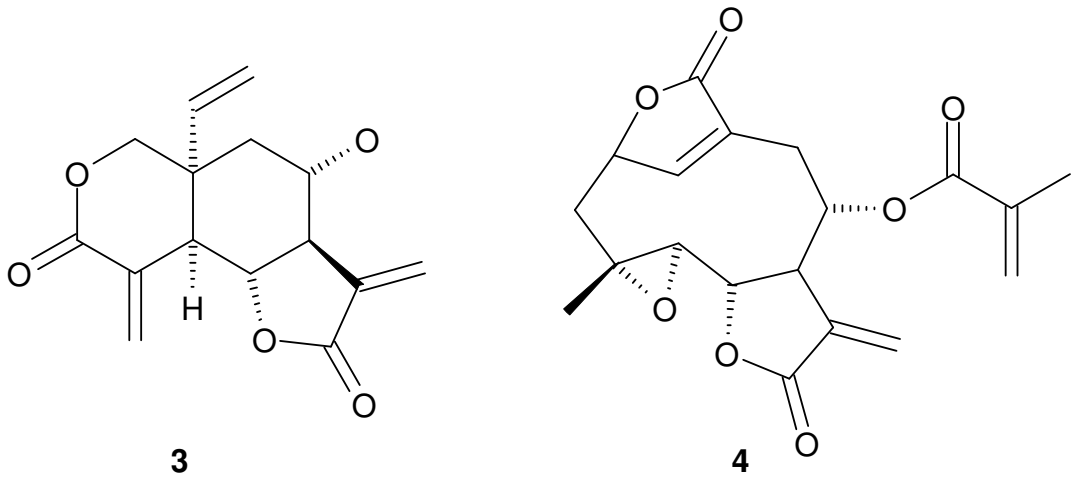
2a,b **1a,b**

Scheme 1

In the next chapter the occurrence and biological properties of α-alkylidene-γ-butyrolactones **1a** and α-alkylidene-γ-butyrolactams **1b** are very briefly described. In chapter 3, the various concepts of their synthesis employing organophosphorus reagents are presented.

2. Occurrence and biological activity

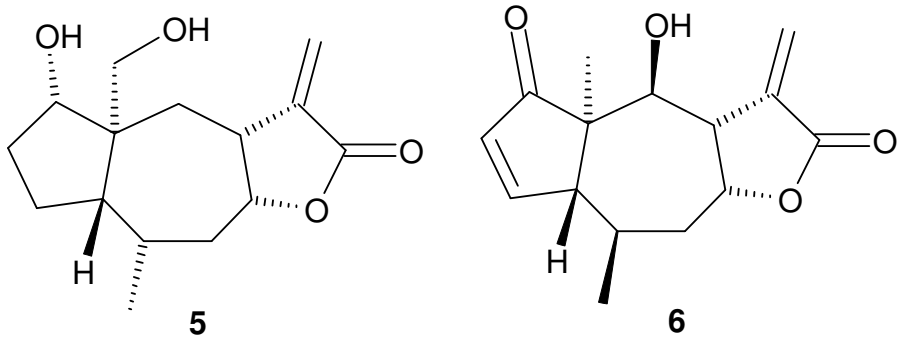
α-Alkylidene-γ-butyrolactones **1a** are widely distributed in nature. Especially interesting are α-methylidene-γ-butyrolactones and among them sesquiterpene lactones, which can be found in plants from *Compositae* family and also in several sea invertebrates. Their cytotoxic, allergenic, fungicidal, phytotoxic, antiinflammatory and antimicrobial properties make them an interesting group of potentially useful compounds. Relatively high cytotoxic activity was found for vernolepin **3**[4] and elefantopin **4**[5] (Figure 2) which were isolated in the 1960s from *Vernonia hymenolepis*[6] and *Elephantopus elatus*,[7] respectively.



3 **4**

Figure 2

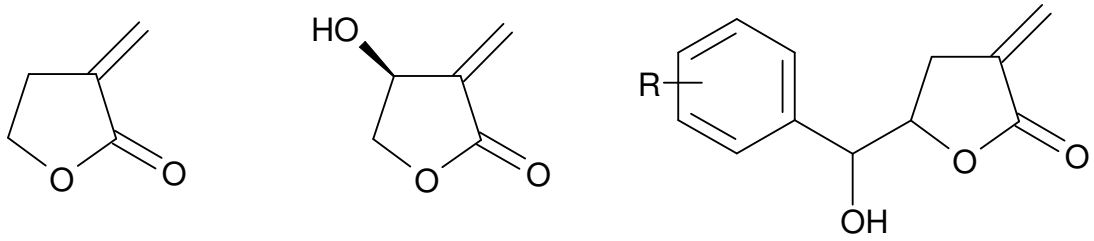
Rudmollin **5** obtained from cones of the pine tree *Rudbeckia mollis*[8] and helenalin **6** (Figure 3) isolated from the sunflower, *Helianthus annuus*,[9] elicit strong cytotoxic activity *in vitro* on neoplastic cells.[8,10] Helenalin additionally induces antibacterial and fungicidal activity.[11]



5 **6**

Figure 3

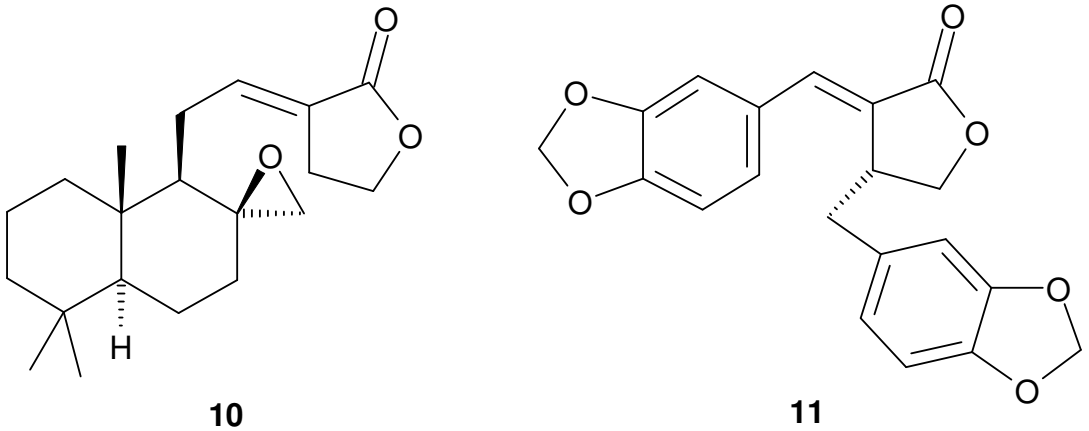
Some compounds with a much simpler chemical structure than those mentioned above can also produce strong biological effects. For example tulipalin A **7** and tulipalin B **8** isolated from *Tulipa gesneriana*[12] possess strong fungicidal properties.[13] Furthermore, simple, synthetic γ-arylhydroxymethyl-α-methylidene-γ-butyrolactones **9** exhibit significant cytotoxicity (Figure 4).[14,15]



7 **8** **9**

Figure 4

Also, γ-butyrolactones with the alkylidene substituent in the α position, such as galanolactone **10**,[16] a diterpene obtained from *Alpinia galanga* seeds and savinin **11**[17] display strong anticancer and fungicidal properties (Figure 5).

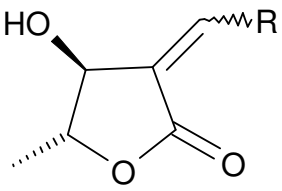


10 **11**

Figure 5

An interesting group of compounds, both in terms of antitumor activity and the variety of naturally occurring stereoisomers, are 3-alkylidene-4-hydroxy-5-methyldihydrofuran-2-ones, which are characteristic for plants from the *Lauraceae* family. A series of litsenolides **12a-c** of this structure was isolated from leaves of *Litsea japonica*.[18] These compounds have the 4*S*,5*R* configuration, whereas the olefin bond has *E* or *Z*

geometry. Litseakolide B (*E*)-**12d** and litseakolide A (*E*)-**12e** were isolated from the bark of an evergreen Taiwan tree *Litsea akoensis.*[19] On the other hand (*E*) and (*Z*)-(4*S*,5*S*)-3-alkylidene-4-hydroxy-5-methyldihydrofuran-2-ones **13a-c** are present in the bark of a Brazilian tree *Clinostemon mahuba* (Figure 6).[20]



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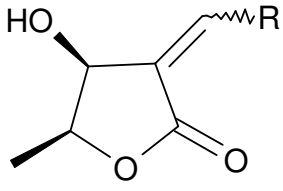


13

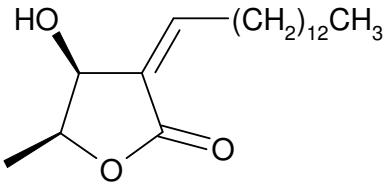
a: R = $(CH_2)_{10}CH_3$
b: R = $(CH_2)_9CH{=}CH_2$
c: R = $(CH_2)_{11}C{\equiv}CH$
d: R = $(CH_2)_9CH{=}CH{-}CH{=}CH_2$
e: R = $(CH_2)_9CH{=}CH{-}CHO$

a: R = $(CH_2)_{10}CH_3$
b: R = $(CH_2)_9CH{=}CH_2$
c: R = $(CH_2)_{11}C{\equiv}CH$

Figure 6

New alkylidenelactones are continuously isolated from natural sources and characterized. Some recent examples are epilitsenolide C_1 **14** from *Aiouea trinervis*,[21] andropanolide **15** from *Andrographis paniculata*[22] or luffarin **16** from the Sea sponge *Fasciospongia carvernosa* (Figure 7).[23]

2-Methyl-4-methylideneisoxazolidin-5-ones **17**, a new class of unnatural α-methylidene-γ-lactones exhibiting high cytotoxic activity, also deserves mentioning (Figure 7).[24]



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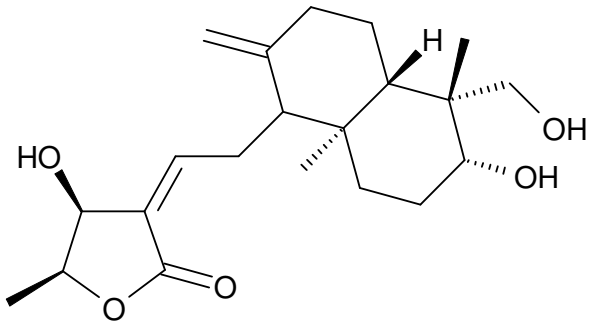

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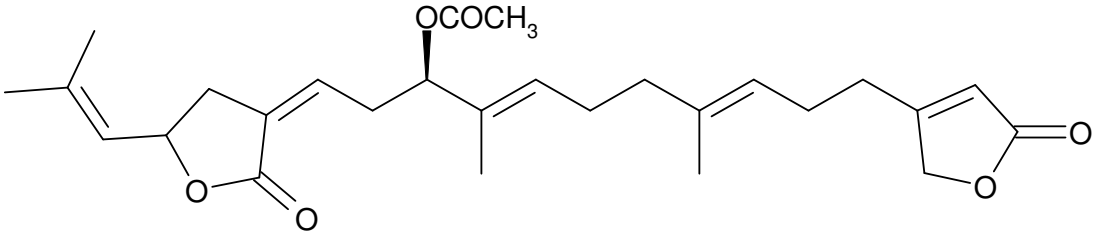

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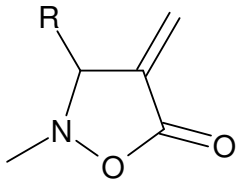
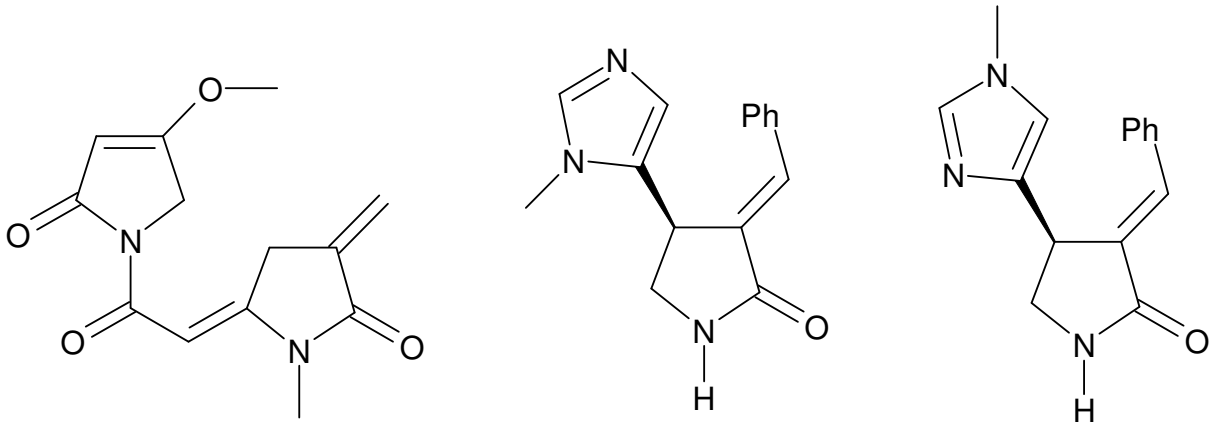


17

Figure 7

α-Alkylidene-γ-butyrolactams **1b** are much less common in nature than α-alkylidene-γ-butyrolactones **1a**. One example of naturally occurring α-alkylidene-γ-butyrolactam is pukeleimid E **18** isolated from the

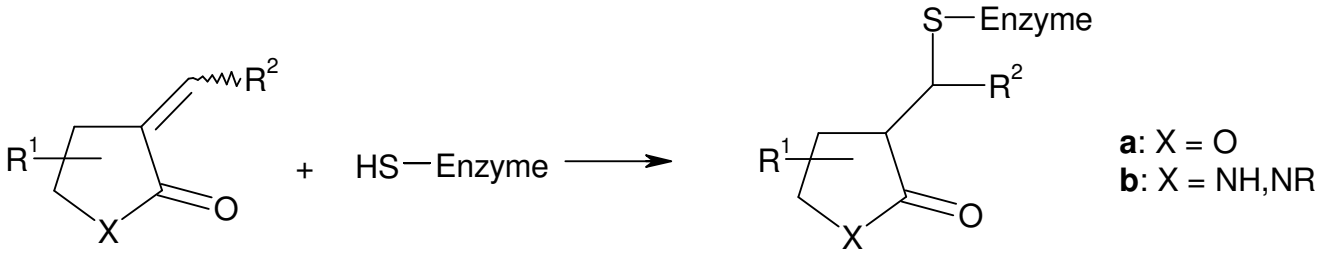
cyanobacteria *Lyngbya* majuscule.[25] Two imidazole alkaloids, anantin **19** and isoanantin **20** were found in leaves of *Cynometra*, a plant used in African folk medicine as a remedy for pain (Figure 8).[26]



18 **19** **20**

Figure 8

Numerous studies revealed that biological activity of natural products containing α-alkylidene-γ-butyrolactone **1a** or α-alkylidene-γ-butyrolactam **1b** rings is associated with the presence of α,β-unsaturated ester or amide groups, which are Michael acceptors in the reaction with mercapto groups of bionucleophiles[27] (Scheme 2).



1a,b **21a,b**

Scheme 2

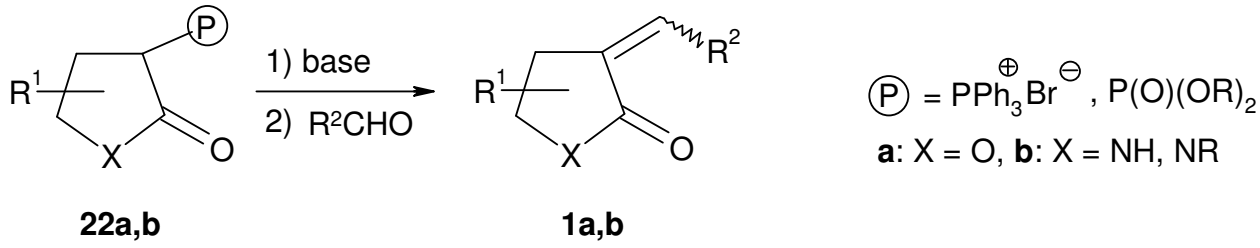
This mechanism can be further confirmed by the observation that α-alkylidene-γ-butyrolactones show much higher cytotoxicity than their nitrogen analogues[28,29] which are less effective Michael acceptors. Cytotoxicity of these compounds is also influenced by the presence of functional groups increasing lipophilicity, and also hydroxy, alkoxy or amino groups, especially in the vicinity of the olefin bond, which can induce a reaction with thiols.[30-32] Furthermore, light-activated 2 + 2 additions of α-alkylidene-γ-lactones to the DNA base, thymine,[33] as well as their role as inhibitors of the transcription factor NF-κB[34] have been recently described.

3. Syntheses of α-alkylidene-γ-butyrolactones and α-alkylidene-γ-butyrolactams *via* Wittig type reactions

As it was mentioned in the introduction the Wittig type reactions provide a very useful technique of the construction of the alkylidene bond in α-alkylidene-γ-butyrolactones and γ-butyrolactams. For the clarity of

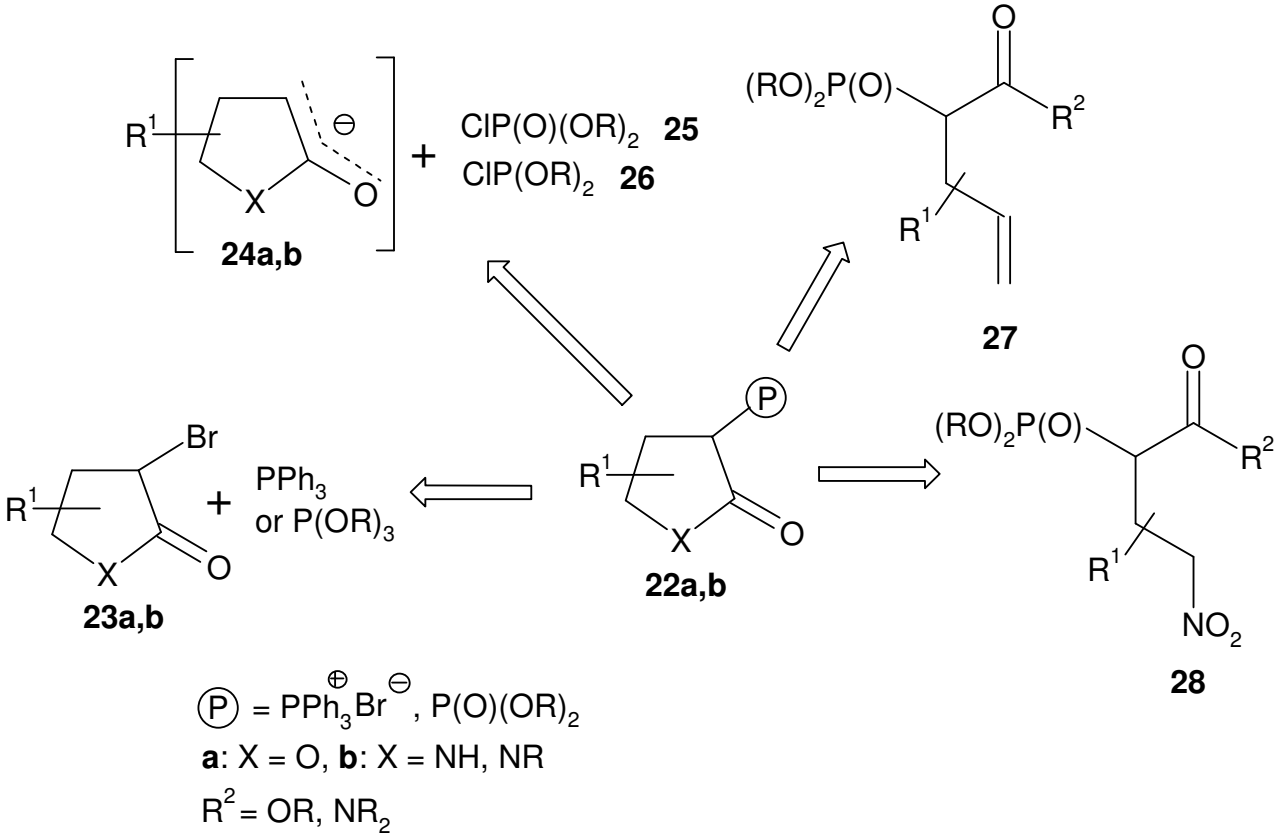
description, from now on, these compounds will be named according to the systematic nomenclature, *i.e.* as 3-alkylidenedihydrofuran-2-ones or 3-alkylidenepyrrolidin-2-ones, respectively.

3-Phosphylated tetrahydrofuran-2-ones **22a** and pyrrolidin-2-ones **22b** can react in the presence of bases with aldehydes producing, after the elimination of phosphine oxide (Wittig reaction) or phosphate (Horner-Wadsworth-Emmons reaction), 3-alkylidenedihydrofuran-2-ones **1a** or 3-alkylidenepyrrolidin-2-ones **1b** (Scheme 3).



22a,b **1a,b**

Scheme 3



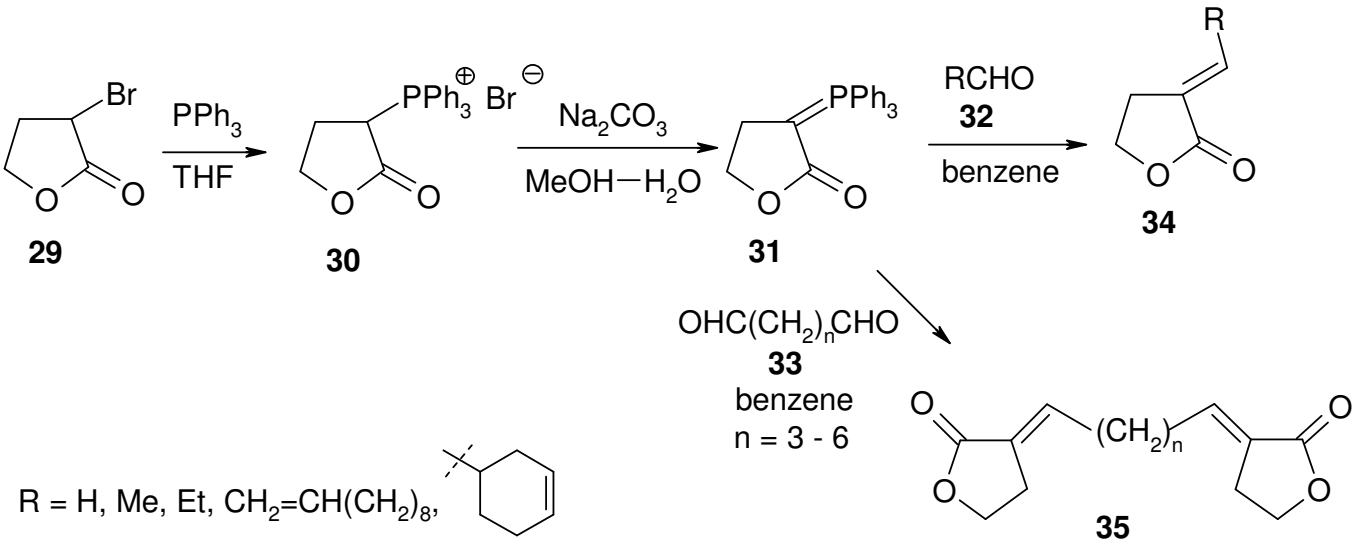
Scheme 4

In general, phosphonium salts or phosphonates **22a,b** required for the Wittig or Horner-Wadsworth-Emmons (HWE) olefination respectively, can be conveniently obtained in the reaction of 3-bromotetrahydrofuran-2-ones **23a** or 3-bromopyrrolidinones **23b** with triphenylphosphine or trialkyl phosphites, as well as in the reaction of enolates **24a,b** with dialkyl chlorophosphates **25** or chlorophosphites **26** (Scheme 4). 3-Dialkoxyphosphoryltetrahydrofuran-2-ones **22a** were also prepared from esters and amides **27** or nitroesters **28**. Some miscellaneous methods have also been described.

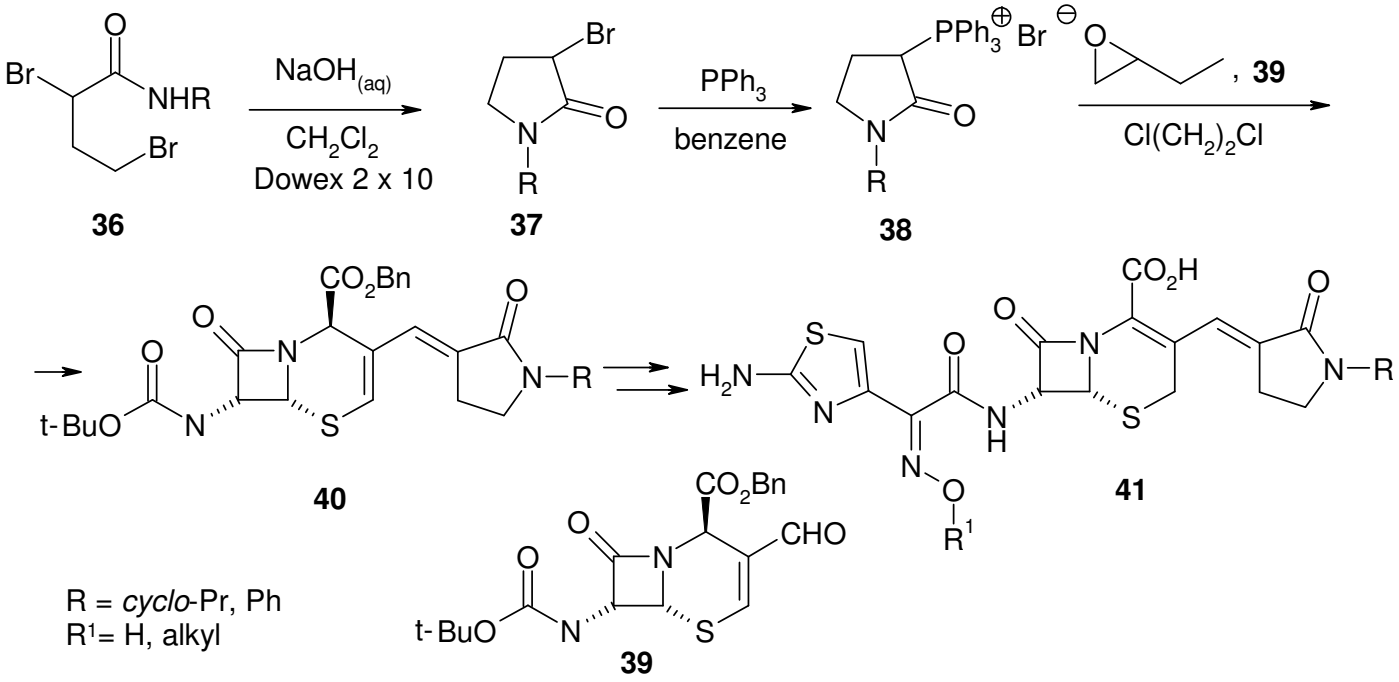
In the next two chapters, the most representative of these methods will be systematically presented, together with the application of the organophosphorus reagents **22a,b** in the Wittig or HWE reaction.

3.1. Syntheses of α-alkylidene-γ-butyrolactones and α-alkylidene-γ-butyrolactams *via* the Wittig reaction

The Wittig reaction was the first which was used to introduce the alkylidene group onto the dihydrofuran-2-one ring. In 1965 Zimmer and Pampalone[35] described the synthesis of substituted 3-benzylidenedihydrofuran-2-ones and in 1974 Grieco and Pogonowski[36] reported a near-quantitative yield of 3-methylidenedihydrofuran-2-one starting from the corresponding 3-(triphenylphosphanylidene) dihydrofuran-2-ones and benzaldehyde or paraformaldehyde, respectively. Also, in 1974 Howie *et al.*[37] performed a sequence of reactions in which triphenylphosphonium salt **30**, obtained from 3-bromotetrahydrofuran-2-one **29** and triphenylphosphine, was converted into ylid **31** which reacted with various aldehydes **32** or dialdehydes **33** (Scheme 5). The olefin bond in the formed 3-alkylidene-dihydrofuran-2-ones **34** and **35** was of the *E*-configuration when the reaction was performed in benzene or DMF.



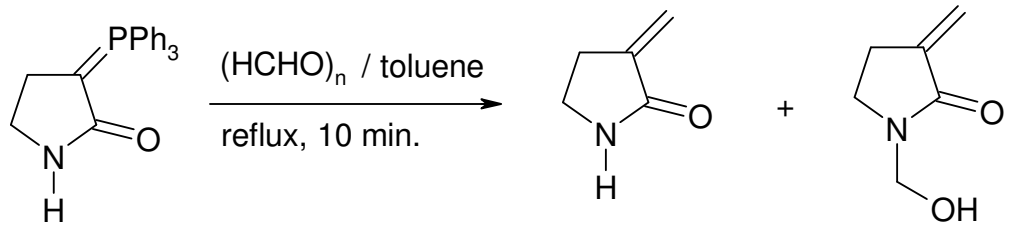
Scheme 5



Scheme 6

Later on, this approach was often used for the synthesis of 3-alkylidenedihydrofuran-2-ones,[38,39] as well as 3-alkylidenepyrrolidin-2-ones.[40-42] For example, Heinze-Krauss *et al.*[41] converted bromopyrrolidinones **37** (obtained from 2,4-dibromopentanoic acid amides **36**) into phosphonium salts **38**, which were allowed to react with aldehyde **39** in the presence of 1,2-epoxybutane, affording olefines **40** with high *E*-selectivity (>95%). Next, these compounds were transformed into γ-lactamyl-(*E*)-vinyl-cephalosporins **41** which exhibited excellent activity against Gram-positive and Gram-negative microbes (Scheme 6).

It should be noted that in the reaction of formaldehyde with ylid **42**, containing an unprotected amide group, N-hydroxymethylene-3-methylidenepyrrolidin-2-one **44** can be formed as a by-product (Scheme 7). Buono *et al.*[42] noticed also that when a three-fold molar access of formaldehyde was used, pyrrolidinone **44** could be obtained with 71% yield.

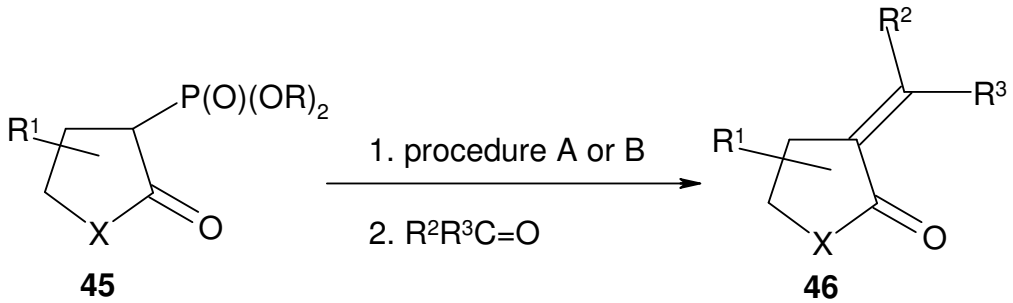


42 **43** **44**

Scheme 7

3.2. Syntheses of α-alkylidene-γ-butyrolactones and α-alkylidene-γ-butyrolactams *via* the Horner-Wadsworth-Emmons reaction

With time, the Wittig technique of the construction of the alkylidene bond in tetrahydrofuran-2-ones and pyrrolidin-2-ones was replaced by HWE methodology. This methodology proved to be more efficient, simple and cheaper than the Wittig approach. Two main procedures were applied to perform the HWE olefinations (Scheme 8).



45 **46**

A: NaH, benzene, toluene or THF X = O, NH

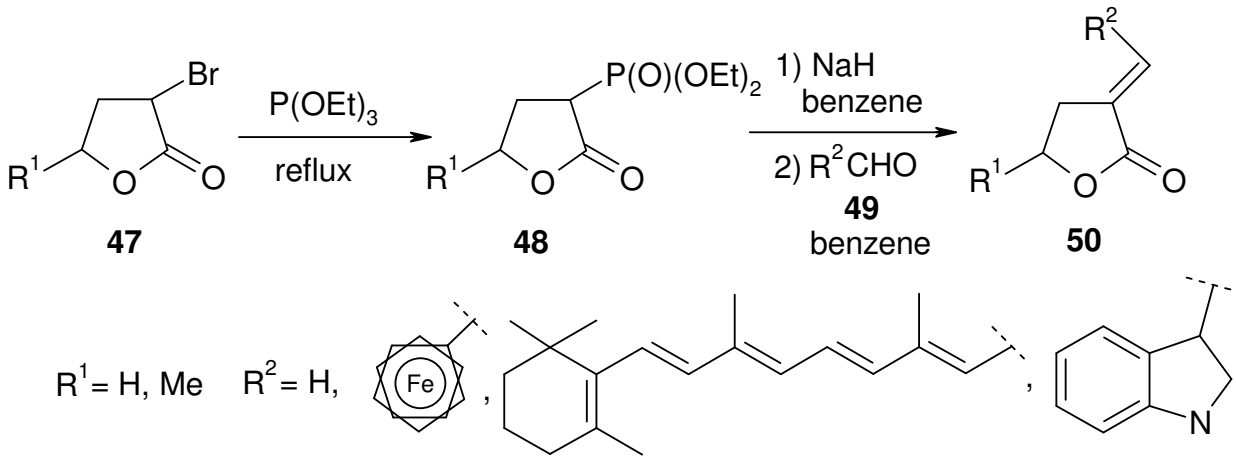
B: K_2CO_3, H_2O or H_2O/THF X= O

Scheme 8

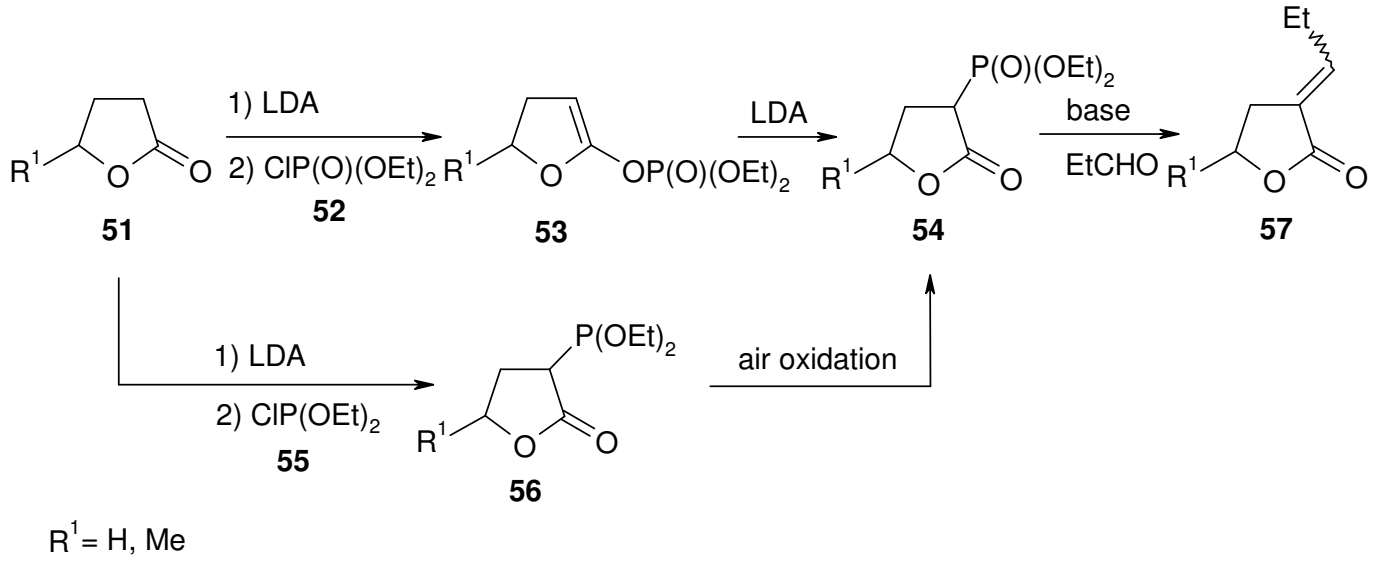
In the first procedure sodium hydride is used as a base in benzene,[43-45] toluene[46,47] or THF[48-50] at elevated or room temperatures. It is worth stressing that this procedure is also suitable for the synthesis of 3-methylidenepyrrolidin-2-ones.[51,52] The second procedure, introduced by Villieras and co-workers,[53,54] is especially worth noting for its mild conditions which allow it to be used for the synthesis of 3-alkylidene-

dihydrofuran-2-ones which cannot tolerate strongly basic conditions and high temperatures. In this method sodium hydride is replaced by potassium carbonate, 36% formalin is used as the source of formaldehyde and the reaction is carried out at 0-5 °C. Other aldehydes,[55,56] as well as acetone,[56] were also successfully olefinated in these conditions. Comparative studies of the two procedures mentioned above were also performed.[57] Furthermore, the influence of various conditions (bases, solvents and temperatures) on stereoselectivity of the HWE reaction was studied.[58]

As it was mentioned in the introduction, the main restriction in the application of the HWE reaction in the construction of the alkylidene bond is not the reaction itself but the limited availability of the starting phosphonates **45** of suitable structure. The first method, applied for the synthesis of these compounds, was the Arbuzov reaction. In 1983 Falsone and Spur[45] obtained 3-diethoxyphosphoryltetrahydrofuran-2-ones **48** by the reaction of 3-bromotetrahydrofuran-2-ones **47** with triethylphosphite (Scheme 9). Organophosphorus reagents **48** were next used in the olefination of the aldehydes **49**, which was performed in boiling benzene in the presence of sodium hydride, to give 3-alkylidenedihydrofuranones **50** in good yields (>85%) and high (*E*) selectivity (>92%).



Scheme 9

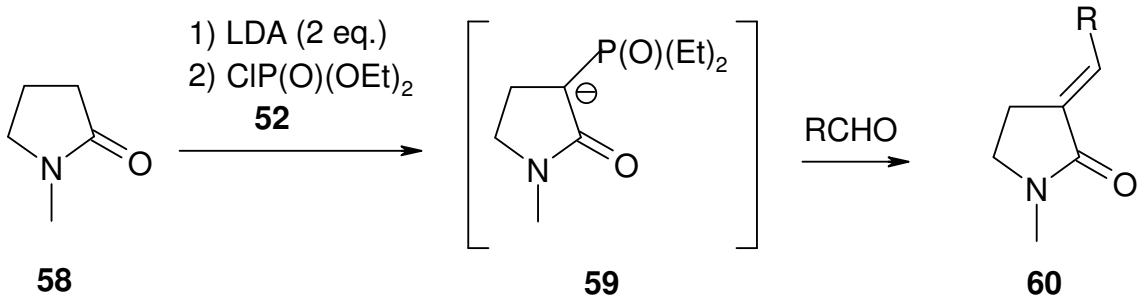


Scheme 10

An alternative synthesis of 3-dialkoxyphosphoryltetrahydrofuran-2-ones was proposed by Wiemer *et al.*[59] in 1989. This method was based on the reaction of enolates, generated from tetrahydrofuran-2-ones **51**,

with chlorophosphates **52**, and yielded vinylphosphates **53**. The rearrangement of vinylphosphates **53** in basic conditions led to 3-dialkoxyphosphoryltetrahydrofuran-2-ones **54** (Scheme 10). Later on, the same authors proposed a modified approach to the synthesis of **54**, in which the same enolates reacted with diethyl chlorophosphite **55** followed by air oxidation of thus formed phosphites **56** (Scheme 10).[60] Reported yields for both methods were good and, more recently, products **54** were used as HWE reagents for the olefination of propionaldehyde, affording mixtures of (*E*) and (*Z*)-3-propylidenedihydrofuran-2-ones **57** in different ratios depending on the temperature, base, and solvent used.[61]

Savignac *et al.*[62] performed a similar reaction sequence starting with *N*-methylpyrrolidin-2-one (**58**). Reaction of **58** and diethyl chlorophosphate **52** in the presence of two equivalents of LDA, gave an enolate anion of 1-methyl-3-diethoxyphosphorylpyrrolidin-2-one **59** (Scheme 11). The formed anion **59** reacted stereoselectively with aromatic aldehydes, yielding (*E*)-3-arylidenepyrrolidin-2-ones **60**.



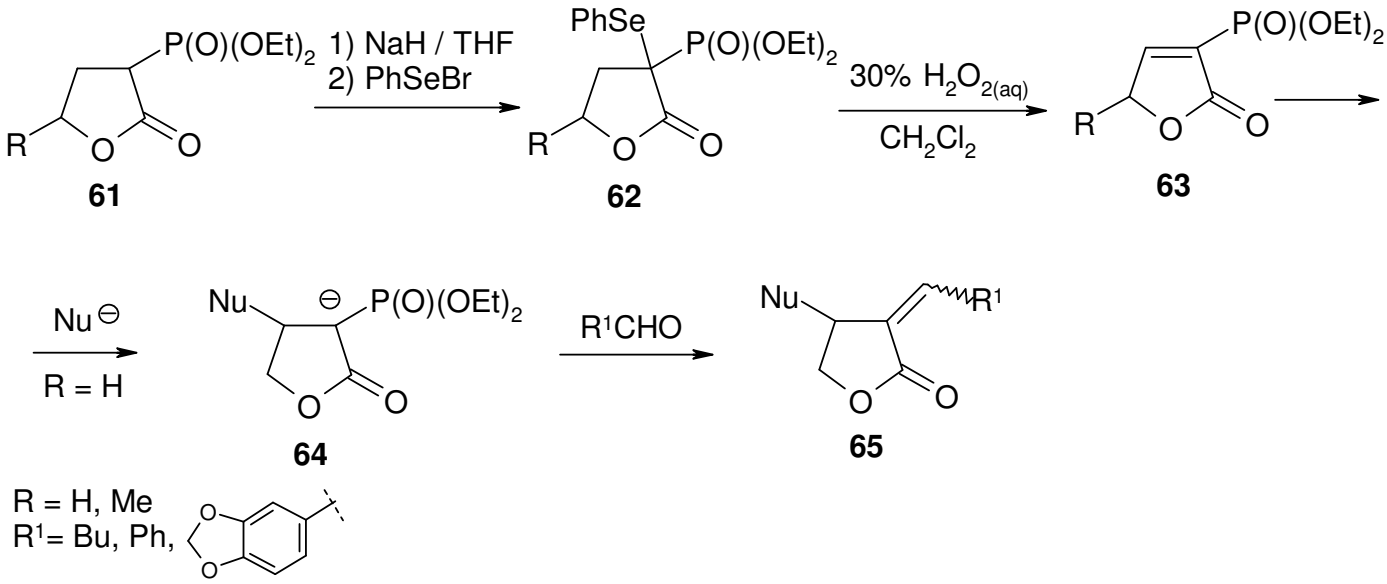
58 **59** **60**

R = 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 11

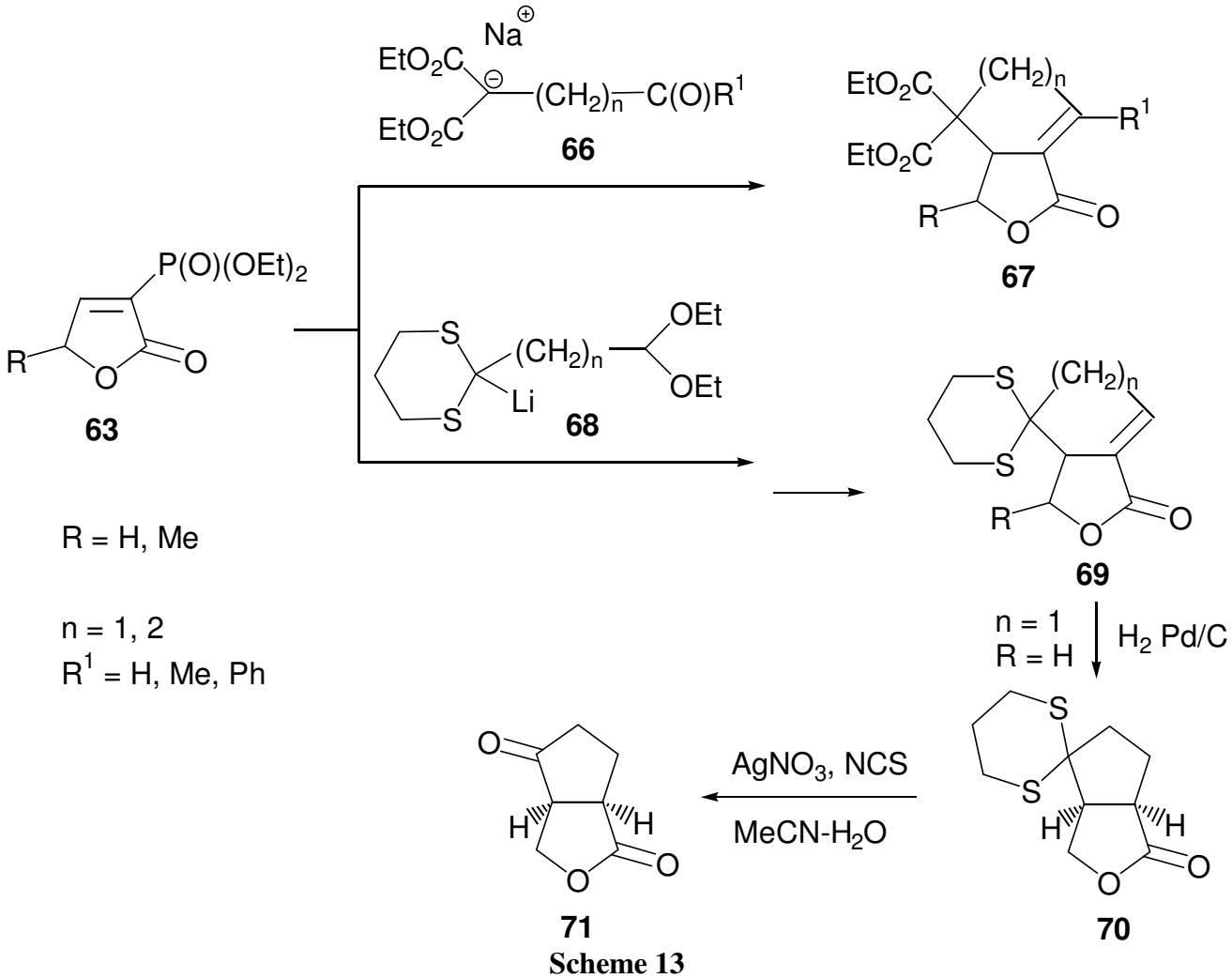
A new approach to HWE reagents of more diverse structure, based on the functionalization of simple 3-diethoxyphosphoryltetrahydrofuran-2-ones **61**, has been proposed by Minami *et al.*[63] This functionalization was achieved through the conversion of **61** into 3-diethoxyphosphoryldihydrofuran-2-ones **63** by phenylselenylation of the corresponding 3-diethoxyphosphoryltetrahydrofuran-2-one anions to afford **62** and the subsequent oxidative elimination of the phenylselenyl residue (Scheme 12). Dihydrofuranones **63** are excellent Michael acceptors and can react with various nucleophiles to give adducts **64** which can be used directly in the HWE olefination. Thus, the reaction of nucleophiles such as lithium *tert*-butyl acetate, lithium dibutyl cuprate, benzylmagnesium chlorides or piperonylmagnesium chloride with 3-diethoxy-phosphoryldihydrofuran-2-one **63** (R = H) gave phosphonate carboanions **64** which were trapped with butanal or aromatic aldehydes to yield corresponding 3-alkylidenetetrahydrofuran-2-ones **65** (Scheme 12).

The same authors[64,65] performed a reaction of 3-diethoxyphosphoryldihydrofuran-2-ones **63** with sodium derivatives of diethyl 2-oxoalkyl- and 3-oxoalkylmalonate **66** which yielded diethyl 1-oxodihydrocyclopenta[c]furan-4,4-dicarboxylates **67** (n = 1) or diethyl-1-oxotetrahydroisobenzofuran-4,4-dicarboxylates **67** (n = 2) , respectively (Scheme 13). The same substrates **63** when reacted with lithium derivatives of 2-alkyldithianes **68** containing the masked carbonyl moiety provided the corresponding Michael adducts. Deprotection of the masked carbonyl group, followed by the HWE reaction led to tetrahydrocyclopenta[c]furan-1-ones **69** (n = 1) or tetrahydroisobenzofuran-1-ones **69** (n = 2), respectively. Hydrogenation of **69** (n = 1, R = H) and subsequent hydrolysis of hexahydroisobenzofuran-1-one **70** led to cyclosarkomycin **71** in good yield.



NuY = $LiCH_2CO^2$*tert*-Bu, Bu_2CuLi, $PhCH_2MgCl$, 3,4-$(OCH_2O)C_6H_3CH_2MgCl$, 3,4-$(MeO)_2C_6H_3CH_2MgCl$

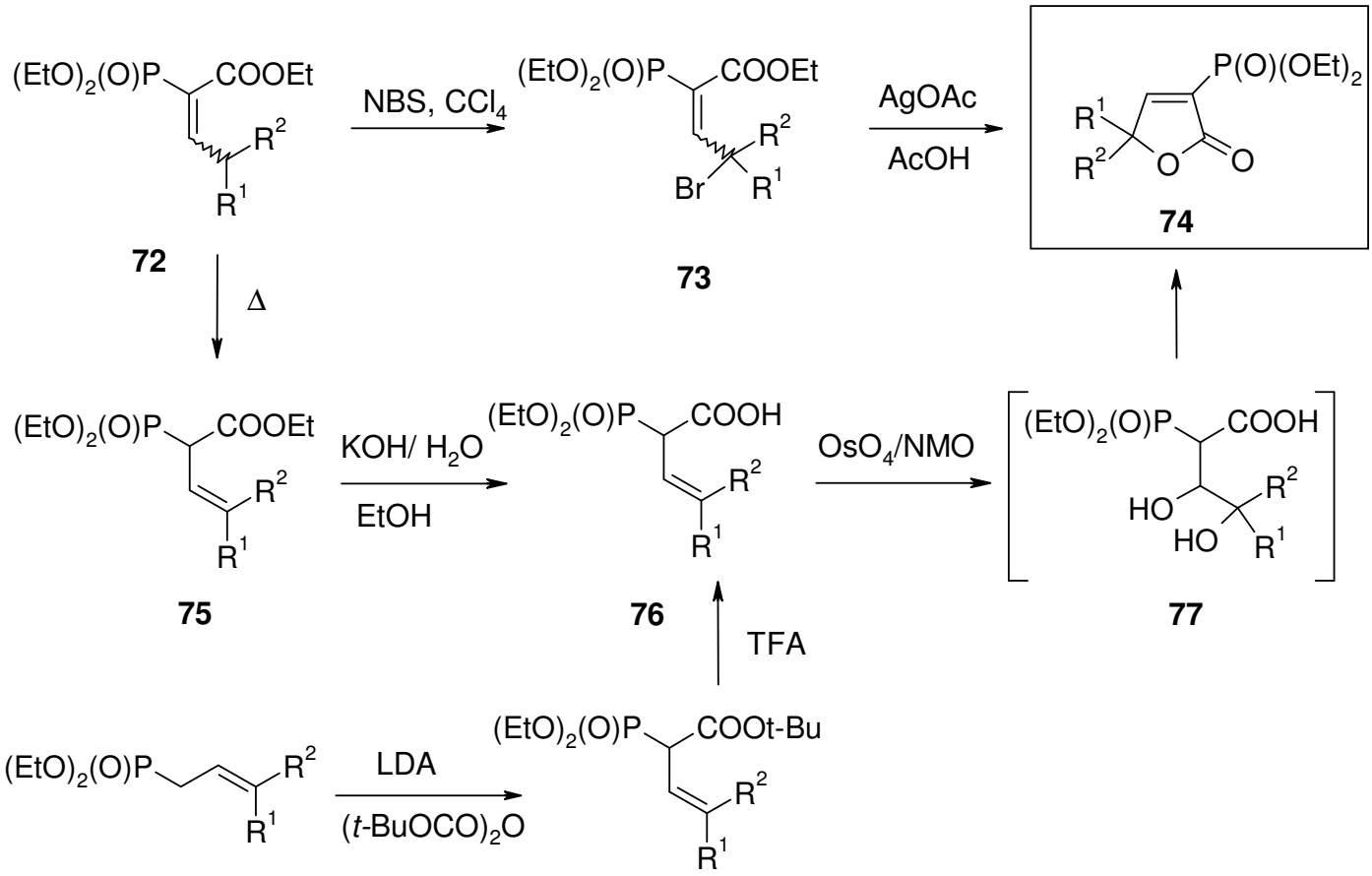
Scheme 12



Scheme 13

Dihydrofuran-2-ones **63** proved to be very efficient Michael acceptors and therefore very useful precursors of the HWE reagents. However, their availability was restricted to simple 3-diethoxyphosphoryldihydrofuran-2-one **63** (R = H) and its 5-methyl homologue **63** (R = Me).

This availability was significantly broaden when Janecki *et al.*[66] described two new and general methods for the synthesis of mono- and disubstituted 3-diethoxyphosphoryl-2,5-dihydrofuran-2-ones **74** from easily accessible 2-diethoxyphosphoryl-2-alkenoates **72** or 2-diethoxyphosphoryl-3-alkenoic acids **76** (Scheme 14).



R^1 = Me, Pr, Ph

R^2 = H, Me

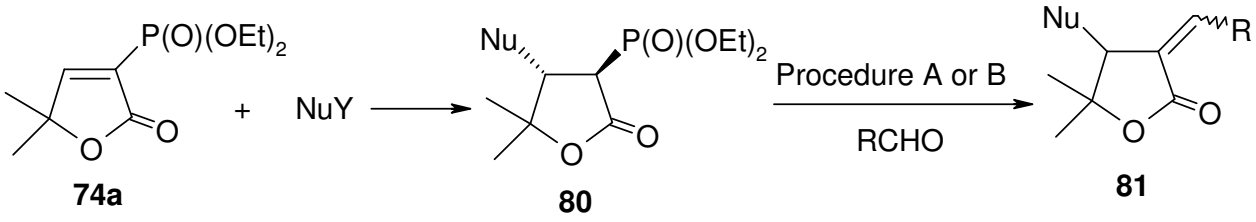
R^1----R^2 = -$(CH_2)_5$-

Scheme 14

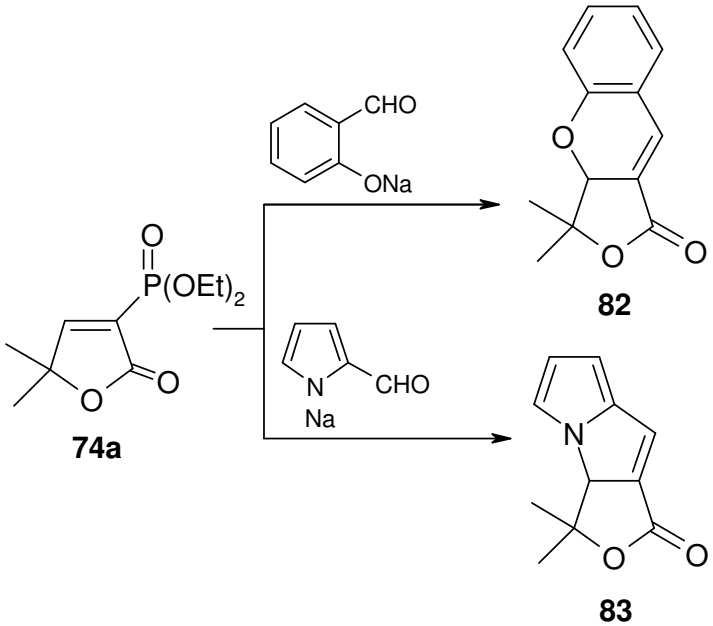
The first method involved an allylic bromination of 2-alkenoates **72** using *N*-bromosuccinimide and subsequent treatment of the crude allylic bromides **73** with silver acetate in acetic acid. The final 3-diethoxyphosphoryl-2,5-dihydrofuran-2-ones **74** were obtained in good to excellent yields. Substrates **72** were prepared by the Knoevenagel condensation of ethyl phosphonoacetate with appropriate aldehydes in the presence of a catalytic amount of acetic acid and piperidine. The key step in the synthetic protocol of the second method is *syn*-hydroxylation of 2-diethoxyphosphoryl-3-alkenoic acids **76** using the osmium tetroxide/*N*-methylmorpholine *N*-oxide system, which gave the diols **77**. The spontaneous lactonization and elimination of water from the crude **77** produced 3-diethoxyphosphoryldihydrofuran-2-ones **74** in good to excellent yields. The intermediate 3-alkenoic acids **76** were obtained in two ways: (a) from 2-alkenoates **72** by a thermally induced [1,5] sigmatropic shift followed by keto-enol tautomerization and chemoselective hydrolysis of the obtained 3-alkenoates **75** and (b) by the treatment of allyl phosphonates **78** with two

equivalents of LDA and then with di-*tert*-butyldicarbonate to yield *tert*-butyl 3-alkenoates **79**. The dealkylation of **79** with trifluoroacetic acid yielded 3-alkenoic acids **76**.

The same group performed systematic studies oriented on the scope and limitations of the reaction sequence involving the Michael addition of various nucleophiles to dihydrofuran-2-ones **74** and the subsequent transformation of the resultant products into substituted 3-alkylidenetetrahydrofuran-2-ones, *via* the HWE olefination.[57] Furanone **74a** ($R^1 = R^2 = Me$) was chosen as a model compound. Various Grignard reagents and other nucleophiles (see Scheme 15) were tested as Michael donors.



NuY = R^1MgX, O_2NCH_2Na, $(EtO(O)C)_2CHNa$, $(EtO)_2(O)PNa$
R = H, *i*-Pr, Ph

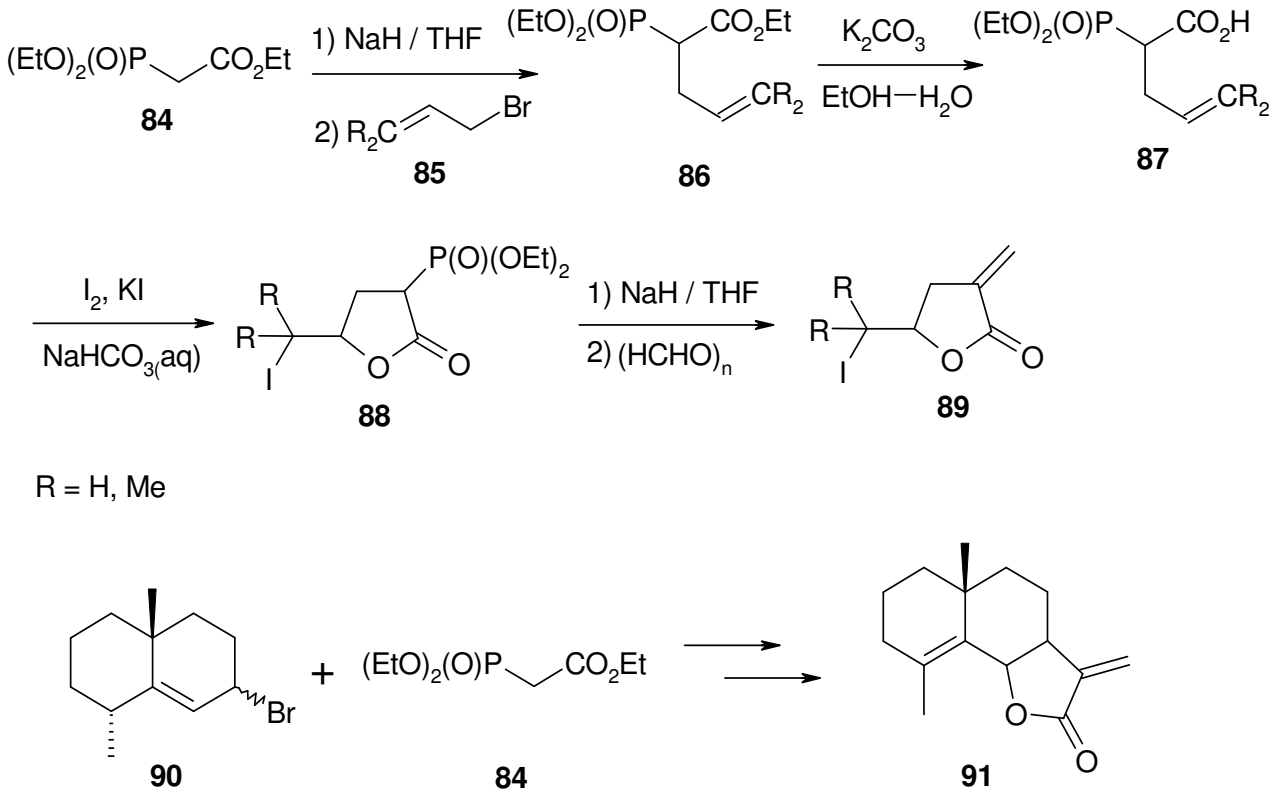


Scheme 15

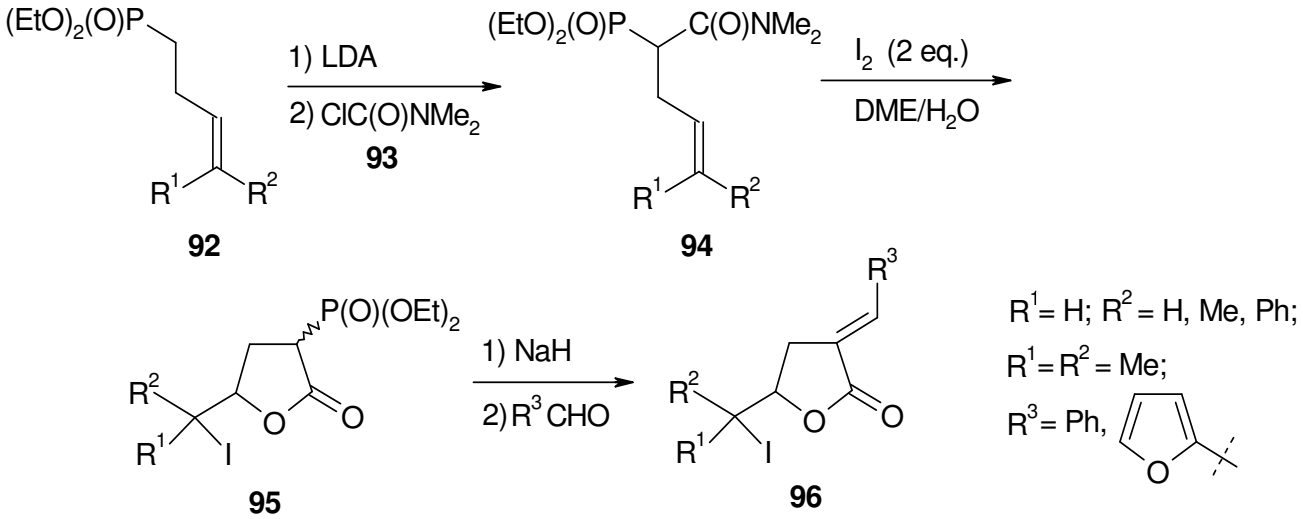
These Michael additions proved to be fully diastereoselective and all adducts **80** were obtained as single *trans*-isomers in good to excellent yield. Next, adducts **80** were transformed into 3-methylidene-tetrahydrofuran-2-ones **81**. Two procedures, commonly used for the olefination of formaldehyde, were tested. Adducts were treated with sodium hydride and paraformaldehyde in refluxing THF (procedure A), and with potassium carbonate and 36% formalin at 0-5 ^oC (procedure B). This latter procedure appeared to be more efficient and versatile. Olefinations of adducts **80** with aldehydes other than formaldehyde were also performed. Furthermore, furanone **74a** was subjected to a tandem Michael addition/olefination reaction. Thus, the treatment of **74a** with the sodium salts of salicylaldehyde or pyrrole-2-carboxyaldehyde gave the expected furochromenone **82** and furopyrrolizinone **83** in 33% and 52% yields, respectively.

Yet another method of the synthesis of 3-diethoxyphosphoryltetrahydrofuran-2-ones is based on the cyclization of esters and amides of 2-dialkoxyphosphoryl-4-alkenoic acids.

Minami *et al.*[48] used allyl bromides **85** for the alkylation of ethyl diethoxyphosphorylacetate **84** and obtained esters **86**. These esters, after hydrolysis to acids **87** followed by iodolactonization, were converted into 3-diethoxyphosphoryltetrahydrofuran-2-ones **88** (Scheme 16). The methylidenation of these furanones with formaldehyde produced 3-methylidenedihydrofuran-2-ones **89** in good yields. The treatment of the iodofuranones **88** with diazabicycloundecane (DBU) led to dehydroiodination products which were also used for the olefination of formaldehyde. Choosing 7-bromooctahydronaphthalene **90** and phosphonoacetate **84** as substrates the authors successfully applied this methodology to the synthesis of the natural product *frullanolide* **91**, which is an allergenically active sesquiterpene.



Scheme 16

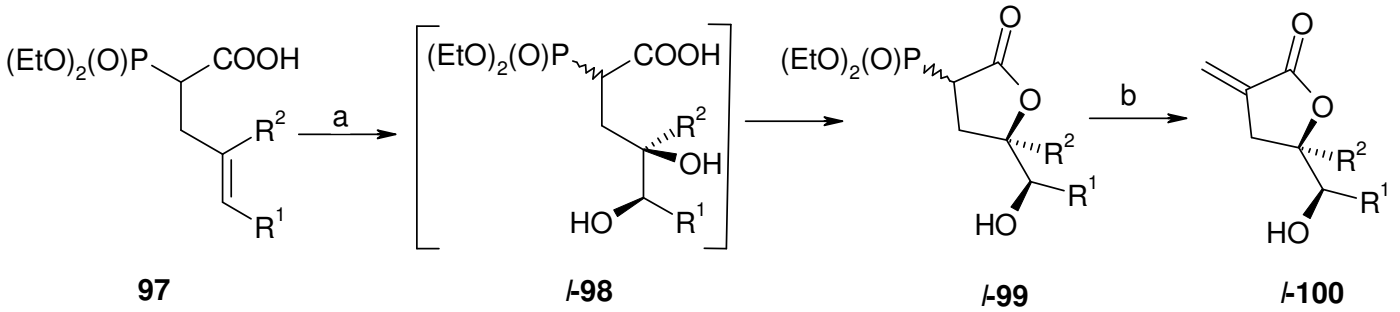


Scheme 17

Iodolactonization was also utilized by Oh *et al.*[50] in the synthesis of 3-arylideneiododihydrofuranones **96**. Homoallyl phosphonates **92** treated with LDA and then with *N,N*-dimethylchloroformamide **93** gave

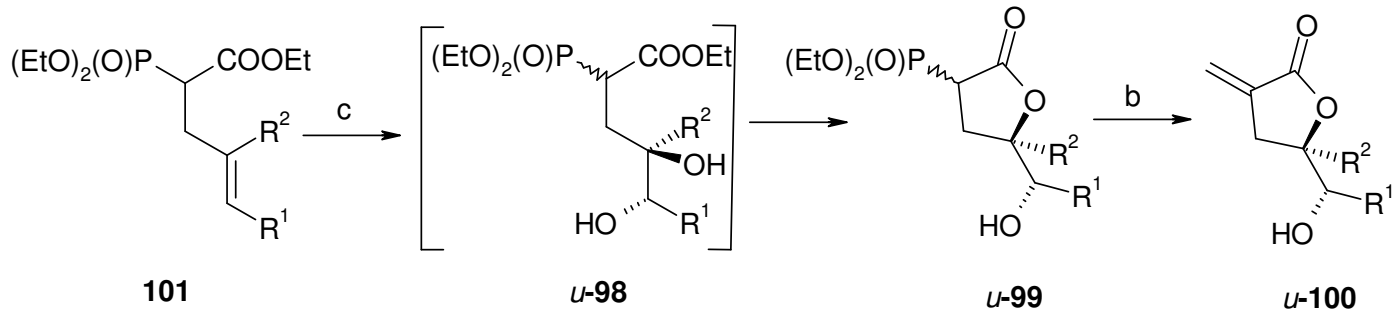
homoallyl amides **94** (Scheme 17). The hydrolysis of an amide group in **94** followed by iodolactonization produced 3-phosphorylated iodofuranones **95**, which reacted with aromatic aldehydes affording (*E*)-3-arylideneiododihydrofuran-2-ones **96** in very good yields.

On the other hand, Janecki and co-workers[15,67] developed an efficient and stereocontrolled route to a variety of *l*- and *u*-5-(1'-hydroxyalkyl)-3-methylidene-2-furanones **100** by a unique combination of *syn*- or *anti*-dihydroxylation of 2-diethoxyphosphoryl-4-alkenoic acids **97** or 2-diethoxyphosphoryl-4-alkenoates **101** and HWE olefination techniques (Scheme 18).



97 ***l*-98** ***l*-99** ***l*-100**

(a) OsO_4/NMO or AD-mix-α or AD-mix-β
(b) 36% formalin, K_2CO_3



101 ***u*-98** ***u*-99** ***u*-100**

(c) MCPBA then 30% $HClO_4$
(b) 36% formalin, K_2CO_3

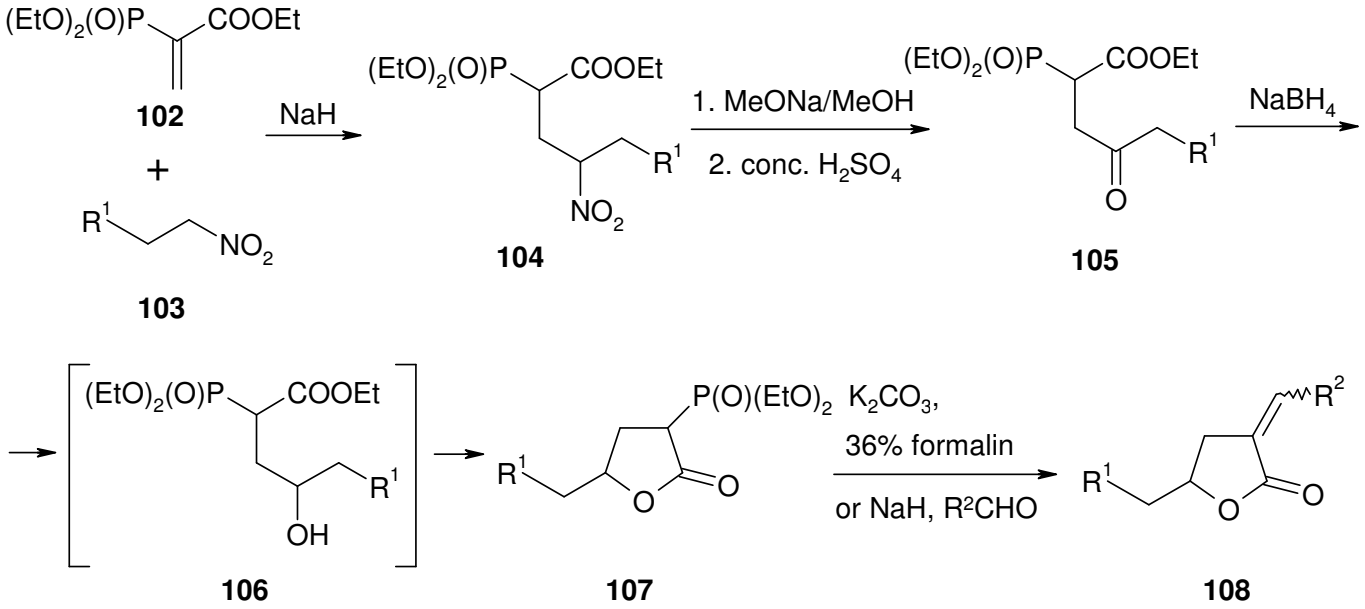
R^1 = H, Me, *n*-Pr, Ph, 4-F-C_6H_4, 4-MeO-C_6H_4, 1-naphtyl
R^2 = H, Me

Scheme 18

Completely diastereoselective *syn*-dihydroxylation of acids **97** was performed using OsO_4/*N*-methylmorpholine oxide protocol, whereas *anti*-dihydroxylation of alkenoates **101** was achieved by a standard reaction sequence involving oxidation with MCPBA, followed by the cleavage of epoxides with perchloric acid. Diols **98** formed in both these transformations, lactonized spontaneously to the desired furanones **99** possessing complementary stereochemistry. The olefination of formaldehyde using these furanones yielded a series of the target *l*- or *u*-3-methylidene-2-furanones **100** as defined diastereoisomers. The enantioselective synthesis of the same class of compounds was also realized using the commercially available Sharpless reagents (AD-mix-α and AD-mix-β) which were employed in *syn*-dihydroxylation reactions of the alkenoic acids **97**. The enantiomeric excesses and absolute configurations of optically active furanones *l*-**100** were determined by Mosher's esters method and the obtained *ee* varied from 20 to 95%.

A novel and quite general method of the synthesis of 5-substituted 3-alkylidenedihydrofuran-2-ones **108** in which 2-diethoxyphosphoryl-4-nitroalkanoates **104** are the key intermediates was also proposed by Janecki's group[51] (Scheme 19). Nitroalkanoates **104** were obtained in the Michael addition of nitroalkanes

103 to ethyl (2-diethoxyphosphoryl)acrylate **102**. The nitro functionality in nitroalkanoates **104** was converted into carbonyl group (Nef reaction) using mild oxidative conditions to give 2-diethoxyphosphoryl-4-oxoalkanoates **105**, usually in excellent yields. A chemoselective reduction of the carbonyl group in alkanoates **105** using $NaBH_4$ gave 4-hydroxyalkanoates **106** which lactonized spontaneously to 3-(diethoxyphosphoryl)tetrahydrofuran-2-ones **107**. Finally, furanones **107** treated with a base and various aldehydes yielded the expected 3-alkylidenedihydrofuran-2-ones **108**.

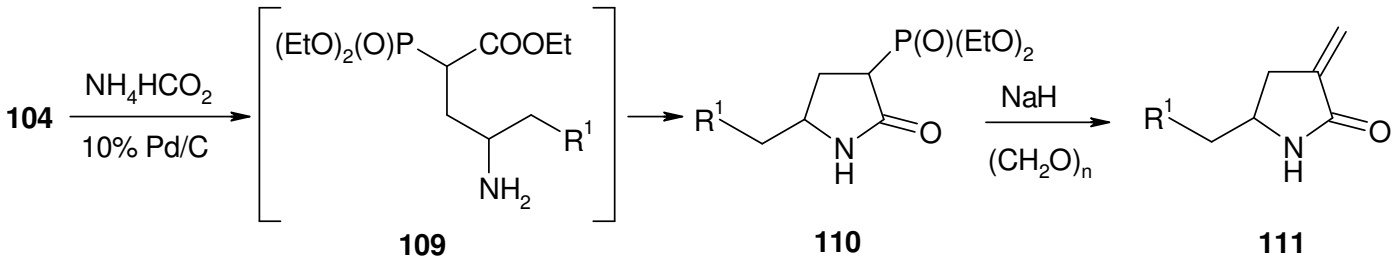


R^1 = H, Me, *n*-Bu, Ph, 3,4-diMeO-C_6H_4, *p*-$NO_2C_6H_4$

R^2 = H, *i*-Pr, Ph, 1-naphthyl

Scheme 19

The same nitroalkanoates **104** were also applied in the synthesis of 3-methylidenepyrrolidin-2-ones **111** (Scheme 20). A palladium catalyzed, ammonium formate reduction of the nitro group in nitroalkanoates **104** gave, after spontaneous lactamization, 3-(diethoxyphosphoryl)pyrrolidin-2-ones **110** which, when used in the HWE olefination of formaldehyde, yielded the expected pyrrolidinones **111**. Attempts to olefinate other aldehydes were unsuccessful.

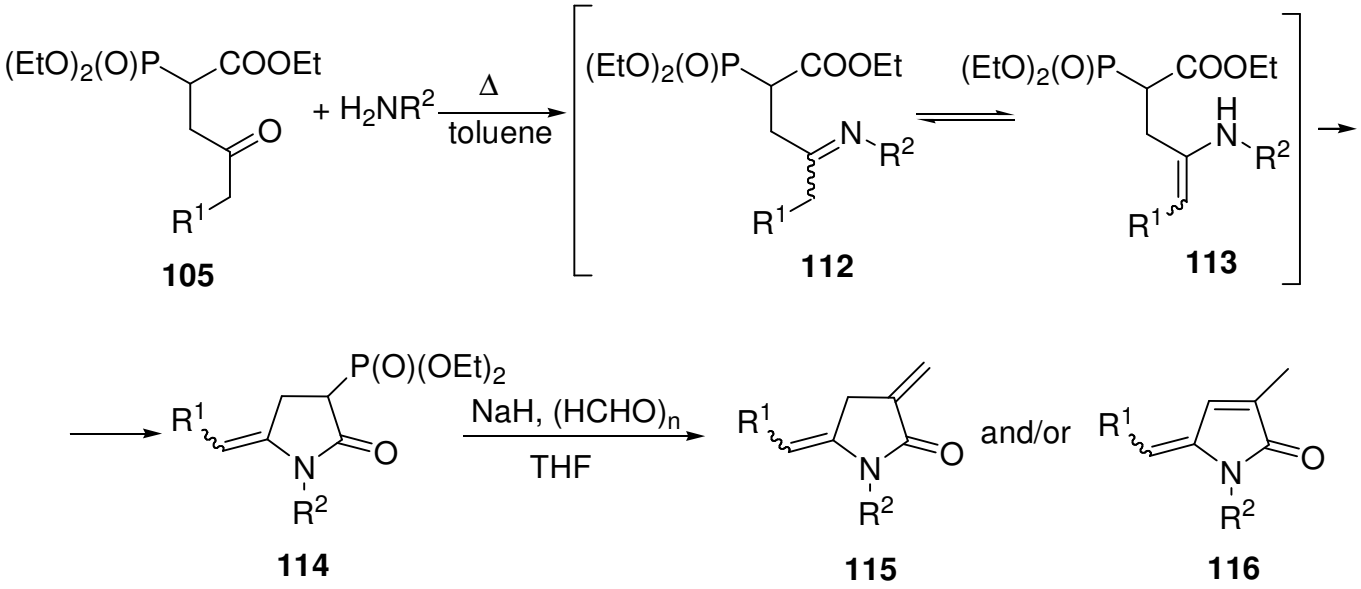


R^1 = H, Me, *n*-Bu, Ph, 3,4-diMeO-C_6H_4, *p*-$NO_2C_6H_4$

Scheme 20

Another application of 4-oxoalkanoates **105** in the synthesis of a so far very poorly recognized group of natural compounds, namely 5-alkylidene-3-methylidenepyrrolidin-2-ones **115**, is also worth mentioning. These oxoalkanoates, when treated with hexyl- or benzylamine in the presence of *p*-toluenesulphonic acid in

boiling toluene, gave 1-alkyl-5-alkylidene-3-diethoxyphosphorylpyrrolidin-2-ones **114** (Scheme 21).[52] This rather unexpected reaction can be rationalized assuming that there is an equlibrium between imines **112** and enamines **113**. The lactamization of enamines **113** gives 5-alkylidene-3-diethoxyphosphorylpyrrolidinones **114**. A HWE olefination of paraformaldehyde using pyrrolidinones **114** performed in boiling THF in the presence of NaH as a base gave 1-alkyl-5-alkylidene-3-methylidenepyrrolidin-2-ones **115** and/or their rearrangement products 1-alkyl-5-alkylidene-3-methylpyrrol-2-ones **116**, usually in moderate yields.

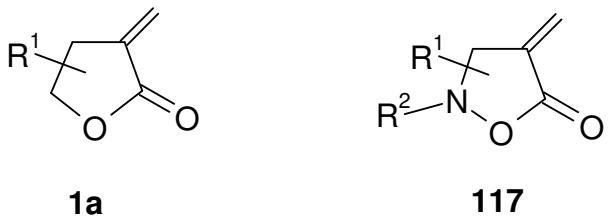


R^1 = Me, *n*-Bu, Ph, 3,4-diMeO-C_6H_4

R^2 = *n*-C_6H_{13}, $PhCH_2$

Scheme 21

A very interesting new group of compounds, whose structure is closely related to 3-methylidene-dihydrofuran-2-ones **1a**, are 4-methylideneisoxazolidin-5-ones **117** where one of the carbon atoms in the lactone ring is replaced by a nitrogen atom (Figure 9). Compounds of this structure are almost unknown.[68,69]

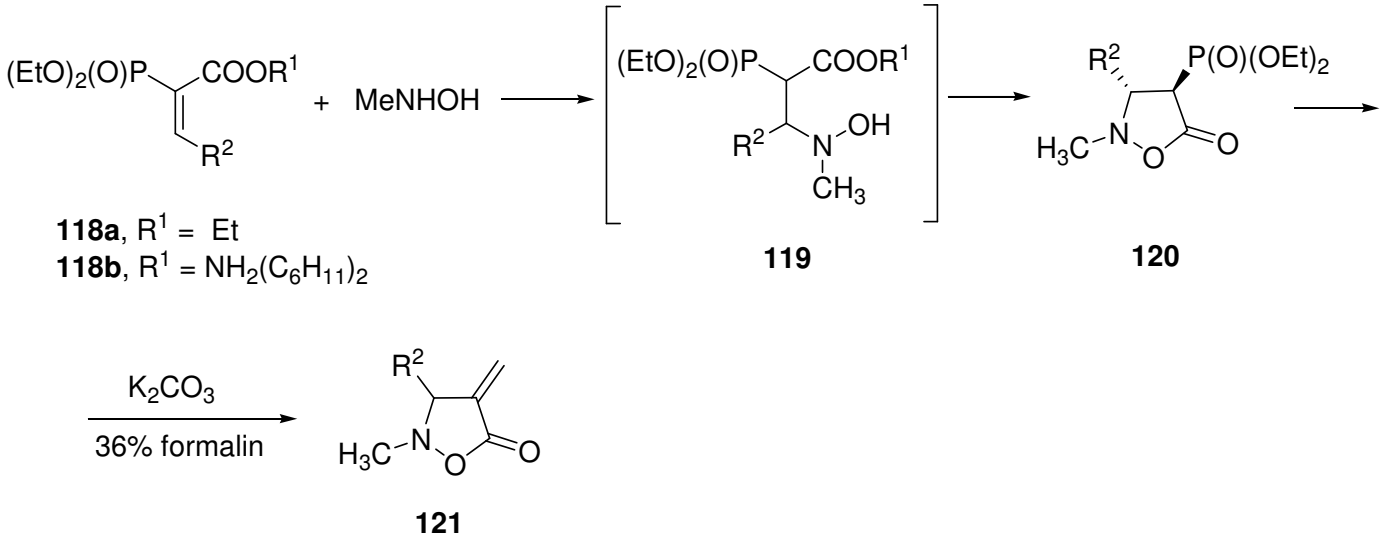


1a **117**

Figure 9

Very recently, a convenient and general route to 3-substituted 2-methyl-4-methylideneisoxazolidin-5-ones **121** was described by Janecki *et al.* (Scheme 22).[24] Ethyl 2-diethoxyphosphoryl-2-alkenoates **118a** or dicyclohexylammonium 4-diethoxyphosphoryl-2-alkenoates **118b** were used as Michael acceptors in the reaction with *N*-methylhydroxylamine hydrochloride. Adducts **119** formed in these additions were not isolated and lactonized spontaneously to *trans*-4-diethoxyphosphorylisoxazolidin-5-ones **120**. Isoxazolidin-

5-ones **120** when used in the HWE olefination of formaldehyde, in the presence of K_2CO_3 as a base, gave the expected 4-methylideneisoxazolidin-5-ones **121** in good to excellent yields.



118a, R^1 = Et
118b, $R^1 = NH_2(C_6H_{11})_2$

119 **120**

121

R^2 = *i*-Pr, 1-methylpentyl, Ph, *p*-MePh, *p*-MeOPh, *p*-BrPh, *p*-NO_2Ph, 1-naphthyl

Scheme 22

4. Conclusions

The discovery of the diverse biological properties and, in particular, high cytotoxic activity of many α-alkylidene-γ-butyrolactones and γ-butyrolactams stimulated a rapid development of synthetic methods leading to these compounds. Among many different synthetic approaches corroborated so far, the one which employs the Wittig or Horner-Wadsworth-Emmons olefination for the construction of the alkylidene moiety emerged recently as a very versatile and promising tool. Simple and efficient synthetic protocols for these olefination reactions are now well established. Also, the limited availability of the appropriate organophosphorus reagents which was until very recently, the main drawback of this approach, is now increasing. Many of these reagents with a precisely defined structure can now be prepared using one of the general methods described in the literature. However, there is still a strong demand for stereo- and especially enantioselective methods which would provide organophosphorus reagents in enantiomerically pure or at least enantiomerically enriched form.

There is no doubt that the methodology presented in this review will be developed further and has the potential to become one of the most versatile approaches to the synthesis of α-alkylidene-γ-butyrolactones and α-alkylidene-γ-butyrolactams.

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SYNTHESIS OF NITROBENZAZOLES. PART 2

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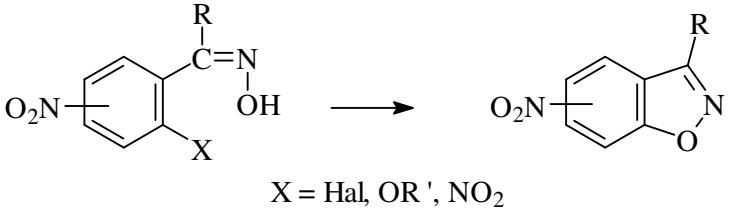
Abstract. *Methods of the preparation of C- and N-nitrated benzazoles for over thirty years are summarized and critically discussed. Part 1 was devoted to the nitration of all types of benzazoles and the preparation of nitroindazoles and nitrobenzimidazoles by heterocyclization. In the Part 2 we describe the preparation of other nitrobenzazoles (nitrobenzoxazoles, nitrobenzothiazoles, nitrobenzoselenazoles and nitrobenzotriazoles) via heterocyclization and other methods of synthesis of nitrated benzazoles.*

Contents

1. Synthesis of nitrobenzazoles via heterocyclization

1.1. Nitrobenzisoxazoles, nitrobenzoxazoles, nitrobenzoxadiazoles

The main method of producing 1,2-benzisoxazoles with the nitro group in the arylene fragment of the molecule is intermolecular condensation in an alkaline medium of the corresponding oxymes containing an easily eliminated group in the *ortho*-position (Scheme 1).[1-12] The same is true for halogens (bromine in most cases), hydroxy-, aryloxy- or nitro group.

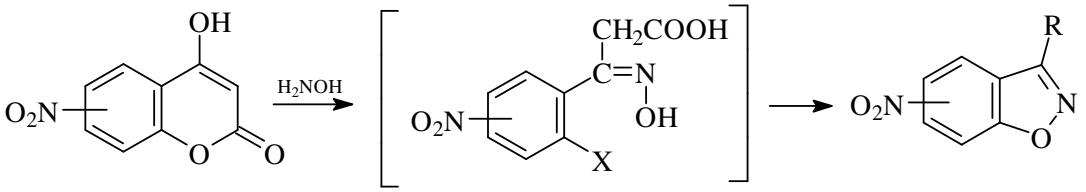


X = Hal, OR ', NO_2

Scheme 1

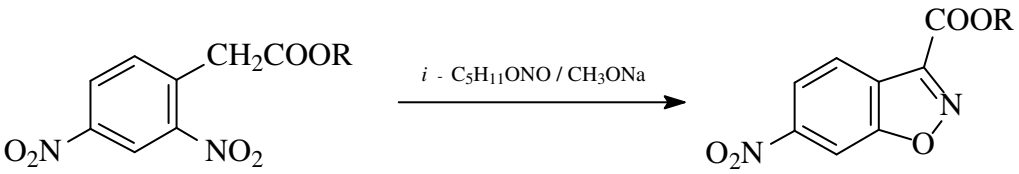
The reaction of 4-hydroxycumarines with hydroxylamine proceeds in the same way (Scheme 2).[7,13]

An attempt to substitute hydroxynitrocumarines by nitrocumarines failed: the yield of the final products fell to 5–17%.[14]



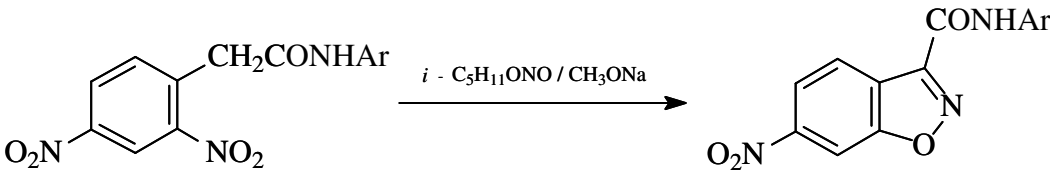
Scheme 2

In 1912 Borsche found out that the esters and amides of 6-nitro-1,2-benzisoxazole-3-carboxylic acid could be obtained in high yield in the reaction of isoamylnitrite with 2,4-dinitrophenylacetic acid derivatives in the presence of sodium methoxide (Scheme 3).[15]



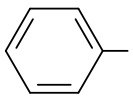
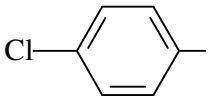
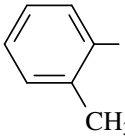
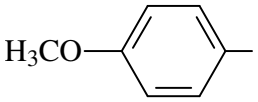
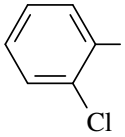
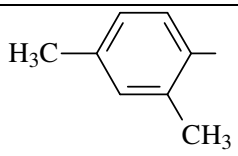
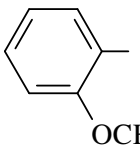
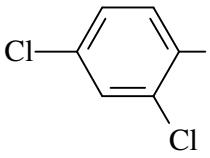
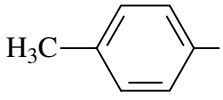
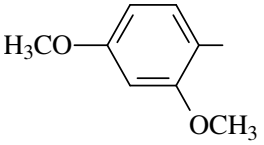
Scheme 3

This reaction was successfully used for the preparation of arylamides of 6-nitro-1,2-benzisoxazole-3-carboxylic acid (Scheme 4 and Table 1).[16,17]



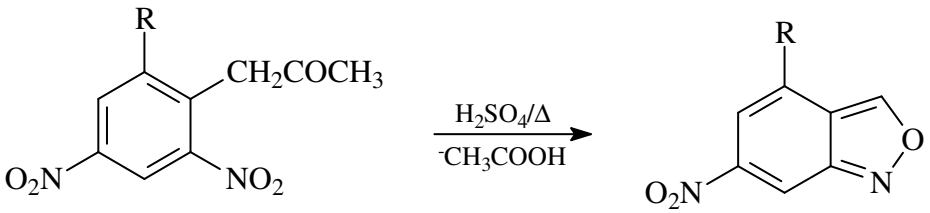
Scheme 4

Table 1. Characteristics of 3-substituted 6-nitro-1,2-benzisoxazoles.

Ar	yield, %	mp, °C (recryst.)	Ar	yield, %	mp, °C (recryst.)
	60	214-216 (benzene)		50	236 (alcohol/acetic acid)
	58	205-206 (CCl_4)		50	220-222, (alcohol/acetic acid)
	40	211-214 (CCl_4)		65	228-230 (alcohol/acetic acid)
	50	202 (CCl_4)		57	232 (alcohol/acetic acid)
	55	201 (CCl_4)		25	235 (CCl_4)

6-Nitro-1,2-benzisoxazolylketones can be obtained in an analogous manner.[15] 5-Nitrosalicilic aldehyde in an acid medium reacts with HN_3 to form a mixture of 5-nitro-1,2-benzisoxazole and 5-nitrobenzoxazole;[18] the latter being formed from 5-nitrosalicilic acid nitrile, a product of 5-nitro-1,2-benzisoxazole hydrolysis.

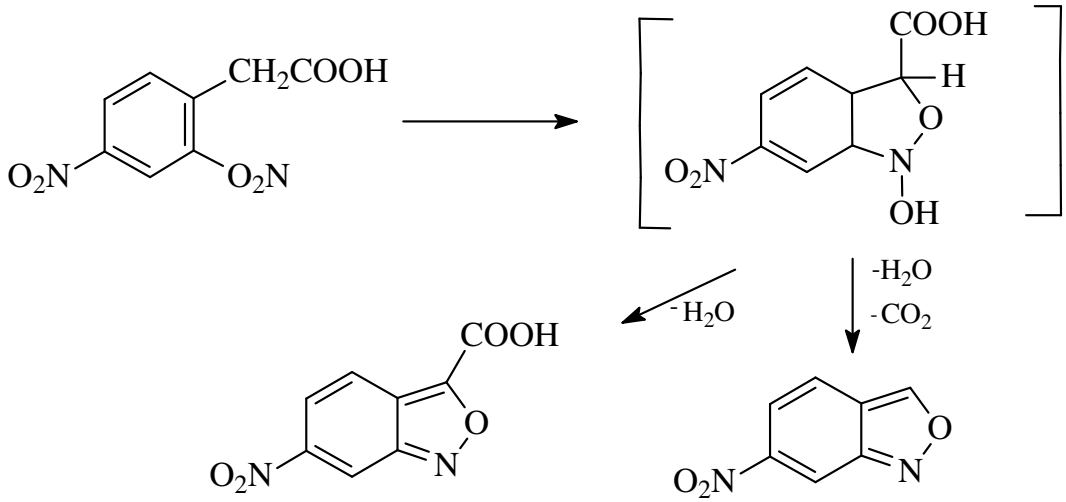
On heating with concentrated sulfuric acid 2,4-dinitrophenylacetone turns into 6-nitro-2,1-benzisoxazoles (6-nitroanthranils) (Scheme 5).[19]



R = Cl (50 %), Br (49 %), I (46 %)

Scheme 5

2,4-Dinitrophenylacetic acid reacts in a similar way and involves partial decarboxylation to form a mixture of 6-nitroanthranil-3-carboxylic acid and 6-nitroanthranil.[20-22] The reaction mechanism is a nucleophilic attack of the methylene carbon by the nitro group oxygen atom, as shown in Scheme 6. The formed cyclic product undergoes dehydration or dehydration with simultaneous decarboxylation.



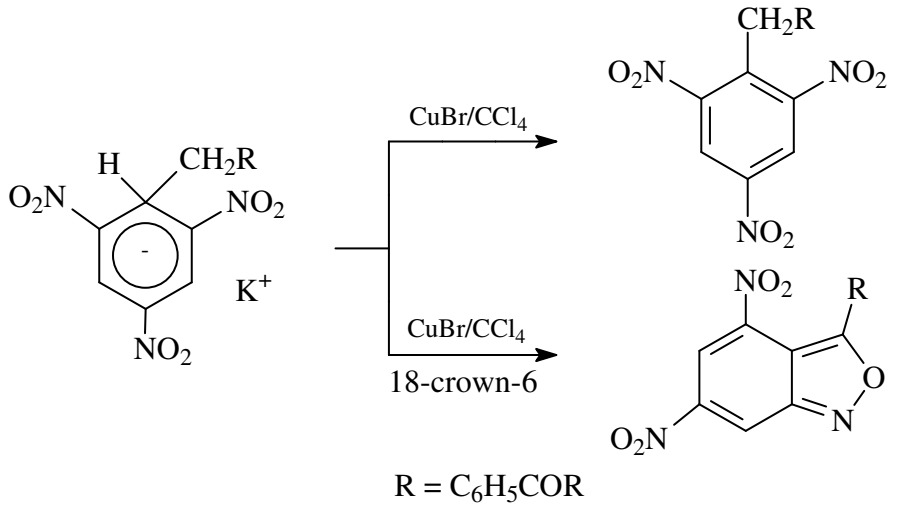
Scheme 6

The methylene ester of 6-nitro-2,1-benzoxazole-3-carboxylic acid is obtained in a similar manner.[23] The reaction of oxidation of 1,3,5-trinitrobenzene σ-complexes, containing the C–C bond in the side-chain follows an interesting pathway.[23]

Under the influence of oxidizing systems [copper(I) bromide – CCl_4] these systems are oxidized into the corresponding 1,3,5-trinitrobenzene derivatives, whereas in the presence of the same system and crown-esters (for example, 18-crown-6) 4,6-dinitroanthranils are formed (Scheme 7). So, the presence of the group in the geminal center of the σ-complex is a necessary condition for conversion of this type.[24]

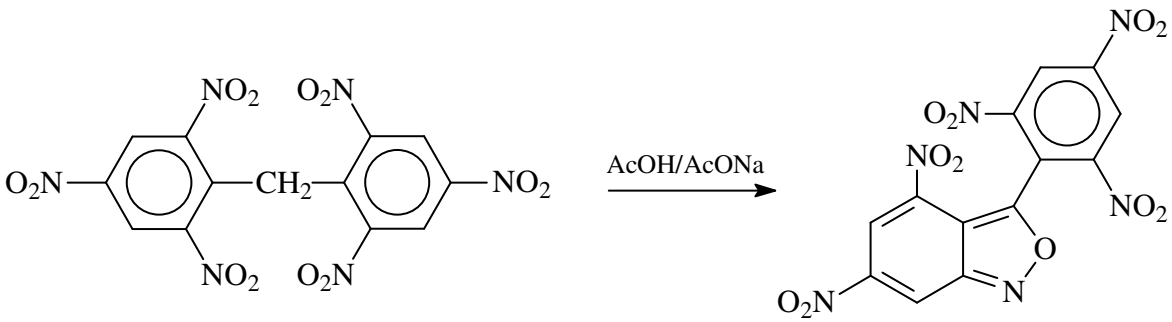
3-Aryl-6-nitroanthranils are obtained on heating of 2,4-dinitrobenzaldehydes in sulfuric acid or poly-phosphoric acids with aromatic carbohydrates.[25-29] Reductive heterocyclization of 2,6-dinitrobenzaldehyde in

the presence of 2-bromo-2-nitropropane and indium (2:5) in a MeOH/H_2O solution leads to 4-nitro-2,1-benzisoxazole in good yield.[30] 3,6-Dichloro-2,5-dinitro-*para*-xylol on heating in oleum transforms to 4,7-dichloro-5-nitro-6-methyl-2,1-benzisoxazole.[31,32]



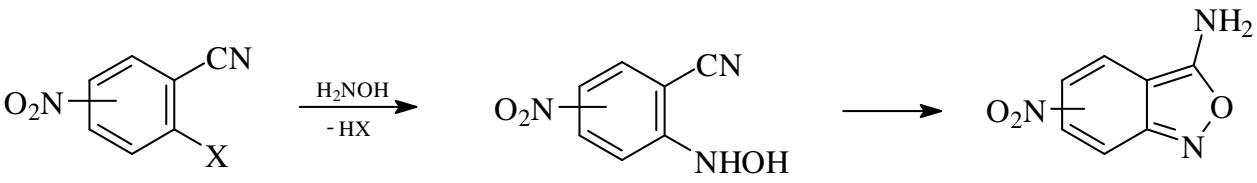
Scheme 7

In the reaction with sodium acetate 2,2',4,4',6,6'-hexanitrodiphenylmethane undergoes an intermolecular cyclization, giving in a good yield 3-picryl-4,6-dinitroanthranil, a rather thermally stable explosive (Scheme 8).[33]



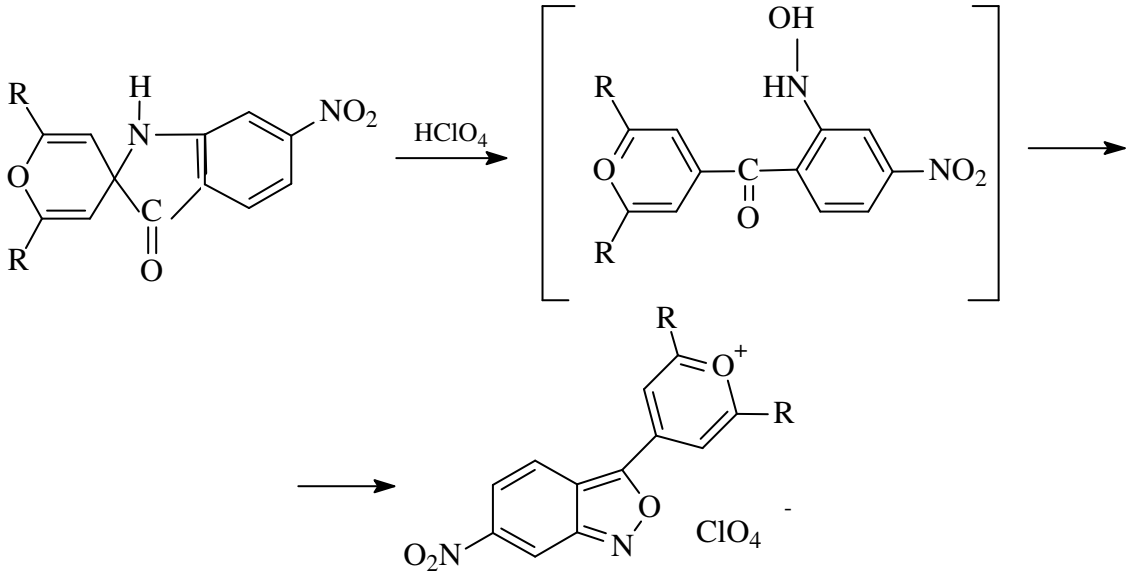
Scheme 8

2,1-Benzisoxazoles are obtained from *ortho*-nitroacetylbenzenes in the reaction with 3-phenylphosphate. 2-Amino-4-nitropropiophenone was obtained in the presence of a nitro group in the benzene-ring along with nitroanthranil.[34] In hydrochloric acid, the cyclization is accompanied by chlorination of the phenylene fragment.[35] The nitriles of *ortho*-halogenonitrobenzoic acids react with hydroxylamine to form nitrated 3-amino-2,1-benzisoxazoles (Scheme 9).[36]



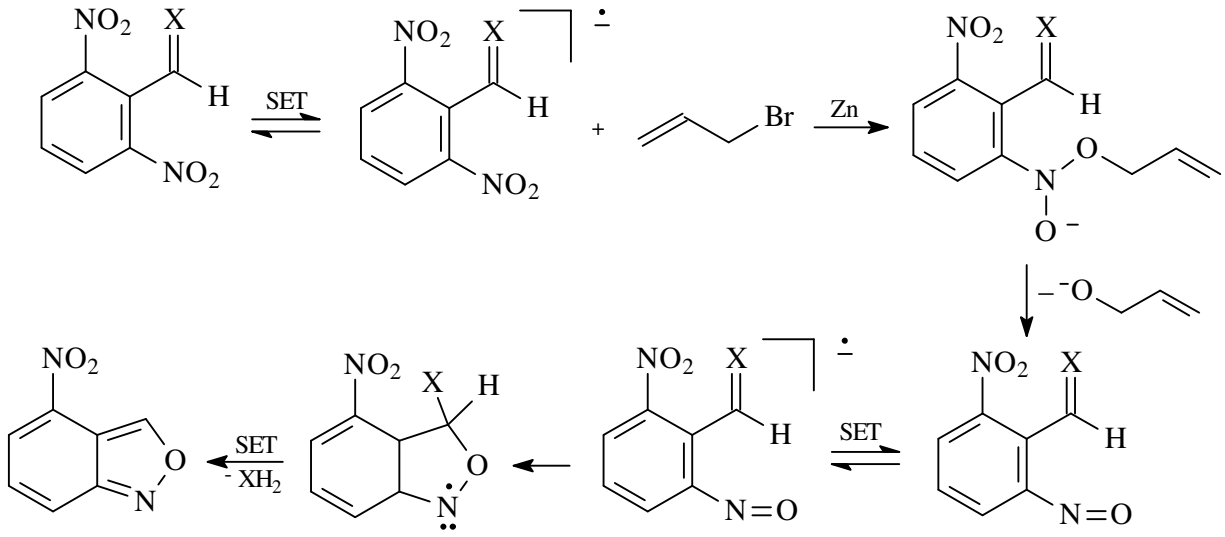
Scheme 9

(6-Nitro-2,1-benzisoxazolyl-3)pyrilium perchlorates have been obtained from the corresponding oxaspiroindolines (Scheme 10).[37]



Scheme 10

A mild and novel reaction route to 2,1-benzisoxazoles from 2-nitrobenzaldehydes in the presence of allyl bromide and zinc dust has been established.[38] The reductive cyclization of 2,6-dinitrobenzaldehyde was strongly retarded probably because of the inhibitory effect of the second nitro group.[38,39] The authors assume a radical mechanism of the reaction, as demonstrated in Scheme 11.[38]



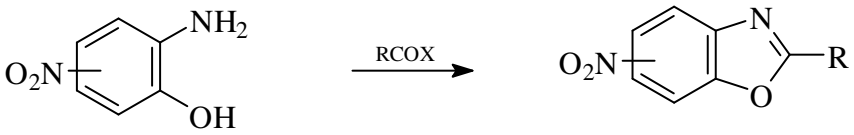
SET – single electron transfer, X = O, N - Ph

Scheme 11

This way would provide a useful synthetic technique along with reductive *N*,*O*-diallylation of nitrobenzene.

6-*tert*-Butyl-5-methoxy-4-nitro-2,1-benzisoxazole along with other products have been isolated on photolysis of 4-*tert*-butyl-3-methoxy-2,6-dinitrotoluene.[40]

Nitrobenzoxazoles, like their non-nitrated analogs, are easily obtained in the reaction of the corresponding *ortho*-aminophenols with carboxylic acids,[41-46] aldehydes[47-49] or chloroanhydrides[50-54] (Scheme 12).



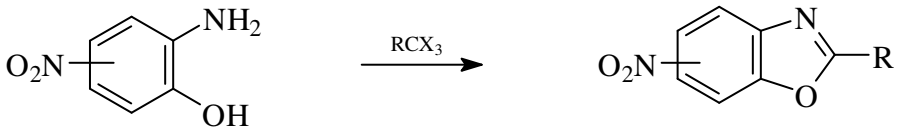
X = H, OH, Cl

Scheme 12

Mono- or diacyl derivatives undergone cyclization to benzoxazoles on heating or under the influence of dehydrating agents, are formed as intermediates in this reaction.[50,41,42,48,51-63] Phosphorus oxychloride,[42,46] boric anhydride[44,51,52] or polyphosphoric acid[50,60] are used as condensing agents. In particular, 2-hydroxy-5-nitrobenzoxazole, used for the synthesis of antivirus medicines, has been obtained by the reaction of condensation of 4-nitro-2-aminophenol with $(NH_2)_2CO$ in pyridine.[64]

To prepare 2-trichloromethylbenzoxazole, nitrated *ortho*-aminophenols are treated with iminoesters of trichloroacetic acid.[65-67] Some other 2-substituted nitrobenzoxazole derivatives were obtained in the same way.[50,68,69]

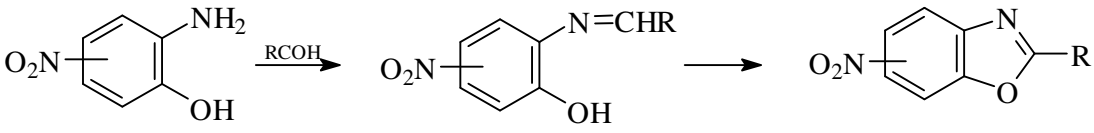
For the formation of the benzoxazole cycle can be use of compounds containing trichloromethyl[70,71] or trialkoxymethyl groups (Scheme 13).[71-73]



X = Hal, OR

Scheme 13

Nitrated *ortho*-aminophenols react with aldehydes to form Schiff's bases, which are easily oxidized into the corresponding benzoxazoles (Scheme 14).[74]

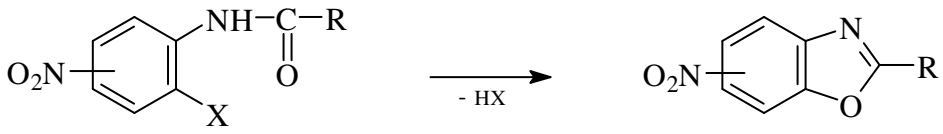


Scheme 14

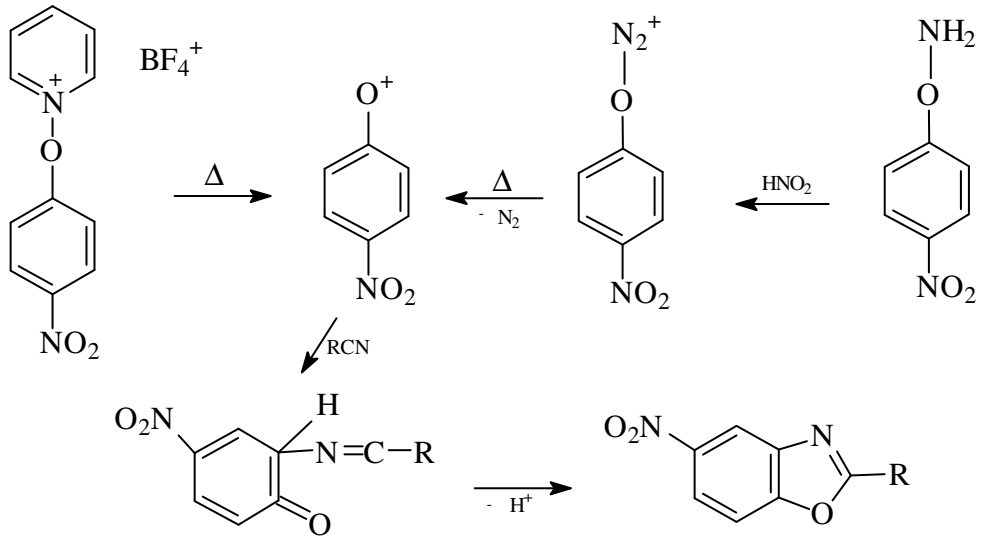
Lead acetate,[50,75-78] nickel peroxide[78,79] and some other substances[80-82] are used as oxidants in most cases.

Sometimes, the corresponding *ortho*-bromo- or *ortho*-nitroacylanilides are used in place of aminophenols for the synthesis of nitrobenzoxazoles (Scheme 15).[83,84]

N-Aryloxypyridinium salts or diazotized aryloxyamines on heating generate aryloxene ions, which turn into benzoxazoles in the presence of acetonitrile or benzonitrile, as shown in Scheme 16.[85,86]



Scheme 15

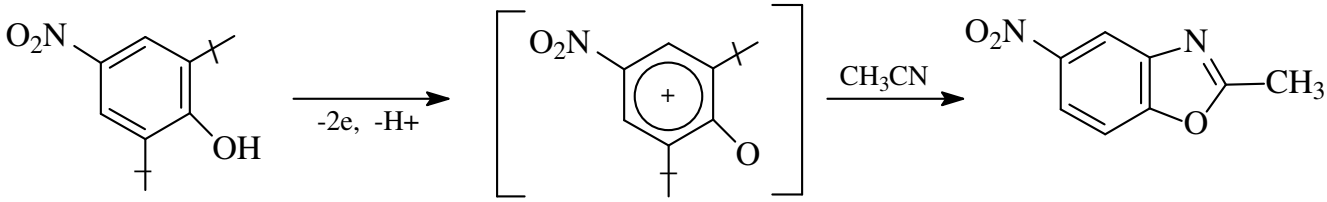


R = CH_3, C_6H_5

Scheme 16

Suschitzky *et al*. have proposed an original synthesis of benzoxazole nitro derivatives in a mixture of carboxylic and polyphosphoric acids by heating aromatic aldehydes containing the nitro group in the *para*-position.[61]

7-*tert*-Butyl-2-methyl-5-nitrobenzoxazole has been synthesized by electrochemical oxidation of 4-nitro-2,6-di-*tert*-butylphenol, according to Scheme 17.[87]

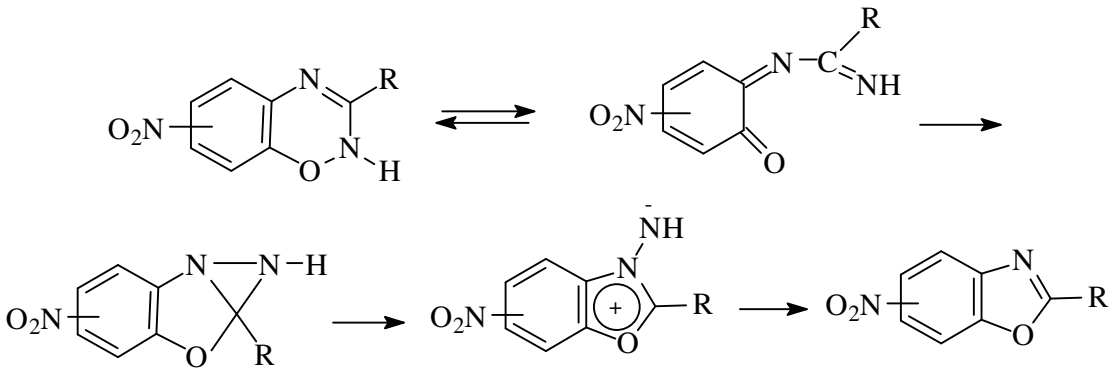


Scheme 17

7-*tert*-Butyl-4-methyl-5-nitrobenzoxazole and 6-*tert*-butyl-5-methoxy-4-nitro-2,1-benzisoxazole were found among the products of photolysis of 4-*tert*-butyl-3-methoxy-2,6-dinitrotoluene.[40]

When heated, benzoxadiazines give benzoxazoles in good yield.[88,89] Based on the proposed mechanism of recyclization the intermediate formation of *ortho*-quinonimine has been suggested (Scheme 18).

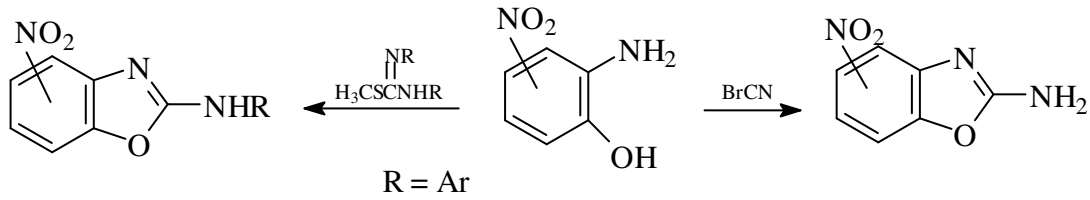
Heating of 7-nitro-1,2,4-benzoxadiazine-3-carboxylic acid or basic hydrolysis of its ethyl ester results in 2-amino-6-nitrobenzoxazole.[88,89] Earlier this compound was wrongly ascribed a structure of 7-nitro-1,2,4-benzoxadiazine.[90]



R = Alk, Aryl

Scheme 18

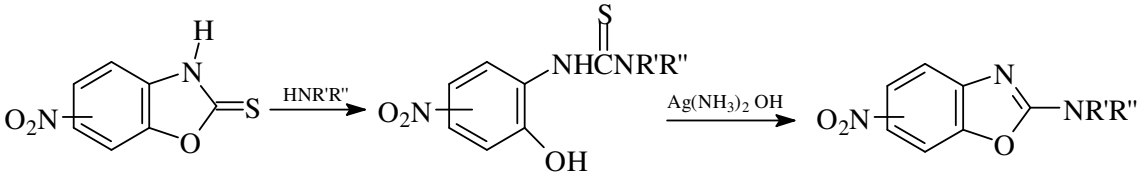
Nitrated 2-aminobenzoxazoles are obtained in good yield in the reaction of *ortho*-aminophenols with cyanogen bromide[91-93] or with *S*-methylisothiourea derivatives,[94] as shown in Scheme 19.



R = Ar

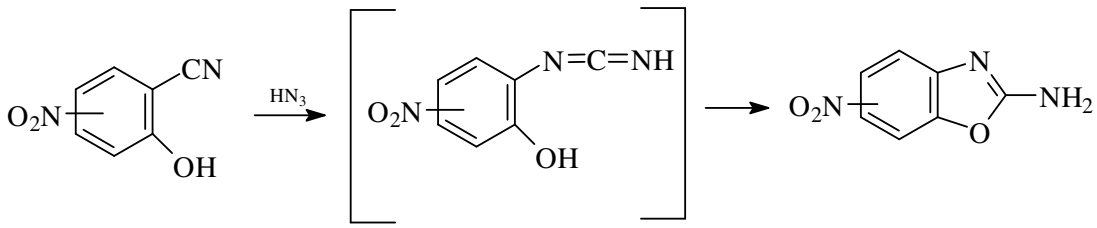
Scheme 19

5- or 6-Nitrobenzoxazoline-2-thiones react with morpholine and aromatic amines to form 2-amino-benzoxazoles.[95] When butylamines and some other amines are used, the reaction stops at a stage of the formation of thiourea 2-oxyphenyl derivatives and for further cyclization to 2-aminobenzoxadiazoles the presence of silver salts is necessary (Scheme 20).



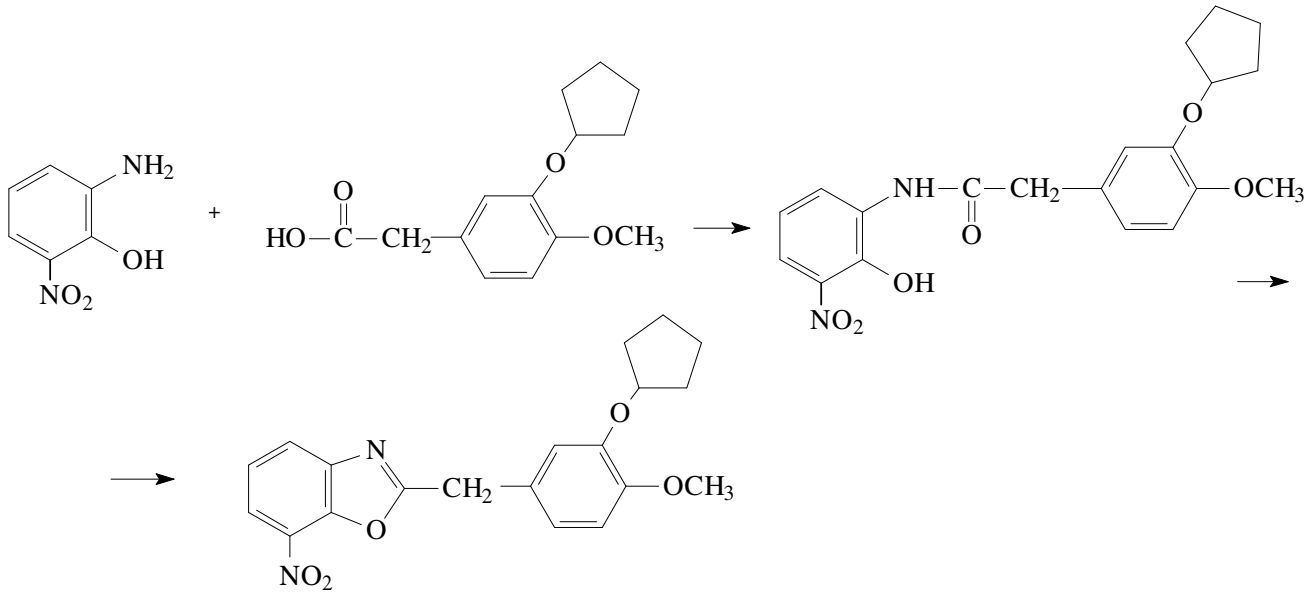
Scheme 20

The nitrile of salicylic acid and its nitroderivatives react with HN_3 to form 2-aminobenzoxazoles, as illustrated Scheme 21.[96,97]



Scheme 21

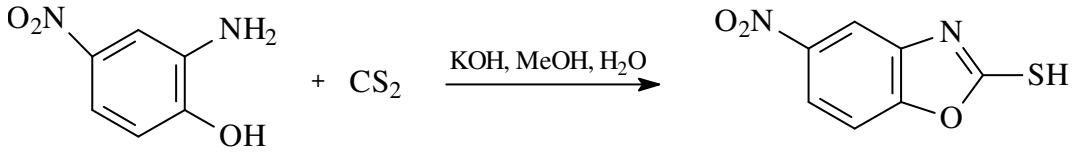
2-(3-Cyclopentyloxy-4-methoxybenzyl)-7-nitrobenzoxazole used in the therapy of asthma has been obtained by condensation of *N*-(2-hydroxy-3-nitrophenyl)-3-cyclopentyloxy-4-methoxyphenylacetamide (Scheme 22).[98]



Scheme 22

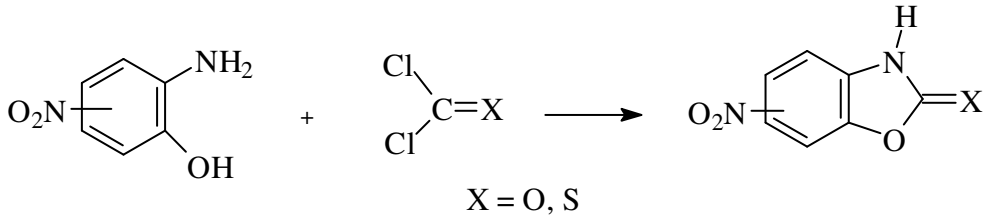
Molecular design of nonlinear optical organic materials based on 6-nitrobenzoxazole chromophores has been developed.[99]

2-Thiol-5-nitrobenzoxazole, the structural material for the preparation of potential enantioselective inhibitors of leukotriene biosynthesis, has been synthesized by condensation of nitro-*ortho*-aminophenol with CS_2 (Scheme 23).[100]



Scheme 23

Nitroderivatives of *ortho*-aminophenols react with phosgene and thiophosgene to form benzoxazolones-2[101] and benzoxazolthiones-2,[102] respectively (Scheme 24).

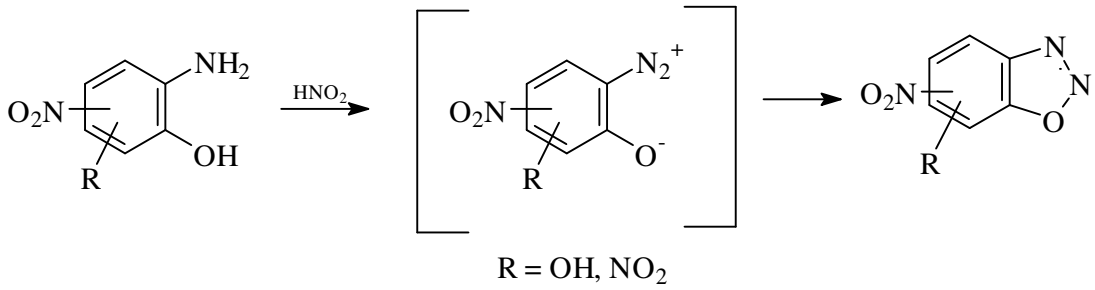


Scheme 24

A synthesis of nitrobenzoxazolones-2 by a Beckman's rearrangement of 4-nitrosalicylhydroxamine acid has been reported.[103] The process is carried out on heating (4-nitro-2-oxyphenyl)-urea[104] or 4-(4-nitro-2-oxyphenyl)semicarbazide[105] with mineral acids and by oxidation of 6-nitro-2-hydroxymethylquinoline and its derivatives.

The most widespread preparative synthetic route to nitrobenzoxazolothione-2 is the reaction of nitroaminophenols with CS_2.[94,106,107]

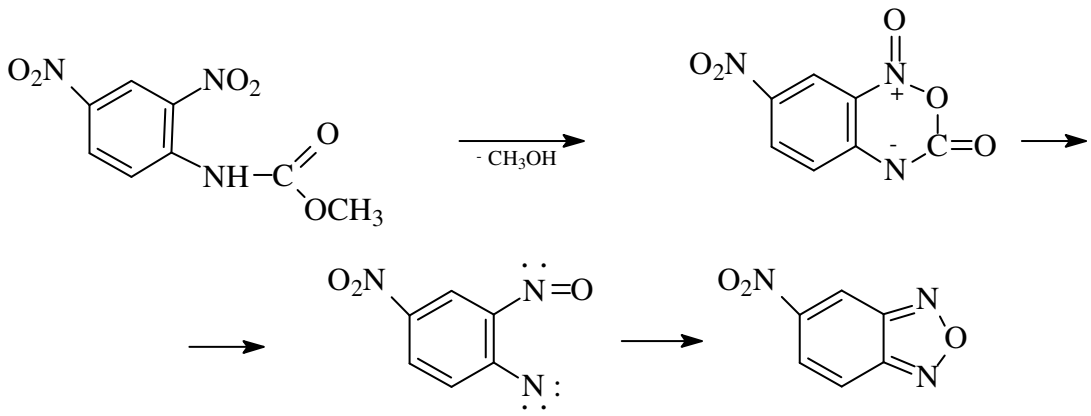
Nitroderivatives of *ortho*-aminophenol on diazotization form the corresponding *ortho*-diazophenols, which readily undergo cyclization into 1,2,3-benzoxadiazoles (Scheme 25).[107-112]



R = OH, NO_2

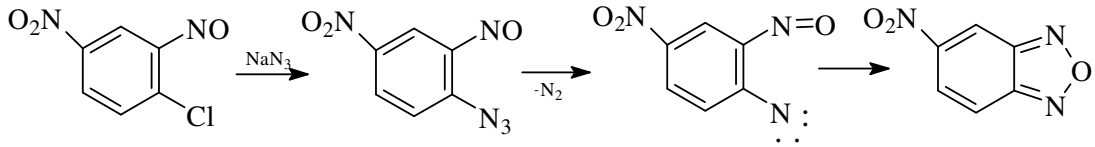
Scheme 25

On pyrolysis of methyl-*N*-(2,4-dinitrophenyl)carbamate, 5-nitro-2,1,3-benzoxadiazole (5-nitrobenzofurazan) was isolated in a yield of 35% (Scheme 26).[113]



Scheme 26

The key-product in this process is *ortho*-nitrosophenylnitrene from which benzofurazan is formed later. The reaction of 2-chloro-5-nitronitrozobenzene with sodium azide in an aqueous-acetone medium is likely to follow a similar pathway. In this case the yield of 5-nitrobenzofurazan reaches 73% (Scheme 27).[114]

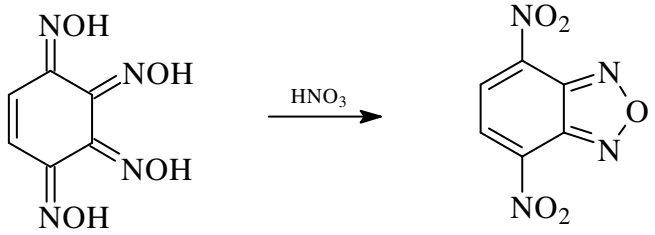


Scheme 27

In the reaction of nitric acid with tetraoximecyclohex-5-ene-1,2,3,4-tetraone, the oxidation of two oxyme groups with simultaneous cyclization to 4,7-dinitro-2,1,3-benzoxadiazole take place (Scheme 28).[115]

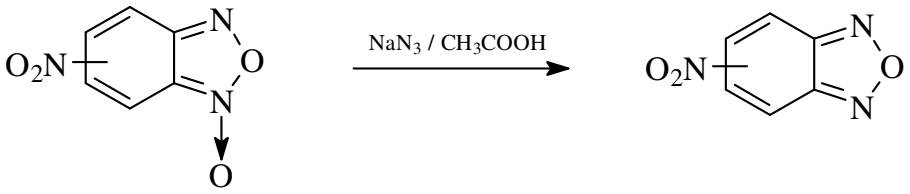
The most common method of the synthesis of nitrobenzofurazans is reduction of benzofuroxan nitroderivatives. A lot of examples of the synthesis of nitro-2,1,3-benzoxadiazoles from the corresponding

N-oxides have been described.[116-123] Here the results of electrochemical investigations of a more difficult reduction of exocyclic N→O bond, in comparison with the endocyclic one, look unexpected.[124] The following explanation for this apparent contradiction can be given. On the one hand, the process of chemical reduction can differ significantly from the mechanism of electrochemical reduction. On the other hand, the primary opening of the furoxan cycle with subsequent closing into furazan is possible; it is the endocyclic N→O bond that undergoes primary opening. Triphenylphosphine is used as a reducing agent in most cases.[116,117,120,121]



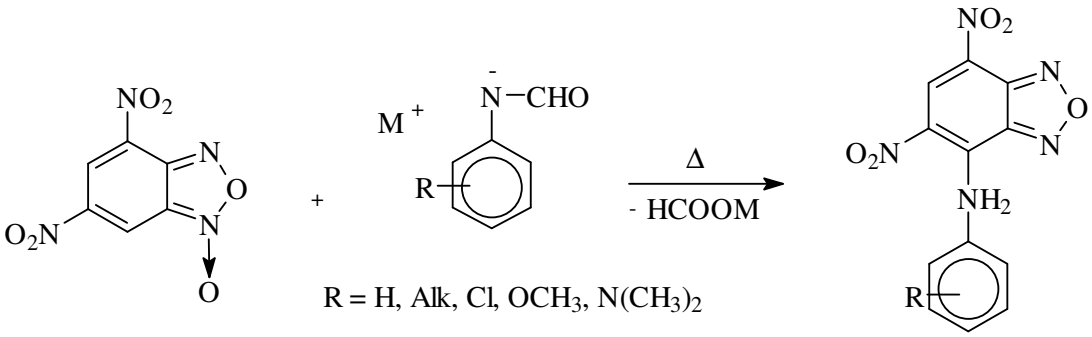
Scheme 28

On heating of sodium azide with benzofuroxans in ethylenglycole or DMSO, the corresponding benzofurazans are formed.[120,122] If the reaction is carried out in a medium of acetic or *iso*butyric acids, *i.e.*, actually using HN_3, the nitrobenzofurazans sought are formed in good yield (Scheme 29).[123]



Scheme 29

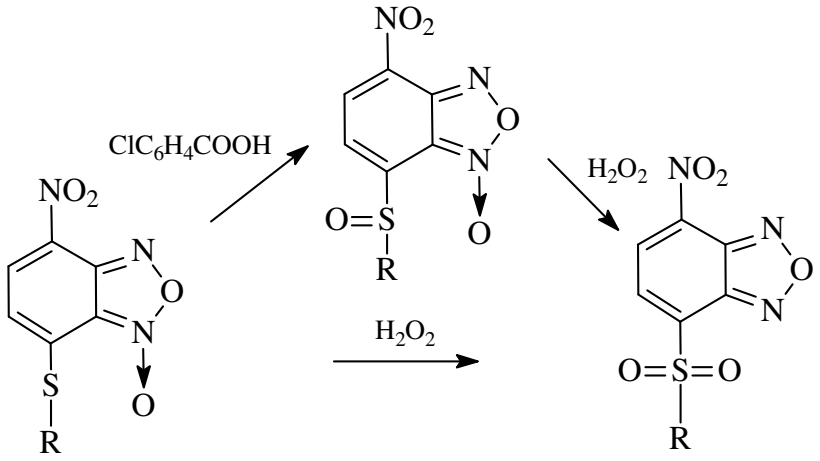
4,6-Dinitrobenzofurazan 7-aminoderivatives have been obtained by the reaction of 4,6-dinitrobenzofuroxan with alkali metal salts of the corresponding formanylidines (Scheme 30).[124-126]



Scheme 30

In recent years, particular attention focuses on reactivity of nitrobenzofuroxans and nitrobenzofurazans.[127-132] The latest are represented a class of neutral 10-π-electron-deficient heteroaromatic substrates which exhibit an extremely high electrophilic character in many covalent nucleophilic addition and substitution processes.

On oxidation of 4-nitro-7-arylthiobenzfuroxanes with excess hydrogen peroxide, the corresponding sulfonylbenzofurazans are obtained; whereas in mild conditions (*meta*-chloroperoxobenzoic acid, 0–20 ºC) intermediate nitro derivatives of sulfonylbenzofuroxan were isolated (Scheme 31).[133]



100-120ºC, in Ac_2O, AcOH, $C_6H_5CH_3$ 1- 9 h

R = C_6H_5, 4- $H_3CC_6H_4$, 3- $H_3COC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, $H_2CC_6H_5$

Scheme 31

On heating, the latter ones form 4-nitro-7-arylsulfonylbenzofurazans in high yield (Figure 1).

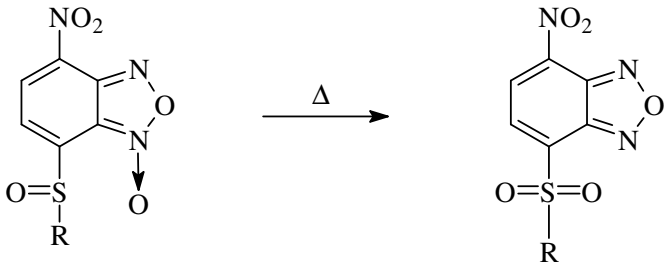


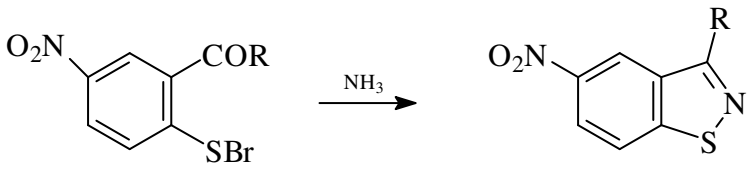
Figure 1

In this case, the observed migration of the furoxan cycle exocyclic oxygen to the neighboring sulfoxide group follows an intermolecular mechanism. The rate of this rearrangement increases with introducing electron-donating substituent into the phenyl-ring of the sulfoxide-fragment. It should be noted that the oxygen atom migration from the furoxan ring moves only to the sulfoxide group, and not to the sulfide one. In some cases the reaction goes without intermediate isolation of the furoxan cycle. For example, on heating 1,3-diamino-2,4,6-trinitrobenzene, 4-amino-5,7-dinitrobenzofurazan is formed.[134]

1.2. Nitrobenzisothiazoles, nitrobenzothiazoles, nitrobenzothiadiazoles

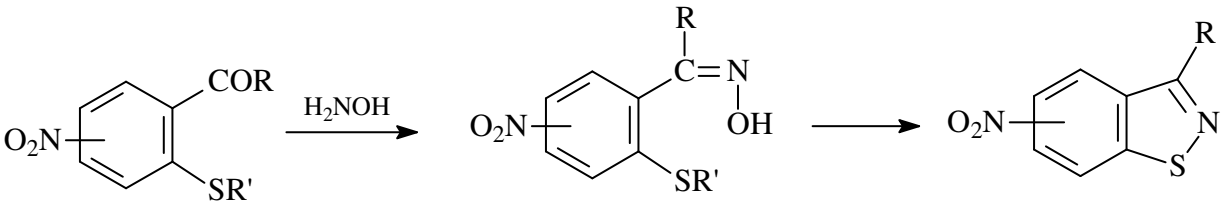
Nitroderivatives of aromatic aldehydes or ketones, containing a sulfohalogen group in the *ortho*-position, undergo cyclization into the corresponding 1,2-benzisothiazoles under the influence of ammonia (Scheme 32).[135]

Later this process has been significantly simplified by using *ortho*-chloro substituted aldehydes or ketones as the initial products.[136-140]



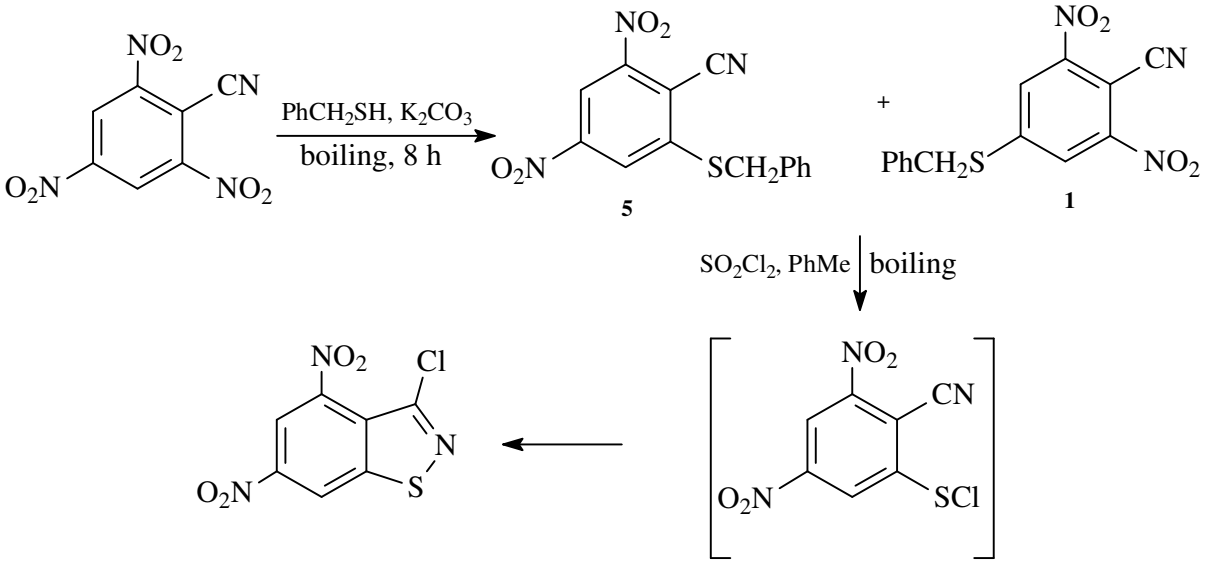
Scheme 32

Another rather widely accepted synthesis of the above compounds is the condensation of oxymes of aldehyde or ketone nitro derivatives, containing sulfohydryl or sulfoalkyl groups in the *ortho*-position (Scheme 33).[141-143]



Scheme 33

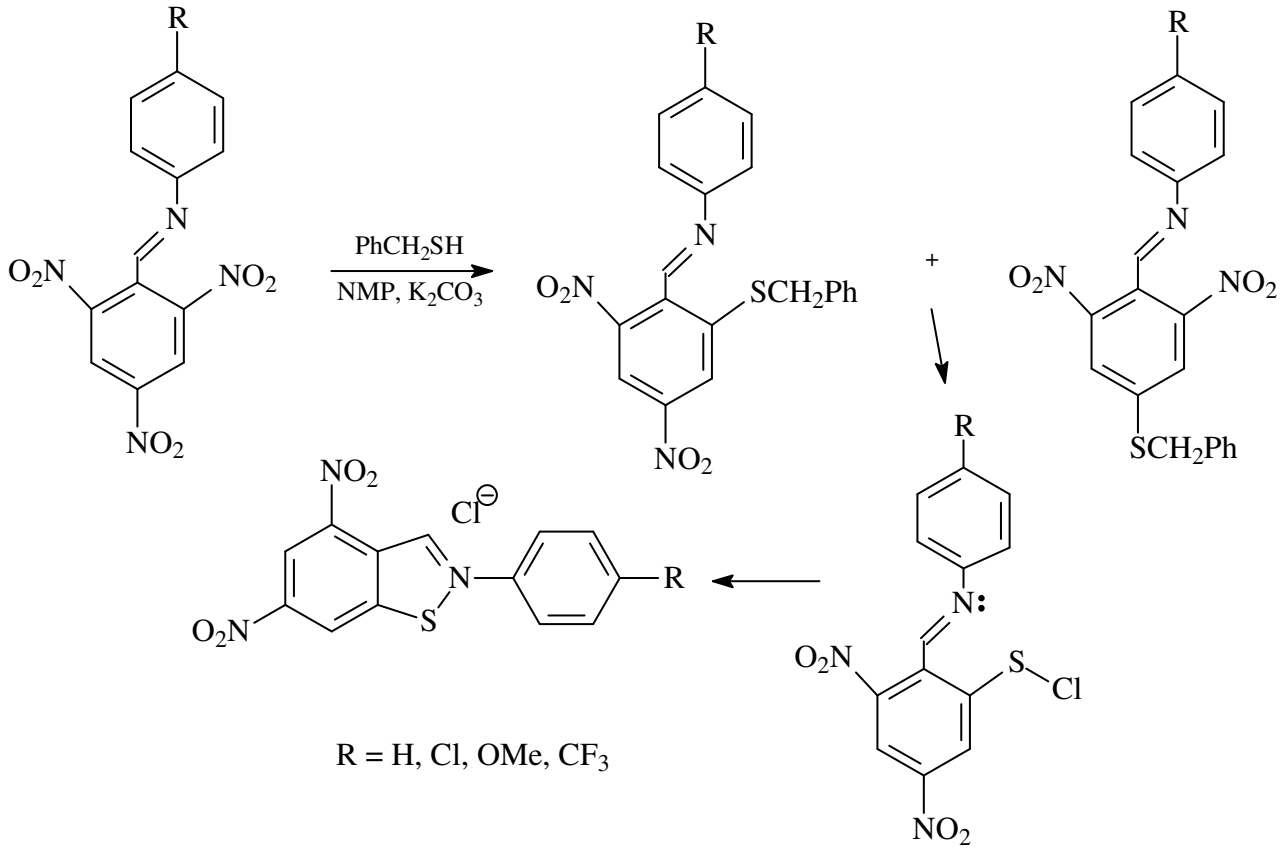
4,6-Dinitrobenzisothiazole derivatives and their salts[144-146] and 4,6-dinitro-1,2-benzisothiazol-3-ones[147] have been prepared in the course of utilization of explosive 2,4,6-trinitrotoluene. 3-Cloro-4,6-dinitrobenzisothiazole was prepared on using 2,4,6-trinitrotoluene, which can easily be transformed to 2,4,6-trinitrobenzonitrile (TNBN) by treatment with nitrosylchloride.[144] The reaction of TNBN in the presence of K_2CO_3 led to both *ortho* and *meta* isomers, the products of substitution of NO_2 groups by a $PhCH_2S$ unit, the ratio of isomers being dependent on the solvent polarity (Scheme 34).



Scheme 34

The fraction of *ortho* substitution considerably increases with decreasing the solvent polarity. The mixture (5:1) of *ortho* and *meta* isomers prepared in toluene was treated with SO_2Cl_2 to give 3-cloro-4,6-dinitrobenzisothiazole as a result of intramolecular cyclization.[144]

2-Aryl-4,6-dinitrobenzoisothiazolium chlorides can be obtained even at room temperature by treatment of the corresponding sulfurylchlorides in dichloroethane without separation, as shown in Scheme 35.[145]

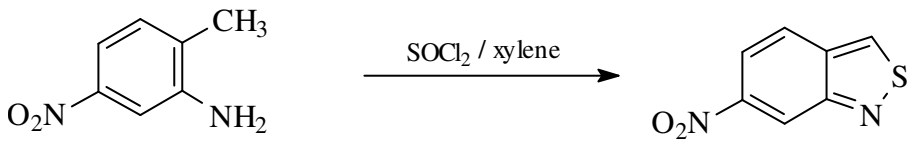


Scheme 35

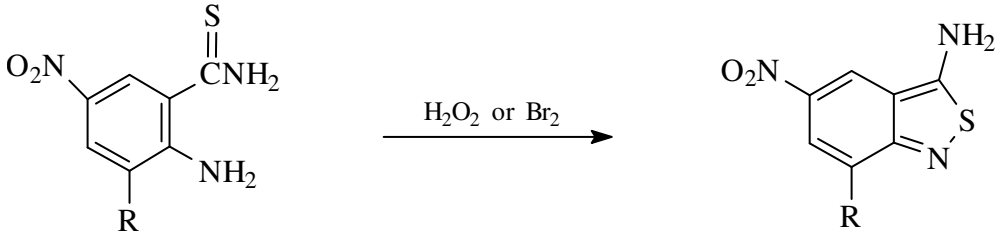
Similarly to 1,2-benzisoxazoles, 1,2-benzisothiazoles with the nitro group in the arylene fragment can be obtained from 4-mercaptotocumarines and from hydroxylamine.[13]

A synthesis of 5-nitro-1,2-benzisothiazolone-3 possessing thrombolytic and antibacterial activity has been described in reference.[148]

The data on the synthesis of nitrated 2,1-benzisothiazoles are rather scarce in comparison with the corresponding benzisoxazoles. It has been reported that, like other 2-aminotoluenes, 2-amino-4-nitrotoluene reacts with thionyle chloride in xylene to form 6-nitro-2,1-benzisothiazole, whereas 2-amino-5-nitrotoluene does not enter into this reaction (Scheme 36).[149]



Scheme 36



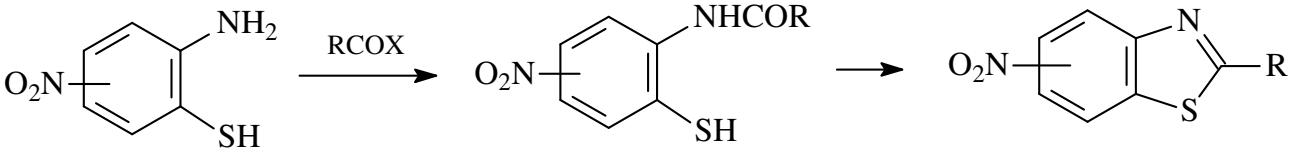
R = H, CN, $CONH_2$, $COOCH_3$

Scheme 37

3-Amino-5-nitro-2,1-benzisothiazole and its 7-substituted derivatives are obtained on oxidation of 5-nitro-2-amino-3-R-thiobenzamides with hydrogen peroxide or bromine (Scheme 37).[150-152]

In these conditions 5-nitrothioanthranilic acid is oxidized to 5-nitro-2,1-benzisoxazolone-3.[153,154]

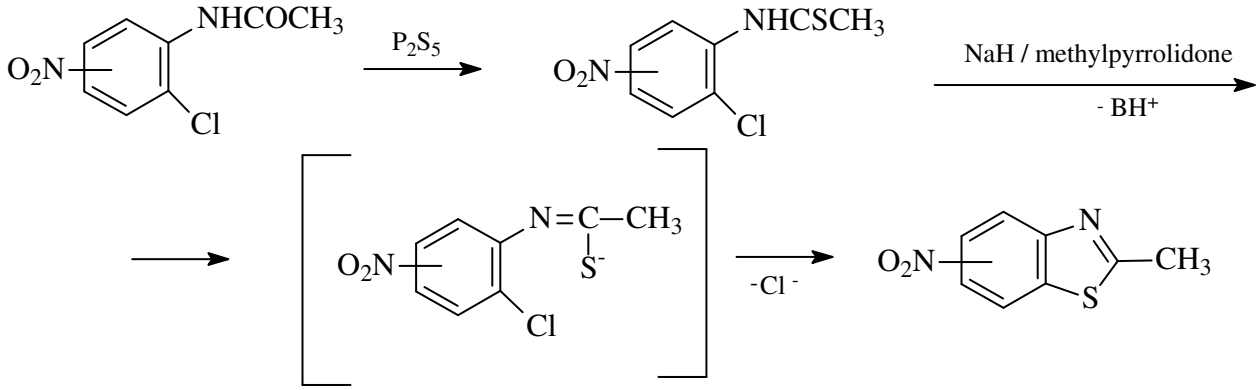
One of the most convenient and widespread syntheses of benzothiazole nitroderivatives is the reaction of the corresponding *ortho*-aminothiophenols with acids,[50,155-158] their anhydrides[157,159,160] or chloroanhydrides, according to Scheme 38.[161,162]



X = OH, OCOR', Cl; R = H, Alk, Ar

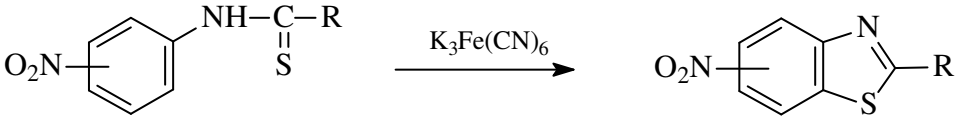
Scheme 38

ortho-Acetylaminothiophenols, which readily undergo cyclodehydratation, are intermediate products in these reactions.[50,163] In this case *ortho*-acetylaminothiophenols are often not separated, instead *ortho*-halogenoacylanilines are treated with alkali metal sulfides.[164-170] In a modification of this process, *ortho*-halogenothioacylanilines are boiled with phosphorus pentasulfide in benzene, and the products, nitroaniline thioacylderivatives, undergo cyclization to nitrobenzothiazoles in amide solvents in the presence of bases (Scheme 39).[171,172]



Scheme 39

Like other benzothiazoles, nitrobenzothiazoles can easily be obtained by Yakobson's method from thioacylanylides under the influence of potassium ferricyanide, as indicated in Scheme 40.[173-176]

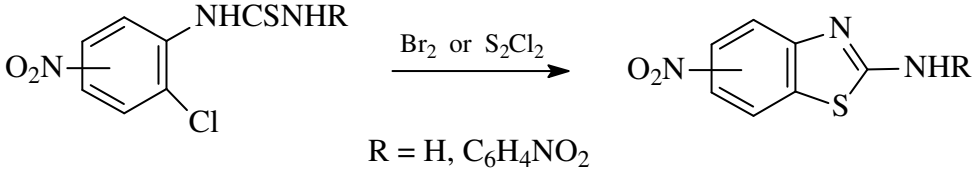


R = Alk, Ar

Scheme 40

Later 2-methyl-6-nitrobenzothiazole was obtained by electrochemical oxidation of 4-nitro-thioacetanylide.[177] Interestingly, that there is no cyclization under the influence of potassium ferricyanide

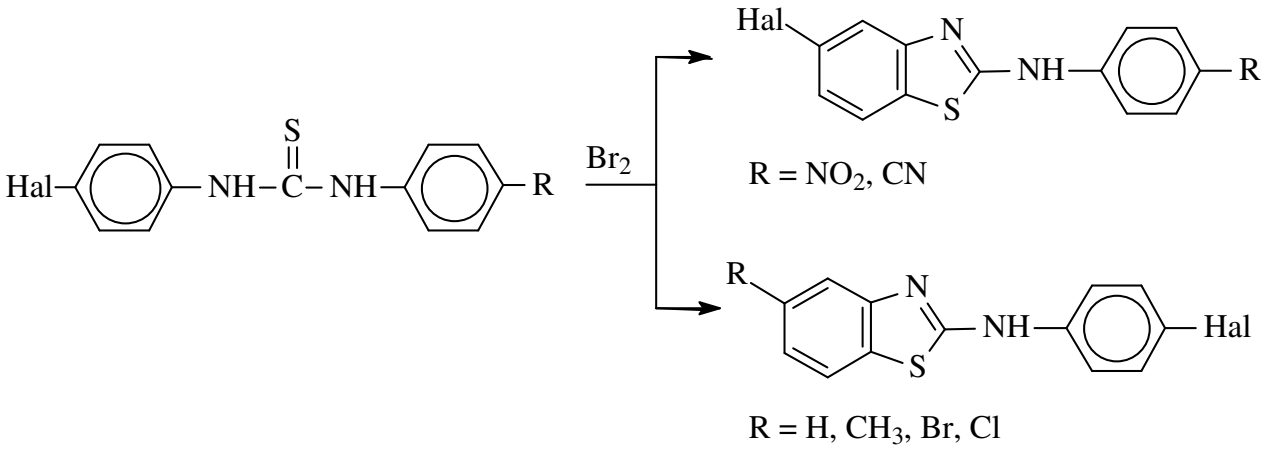
when arylthioureas are used. In this case other cyclizating agents have to be used as oxidizers. Bromine-induced oxidation of nitroarylthiourea with the formation of the corresponding 2-aminobenzothiazole nitroderivatives (Hugershoff's method) is used for preparative purposes.[178-184] Sometimes sulfur monochloride is used as an oxidizer in place of bromine (Scheme 41).[185,186]



Scheme 41

Introduction of the diazoarylamino groups into 2 position of 6-nitrobenzotiazoles leads to the thermical stability of nonlinear optical organic materials on the base nitrobenzazoles.[187-189]

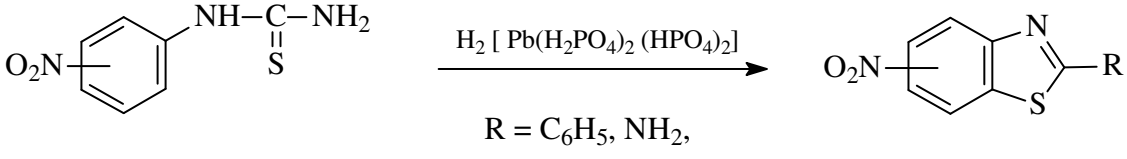
With *N,N'*-diarylthioureas, the cyclization direction is determined by the character of substituent and the introduction of a nitro group or other electron-withdrawing substituent decreases the reactivity of the aromatic ring.[190,191] This can be illustrated by the following Scheme 42.



Scheme 42

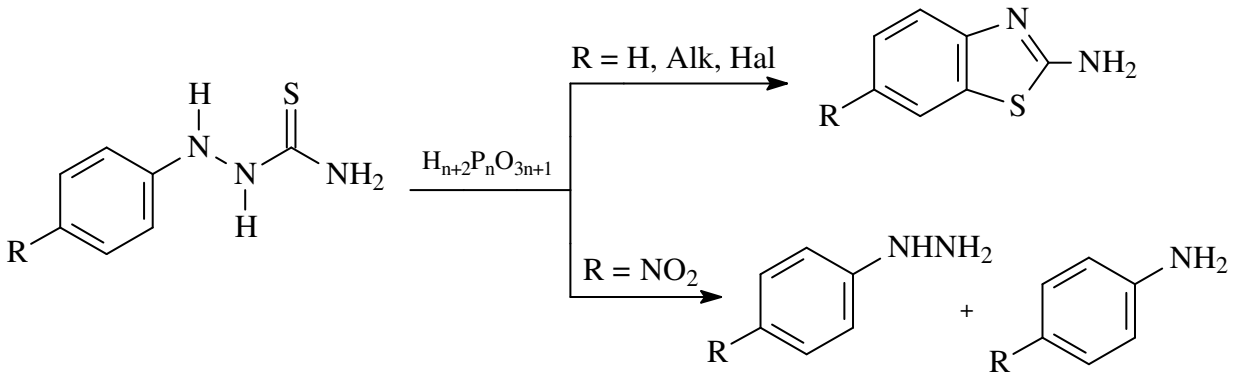
It has been reported about facile and highly efficient synthesis of 2-*N*-alkyl(aryl)amino-7-nitrobenzothiazoles,[192] which are of pharmaceutical interest. The key step involves intramolecular cyclization of a thiourea facilitated by the nitro group.

The using of a mixture of Pb_3O_4 with *ortho*-phosphoric acid as an oxidizer allows the preparation of both 2-aryl- and 2-aminonitrobenzothiazoles (Scheme 43).[80]



Scheme 43

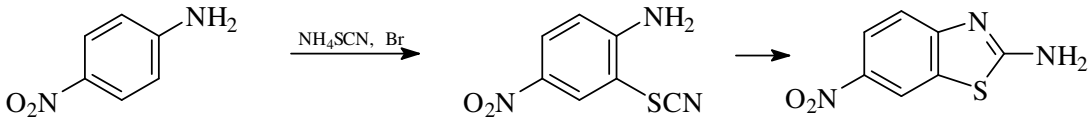
On heating in polyphosphoric acid 1-phenylthiosemicarbazides with alkyl or halogen substituent in the benzene ring turn into 2-aminobenzothiazoles in good yield (Scheme 44).[193]



Scheme 44

However, the presence of the nitro group in the *para*-position to the thiosemicarbazide group blocks the process of cyclization and only the products of N–C and N–N bond splitting are obtained as a result.

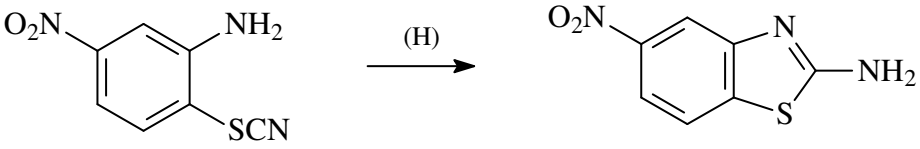
4-Nitroaniline reacts with ammonium rhodanide and bromine to form 2-rhodanyl-4-nitroaniline, which undergoes cyclization into 2-amino-6-nitrobenzothiazole under the reaction conditions on Scheme 45.[194-197]



Scheme 45

Other derivatives of 2-nitroaminobenzene were obtained in the same way,[157,195,198] and in some cases the above mentioned rhodanylaniniles could be isolated.[157,198]

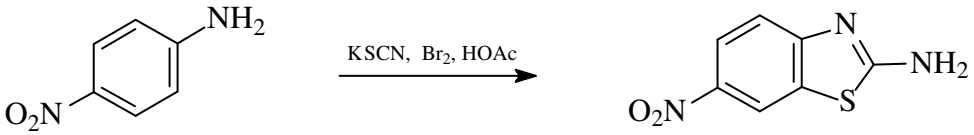
It should be taken into consideration that the rhodanation of substituted anilines goes mainly to the position 4. The reported synthesis of 2-amino-4-nitrobenzothiazole by rhodanation of *ortho*-nitroaniline[199] turned out to be incorrect. In fact the authors obtained 2-nitro-4-rhodanylaniline of the same empirical formula.[200] 2,4-Dinitrophenylthiocyanate is reduced to 2-amino-5-nitrobenzothiazole in acetic acid by iron (Scheme 46).[201,202]



Scheme 46

The same compound can be obtained on heating 2,4-dinitrochlorobenzene with thiourea in sulfolane.[203] In the same manner, 2-amino-7-trifluoromethyl-5-nitrobenzothiazole and 2-amino-7-nitro-benzothiazole were synthesized.

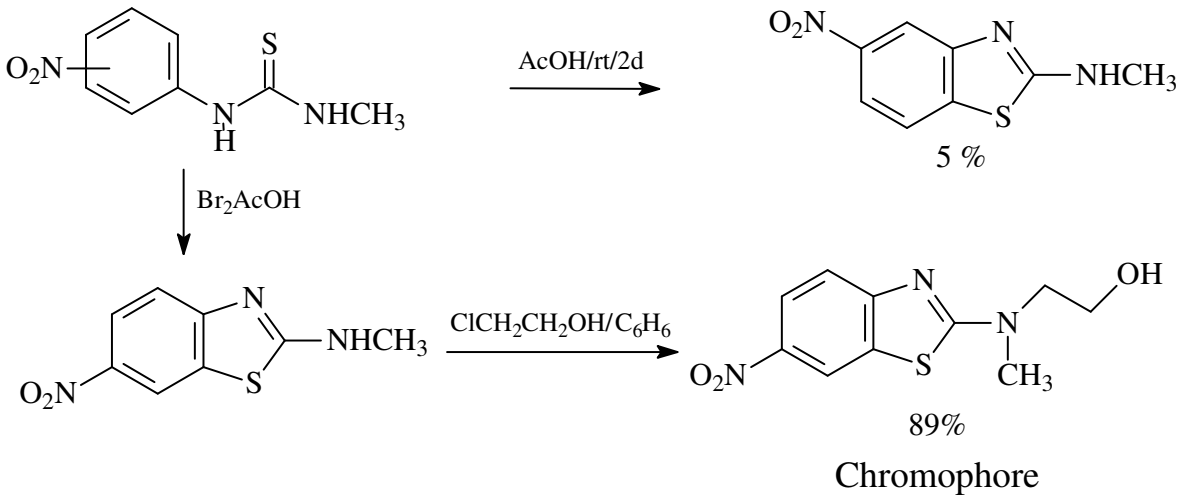
2-Amino-6-nitrobenzothiazole as a sodium flux inhibitor (anticonvulsant activity) has been synthesized from nitroaniline *via* a one-pot procedure (Scheme 47).[204]



Scheme 47

In this route, the thiourea is produced *in situ* and then oxidatively cyclized to the nitrobenzothiazole. This method failed for anilines containing an electron-withdrawing substituent in the *meta*-position.

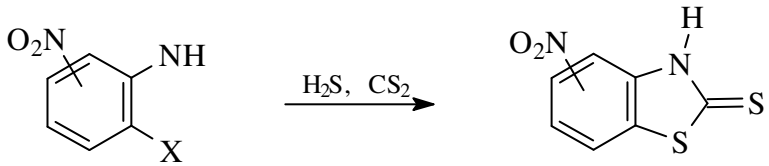
Nitrobenzothiazole chromophores[205,206] and their precursors[207] are building blocks of nonlinear optical materials which extensively use in the field of optical information processing, optical sensing, data storage, and telecommunications.[205,208] 5-Nitro-[207] and 6-nitro-2-(methyamino)benzothiazole[206] have been prepared from 3-nitro- and 4-nitrophenyl-thiourea corresponding, as illustrated in Scheme 48.



Scheme 48

Preparation method of the chromophore involves the condensation of *para*-nitroaniline with thiocyanate in methanol and the bromine radical cyclization using bromine in acetic acid. In this case only one product – 2-(methylamino)-6-nitrobenzothiazole – was obtained, which is easily purified over column chromatography using neutral alumina.[206]

6-Methyl-5-nitrobenzothiazolone-2 has been obtained from (5-methyl-2,4-dinitro-phenylthio)acetic acid and acetic anhydride.[209] Benzothiazolethione-2 nitroderivatives can readily be obtained by the following Scheme 49.[168]

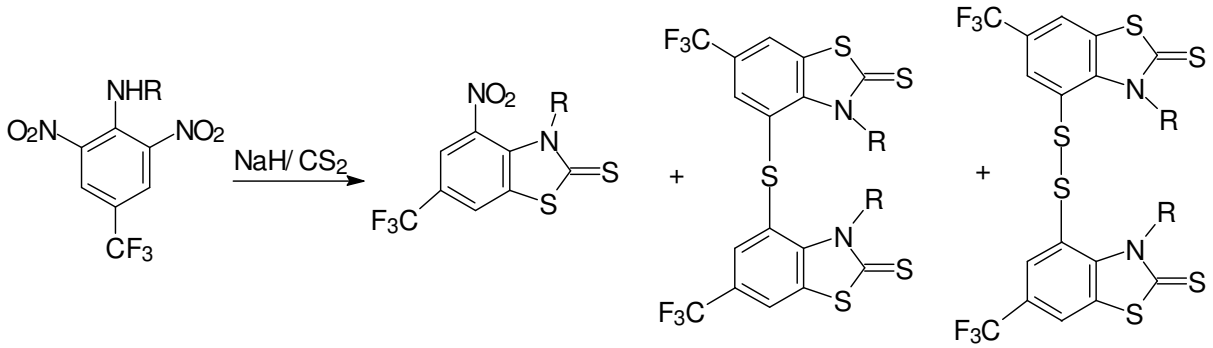


X = Cl, Br

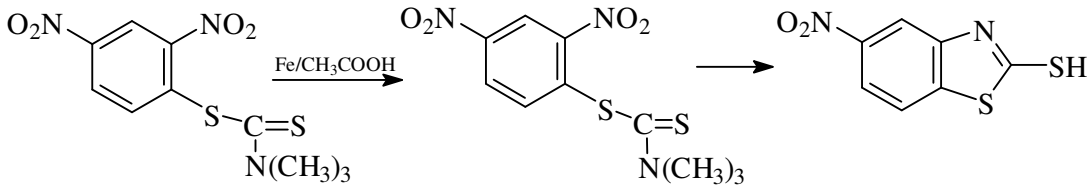
Scheme 49

An analogous reaction takes place with *ortho*-nitroanilines. For example, 4-amino-3,5-dinitrobenzotrifluoride and its *N*-alkylsubstituted derivatives react with CS_2 in dry dimethylformamide in the presence of sodium hydride to form the corresponding benzothiazolethiones, as shown in Scheme 50.[210]

2,4-Dinitrophenyl ester of *N,N*-dimethyldithiocarbamic acid is reduced with iron powder in glacial acetic acid with the formation of 5-nitrobenzothiazolethione-2[201,202] (Scheme 51) which is extensively used in coordinating chemistry.[211-214]



Scheme 50

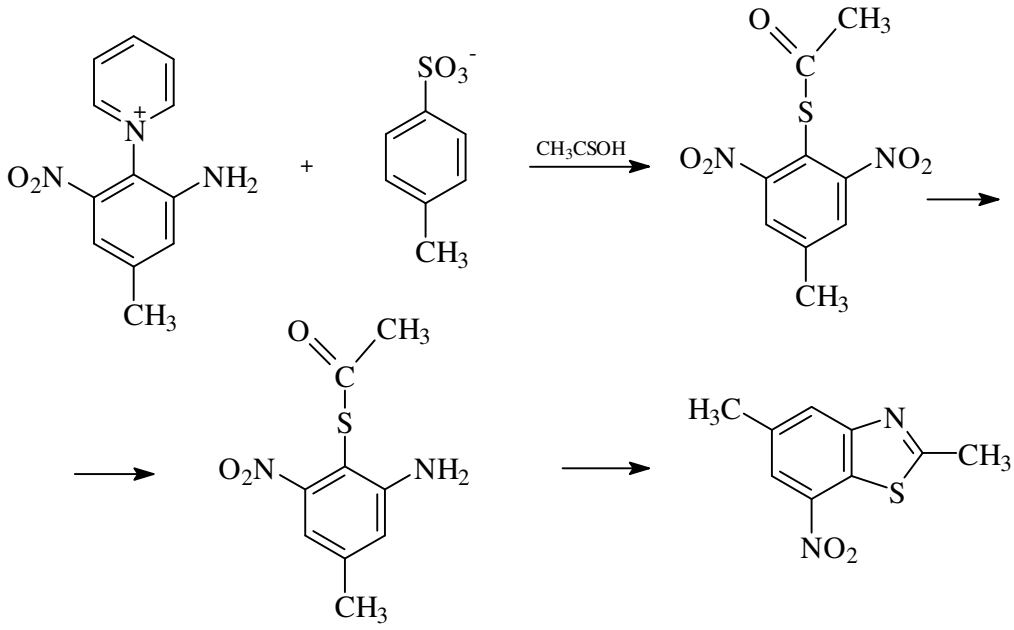


Scheme 51

The heteroaromatic thioles, in particular 2-mercapto-6-nitrobenzothiazole, were studied in regard to their abilities to function as co-initiators in free-radical photopolymerizations induced by camphorquinone and isopropylthioxanthone.[215]

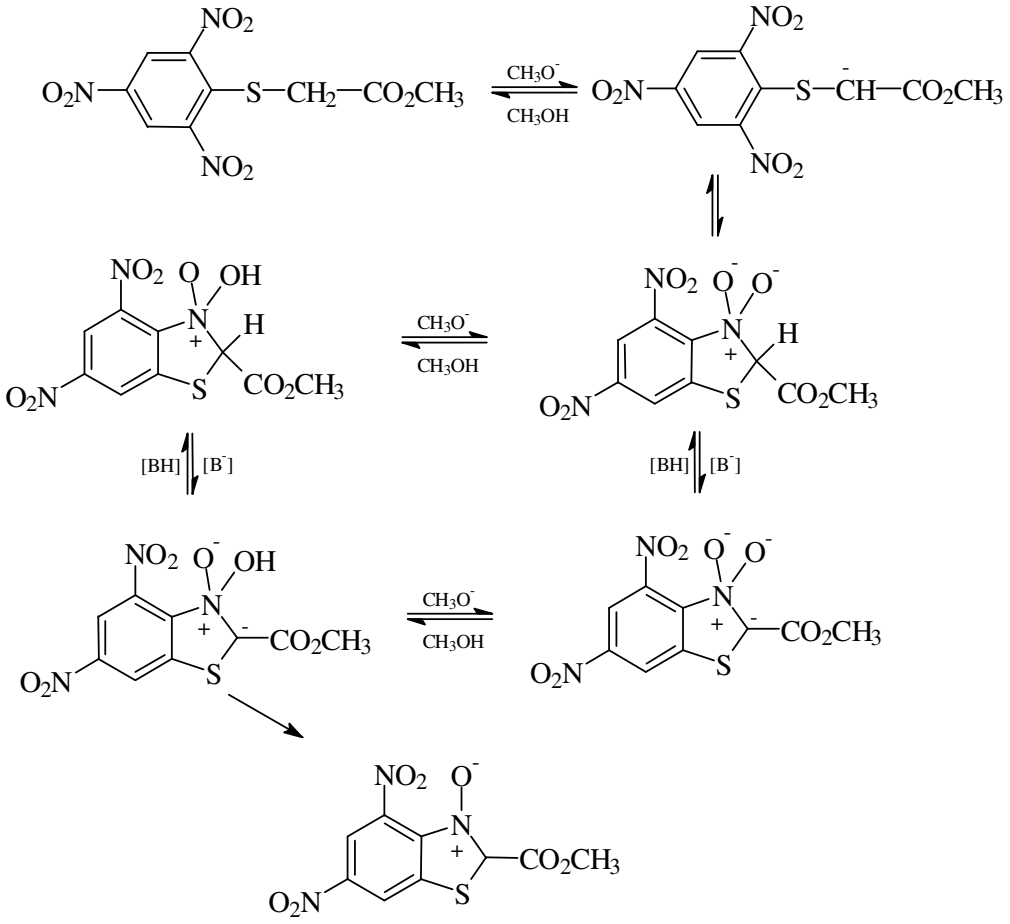
A formation of 2-propyl-5-nitrobenzothiazole on reduction of 2,4-dinitro-butylthiobenzene with sodium polysulfite or trimethylphosphite has been observed.[216]

para-Toluenesulfonate 2,5-dimethyl-7-nitrobenzothiazole was obtained under the action of excess thioacetic acid on *N*-(4-methyl-2,6-dinitrophenyl)pyridinium.[217] The reaction involves the formation of 4-methyl-2,6-dinitrothiophenol acetate in which, under experimental conditions, one of the nitro groups is reduced to an amino group with subsequent cyclization, as shown in Scheme 52.



Scheme 52

Kinetics of the formation of 2-methoxycarbonyl-5,7-dinitrobenzothiazole-3-oxide by cyclization of *S*-(2,4,6-trinitrophenyl)mercaptoacetate in acetate, methoxyacetate or *N*-methylmorfoline buffers has been studied.[218] In the first two buffers the cyclization follows two reaction pathways, which differ in the order of reaction steps, the proton splitting off from the C-H group being the rate-limiting step in either pathway (Scheme 53).



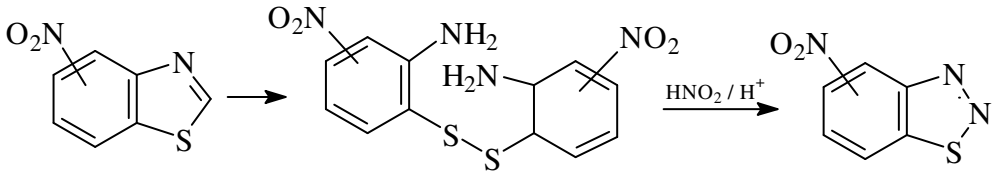
Scheme 53

In *N*-methylmorpholine buffer an increase in the concentration of the base results in a gradual decrease of the reaction order in the base and a change in the rate-limiting step of cyclization.[218]

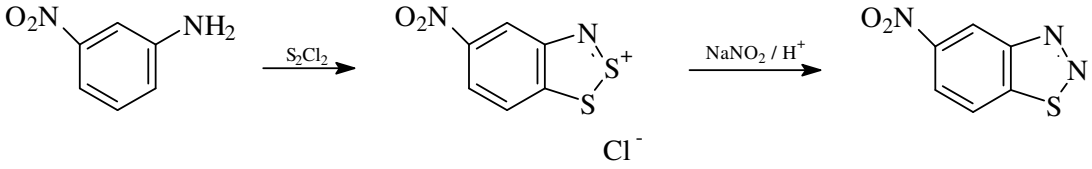
The synthesis, structure and superoxide dismutase mimetic activity *in vitro* and the protection against reactive oxygen species *in vivo* of mononuclear copper complexes with 2-(4-methylphenylsulfamoyl)-6-nitrobenzothiazole have been reported.[219]

Like 1,2,3-benzoxadiazoles, nitroderivatives of 1,2,3-benzothiadiazoles were obtained on diazotization of the corresponding *ortho*-aminothiophenoles.[164,220,221] The initial *ortho*-thiophenols for this reaction were synthesized by nucleophilic substitution of halogen in *ortho*-halogenoanilines. It turned out that 4-nitro- and 6-nitrobenzothiazoles on boiling with hydrazine in ethanol transformed to the corresponding disulfides, which form 4- or 6-nitro-1,2,3-benzothiadiazoles under the effect of nitrous acid (Scheme 54).[222]

An attempt to synthesize 5- or 7-nitro-1,2,3-benzothiadiazoles in this way was unsuccessful. *meta*-Nitroaniline reacts with sulfur monochloride (Herz's reaction), whilst 1,2,3-benzothiazathiolium chloride with nitrous acid gives a small amount of 5-nitro-1,2,3-benzothiadiazole, according to Scheme 55.[221,223]

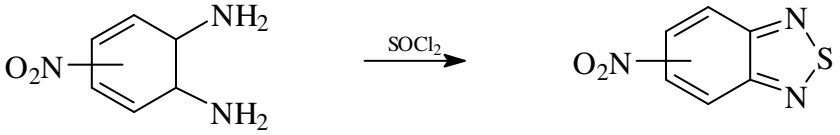


Scheme 54



Scheme 55

Different derivatives of 2,1,3-nitrobenzothiadiazole (earlier called nitropiazthiole) are obtained in the reaction between thionylchloride and the corresponding 1,2-diaminobenzenes.[224-231] Some of them, in particular, 4-nitro-2,1,3-benzothiadiazole (and also 4-nitro-2,1,3-benzoselenodiazole - nitropiazselenols), are effective against fungus diseases of cotton plants and grapes (Scheme 56).[231]

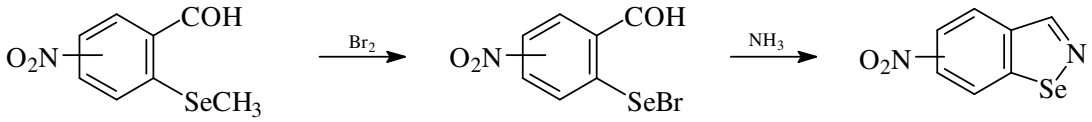


Scheme 56

Sulfinylaniline[229,232] or sulfur monochloride[233] can be used as cyclizing agents. The formation of 5-nitro-2,1,3-benzothiadiazole in the reaction of 2,4-dinitroaniline with sulfur monochloride has been observed. Here the reduction of substrate to 4-nitro-1,2-diaminobenzene followed by cyclization takes place.[233]

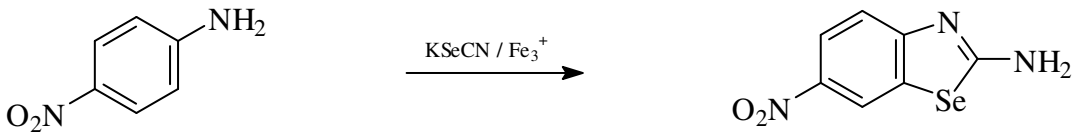
1.3. Nitrobenzisoselenazoles, nitrobenzoselenazoles, nitrobenzoselenodiazoles

Analogously to the formation of 5-nitrobenzisothiazole,[135] 5- and 7-nitrobenzisoselenazoles can be obtained in the reaction of 3- or 5-nitro-2-methylseleno-benzaldehyde with bromine and ammonia (Scheme 57).[234]



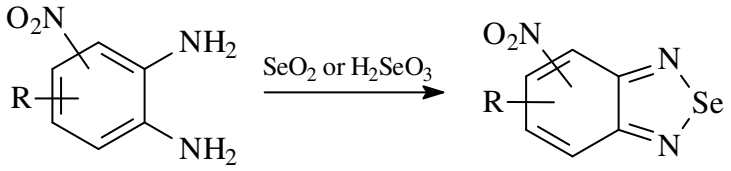
Scheme 57

para-Nitroaniline reacts with potassium selenocyanate in the presence of iron(III) salts to form 2-amino-6-nitrobenzoselenazole (Scheme 58).[235]



Scheme 58

The reaction of selenium dioxide or selenic acid with nitro-1,2-diaminobenzenes leads to the corresponding nitro-2,1,3-benzoselenodiazoles (Scheme 59).[225,227,231,236-246]



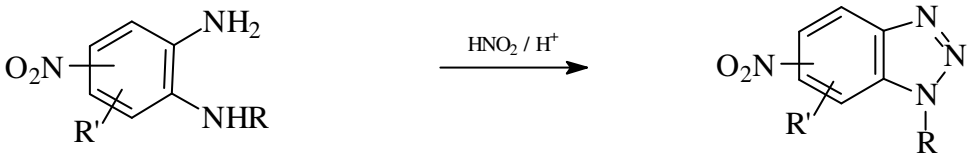
R = H, Alk, OAlk, Hal, Aryl

Scheme 59

In the literature[242-246] there are the results of quantitative investigations into the reaction of complex formation of H_2SeO_3 and aromatic *ortho*-diamines, –R–$C_6H_3(NH_2)_2$, which allow an accurate determination of the composition of the mixture at any pH, which is widely used in analytical chemistry of selenium.

1.4. Nitrobenzotriazoles

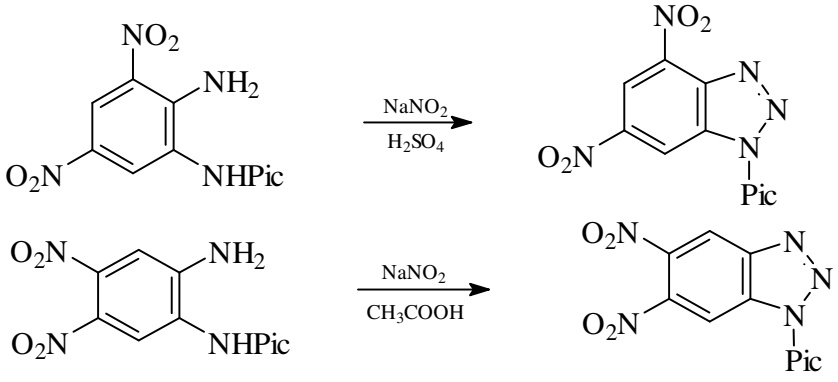
The most common and convenient way of obtaining nitro-1(*H*)-benzotriazoles is the condensation of nitro-1,2-phenylendiamines with nitrous acid.[247-261] In most cases this reaction is undertaken in the medium of hydrochloric acid or lower carboxylic acids - HCOOH, CH_3COOH (Scheme 60).



R = H, Alk, Ar, OH, OAlk, Het, SO_2Alk, SO_2Ar', R' = Alk, OCH_3

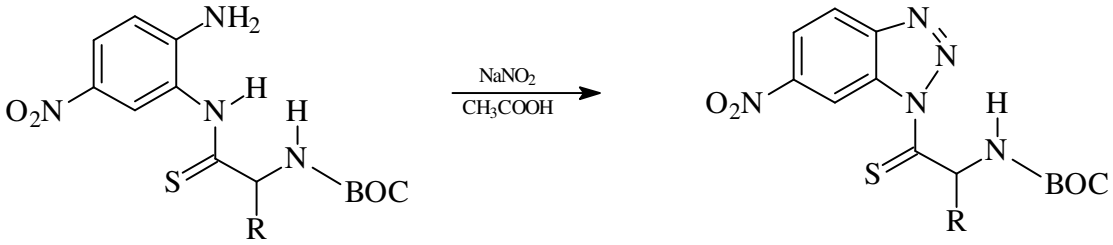
Scheme 60

High energy materials such as 4,6-dinitro-1-(2',4',6'-trinitrophenyl)- and 5,6-dinitro-1-(2',4',6'-trinitrophenyl)benzotriazole have been obtained by treating the corresponding *ortho*-phenylendiamines with sodium nitrite in sulfuric and acetic acids, respectively (Scheme 61).[262]

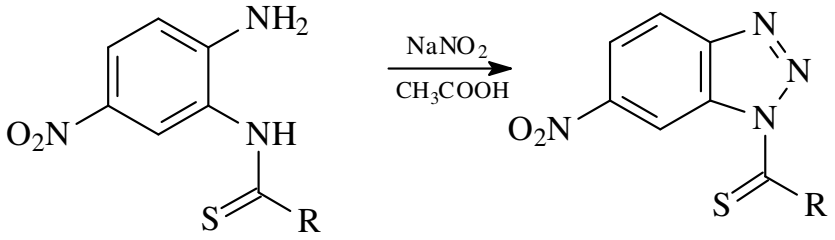


Scheme 61

The derivatives of nitrobenzotriazole α-aminothionic acids, used as thioacylating agents in the synthesis of thiopeptides and nitrobenzotriazole thioacylating reagents have been obtained in a similar way (Scheme 62).[263,264]



R = CH_3, CH_2Ph, $CH(CH_3)_2$, CH_2OBn, $CH_2CO_2CH_3$, $CH_2CO_2Bu^t$

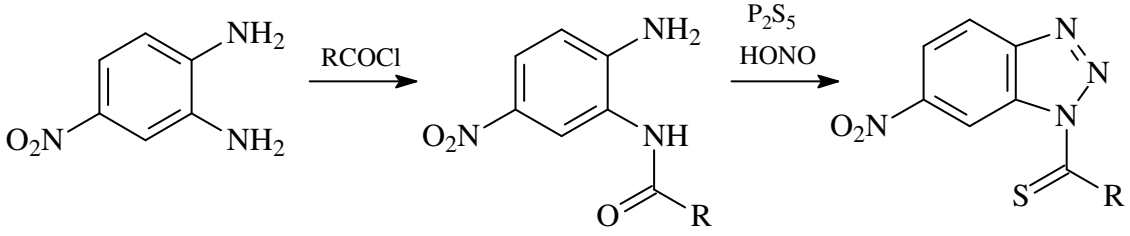


R = $CH(OAc)CH_2CO_2CH_3$, $CH(OAc)Ph$, $CH{=}CHCO_2CH_3$—
$CH{=}CHCH_3$, $CH{=}CH_2$, $CH{=}CHPh$

Scheme 62

Thioanilides are treated with sodium nitrite either in the medium of glacial acetic acid or in 70% acetic acid to form the corresponding nitrobenzotriazoles in good yield (72–83%). In general, terms the stability of non-benzenoid thiocarbonylbenzotriazoles is poor. Rapoport[263,264] obtained aliphatic nitrated thiocarbonylbenzotriazoles. Probably, the electron-withdrawing nitro group in the benzotriazole ring improves the stability and allows to isolate aliphatic thiocarbonylbenzotriazoles.

Following this method, the Katritzky team has prepared several novel aliphatic and aromatic thiocarbonyl-1*H*-6-nitrobenzotriazoles, as shown in Scheme 63.[265]



Yeilds of thiocarbonyl-1*H*-6-nitrobenzotriazoles (R, %)

R	%	R	%
ethyl	84	4-methoxyphenyl	86
4-methylphenyl	98	4-bromophenyl	99
2-furanyl	95	pentyl	81
4-nitrophenyl	83	2-thienyl	91

Scheme 63

Interaction of 4-nitro-1,2-phenylendiamines with the respective acid chlorides gave regioselectively amides (83-99%). Resonance and inductive effect of the nitro group lowered the nucleophilicity of the amino group in the *para*-position, leaving the *meta*-amino group to attack the carbonyl of acid chloride. Intermediated amides were converted to thiocarbonyl-1*H*-6-nitrobenzotriazoles crude yields by stirring at room temperature with phosphorus pentasulfide.

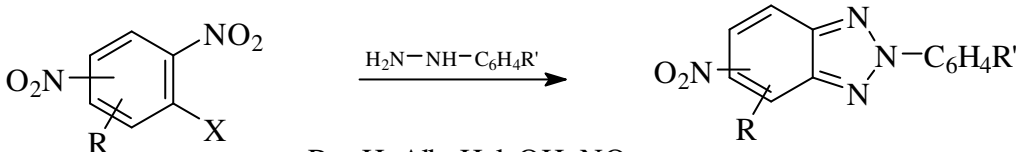
1-Alkyl-5-nitro-1*H*-benzotriazoles in excellent yield (90%) and purities (95%) were obtained, as illustrated in Scheme 64.[266]

Scheme 64

Commercially available 2-fluoro-5-nitroaniline was diazotized and coupled to benzylamino-methylpolystyrene to give the immobilized triazene. After nucleophilic displacement with primary amines to furnish an aniline resin, the cleavage with trifluoroacetic acid in dichloromethane proceeded smoothly at room temperature within minutes, resulting to nitrobenzotriazoles.[266]

4-Nitrobenzotriazole possessing an excellent herbicidal activity[267] has been prepared on oxidizing 2-acetylamino-6-nitrophenylhydrazine with chlorine.[268] *N*-Chloro derivative of 4-nitrobenzotriazole is used as oxidizer of alkylamines.[269]

The most widely accepted way to the synthesis of 2*H*-benzotriazole nitroderivatives is the condensation of *ortho*-substituted halogenodinitro- or halogenopolynitrobenzenes with phenylhydrazine (Scheme 65).[251,256,270-281]

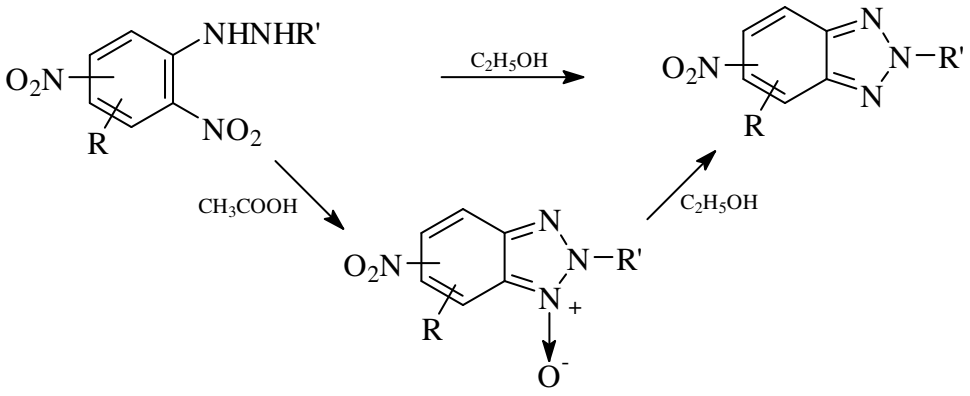


R = H, Alk, Hal, OH, NO_2

R' = Alk, Hal, NO_2 X = Hal

Scheme 65

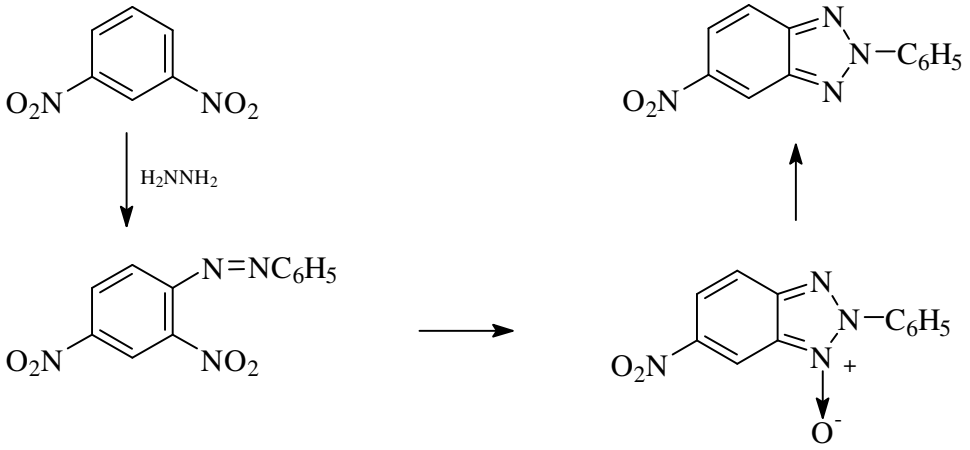
The initial stage of this reaction involves a nucleophilic halogen substitution followed by intermolecular redox cyclization of *ortho*-nitrohydrazobenzenes.[282] Instead of halogen, the substrate can contain another group (NO_2, OAlk).[283-285] It has been shown that in ethanol the above-mentioned reaction proceeds with the formation of 2*H*-benzotriazole nitro derivatives, whereas in acetic acid their *N*-oxides are formed and, when boiled in ethanol, turn into the final products (Scheme 66).[277,278,286]



R = H, Alk, Hal, OH, NO_2; R' = Ar

Scheme 66

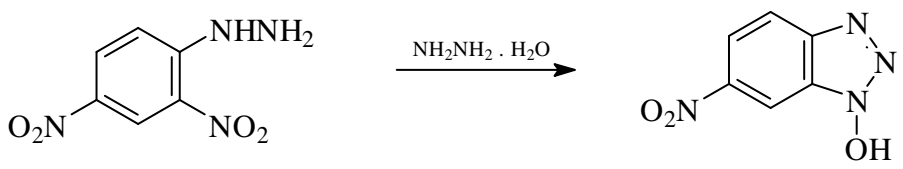
The reduction of 2,4-dinitroazobenzene by hydrazine in ethanol to 6-nitro-2-phenylbenzotriazole has been carefully studied.[287] The authors have proved that it goes *via* the formation of two intermediate products, *i.e.* 2,4-dinitrohydrazobenzene and 6-nitro-2-phenylbenzotriazol-1-oxide which is obtained from the former as a result of cyclization (Scheme 67).



Scheme 67

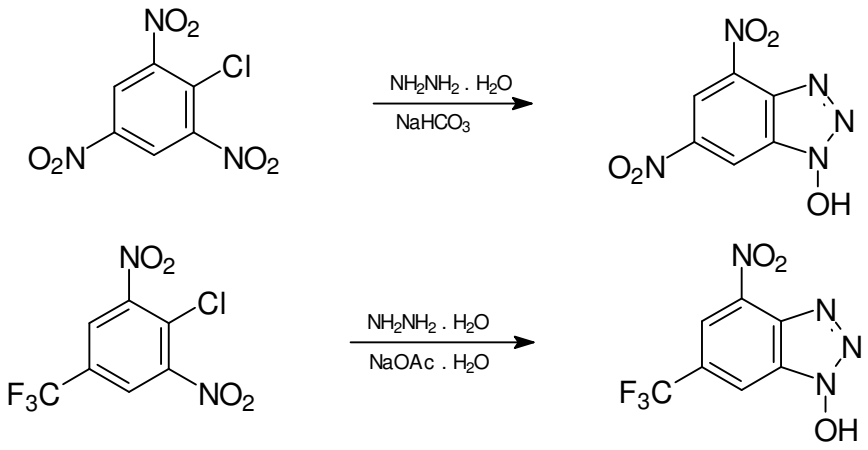
The reaction of cyclization of 2,4-dinitrohydrazobenzene is described with a first order kinetic equation. The reaction rate depends on the pH-value. In the pH range of 6.5–9.5 the rate constant is linearly dependent on the concentration of OH-ions.

A synthesis of 1-hydroxy-6-nitrobenzotriazole from 2,4-dinitrophenylhydrazine has been described (Scheme 68).[287]



Scheme 68

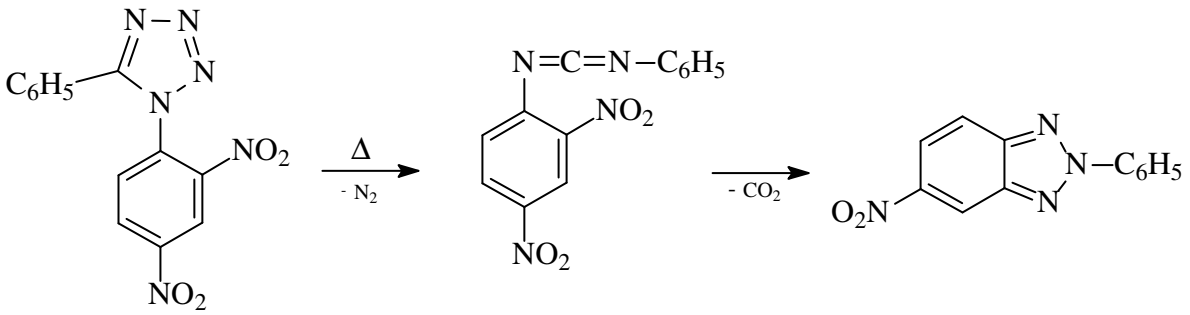
1-Hydroxy-4,6-dinitrobenzotriazole[288,289] and 1-hydroxy-4-nitro-6-trifluoromethylbenzotriazole[289] have been synthesized in a similar manner. Later[290] an improved synthesis of these compounds from the corresponding chlorinated nitrobenzenes with excess hydrazinium hydrate has been proposed (Scheme 69).



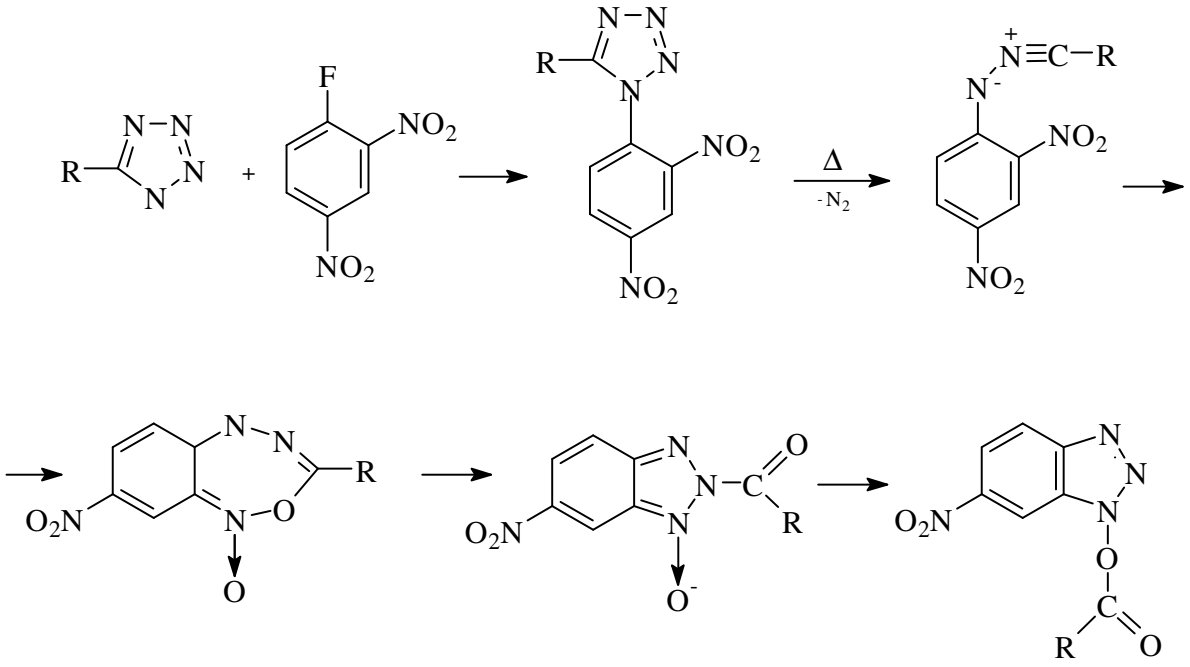
Scheme 69

The melting points of these compounds are significantly higher than those of compounds obtained by the method described in reference.[289]

1-(2,4-Dinitrophenyl)-5-phenyltetrazole on heating turns to 2-phenyl-5-nitrobenzotriazole, according to Scheme 70.[291,292]



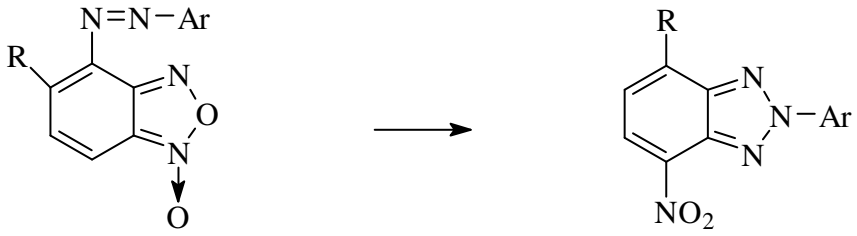
Scheme 70



Scheme 71

At the same time, the pyrolysis of its isomeric 2-substituted tetrazole results in 1-aroyloxy-6-nitrobenzotriazoles, as demonstrated in Scheme 71.[293]

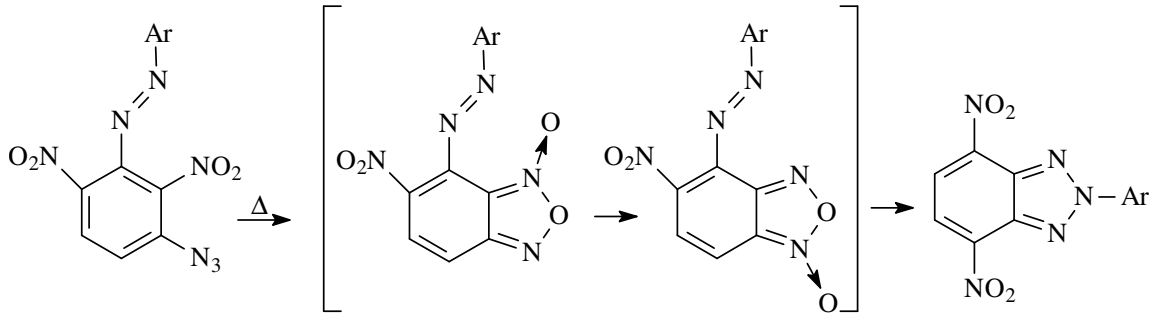
4-Azobenzofuroxanes undergo intermolecular rearrangement to form 2-aryl-7-nitrobenzotriazoles (Scheme 72).[268]



R = $N(CH_3)_2$, Cl

Scheme 72

2-Aryl-4,7-dinitrobenzotriazoles are formed as a result of two rearrangements, as shown in Scheme 73.[294]



Scheme 73

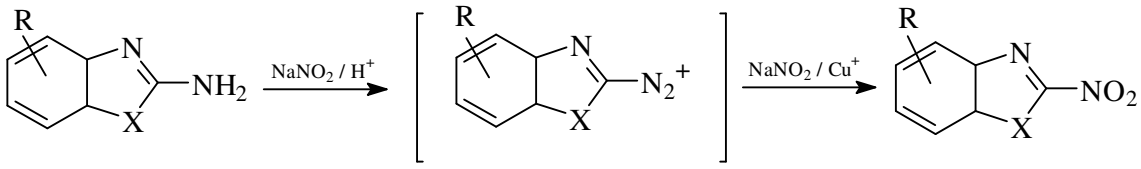
The second transformation is a version of the above-mentioned Boulton-Katrizky rearrangement.[618] Benzofuroxan was not isolated but appeared as an intermediate on heating 2,6-dinitro-3-azido-aryldiazenobenzene. The reaction starts with nucleophilic attack of the diazene fragment on the furoxan cycle nitrogen atom.[294]

2,5-Diamino-4-nitroazobenzene turns into 2-phenyl-5-amino-6-nitrobenzotriazole in the presence of copper sulfite.[295]

2. Other methods of synthesis

2.1. The Sandmeyer reaction

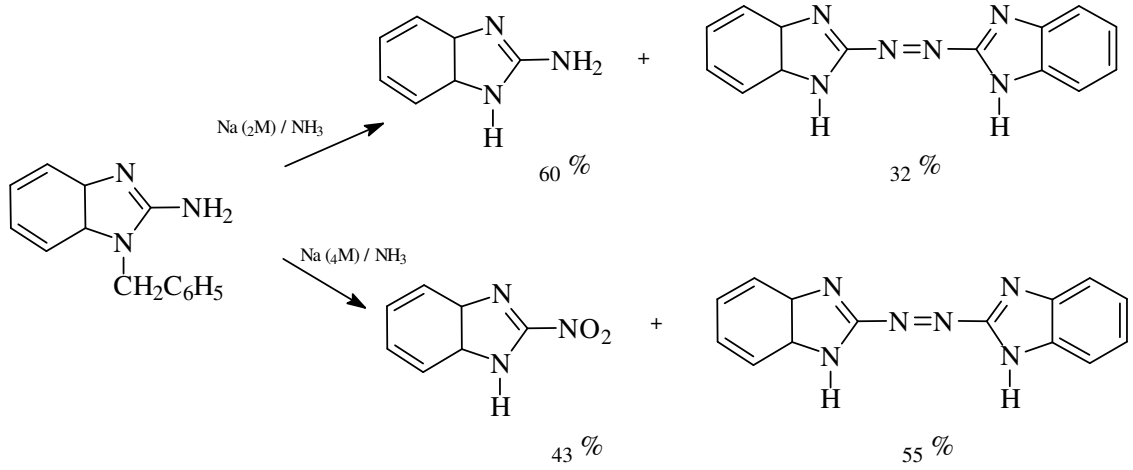
The main method of introducing of the nitro group into the benzazole cycle position 2 is Sandmeyer's reaction (Scheme 74).[296-299]



X = NH, S

Scheme 74

Pozharskii and his colleagues have established that 1-benzyl-2-aminobenzimidazole in liquid ammonia in the presence of metallic sodium turns into 2-nitrobenzimidazole and 2,2'-azobenzimidazole, as shown in Scheme 75.[300-302]

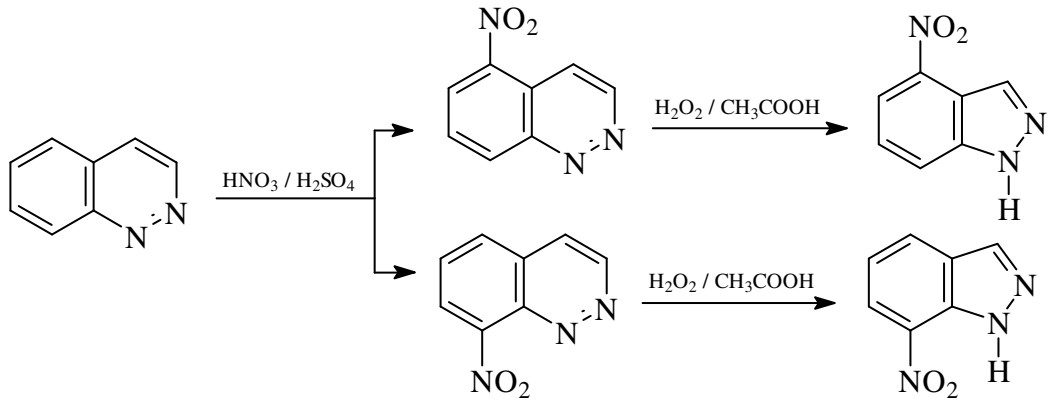


Scheme 75

The first stage of this unusual reaction involves debenzylation of the substrate to form 2-aminobenzimidazole polyanions. The formation of 2,2'-azobenzimidazolone is the result of autooxidation of 2-aminobenzimidazole di- and trianions, when 2-nitrobenzimidazole is formed, on oxidizing of anion-radicals.[301]

2.2. Recyclization

It is known that 5- and 8-nitrozinecolynes are oxidized to 4-nitro- and 7-nitroindazoles, respectively, by hydrogen peroxide in acetic acid (Scheme 76).[303]

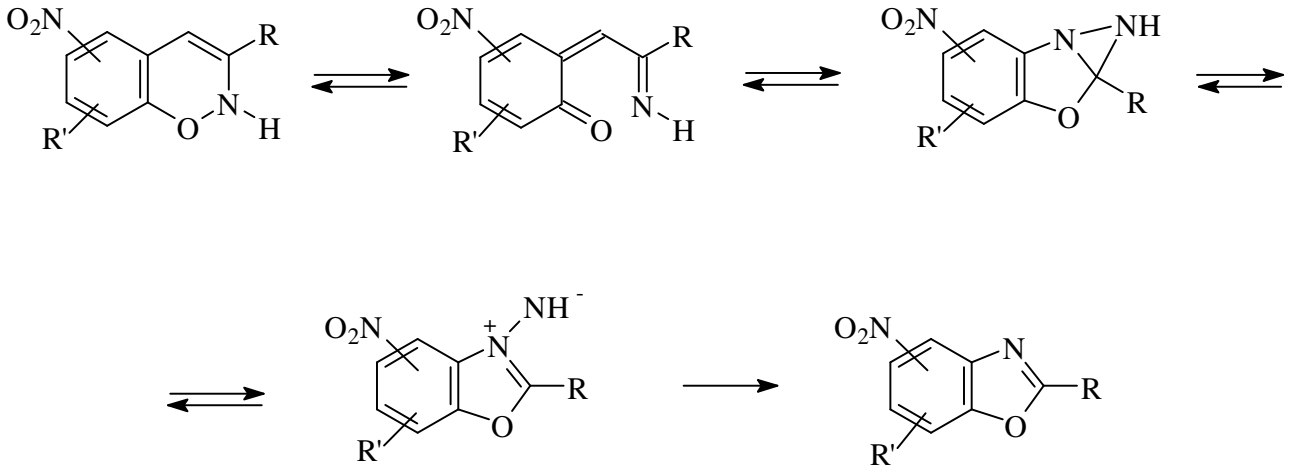


Scheme 76

This is the way the synthesis of 4-nitro[3-^{14}C]- and 7-nitro[3-^{14}C]indazole has been performed.[303]

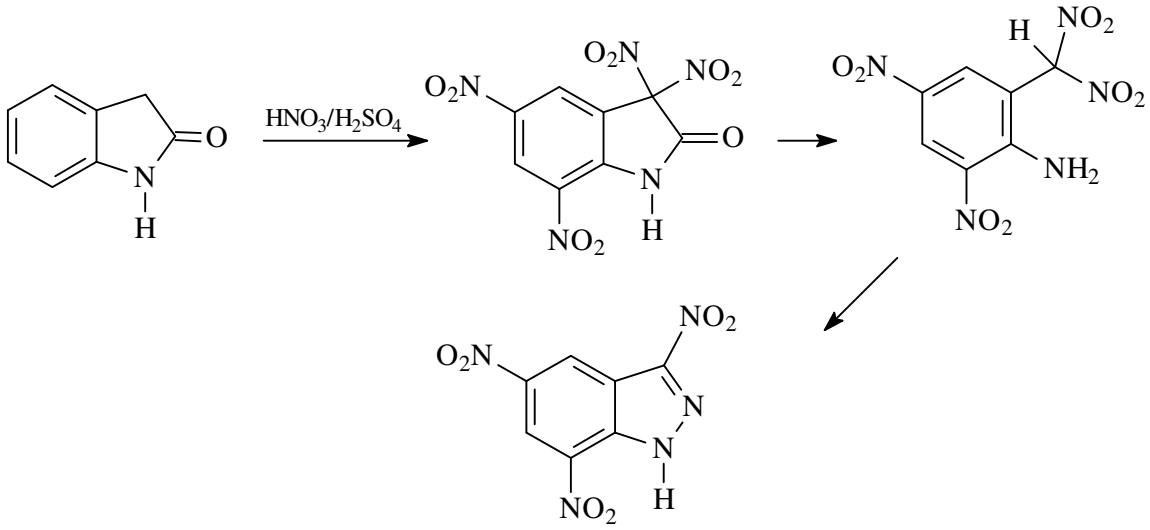
A possible mechanism of the recyclization of 1,2,4-benzoxadiazones to form the corresponding benzoxazoles has been described, as illustrated in Scheme 77.[304]

The nitration of oxyindole leads to 3,3,5,7-tetranitrooxyindole which transforms with ring-opening and undergoes decarboxylation to form 4,6-dinitro-2-(dinitromethyl)aniline. The latter is cyclized into 3,5,7-tri-nitroindazole.[305] The mechanism of ring transformation leading to nitroindazole is not clear yet and needs detailed examination (Scheme 78).

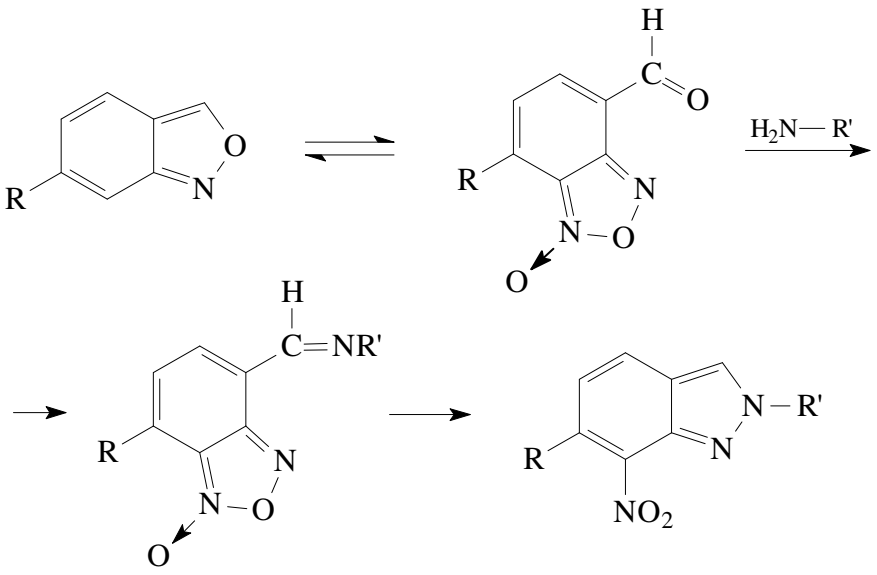


R = Ph, XPh, COOR'' ; R' = H, Ph, Hal

Scheme 77



Scheme 78



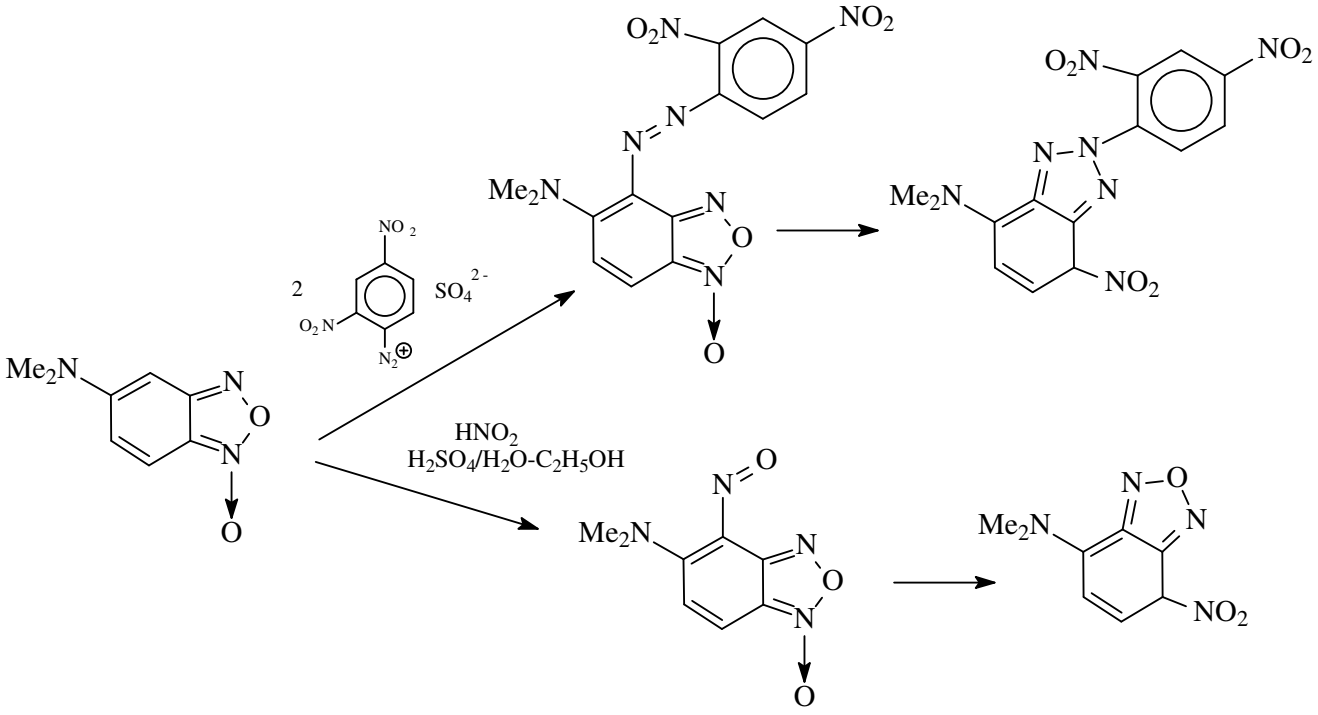
R = H, OMe, Cl; R' = Alk, Ph, CH_2Ph, OAlk, OPh, OCH_2Ph, NMe_2, NHPh

Scheme 79

Interconversions of nitroanthranils equilibrated on heating with benzofurazan *N*-oxides lead to the formation of the corresponding nitroindazoles (Scheme 79).[306,307]

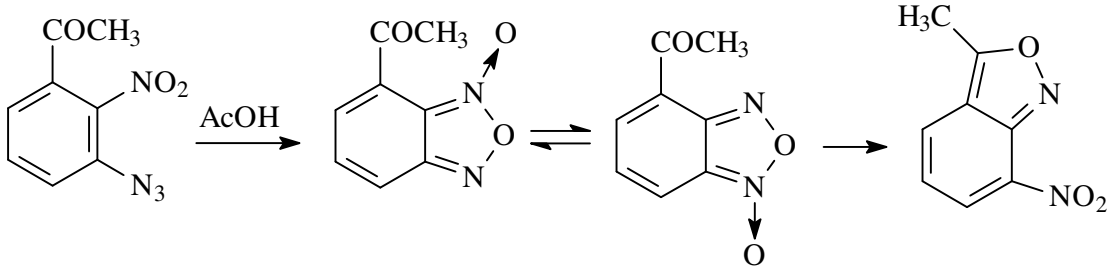
Selective reduction of nitrobenzothiazole *N*-oxides makes it possible to synthesize nitrobenzothiazoles, which so far were difficult or inaccessible to prepare.[308-311]

Nitrated benzotriazole and benzofurazan were obtained as a result of an interesting rearrangement in the reaction of 5-dimethylaminobenzofuroxan with 2,4-dinitrobenzenediazonium sulfate or with HNO_2 in H_2SO_4/H_2O-C_2H_5OH (Scheme 80).[312]



Scheme 80

Similarly, heating of 2-NO_2-3-N_3-$C_6H_3COCH_3$ in AcOH to 120 ^oC gave nitroanthranyl, and not the intermediate benzofuroxan system, as shown in Scheme 81.[312]



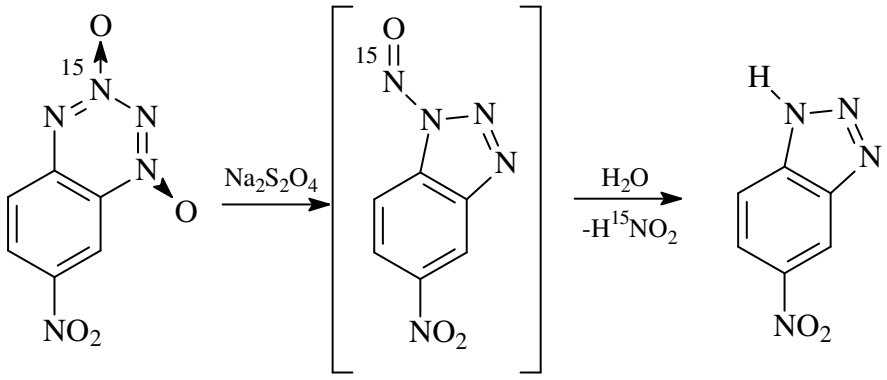
Scheme 81

4,6-Dichloro-5,7-dinitrobenzofuroxan was transformed to 4,6-dichloro-5,7-dinitrobenzofurazan by PPh_3 polymer support.[313]

5(6)-Nitrobenzotriazole was obtained by reduction of benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) with $Na_2S_2O_4$ or $SnCl_2$ *via* intermediate *N*-nitrosobenzotriazoles (Scheme 82).[314]

The ^{15}N-labeling experiments have shown that the ^{15}N-3-labeling atom of N →O fragment of the tetrazine ring is incorporated into the nitroso group of benzotriazole. The authors[314] have suggested the

biological activity of BTDOs to be due to their ability to release nitrosating species, *i.e.*, *N*-nitroso-benzotriazole, in the course of reduction.



Scheme 82

It has already been shown that the nitration with nitric acid in acetic anhydride provides the general way of obtaining *N*-nitroheterocycles. As an alternative synthesis of the above compounds, and, in particular, 1-nitrobenzotriazole, the reaction of 1-chlorobenzotriazole with the silver nitrate-triphenylphosphite-complex can be suggested.[315]

3. Conclusions

The azoles occupy an important place in the chemistry of heterocyclic compounds. Their unique properties and specific biological activity attract much attention of scientists worldwide. A much used and convenient method for the preparation of nitroazoles is the electrophilic nitration. Electrophilic substitution reaction of azoles and benzazoles is a complex process in which the experimental conditions can modify the product orientation. The ability of azoles to electrophilic substitution is determined by the activity of reagents, the basicity of substrates and the acidity of medium. The existence of an annelated benzene ring in the benzazole molecule influences much its ability for electrophilic substitution – all benzazoles are more easily nitrated than their five-membered analogs – and the nitro group is generally introduced into the arylene fragment of the molecule.

The nitration of benzazoles are usually effected using concentrated (65%) to fuming (100%) nitric acid generally at temperature between 0 – 5 ^{o}C. Indazoles are usually nitrated into 5 position, benzimidazoles – as rule into 5- or 6-position of the phenylene fragment whereas benzotriazole – into position 4 or 7. For the preparation of other nitrobenzazoles the reaction of heterocyclization is used.

The nitrobenzazoles are adequate precursors for the preparation of high energy aminonitro compounds. With this aim in view, the nitroazoles are widely used in the reaction of vicarious nucleophilic substitution (VNS) of hydrogen. Vicarious nucleophilic *C*-amination, practically, the single method of direct introduction of the amino group into nitro compounds. Using the VNS reaction we have successfully carried out the *C*-amination of some representatives of nitrobenzazoles, nitroazoles and model compounds thereof and studied the structure of aminated products and the *C*-amination mechanism.[316-320]

Acknowledgments

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