3-ACYLAMINO-2*H*-PYRAN-2-ONES AS DIENES IN DIELS-ALDER REACTIONS

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Krištof Kranjc

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia

(e-mail: kristof.kranjc@fkkt.uni-lj.si)

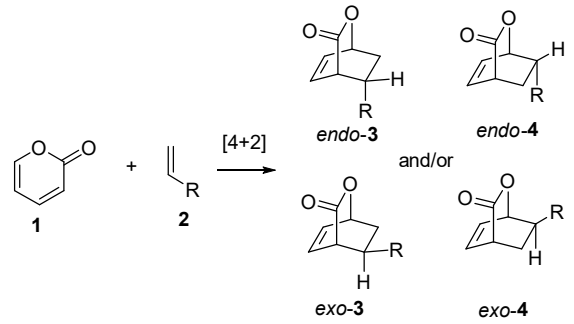
Abstract. *3-Acylamino-2H-pyran-2-ones represent dienes useful for a wide variety of Diels-Alder reactions. When alkynes are used as dienophiles unstable 4-acylamino-2-oxabicyclo[2.2.2]octa-5,7-dien-3-one systems formed initially are in situ transformed (with the elimination of CO_2) into the final aromatic products (aniline derivatives). However, when alkenes are used as dienophiles, the primary cycloadducts 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-ones can be isolated in some cases; otherwise elimination of CO_2 yields cyclohexa-1,3-diene intermediates (also these can be occasionally isolated), which most often react as new dienes yielding final "double" cycloadducts (1-acylaminobicyclo[2.2.2]oct-2-enes) or they undergo aromatization (oxidation) to final aromatic products. Albeit all these reactions can yield a multitude of different products and also many regio- and stereoisomers are often possible, recent advances in the field enable to carefully select reaction conditions and thus steer the transformations toward the desired product, moreover, toward the desired regio- or stereoisomer.*

Contents

1. Introduction

The centennial of the appearance of the landmark paper by Diels and Alder[1] is approaching and the reaction named after them has in this time advanced to one of the most important strategies for the construction of new C–C bonds, in particular cyclic six-membered carbocycles.[2] When there is one (or more) hetero atom in the reacting partners, such cases being termed hetero-Diels-Alder reactions, synthesis of heterocyclic rings is also possible. Diels-Alder reaction, known also as [4+2]-cycloaddition is one example of a pericyclic reactions taking place between a diene (having 4π electrons) and a dienophile (with 2π electrons). For this reaction to be thermally allowed, both partners have to react suprafacially according to the Woodward–Hoffmann rules.[3] Pericyclic reactions are controlled by orbital symmetry and their course is thus highly regio- and stereospecific.[4-6] Certain rules, partially empirical, help to predict the structure of the major (or the only) product obtained.[7] Such is the *cis* rule, which states that the configuration of diene and dienophile is conserved in the product; the other one is (Alder) *endo* rule stating that products will be preferentially formed *via endo* transition state, its stability often explained by secondary orbital interactions.[8,9] Regioselectivity is controlled by the orbital coefficients of the terminal atoms of both

partners. Thus a [4+2]-cycloaddition between a 2*H*-pyran-2-one ring **1** acting as a diene and a suitable dienophile (alkene), such as **2**, yields in the first step a carbon dioxide-bridged 2-oxabicyclo[2.2.2]oct-5-en-3-one system (Scheme 1). If the dienophile **2** was not symmetric, two different regioisomers **3** or **4** can be formed and each of these can exist as two different stereoisomers (*endo* and *exo*); all of these products being pairs of enantiomers.



Scheme 1. General Diels-Alder reaction between 2*H*-pyran-2-one ring **1** and alkene **2** as dienophile yielding four stereoisomers of 2-oxabicyclo[2.2.2]oct-5-en-3-one systems (each of the products shown can exist as a pair of enantiomers).

Even though pericyclic reactions do not include charged intermediates, the electronic effects of the substituents are still important for the reactivity and regioselectivity. In this regard, three possibilities can be discerned: (i) Diels-Alder reactions with normal electron demand (NED) are when electron flow is from the HOMO of the diene to the LUMO of the dienophile (meaning that this energy gap is far smaller than the other one, *i.e.* between HOMO of the dienophile and LUMO of the diene), (ii) with inverse electron demand (IED) when electron flow is taking place from the HOMO of the dienophile to the LUMO of the diene, (iii) neutral electron demand when the energies of both gaps are comparable and electron flow can take place either between HOMO of the diene and LUMO of the dienophile or HOMO of the dienophile and LUMO of the diene. Thus, when a diene is electron rich (*i.e.* contains electron-donating groups) and/or dienophile is electron poor (*i.e.* contains electron-withdrawing groups), NED Diels-Alder reactions are taking place.

Two other mechanistic aspects of cycloadditions are important, namely the concept of the reaction being concerted and/or synchronous; both of these are connected with the symmetry or asymmetry of the transition state. Albeit for a transformation to be classified as a pericyclic reaction, it is required to be concerted, the synchronicity of pericyclic reactions is far more debatable, however in this regard mostly only computation studies are available.[10-14] On the other hand, both aspects are reflected in the regio- and stereoselectivity of the product(s) obtained in pericyclic reactions, including Diels-Alder reaction.

However, a word of caution is necessary; not all reactions yielding products that look like Diels-Alder cycloadducts actually take place *via* pericyclic mechanisms. For example, when reacting partners are strongly electronically perturbed, zwitterionic or biradical intermediates might be formed (such reactions are of course not pericyclic anymore), thus decreasing or changing the regio- and stereoselectivities predicted (and expected) for a pericyclic process.

Diels-Alder reactions can also take place in an intramolecular fashion. Pericyclic reactions are in general reversible processes and thus retro-Diels-Alder reactions can take place; they can sometimes cause unfavourable position of the equilibrium thus diminishing the synthetic utility of such processes in some cases.

Preparation of a variety of substituted 3-acylamino-2*H*-pyran-2-ones is rather straightforward, the most often-used procedure[15-18] starts from a carbonyl compound (containing an activated CH_2 or CH_3 group) and a suitable C_1-synthon (for example, *N*,*N*-dimethylformamide dimethyl acetal, diethoxymethyl acetate, triethyl ortoformate, trimethyl ortoformate) which upon heating form the intermediary *N*,*N*-dimethylaminomethylene derivative. Thereafter, volatile components (excess of C_1-synthon and methanol formed as the side product) are removed in vacuum and the remainder is reacted with an

N-acylglycin (hippuric acid, aceturic acid *etc.*). Acetic anhydride is used as the solvent and concomitant dehydration agent transforming *N*-acylglycin into corresponding 2-substituted oxazol-5(4*H*)-one which reacts with the intermediate from the first step *via* ring-opening/ring-closing mechanism towards the desired 2*H*-pyran-2-one skeleton. Their structures were in some cases also confirmed by single-crystal X-ray diffraction.[19] When *N*,*N*-dimethylacetamide dimethyl acetal is used as the C_1-synthon, 4-methyl substituted derivatives are formed.[20] In some cases, efficient access to substituted 2*H*-pyran-2-ones can also be established by reacting 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone with a variety of activated methylene compounds under acidic or basic conditions.[21] Additionally it is worth mentioning that 2*H*-pyran-2-one rings can be efficiently transformed into a variety of hetero- and carbocycles,[22] as well as into α,β-didehydro-α-amino acid derivatives.[23,24]

2. 3-Acylamino-2*H*-pyran-2-ones as dienes in Diels-Alder reactions: general reaction pathways

Classically, 2*H*-pyran-2-ones can be represented as cyclic dienes, although they display some properties of aromatic compounds (thus being prone to electrophilic substitutions). Their partial aromaticity was demonstrated by some spectroscopic properties (NMR, UV), however it is estimated that 2*H*-pyran-2-ones possess only 20-40% of aromatic stabilization energy that benzene has.[25,26] However, it would be more appropriate to compare 2*H*-pyran-2-ones with phenol (and its derivatives) and not with benzene.

Aromatic stabilization can have two important effects on the outcome of Diels-Alder reactions. Activation energy for reactions of (at least partially) aromatic systems (1,3-dienes) is higher when compared with nonaromatic systems, thus the latter need less energy to overcome the activation barrier. For a practical synthetic application, this often means that 2*H*-pyran-2-ones need harsher reaction conditions (higher temperatures) to react as dienes in Diels-Alder reactions than other nonaromatic cyclic dienes. The other important property of Diels-Alder reactions is their reversibility (at least generally); thus starting materials that are aromatically stabilized (meaning they are more stable) are more likely to prevail when the equilibrium is reached, consequently decreasing the conversion of such cycloadditions. The latter is in the case of 2*H*-pyran-2-ones used as dienes important only in the first cycloaddition step, before CO_2 elimination (*vide infra*). Overall, it is easy to imagine that substituents that enable additional electron delocalization increase the aromatic stabilization of such substituted 2*H*-pyran-2-ones and thus decrease their reactivity as dienes in Diels-Alder reactions.

Unsubstituted 2*H*-pyran-2-ones are *per se* polarized dienes; their polarization can be roughly compared with acyclic 1,3-diene system having at one terminal an electron-withdrawing carboxylate group (ester) and at the other end an electron-donating oxycarbonyl group. With this approximation, it is possible to estimate regioselectivity of Diels-Alder reactions. Empirically it was established that unsubstituted 2*H*-pyran-2-ones are electron-rich (nucleophilic partners) and thus appropriate for participation in NED Diels-Alder reactions (meaning that electron-poor dienophiles react best). However, regioselectivity of such transformations is usually found to be rather low, most probably due to weak polarization of 2*H*-pyran-2-one diene system. Additional electron-donating substituents can thus further increase reactivity with electron-poor dienophiles (NED reactions). On the other hand, strong electron-withdrawing group(s) can decrease the electron density of 2*H*-pyran-2-one systems profoundly enough to enable them to react with electron-rich dienophiles (thus reacting in IED reactions). Both cases of electron density perturbation, however, result in markedly increased regioselectivity.

To approximately predict the electronic demand of a particular Diels-Alder reaction with substituted 2*H*-pyran-2-ones, a correlation with the effect that these substituents have on the activation or deactivation of a benzene ring for electrophilic aromatic substitution is a useful estimation.[27] Groups that activate aromatic system for electrophilic aromatic substitution (*i.e.* electron-donating substituents) also increase the likelihood that a 2*H*-pyran-2-one substituted with such groups will react according to NED Diels-Alder reaction. On the other hand, groups that deactivate the benzene ring for electrophilic aromatic substitution (*i.e.* electron-withdrawing groups), increase the possibility for the IED Diels-Alder reactions. Posner *et al.*[28] correlated ^{13}C NMR shifts of C-6 nuclei of 3-substituted 2*H*-pyran-2-ones with electron demand, however this approach was successful only in the cases having similar substitution patterns. Recently, Afarinkia *et al.*[29] reported on 5-*tert*-butylcarbamate substituted 2*H*-pyran-2-one that was shown to be an adequate diene for cycloaddition reactions with both, electron-rich and electron-deficient dienophiles, thus termed to be a

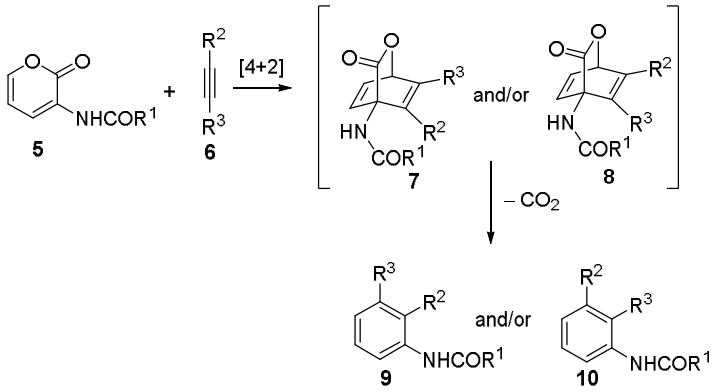
"chameleon" diene, forming oxabicyclo[2.2.2]octenes in both cases, however dienophiles with electron-withdrawing groups reacted faster.

The situation in the case of 3-acylamino substituted 2*H*-pyran-2-ones is analogous to that elaborated above. Clearly, the amide group contributes to the electron density, but as its electron-donating effect is rather weak, the main contribution on the electron perturbation is still the consequence of the lactone group of the 2*H*-pyran-2-one itself, as well as other groups (if they are present).

Two different possibilities of [4+2]-cycloaddition reactions with 2*H*-pyran-2-ones should be described: (i) when alkynes react as dienophiles and (ii) when alkenes are used as dienophiles. The initial attack is identical in both cases, also the initially formed primary cyloadducts are analogous, but further transformations can differ depending upon the dienophiles used. Already in 1931 Diels and Alder reported[30] application of 2*H*-pyran-2-ones as partners in the newly discovered reaction, thus triggering a plethora of later applications and publications,[31-33] including versatile applications of cycloadditions of 2*H*-pyran-2-ones as key steps in total synthesis.[34,35]

2.1. Alkynes as dienophiles in cycloadditions with 3-acylamino-2*H*-pyran-2-ones

The first step of the cycloaddition between a 3-acylamino-2*H*-pyran-2-one system **5** (acting as a diene) and an alkyne **6** (as a dienophile) leads to carbon dioxide-bridged systems **7** or **8** (*i.e.* 2-oxabicyclo[2.2.2]octa-5,7-dien-3-one), which are very unstable (such systems were not isolated yet) and spontaneously a retro-hetero-Diels-Alder reaction takes place (elimination of a carbon dioxide molecule) yielding regioisomeric benzene systems **9** or **10** (Scheme 2). The first example of such a transformation was already reported in 1937 by Alder and Rickert.[36] The initial cycloadduct can be formed as one of two possible regioisomers **7** or **8**, however each of this can exist as a pair of enantiomers. This stereoinformation is lost upon the elimination of CO_2, thus the only structural question is the problem of regioselectivity (formation of **9** or **10**). In general terms, when substituted 3-acylamino-2*H*-pyran-2-ones **11** are involved in cycloadditions with unsymmetrically substituted alkynes the predominant (or often the only) regioisomer obtained will have substituent stemming from the dienophile positioned *ortho* relatively to the 3-acylamino group, consistent with the theoretical predictions.[7]

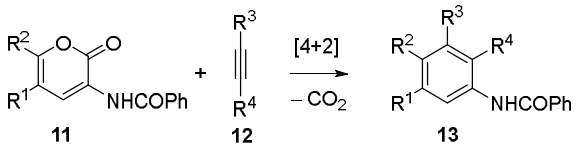


Scheme 2. Diels-Alder reaction between 3-acylamino-2*H*-pyran-2-one **5** and an alkyne **6** as dienophile.

Such cycloadditions represent a straightforward approach towards the synthesis of a wide variety of highly substituted anilines **13** as well as bi- and terphenyl systems, as demonstrated by the examples presented in Table 1.[37-42] Substituents on both partners with their variable electronic properties change electron density and thus reactivity, as is clearly reflected in the different reactions conditions needed to bring these cycloadditions to completion. When alkynes **12** used as dienophiles are unsymmetrically substituted, the regioselectivity of the cycloadditions can be investigated. In the cases presented in Table 1 only one regioisomer was obtained, the general rule being that when the starting 2*H*-pyran-2-one **11** is

4-unsubstituted (*i.e.* on the position 4 is hydrogen) and the dienophile **12** has R^3=H (for example, phenylacetylene, methyl or ethyl propiolate), the product **13** contains both hydrogens in 1,4-arrangement.

Table 1. Cycloadditions of various alkynes **12** on 3-acylamino-2*H*-pyran-2-ones **11**, yielding aromatic products **13**.



11 **12** **13**

	R^1	R^2	R^3	R^4	solvent	*T*	*t* (h)	yield (%)[d]	ref.
1	COMe	Me	CO_2Et	CO_2Et	tetralin	reflux	5	67	37
2	COMe	Me	CO_2Et	CO_2Et	neat[a]	170 °C[b]	1.5	95	38
3	COMe	Me	H	CO_2Et	tetralin	reflux	7.5	94	37
4	COMe	Me	CO_2Me	CO_2Me	neat[a]	170 °C[b]	3	93	38
5	COMe	Me	H	COMe	neat[a]	170 °C[b]	1.5	88	38
6	COMe	Me	Ph	Ph	tetralin	reflux	12	62	37
7	COMe	Me	H	Ph	tetralin	reflux	1	98	37
8	COMe	Me	H	Ph	neat[a]	170 °C[b]	0.17	91	38
9	COMe	Me	H	4-MeC_6H_4	neat[a]	170 °C[b]	0.33	87	38
10	COMe	Me	Me	NEt_2	CH_2Cl_2	r.t.	0.5	95	37
11	COPh	Me	CO_2Et	CO_2Et	tetralin	reflux	5	74	37
12	COPh	Me	H	CO_2Et	tetralin	reflux	9.75	65	37
13	COPh	Me	CO_2Me	CO_2Me	neat[a]	170 °C[b]	1.5	85	38
14	COPh	Me	H	COMe	neat[a]	170 °C[b]	1.75	82	38
15	COPh	Me	H	Ph	tetralin	reflux	1.75	88	37
16	COPh	Me	H	Ph	neat[a]	170 °C[b]	0.5	92	38
17	COPh	Me	H	4-MeC_6H_4	neat[a]	170 °C[b]	1	92	38
18	CO_2Et	Me	CO_2Et	CO_2Et	tetralin	reflux	6	75	37
19	CO_2Et	Me	H	CO_2Et	tetralin	reflux	11.5	82	37
20	CO_2Et	Me	H	CO_2Et	neat[a]	170 °C[b]	2	90	38
21	CO_2Et	Me	CO_2Me	CO_2Me	neat[a]	170 °C[b]	1.5	85	38
22	CO_2Et	Me	H	CO_2Me	neat[a]	170 °C[b]	3	86	38
23	CO_2Et	Me	H	Ph	tetralin	reflux	6	96	37
24	CO_2Et	Me	H	Ph	neat[a]	170 °C[b]	1.5	96	38
25	CO_2Et	Me	Me	NEt_2	CH_2Cl_2	r.t.	0.5	79	37
26	CO_2Me	CH_2CO_2Me	CO_2Et	CO_2Et	tetralin	reflux	6	78	37
27	CO_2Me	CH_2CO_2Me	CO_2Et	CO_2Et	neat[a]	170 °C[b]	3.5	92	38
28	CO_2Me	CH_2CO_2Me	H	CO_2Et	neat[a]	170 °C[b]	3	87	38
29	CO_2Me	CH_2CO_2Me	CO_2Me	CO_2Me	neat[a]	170 °C[b]	2	80	38
30	CO_2Me	CH_2CO_2Me	H	CO_2Me	neat[a]	170 °C[b]	3	93	38
31	CO_2Me	CH_2CO_2Me	H	Ph	tetralin	reflux	6	76	37
32	4-$MeOC_6H_4$	Me	CO_2Et	CO_2Et	toluene	reflux	8	72	39
33	4-$MeOC_6H_4$	Me	H	CO_2Et	xylene	reflux	15	75	39
34	4-$MeOC_6H_4$	Me	CO_2Me	CO_2Me	toluene	reflux	8	86	39
35	4-$MeOC_6H_4$	Me	H	CO_2Me	xylene	reflux	15	76	39
36	4-$MeOC_6H_4$	Me	H	COMe	xylene	reflux	5.75	90	39
37	4-$MeOC_6H_4$	Me	H	Ph	xylene	reflux	15.5	75	39
38	4-$MeOC_6H_4$	Me	H	Ph	neat[a]	170 °C[b]	2.5	89	38
39	4-$MeOC_6H_4$	Me	H	4-MeC_6H_4	neat[a]	170 °C[b]	2.5	89	38
40	3,4-$(MeO)_2C_6H_3$	Me	CO_2Et	CO_2Et	toluene	reflux	9	74	39

41	3,4-$(MeO)_2C_6H_3$	Me	H	CO_2Et	xylene	reflux	15	68	39
42	3,4-$(MeO)_2C_6H_3$	Me	CO_2Me	CO_2Me	toluene	reflux	9.5	78	39
43	3,4-$(MeO)_2C_6H_3$	Me	H	CO_2Me	xylene	reflux	16.5	87	39
44	3,4-$(MeO)_2C_6H_3$	Me	H	COMe	xylene	reflux	6	80	39
45	3,4-$(MeO)_2C_6H_3$	Me	H	Ph	xylene	reflux	15.5	78	39
46	3,4-$(MeO)_2C_6H_3$	Me	H	4-MeC_6H_4	neat[a]	170 °C[b]	2.5	92	38
47	H	Me	CO_2Et	CO_2Et	xylene	reflux	10.5	69	39
48	H	Me	H	CO_2Et	tetralin	220 °C	48	44	40
49	H	Me	H	CO_2Et	neat[a]	170 °C[b]	2.5	86	38
50	H	Me	CO_2Me	CO_2Me	xylene	reflux	13.5	66	39
51	H	Me	H	Ph	neat[a]	170 °C[b]	2.5	91	38
52	CO_2Et	CF_3	H	Pr	neat	150 °C[b]	1	90	41
53	CO_2Et	CF_3	H	*i*-Pr	neat	150 °C[b]	1.5	64	41
54	CO_2Et	CF_3	H	cyclopropyl	neat	150 °C[b]	1.5	68	41
55	CO_2Et	CF_3	H	*t*-Bu	neat	150 °C[b]	3	55	41
56	CO_2Et	CF_3	H	-$(CH_2)_2$CN	neat	150 °C[b]	1	73	41
57	CO_2Et	CF_3	H	-CH_2OH	neat	150 °C[b]	0.5	58	41
58	CO_2Et	CF_3	H	-$(CH_2)_2$OH	neat	150 °C[b]	1	74	41
59	CO_2Et	CF_3	H	-$(CH_2)_3$OH	neat	150 °C[b]	1	81	41
60	CO_2Et	CF_3	H	-$(CH_2)_4$OH	neat	150 °C[b]	1	70	41
61	CO_2Et	CF_3	H	-$(CH_2)_5$OH	neat	150 °C[b]	1	89	41
62	CO_2Et	CF_3	H	-(CH_2)-CH(OH)-CH_3	neat	150 °C[b]	1.5	67	41
63	CO_2Et	CF_3	H	-(CH_2)O-$(CH_2)_2$OH	neat	150 °C[b]	0.5	84	41
64	H	CF_3	H	Ph	neat	120 °C[c]	168	91	42
65	H	CF_3	H	*n*-pentyl	neat	120 °C[c]	168	68	42
66	H	CF_3	H	-CH_2Cl	neat	120 °C[c]	168	62	42
67	H	CF_2Cl	H	Ph	neat	120 °C[c]	168	86	42
68	H	C_3F_7	H	Ph	neat	120 °C[c]	168	80	42
69	CO_2Et	CF_3	H	Ph	neat	120 °C[c]	168	91	42
70	C(O)CF_3	CF_3	H	Ph	neat	120 °C[c]	168	76	42

[a]With the addition of small amount of *n*-BuOH. [b]Under microwave irradiation. [c]In a closed vessel. [d]Yield of isolated products.

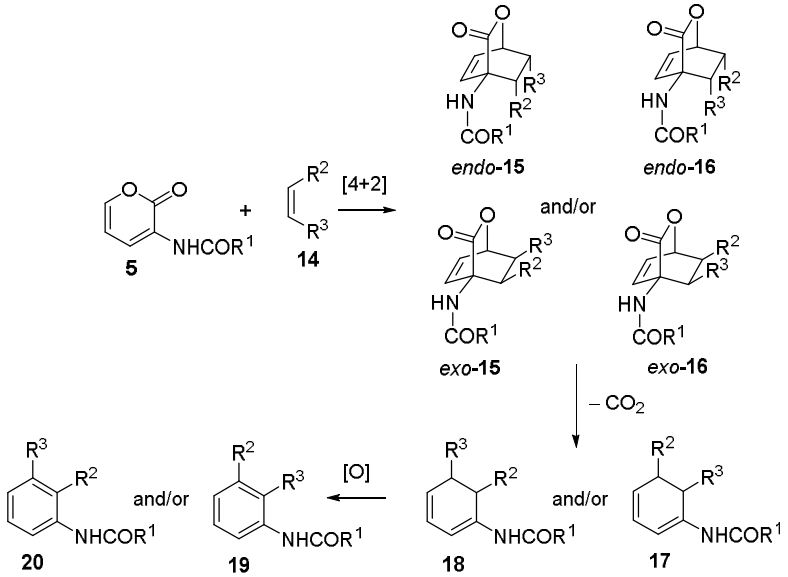
Cycloadditions that were conducted under microwave irradiation,[38] were first investigated under neat conditions (without the addition of solvent), however, it was found that the conversions were low (unless unsuitably high excess of dienophile is used). The main reason for low conversions was the volatility of the dienophiles; they were evaporating from the bottom part of the reaction vessel and depositing on the upper (cooler) part thus not being available for the cycloaddition with non-volatile 2*H*-pyran-2-one derivatives. Solution to this problem was addition of a small amount of another liquid having boiling point near the reaction temperature (typically 100 mg of *n*-BuOH was used in the case of 10 mL reaction vessels). The liquid additive helps to rinse the deposited droplets of the dienophile from the upper part of the reaction vessel back to the bottom where the cycloaddition is taking place (and where the microwave irradiation is focused). Thus, these reactions can still be termed solvent-less, albeit a liquid additive is necessary.

Some attempts on estimating relative reactivity of variously substituted 2*H*-pyran-2-ones and alkynes were also made[39] by carrying out competitive experiments, where two (or more) dienes (or dienophiles) were reacted simultaneously. Thus, the following order of decreasing reactivity for 5-substituted 3-benzoylamino-6-methyl-2*H*-pyran-2-ones was established: 5-acetyl>5-benzoyl>5-ethoxycarbonyl (with comparable reactivity to 5-methoxycarbonyl-6-methoxycarbonylmethyl derivative). Reactivity of various alkynes was estimated to be: *N*,*N*-diethylpropynamine>styrene>diethyl acetylenedicarboxylate>ethyl propynoate>diphenylacetylene. Based on these data it was concluded that cyloadditions of phenylacetylene

proceed according to IED with 5-acetyl-, 5-benzoyl-, 5-ethoxcarbonyl- and 5-methoxycarbonyl-6-methoxycarbonylmethy; 5-(4-methoxyphenyl) and 5-(3,4-dimethoxyphenyl) derivatives react *via* NED; whereas 5-unsubstituted derivative reacts according to neutral electron demand (and is the least reactive among all 2H-pyran-2-ones investigated). On the other hand, all of the above mentioned 2*H*-pyran-2-ones react according to NED with dimethyl- and diethyl acetylenedicarboxylate (in the decreasing order of reactivity: 5-(4-methoxyphenyl) and 5-(3,4-dimethoxyphenyl)>5-unsubstituted>5-acetyl>5-benzoyl>ethoxycarbonyl>5-methoxycarbonyl-6-methoxycarbonylmethy. Cycloaddition of ethyl- and methyl propynoates proceeds according to NED with 5-(4-methoxyphenyl) and 5-(3,4-dimethoxyphenyl); according to IED with 5-acetyl>5-benzoyl>ethoxycarbonyl> 5-methoxycarbonyl-6-methoxycarbonylmethy and according to neutral electron demand with 5-unsubstituted 2*H*-pyran-2-one derivative.

2.2. Alkenes as dienophiles in cycloadditions with 3-acylamino-2*H*-pyran-2-ones

As with alkynes, the first cycloaddition between an alkene **14** (acting as a dienophile) and a 3-acylamino-2*H*-pyran-2-one system **5** (as a diene) yields carbon dioxide-bridged systems **15** or **16** (*i.e.* 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-one), but these now contain just one double bond (and not two as is the case when an alkyne was used as a dienophile, *cf.* **15**, **16** and **7**, **8**) (Scheme 3). Albeit such initial cycloadducts **15** or **16** possessing 2-oxabicyclo[2.2.2]oct-5-en-3-one core are somewhat stable and can be isolated (especially if the cycloaddition does not demand high reaction temperatures, see Section 3.1.), most often the reaction conditions necessary for the cycloaddition to take place, cause a spontaneous elimination of carbon dioxide (*via* retro-hetero-Diels-Alder reaction) yielding a 1-acylaminocyclohexa-1,3-diene systems **17** or **18** (dihydrobenzenes) (Scheme 3). Even though also these intermediates are not very stable, some of them were isolated (see Section 3.2.).

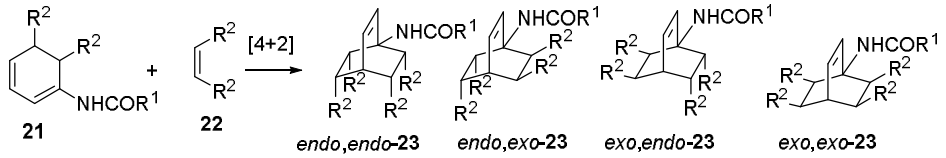


Scheme 3. Diels-Alder reaction between 3-acylamino-2*H*-pyran-2-one **5** and an alkene **14** as dienophile yielding final aromatic products **19** or **20**.

On the other hand, if 1-acylaminocyclohexa-1,3-diene systems **17** or **18** react further, two different scenarios can unfold: (i) they can be aromatized (dehydrogenation or elimination of a suitable stable small molecule, such as HCl, EtOH *etc.*) to benzene systems **19** or **20** (generally analogous to those obtained with alkynes as dienophiles) (Scheme 3) or (ii) they can serve as a new diene system **21** and another molecule of

dienophile **22** (if still available) can cycloadd thus leading to the final 1-acylaminobicyclo[2.2.2]oct-2-ene systems **23**. In contrast to more complex cases when dienophiles **14** are not symmetric (or are even different), the case when both molecules of the dienophile have symmetrical arrangement of substituents, such as **22** (Scheme 4), the double cycloadducts **23** formed can exist (at least theoretically) as only four different stereoisomers: as *exo*,*exo*-**23** or *endo*,*endo*-**23** (both of these have a plane of symmetry and are thus *meso* compounds) or as an enantiomeric pair of *exo*,*endo*-**23** and *endo*,*exo*-**23**.[43]

When symmetric dienophiles **22** are allowed to react with substituted 3-acylamino-2*H*-pyran-2-ones of the type **11**, most often symmetric bicyclo[2.2.2]oct-2-enes *exo*,*exo*-**23** are formed as predominant or even exclusive products. This seems to be the case in all examples (regardless of the reaction conditions) except where very high steric hindrance arises between the reaction partners **21** and **22** on their way to the transition state thus inversing the stereocourse of the second cycloaddition step. Such is the case when an eight-membered ring is fused to a 3-acylamino-2*H*-pyran-2-one frame; cycloadditions of *N*-phenylmaleimide yield unexpected asymmetric product (racemic mixture of *exo*,*endo*-**23** and *endo*,*exo*-**23** bicyclo[2.2.2]oct-2-enes), however when sterically less demanding maleic anhydride is used, the cycloaddition takes place according to normal stereocourse thus again yielding symmetric *meso* bicyclo[2.2.2]oct-2-ene product of the *exo*,*exo*-**23** type.[44] This observations demonstrate that only when both reaction partners are bulky enough, the second cycloaddition step (*i.e.* transformation of the cyclohexadiene system **20** into the bicyclo[2.2.2]oct-2-ene **23**) takes place *via* a changed stereocourse (opposite as usually) yielding different stereomeric product.



Scheme 4. Diels-Alder reaction between 1-acylaminocyclohexa-1,3-diene **21** and a symmetric alkene **22** as dienophile yielding 1-acylaminobicyclo[2.2.2]oct-2-ene systems **23**.

On the other hand, if the dienophile had different substituents on both ends (*i.e.* it is not symmetric, for example H_2C=CHR), then the following possibilities of regioisomers of the final 1-acylaminobicyclo[2.2.2]oct-2-ene systems can be the outcome of such a transformation: (i) both substituents R stemming from the dienophile can be on the same side of the skeleton as 3-acylamino group, (ii) or on the opposite side, (iii) or one can be on the same and the other on the opposite side (in general two different possibilities, the other being (iv)) (Figure 1). However, all of these regioisomers can exist as multiple stereoisomers: for the regioisomer (i) two different *meso* stereoisomers are possible: (i-a) and (i-b), as well as a pair of enantiomers (i-c) and (i-d). The situation is analogous for regioisomer (ii): again two *meso* compounds (ii-a) and (ii-b) and a pair of enantiomers (ii-c) and (ii-d) are possible (Figure 1). Whereas for regioisomers (iii) and (iv) this means four different diastereoisomers, each of which being a pair of enantiomers (pairs being: (iii-a)–(iv-a), (iii-b)–(iv-b), (iii-c)–(iv-c), and (iii-d)–(iv-d)).

In contrast to the first cycloaddition step, which is most often followed by the elimination of CO_2 consequently not enabling the retro-cycloaddition to take place (thus precluding any possible re-formation of the starting 3-acylamino-2*H*-pyran-2-one system), the last cycloaddition step can be reversible. Indeed, it was often demonstrated that with changing reaction conditions, either bicyclo[2.2.2]oct-2-enes can be obtained or corresponding aromatic benzene systems. Experimental data show that when the reaction is taking place under kinetic control (relatively shorter reaction times and lower temperatures), the bicyclo[2.2.2]oct-2-enes are formed, however when the reaction conditions are changed so that the thermodynamic control prevails (longer reaction times and higher temperatures) the previously formed bicyclo[2.2.2]oct-2-enes are converted *via* retro-Diels-Alder reaction into cyclohexadiene intermediates which are then after aromatized (*via* dehydration or elimination of some other molecule) into benzene systems. These, obviously, represent the end of the reaction and cannot be transformed back into any of the previously encountered intermediates.

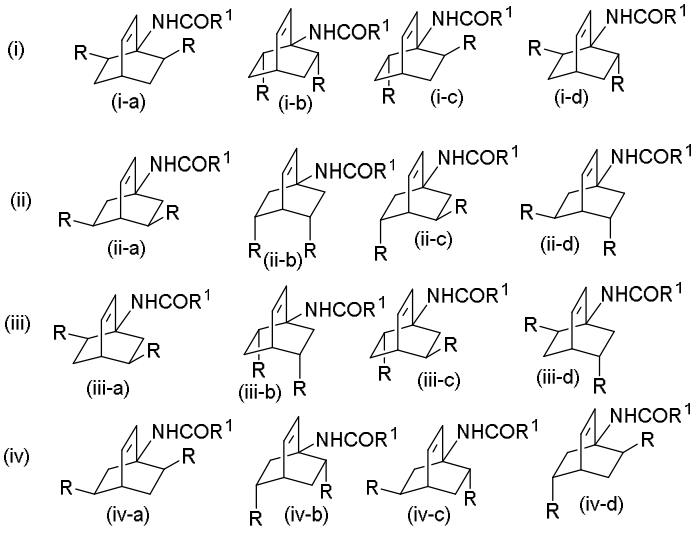


Figure 1. Possible regio- and stereoisomers of disubstituted 1-acylaminobicyclo[2.2.2]oct-2-ene adducts.

3. Adjusting reaction conditions of 3-acylamino-2*H*-pyran-2-one cycloadditions with alkenes to yield various types of desired products

As mentioned in the Section 2.2., when 3-acylamino-2*H*-pyran-2-ones react with various alkene dienophiles, a plethora of different products can be obtained. However, there are many cases where suitably selected reaction conditions can change the reaction course and thus provide just one among the possible products. According to the literature data, some general guidelines can be provided (see below).

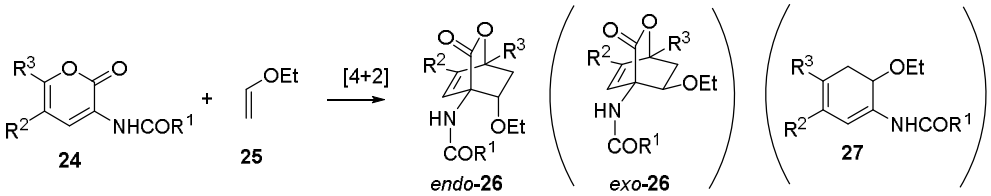
3.1. Favouring the formation of 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-ones: high pressure conditions

To obtain the primary cylcoadduct (*i.e.* 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-one systems) of a cycloaddition between 3-acylamino-2*H*-pyran-2-one and an alkene acting as a dienophile, it is necessary that the reaction conditions are mild, meaning that reaction temperatures are not much above room temperature. In some cases, reflux of methanol still enables the preparation and isolation of these CO_2-containing adducts; in some other cases a careful selection of the starting 3-acylamino-2*H*-pyran-2-ones (such as 6-trifluoromethyl substituted) as demonstrated by Haufe *et al.*[45] was appropriate to synthesize 2-oxabicyclo[2.2.2]oct-5-en-3-ones even at higher temperatures (*e.g.* 120 °C). On the other hand, mild reaction conditions (that are generally needed) often do not provide enough activation energy to enable the cycloadditions to proceed with good conversions. Thus, different activation methods have been successfully used, one of them is activation of the reaction (in the liquid phase) with the application of high pressure (7-20 kbar) at room temperature. Such high pressures accelerate reactions having negative activation volume, and bimolecular reactions (such as intermolecular Diels-Alder reactions) often fulfill this criterion.[46-48] Of course, when the reactants are dissolved in a solvent, the volume change upon proceeding from the reactants to the transition state needs to include the solvent as well, thus slightly complicating the explanation and predictability. Nevertheless, high pressure conditions often enable cycloadditions to proceed towards the formation of 2-oxabicyclo[2.2.2]oct-5-en-3-one adducts and concomitantly prevent further elimination of CO_2 (as the evolution of a gas is strongly hindered by the increase of pressure). However, there are some drawbacks in the use of this technique: reaction times are typically very long (days); most high pressure apparatuses do not enable monitoring of the reaction process; additionally the reaction mixtures cannot be stirred (at least in the most common types of equipment). All these, coupled by the fact that an augment of pressure increases the viscosity of liquids, increases their melting points and decreases the solubility of solids, means that the optimization of cycloadditions conducted under high pressure is

cumbersome and time-consuming. Moreover, the fact that cycloadditions are (at least theoretically) reversible also means that after the equilibrium is reached, the concentration of the adduct does not increase any more (there is no way to remove the product during a high pressure reaction). An additional problem can arise when the reaction vessels are de-pressurized, as it is possible that the equilibrium is shifted back to the starting material (thus destroying the adducts formed previously) or, alternatively, CO_2 elimination can take place thus also disabling the possibility to obtain 2-oxabicyclo[2.2.2]oct-5-en-3-ones.

High pressure conditions (13-15 kbar) were thus successfully applied for the cycloadditions of substituted 3-acylamino-2*H*-pyran-2-ones **24** and various vinyl ether moiety containing dienophiles taking place in dichloromethane. The largest number of such transformations under high pressure conditions were carried out by the application of ethyl vinyl ether **25** (Table 2, entries 1-8).[49] All of these cycloadditions take place *via* inverse electron demand mechanism[50] and have yielded CO_2-bridged adducts 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-ones **26** as single regioisomers (all of the same type) and as just one of the two possible stereoisomers (only *endo*), however occasionally some starting 3-acylamino-2*H*-pyran-2-one **24** remained (Table 2, entries 7 and 8). When ethyl vinyl ether **25** (Table 2, entries 1-8) or cyclohexyl vinyl ether (**28**, R^3=R^5=H, R^4=cyclohexyl) (Table 3, entries 1 and 2) were used under high pressure reaction conditions (neat or in dichloromethane), the cycloadditions were stereospecific, *i.e.* yielding just *endo*-**26** and *endo*-**29** stereoisomers of the 2-oxabicyclo[2.2.2]oct-5-en-3-one framework, as additionally proven by single-crystal X-ray diffraction analyses in some cases.[43,49]

Table 2. Cycloadditions of ethyl vinyl ether **25** on 3-acylamino-2*H*-pyran-2-ones **24** to yield 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-one systems **26**.

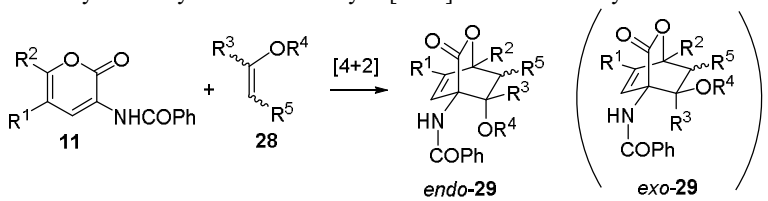


	R^1	R^2	R^3	solvent	*T*	*t* (h)	product(s) (yield)	ref.
1	Ph	COMe	Me	neat	r.t.[a]	312	*endo*-**26** (69%)[d]	49
2	Ph	COPh	Me	neat	r.t.[a]	312	*endo*-**26** (69%)[d]	49
3	Me	COMe	Me	neat	r.t.[a]	432	*endo*-**26** (72%)[d]	49
4	2-Cl-3-pyridyl	COMe	Me	CH_2Cl_2	r.t.[a]	360	*endo*-**26** (61%)[d]	49
5	2-furyl	COMe	Me	CH_2Cl_2	r.t.[a]	360	*endo*-**26** (67%)[d]	49
6	3,4,5-$(MeO)_3$-C_6H_2	COMe	Me	CH_2Cl_2	r.t.[a]	360	*endo*-**26** (62%)[d]	49
7	3,4,5-$(MeO)_3$-C_6H_2	COMe	Me	CH_2Cl_2	r.t.[a]	336	**24**:*endo*-**26**=0.15:1[e]	49
8	3,4,5-$(MeO)_3$-C_6H_2	COMe	Me	CH_2Cl_2	r.t.[a,b]	336	**24**:*endo*-**26**=0.15:1[e]	49
9	Ph	CO_2Et	CF_3	neat	120 °C	1.5	*endo*-**26** (87%)[d] **24**:*endo*-**26**:*exo*-**26**=0.02:1:0.5[e]	45
10	Ph	CO_2Et	CF_3	neat	80 °C[c]	0.5	*endo*-**26** (24%)[d] **24**:*endo*-**26**:*exo*-**26**= 0.65:1:0.16[e]	45
11	Ph	CO_2Et	CF_3	neat	120 °C[c]	1	*endo*-**26** (51%)[d] **24**:*endo*-**26**:*exo*-**26**:**27**=0:1:0.26:0.05[e]	45
12	Ph	CO_2Et	CF_3	neat	150 °C[c]	0.5	*endo*-**26** (60%)[d] **24**:*endo*-**26**:*exo*-**26**:**27**=0:1:0.21:0.1[e]	45

[a]At high pressure (13-15 kbar). [b]With addition of 15 mol% DABCO. [c]Under microwave irradiation (200 W). [d]Yield of isolated products. [e]Molar ratio estimated from ^{1}H-NMR spectra of crude reaction mixtures.

However, under thermal reaction conditions (conventional or microwave heating of up to 150 °C) starting from substituted 2*H*-pyran-2-one **24** (R^1=Ph, R^2=CO_2Et, R^3=CF_3), as applied by Haufe *et al.*[45] the cycloadditions of ethyl vinyl ether (Table 2, entries 9-12), 1-ethoxyprop-1-ene (Table 3, entries 3 and 4) or 1-methoxyprop-1-ene (Table 3, entries 5 and 6) were not stereospecific, instead mixtures of *endo*-**26** (predominant product) and *exo*-**26** adducts (together with some unreacted starting 2*H*-pyran-2-ones **24** or cyclohexadiene products **27** as the result of CO_2 elimination) were isolated. It was also very challenging for the authors to adjust the reaction parameters so that complete conversions would be achieved without concomitantly causing CO_2 eliminations. Because of this, the reactions mostly yielded mixtures of products that necessitated chromatographic separations.

Table 3. Cycloadditions of substituted vinyl ethers **28** on 3-acylamino-2*H*-pyran-2-ones **11** to yield 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-one systems **29**.



	R^1	R^2	R^3	R^4	R^5	solvent	*T*	*t* (h)	product(s) (yield)	ref.
1	COMe	Me	H	Cy	H	CH_2Cl_2	r.t.[a]	384	*endo*-**29** (52%)[c]	49
2	COPh	Me	H	Cy	H	CH_2Cl_2	r.t.[a]	384	*endo*-**29** (64%)[c]	49
3	CO_2Et	CF_3	H	Et	Me	neat	120 °C	1.5	*endo*-**29** (31%),[c] *exo*-**29** (19%)[c] **11**:*endo*-**29**:*exo*-**29**=0.3:1:0.83[d]	45
4	CO_2Et	CF_3	H	Et	Me	neat	120 °C[b]	1	*endo*-**29** (36%),[c] *exo*-**29** (13%)[c] **11**:*endo*-**29**:*exo*-**29**=0.4:1:0.49[d]	45
5	CO_2Et	CF_3	Me	Me	H	neat	120 °C	1.5	**11** (81% rec.) **11**:*endo*-**29**:*exo*-**29**=1:0.17:0.06[d]	45
6	CO_2Et	CF_3	Me	Me	H	neat	120 °C[b]	1	*endo*-**29** (60%),[c] *exo*-**29** (11%)[c] **11**:*endo*-**29**:*exo*-**29**=0:1:0.39[d]	45

[a]At high pressure (13-15 kbar). [b]Under microwave irradiation (200 W). [c]Yield of isolated products. [d]Molar ratio estimated from ^{1}H-NMR spectra of crude reaction mixtures (cyclohexadiene products were not detected).

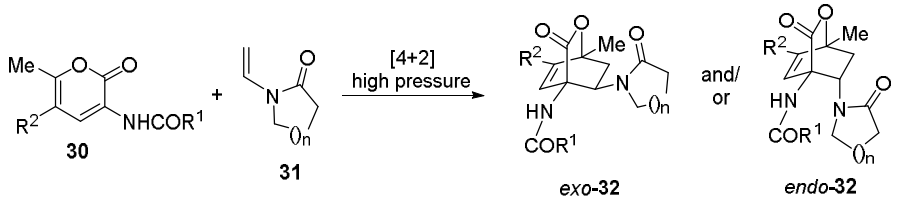
On the other hand, when 1-vinyl-2-pyrrolidone **31** (n=1) was used as dienophiles reacting with 3-acylamino-2*H*-pyran-2-ones **30** under high pressure conditions (13-15 kbar) in dichloromethane as the solvent (Table 4, entries 1 and 2),[49] an *exo*-**32** isomer of the 2-oxabicyclo[2.2.2]oct-5-en-3-one system was obtained as the predominant (or the only) adduct. In the case when *N*-vinylcaprolactam **31** (n=2) was used (Table 4, entries 3 and 4)[49] the stereoselectivity of the cycloaddition depended upon the reaction time: after 16 days a mixture of *exo*-**32** and *endo*-**32** adducts was obtained, whereas after 106 days only *exo*-**32** adduct was detected and isolated. Structures of these cycloadducts **32** were additionally confirmed by single-crystal X-ray diffraction analysis.[43,49]

Therefore, high pressure conditions (13-15 kbar) seem to be superior as regards stereoselectivity of the formation and isolation (purification) of the 2-oxabicyclo[2.2.2]oct-5-en-3-ones, but the reaction times and necessary equipment might in many cases complicate such syntheses. In some cases access to these bicyclic systems is possible under thermal conditions as well.

3.2. Favouring the formation of 1-acylaminocyclohexa-1,3-diene systems

To stop the reactions when a 1-acylaminocyclohexa-1,3-diene system is formed is rather difficult and consequently there are just a few literature examples for this. Such cyclohexadiene systems are namely highly prone to the aromatization (oxidation) *via* elimination of hydrogen or some other small molecules or alternatively they can react as dienes with new molecules of dienophiles.

Table 4. Cycloadditions of *N*-vinyl lactams **31** on 3-acylamino-2*H*-pyran-2-ones **30** to yield 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-one systems **32**.



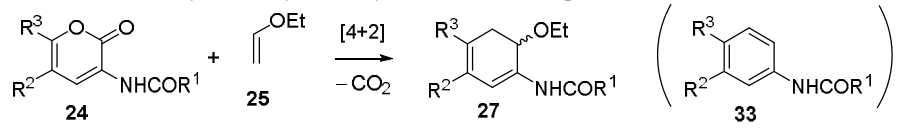
	R^1	R^2	n	solvent	*t* (h)	product **32** (yield)[b]	ref.
1	3,4,5-$(MeO)_3$-C_6H_2	COMe	1	CH_2Cl_2	384[a]	*exo*-**32** (64%), *endo*-**32** (0.5%)	49
2	Ph	COPh	1	CH_2Cl_2	408[a]	*exo*-**32** (61%)	49
3	Ph	COMe	2	CH_2Cl_2	384[a]	*exo*-**32** + *endo*-**32** (63%),[c] ratio 1:1[d]	49
4	Ph	COMe	2	CH_2Cl_2	2544[a]	*exo*-**32** (67%)	49

[a]At high pressure (13-15 kbar) at room temperature. [b]Yield of isolated products. [c]Combined yield for both stereoisomers together. [d]Molar ratio between *exo*-**32** and *endo*-**32** was estimated from ^{1}H-NMR spectra of crude reaction mixtures (cyclohexadiene products were not detected).

An instructive example from the literature is formation of ethoxycyclohexadiene systems **27** *via* cycloaddition of ethyl vinyl ether on various 3-acylamino-2*H*-pyran-2-ones **24** (Table 5).[49] These reactions were conducted under microwave irradiation (1.5-2 h at 120 °C) in acetonitrile without the addition of a base (Table 5, entries 1-3),[49] however even with careful adjustment of reaction conditions, it was not possible to obtain exclusively cyclohexadiene products **27**, as in all cases investigated, at least some starting 2*H*-pyran-2-one **24** remained unreacted and some aromatic final product **33** (after the elimination of ethanol) was already produced. It is worth noting that analogous reaction conditions, but with the addition of DABCO (or other sterically hindered bases), yield exclusively aromatic products **33** upon the elimination of ethanol.[49]

Haufe *et al.*[45] met with similar limitations when they tried to prepare cyclohexadiene systems starting from substituted 2*H*-pyran-2-one **24** (R^1=Ph, R^2=CO_2Et, R^3=CF_3), as the diene in the cycloaddition with ethyl vinyl ether **25** acting as dienophile (Table 5, entries 4-6). They were, however, able to adjust the reaction conditions to bring the process towards complete conversion, but nevertheless some of the desired cyclohexadiene product **27** already underwent elimination of ethanol thus yielding the final benzene system **33** as an undesired side product.

Table 5. Cycloadditions of ethyl vinyl ether **25** on 3-acylamino-2*H*-pyran-2-ones **24** to yield 1-acylaminocyclohexa-1,3-diene products **27**.



	R^1	R^2	R^3	solvent	*T*	*t* (min)	**24**:**27**:**33**[b]	ref.
1	Ph	CO_2Me	Me	CH_3CN	120 °C[a]	120	0.3:1:0.04	49
2	3,4,5-$(MeO)_3$-C_6H_2	COMe	Me	CH_3CN	120 °C[a]	90	0.03:1:0.4	49
3	4-NO_2-C_6H_4	COMe	Me	CH_3CN	120 °C[a]	90	0:1:0.4	49
4	Ph	CO_2Et	CF_3	neat	180 °C[a]	30	0:1:0.28	45
5	Ph	CO_2Et	CF_3	neat	180 °C[a]	60	0:0.45:1	45
6	Ph	CO_2Et	CF_3	neat	180 °C	480	0:0.15:1	45

[a]Under microwave irradiation. [b]Molar ratio estimated from ^{1}H-NMR spectra of crude reaction mixtures (CO_2-bridged intermediates were not detected).

3.3. Favouring the formation of 1-acylaminobicyclo[2.2.2]oct-2-enes: kinetic control

To obtain 1-acylaminobicyclo[2.2.2]oct-2-enes of the type **36** (also known as "double cycloadducts"),[51] generally, thermal reaction conditions are applicable. Bicyclo[2.2.2]oct-2-ene as the product of a [4+2]-cycloaddition is one of those most often encountered, for the first time described already in 1931 by Diels and Alder,[30] when a reaction between an unsubstituted 2*H*-pyran-2-one (coumalin) and maleic anhydride was conducted. Most of the related cases in the literature use reflux combined with conventional heating. Some of these syntheses were also successfully conducted with microwave irradiation. There are quite many examples in the literature of such cycloadducts obtained from variously substituted 2*H*-pyran-2-one systems, however there are far less reports on the application of 3-acylamino-2*H*-pyran-2-ones as dienes. Most common dienophiles being, beside maleic anhydride,[52] various *N*-substituted maleimides (methyl, ethyl, phenyl *etc.*),[53-55] styrene *etc*. (see Section 4.2.).

As already presented in Section 2.2., formation of bicyclo[2.2.2]oct-2-enes **36** also brings interesting issues of stereoselectivity (when symmetric dienophiles are used) in addition to the problems of regioselectivity (if the dienophile is not symmetric).[44] In general, when a symmetric (cyclic) alkene, such as **35**, is used as the dienophile (maleic anhydride, for example) reacting with a 3-acylamino-2*H*-pyran-2-one, the first cyloaddition step can yield just one regioisomer of the initially formed 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-one adducts, but it can exist as two different stereoisomers (*exo* and *endo*), each of them, of course, as a pair of enantiomers, thus altogether forming 4 stereoisomers (2 pairs of enantiomers). However, regardless of the stereocourse of this first step, the elimination of the CO_2 in the next step eliminates one element of asymmetry as well, thus reducing the total number of stereoisomers of 1-acylaminocyclohexa-1,3-diene systems to 2 (one pair of enantiomers). If aromatization takes place, another element of asymmetry is lost and just one possible aromatic product (fused aniline derivative) is formed. On the other hand, if cyclohexadiene system serves as a new diene thus forming 1-acylaminobicyclo[2.2.2]oct-2-ene adducts, an additional element of asymmetry is formed, making possible the following four stereoisomeric options: (i) both rings stemming from maleic anhydride are *syn* to the double bond of the bicyclo[2.2.2]octene skeleton (termed *exo*,*exo* product); (ii) both rings from maleic anhydride are *anti* to the double bond of the skeleton (*endo*,*endo* product); (iii) one ring is *anti* and the other *syn* (*endo*,*exo* product); (iv) the opposite possibility *exo*,*endo* being enantiomer of (iii). Options (i) and (ii) are *meso* compounds, since they contain a plain of symmetry.

Thus, at least theoretically, one might expect a plethora of different stereoisomeric products and thus a very limited utility of such cycloadditions. The reality, however, is different: pericyclic reactions, including Diels-Alder cycloadditions are highly regio- and stereoselective, thus bicyclo[2.2.2]oct-2-enes are in the majority of cases formed as just one isomer: when maleic anhydride **35** (X=O) and its analogues (such as *N*-substituted maleimides) is used in the cycloaddition with **34** and the conditions are selected in such a way as to favour the formation of bicyclo[2.2.2]oct-2-enes **36**, exclusively *exo*,*exo* adducts (*meso* compounds) are obtained. The cycloadditions yielding bicyclo[2.2.2]oct-2-enes **36** were conducted under thermal reaction conditions (Table 6),[52-55] either conventionally (reflux of tetralin in the case of cycloaddition of maleic anhydride) or under microwave irradiation (at 150 °C neat, in water of with a small addition of *n*-butanol); the reaction times for the latter being in the majority of the cases somewhat shorter than for the former, but in both cases yielding the same stereoisomers (*i.e. exo*,*exo*-**36**) of the bicyclo[2.2.2]oct-2-enes in good yield (on average 86%).

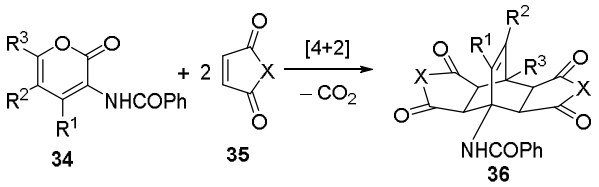
3.4. Favouring the formation of aromatic products: thermodynamic control

When the reaction conditions are harsh enough to enable the last cycloaddition step to be reversible (*i.e.* enabling retro-Diels-Alder reaction) then with longer reaction times the amount of aromatic product formed will increase, regardless of the fact that initially the bicyclo[2.2.2]octene was the predominant (or even the only) product formed. Thus, long reaction times coupled with higher temperatures in general always yield aromatic systems as final products. Of course, these are unable to undergo any reversible reaction and thus they accumulate in the reaction mixture; most often being stable enough not to be affected by high reaction temperatures.

There is also another approach towards aromatic products, namely, application of suitable dehydrogenation catalysts; initially, analogously to the hydrogenation reactions, also here precious metals on activated carbon were used, however later it was found out that in many cases activated carbon (without

metals) works as well, if not even better. Clearly, when a dehydrogenation reaction is taking place, the eliminated hydrogen is most often taken by a suitable hydrogen acceptor (except in acceptor-less dehydrogenations)[56] it turns out that the excess amount of dienophile often can serve exactly as such an acceptor.

Table 6. Cycloadditions of maleic anhydride **35** (X=O) and *N*-substituted maleimides **35** (X=NR) on 3-acylamino-2*H*-pyran-2-ones **34** yielding bicyclo[2.2.2]oct-2-ene systems **36**.



	R^1	R^2	R^3	X	solvent	*T*	*t* (min)	yield of **36** (%)[c]	ref.
1	H	H	Me	O	tetralin	reflux	15	64	52
2	H	H	Me	NEt	neat[a]	150 °C[b]	15	93	53
3	H	H	Ph	O	tetralin	reflux	120	76	52
4	H	H	Ph	NEt	neat[a]	150 °C[b]	45	85	53
5	H	H	Ph	NPh	neat[a]	150 °C[b]	25	94	53
6	H	H	2-thienyl	O	tetralin	reflux	60	76	52
7	H	H	2-thienyl	NEt	neat	150 °C[b]	150	96	54
8	H	H	2-thienyl	NPh	neat[a]	150 °C[b]	40	98	53
9	H	H	2-furyl	O	tetralin	reflux	60	72	52
10	H	H	2-furyl	NMe	neat[a]	150 °C[b]	45	93	53
11	H	H	2-furyl	NEt	neat[a]	150 °C[b]	45	95	53
12	H	H	2-furyl	NPh	neat	150 °C[b]	90	99	54
13	H	COMe	Me	O	tetralin	reflux	90	39	52
14	H	COMe	Me	NH	neat	150 °C[b]	20	82	55
15	H	COMe	Me	NMe	water	150 °C[b]	30	87	55
16	H	COMe	Me	NEt	water	150 °C[b]	30	92	55
17	H	COMe	Me	NPh	water	150 °C[b]	30	94	55
18	H	CO_2Et	Me	NMe	water	150 °C[b]	45	86	55
19	H	CO_2Et	Me	NEt	water	150 °C[b]	45	87	54
20	H	CO_2Et	Me	NPh	water	150 °C[b]	60	91	54
21	H	CO_2Me	CH_2CO_2Me	NEt	neat	150 °C[b]	30	82	54
22	H	CO_2Me	CH_2CO_2Me	NPh	neat	150 °C[b]	30	81	55
23	H	4-$MeOC_6H_4$	Me	O	tetralin	reflux	10	94	52
24	H	4-$MeOC_6H_4$	Me	NEt	neat[a]	150 °C[b]	15	86	53
25	H	4-$MeOC_6H_4$	Me	NPh	water	150 °C[b]	10	93	55
26	H	3,4-$(MeO)_2C_6H_3$	Me	NEt	water	150 °C[b]	10	92	53
27	Me	H	Ph	O	tetralin	reflux	90	80	52
28	Me	H	Ph	NEt	neat[a]	150 °C[b]	90	88	53
29	Me	H	Ph	NPh	neat[a]	150 °C[b]	50	97	53
30	Me	H	2-thienyl	O	tetralin	reflux	90	80	52
31	Me	H	2-thienyl	NEt	neat[a]	150 °C[b]	60	96	53
32	Me	H	2-thienyl	NPh	neat[a]	150 °C[b]	90	98	53

[a]With addition of small amount (100 mg) of *n*-BuOH. [b]Under microwave irradiation. [c]Yield of isolated products.

This sometimes brings difficulties when bicyclo[2.2.2]octene adducts are desired products, namely the 2 equivalents of the dienophile (added to enable double cycloaddition) can be used as just 1 equivalent for

the cycloaddition and the remaining equivalent can act as hydrogen acceptor thus steering the reaction towards aromatic products. However, the change of the amount of dienophiles applied, generally does not cause the reaction to proceed towards double cycloadduct (bicyclo[2.2.2]octenes) or towards aromatic benzene systems; far greater is the importance of other reaction parameters, especially reaction time and temperature.

In some cases, the formation of aromatic products was achieved by dienophiles, strategically selected in such a way to possess groups that are able to eliminate (easily) after the cycloaddition. A broad family of such dienophiles are vinyl-moiety containing compounds, which can serve as synthetic equivalents of corresponding alkynes (which are typically more difficult to obtain and often are also more expensive). In this regard cycloaddition of ethyl vinyl ether is of interest, being a synthetic equivalent of acetylene. Albeit acetylene is easily available, it is more cumbersome to work with due to its gaseous state; it is also less reactive as it lacks substituents with electronic effects. There were many reports on various synthetic equivalents of acetylene applied in related cases; recently Crews *et al*.[57] reported on a regioselective and highly efficient preparation of 3,4-unsubstituted isoquinolones and isocoumarins, where the crucial step consisted of vinyl boronate acting as a C_2 synthon, equivalent of acetylene. There are some other reports where the synthetic equivalent is nevertheless based on acetylenes, such as ethynyl *para*-tolyl sulfone,[58] and 1-benzenesulfonyl-2-trimethylsilylacetylene;[59] whereas some others are also based on vinyl-moiety containing derivatives, such as phenyl vinyl sulfide,[60] phenyl vinyl sulfoxide,[61] and fluoroalkyl vinyl sulfoxides.[62] However, ethyl vinyl ether could be superior to the other options, as the side product of the elimination step (that is, ethanol) is far less environmentally problematic than other sulfur compounds that are formed as side products in most of the other cases.

Reactions of a variety of substituted 2*H*-pyran-2-ones **24** with vinyl-moiety containing dienophiles, such as ethyl vinyl ether **25** or 1-vinyl-2-pyrrolidone **31a** were investigated under thermal reaction conditions and the most appropriate reaction parameters to prepare aromatic products **33** in good yields (on average 71%) were found to be irradiation with microwaves at 120 or 150 °C in acetonitrile (Table 7).[49,63] Additionally, however, it was found that application of a sterically hindered base, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is beneficial for the formation of the required aromatic products **33** (*via* elimination of ethanol), necessitating lower reaction temperatures (120 °C instead of 160 °C) and shorter reaction times. In addition to ethyl vinyl ether and 1-vinyl-2-pyrrolidone, also vinyl acetate, vinyl propionate, cyclohexyl vinyl ether, and *N*-vinylcaprolactam were found to be adequate synthetic equivalents of acetylene, as they also enable aromatization *via* elimination of a small stable volatile molecule thus yielding the desired products **33**.[49] This strategy was also extended to fused 3-acylamino-2*H*-pyran-2-one derivatives where upon cycloaddition of ethyl vinyl ether under analogous reaction conditions naphthalene derivatives were isolated.[64]

4. Selected examples

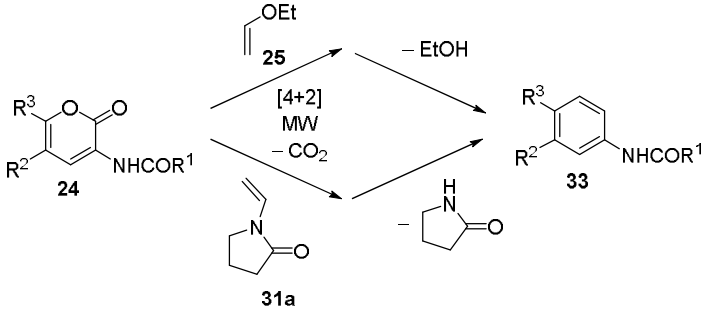
4.1. Synthesis of indole derivatives

Indole heterocyclic core being a very important part of many natural molecules as well as biologically active compounds is gaining recognition also as a constituent part of various chiral heterocycles; as clearly demonstrated in a recent review paper.[65] A successful synthesis of indole derivatives was developed,[66] based on a two-step process: in the first step cycloaddition of (*Z*)-1-methoxybut-1-en-3-yne **37** with a substituted 3-acylamino-2*H*-pyran-2-one **24** is carried out forming intermediates **38** with strategically positioned 2-methoxyethenyl substituent *ortho* relative to the acylamino group, thus appropriate for acid-catalyzed cyclization towards substituted *N*-acylindoles **39** (Scheme 5). It is worth noting that in the first step exclusively triple bond of **37** is involved in the cycloaddition, whereas the double bond does not react. These transformations were taking place under microwave irradiation, some of them even as a one-pot process without the isolation of the intermediates **38**. However, the activation with high pressure did not change the selectivity and products obtained were analogous to those formed under thermal conditions.

One of the obtained *N*-benzoylindoles **39** (R^1=Ph, R^2=COMe, R^3=Me) was further deprotected and derivatized *via* Mannich reaction (with formaldehyde and dimethylamine in the presence of catalytic amount of zinc(II) chloride in ethanol as the solvent) to 6-acetyl-5-methylgramine, its structure was further confirmed by single-crystal X-ray diffraction.[67] Furthermore, the cyclization step of the primary adduct **38**

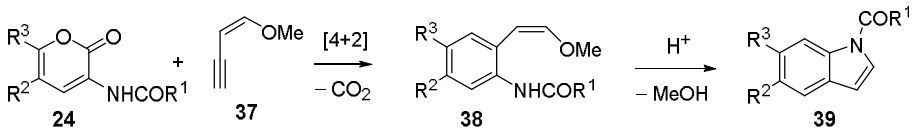
into the indole **39** and the deprotection of the indole nitrogen atom (removal of benzoyl group), was executed as a one-pot reaction without the isolation of the intermediary *N*-protected indole **39**.[67]

Table 7. Cycloadditions of ethyl vinyl moiety containing dienophiles **25** and **31a** as synthetic equivalents of acetylene on 3-acylamino-2*H*-pyran-2-ones **24** to yield aromatic products **33**.



	R^1	R^2	R^3	dienophile	*T* (°C)	*t* (min)	yield of **33** (%)[b]	ref.
1	Ph	CO_2Me	CH_2CO_2Me	**25**	120	100	73	63
2	Ph	CO_2Et	CH_2CO_2Et	**25**	120	100	70	63
3	Ph	CO_2Me	Me	**25**	120	90	68	63
4	Ph	CO_2Et	Me	**25**	120	90	64	63
5	Ph	COMe	Me	**25**	120	60	85	63
6	Ph	COPh	Me	**25**	120	60	82	63
7	Me	COMe	Me	**25**	120	60	78	63
8	2-chloro-3-pyridyl	COMe	Me	**25**	120	120	60	49
9	2-furyl	COMe	Me	**25**	120	120	69	49
10	3,4,5-$(MeO)_3$-C_6H_2	COMe	Me	**25**	120	120	70	49
11	4-NO_2-C_6H_4	COMe	Me	**25**	120	120	69	49
12	6-chloro-3-pyridyl	COMe	Me	**25**	120	120	74	49
13	cyclobutyl	COMe	Me	**25**	120	120	63	49
14	cyclopropyl	COMe	Me	**25**	120	120	65	49
15	Ph	CO_2Me	Me	**31a**	120	120	74	49
16	Ph	CO_2Et	Me	**31a**	120	150	71	49
17	Ph	COMe	Me	**31a**	120	120	71	49
18	Ph	CO_2Et	CH_2CO_2Et	**31a**	150	120	73	49

[a]Under microwave irradiation with DABCO in acetonitrile. [b]Yield of isolated products.



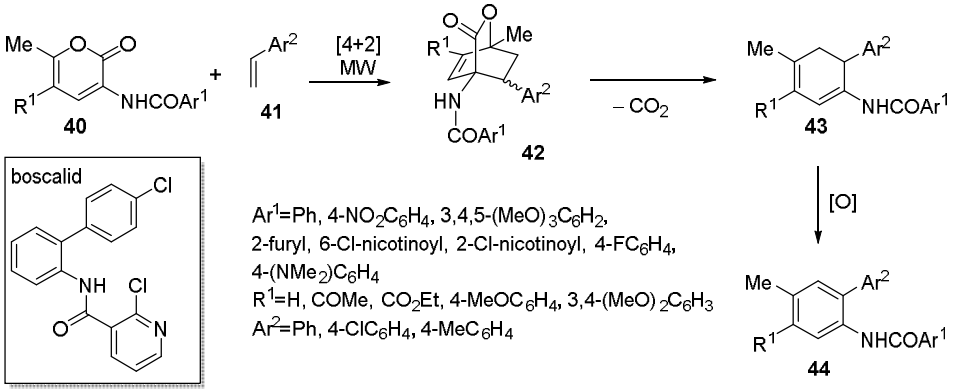
Scheme 5. Diels-Alder reaction between 3-acylamino-2*H*-pyran-2-one **24** and (*Z*)-1-methoxybut-1-en-3-yne (**37**) as dienophile yielding substituted indoles **39**.

Haufe *et al.*[41] developed another approach, starting by cycloaddition of but-3-yn-1-ol on a 2*H*-pyran-2-one **24** (R^1=Ph, R^2=CO_2Et, R^3=CF_3) forming the 2-hydroxyethyl substituted aromatic system; next step required protection of hydroxy group with methanesulfonyl chloride leading to a precursor that is suitable for cyclization to 2,3-dihydroindole system. Cyclization was achieved by the application of cesium carbonate in dioxane. The final step was dehydrogenation with DDQ yielding the final indole product.

Both of these approaches lead to *N*-benzoyl (or *N*-acyl) protected indoles **39** without substituents on positions 2 and 3, however our approach[66] is shorter as it necessitates just two steps starting from 2*H*-pyran-2-one *vs.* four steps needed for the approach by Haufe *et al.*[41] The first approach is more general as it was successfully applied for the synthesis of 6 different indole systems **39**, whereas the second one was demonstrated on a single case. The first approach is somewhat limited by the lack of reactivity of (*Z*)-1-methoxybut-1-en-3-yne **37** with electron rich 2*H*-pyran-2-one systems **24**, but it is also to be expected that but-3-yn-1-ol is not very reactive dienophile and certainly not applicable for cycloadditions with all types of 2*H*-pyran-2-ones.

4.2. Synthesis of boscalid derivatives

Boscalid (Scheme 6), also known as nicobifen, is an important fungicide, commercially introduced by BASF in 2003. It is used to prevent ascomycetes infections (pathogen sac fungi) on agricultural plants (fruits and vegetables) acting as a succinate dehydrogenase inhibitor.[68,69] Boscalid possesses an arylamino-biphenyl core, and is industrially prepared on a 10^3 ton/year scale according to a patent[70] and on the Gooßen procedure[71] that involves a palladium(0)-catalyzed Suzuki-Miyaura cross-coupling reaction between 4-chlorophenylboronic acid and 1-chloro-2-nitrobenzene. Glasnov and Kappe have additionally shown that this approach could be further streamlined by the application of a continuous-flow technique.[72] A similar approach by Felpin *et al.*[73] incorporated palladium nanoparticles that were uniformly dispersed on an active carbon surface leading to increased efficiency.



Scheme 6. Diels-Alder reaction between substituted 3-acylamino-2*H*-pyran-2-ones **40** and styrene or its derivatives **41** as dienophiles yielding substituted boscalids **44**.

Arylamino-biphenyl core, however, could also represent a suitable target for the synthesis *via* Diels-Alder cycloaddition of 2*H*-pyran-2-ones **40**. To incorporate a 4-chlorophenyl ring (as part of the biphenyl moiety), two different approaches were investigated: (i) use of 4-chlorophenylacetylene as the dienophile where the cycloaddition would directly yield the desired biphenyl system **44** or (ii) use of 4-chlorostyrene **41** (Ar^2=4-ClC_6H_4) where an additional dehydrogenation (aromatization) step **43**→**44** is necessary following the Diels-Alder reaction yielding the primary cycloadduct **42** followed by the CO_2 elimination to **43** (Scheme 6). Although the alkyne approach is more direct, alkynes are in general more expensive and the variability of (commercially) available analogues is lower in comparison with styrenes, thus making the approach (ii) more attractive. Indeed, application of chloranil (or activated carbon Darco KB) as dehydrogenation agents enabled one-pot synthesis of the biphenyl core **44** when styrene or 4-chlorostyrene was used.[74] These metal-free reactions were fast (1-3 h), taking place at moderate temperatures (120-140 °C) by conventional heating or by microwave irradiation in environmentally acceptable solvents (acetonitrile, decalin or *n*-BuOH) providing access to a set of 18 differently substituted boscalid derivatives **44** in moderate to good yields (38-86%), 14 of these were previously not yet described in the literature. Later we extended this approach by using other styrene and 2*H*-pyran-2-one derivatives thus

obtaining an additional set of boscalid analogues (15 new compounds), as well as comparing the application of Darco KB and chloranil under various reaction conditions to find the most appropriate oxidizing agent.[75]

4.3. Further transformations of 1-acylaminobicyclo[2.2.2]oct-2-ene systems with nitrogen nucleophiles

When 1-acylaminobicyclo[2.2.2]oct-2-enes are obtained by the cycloaddition of maleic anhydride on substituted 2*H*-pyran-2-ones, the ensuing adducts contain two anhydride moieties (fused succinic anhydride rings) that are highly amenable for further transformations. In this regard, the most diverse possibilities are offered by nitrogen nucleophiles, such as primary amines, hydrazine and its derivatives (substituted hydrazines, hydrazides *etc.*).[51] Transformation with hydrazine hydrate and methyl-, phenyl-, and 2-pyridylhydrazine (10-20 mol% excess) were carried out under microwave irradiation at 100-160 °C in aqueous suspensions; 14 new *N*-aminosuccinimide derivatives were isolated in excellent yields (90% on average).[76] In continuation of this research, further 16 *N*-aminosuccinimide products were obtained under analogous reaction conditions.[77] Also primary amines were found to be useful for derivatizations into succinimide derivatives; additionally comparison of aqueous versus neat reaction conditions (under microwave irradiation) was investigated on the case of bicyclo[2.2.2]oct-2-enes stemming from 5-acetyl-3-benzoylamino-2*H*-pyran-2-one.[78] Aqueous conditions enabled the acetyl group to remain unchanged in the products, whereas neat conditions (with a small amount of a suitable liquid additive, such as toluene), enabled the transformation into corresponding imines.

Various hydrazinylpyridines were prepared by efficient nucleophilic aromatic substitution of chlorine in different chloronitropyridines upon heating in closed vessels using 1-propanol as the solvent. The hydrazines thus prepared were used to derivatize a set of 1-acylaminobicyclo[2.2.2]oct-2-enes, products were isolated in moderate yields (61% on average).[79]

2-, 3- and 4-Pyridylcarbohydrazides were also used to derivatize a set of 6 different 1-acylaminobicyclo[2.2.2]oct-2-enes upon heating in closed vessels at 160 °C for 9 h and using *n*-butanol as the solvent. In this way 15 novel pyridine-ring containing *N*-aminosuccinimide derivatives were formed (69% yield on average).[80] Their approximately square planar arrangement of four aromatic rings represents substantial structural similarity (additionally demonstrated by molecular docking) with some known HIV-1 protease inhibitors (such as lopinavir and nelfinavir) that also inhibit the replication of SARS-CoV-2 virus by binding to the major protease $3CL^{pro}$. Therefore, we envisaged the potential of these *N*-aminosuccinimide derivatives as non-covalent inhibitors of SARS-CoV-2 $3CL^{pro}$ main protease. Indeed, two compounds were found to be moderately active, with IC_{50} values in micromolar range (the best value was IC_{50}=102.2 μM, Figure 2).[80] Molecular simulations of the target–ligand complex together with the dynophore analyses and endpoint free energy calculations enabled additional insight as well as valuable hints for further optimizations.

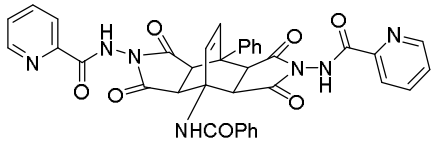
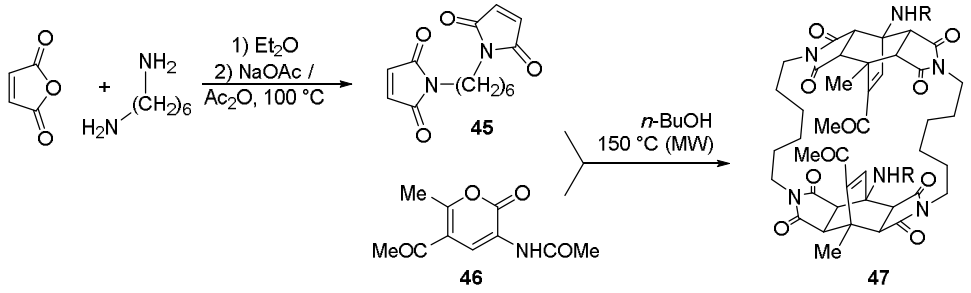


Figure 2. *N*-[8-Phenyl-2,3,3a,4a,5,6,7,7a,8,8a-decahydro-1,3,5,7-tetraoxo-2,6-bis(2-pyridylcarboamino)-4,8-ethenobenzo[1,2-*c*:4,5-*c*']dipyrrol-4(1*H*)-yl]benzamide.

Another option is hydrolysis of the anhydride rings towards tetraacids or tetraester derivatives by the application of trimethyl or triethyl orthoacetate in the appropriate alcohol with the addition of a suitable ionic liquid, such as $[emim]BF_4$. These reactions were conducted at 120 °C under microwave irradiation (25-100 min) to yield corresponding tetramethyl or tetraethyl esters of bicyclo[2.2.2]octenes in excellent yields (90% on average).[81] The products thus obtained were isomerized with *t*-BuOK in reflux of a suitable alcohol (25-360 min) to yield less sterically congested bicyclo[2.2.2]octenes that could undergo catalytic hydrogenation on Pd/C (5 h at 3 bar in ethanol at room temperature).[81] It is worth mentioning that starting *exo*,*exo*-bicyclo[2.2.2]octene adducts are very resistant to hydrogenation.[55,82-84]

4.4. Formation of macrocycles

By connecting two maleimide rings *via* an alkyl tether, for example, 1,1'-(hexane)-1,6-diyl)bis(1*H*-pyrrole-2,5-dione), a double dienophile **45** thus formed was shown to be a suitable partner to react with two molecules of 5,6-disubstituted 3-benzoylamino-2*H*-pyran-2-ones **46** under solvent-free reaction conditions with a minor amount of *n*-BuOH as an additive under microwave irradiation (at 150 °C) forming an interesting 26-membered tetraaza heteromacrocyclic system **47** (Scheme 7). The structure of the dienophile **45** and of the novel macrocycle **47** were further confirmed by single-crystal X-ray diffraction analysis.[85]



Scheme 7. Diels-Alder reaction between a 3-acylamino-2*H*-pyran-2-one derivative **46** and a double dienophile **45** yielding 26-membered macrocycle **47**.

5. Conclusions

3-Acylamino-2*H*-pyran-2-ones represent a very versatile diene scaffold appropriate for a wide range of different cycloadditions. The diversity of products obtained by alkynes as dienophiles is rather limited (only aniline derivatives could be prepared), whereas when alkenes are used as dienophiles the following types of products can be synthesized: (i) 4-acylamino-2-oxabicyclo[2.2.2]oct-5-en-3-ones; (ii) 1-acylaminocyclohexa-1,3-dienes; (iii) 1-acylaminobicyclo[2.2.2]oct-2-enes; and (iv) aniline derivatives. Products of the type (i) are formed as primary cycloadducts; if a CO_2 elimination takes place, products of the type (ii) are formed. These can in turn either act as new dienes for a second cycloaddition step thus yielding products of the type (iii) or they can undergo aromatization (*via* dehydrogenation or elimination of some other, small, volatile molecule, such as ethanol) to form products of the type (iv). Based on these principles, novel routes toward substituted indoles, gramines, derivatives of boscalid, or macrocyclic products were opened. Additionally, products of the type (iii) are of interest for further transformations as well, as their fused succinic anhydride moieties can react with a variety of nitrogen nucleophiles (such as primary amines, hydrazine and its derivatives) toward more complex products. Anhydride moieties can also be hydrolized towards tetraesters which open the possibility of various isomerizations.

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