MICROWAVE AND MECHANOCHEMISTRY: TOOLS FOR THE SUSTAINABLE SYNTHESIS OF PYRROLES, PORPHYRINS AND RELATED MACROCYCLES

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Abstract. *Microwave-assisted synthesis and mechanochemistry are two powerful tools for the sustainable synthesis of heterocycles that could contribute to reduce cost, energy, environmental impact, risk and hazard as well as waste in the research and production of these type of compounds. Herein the synthesis of pyrroles and porphyrins, two natural heterocycles with multiple applications, under microwave irradiation or through mechanochemistry is reviewed.*

Contents

1. Introduction

The use of new technologies in the synthesis of *N*-heterocycles, structural components of many bioactive natural products such as vitamins, hormones, antibiotics or alkaloids, and natural drugs such as quinine, atropine or morphine, is specially relevant because they are considered privileged structures for the synthesis and development of new drugs.[1] The pharmaceutical industry was one of the industrial sectors that firstly embraced the field of green chemistry. Pfizer, in the late 1990s, led the world's first corporate program to grow and develop green chemistry within the pharmaceutical industry. The pharmaceutical industry has some widely used examples of reduced manufacturing costs of active pharmaceutical ingredients (APIs), many of which are award-winning green chemistry technologies.[2] To address de goals of green chemistry new methods, solvents and techniques were developed. Alternative activation methods and alternative reaction media are required for the purpose of reducing cost, energy, environmental impact, risk,

hazard and waste. From the point of view of sustainability greener methodologies with higher energy efficiency such as microwave (MW), mechanochemistry, and ultrasound are recommended.[3] Microwave irradiation is, nowadays, fully recognized as a useful tool for organic synthesis used in multi-step total synthesis,[4] medicinal chemistry and drug discovery,[5] polymer synthesis,[6] material science,[7] nanotechnology[8] and biochemical processes.[9]

Mechanochemical synthesis, the branch of synthesis that studies reactions induced by mechanical action (MA),[10] is one of the most recent techniques in organic synthesis and holds great promise in the development of solvent-free synthetic methodologies. The synthesis of pyrroles, porphyrins and related compounds under microwave irradiation or using mechanical activation are reviewed herein.

2. Pyrroles

2.1. Introduction

Pyrroles are broadly recognized as one of the simplest and most important aromatic heterocycles. Pyrroles can be found in a wide range of natural products such as bacteria and marine natural products, and both natural and synthetic pyrroles, exhibit interesting biological properties. Indeed a considerable number of drugs containing pyrroles exits. For example, pioluteorine and nakamuric acid, isolated from bacterial sources and from marine natural products, respectively, exhibit antibacterial activity; tolmetin and zomepirac are non-steroidal anti-inflammatory synthetic drugs; sunitinib is used for the treatment of renal cell carcinoma, and atorvastatin, one of the best-selling drugs in pharmaceutical history, is a cholesterol-lowering agent (Figure 1).

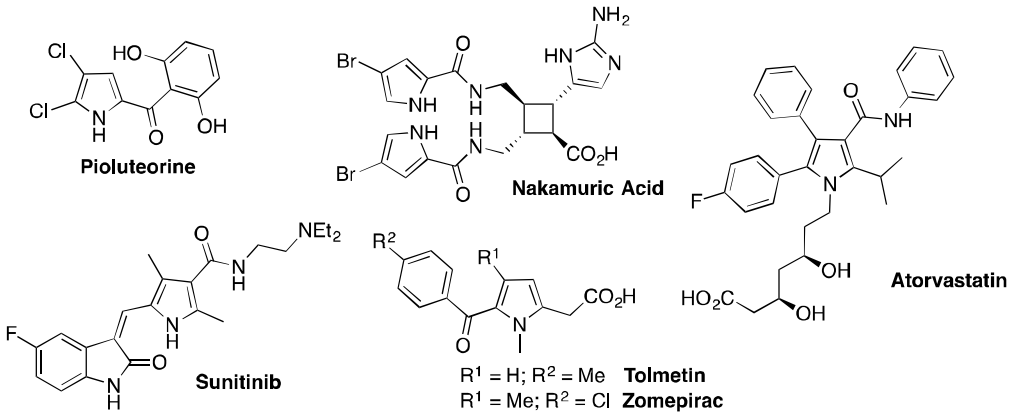
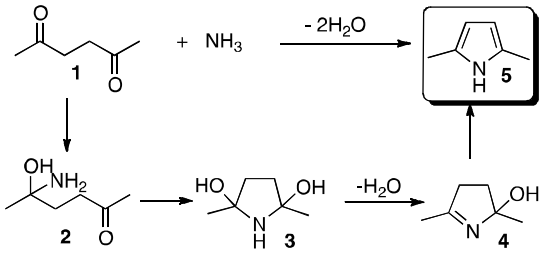


Figure 1. Natural and synthetic pyrroles with biological activity.

Since the end of the 19th century, when Knorr, Paal and Hantzsch developed the synthesis of pyrroles, a large variety of synthetic strategies for the synthesis of pyrrole derivatives has been developed and largely reviewed.[11] The Paal-Knorr synthesis involves the treatment of suitable substituted 1,4-dicarbonyl compounds with ammonia, primary amines, ammonium or alkyl ammonium salts in ethanol or acetic acid leading to 2,5-disubstituted pyrroles.[12] According to the mechanistic proposal of Amarnath,[13] exemplified by the synthesis of 2,5-dimethyl-1*H*-pyrrole in Scheme 1, the reaction of 2,5-hexadione (**1**) with ammonia gives

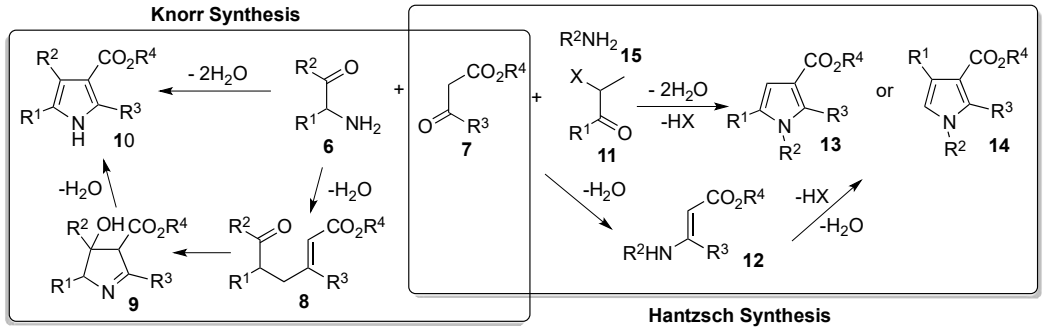
double hemiacetal **3** which, through the elimination of water, yields imine **4** and 2,5-dimethyl-1*H*-pyrrole (**5**).



Scheme 1. Paal-Knorr synthesis of pyrroles.

Ludwig Knorr, 130 years ago, published the cyclocondensation of α-aminoketones **6** with β-ketoesters **7** or β-diketones **8** to affords 3-alkoxycarbonyl-or 3-acyl-substituted pyrroles **10** (Scheme 2).[14]

Hantzsch developed the first multicomponent synthesis of pyrroles.[15] The reaction of β-ketoesters **7** with ammonia or primary amines and α-haloketones **11** yield, through β-aminoacrylic ester intermediate **12**, substituted pyrroles **13** or **14**. The regioselectivity of the product depends on the substituents in the starting materials, *C*-alkylation of enamine **12** leads to 1,2,3,5-tetrasubstituted pyrroles **13** while *N*-alkylation gives 1,2,3,4-tetrasubstituted pyrroles **14** (Scheme 2). The use of this reaction has grown recently due to the increased interest in multicomponent reactions to enhance the sustainability of synthetic processes.[11c]

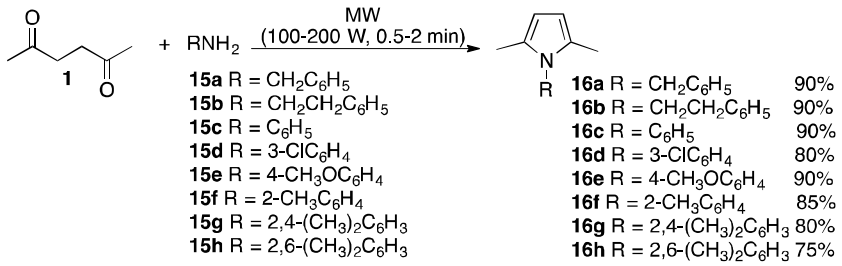


Scheme 2. Knorr and Hantzsch synthesis of pyrroles.

2.2. Microwave-assisted synthesis

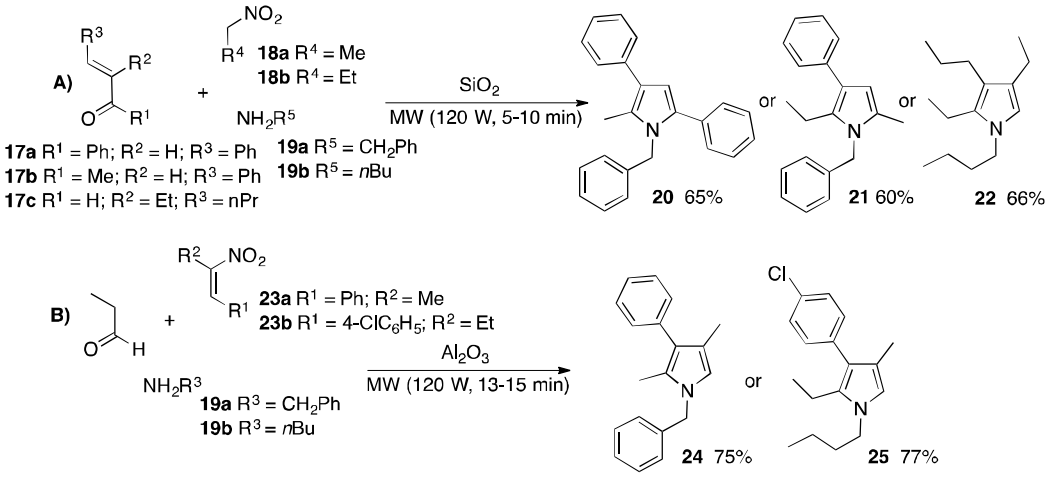
Microwave-assisted synthesis has been successfully applied to the preparation of heterocyclic compounds[16] including pyrroles.

The first microwave-assisted Paal-Knorr reaction was reported in 1999 when Danks described the synthesis of 2,5-dimethylpyrroles **16a-h** from 2,5-hexanedione (**1**) and primary amines **15a-h** using a domestic microwave oven, in less than 2 minutes (Scheme 3).[17] Ring-fused pyrroles were obtained using cyclic amines in xylene and *p*-toluenesulfonic acid under microwave irradiation at 280 ºC during 20-40 min.[18]



Scheme 3. Synthesis of *N*-substituted-2,5-dimethylpyrroles under microwave irradiation without solvent.

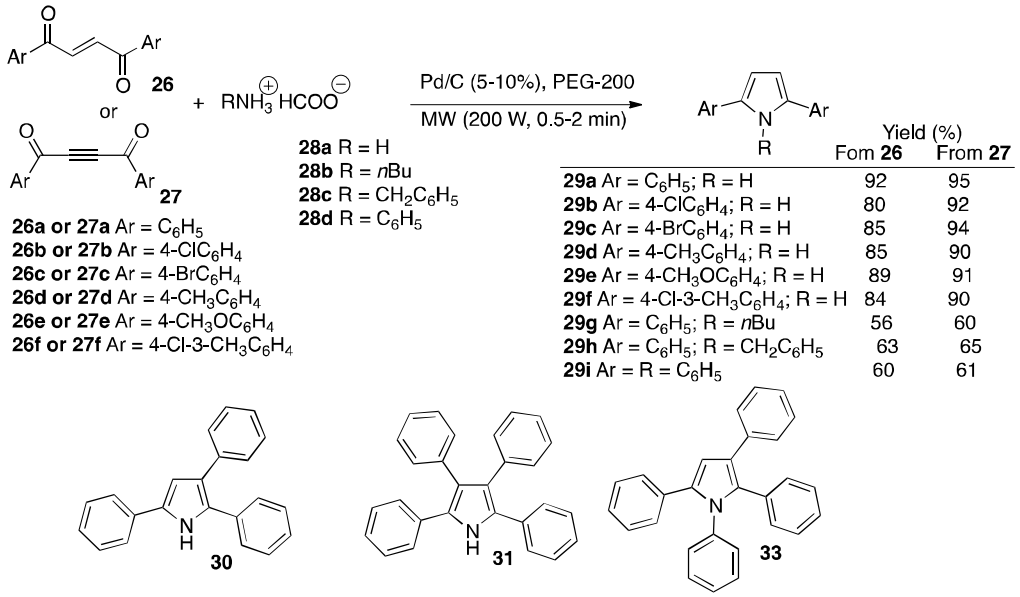
Solid supported three-component condensation of α,β-unsaturated aldehydes or ketones **17a-c**, primary amines **19a**,**b** and nitroalkanes **18a**,**b** on silicon dioxide (see selected examples in Scheme 4A) or the solid supported condensation of aldehydes or ketones, primary amines and nitroalkenes **23a**,**b** on aluminium oxide (Scheme 4B) under microwave irradiation in a domestic oven during 5 to 15 minutes afforded pyrroles with diverse substitution patterns **20**-**22**,**24** and **25** in moderate to high yields.[19] 3-Naphthyl, 3-antracenyl and 3-pyrenyl analogs of pyrrole **20** were obtained using this methodology, however the use of a mono-mode microwave reactor for synthesis, the use of different solid supports, the increase of the reaction time, temperature or MW power did not allow the formation of the desired products in yields higher than 28%.[20] The cycloaddition of nitroalkenes and α-(alkylideneamino)nitriles under microwave irradiation in DMF affords *N*-unsubstituted pyrroles in low to moderate yields.[21]



Scheme 4. Solid supported three-compoent synthesis of pyrroles under microwave irradiation.

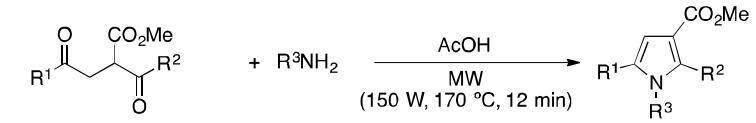
2,5-Diarylpyrroles were prepared under microwave irradiation in very short reaction times (0.5-2 min) using the Paal-Knorr strategy. Starting from ammonium, alkyl or aryl ammonium formates **28b-d** and but-2-ene-1,4-diones **26a-f** or but-2-yne-1,4-diones **27a-f**, using polyethylene glycol (PEG-200) as solvent and Pd/C as catalyst, pyrroles **29a-i** were obtained in high yields *via* palladium-mediated transfer hydrogenation

of the carbon-carbon double or triple bond, followed by a reductive amination-cyclization process (Scheme 5). Starting from highly substituted but-2-ene-1,4-diones and using this methodology, pyrroles with three and four phenyl substituents **30-32** were obtained in good yields, however it fails for the synthesis of the pentaphenyl substituted pyrrol.[22]



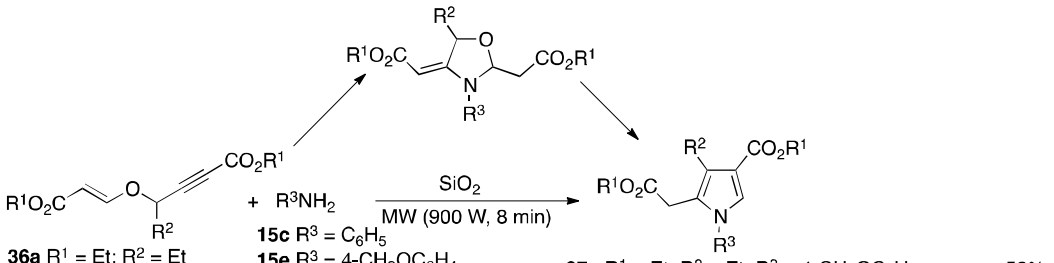
Scheme 5. Synthesis of aryl substituted pyrroles under microwave irradiation using PEG-200 as solvent.

Pyrroles with a methylcarboxylate substituent at position 3, **35a-e**, were prepared from 3-methylcarboxylate-1,4-dicarbonyl compounds, previously synthetized from the corresponding β-ketoester and aldehyde, and primary amines *via* Paal-Knorr procedure using acetic acid as solvent and microwave irradiation (single-mode microwave reactor) in the cyclisation step in moderated to high yields (Scheme 6).[23] This procedure was adapted for the synthesis of a library of pyrrole-based amino acids and some constrained oligopeptides[24] and for the solution-phase microwave-assisted synthesis of a large library of pyrrole amide derivatives.[25]



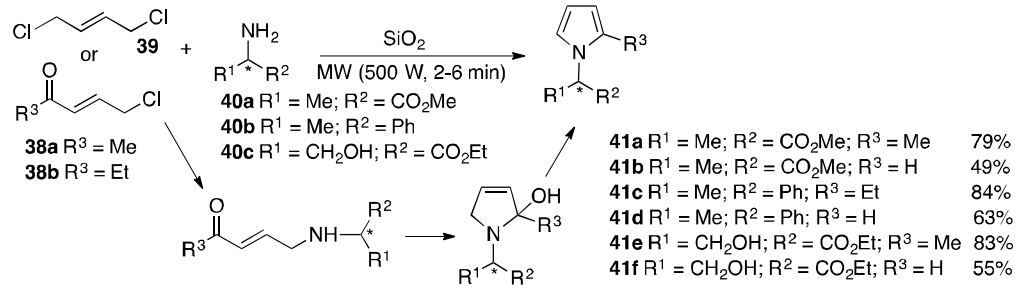
Scheme 6. Synthesis of 3-carboxymethyl substituted pyrroles under microwave irradiation.

Tetrasubstituted pyrroles **37a-f**, also with a methylcarboxylate substituent at position 3 and unsubstituted at position 2, could be obtained through rearrangement of 1,3-oxazolidines synthetized under microwave irradiation, from the reaction of enol ethers **36a-f** with primary amines using silica dioxide as solid support, in 8 minutes (Scheme 7).[26]



Scheme 7. Synthesis of 3-methylcarboxylate substituted pyrroles through *in situ* rearrangement of 1,3-oxazolidines under microwave irradiation.

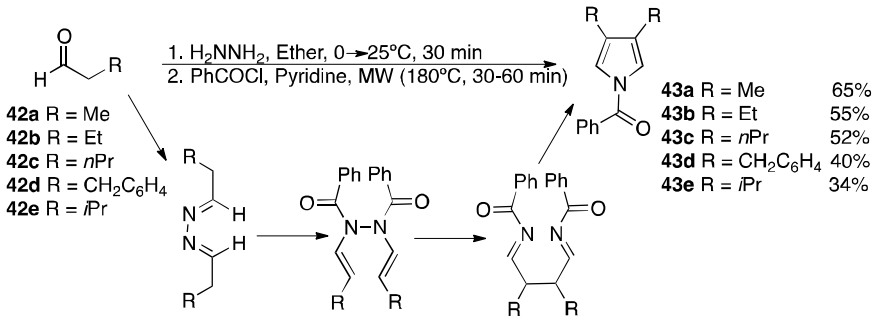
Microwave-assisted solid support coupling of chloroenones **38a**,**b** or 1,4-dichlorobut-2-ene (**39**) and chiral amines **40a-c** allows the synthesis of *N*-substituted chiral pyrroles **41a-f** in less than 6 minutes in moderate to high yields, comparable with those obtained under conventional heating in 6 h. The suggested mechanism for the formation of pyrroles involves the initial reaction of the amine with the allylic chloride followed by cyclisation and water or HCl elimination; no racemization was observed in the reaction products (selected examples in Scheme 8).[27]



Scheme 8. Synthesis of *N*-substituted chiral pyrroles under microwave irradiation.

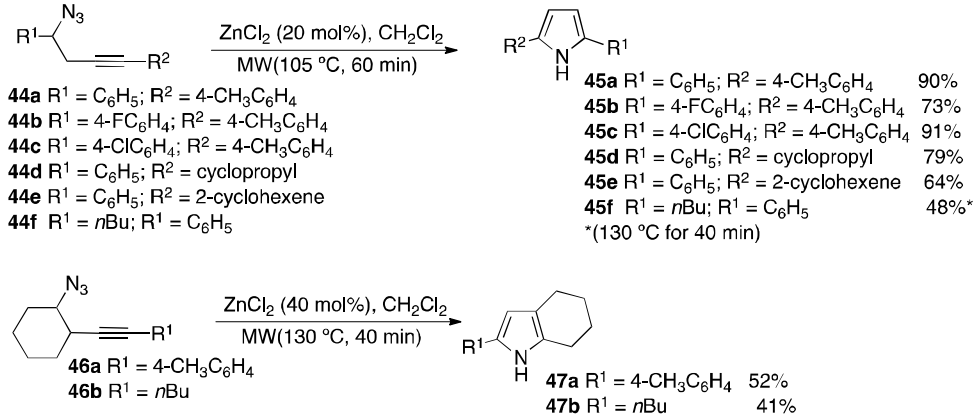
The microwave-assisted two-step, one-pot synthesis of 3,4-disubstituted *N*-acylpyrroles reported by Milgram *et al.* offers a straightforward approach for the synthesis of octaethylporphyrin and octaethyltetraphenylporphyrin. Starting from hydrazine and alkyl aldehydes **42a-e**, *via* Piloty-Robinson reaction, *N*-acylpyrroles **43a-e** were obtained through cyclization under microwave irradiation in moderate

to high yields, greatly reducing the reaction time when compared with the conventional conditions (Scheme 9). The overall sequence involves the synthesis of a symmetric azine which, under microwave irradiation in the presence of aryl chloride, promotes tautomerization and subsequent [3,3]-sigmatropic rearrangement delivering a 1,4-bis imine that after cyclization and aromatization generate the desired 3,4-disubstituted *N*-acylpyrroles.[28]



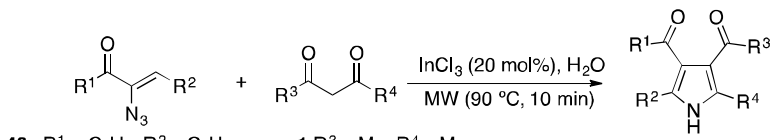
Scheme 9. Microwave-assisted two-step one-pot synthesis of 3,4-disubstituted *N*-acylpyrroles.

Azides offer an interesting synthetic alternative for the synthesis of pyrroles. 5-Endo-dig cyclization of previously prepared homopropargyl azides **44a-f**, in the presence of zinc chloride in dichloromethane under microwave irradiation provides 2,5-disubstituted pyrroles **45a-f**. Fused pyrroles **47a**,**b** were obtained when ciclohexylazide derivatives **46a**,**b** were used. Both conventional and microwave protocols furnished comparable results: diaryl substituted pyrroles were obtained in good yields while the synthesis of fused pyrroles or alkyl substituted pyrroles require higher quantities of catalyst and higher temperature to afford moderates yields. Despite the unusually long reaction time under microwave irradiation, it is still significant decrease when compared with the 16 h necessary under conventional heating conditions (Scheme 10).[29]



Scheme 10. Microwave-assisted synthesis of pyrroles from homopropargyl azides.

α-Azido chalcones **48a-c**, obtained from benzylidene acetophenones, react with 1,3-dicarbonyl compounds **1** and **49a-c** in the presence of indium chloride as Lewis acid catalyst and water as solvent under microwave irradiation during 10 minutes to afford highly substituted pyrroles **50a-d** in high yields (see selected examples in Scheme 11).[30]



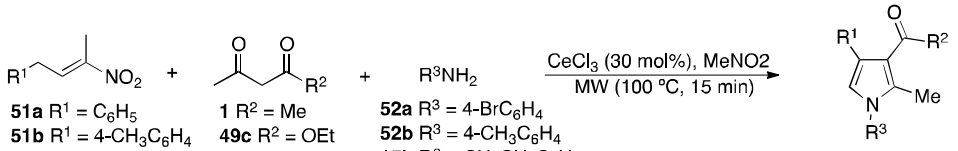
48a $R^1 = C_6H_5$; $R^2 = C_6H_5$
48b $R^1 = C_6H_5$; $R^2 = 4\text{-}ClC_6H_5$
48c $R^1 = 4\text{-}ClC_6H_5$; $R^2 = C_6H_5$

1 R^3 = Me; R^4 = Me
49a R^3 = Me; $R^4 = CF_3$
49b R^3 = Me; $R^4 = C_6H_5$
49c R^3 = Me; R^4 = OEt

50a $R^1 = C_6H_5$; $R^2 = C_6H_5$; R^3 = Me; R^4 =Me 94%
50b $R^1 = C_6H_5$; $R^2 = 4\text{-}ClC_6H_5$; R^3 = Me; $R^4 = CF_3$ 79%
50c $R^1 = 4\text{-}ClC_6H_5$; $R^2 = C_6H_5$; R^3 = Me; $R^4 = C_6H_5$ 88%
50d $R^1 = 4\text{-}ClC_6H_5$; $R^2 = C_6H_5$; R^3 = Me; R^4 = OEt 71%

Scheme 11. Microwave-assisted synthesis of pyrroles from α-azido chalcones.

Using Cerium(III) chloride as catalyst tetra- and pentasubstituted pyrroles were synthesized in a multicomponent microwave-assisted reaction. Equimolar amounts of β-nitrostyrenes **51a-d**, acetylacetone (**1**) or ethylacetylacetonate (**49c**) and several aniline derivatives react under microwave irradiation in the presence of $CeCl_3.7H_2O$ in nitromethane during 15 min affording pyrroles **53a-h** in good yields. The reaction yield is influenced by the substituent at the *para* position of the phenyl ring of nitrostyrene, with methyl substituents giving the pyrroles in high yields (67-80%) while the substitution with chlorine decreases the reaction yield (46-58%). Substitution of acetylacetone (**1**) for ethylacetylacetonate (**49c**) or the introduction of substituents at the phenyl ring of aniline have little influence on the reaction yield. However, using cyclic 1,3-dicarbonyl compounds, the reaction does not afford the expected product. Using primary aliphatic amines the reaction yield decreases (25% with 2-phenylethylamine (**15b**)) but using 60 mol% of $CeCl_3.7H_2O$ the reaction yield increases to 43% which compares favorably with the 13% yield obtained after 15 h of heating under conventional conditions (Scheme 12).[31]



51a $R^1 = C_6H_5$
51b $R^1 = 4\text{-}CH_3C_6H_4$
51c $R^1 = 4\text{-}ClC_6H_4$
51d $R^1 = C_6H_5$

1 R^2 = Me
49c R^2 = OEt

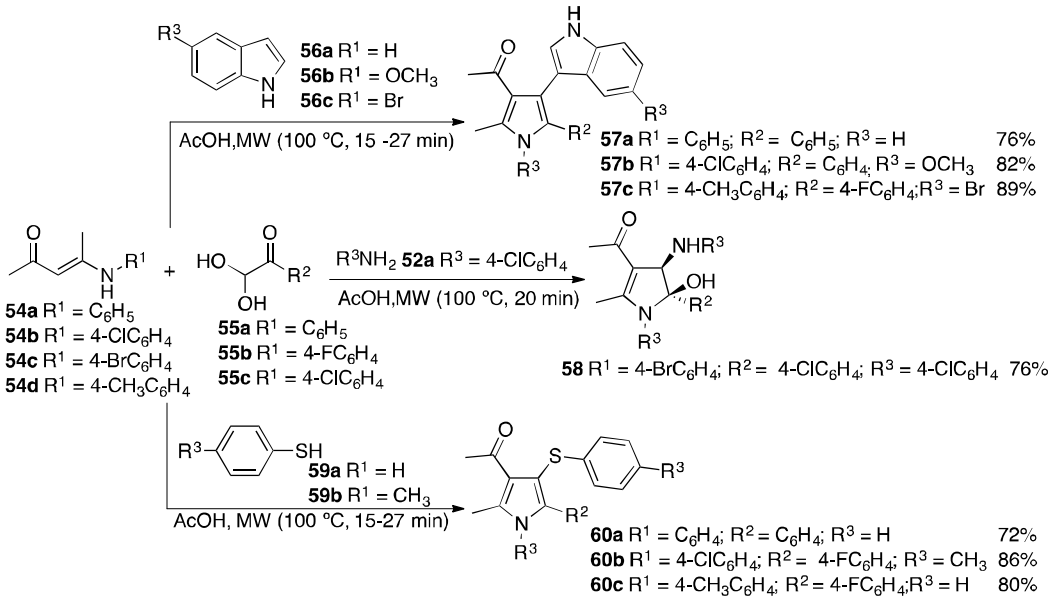
52a $R^3 = 4\text{-}BrC_6H_4$
52b $R^3 = 4\text{-}CH_3C_6H_4$
15b $R^3 = CH_2CH_2C_6H_4$
15c $R^3 = C_6H_5$
15e $R^3 = 4\text{-}CH_3OC_6H_4$

53a $R^1 = C_6H_5$; R^2 = Me; $R^3 = C_6H_5$ 75%
53b $R^1 = 4\text{-}CH_3C_6H_4$; R^2 = Me; $R^3 = C_6H_5$ 80%
53c $R^1 = 4\text{-}ClC_6H_4$; R^2 = Me; $R^3 = C_6H_5$ 59%
53d $R^1 = C_6H_5$; R^2 = Me; $R^3 = 4\text{-}CH_3C_6H_4$ 77%
53e $R^1 = C_6H_5$; R^2 = Me; $R^3 = 4\text{-}CH_3OC_6H_4$ 60%
53f $R^1 = C_6H_5$; R^2 = Me; $R^3 = 4\text{-}BrC_6H_4$ 61%
53g $R^1 = C_6H_5$; R^2 = OEt; $R^3 = C_6H_5$ 64%
53h $R^1 = C_6H_5$; R^2 = Me; $R^3 = CH_2CH_2C_6H_5$ 43%*
*(60 mol%) $CeCl_3.7H_2O$

Scheme 12. Multicomponent microwave-assisted synthesis of pyrroles promoted by $CeCl_3.7H_2O$.

β-Enaminones and 2,2-dihydroxy-1-phenylethanones were use for the multicomponent synthesis of pentasubstituted pyrroles with the indole, thiol or amine functionalization at C-3. The reaction of β-

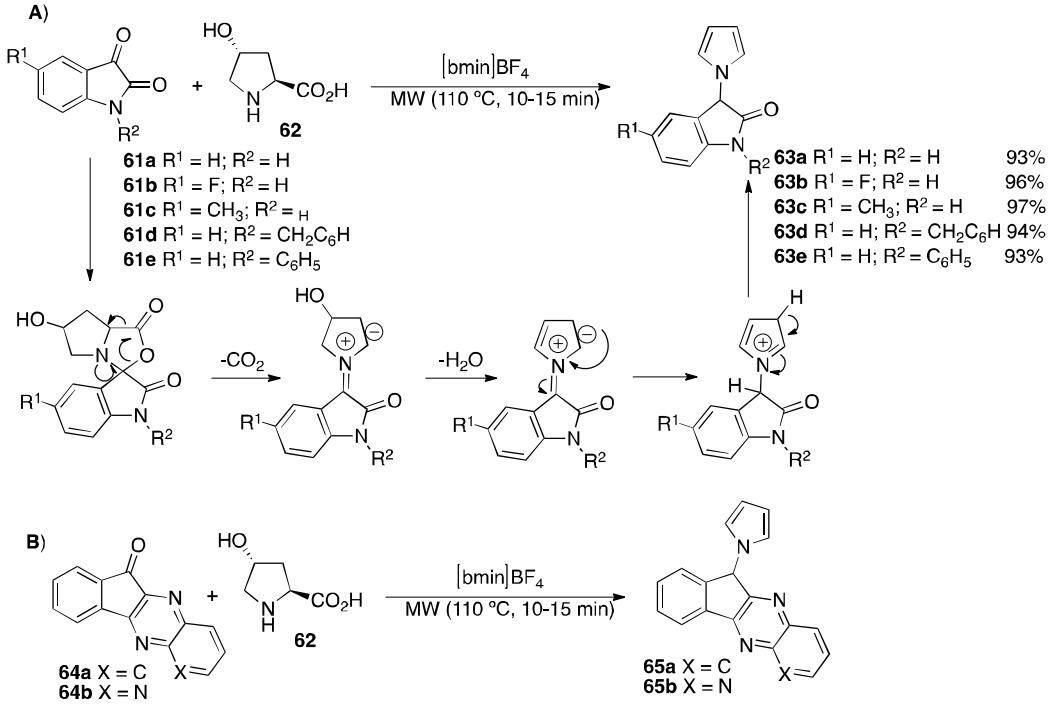
enaminones **54a-d** with 2,2-dihydroxy-1-phenylethanones **55a-c** and indole derivatives **56a-c** in acetic acid under microwave irradiation for 15 to 27 min, affords pentasubstituted pyrroles **57a-c** with the indole moiety in high yields. Substituting indole by benzenethiol derivatives **59a**,**b** the corresponding pyrroles were also obtained in very good yields, while using aromatic amines the reaction affords 4,5-dihydro-1*H*-pyrroles **58** (selected examples in Scheme 13).[32]



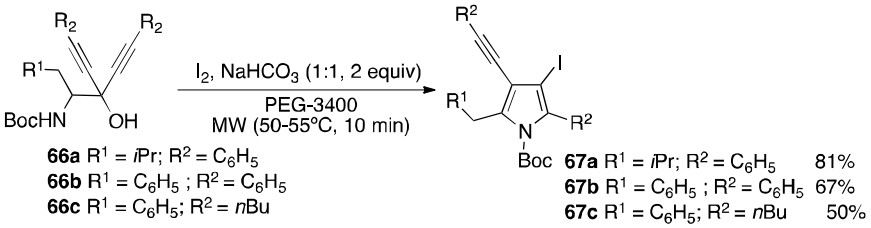
Scheme 13. Multicomponent microwave-assisted synthesis of pyrroles from β-enaminones and 2,2-dihydroxy-1-phenylethanones.

Pyrroles with an *N*-indolinone moiety **63a-e** were synthetized through the microwave-assisted condensation of 4-hydroxyproline (**62**) and several substituted isatins **61a-e** using an ionic liquid as solvent. Microwave irradiation results in very high yields in 10-15 min, while under conventional heating conditions the reaction remained incomplete even after 24 h at 110 ºC. The reaction proceeded without the addition of any acid promoter and the recovered ionic liquid was reused for six cycles. The formation of the desired products may be explained by the formation of an azomethine ylide *via* decarboxylation and subsequent 1,5-proton shift to give the more stable zwitterion, which can be easily transform to the more stable product with aromatic character (Scheme 14A). It was also observed that (ethylideneamino)-2,3-dihydroindene-1-ones **64a**,**b** underwent condensation with 4-hydroxyproline (**62**) under similar conditions to produce the corresponding 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-b]quinoxalin-11-ones **65a**,**b** in good yields (Scheme 14B).[33]

Highly substituted pyrroles **67a-c** were obtained through microwave-assisted iodocyclization of 1,2-amino alcohol derivatives with alkynyl substituents **66a-c** in the presence of an equimolar mixture of molecular iodine and $NaHCO_3$ (1:1, 2 equiv) in PEG-3400 at 50 °C for 15 minutes (Scheme 15).[34]



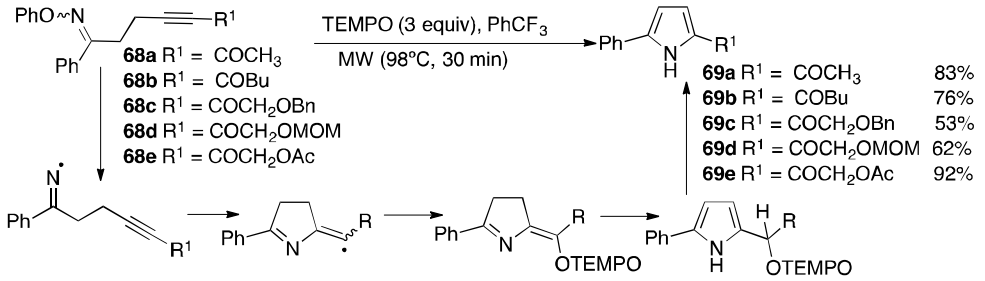
Scheme 14. Microwave-assisted synthesis of *N*-indolinone pyrroles derivatives.



Scheme 15. Microwave-assisted synthesis of iodopyrroles in PEG-3400.

Microwave irradiation of *O*-phenyl oxime ethers with alkynyl substituents **68a-e**, in the presence of TEMPO (2,2,6,6-tetramethylpiperidinyloxy) as a radical trapping agent and trifluoromethylbenzene, for 30 min afforded 2-acylpyrroles **69a-e** in moderate to good yields. The mechanism proposed involves the homolytic cleavage of the N-O bond producing an iminyl radical which undergoes 5-exo-dig cyclization to afford a vinyl radical which is trapped by TEMPO; after isomerization and fragmentation, probably triggered by abstraction of the hydrogen atom geminal to the OTEMPO substituent, the desired pyrroles are obtained (Scheme 16). Pyrroles with alkyl substituents at the C-3 and C-4, such as **70**-**73** can also be obtained in high yields (Figure 2).[35]

Microwave-assisted enyne cross-metathesis of propargylamines **73a-e** with ethyl vinyl ether (**74**) in the presence of Grubbs' catalyst (G-II) and copper sulfate, in toluene for 3x10 min, affords an easy approach to the synthetically challenging 1,2,3-substituted pyrroles **75a-e** (selected examples in Scheme 17).[36]



Scheme 16. Pyrrole synthesis through TEMPO-terminated iminyl radical cyclization under microwave irradiation.

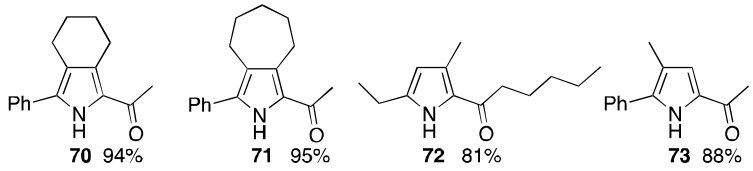
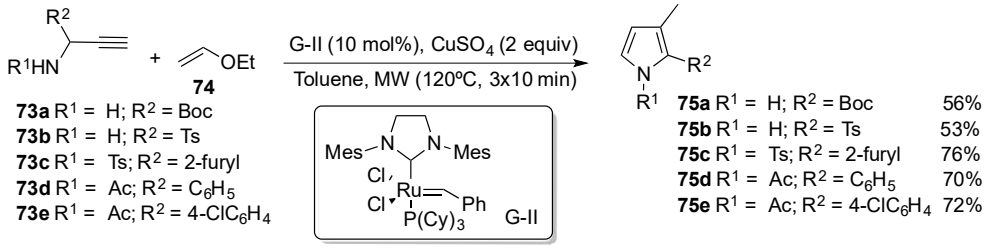
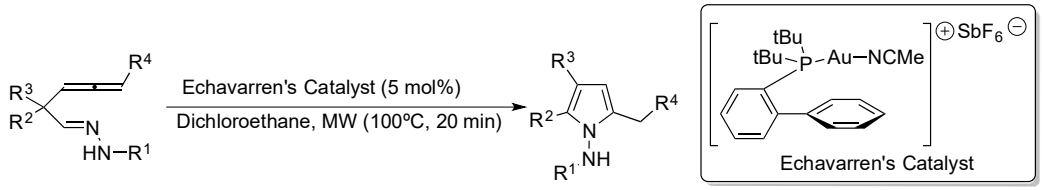


Figure 2. pyrroles with diferent substitution patterns obtained from *O*-phenyl oxime ethers.



Scheme 17. Microwave-assisted synthesis of pyrroles through enyne cross-metathesis.

The gold(I)-catalyzed intramolecular cycloisomerization of alkyl or aryl β-allenylhydrazones **76a-e** under microwave irradiation provides and efficient access to multisubstituted *N*-aminopyrroles **77a-e** in good to excellent yields(selected example in Scheme 18).



76a R^1 = Ts; R^2 = R^3 = Me; R^4 = Me
76b R^1 = Ts; R^2 = R^3 = C_6H_5; R^4 = Me
76c R^1 = Ts; R^2 = Me; R^3 = Et; R^4 = Me
76d R^1 = 2,4-$(NO_2)_2C_6H_3$; R^2 = R^3 = C_6H_5; R^4 = Me
76e R^1 = CO_2CH_3; R^2 = R^3 = Me; R^4 = C_6H_5

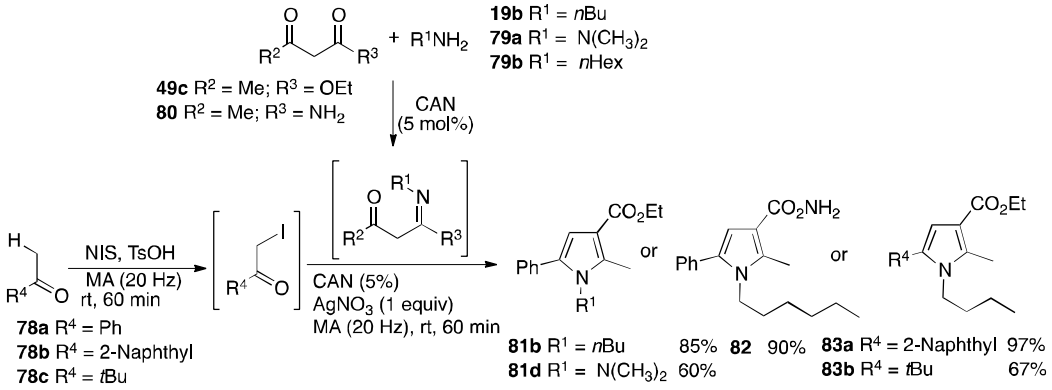
77a R^1 = Ts; R^2 = R^3 = Me; R^4 = Me 55%
77b R^1 = Ts; R^2 = R^3 = C_6H_5; R^4 = Me 69%
77c R^1 = Ts; R^2 = Me; R^3 = Et; R^4 = Me 94%
77d R^1 = 2,4-$(NO_2)_2C_6H_3$; R^2 = R^3 = C_6H_5; R^4 = Me 90%
77e R^1 = CO_2CH_3; R^2 = R^3 = Me; R^4 = C_6H_5 67%

Scheme 18. Gold(I)-catalyzed cycloisomerization of β-allenylhydrazones under microwave irradiation.

The cycloisomerization occurs in dichloroethane at 100 ºC for 20 min with 5% of Echavarren's catalyst.[37]

2.3. Mechanochemical synthesis

A sequential multicomponent synthesis of polysubstituted, functionalized pyrroles under solvent-free mechanochemical conditions using ketones, primary amines and β-dicarbonyl compounds as building blocks was reported by Menéndez, Estevez and Villacampa in 2013.[38] As expressed by the authors "*this is the first multicomponent reaction carried out under high-speed vibration milling conditions using a simple instrument without temperature control and with the sole input of mechanical energy*". The sequential three-component pyrrole synthesis involves the high-speed vibration milling of ketones **78a-c** with *N*-iodosuccinimide and *p*-toluenesulfonic acid for 60 min, followed by addition of a mixture of primary amines and β-dicarbonyl compounds **49c** and **80** previously stirred at room temperature for 30 min with cerium(IV) ammonium nitrate and sequential high-speed vibration milling with cerium(IV) ammonium nitrate and silver nitrate for an additional 60 min. This methodology allowed the synthesis of a set of 35 tetra- and pentasubstituted pyrroles and, in most of the cases, in higher yields than those obtained under conventional conditions in solution (see selected examples in Scheme 19).[39]



Scheme 19. Solvent-free mechanochemical three-component pyrrole synthesis.

Starting from diacetylbenzene derivatives under the same reaction conditions, using two equivalents of *N*-iodosuccinimide and 20% of *p*-toluenesulfonic acid for the iodination step, pyrrole derivatives **84-86** were obtained in high yields (Figure 3).

A straightforward and solventless Paal-Knorr pyrrole synthesis was developed involving mechanical activation in a laboratory-scale ball mill, using citric acid a biosourced organic acid as catalysts. This allowed the synthesis of pyrroles **89a-f** in very short reaction times at room temperature with moderate to good yields. The difference in reaction yields was not attributed to the dicarbonyl compound structure but to the different physical state of the amines. While iodoaniline **88a** and dodecylamine **88c** are solids at room temperature, but have very low melting points that allow them to achieve a molten or liquid phase under

mechanical activation which favours high yields, amines with higher melting points, such as naphthylamine **88d**, remain solid, giving lower yields (Scheme 20).[40]

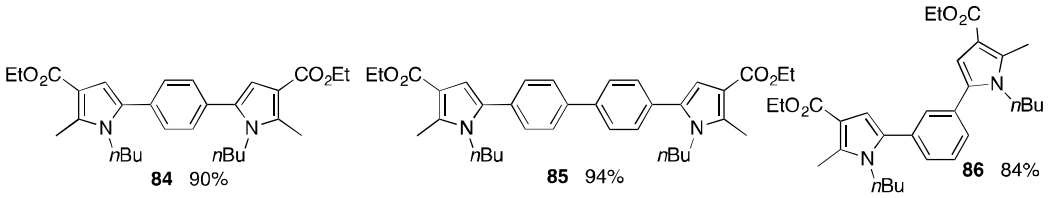
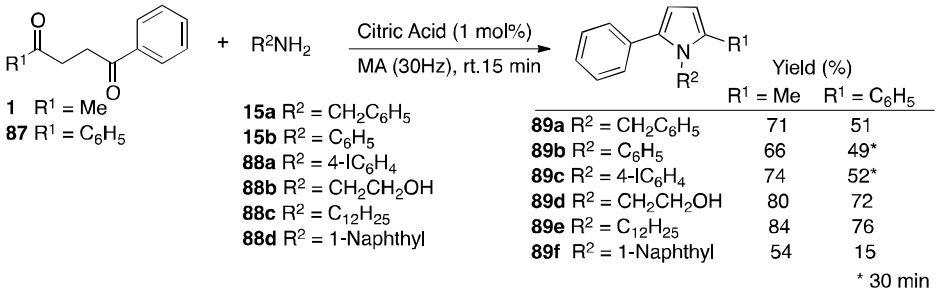


Figure 3. *Ter*- and *quarter*-aryl derivatives contained the pyrrole moiety obtained under mechanical action conditions.



Scheme 20. Paal-Knorr synthesis under mechanical activation.

3. Porphyrins

3.1. Introduction

The best-known natural tetrapyrrolic macrocycles are heme and chlorophyll, Figure 1. The remarkable popularity and versatility of porphyrins and their derivatives[41] relies in great length, on the development and improvement of synthetic strategies over the years that make the huge availability of these compounds possible. Since Rothemund's report on the one-pot synthesis of *meso*-substituted porphyrins starting from pyrrole and an aldehyde[42] several simple one-step or two-step approaches have been developed for the preparation of these compounds.

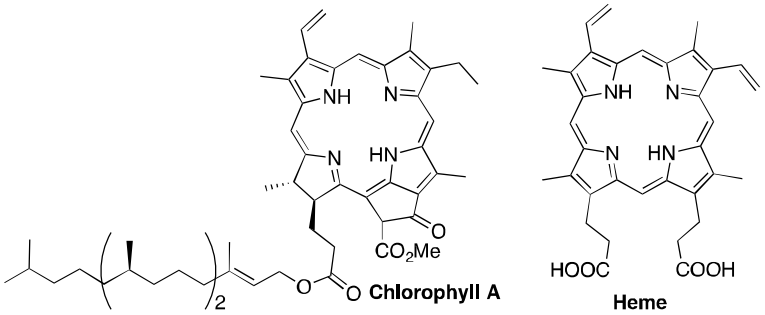


Figure 1. Natural tetrapyrrolic macrocycles.

The characteristics of the most significant methods for the synthesis of *meso*-porphyrins under conventional heating conditions are summarized in Table 1. More complex multi-step protocols involving the preparation of multi-substituted pyrrolic precursors, were used to prepare porphyrins substituted at the *β*-position, namely the MacDonald methodology also known as [2+2] strategy[43], the "head to tail" condensation of four molecules of pyrrole,[44] the [3+1] condensation between diformyl pyrrole and tripyrrane[45] and the cyclisation of linear tetrapyrroles, b-bilenes and a,c-biladienes.[46]

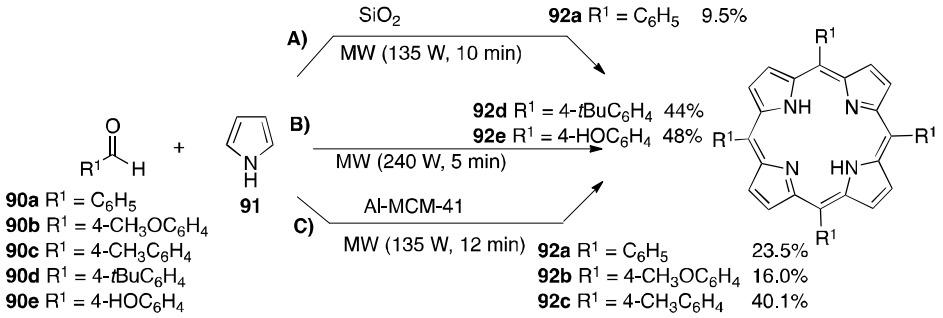
Table 1. Methods for the synthesis of *meso*-porphyrins under conventional heating conditions.

	Rothemund[42]	**Adler**[47]	**Lindsey**[48]	**Gonsalves**[49]
Solvent	Pyridine	Propionic or acetic acid	DCM or Chloroform	Acetic acid/ nitrobenzene
Temperature (ºC)	220	140-120	rt	120
Time (h)	24-48	1	1	1.5
Catalyst	-	-	TFA or BF_3	-
Oxidant	-	O_2	DDQ or *p*-chloranil	-
Reactants Conc. (M)	3.6	0.02	0.001-0.1	0.08
Work-up	Filtration	Filtration	Chromatography	Filtration
Yield	<10 %	20 %	40 %	20%

3.2. Microwave synthesis

3.2.1. Solventless reaction conditions

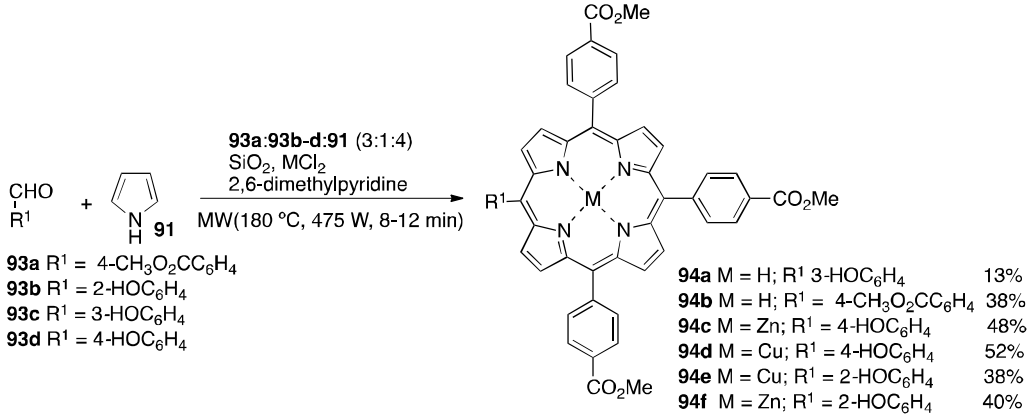
The preparation of porphyrins under microwave irradiation was first described by Loupy *et al* in 1992[50] and later adapted for undergraduate experimental teaching.[51] Irradiation of a mixture of pyrrole (**91**) and benzaldehyde (**90a**), pre-adsorbed on the surface of silica dioxide for 10 minutes, afforded 5,10,15,20-tetraphenylporphyrin (**92a**) in 9.5% yield (Scheme 21A). Using Al-MCM-41 mesoporous molecular sieves as solid acidic catalysts and a domestic microwave apparatus operating at 1200 W for 12 minutes, *meso*-substituted porphyrins **92a-c** were obtained in yields comparable to the classical methodologies (Scheme 21C).[52]



Scheme 21. Solventless microwave-assisted synthesis of porphyrins using SiO_2, Al-MCM-41 or in the absence of solid support.

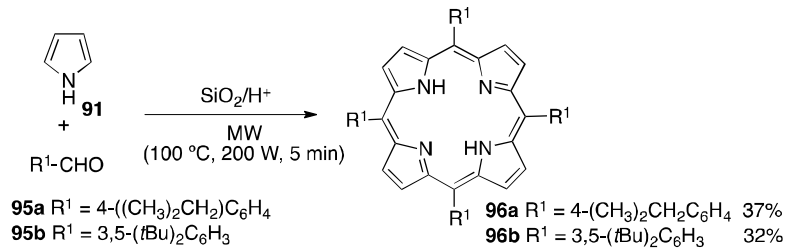
5,10,15,20-*Tetrakis*(4-*tert*-butylphenyl)porphyrin (**92d**) and 5,10,15,20-*tetrakis*(4-hydroxyphenyl)porphyrin (**92e**) were obtained in good yields, heating the corresponding aldehyde and pyrrole under microwave irradiation in a domestic oven at 240 W for 5 min without solvent or solid support (Scheme 21B).[53]

Since the report of Loupy several groups used silica dioxide as solid support for the synthesis of porphyrins. Using 3:1:4 molar ratio of methyl 4-formylbenzoate (**93a**), 3-hydroxybenzaldehyde (**93c**) and pyrrole (**91**), pre-adsorbed on the surface of silica gel and heating for 12 minutes at 450 W in a domestic oven, the desired unsymmetrically substituted porphyrin **94a** and the symmetrical *meso*-substituted porphyrin **94b** were obtained with 13% and 38% isolated yields, respectively. These unsymmetrical porphyrins were typically synthesized in reflux of propionic acid for 3 h with relatively poor yields (~ 10%). Adding $ZnCl_2$ or $CuCl_2$ to the reaction mixture, the corresponding unsymmetrical metaloporphyrins **94c-f** were obtained in higher yields (Scheme 22).[54]



Scheme 22. Microwave-assisted synthesis of asymmetric porphyrins and metaloporphyrins using silica dioxide as solid support.

Yaseen and colleagues[55] reported the solid-supported synthesis of two *meso*-tetraarylporphyrins under microwave heating using silica gel, previously acidified with propanoic acid and dried in an oven at 50 ºC for 12 h as solid support (Scheme 23).

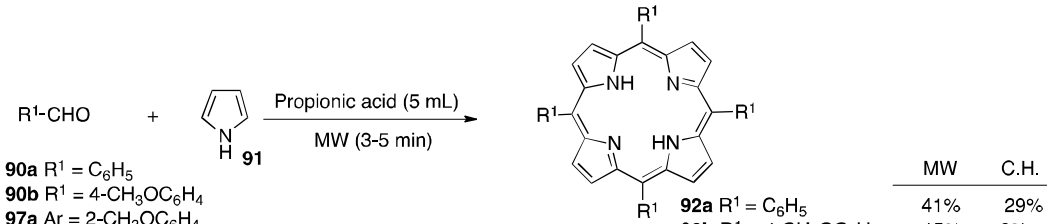


Scheme 23. Synthesis of meso-substituted porphyrins under microwave irradiation using silica dioxide dopped with acid as solid support.

Porphyrins **96a**,**b** were synthesized after 10 minutes under microwave irradiation at 100 ºC in 37% and 32% yields, respectively.

3.2.2. Synthesis in solution

Chauhan and co-workers, in 2001 reported, the condensation of equimolar amounts of a series of aryl aldehydes and pyrrole in an open vessel, employing propionic acid as solvent and making use of a microwave domestic oven in an adaptation of the classical Adler method.[56] *meso*-Substituted porphyrins **92a**,**b** and **98a**-**f** were obtained with poor to moderate isolated yields. Nevertheless, comparing microwave irradiation using 5 mL of propionic acid with conventional heating using 160 mL of propionic acid, all porphyrins were obtained with higher isolated yields under microwave irradiation (Scheme 24).



90a $R^1 = C_6H_5$
90b $R^1 = 4\text{-}CH_3OC_6H_4$
97a $Ar = 2\text{-}CH_3OC_6H_4$
97b $Ar = 4\text{-}O_2NC_6H_4$
97c $Ar = 2\text{-}O_2NC_6H_4$
97d $Ar = 2,4,6\text{-}(CH_3)_3C_6H_2$
97e $Ar = 4\text{-}ClC_6H_4$
97f $Ar = 3\text{-}ClC_6H_4$

	MW	C.H.
92a $R^1 = C_6H_5$	41%	29%
92b $R^1 = 4\text{-}CH_3OC_6H_4$	15%	9%
98a $R^1 = 2\text{-}CH_3OC_6H_4$	43%	27%
98b $R^1 = 4\text{-}O_2NC_6H_4$	28%	6%
98c $R^1 = 2\text{-}O_2NC_6H_4$	25%	5%
98d $R^1 = 2,4,6\text{-}(CH_3)_3C_6H_2$	19%	13%
98e $R^1 = 4\text{-}ClC_6H_4$	7%	3%
98f $R^1 = 3\text{-}ClC_6H_4$	4%	trace

Scheme 24. Microwave-assisted synthesis of *meso*-substituted porphyrins using proprionic acid as solvent.

5,10,15,20-*Tetrakis*(4-*t*butylphenyl)porphyrin (**92d**),[57] 5,10,15,20-*Tetrakis*[4'-(terpyridinyl)phenyl]porphyrin (**99**)[58] and a series of resorcin[4]arene cavitand-capped porphyrin capsules **100a-f**[59] were synthesized using this methodology in moderated to good yields (Figure 5).

The adaptation of the classical Rocha Gonsalves one-step synthesis of *meso*-tetraarylporphyrins to microwave technology was reported by Pineiro and Gonsalves in 2007,[60] using a single-mode microwave reactor. The selected aryl aldehyde and pyrrole were added to propionic acid (3.5 mL) and nitrobenzene (1.5 mL) thoroughly mixed and heated at 200 ºC for 5 min under focused microwave with an initial power setting of 250 W. Seven porphyrins were obtained in 5 min reactions, with improved yields ranging from 5% to 55%, affording from 0.5 to 1.1 gram of product (Scheme 25).[61] A similar procedure was adopted by Pan and co-workers to synthesized fluorinated prophyrins in good yields[62] and asymmetrically substituted 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin in 20% yield.[63]

Zerrouki and co-workers described a microwave-assisted, iodine-catalysed, one-pot-two-step synthesis of *meso*-tetraphenylporphyin (**92a**) in 2008.[64] First, pyrrole, benzaldehyde, dichloromethane and a 10% molar equivalent of molecular iodine were activated under microwave irradiation (100 W, 30 ºC), then *p*-chloranil was added and a second period of microwave irradiation was performed (100 W, 30 ºC). A maximum isolated yield of 47% was achieved after chromatographic work-up.

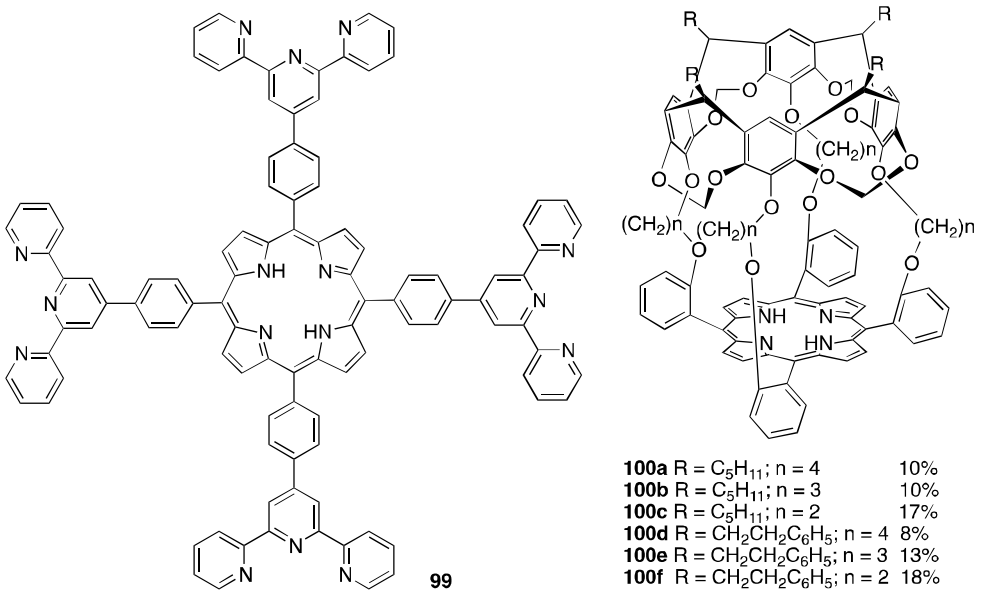
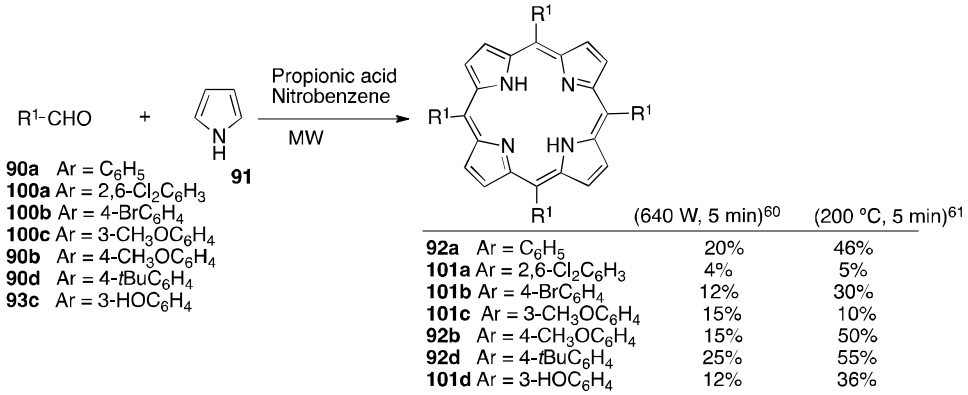


Figure 5. 5,10,15,20-*Tetrakis*[4'-(terpyridinyl)phenyl]porphyrin and a series of resorcin[4]arene cavitand capped porphyrin capsules synthesized under microwave irradiation using proprionic acid as solvent.

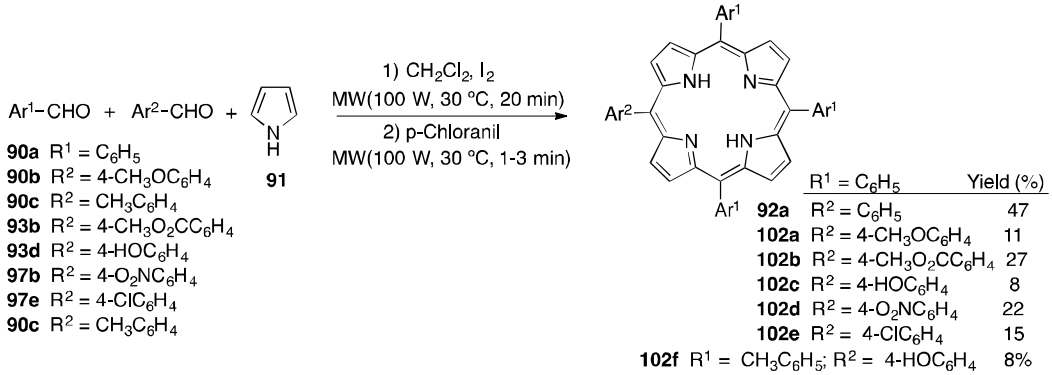


Scheme 25. Microwave-assisted synthesis of *meso*-substituted porphyrins using proprionic acid/nitrobenzene.

The same authors subsequently employed this microwave-activated synthetic approach to the preparation of some A_3B unsymmetrical *meso*-tetraarylporphyrins, **102a-e**, in moderate yields,[65] including A_3B type porphyrin **102f** with 8% yield, suitable for the generation of a large range of peptidic porphyrin derivatives[66] (Scheme 26).

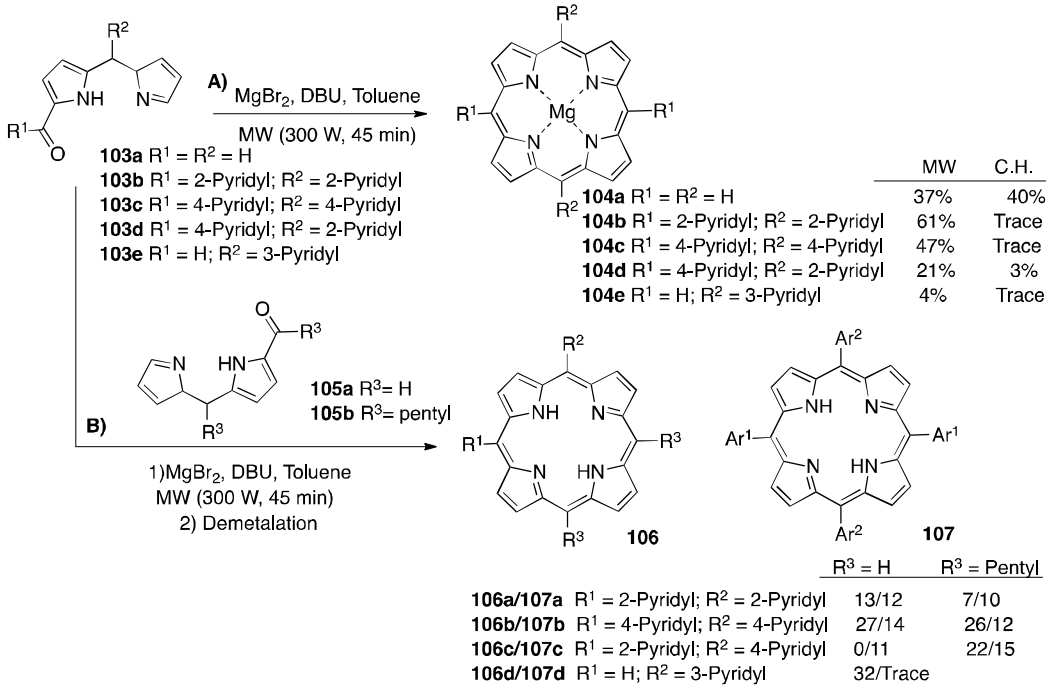
Porphine (**104a**), the structurally simplest porphyrin, was synthesized as the Mg(II) complex through microwave-assisted self-condensation of 1-acyldipyrromethane **103a** in toluene with 10 equiv. of DBU and

3 equiv. of $MgBr_2$ in 45 minutes with 37% yield, a notably short reaction time when compared with the 19 h necessary to obtain porphine in 40% yield under classical heating conditions.[67]



Scheme 26. Iodine-catalysed microwave-assisted synthesis of *meso*-substituted porphyrins.

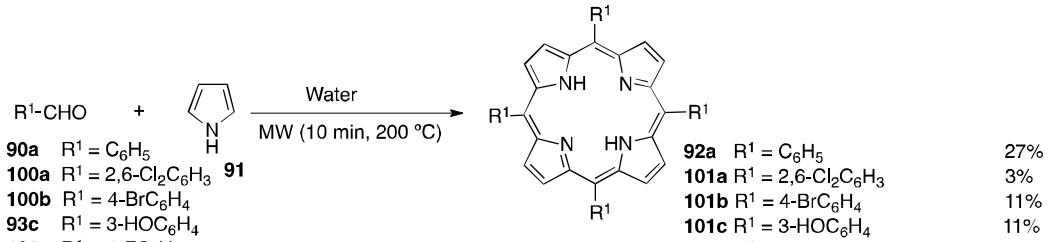
Using this approach and starting from 1-acyl-5-aryl-dipyrromethanes, Mg(II) complexes of A_2B_2 type *meso*-tetraarylporphyrins **104a-e** were obtained in low to moderate yield (see selected examples in Scheme 27A).[68] Using two non-identical 1-acyldipyrromethanes bearing pyridyl or alkyl substituents at the 5-position, followed by demetallation,



Scheme 27. Microwave-assisted synthesis of porphine, A_2B_2 type and unsymmetrical porphyrins.

Lindsey and co-workers synthesized unsymmetrical substituted *meso*-porphyrins **106a-d** and **107a-d** (selected examples in Scheme 27B).[68]

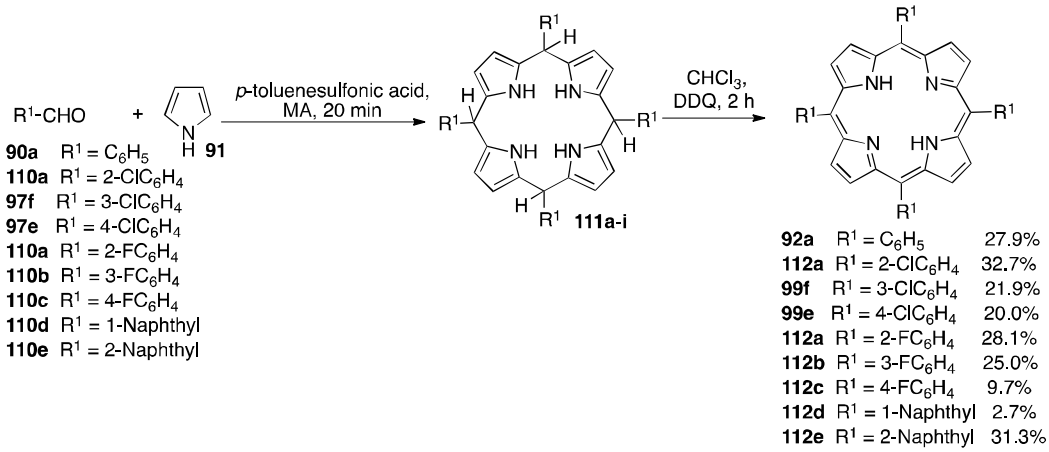
meso-Arylporphyrins were synthetized exploring the unique characteristics of overheated water under microwave irradiation. Thus, a mixture of pyrrole (9.8 mmol), arylaldehyde (9.8 mmol), and water (0.2 mL) subjected to microwave irradiation for 10 min at 200 ºC and initial MW power of 300 W afforded both the aryl and alkyl meso-substituted pophyrins in moderate to good yields. Sustainability of the reaction was assessed by E-Factor = 35 and EcoScale value of 50.5, the highest so far obtained for porphyrin synthesis (Scheme 28).[69]



Scheme 28. Microwave-assisted synthesis of porphyrins using water as additive.

3.3. Mechanochemical synthesis

In 2014 Hamilton and co-workers report the first and, until now, only example of mechanochemical synthesis of porphyrins (Scheme 29). The manual grinding of pyrrole, arylaldehyde and *p*-toluenesulfonic acid, as catalyst, for one minute followed by the addition of an arylaldehyde and grinding for *ca* 20 min yields a pink solid indicative of the formation of the corresponding porphyrinogen **111a-i**.

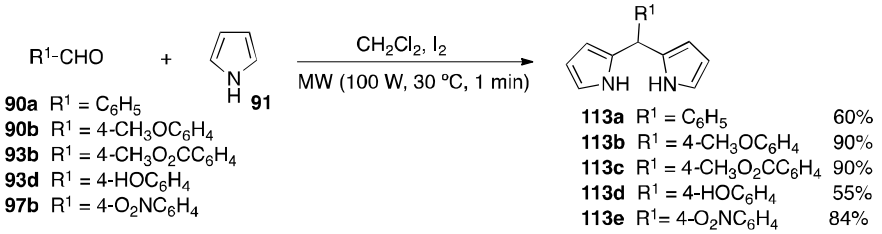


Scheme 29. Mechanochemical synthesis of *meso*-arylporphyrins.

The stirring of the porphyrinogen for two hours in chloroform with DDQ (1.5 equivalents to aryldehyde) gives the corresponding porphyrin in yields similar to those reported for the solution synthesis. The use of different oxidants, namely, iodine, nitric acid, sodium perborate or oxone does not afford better yields.[70]

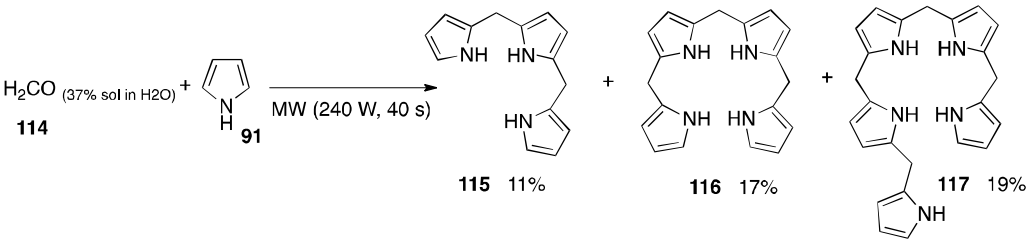
4. Related compounds

Some porphyrin precursors such as dipyrrylmethanes were synthesized under microwave irradiation. Zerrouki and co-workers used molecular iodine as catalyst for the synthesis of dipyrrylmethanes **113a-e** from pyrrole and benzeldehyde in a (1:10) molar ratio in dicloromethane (Scheme 30).[71]



Scheme 30. Microwave-assisted synthesis of 5-aryldipyrrylmethanes.

Preparation of tri-, tetra- and penta- unsubstituted pyrranes (**115-117**), was also achieved in moderate yields and short reaction times by microwave-assisted one-step condensation of aqueous formaldehyde with pyrrole (Scheme 31).[72]

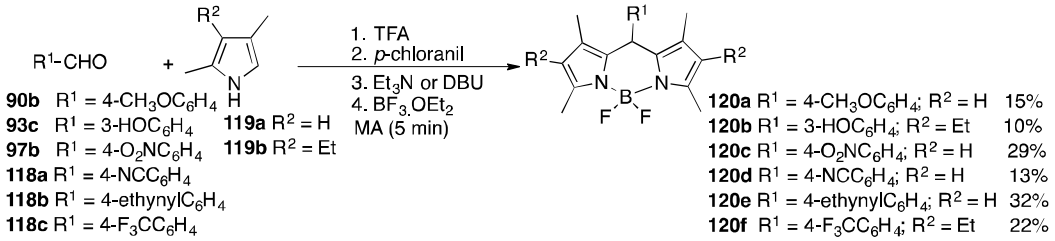


Scheme 31. Aqueous synthesis of tri- tetra- and pentapyrranes under microwave irradiation.

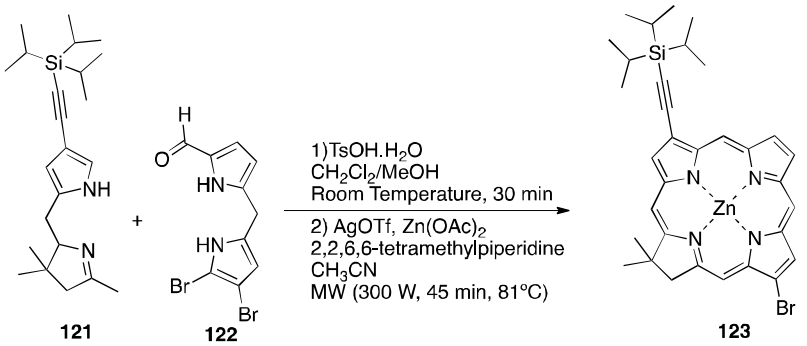
The condensation of alkylpyrroles **119a**,**b** and arylaldehydes by grinding in the presence of a few drops of TFA followed by oxidation with *p*-chloranil affords dipirrylmethenes in yields comparable to those obtained with classical methodologies but with a drastic reduction of the reaction times from hours or days to 5 minutes. These were subsequently transformed into the corresponding boron-dipyrromethenes (BODIPYS) **120a-f** (Scheme 32).[73]

Hydroporphyrins, namely chlorins and bacteriochlorins are accessible through microwave-assited methodologies such as the adaptation of the classical Withlock methodology[74] recently reviewed by Taniguchi and Lindsey.[75] Although, the synthesis of *beta*-subtituted porphyrins under microwave irradiation is only achieved through derivatization of the previously formed porphyrin ring, it is worth mentioning the

synthesis of a *beta*-substituted chlorin through *in situ* cyclization, oxidation and metal insertion under microwave irradiation with 5% yield, while the yield under conventional heating did not exceed 2% (Scheme 33).[76]



Scheme 32. Synthesis of dipyrrilmethanes by mechanical activation.



Scheme 33. Microwave-assisted synthesis of Zn(II) *beta*-substituted chlorin.

5. Conclusions

Microwave assisted synthesis had been proved to be an excellent tool for the synthesis of pyrroles and porphyrins. Under microwave irradiation it was possible to synthetize pyrroles with different substitution patterns, from simpler 2,5-disubstituted to more challenging highly substituted pyrroles, taking advantage of the reduction of reaction time and solvent consumption, use of alternative reaction media and increase of the reaction yields that characterize this technique. Porphyrins, particularly *meso*-substituted porphyrins, were also successfully synthetized using microwave irradiation. The new reaction conditions allow the synthesis of these compounds in good yields and, above all, in more sustainable ways. The first reports on the synthesis of pyrroles and porphyrins through mechanical activation demonstrate that mechanochemistry is emerging as a powerful tool for organic synthesis with high potential to develop more sustainable and secure methodologies.

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