

Microwave-assisted organic synthesis of pyrroles (Review)

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Abstract

The detection of pyrrole rings in numerous organic compounds with various pharmacological activities, emphasizes its huge importance in medicinal chemistry. Thus, the synthesis of pyrroles continues to arouse interest and Paal-Knorr condensation is considered to be the main synthetic route. A significant advance has been made since the MW activation was introduced in the organic synthesis which can be confirmed with the rapid growth of the published papers on that topic. Microwave irradiation is gaining popularity since faster reaction time, higher yields, easier work-up and reduced energy input can be achieved. Furthermore, it appears in numerous green chemistry protocols. The aim of the current article was to provide insights into the microwave syntheses of pyrrole derivatives, focusing on the most used synthetic approaches - Paal-Knorr, Clauson-Kaas, Barton-Zard, Hantzsch and others. The article was divided into several sections starting with the principles of the microwave organic synthesis. Thereafter the structure and the main pharmacological effects of the pyrrole derivatives were examined. Subsequently, articles describing the synthesis of pyrroles via Paal-Knorr, Hantzsch, Clauson-Kaas and Barton-Zard were discussed. All the reviewed papers conclude a significant reduction of the reaction times after MW irradiation compared to conventional heating.

Keywords

Green synthesis, Microwave synthesis, Paal-Knorr, Pyrrole

Green chemistry

Green chemistry consists of 12 principles described for the first time by Paul Anastas and John Warner. One major concern of Green chemistry is the usage of dangerous solvents throughout the chemical reactions. Moreover, problems associated with global issues such as energy production, climate change and the presence of toxic substances in the environment, form the basic concepts of Green chemistry (Donato et al. 2022). MW irradiation as a tool for greener chemistry was mentioned for the first time in the Green Chemistry journal (Bandgar et al. 1999). MW heating is an alternative energy-input system and has been

part of the development of greener processes in chemical reactions. Furthermore, advances in MW synthesis such as solvent-free reactions and in some cases absence of acid catalyst lead to the implementation of MW irradiation for green protocols (Pawelczyk et al. 2018).

Principles of microwave assisted organic synthesis

The microwave oven was first introduced in 1955 and the application of microwave technology to chemistry was initially done in the late 1980s (Gerling 1987). Microwave

radiation region is located between infrared radiation and radio-waves (Fig. 1). Household and industrial microwave ovens usually operate at a fixed frequency of 2.45 GHz. However, 5.8-GHz microwave radiation has been examined in the synthesis of ionic liquids and few advantages over 2.45GHz have been pointed out (Horikoshi et al. 2008). The interaction with microwaves is determined by the dielectric properties of the studied materials that are highly dependent on their chemical composition and physical state. To efficiently absorb microwave energy, the reaction mixture should possess polarization or ionic conducting mechanism (Sun et al. 2016). In general, this means that the solvent used for a specific transformation must be microwave absorbing. Therefore, molecules which align themselves with the electric field are microwave – active. Examples are DMF, CH_2Cl_2 , H_2O , acetic acid, ethanol, and acetonitrile. However, nonpolar molecules such as carbon tetrachloride, diethyl ether, toluene, benzene are microwave – inactive (Rodríguez et al. 2015). MW activation of solids relies on energy transfer from microwaves to materials, through either resonance or relaxation (Yang et al. 2019).

Selective heating using MW irradiation has been utilized for catalysts (Jie et al. 2021) and solvents (Nandihalli et al. 2022). The major advantages of MW irradiation are given in Fig. 2.

Since it has been introduced in the field of synthetic chemistry, the applications of MW irradiation have been growing rapidly (Fig. 3). The implementation of Microwave Assisted Organic Synthesis (MAOS) has received increased attention mainly in the process of synthesizing and enhancing heterocyclic compounds (Meera et al. 2020; Frecentese et al. 2023). Furthermore, reports of the microwave assisted synthesis of beta-lactams (Troisi et al. 2010), indoles (Patil et al. 2011), quinazolines (Mohammadkhani et al. 2020), benzothiazoles (Algul et al. 2008), imidazoles (Asressu et al. 2021) have all recently appeared.

The MW heating process of the Paal-Knorr reaction is viewed as more valuable and beneficial to the environment compared to the conventional route (Bandyopadhyay et al. 2010). Therefore, MW heating has been heavily applied for Paal-Knorr condensation since it reduces the reaction time, increases the yields and provides benign reaction conditions.

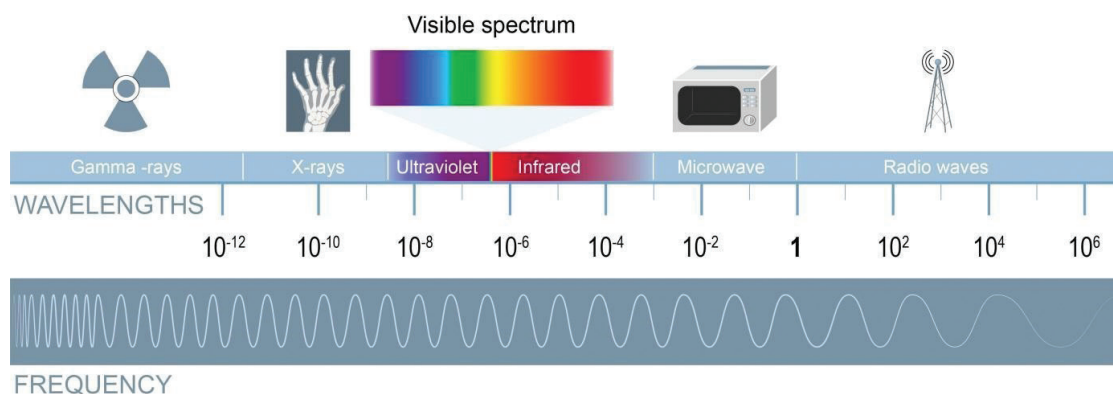


Figure 1. Electromagnetic spectrum.

Applying MW irradiated heating leads to numerous improvements in comparison with conventional conditions. Essentially, the MW irradiation achieves high temperatures which is due to the direct heating effect. Another notable utilization of the microwaves involves the modification of the regioselectivity of the final product in comparison to conventional heating (Torres-Moya et al. 2022). Additionally, the maintenance of the temperatures in MW ovens appears to be controlled. Furthermore, better yields, decreased reaction times, fast cooling potential, higher product purities, minor pollution of the environment and significantly easier work-up practices were reported (Bhatewara et al. 2013; Henary et al. 2020). A difference in the energy input for MW synthesis and a conventional oil-bath has been noted. On a laboratory scale approximately 80-fold of energy reduction is expected when using a microwave reactor (Gronnow et al. 2005). Moreover, microwave heating is selective since only polar substances convert microwave irradiation into heat and thus, they can be selectively heated when combined with apolar substances (Călinescu et al. 2021).

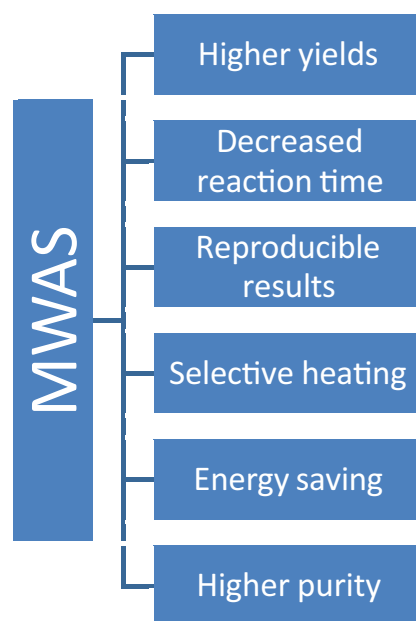


Figure 2. Major advantages of MW assisted synthesis.

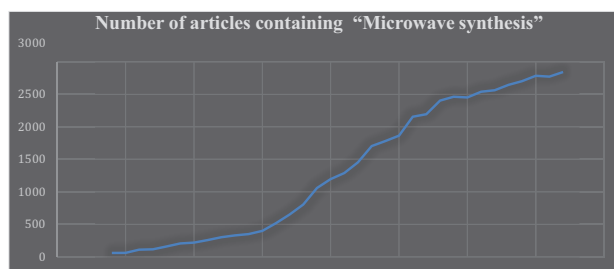


Figure 3. Number of published articles containing “microwave synthesis” indexed in Scopus (accessed 09.2023).

Pyrrole and its pharmacological properties

Pyrrole is a colorless, volatile liquid that becomes dark upon exposure to air. It has a low pKa of about - 3.8 which determines its weak basicity (Jeelan et al. 2022). Pyrrole can participate in several major chemical reactions given in Fig. 4.

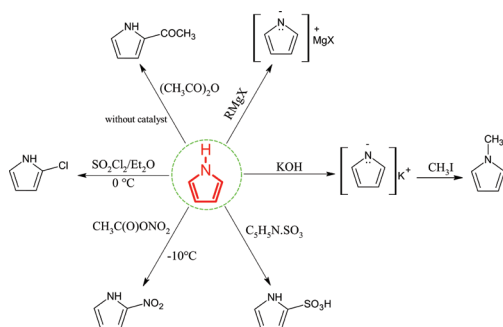
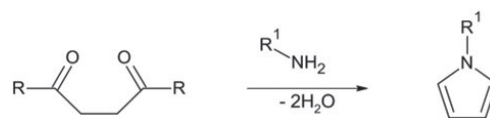


Figure 4. Chemical reactions of the pyrrole.

Moreover, the pyrroles and their substituted derivatives are heterocyclic compounds of great importance. The presence of pyrroles is found in various naturally occurring, biological and drug molecules (Ahamad et al. 2018; Ivan et al. 2022). Pyrrole derivatives have effects, such as anti-inflammatory, anticancer, antihypertensive, antimalarial, etc. Moreover, it has been found that the pyrrole based molecules are inhibitors of 5-hydroxytryptamine transporters, agonists of the cannabinoid receptors, and modulators of AMPA (Mateev et al. 2022). Large numbers of pyrroles are successfully utilized as catalysts for polymerization, corrosion inhibitors, and preservatives (Lu et al. 2013; Wan et al. 2023). Furthermore, it has been discussed that pyrrole derivatives are major intermediates for the syntheses of heterocyclic derivatives (Mir et al. 2022) and alkaloids (Seipp et al. 2021).

Paal-Knorr reaction

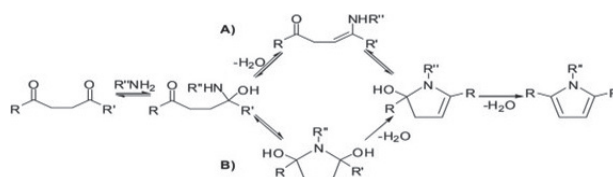
In 1884 Paal and in 1885 Knorr independently reported condensation of primary amines and 1,4- dicarbonyl compounds in the presence of an acid as catalyst. The reaction occurs via the elimination of two moles of water. Using this synthetically valuable method pyrroles and furans were obtained (Scheme 1).



Scheme 1. General Paal-Knorr synthesis of pyrroles.

Since then, the Paal-Knorr reaction has been widely accepted and utilized in the process of synthesizing pyrroles and furans. Advantages such as easy to obtain and stable starting reagents, high efficiency and simplicity granted Paal-Knorr condensation immense application in the organic synthesis. Furthermore, numerous reports have been published discussing the use of different Lewis acids as catalysts of the condensation (Zhang et al. 2017; Nguyen et al. 2019). However, one of the drawbacks of Paal-Knorr reaction, under conventional conditions, is the lack of regioselectivity (Kornienko et al. 2017). Moreover, carrying out a classical synthetic route requires harmful organic solvents, long reaction time, extreme amounts of solid catalysts and use of excess amounts of acids (Nguyen et al. 2019). Long and high heating and waste of energy also present as problems (Werner et al. 2006). Hence, numerous developments and modifications of the Paal-Knorr reaction have been published ranging from variation of different catalysts, solvents to activation via MW irradiation and ultrasound (Wang et al. 2011; Philkhana et al. 2021).

Few studies were carried out to explore the mechanism of Paal-Knorr reaction. In 1991 V. Amarnath et al. published a paper proposing a differentiation between numerous pathways for Paal-Knorr synthesis. The research gave a prediction that throughout the Paal-Knorr condensation, the rate-determining step is the cyclization of the hemi-aminal intermediate. This theory has been confirmed in a density functional study held in 2007 which determines the hemiaminal pathway as most preferred for the Paal-Knorr pyrrole synthesis (Mathana et al. 2007). Furthermore, quantum chemical studies have been carried out to affirm the latest hemiaminal route as the rate-determining step (Scheme 2) (Abbat et al. 2015).

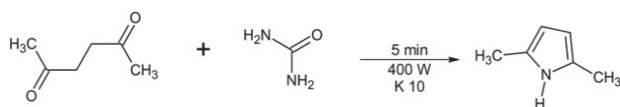


Scheme 2. Pathways for the Paal-Knorr synthesis of pyrroles: A. the enamine pathway and B. the hemiaminal pathway.

Other frequently applied reactions for the synthesis of pyrroles are Barton-Zard (Nguyen et al. 2019), Clauson-Kaas (Singh and Kumar 2023), Hantzsch (Leonardi et al. 2019), and Van Leusen (Trilleras et al. 2022).

Due to the aforementioned numerous pharmacological actions of pyrrole, researchers have been developing novel methods, including MW irradiation, for rapid synthesis of the 5-membered heteroatom. The MW synthesis

of the prominent pyrrole has been discussed in numerous papers. One of the first reports about the MW synthesis of pyrroles was posted in 1994 by Ruault et al. They have described a microwave irradiated synthetic production of 2,5-substituted pyrroles starting from urea and acetylacetone. A domestic microwave oven was utilized for the examined synthesis (Scheme 3).

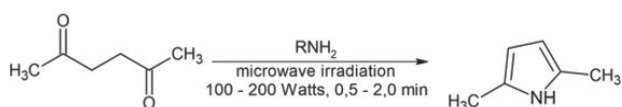


Scheme 3. Formation of N-unsubstituted pyrrole by the reaction of urea and acetylacetone absorbed over K10 in a microwave oven.

It was clear that the performed microwave irradiation significantly accelerated the production of pyrroles compared to the conventional approaches.

Microwave synthesis of pyrrole derivatives by Paal-Knorr condensation

Danks et al. (1999) were the first to examine the interaction between hexane-2,5-dione and primary amines using microwave activation (Scheme 4). The authors have found that the microwave irradiation significantly decreases the reaction time compared to classical conditions. Under classical synthesis, more than 12 hours were needed, whereas MW irradiation has drastically reduced the reaction time. A steric hindrance which requires higher power and longer irradiation times has been reported. Furthermore, it was noted that the use of MW heating removes the need for Lewis acids.

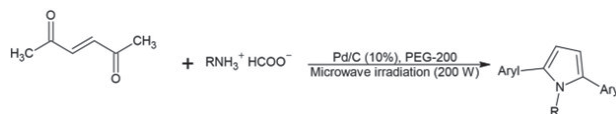


Scheme 4. Microwave irradiated condensation of diketone with primary amine.

Rao et al. (2001) have applied and discussed polyethylene glycol 200 (PEG-200) as a solvent in MW assisted synthesis in a one-pot operation through domino-pathway followed by Paal-Knorr reaction (Scheme 5). The reaction was carried out in a domestic microwave oven and the time of the reaction was drastically reduced compared to conventional heating. Furthermore, the paper utilized alkyl/aryl ammonium formates as enone reductors and pyrrole moiety initiators.

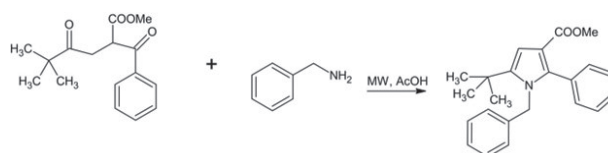
Microwave-assisted Paal-Knorr cyclization was carried out on substituted 1,4-diketoeater in the presence of different amines and acetic acid. The reactions gave expected pyrroles with good yields. Initially, the absence of an acid did not produce the desired products. Therefore, the

syntheses were executed in the presence of acetic acid. The reaction proceeded in a sealed tube in a microwave cavity heated to 180 °C for 3 min. Saponification of the carboxylic ester with



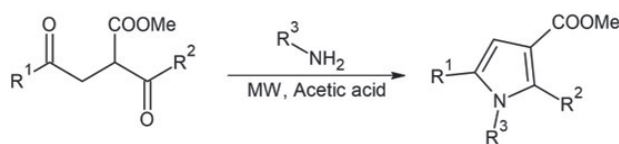
Scheme 5. Synthesis of substituted pyrroles from 1,4-diaryl-2-butene-1,4-diones and ammonium formate.

NaOH has given acid, which could be decarboxylated in boiling toluene. Subsequently, a reduction with DIBAL-H gave aldehyde which could be submitted to the Wittig reaction (Scheme 6). It has been noted that the conduction of the reaction under classical conditions did not obtain desirable yields (Minetto et al. 2004).



Scheme 6. Cyclization of diketons with amines under microwave irradiation. Conditions: (a) NaOH, EtOH/H₂O, reflux, 10 min. (b) Toluene, reflux, 12 h.

In another work, Minetto et al. (2005) have reported synthesis of various pyrroles through Paal-Knorr condensation starting from β -ketoesters, in the presence of acetic acid using MW reactor at 120–150 °C from 2 to 10 min, depending on the nature of the starting products (Scheme 7). The yields obtained were ranging from 65 to 89%. Further functionalizations of the heterocyclic substituents have been carried out to improve the molecular diversity. The methoxycarbonyl moiety has been transformed into an NH₂ group. First step was hydrolyzing the -COOMe group. Thereafter, in the presence of DPPA/water the acid gave amine through a Curtius rearrangement. Furthermore, different amides were produced from the -COOMe group in the presence of AlMe₃ in CH₂Cl₂.



Scheme 7. MW synthesis of pyrroles from diketons and acetic acid.

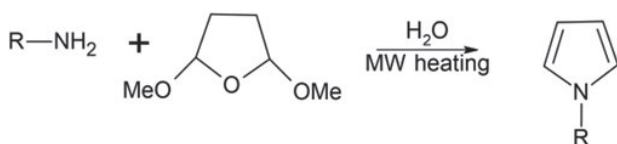
Werner et al. (2006) reported Paal-Knorr cyclization of tricyclic pyrrole-2-carboxamides under microwave irradiation (Scheme 8). The starting substrate-amido-1,4-diketone was obtained after Pauson-Khand cyclization of cyclopentenone and subsequent Stetter reaction with aldehyde.



Scheme 8. MW assisted Paal-Knorr condensation of cyclopentenone to a set of tricyclic pyrrole-2-carboxamides.

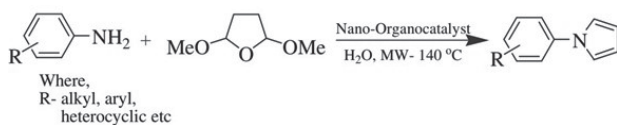
Additionally, the authors analyzed the synthesis of pyrrole-2-carboxamides under microwave irradiated and conventional heating. It was noted that besides shorter reaction times and higher yields the microwave-assisted synthesis facilitates the production of a larger library of tricyclic pyrrole-2-carboxamides.

Simplified approach to an uncatalyzed Paal-Knorr condensation is reported by Wilson et al. (2009) (Scheme 9). The reactions were carried out in water as a solvent without catalyst and a wide range of commercially available aryl sulfonamides and anilines were used. The optimal temperature was set at 150 °C since a small precipitation was observed above that mark. High yields were achieved (81–99%). Additionally, the authors noted a correlation between the pKa of the nucleophiles and the possibility of successful reaction. They concluded that when the nucleophile had a lower pKa, for example, a sulfonamide, the reaction proceeds easier.



Scheme 9. Microwave induced uncatalyzed reaction of 2,5-dimethoxytetrahydrofuran with aryl sulfonamides and anilines in water.

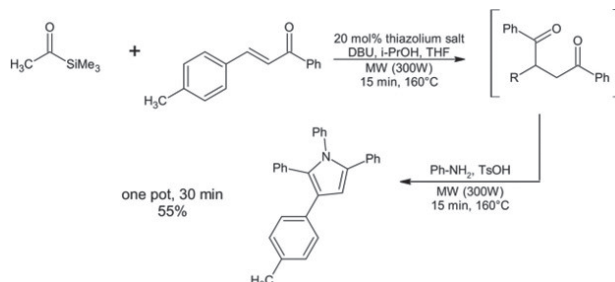
Polshettiwar et al. (2010) have reported MW-assisted Paal-Knorr synthesis of pyrroles using nano-organocatalyst in aqueous medium at 140 °C in 20 min (Scheme 10). Glutathione has been used for functionalization of the magnetic nanoparticles. The catalyst has shown high activity after it had reacted with aliphatic, aromatic, heterocyclic amine and even acid hydrazide. However, hydrazines and amides yielded no product. The dramatically increased contact between reactants and catalyst, hence mimicking the homogeneous catalysts has been pointed out. Furthermore, the ability of the nano-organocatalyst to be magnetically separated, led to the elimination of catalyst filtration after completion of the reaction.



Scheme 10. Nano-organocatalyst promoted Paal-Knorr reaction.

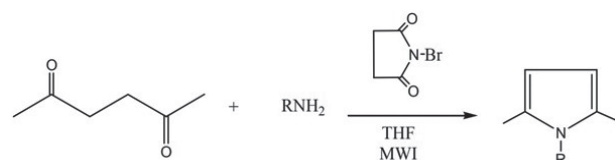
Bharadwaj et al. (2004) discussed one pot synthesis of substituted pyrroles under MW irradiation. The process

followed the Sila-Stetter/Paal-Knorr sequence. Initially, the reaction sequence was carried out in classical conditions. Further investigations using MW heating were made and drastically reduced reaction times were documented. The first heating cycle advanced for 15 min at 160 °C in the presence of DBU, thiazolium and 2-propanol. It was followed by the addition of aniline and TsOH and the sequence was followed by a second 15 min heating at 160 °C. Thus the obtained pyrrole derivative was in good yield (Scheme 11).



Scheme 11. Microwave-Assisted Sila-Stetter/Paal-Knorr Reaction

Andoh-Baidoo et al. (2011) have developed a method for synthesis of N-substituted pyrroles from 2,5-hexanedione and primary amine applying microwave irradiation (Scheme 12). The reaction has been catalyzed with N-bromosuccinimide (NBS) and no solvent has been used. NBS drastically reduced the time of the reaction. The paper has reported a plausible trace of hydrobromic acid from the N-bromosuccinimide. The slow production of pyrroles when the catalyst was not present has been noted. However, when NBS was used the products were formed within 8 minutes. Furthermore, NBS can be used for certain reactions in which mild acidic reagent is required.

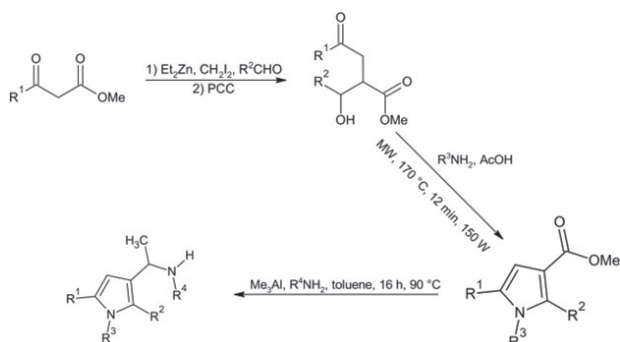


Scheme 12. Synthesis of N-substituted pyrroles starting from 2,5-hexanedione and amine using N-bromosuccinimide as catalyst and microwave oven.

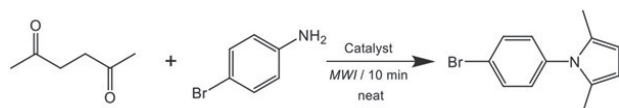
A paper for Paal-Knorr MW assisted synthesis of pyrrole amides was reported by Bianchi et al. (2006). Initially, a series of substituted 1,4-dicarbonyl compounds were obtained from the oxidation of aldehydes and after rapid cyclization 24 pyrrole esters were produced. However, work up with NaHCO_3 was necessary. The method was further developed by functionalizing the ester group with trimethylaluminum. Aminolysis occurs to produce 288 non-identical pyrrole-3-amides (Scheme 13). The Weinreb reaction was used for synthesis of the final pyrrole amide.

A microwave-mediated preparation of a series of pyrroles by Paal-Knorr conversion, in the presence of various alkali and alkaline-earth chlorides, has been described

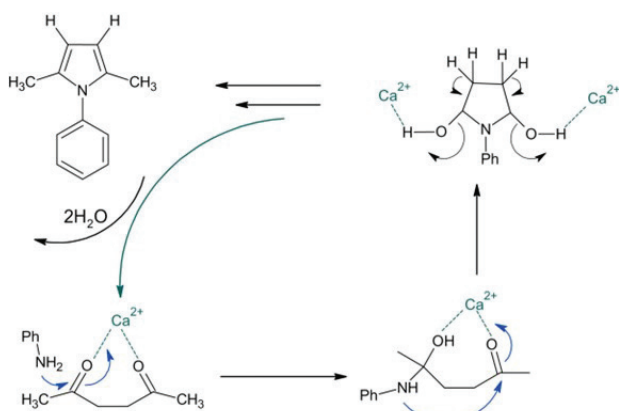
by Aghapoor et al. (2018) as shown in Scheme 14. $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ has been reported as the most prominent, low-cost, widely available, nontoxic Lewis acid catalyst in MW assisted Paal-Knorr condensation. When different alkali and alkaline-earth catalysts had been used in the process, the yields have been reduced. Furthermore, the condensation, catalyzed by $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, has been carried out in MW irradiated and conventional heating. A significantly reduced reaction time when using MW irradiation was discussed. A plausible mechanism of the reaction is given in Scheme 15.



Scheme 13. Synthesis of Tetra-substituted Pyrrole Amide Library.



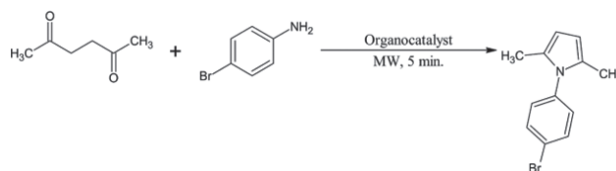
Scheme 14. Paal-Knorr MW synthesis in the presence of alkaline salts as catalysts.



Scheme 15. A plausible mechanism of calcium(II) chloride catalyzed Paal-Knorr condensation under MW irradiation.

The authors consider an activation of the carbonyl group and subsequent promotion reaction via nucleophilic attack by primary amines.

Aghapoor et al. (2021) reported solvent-free Paal-Knorr pyrrole synthesis by applying microwave irradiation and an organocatalyst. A wide range of organocatalysts were used, such as benzoic acid, 4-methoxybenzoic acid, salicylic acid, thiosalicylic acid, benzoic acid, lactic acid and others. It was found that using salicylic acid led to nearly full conversion of 4-bromoaniline (92%), in 15 seconds (Scheme 16).



Scheme 16. Solvent-free MW synthesis of pyrroles with organocatalyst.

The aforementioned article demonstrated the major advantage of the MW irradiation - the potential of achieving solvent-free conditions.

Hantzsch synthesis of pyrroles

Although highly accepted and applicable for the production of pyrroles, Paal-Knorr condensation has one major limitation-it is limited to the presence of 1,4-diketones (Kornienko et al. 2017). Another reaction for synthesis of pyrroles that has been extensively used is Hantzsch-type synthesis. Applying MW energy has drastically reduced the time of the process. Recently, Cores et al. (2016) have reported the synthesis of a library of 2-pyrrolin-5-ones. The authors have used MW irradiation in solventless Hantzsch reaction (Scheme 17).

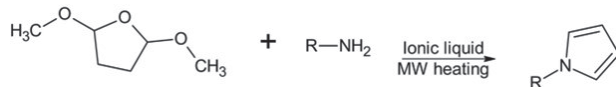


Scheme 17. Synthesis of 2-pyrrolin-5-ones by Hantzsch-type reaction.

Similarly, one pot microwave synthesis of pyrroles has been developed by Estevez et al. (2016). Solvent free Hantzsch-type reactions have been used and high yields were produced. However, no regioselectivity has been obtained.

Clauson-Kaas synthesis of pyrroles

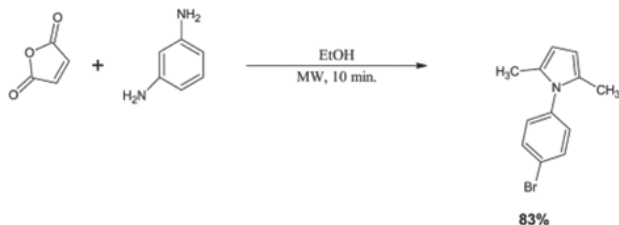
Aydogan et al. (2013) have discussed a Clauson-Kaas pyrroles synthesis under MW irradiation and acidic ionic liquid (Scheme 18). This novel method has provided higher yields and faster reaction time. Moreover, the ionic liquid has been successfully applied as an acid catalyst, and thus has excluded the requirement of a solvent.



Scheme 18. Clauson-Kaas synthesis of pyrroles catalyzed by [hmim][HSO4].

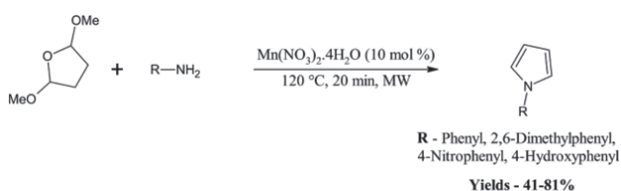
A microwave-assisted synthesis of novel pyrroles was discussed by Reddy et al. (2021). The pyrrole

derivatives were obtained by the reaction of furan-2,5-dione with 3-phenylenediamine with ethanol as a solvent (Scheme 19). The reaction time was 10 min. under microwave heating at 130 °C. The authors reported a good yield of 83%. The novel structure was fully characterized by ^1H , ^{13}C and HRMS.



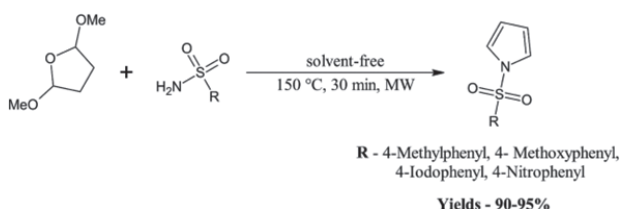
Scheme 19. MW synthesis of pyrrole by reacting furan-2,5-dione with 3-phenylenediamine.

Rohit et al. (2021) reported the microwave synthesis of pyrrole-based compounds by reacting various amines with 2,5-dimethoxytetrahydrofuran in the presence of the catalyst $\text{Mn}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (Scheme 20). The reaction was optimized by altering the Mn-based catalyst, the reaction temperatures and the reaction times. It was discovered that the optimal conditions are 120 °C for 20 min. without a solvent. Moreover, the paper reported that the amines containing electron-donating moieties produce higher yields.



Scheme 20. MW synthesis of pyrrole starting from 2,5-dimethoxytetrahydrofuran in the presence of an Mn-based catalyst.

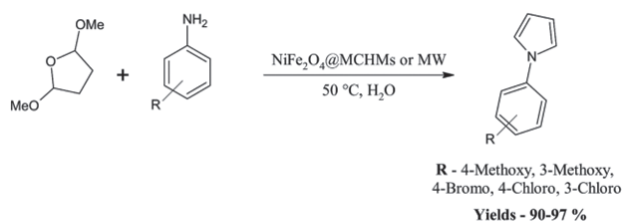
Another report of a Clauson-Kaas synthesis of pyrrole-based sulfonates was reported by Ozaki et al. (2022). The primary conventional protocol was optimized by applying MW heating - 150 °C for 30–60 min (Scheme 21). Importantly, the reactions were completed in solvent-free conditions. With this method, various sulfonamides were converted to the corresponding sulfonylpyrroles.



Scheme 21. Solvent-free synthesis of novel sulfonylpyrroles by MW heating.

Novel N-substituted pyrrole derivatives were synthesized by using nanocatalysts or MW heating (Mousavi et al. 2023). The applied solvent was water. The article follows the reaction of 2,5-dimethoxytetrahydrofuran with various aniline derivatives. Interestingly, the efficiency of $\text{NiFe}_2\text{O}_4 @ \text{MCHMs}$ was higher than the MW heating

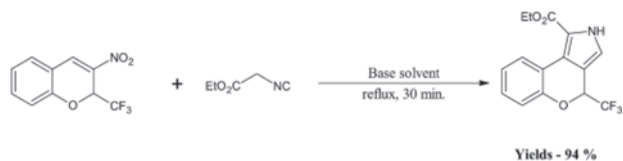
conditions (Scheme 22). The authors reported the ambiguous separation of the catalyst from the reaction mixture.



Scheme 22. Synthesis of N-substituted pyrrole derivatives with nanocatalysts or MW.

Barton–Zard synthesis of pyrroles

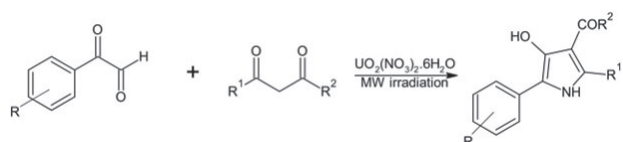
One pot reaction for the synthesis of pyrrole-based chromanes was reported by Kochnev et al. (2022) (Scheme 23). The yield of the final compound was 94%. The conventional reflux led to better yield compared to the non-heating reaction conditions. Therefore, it could be hypothesized that the application of MW heating could drastically decrease the reaction time, as well as the probability to remove the solvent. The novel compound was characterized by ^{19}F , ^{13}C , ^1H and IR.



Scheme 23. Synthesis of new pyrrole-based compound by reaction of 3-nitro-2H-chromenes with an ethyl isocyanoacetate.

Other reactions for the production of pyrrole derivatives

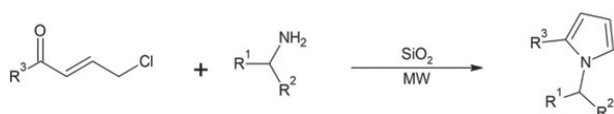
Venkatesan et al. (2020) have developed a simple and efficient MW irradiated method for synthesis of functionalized pyrrole derivatives. $\text{UO}_2(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ has been used as a catalyst (Scheme 24). It has been noted that when ethanol is used as solvent it gives higher yield compared to methanol, chloroform, acetonitrile and DCM. Additionally, the authors have affirmed the advantages of the MW assisted synthesis over classical conditions.



Scheme 24. MW irradiated synthesis of functionalized pyrroles using $\text{UO}_2(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ as a catalyst.

One pot MW assisted synthesis of pyrroles has been developed by Aydogan et al. (2005) (Scheme 25).

The reactions were carried out on the surface of silica gel and no solvent had been used. Furthermore, the paper has reported reduced reaction time, cleaner process due to fewer side-reactions and use of minimal quantities of solvent in contrast with conventional synthesis.



Scheme 25. MW assisted synthesis of 1,2-disubstituted pyrroles on the surface of silica gel.

Conclusion

MW irradiation is affirming its place in modern organic chemistry. The ability of MW heating to carry out chemical transformations in minutes instead of hours is slowly replacing conventional heating. Furthermore, the role of MW assisted synthesis is emerging as immensely important in the green chemistry protocols. All the papers

reviewed above conclude a significant reduction of the reaction time in the synthesis of the pyrroles when using MW heating compared to conventional one. Additionally, higher yields, cleaner reaction profiles and reproducible experimental conditions are examined. The removal of catalysts and solvents in some discussed papers further facilitate the work-up. The cited reports confirm the efficiency of microwave heating in the Paal-Knorr condensation, as well as in the Hantzsch, Clauson-Kaas and Barton–Zard syntheses. Hence, the establishment of MW irradiation is a major improvement in the syntheses of pyrrole derivatives. Moreover, in most papers the reactions could be carried out in solventless conditions, which corresponds to the “Green” chemistry principles.

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