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Review Article

Microwave-assisted synthesis of pyrazoles - a mini-review

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ABSTRACT

Heterocyclic compounds including pyrazole have a serious area in the field of medicinal chemistry and modern drug development studies. Pyrazole is a five-membered ring system containing two adjacent nitrogen atoms. Pyrazole attracts great attention due to its wide biological activity scale and potential in the development of new drug molecules. Traditional methods have been used in the general synthesis methods of pyrazole for a long time, but since these methods can be performed within certain limits, it is necessary to benefit from new and sustainable methodologies. In this review, the use and benefits of microwave (MW)-assisted techniques under the general title of green chemistry will be emphasized. The use of MW techniques stands out with its advantages such as increasing the efficiency of synthesis, obtaining selective products and preventing environmental pollution. The area of use of the MW method in pyrazole synthesis, synthesis mechanisms, organic synthesis methods and benefits are examined in this study. The MW method used in the synthesis of the pyrazole ring, which stands out with its bioactive diversity, will be encountered much more in the coming years.

Keywords: Pyrazole, Microwave, Green Chemistry

1. INTRODUCTION

Heterocyclic compounds, which constitute a large part of organic chemistry, also have a significant use in the field of pharmacy. More than 95% of the drugs and drug candidate molecules used today contain at least one heterocyclic ring [1]. Among these heterocyclic compounds, *N*-based compounds have been an important focus because they are found in the structure of many bioactive natural products such as antibiotics, vitamins, hormones and alkaloids used to improve human health and protect against diseases [2]. Therefore, *N*-based heterocyclic rings are the main focus in the synthesis and development of new drugs [3]. The five-membered pyrazole, which contains two adjacent nitrogens in its structure, is one of the heterocyclic compounds that draws organic and medicinal chemists' attention because of its strong biological activity and the variety that it can create in its chemical structure. It is also found in many drug molecules. Some examples are shown chronologically in Figure 1 and a few of them are shown in Figure 2. [4]. Pyrazole is synthesised through the reaction of a series of substituted hydrazine with an α,β-unsaturated carbonyl molecule, known as chalcones (Figure 3). In some instances, conventional organic synthesis techniques may prove insufficient for the synthesis of these compounds. New methodologies are currently being developed to overcome this limitation [5]. Among these methods, sustainable chemistry, also known as green chemistry, has become the focus [5]. The term 'green chemistry' was introduced in the mid-1990s

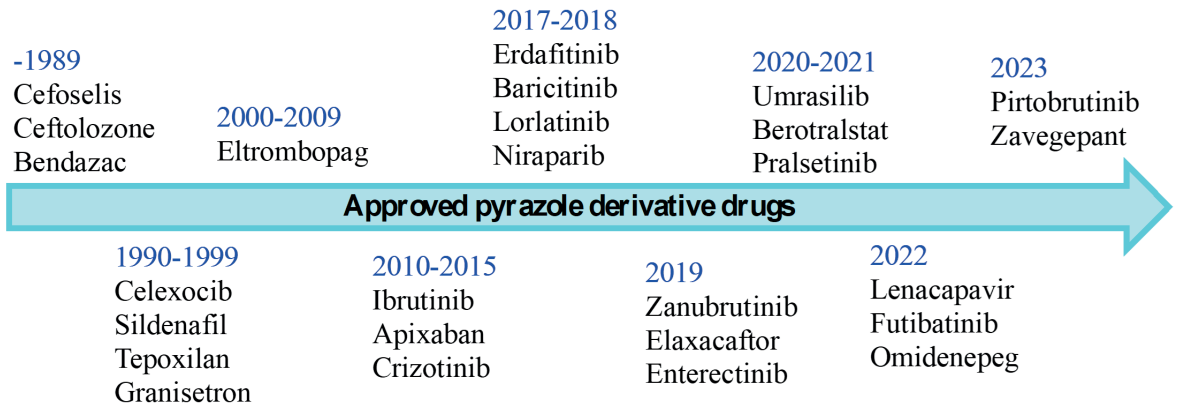


Figure 1. Chronological representation of some approved pyrazole derivative drugs [4,51].

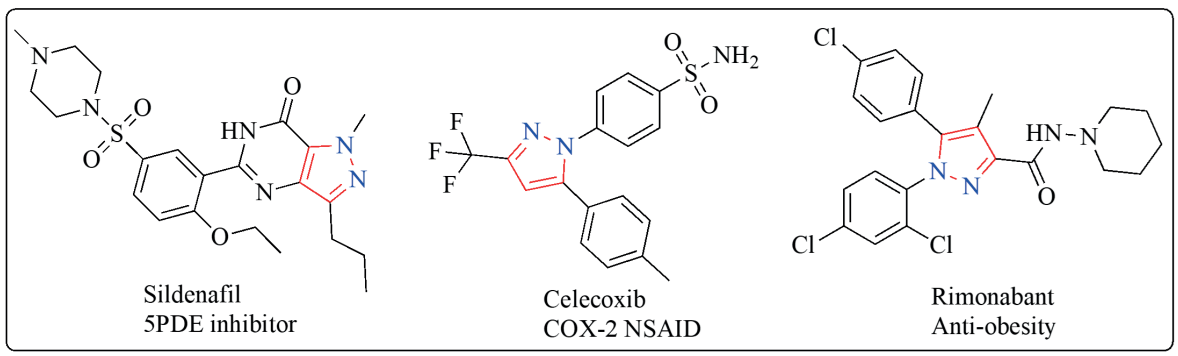


Figure 2. Examples of some biologically active pyrazole-containing drugs and their pharmacological effects [52].

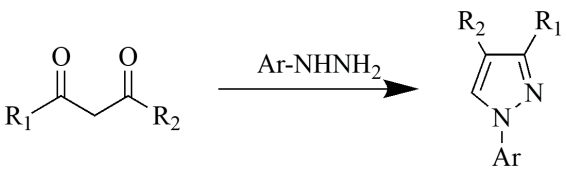


Figure 3. Synthesis of pyrazole from α,β-unsaturated carbonyl molecule [5].

for use in chemical syntheses to improve human health and protect the environment [6]. With green chemistry, the formation of hazardous compounds that may occur as a result of the use of traditional methods is reduced or even eliminated. The need for volatile organic solvents used in the synthesis of many heterocyclic compounds is also eliminated. Thus, sustainable, eco-friendly and clean new synthesis methods are created [6–8]. One of the most used green chemistry techniques in recent years is the microwave (MW) irradiation method [9]. Utilizing the MW technique in the synthesis of organic compounds accelerates the synthesis of compounds. It also offers superior targeting capabilities such as chemo-, regio-, and stereo-selectivity [10]. When past studies are examined, it is seen that MW has a wide range of applications. These can be listed as solvent-free reactions [11], heterocyclic chemistry [12], medicinal and combinatorial chemistry [13], homogeneous and heterogeneous catalysis [14], fullerene chemistry [15], cycloaddition reactions [16] and synthesis of radioisotopes [17]. Dielectric heating resulting from material–wave interactions is the cause of the acceleration rate seen in MW irradiation. MW is a representation of electromagnetic energy as it consists of an electric and magnetic field. This energy does not alter molecule structure, but it can function as a nonionizing radiation that rotates dipoles and generates ion molecular movements [18]. The MW field applied to the components allows the molecules it contains to spend a little more time in the electric field to which they are exposed, allowing the molecules to pass in the event of an arrangement, thus releasing thermal energy. In short, this method allows the absorption of MWs and their ability to withstand heat. Compared to traditional heating, this

interior warmth is substantially more homogeneous [19]. Method development in microwave-assisted organic synthesis is as follows: determination of open or closed application, solvent selection, determination of reaction conditions, adjustment of time and determination of exposure power, as shown in Figure 4 [20].

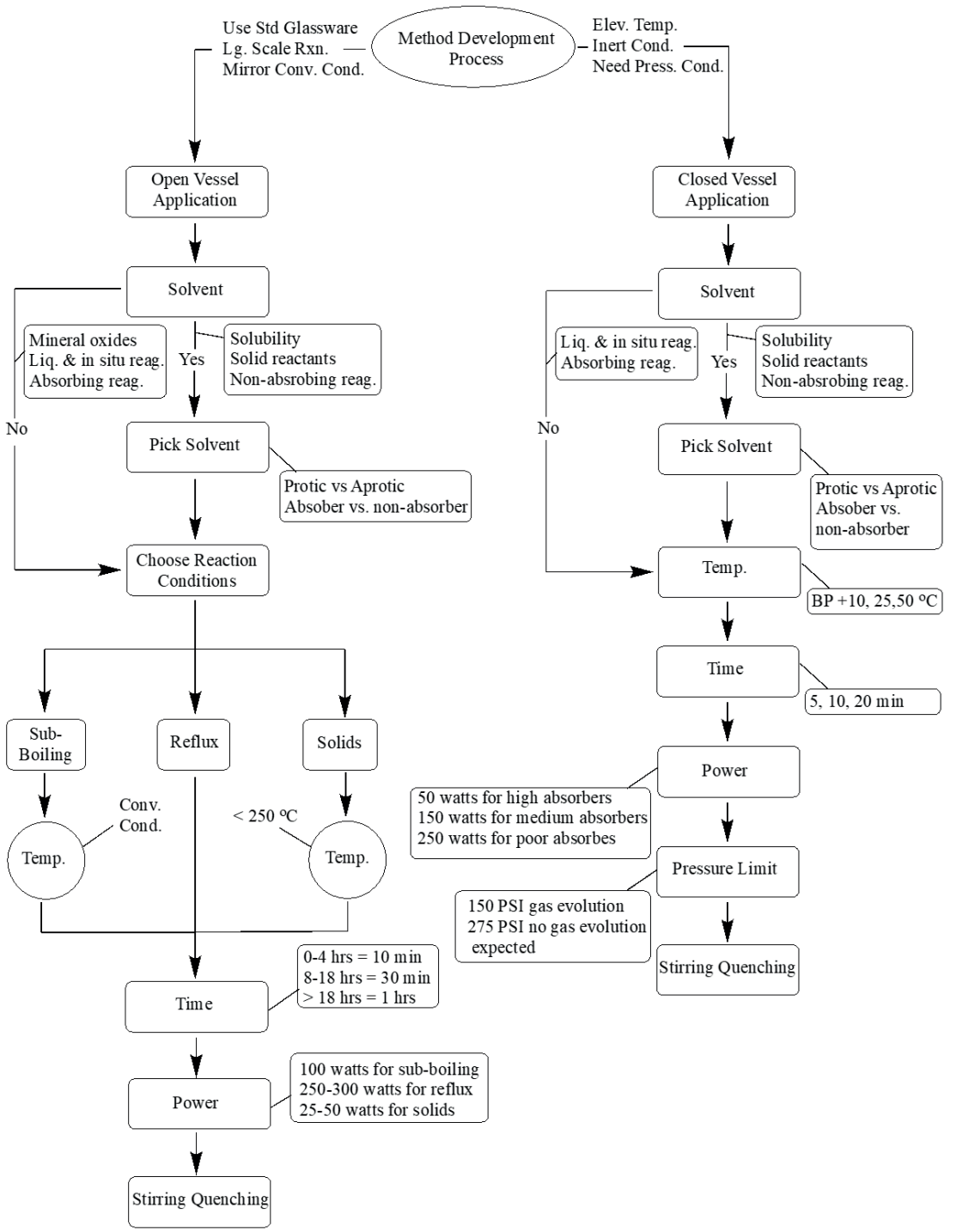


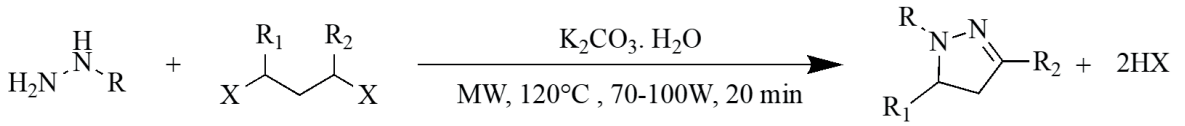
Figure 4. Microwave assisted synthesis method determination steps [20].

2. SYNTHESIS OF PYRAZOLE, USING MW METHOD

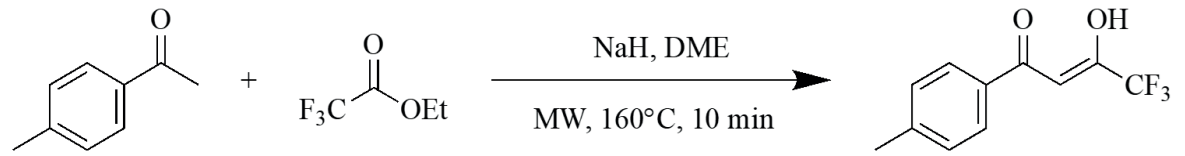
The azole family, which contains 5-membered heterocyclic nitrogenous rings such as pyrazole, imidazole, thiazoline and pyrazolidine, has a wide spectrum of biological activities, including antifungal [21], antiviral [22], anti-inflammatory [23], anti-tumor [24], anti-bacterial [25] and antioxidant [26]. This has caused them to become a focal point in the pharmaceutical industry [27]. With two nitrogen atoms positioned next to each other and a five-membered heterocyclic ring, pyrazole is a significant subgroup of the azole family. Because of their broad biological uses, these chemicals are the most investigated members of the azole family [28]. The first known pyrazole synthesis was described by Knorr [29]. Traditional pyrazole synthesis is not sufficient to obtain products with the desired yield. With the use of newly developed multimode and monomode microwave devices in the field of medicinal chemistry, products with higher yields can be obtained in a shorter time [30]. The results of recent studies indicate that both monomode and multimode microwave methods are reproducible [31,32]. This study will shed light on the MW-supported pyrazole syntheses made from past years to present.

In the study conducted by Ju et al. (2005), MW iridation method was used for pyrazole synthesis. In the method used, MW power was 70-100 W and the reaction took place in 20 minutes in aqueous medium in the presence of a weak base at 120°C. SN_2-like sequential heterocyclization reaction, which is difficult to perform by the conventional method, was carried out with a yield of 60-80%. (Scheme 1) [33].

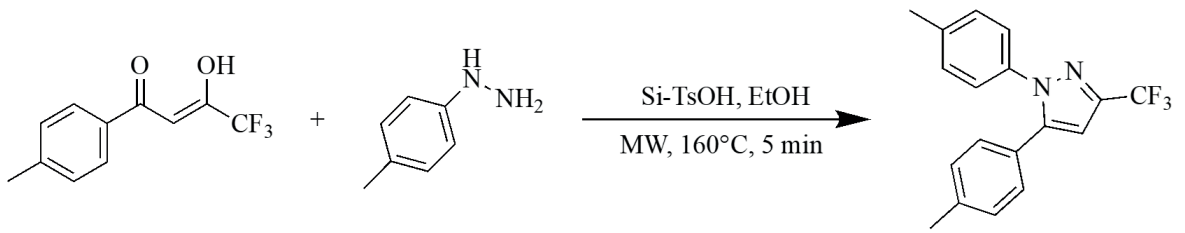
Paul et al. (2006) used the MW-assisted synthesis method for pyrazole synthesis. In the study, the first step of the two-step synthesis was completed in 5 days for the substances without MW application, while the MW-applied substances completed the reaction in a short time of 2 hours. In the first step, 4-methylacetophenone and ethyl trifluoroacetate were used at 160°C for 10 min and the desired enol ketone was obtained with 96% yield. In the second step, the most efficient conditions for the reaction between the obtained enol ketone and 4-methylphenylhydrazine are the method using silica-supported toluenesulfonic acid as a proton source at 160°C in the microwave (Scheme 2 and Scheme 3) [34].



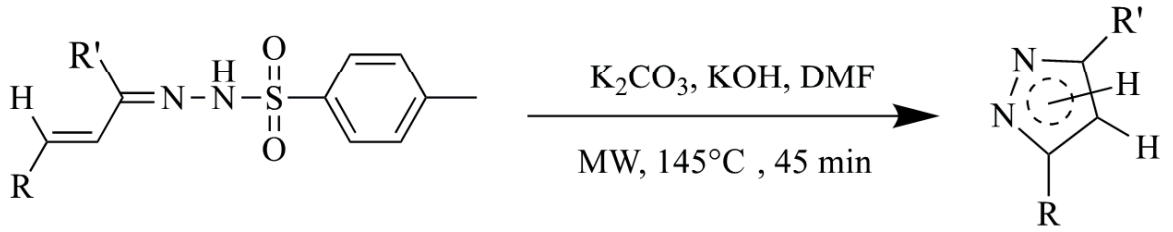
Scheme 1. Double alkylation of hydrazine by alkyl dihalides under MW irridation.



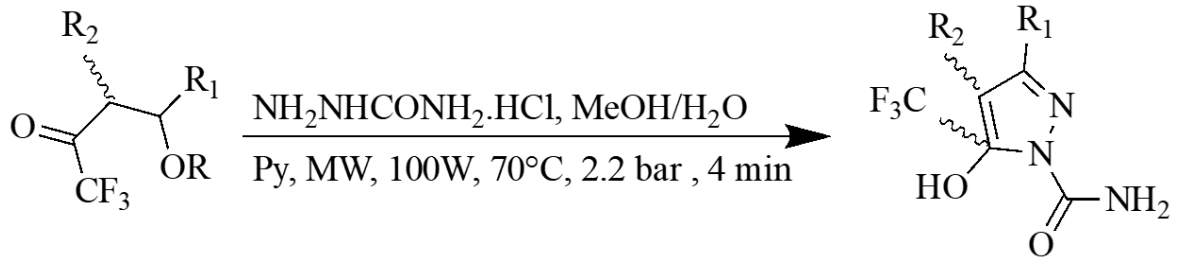
Scheme 2. Synthesis of (*Z*)-4,4,4-trifluoro-3-hydroxy-1-(*p*-tolyl)but-2-en-1-one.



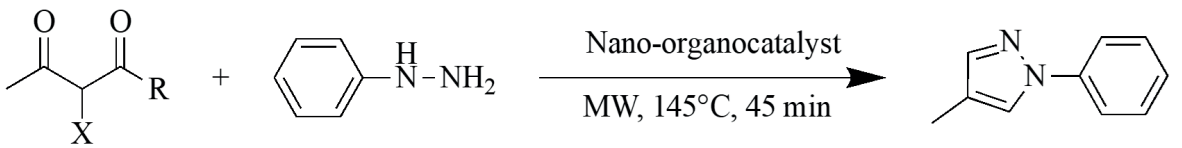
Scheme 3. Synthesis of 1,5-di-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazole.



Scheme 4. Scheme of reaction for converting tosylhydrazones into pyrazoles.



Scheme 5. Synthesis of 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles.



Scheme 6. Synthesis of pyrazole derivatives using nano-organocatalyst by MW heating.

Corradi et al. (2007) synthesized new pyrazole derivatives by microwave method starting from acyclic α,β-unsaturated carbonyl compound. Synthesis is carried out by 1,3-cycloaddition of the corresponding tosylhydrazones of the selected carbonyl compounds using a base in dry medium (Scheme 4) [35].

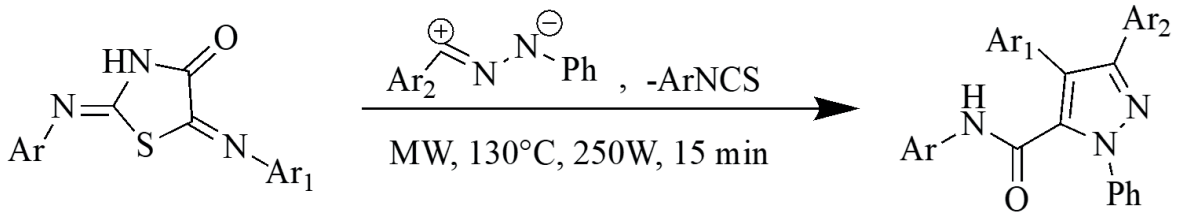
In the study conducted by Sauzem et al. (2008), a new pyrazole derivative compound was synthesised using MW in the second step of a two-step synthesis study. In the initial stage of the process, 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles were synthesised through a cyclocondensation reaction involving enones and semicarbazide hydrochloride. In the second step, a mixture of enones and semicarbazide hydrochloride was reacted in the presence of pyridine and a methanol/water solution (3:1 v/v) as solvent. The solution was subjected to microwave irradiation (100 W) at 70°C and 2.2 bar pressure for 4 minutes, resulting in the production of 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles with an 82-96% yield (Scheme 5) [36].

In the study conducted by Polshettiwar et al. (2009), MW-supported pyrazole derivatives were synthesized to be used as nano-organocatalysts in water. The conditions in this synthesis were as follows: 140°C, 20 minutes (Scheme 6) [37].

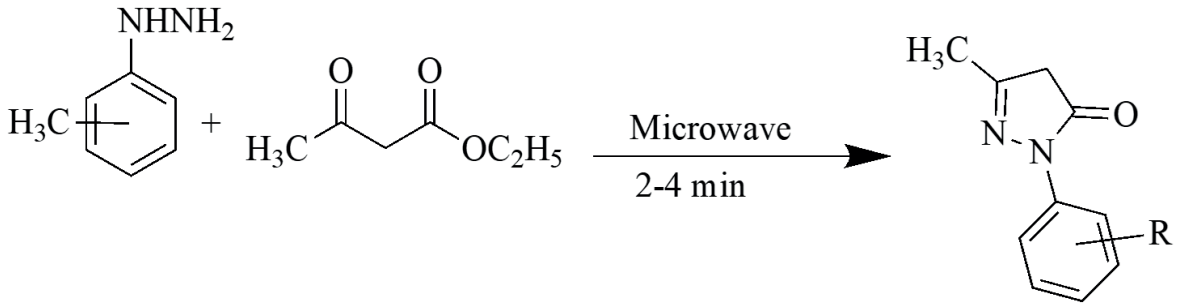
By 1,3-di-polar cycloaddition of nitrilimines with 5-arylidene-2-arylimino-4-thiazolidinones, Hatem et al. (2010) reported synthesizing 1,3,4-triaryl-5-*N*-arylpyrazole-carboxamides at 130°C for 15 minutes without the need of a solvent and with the assistance of MW (Scheme 7) [38].

In the study conducted by Antre et al. (2011), 3-methyl-1-substituted-1*H*-pyrazol-5(4*H*)-ones derivatives were obtained by reacting ethyl acetate with 1-phenylhydrazine under microwave for 2-4 minutes (Scheme 8) [39].

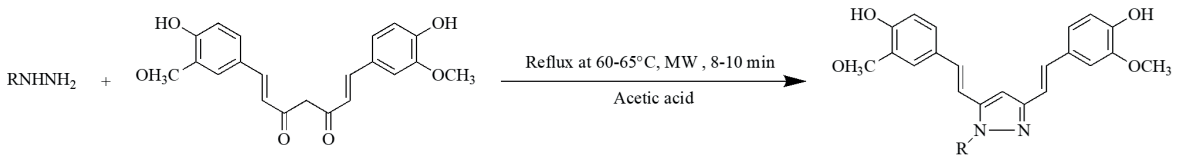
In a study conducted by Sahu et al. (2012), the objective was to obtain the derivatives of benzylidene of curcumin and new pyrazole derivatives using hydrazine. The initial synthesis was conducted



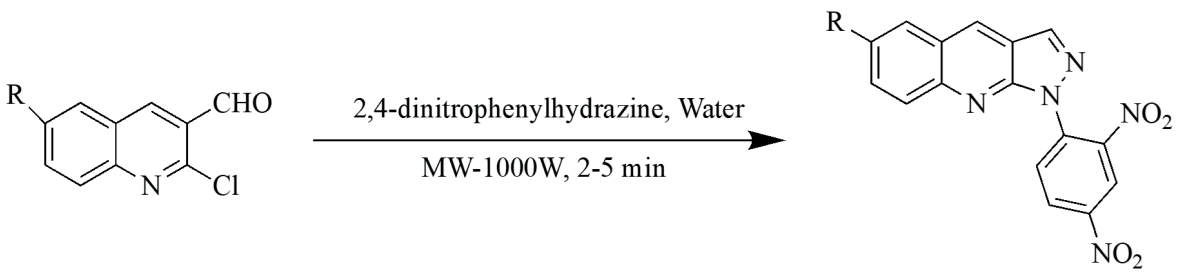
Scheme 7. Synthesis of 1,3,4-triaryl-5-*N*-arylpyrazole-carboxamides under MW irradiation.



Scheme 8. Synthesis of 3-methyl-1-substituted-1*H*-pyrazol-5(4*H*)-ones derivatives.



Scheme 9. Curcumin-pyrazole preparation.

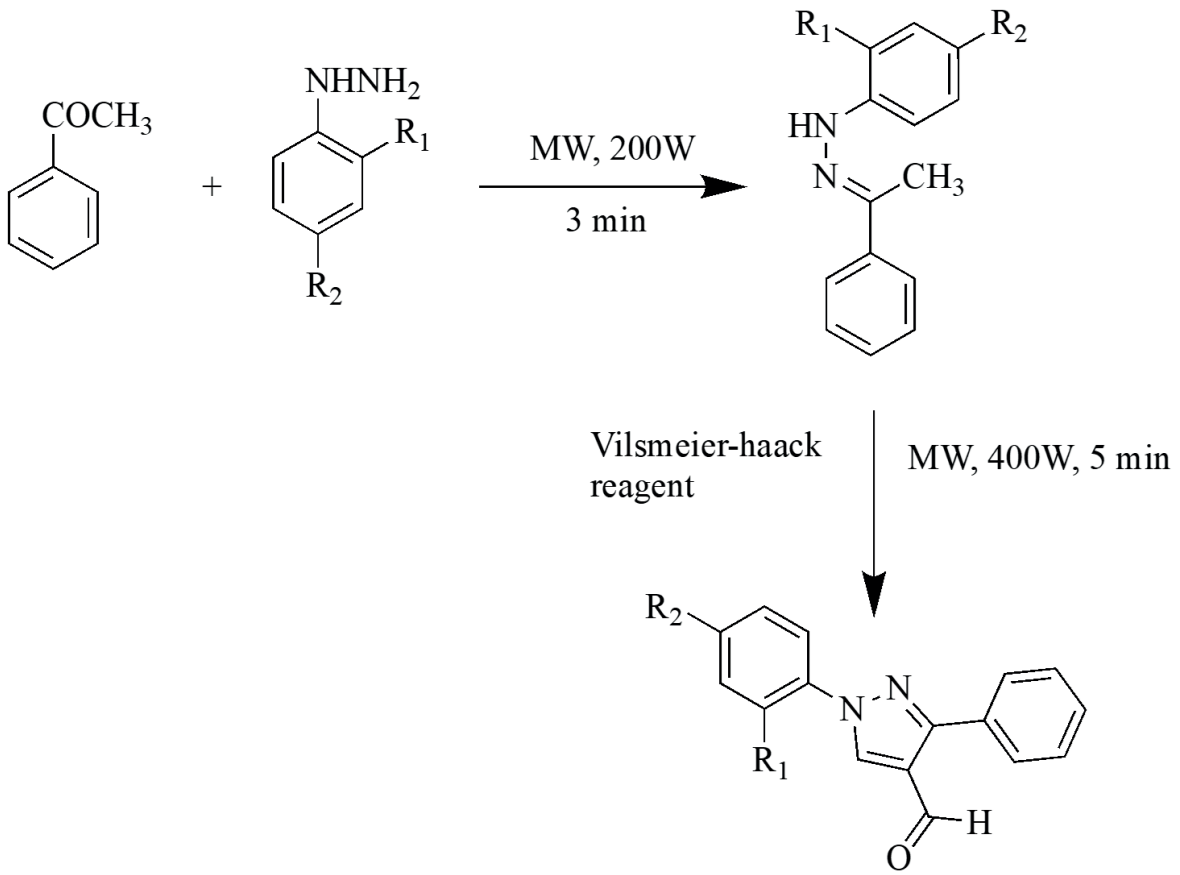


Scheme 10. Synthesis of 1-carboamidopyrazolo[3,4-b]quinolines derivatives.

via reflux in acetic acid at 60-65°C. However, due to the prolonged duration of the classic method (approximately 20 hours), a novel synthesis approach was devised. This involved performing the reaction in a microwave under non-solvent conditions, which proved to be an efficient and expeditious method, with the reaction completing in 8-10 minutes (Scheme 9) [40].

In a study conducted by Alam et al. (2013), a combination of conventional and unconventional methods was employed for the synthesis of 1-carboamidopyrazolo[3,4-b]quinolines. In the conventional synthesis method, it was refluxed in ethanol for a longer time than in the method utilising microwave irradiation. In the unconventional method, 2-chloroquinoline-3-carbaldehyde and 2,4-dinitrophenylhydrazine were refluxed with stirring in water under microwave irradiation at 1000W for 2-5 minutes (Scheme 10) [41].

Selvam T. P. et al. (2014) followed a two-step microwave-assisted synthesis method to synthesize new pyrazole derivatives. In the first step,

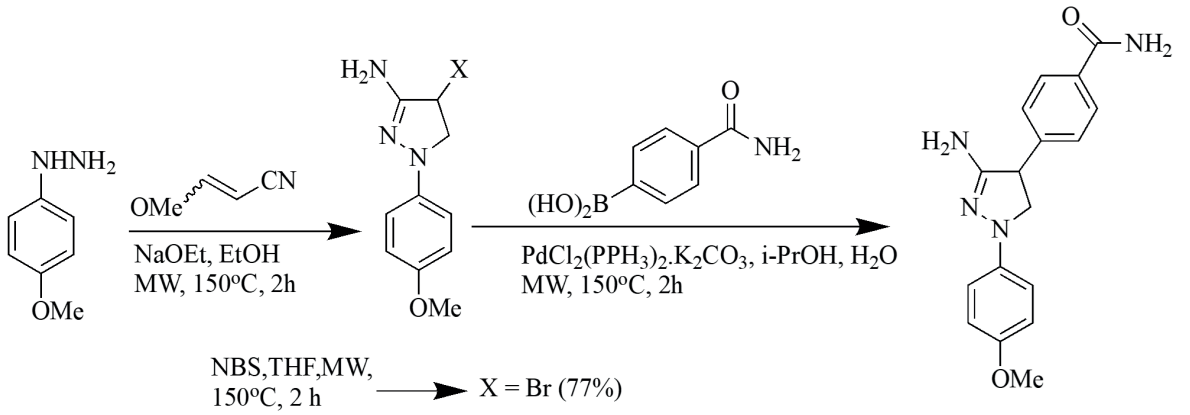


Scheme 11. Synthesis scheme of pyrazole-4-carbaldehyde derivatives.

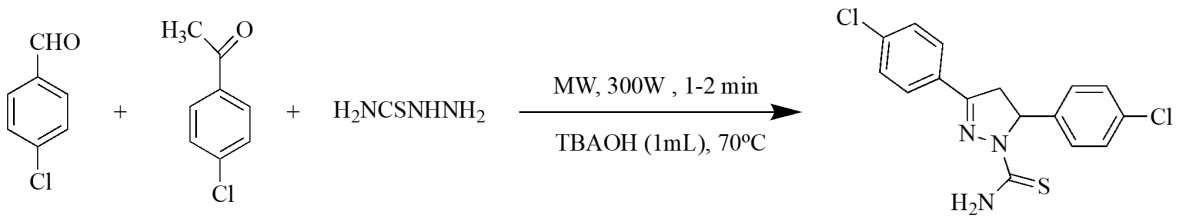
acetophenone, substituted phenylhydrazine and DMF were reacted under 200W microwave for 3 min to obtain 1-substituted phenyl-2-(1-phenylethyldiene) hydrazine. In the second step, 1-substituted phenyl-2-(1-phenylethyldiene)hydrazine was reacted with Vilsmeier-Haack reagent ($POCl_3$–DMF/SiO_2) under 400W microwave. It took a total of 5-6 min to obtain the final product (Scheme 11) [42].

In a study conducted by Bagley et al. (2015), the synthesis of novel pyrazole derivatives as MK2 inhibitors was pursued through the utilization of microwave-assisted Suzuki-Miyaura cross-coupling reactions. To this end, a microwave-assisted three-step synthesis method was developed. In the initial stage of the process, the 4-methoxyphenylhydrazine hydrochloride salt and 3-methoxyacrylonitrile were subjected to a reaction under alkaline conditions (using sodium ethoxide in ethanol) at 150°C for two hours in a microwave irradiation, resulting in the formation of 3-aminopyrazole. The subsequent step involved the synthesis of the pyrazolyl bromide compound, which was achieved by subjecting the reaction mixture to microwave irradiation at 150°C for 2 hours in the presence of NBS in THF, resulting in the formation of a C-4 brominated pyrazole with a 77% yield. To obtain the final pyrazole product, the Suzuki-Miyaura pyrazolyl bromide was combined with the 4-carbamoylphenylboronic acid in *i*PrOH–H2O in the presence of bis(triphenylphosphine) palladium(II) chloride and potassium carbonate under microwave irradiation at 150°C for 2 h, resulting in the formation of the complex pyrazole final product in 54% yield (Scheme 12) [43].

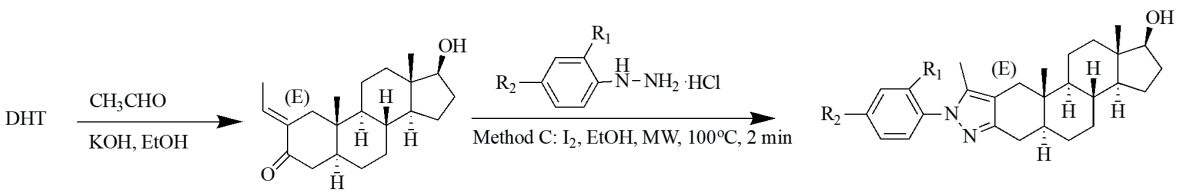
Farmani et al. (2018) devised and synthesised 4,5-dihydro-1*H*-pyrazole-1-carbothioamide in water using a microwave-assisted green chemistry method. In this study, a range of basic catalysts were employed, including NaOH, KOH, Et_3N and DABCO. However, the highest yield was observed in the derivative prepared using tetrabutylammonium hydroxide



Scheme 12. Microwave-assisted synthesis of the complex pyrazoles using a Suzuki-Miyaura cross-coupling.



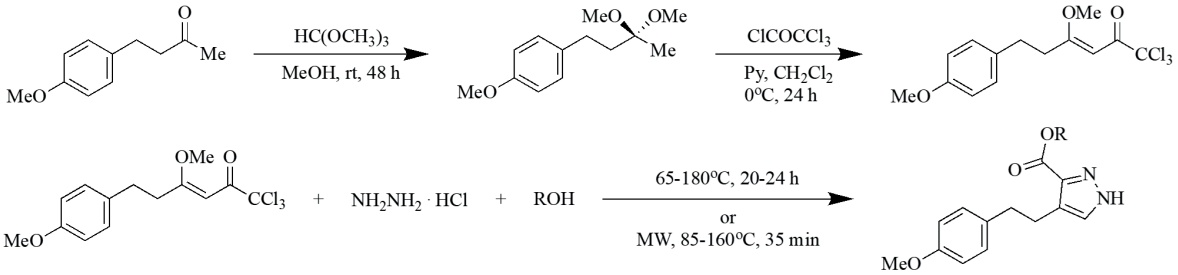
Scheme 13. Synthesis of 4,5-dihydro-1*H*-pyrazole-1-carbothioamides in the presence of TBAOH under microwave irradiation.



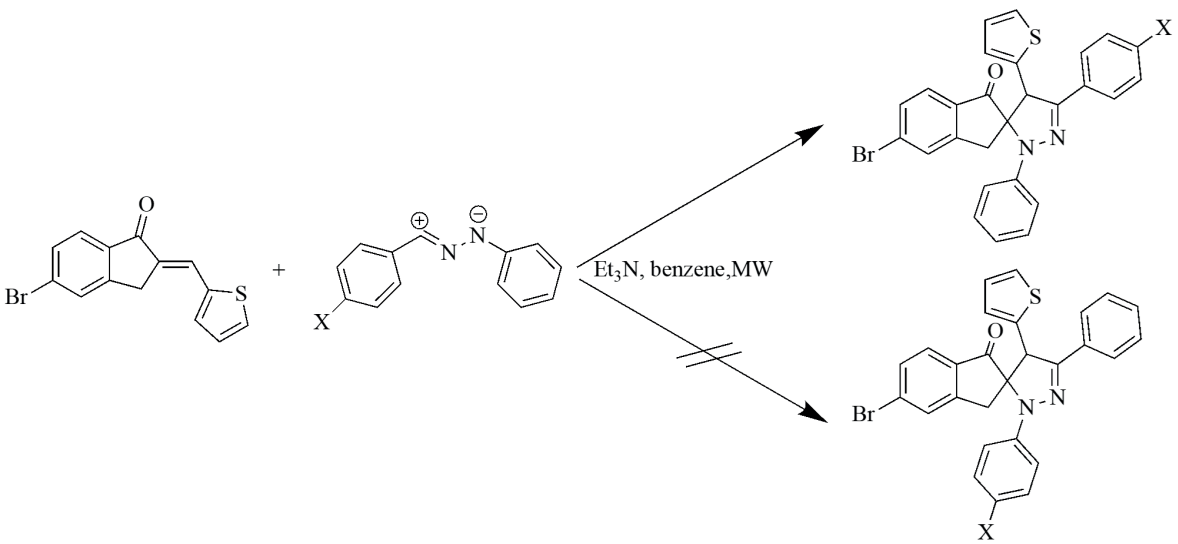
Scheme 14. Synthesis of ring arylpyrazole derivatives of DHT.

(TBAOH). Similarly, a variety of microwave irradiations were attempted, with the highest yield obtained at 300 W. The optimal temperature for the reaction was determined to be 70°C. The reaction of 4-chloro-benzaldehyde, 4-chloroacetophenone and thiosemicarbazide under the aforementioned conditions yielded pyrazole derivative compounds (Scheme 13) [44].

Mótyán et al. (2019) employed a microwave-assisted synthesis method for the design and synthesis of novel arylpyrazol derivatives as 17-keto analogues. In this study, in order to obtain the α,β-enone suitable for heterocyclization required in the pyrazole synthesis, DHT was first subjected to aldol condensation with an excess of acetaldehyde in alkaline ethanol at low temperature. Three distinct methodologies were employed: Method A, Method B, and Method C. While Method A encompasses the synthesis of compounds through conventional techniques, Methods B and C involve the utilisation of microwave-assisted synthesis. Method B was completed in a significantly shorter timeframe compared to Method A; however, the yield did not meet the desired specifications. Method C employs a one-pot procedure that includes I_2-mediated oxidative cyclisation and microwave irradiation. This approach was adopted to circumvent the necessity for a multi-step synthesis and to preclude the formation of unstable pyrazole by-products. In the last step of the synthesis, Jones reagent in acetone was used for the oxidation of the 17-OH group. The yield of the final products was found to be in the range of 81-89% (Scheme 14) [45].



Scheme 15. Synthesis of 1*H*-pyrazole-5(3)-carboxylates derivatives.

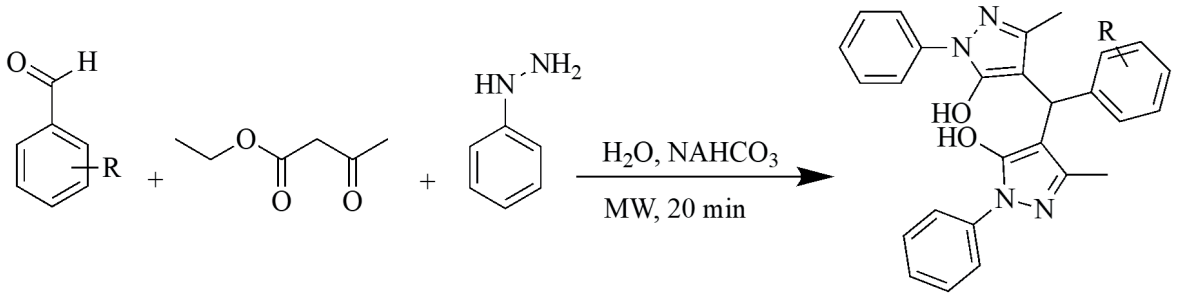


Scheme 16. Synthesis of spiropyrazoles under microwaves irradiation.

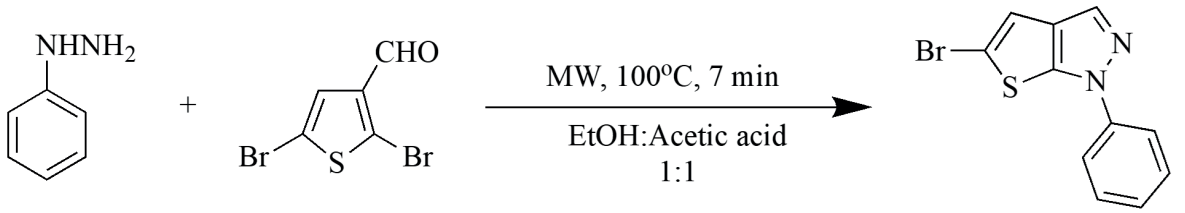
Goulart et al. (2020) synthesized 1*H*-pyrazolecarboxylates by both conventional and microwave-assisted synthesis methods, starting from compounds with antioxidant activity. The desired product was obtained as a result of a three-step synthesis. In the first step, trimethyl orthoformate and 4-(4-methoxyphenyl)butan-2-one were reacted in methanol at room temperature for 48 hours. The resulting product is 1-(3,3-dimethoxybutyl)-4-methoxybenzene. In the second step, benzene derivatives were acetylated with trichloroacetyl to form the precursor compounds required for the synthesis of the target compounds. In the last step, the reaction between $NH_2NH_2 \cdot HCl$ and 1,1,1-trichloro-4-methoxy-6-(4-methoxy-phenyl)hex-3-en-2-one was carried out using both microwave-assisted and conventional techniques. When this reaction was compared, it was observed that the microwave-assisted synthesis was significantly faster. (Scheme 15) [46].

In a study conducted by Masaret (2022), new spiropyrazole derivatives were synthesized using microwave irradiation and their antimicrobial, antiviral activities and effects on the novel coronavirus disease (2019-nCoV) were investigated. In the synthesis stages, the reaction between 5-bromo-2-thiophen-2-ylmethylene-indan-1-one and hydrazonoyl chloride was carried out under the following conditions: the reaction was carried out in benzene under microwave irradiation. In addition to the shortening of the reaction time, when the spectral data of the obtained products were examined, it was observed that substituted derivative products of the 4th position of the phenyl ring at the 5th position of the compound were obtained (Scheme 16) [47].

Anwer et al. (2023) synthesized novel pyrazole derivative compounds that can be used in cancer treatment using green chemistry methodologies. The desired pyrazole derivative compounds were



Scheme 17. Synthesis of bis-pyrazole analogues under MW irridation.



Scheme 18. Synthesis of 5-bromo-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole compound.

obtained by reacting the mixture of enaminonitrile and malononitrile with cyanoacetamide or chloroacetic acid in the presence of sodium ethoxide under microwave radiation. The microwave used in the synthesis is 300 MW and the reaction time is 2-4 minutes [48].

Novel pyrazole derivative compounds based on substituted benzaldehyde were synthesized by Kumar et al. (2024). In this study, a novel pyrazole derivative compound was synthesized by subjecting the mixture of substituted benzaldehyde, ethyl-3-oxobutanoate, phenylhydrazine and water to microwave irradiation at room temperature for 20 min (Scheme 17) [49].

In a recent study, Sharma et al. (2024) employed a microwave-assisted synthesis approach to create novel pyrazole derivatives, beginning with a carbaldehyde derivative compound. The synthesis was conducted using a one-pot microwave irradiation method. A reaction was conducted between phenyl hydrazine and 2,5-dibromo-3-thiophenecarbaldehyde in a solution of ethanol and acetic acid in a 1:1 ratio. The temperature was maintained at 100°C, and the reaction was irradiated in a microwave oven for a period of seven minutes (Scheme 18) [50].

3. CONCLUSION

Many drugs and drug candidates that have been the subject of medicinal chemistry contain heterocyclic rings. Among these rings, pyrazole, an N-based heterocyclic ring, stands out for its diversity of biological activities and ease of access. Until recent years, pyrazole synthesis studies were carried out using classical methods, but with the emergence of the term green chemistry and the widespread use of MW irridation, new environmentally friendly, faster and higher yielding methods have begun to be applied. In this review, studies including MW synthesis methods used for pyrazole synthesis have been examined. The use of microwave radiation is also important in an industrial sense, as it keeps the environment clean and provides clean products. It is obvious that it will be used more frequently in the field of chemistry and medicine in the coming years. Considering the general review, for microwave-assisted pyrazole synthesis, microwave irradiation should be in the range of 100-300 MW, temperature should be in the range of 65-180 °C, and time should be in the range of 5-45 minutes. A comparison of the study conducted by Sahu et al. (2012) with that conducted by Selvam et al. (2014) reveals that the utilisation of solvent in the reaction does not impact reaction time. However, it has been demonstrated that solvent-free reactions

can contribute to the prevention of environmental pollution, less hazardous reaction conditions and reduced consumption, thus being compatible with the principles of 'green chemistry'. Among the studies examined, the conditions that achieved the highest efficiency (82-96%) were as follows: (100 W) at 70°C and 2.2 bar pressure for 4 minutes.

Ethical approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Author contribution

Conceptualization, A.K.; Methodology, A.K.; Software, A.K.; Validation, A.K.; Formal analysis, A.K.; Investigation, A.K.; Resources, A.K.; Data curation, A.K.; Writing—original draft preparation, A.K.; Writing—review and editing, A.K.; Visualization, A.K.; Supervision, A.K.; Project administration, A.K.; Funding acquisition, A.K. The author have read and agreed to the published version of the manuscript.

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Conflict of interest

The author declared that there is no conflict of interest.

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