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A Brief Review on Microwave Assisted Synthesis of Pyrazole Derivatives

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ABSTRACT: Pyrazoles have played an important part in the progression of theory in heterocyclic chemistry and also used extensively in organic synthesis. Pyrazoles are five membered heterocyclic compounds. Compounds which containing pyrazole derivatives are well-known and important nitrogen-containing five-membered heterocyclic compounds. Among the two nitrogen atoms; one is basic and the other is neutral in nature. Pyrazole and its derivatives have displayed broad spectrum of pharmacological important active scaffold that possesses almost all types of pharmacological activities and biological activities such as antimicrobial, antitumor, antiviral, antidepressant, anticonvulsant, antihyperglycemic, and enzymes inhibitory activities. Present paper is emphasizes on microwave assisted synthesis of some schemes Pyrazole Derivatives.

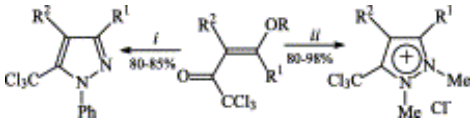
Keywords: Pyrazole, heterocyclic, derivatives, pharmacological, activity.

INTRODUCTION: The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development.[1]By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assembled in a fraction of the time required by classical thermal methods. Presently, thermally driven organic transformations take place by either of two ways: conventional heating or microwave-accelerated heating. In the first way, reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order toreach the solvent and reactants. This is a slow and inefficient method for transferring energy into the reacting system. In the second way, microwaves couple directly with the molecules of theentire reaction mixture, leading to a rapid rise in temperature.Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conduction—the two fundamental mechanisms for transferring energy from microwaves to the substance(s) being heated.[2]

For instance, solvent free heterocyclic compound synthesis includes ultrasound and microwave irradiation[3, 4]. Microwave (MW) irradiation has been widely exploited in the last decades to run various number of organic synthesis. Usually three types of solvent-free procedures can be coupled with dielectric heating provided by a microwave source: reactions among neat reagents, reactions among supported reagents on mineral solid supports and phase transfer catalysis reactions. Among the three types of solvent-free procedures, the neat reagent one is the most routinely employed due to its easy work-up and negligible use of solvents [5]. In particular, applying Microwave Assisted Organic Synthesis (MAOS) becomes more common in heterocyclic chemistry and especially in pyrazole derivative synthesis. [6, 7]

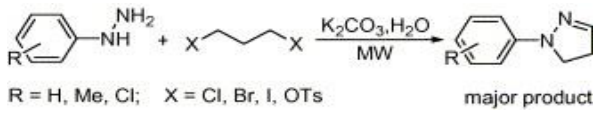
Different Approaches in Synthesis: A series of five 5-trichloromethyl-1-phenyl-1*H*-pyrazoles and six 5-trichloromethyl-1,2-dimethylpyrazolium chlorides have been synthesized in 80–98% yield by environmentally benign microwave induced techniques involving the cyclocondensation of 4-alkoxy-1,1,1-trichloro-3-alken-2-ones [$Cl_3C(O)C(R^2)=C(R^1)OR$, where R^2=H, Me; R^1=H, alkyl, phenyl and R=Me, Et] with phenyl hydrazine and 1,2-dimethylhydrazine dihydrochloride, respectively, using toluene as sol-

vent. The use of microwave and classical methods are comparable for making pyrazoles, but the formation of pyrazolium chlorides can be achieved in a significant shorter time, and in some cases better yield. A series of five 5-trichloromethylpyrazoles and six 5-trichloromethylpyrazolium chlorides have been synthesized by microwave (MW) induced techniques. *Reaction conditions*: (i) $PhNHNH_2$, (ii) MeNHNHMe·2HCl, MW, 45 W, PhMe, 85°C, 5–12 min.[8]



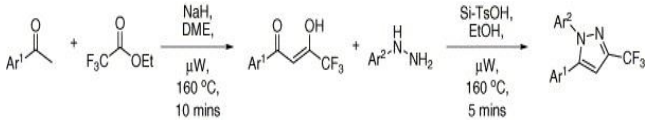
[Scheme 1]

Direct microwave-assisted syntheses of 4, 5-dihydropyrazole, pyrazolidine and 1,2-dihydro-phthalazine derivatives from hydrazines and alkyl dihalides or ditosylates were achieved in aqueous alkaline media.[9]



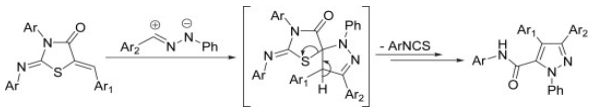
[Scheme 2]

The application of microwave heating to a silica-assisted solution-phase synthesis technique has been utilized to develop a rapid and efficient two-step protocol for the preparation of pyrazoles from arylmethyl ketone and aryl hydrazine monomers.[10]



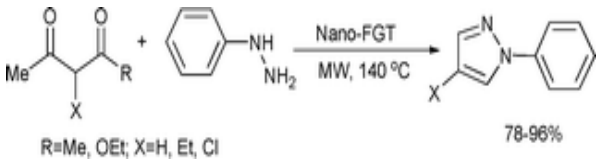
[Scheme 3]

Regioselective 1, 3-dipolar cycloaddition of nitrilimines with 5-arylidene-2-arylimino-4-thiazolidinones and with 2-(4-arylidene)thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones afforded the corresponding 1,3,4-triaryl-5-*N*-arylpyrazole-carboxamides and pyrazolylbenzimidazoles. All reactions were carried out under conventional thermal heating and/or microwave irradiation. Both the pyrazole-5-carboxamides and pyrazolylbenzimidazoles were examined for their *in-vitro* anti-tumor activities against two tumor cell lines, Hep-2 and colon CaCo-2. Most of the obtained compounds exhibited significant activity against CaCo-2 and Hep-2 cell lines.[11]



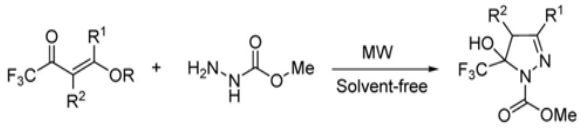
[Scheme 4]

The same catalyst was also employed in the synthesis of pyrazoles by a double condensation reaction of phenyl hydrazine with substituted 2,4-pentanediones under microwave-assisted aqueous conditions .[12]



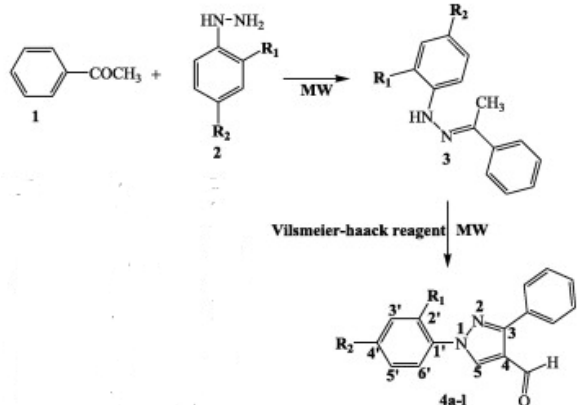
[Scheme 5]

An efficient microwave-assisted synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1*H*-pyrazoles from the cyclocondensation reaction between enones [CF_3C (O) C (R^2) = C (R^1) (OR), where R^2 = H, Me; R^1 = H, Me, Et, Pr, *i*-Pr, *t*-Bu, *i*-Bu, Ph, 4-NO_2-Ph, 4-Cl-Ph, 4-Br-Ph, 4-F-Ph and R = Me, Et] and methyl hydrazinocarboxylate under solvent-free conditions is reported. This process is an efficient alternative to the traditional thermal heating and furnishes the heterocyclic compounds in good to excellent yields in a short reaction time. To show the versatility of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1*H*-pyrazoles, dehydration reactions of these compounds are also demonstrated.[13]



[Scheme 6]

A series of 1-(4-substitutedphenyl)-3-phenyl-1*H*-pyrazole-4-carbaldehydes **4a–l** have been synthesized and tested for their biological activities. Formation of the pyrazole derivatives was achieved by treating with Vilsmeier-Haack reagent. The newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activities compared to Diclofenac sodium as standard drug.[14]



[Scheme 7]

CONCLUSION: Microwave heating is very convenient to use in pyrazole synthesis. The heating is instantaneous, very specific and there is no contact required between the energy source and the reaction vessel. Microwave assisted organic synthesis is a technique which can be used to rapidly explore `chemistry space' and increase the diversity of the compounds produced. Now-days, it could be considered that all of them previously conventionally heated reactions could be performed using this technique. Within these examples, there are also some results that would appear to be unique for microwave assisted pyrazole synthesis.

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