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A Convenient Approach for the Synthesis of Ingenous Imidazole Derivatives Using Microwaves

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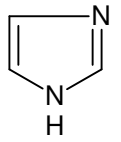
ABSTRACT
Imidazole is a planar, five membered heteroaromatic molecule with pyrrole type and pyridine type annular nitrogens. It is the constituent of several natural compounds like histamine, histidine, biotin, alkaloids and nucleic acid and a very important class among the medicinal compounds. Imidazole moiety has been established as the potential entity in the large growing chemical world of heterocyclic compounds possessing promising pharmacological characterstics, therefore this article aims to review the work reported on the synthesis of imidazole derivatives using microwave reactions as a modern method for synthesis, to get better yield, economic and environment friendly reaction.
Keywords: Heterocycle, Imidazole , Microwave Techniques, Green Chemistry, Ecofriendly

Introduction

As the world's population increases and health problems expand accordingly, need to discover new therapeutics will become even more daring. The design of drug molecules arguably offers some of the greatest hopes for success in present and future era. Heterocyclic compounds are widely distributed in nature and are essential for life. There are vast numbers of pharmacologically active heterocyclic compounds many of which are in regular clinical use[1].. Imidazole belongs to a class of heterocyclic compounds containing a five membered ring made up of two nitrogen as heteroatom with the formula $C_3H_4N_2$.Imidazole[2] is itself a parent comound whereas imidazoles are belong to a class of heterocycles with similar ring stucyure but different substituents. This ring system is present in important biological building blocks, such as histidine[3], and the related hormone histamine[4]. Imidazole can serve as a base and as a weak acid. Many drugs contain an imidazole ring, such as antifungal drugs, Nitroimidazole and sedative midazolam[5].



IMIDAZOLE

In medicinal chemistry, imidazole derivatives have been very well known for their therapeutic applications. Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives had been discovered as early as the 1840s, as shown below, used glyoxal and formaldehyde in ammonia to form imidazole . This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles. The first application of microwave irradiation in chemical synthesis was published in 1986[6]. A microwave (MW) is a form of electromagnetic energy that falls at the lower frequency end of the electromagnetic spectrum (300-300000 MHz). Microwave heating (dielectric heating) is a very efficient process due to the microwave couple directly with the molecules that are present in the reaction mixture, leading to a fast rise in temperature, faster reactions and cleaner chemistry.

Structure And Properties

Imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar five-member ring system with 3C and 2N atom in 1 and 3 positions The simplest member of the imidazole family is imidazole itself, a compound with molecular formula $C_3H_4N_2$. The systemic name for the compound is 1, 3 diazole, one of the annular N bear a H atom and can be regarded as a pyrole type N. It is soluble in water and other polar solvents. It is a colourless organic compound having melting point 89-91 °C and boiling point is 256 °C. It has high boiling point as compared all other five membered heterocyclic compounds[7]..It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring[8] .

Amphoterism

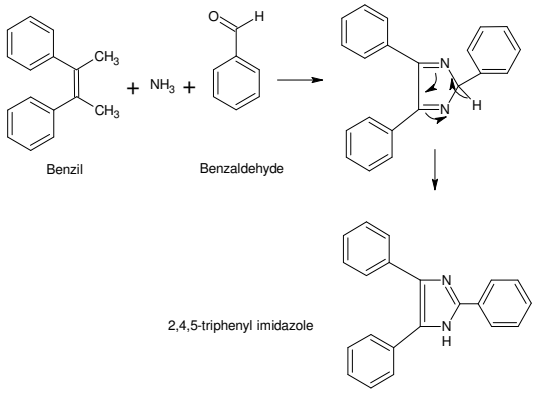
Imidazole is amphoteric, *i.e.* it can function as both an acid and as a base. As an acid, the p*K*a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is located on N-1. As a base, the p*K*a of the conjugate acid (cited above as p*K*b H^+ to avoid

confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is N-3[8].

Major Synthetic Procedures

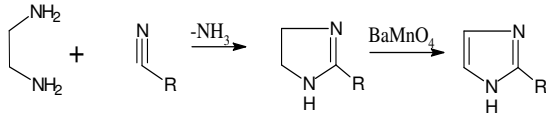
1. Radiszewski Synthesis[9-11]

It consist of condensing a dicarbonyl compound such as glyoxal, a- keto aldehyde or a- diketones with an aldehyde in the presence of ammonia, benzyl for instantce, with benzaldehyde and two molecule of ammonia react to yield 2,4,5-triphenylimidazole. Formamide often proves a convenient substitute for ammonia.



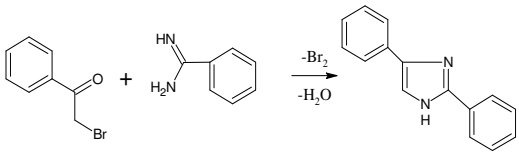
2)From Imidazoline[12]

Knapp and coworkers have reported a milder reagent barium managanate for the conversion of imidazolines to imidazoles in presence of sulphur. Imidazolines obtained from alkyl nitriles and 1, 2 ethanediamine on reaction with BaMnO4 yield 2-substituted imidazoles.



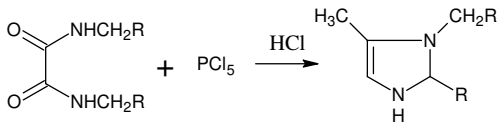
3) From Halo Ketone[12]

This reaction involves an interaction between an imidine and alpha halo ketones. This method has been applied successfully for the synthesis of 2, 4- biphenyl imidazole.



4) Wallach Synthesis[12-16]

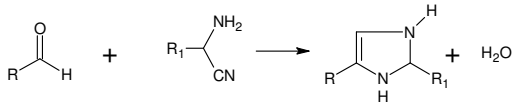
When N, N′ -dimethyloxamide is treated with phosphorus pentachloride, a chlorine containing compound is obtained which on reduction with hydroiodic acid give N- methyl imidazole. Under the same condition N, N′ -diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2- methyl imidazole. The chlorine compound has been shown to be 5- chloral imidazole.



N,N-dimethyloxamide

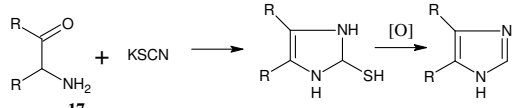
5)From Aminonitrile & Aldehyde[8]

Mixture of an aldehyde and aminonitrile both condensed under suitable reaction condition to give substituted imidazole as shown below



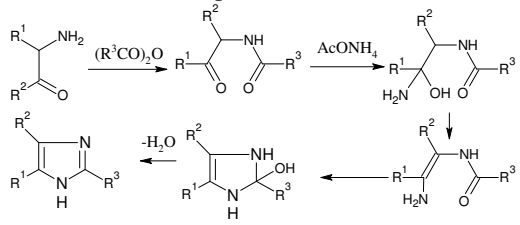
6) Markwald Synthesis[12]

The preparation of 2- mercaptoimidazoles from a- amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulfur can readily be removed by a variety of oxidative method to give the desired imidazoles.



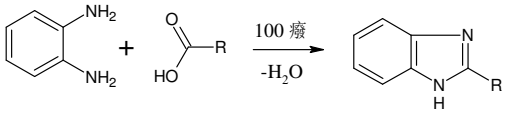
7) Cyclization Of Acylaminoketones[17]

α-acylaminoketones, also behave as 1, 4-diketo compounds.

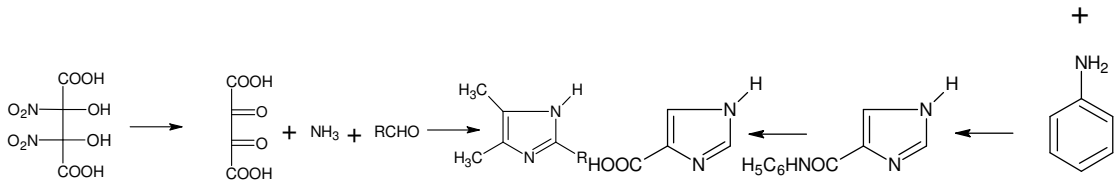


Some Other Methods By Which Imidazole Can Be Synthesized:

8) Benzimidazole is more important than imidazole as the former occur in Vit B12 and has been prepared by a number of methods, 1, 2-diaminobenzene condenses with a carboxylic acid on heating in an acidic medium to give benzimidazole[8].

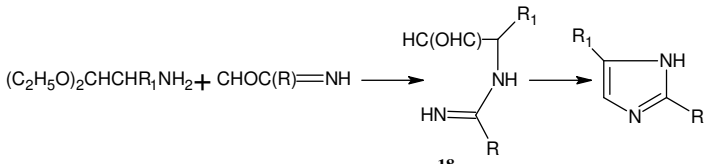


9)Imidazole can best be prepared itself by action of ammonia on a mixture of tartaric acid dinitrate and formaldehyde then heating the dicarboxylic acid with quinoline in the presence of copper to give 2-alkyl substituted 4,5- dicarboxylic acid imidazole further which is reacted with aniline to give 4- substituted benzamide[17].



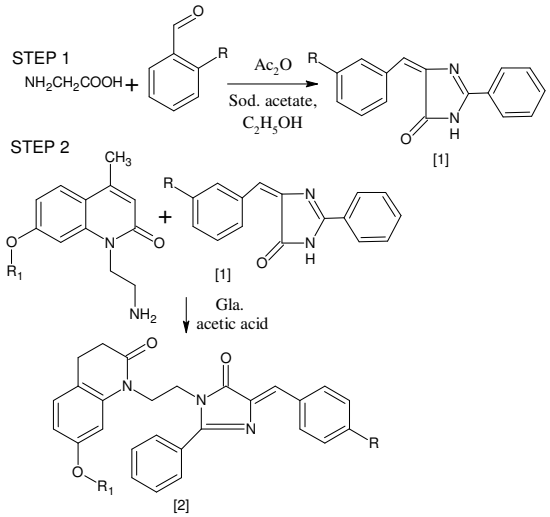
10) By The Formation Of One Bond[8]

The (1,5) or (3,4) bond can be formed by the reaction of an imidate and an α-aminoaldehyde or α-aminoacetal , resulting in the cyclization of an imidine to imidazole . The example below applies to imidazole when R=R1=Hydrogen.

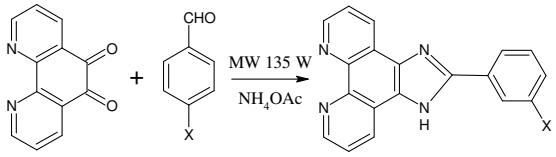


Synthesis Of Imidazole Derivatives By Microwave Reactions[18]

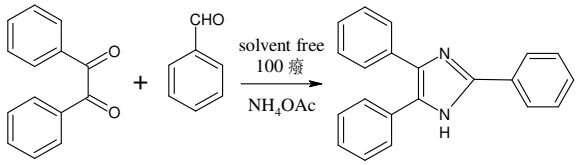
Raghavendra *et al* (2011) A Series of 1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5- oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl imidazolo quinoline analogs were synthesized by condensation of substituted imidazole and substituted quinoline[19].



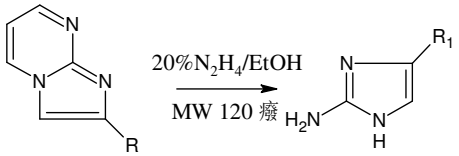
Qasim *et al* (2011) synthesized 2- phenylimidazo [4,5-f] [1,10] Phenanthroline derivatives , by reacting dicarbonyl compound and *p*-substituted benzaldehyde , this is a type of acid catalyzed reaction with excellent yields in a neutral ionic liquid, 1-methyl-3-heptylimidazolium tetrafluoroborate [(HeMIM) BF4], under solvent free and microwave assisted conditions. This particular reaction accompanies all the merits of microwave reactions like easy workup, better yield, environment friendly reaction[20].



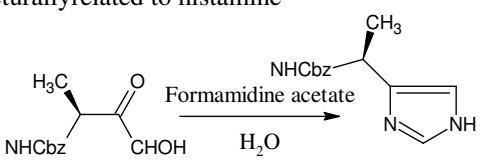
Safari *et al* (2010) rapid synthesis of 2,4,5-trisubstituted imidazoles by a three-component, one-pot condensation of benzyl, aryl aldehydes and ammonium acetate in good yields under solvent-free conditions using microwave irradiation. The reactions in conventional heating conditions were compared with the microwave-assisted reactions[21]



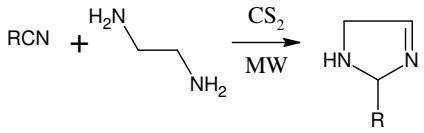
Ermolat *et al* (2009) synthesized mono and disubstituted-2-amino-1H imidazoles via microwave assisted hydrazinolysis of substituted imidazo [1, 2 a] pyrimidines is reported. This method avoids strong acidic conditions and is superior to the conventional cyclocondensation of a haloketones with N-acetyl guanidine [22].



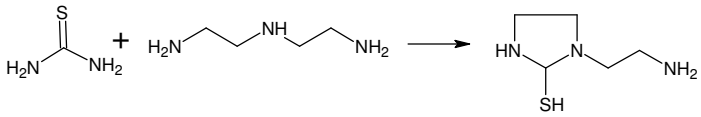
Marek *et al* (2007) synthesized via a facile 4-step reaction sequence starting from commercially available and inexpensive N-Cbz amino acids . The condensation of the corresponding α- bromoketones with formamidine acetate in liquid ammonia was revealed to be a useful method for the synthesis of such imidazole derivatives, derivatives thus prepared are structurallyrelated to histamine[23]



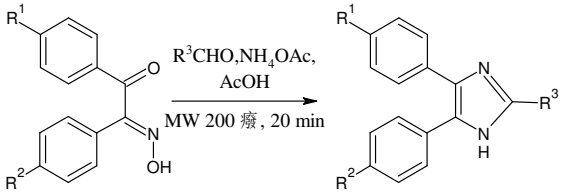
Pathan *et al* (2006) reported the reaction of alkyl cyanide (46) with ethylenediamine (47) in the presence of carbon disulphide give 2-substituted 2-imidazolines (48) under microwave irradiation. The yields of product obtained using this protocol is significantly high and the reaction time is reduced [24]



Hopfl *et al* (2005) 1-(2-aminoethyl)-2-imidazolidinethione (57) synthesis was described. The crystal and molecular structure was determined. The combination of an X-ray crystallographic study and theoretical calculations (DFT) provided insight into the understanding of the high performance of this compound as low toxicity corrosion inhibitor [25].



Sparks *et al* (2004) were synthesized 2,4,5-Triaryl-imidazoles (101) directly from the ketooxime in moderate to good yields via cyclization to the N-hydroxyimidazole (100) and an unprecedented in situ thermal reduction of the N-O bond upon microwave irradiation at 200 degrees C for 20 min [26].



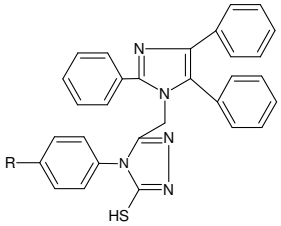
Biological Signicances

Imidazole is incorporated into many important biological molecules. The most pervasive is the amino acid histidine[27] and its decarboxylation product, histamine. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin . Imidazole-based histidine compounds play a very important role in intracellular buffering[28]. histamine is a component of the toxin that causes urticaria , which is another name for allergic hives. One of the applications of imidazole is in the purification of His-tagged proteins in immobilised metal affinity chromatography (IMAC). Imidazole is used to elute tagged proteins bound to Ni ions attached to the surface of beads in the chromatography column. An excess of imidazole is passed through the column, which displaces the His-tag from nickel co-ordination, freeing the His-tagged proteins. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, that stimulates the central nervous system . It is present in the anticancer medication mercaptopurine, which combats leukemia by interfering with DNA activities.[29]

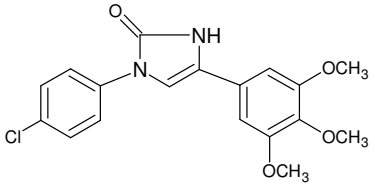
Pharmaceutical Significances[30]

Imidazoles are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents On the basis of various literature surveys Imidazole derivatives shows various pharmacological Activities like Anti fungal and Anti-bacterial activity, Anti inflammatory activity and analgesic activity, Anti tubercular activity, Anti depressant activity, Anti cancer activity, Anti viral activity and Antileishmanial activity[31].

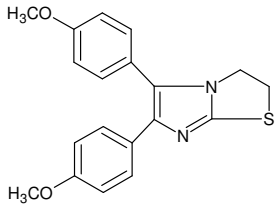
1 Synthesized by Mohd. Adil et. Al show activity against *S. aureus, E. coli, B. subtilis, C. albicans*[32].



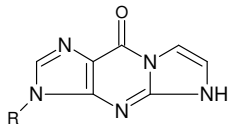
2 Balasubramanian Narasimhan *et al.*[33] synthesised imidazole derivative show activity against NCI human cancer cell.



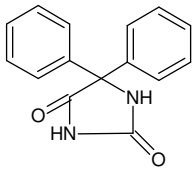
3 Synthesised by Paul E. Bender *et al.* behave analgesic agents. Antiinflammatory[30].



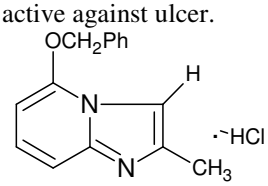
4 Synthesized by Jerzy Boryski *et al.*[34] show antiviral activity.



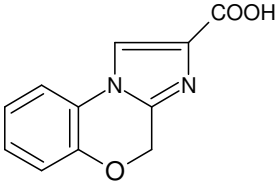
5 Synthesized by Rahul Mishra *et al.*[35]show potent Anticonvulsant activity.



6 Synthesized by James J. Kaminski *et al.*[36] active against ulcer.



7 Synthesized by ian.R. AGER et al.[37] show antiallergic activity.



Industrial Applications

Imidazole has been used extensively as a corrosion inhibitor on certain transition metals, such as copper. Preventing copper corrosion is important, especially in aqueous systems, where the conductivity of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives. The thermostable polybenzimidazole PBI contains imidazole fused to a benzene ring and linked to a benzene, and acts as a fire retardant. Imidazole can also be found in various compounds that are used for photography and electronics[29].

Conclusion

The informational data, available in literature so far, rendered imidazole, a significantly important class of heterocycle and their applications are challenging in chemotherapy of various infections etc. Microwave reactions are extremely attractive to synthetic organic chemists owing to their ability to improve regio and/or chemoselectivity and for ecofriendly & lesser reaction times. In case of imidazole derivatives which are proved to be having great potential for the different pharmacological activities, therefore synthesis of these by using microwave techniques are found to be further advantageous.

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