THERAPEUTIC AND SYNTHETIC IMPORTANCE OF 1, 3-IMIDAZOLE DERIVATIVES

Abstract

Imidazole is a biologically and medicinally important heterocyclic compounds made up of a five-membered ring with three carbons and two nitrogens are at alternate position, this compound is having the molecular formula $C_3H_4N_2$. This nitrogen containing five mebered ring system is the part of important biological building blocks, like histidine and hormone histamine. The important biomolecules nucleotides adenine and guanine in DNA also contains the Imidazole ring. This ring is also observed in the sub groups of vitamin B. it is also found in the paints and polymer. Considering its importance, different scientist and research scholar are interested to synthesize it by applying different methods of synthesis and also utilize different catalyst. The present article aims to review the various methods of synthesis reported by different scientists and research scholars.

Keywords: Imidazole, hetrocyclic, nitrogens, histidine, adenine, guanine, DNA

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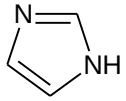
I. INTRODUCTION

Imidazole and Diazolium compounds are present in most of the important biological and chemical systems. As it is found in nature it may performs many important biological functions in an organism. This compound is made up of a five-membered ring with three carbons and two nitrogens are at alternate position, two nitrogen atoms in Imidazole molecule are arranged in the 1 and 3 positions. This is having the molecular formula $C_3H_4N_2$. The imidazole molecule term as "1, 3-diazole" and is comes under an alkaloid class. Imidazole (1) considered as the parent compound, but Diazoles comes under the category of heterocycles with identical ring structure, but substituents are different. This nitrogen containing five mebered ring system is the part of important biological building blocks, like histidine (2), the harmone histamine (3) are also contains the similar rings as in histamine. The lone pair present on two nitrogen of imidazole ring make this molecule as a base but the hydrogen atom present on one nitrogen make this compound a weak acid. The number of heterocyclic compounds showing the drug like properties like antifungal and antibacterial bears a Imidazole ring, Nitroimidazole (4) .[1-5] is one of the group of the compounds bearing imidazole ring act as a drug like properties.



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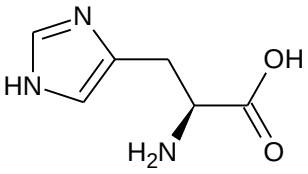

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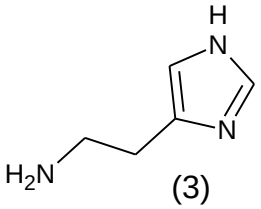

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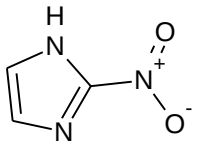
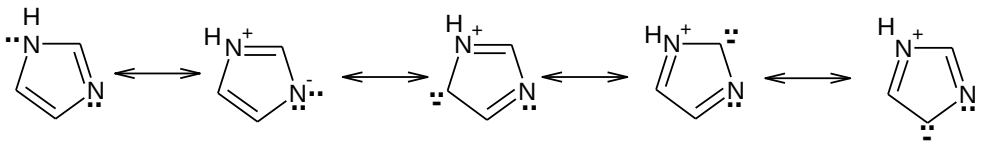
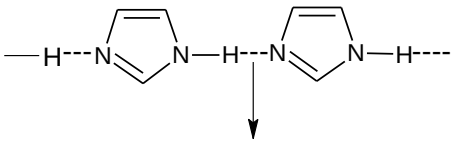


(4)

The monobasic character of imidazole molecule can easily salts with acids which is crystalline in nature. It was proved from the melting point of various crystalline salt of imidazolium [6]. This molecule is having planar geometry and highly polar in nature the calculated dipole moment 3.61D this makes the molecule easily soluble in water and other polar solvent. The hydrogen atom present in this 5 member heterocyclic ring is responsible for the isomerism in this molecule therefore the molecule exist in two taotomeric forms like 1*H*-Imidazoleand 3*H*-Diazole. The compound diazole is aromatic in nature due to the presence of a sextet of π-electrons, the lone pair of electron present on nitrogen involves in delocalization and makes the Diazoles ring as an aromatic compound. Some resonance structures of Diazoles are as shown below [7].



As the imidazole molecule acts both as a base and as a weak acid it is amphoteric in nature. The imidazole molecule is considered as higly basic than pyridine as it is observed from its pKa is found to be near about 7. This molecule is colourless and its melting point was found to be 89-91°C and boiling point is 256 °C. the boiling point of imidazole molecule is exceptionally high as compaired to the other five membered heterocyclic compounds [8]. The hydrogen atom attached to one of the nitrogen atom of this molecule responsible for the intermolecular hydrogen bonding. The existence of intermolecular hydrogen bonding in Imidazole ring is shown below.



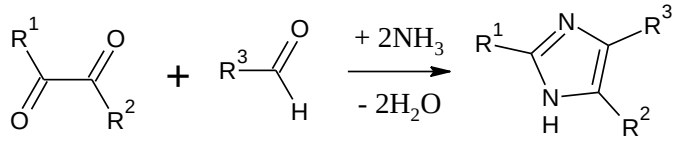
Intermolecular H-Bonding in Diazole

From the literature it reveals that Imidazoleplays various important roles in diverse field. Imidazole is found in the uses of immobilized metal affinity chromatography for purification of His tagged proteins. The important biomolecules nucleotides adenine and guanine in DNA also contains the Imidazole ring. This ring is also observed in the sub groups of vitamin B. it is also found in the paints and polymer [9]. In the recent years, lot of research is going to replace the toxic solvents by Imidazole compounds as a alternative solvents in various industries and organic synthesis [10]. Various biologically important natural products also have the imidazole ring systems. The chemical stimulant present in the tea and coffee like theophylline[11] also contains the Imidazole rings.

Imidazole compounds show versatile biological properties such as angiotensin inhibitors[12], anti-inflammatory[13], glucagonantagonist[14], antiviral[15], antimicrobial[16], fungicidal[17], inhibitors of p38 MAP Kinase[18], B-Raf kinase[19], anti-HIV[20], anticonvulsant, HIV-1 protease[21], calcium antagonist and inhibitors of thromboxane A_2 synthesase[22], therapeutic agent[23], antihistaminic[24], tranquilizer[25], antimuscarinic[26], antiarthritic[27],cardiotonic[28], HMG CoA reductase(HMGR)[29], and antitumor agents[30]. Many Imidazole derivatives plays important role in pharmaceuticals[31-32]. These ring is present in the important amino acids biotin, histamine and histidine derivatives have biological role in the formation of protiens [33]. The drug which is prescribed to reduced the blood pressure eprosartan and Losartan [34] contains the active part of imidazole ring.

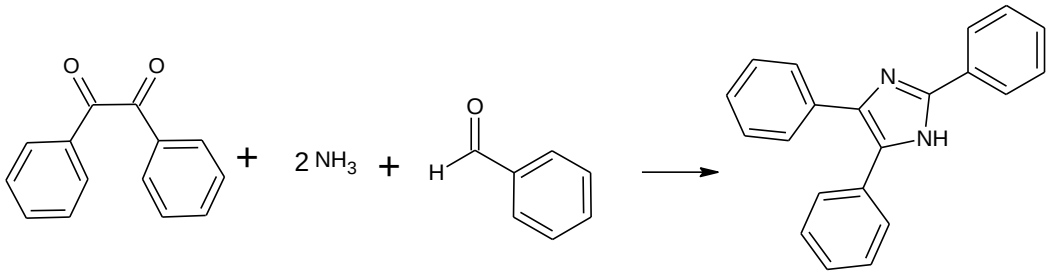
From the above discussion, it is observed that Imidazoleis most important organic compounds due to its versatile role in different chemistry. Considering its importance, different scientist and research scholer are intrested to synthesize it by applying different methods of synthesis and also utilizes different catalyst. Literature survey revealed the synthesis of Imidazoleand its different substituted derivative. Some of the methods available in the literarture survey are as follow.

This biologically and pharmacologically important compounds was synthesized from simple molecule glyoxal (5) and formaldehyde (6) in ammonia to give imidazole (7) this reaction was first discovered by Heinrich Debus [35] in 1858. This method of synthesis of imidazole produces low yields.



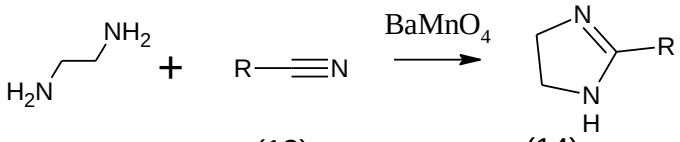
(5) (6) (7)

To overcome the yields obtained by the H. Debus methods for synthesis of imidazole derivatives. the trisubstituted derivatives of imidazoles (11) synthesis from, benzil (8) and α-ketoaldehyde, benzaldehyde (10) or α-diketones in the presence of ammonia (9) were reported [36-38]



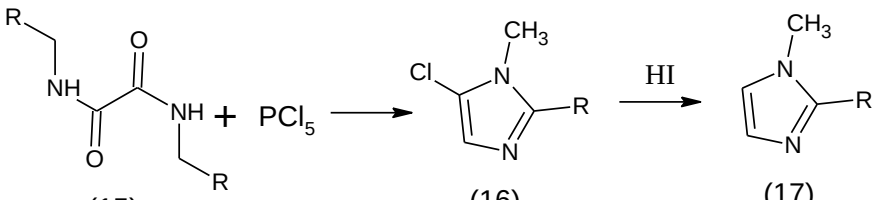
(8) (9) (10) (11)

2-substituted derivative of imidazole(14) were obtained by using the barium magnate a milder reagent[39]. In this reaction diazolones converted to diazoles in the presence of sulphur diazolines. Where 1, 2 ethanediamine (12) and alkyl nitriles (13) on reaction with BaMnO4 yield 2-substituted Diazoles



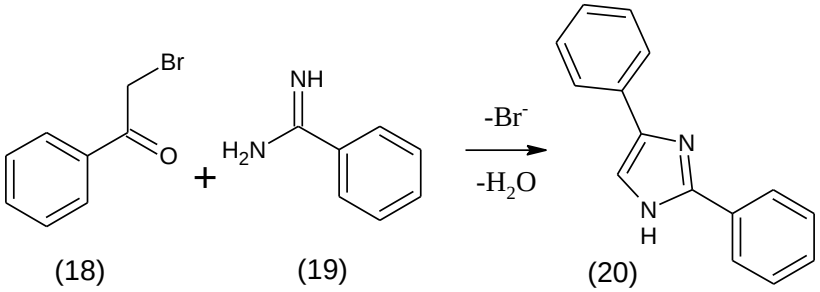
(12) (13) (14)

Wallach [40-43] reported the new precursor for the synthesis of substituted derivatives of imidazoles by multiple steps. In this the chlorosubstituted derivatives of imidazole (16) obtained first by the treatment of N, N- dimethyloxamide (15) with phosphorus pentachloride. The compound (16) on reduction in next step with hydroiodic acid give N- substituted methyl derivatives of Imidazole(17).



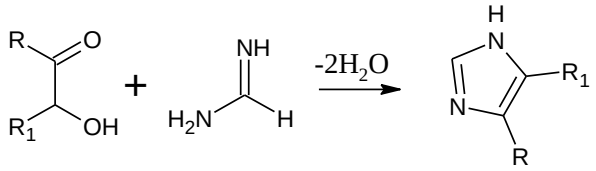
(15) (16) (17)

Simple and efficient methods of synthesis of substituted imidazole derivatives are reported phenacyl bromide or alpha halo ketones [44-45]. In this 2, 4- or 2, 5- biphenyl Imidazole (20) can be prepared by interaction between an alpha halo ketones (18) and imidine (19). This method of synthesis has been successfully employed for the convinient preparation.



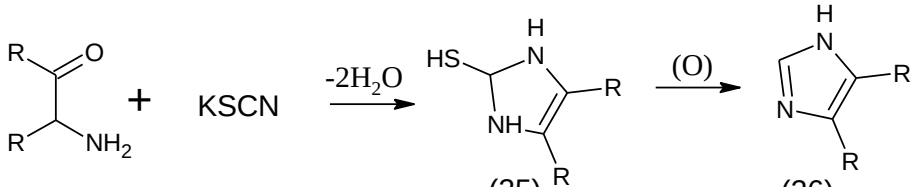
(18) (19) (20)

Cornforth and Huang [46] reported the synthesis of 4, 5 substituted derivatives of imidazoles (23) by the condensation of alpha hydroxyl ketones or alpha halo ketones (21) with amidine (22) to yields the desired products.



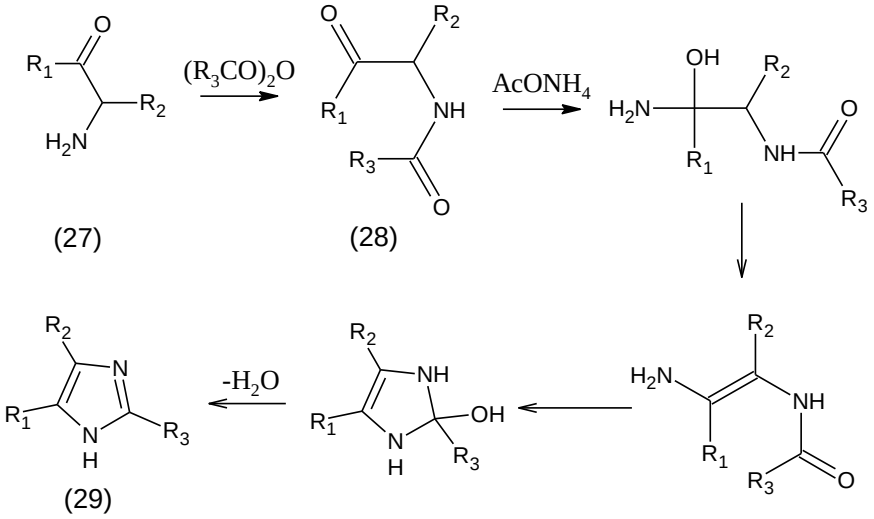
(21) (22) (23)

H. Bredereck *et al.* reported [47] the synthesis of substituted imidazole (26) by multiple steps by utilizing the new precursor α-amino ketones (24) in presence of potassium thiocyanate first give the sulphur derivative of imidazole called 2- mercaptodiazoles (25). After that sulphur can easily be removed by various oxidative methods to obtain the imidazole.

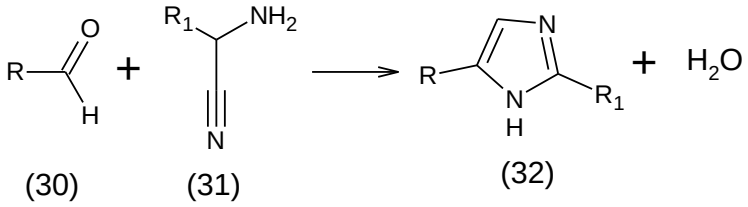


(24) (25) (26)

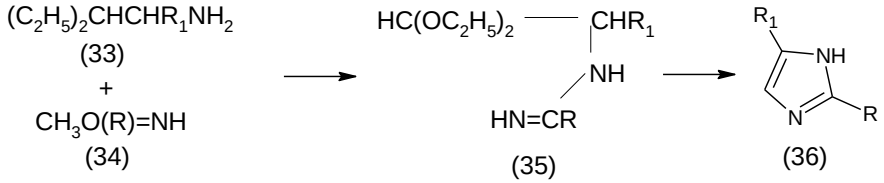
C.Robert reported [48] the cyclization method of synthesis of imidazole derivatives by multiple step synthesis. In this the α-acylaminoketones (27) on treatment with acetic anhydride converted to 1, 4-diketo compounds (28) this compound on intermolecular rearrangement undergo cyclization in presence of ammonium acetate to produces the trisubstituted imidazole derivatives (29).



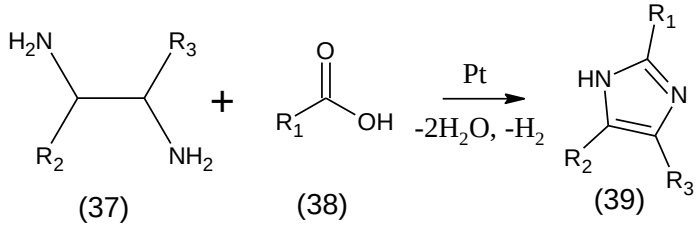
1,3 substituted derivatives of imidazole (32) synthesis was reported [49] by the condensation of a mixture of an aldehyde (30) and amino derivaties of nitrile (31) in proper condition to give substituted imidazoles (32) as shown below.



α-aminoaldehydeor α-aminoacetal (34) is found to be an efficient precursor in the synthesis of imidazole (36) when it is treated with imidate (33) first gives the intermediate an imidine (35). The resulting intermediate imidine undergo cyclization to produce the desired imidazole derivatives.

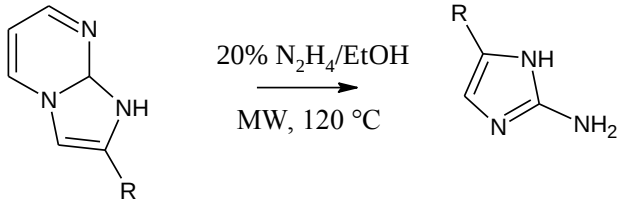


One of the efficient methods found to prepare the trisubstituted imidazole derivative (39) by two bond formation process by utilizing platinum on alumina a dehydrogenating catalyst. In this method of synthesis 1, 2-diaminoalkane (37) and aldehyde, or carboxylic acid (38) with an alcohol heated at high temperature give the desired products.



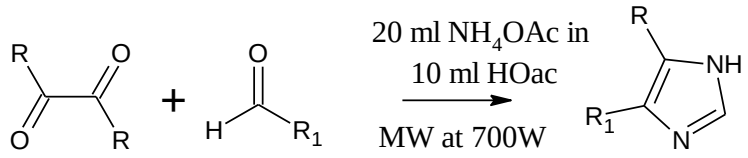
To overcome the classical method of synthesis Microwaves assisted technique of synthesis is a modern and ecofriendly method this method has characteristics of less time and maximum yields of the reaction. Other advantages of microwave assisted method of synthesis minimize the use of toxic solvent and energy.

Bhatnagar *et al.* [50] reported the replacement of classical method by modern method for synthesis of various substituted-2-amino-1*H*Diazoles (41) in this method he synthesizes the target compounds by hydrazinolysis of diazo [1,2 a] pyrimidines (40) under microwave irradiation. According to Bhatnagar *et al.*this method is beneficial as it replace the use of strong acidic condition.



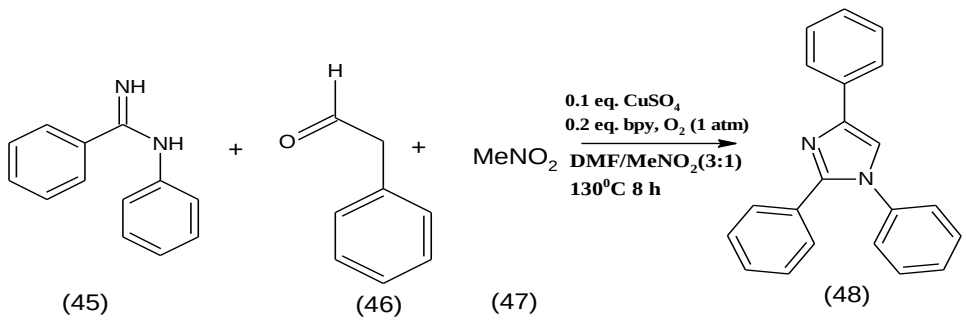
(40) (41)

Ermolat'ev *et al.* reported[51] corrosion inhibition activity of imidazole on carbon steel surface and microwave assisted method of synthesis of 4,5-substituted Imidazole derivatives (44) by using the ammonium acetate as a simple easily available catalyst in acetic acid. in this reaction diketone (42) and some aldehyde or ketone (43) on microwave irradiation under suitable condition gives the desired products.



(42) (43) (44)

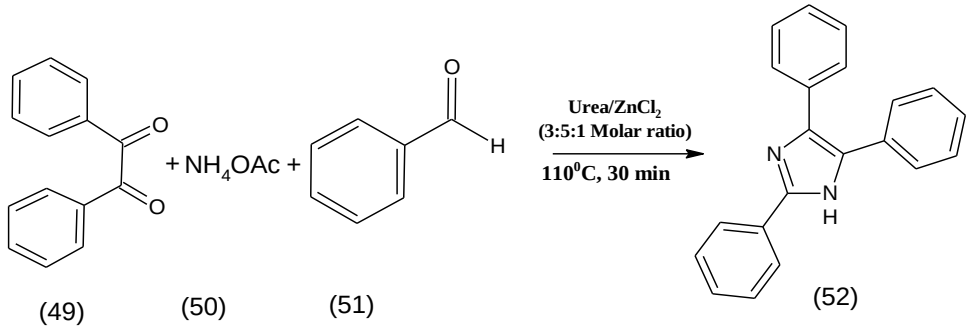
Pardesi *et.al.* reported[52] the use of low cost catalyst such as copper sulfate and easily available precursor in the synthesis of the multisubstituted derivatives of imidazole (48). This is environmental friendly and economic method. In this arylacetic acids(46), *N*-arylbenzamidines (45), and nitroalkanes (47) on long time heating under 1 atmospheric pressure produces the desired product.



(45) (46) (47) (48)

Higuera *et al.* reported [53] the use of reusable both solvent and catalyst up to five times in the synthesis of imidazoles (52). This is a short period synthetic method, where

benzyl (49), ammonium acetate (50), and an aromatic aldehyde (51) on heated in low-melting mixture urea-$ZnCl_2$ as reaction medium provide the product in high yield.



II. CONCLUSIONS

From the above discussion, it is observed that an imidazole derivative is most important organic compounds due to its versatile role in different chemistry. This molecule performs various biological activities in different biological systems. Considering its importance, different scientist and research scholar are interested to synthesize it by applying different methods of synthesis and also utilize different catalyst. But the simple economic and environmental friendly methods are still in demands.

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