Therapeutic and synthetic importance of 1, 3-imidazole derivatives

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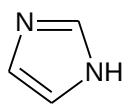
ABSTRACT

Imidazole is a hetrocyclic; planar organic molecule that consisting of a five-membered ring containing three carbons and two nitrogens, this compound is having the molecular formula $C_3H_4N_2$. The Imidazole ring system is present in important biological building blocks, such as histidine and the related hormone histamine. The Imidazole ring is found in the nucleotides adenine and guanine in DNA and in biotin (also known as Co-enzyme R), a member of the B group of vitamins. Diazoles containing compounds can also be found as polymers and which are used in the paint industry as optical brighteners. 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.

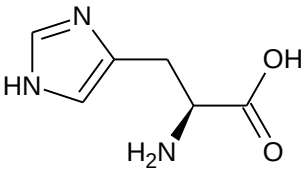
Keywords: Imidazole, hetrocyclic, nitrogens, histidine, adenine, guanine, DNA

I. INTRODUCTION

Imidazole and Diazolium compounds are present in most of the biological and chemical systems. As it is found in nature it may performs many important biological functions in an organism. Imidazole is a heterocyclic; planar organic molecule that consisting of a five-membered ring containing three carbons and two nitrogens, the two nitrogen's in Imidazolemolecule are arranged in the 1 and 3 positions. This is having the molecular formula $C_3H_4N_2$. This heterocyclic compound is a "1, 3-diazole" and is comes under as an alkaloid class. Imidazole(1) refers to the parent compound, whereas Diazoles are a class of heterocycles with similar ring structure, but varying substituents. The Diazoles ring system is present in important biological building blocks, such as histidine (2), and the related hormone histamine (3). Diazoles can serve as a base and as a weak acid. Many, drugs contain a Imidazolering, such as antifungal drugs and Nitroimidazole (4)[1-5]



(1)



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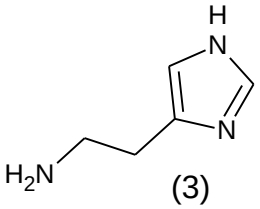

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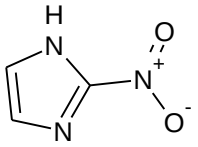
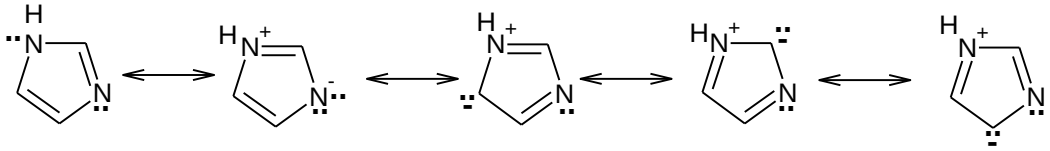
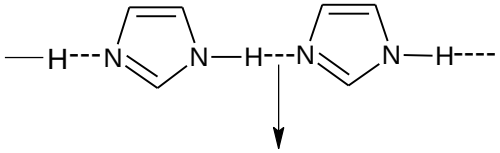


(4)

Imidazolebehaves as a monoacidic base, which can easily form crystalline salts with acids.The melting points of number of characteristic imidazolium salts are reported[6]. Imidazolecompound is a 5-membered planar ring, which is soluble in water and other polar solvents. This molecule exists in two equivalent tautomeric forms such as 1*H*-Imidazoleand 3*H*-Diazole, because the hydrogen atom can be located on either of the two nitrogen atoms. Imidazoleis a highly polar compound, as evidenced by a calculated dipole of 3.61D and is entirely soluble in water.The compound is comes under the class as aromatic 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].



Further Imidazolealso acts amphoteric in nature. That is, it can function as both an acid and as a base. As an acid, the p*K*a of Imidazoleis 14.5. As a base, the p*K*a of the conjugate acid is approximately 7, making Diazoles approximately sixty times more basic than pyridine. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimise solubility and bioavailability parameters of proposed poorly soluble lead molecules. 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[8].it is observed that intermolecular hydrogen bonding exists in Imidazolering. The intermolecular hydrogen bonding exists in Imidazolemolecule as shown below.



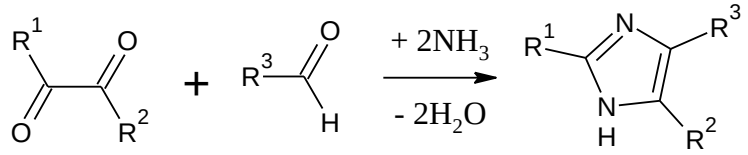
Intermolecular H-Bonding in Diazole

From the literature it reveals that Imidazoleplays various important roles in diverse field. One of the applications of Imidazoleis in the purification of His tagged proteins inimmobilized metal affinity chromatography (IMAC). The Imidazolering is found in the nucleotides adenine and guanine in DNA and in biotin (also known as Co-enzyme R), a member of the B group of vitamins. Diazoles containing compounds can also be found as polymers and which are used in the paint industry as optical brightners[9].in the recent years, research is focused on the possible use of Diazoles as ionic liquids as an alternative to toxic solvents[10].Imidazoleis also found as an entity in natural Products, such as theophylline[11]which is a stimulant found in tea and coffee.

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]. They also have many applications in various chemical processes, such as in pharmaceuticals[31-32]. Diazoles play an important role in pharmacology, for instance histidine, histamine, and biotin[33].These aromatic hetrocycle play an active parts in drugs such as Losartan and eprosartan[34].

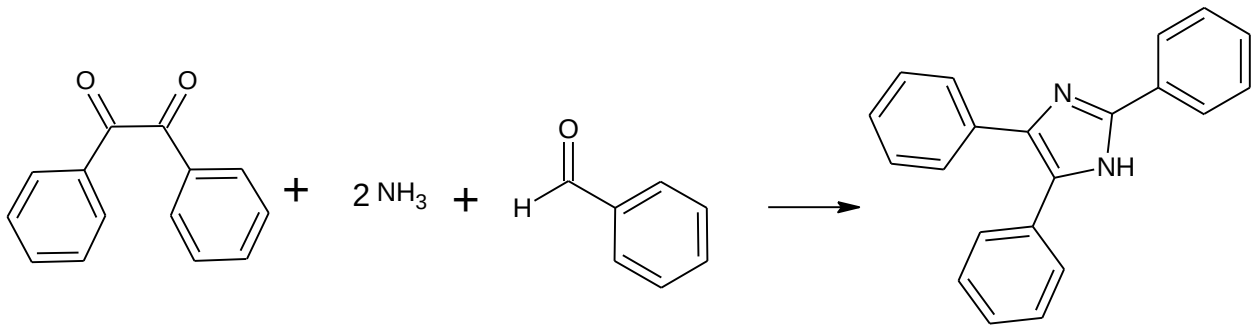
From the above discussion, it is observed that Imidazoleis most important organic compounds due to its versatile role in different chemistry. Considering its importance, different scientist and research scholer are intrested to synthesize it by applying different methods of synthesis and also utilizes 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.

Imidazole was first synthesized by Heinrich Debus in 1858, but various Diazoles derivatives (7) had been discovered as early as the 1840s, he was synthesized Imidazoleby utilysing glyoxal (5) and formaldehyde (6) in ammonia to form Diazole[35]. This synthesis, while producing relatively low yields, is still used for creating C-substituted Diazoles.



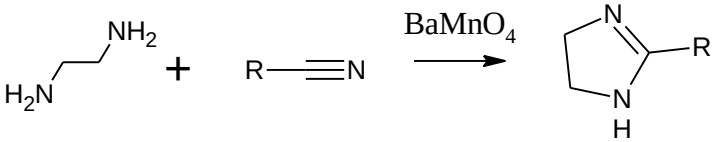
(5) (6) (7)

Radiszewski[36-38] reported the condensation of a dicarbonyl compound, benzil (8) and α- ketoaldehyde, benzaldehyde (10) or α-diketones in the presence of ammonia (9), yield 2, 4, 5 triphenylimidazole (11).



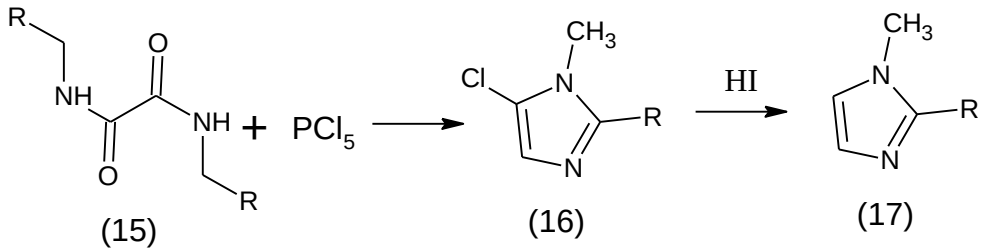
(8) (9) (10) (11)

A milder reagent barium mangnate to convert diazolines to diazoles in the presence ofsulphur diazolines obtained[39]from 1, 2 ethanediamine (12) and alkyl nitriles (13) on reaction with BaMnO4 yield 2-substituted Diazoles (14).



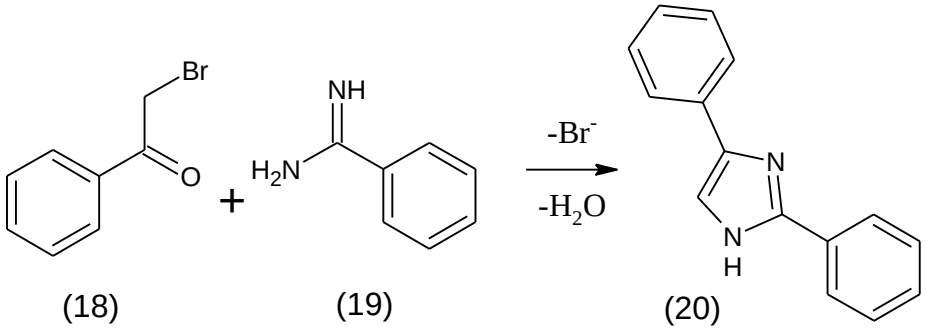
(12) (13) (14)

Wallach[40-43] reported that when N, N- dimethyloxamide (15) was treated with phosphorus pentachloride, a chlorine containing compound (16) was obtained which on reduction with hydroiodic acid give N- methyl Imidazole(17). Under the same condition N, N-diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2- methyl Diazole.



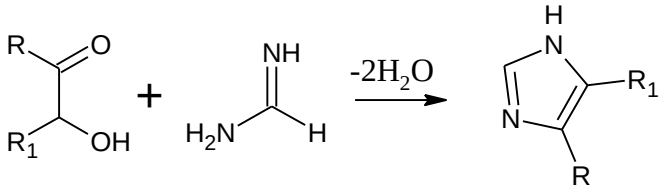
(15) (16) (17)

Diazoles can also be prepared from α- Halo Ketone this method[44-45] is based on an interaction between an alpha halo ketones (18) and imidine (19).This method has been applied successfully for the synthesis of 2, 4- or 2, 5- biphenyl diazole(20).



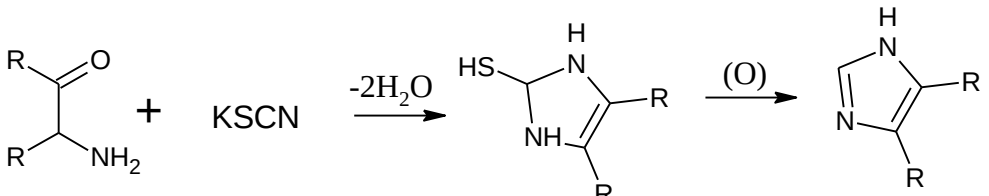
(18) (19) (20)

Similarly, acyloin (21) reacts with amidine (22) or alpha halo ketones to yield Diazoles(23) [46].



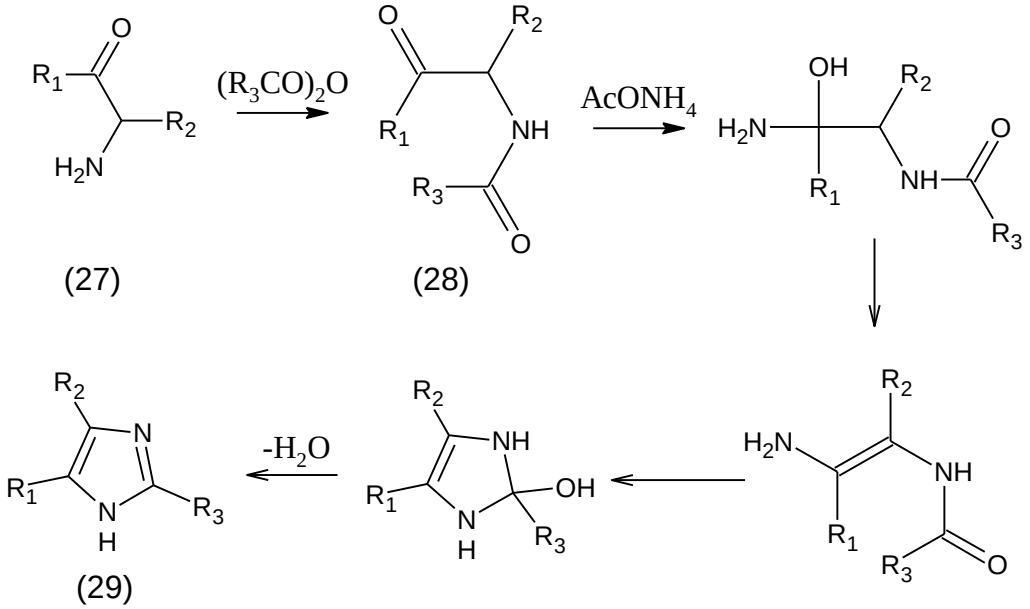
(21) (22) (23)

The preparation of 2- mercaptodiazoles from α-amino ketones (24) or aldehyde and potassium thiocyanate is used[47] for the synthesis of 2-thiol substituted Diazoles (25). The sulfur can readily removed by a variety of oxidative method to give the desired Diazoles (26).



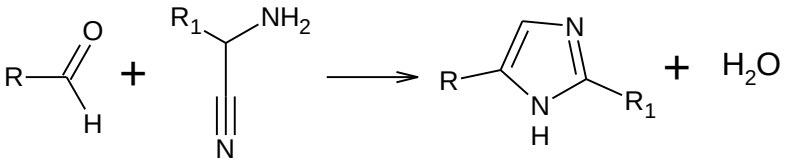
(24) (25) (26)

α-acylaminoketones (27), also behave as 1, 4-diketo compounds (28). This compound lead to ready cyclization (29), in the presence of anhydride followed by presence of ammonium acetate[48].



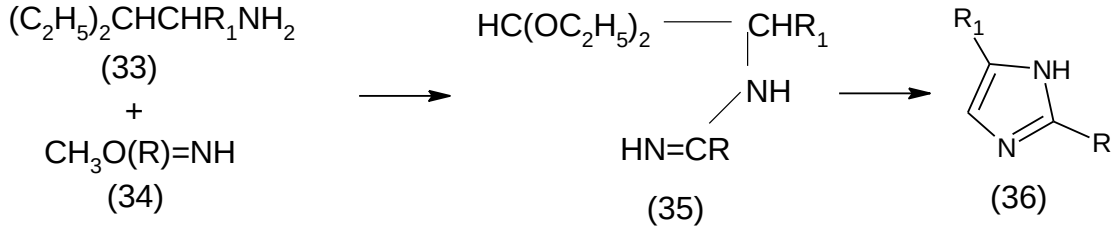
(27) (28) (29)

1,3-Imidazolecan also be prepared from aminonitrile and aldehyde[49]a mixture of an aldehyde (30) and aminonitrile (31) both condensed under suitable reaction condition to give substituted diazoles (32) as shown below.



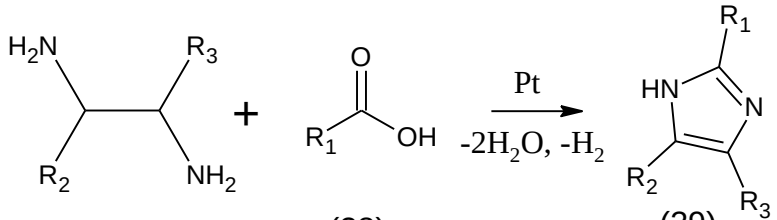
(30) (31) (32)

1,3-Imidazolecan also be synthesized by formation of one bond. The (1, 5) or (3, 4) bond can be formed by the reaction of an imidate (33) and a α-aminoaldehydeor α-aminoacetal (34), resulting in the cyclization of an imidine (35) to Diazoles (36). The example below applies to Imidazolewhen R=R_1=Hydrogen.



(33) + (34) (35) (36)

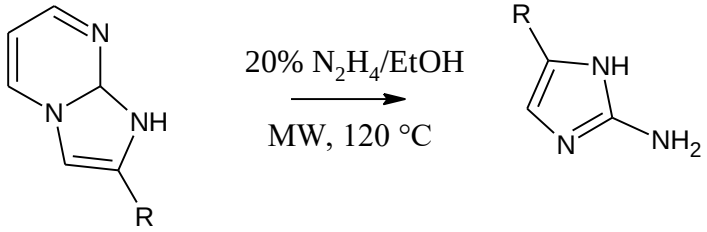
The compound (39) also prepared by two bond formation method. The (1,2) and (2,3) bonds can be formed by treating a 1, 2-diaminoalkane (37), at high temperatures, with an alcohol, aldehyde, or carboxylic acid (38). A dehydrogenating catalyst, such as platinum on alumina is required.



(37) (38) (39)

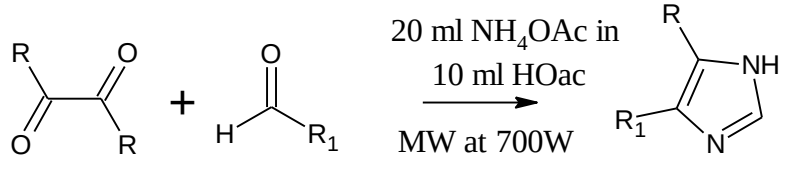
Microwaves assisted modern time-consuming procedure it has advantages compared to classical methods yield increase, substantial reduction of reaction time, solvents consumption and waste minimization.

Synthesis of mono and disubstituted-2-amino-1*H*Diazoles (41) via microwave assisted hydrazinolysis of substituted diazo [1,2 a] pyrimidines (40) is reported[50].This method avoids strong acidic conditions and is superior to the conventional cyclocondensation of a haloketones with N-acetyl guanidine.



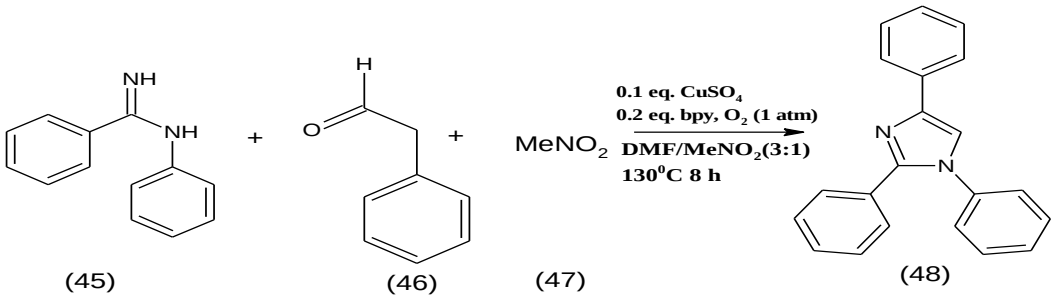
(40) (41)

4,5-substituted Imidazole derivatives (44) have been synthesized[51]by utilizing microwave assisted organic synthesis (MAOS) method, by reacting with suitable diketone (42) and some aldehyde or ketone (43), in order to investigate their corrosion inhibition mechanism on carbon steel surface.



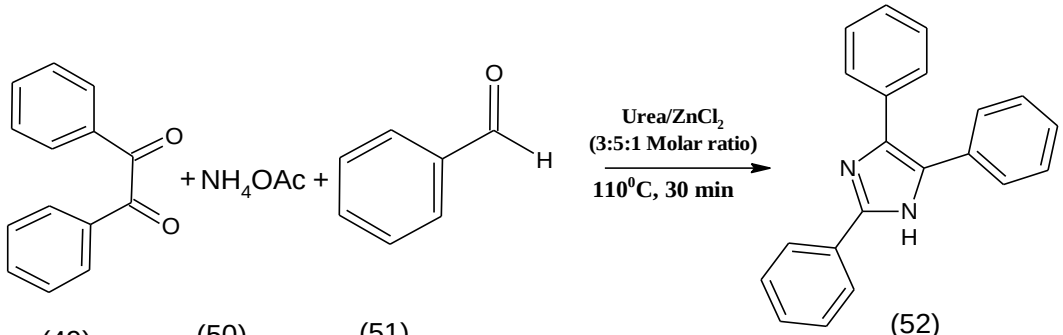
(42) (43) (44)

Pardesi *et.al.* reported[52] the multisubstituted derivatives of imidazole (48) ecofroiendly by one pot multicomponent synthesis catalysed by copper. from arylacetic acids(46), *N*-arylbenzamidines (45), and nitroalkanes (47) involves simultaneous activation of C–H and N–H bonds. The use of inexpensive copper sulfate as a catalyst and readily available starting materials makes this protocol economically viable.



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

Higuera *et al.* reported [53] the synthesis of imidazoles (52) from a dicarbonyl compound(49), ammonium acetate (50), and an aromatic aldehyde (51) in very good yields. by using the low-melting mixture urea-$ZnCl_2$ as reaction medium efficiently catalyzes to provide a broad range of triaryl-1*H*-imidazoles or 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles. In addition, the eutectic solvent can be reused five times without loss of catalytic activity.



(49) (50) (51) (52)

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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