CHAPTER II

2.0 Introduction

2.1 Review on Imidazole formation

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 itself, a compound with molecular formula C$_3$H$_4$N$_2$. The systematic name for the compound is 1,3 of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives. The thermo stable polybenzimidazole (PBI) contains imidazole fused to benzene ring and linked to benzene, and acts as a fire retardant. Imidazole can also be found in various compounds which are used for photography and electronics.

1. Radziszewski synthesis [1-8]

In 1882, Radziszewski and Japp reported the first synthesis of the highly substituted imidazole from a 1,2-dicarbonyl compound, different aldehydes, and
ammonia. Also a number of methods have been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles and 2,4,5-trisubstituted imidazoles. The syntheses of 1,2,4,5-tetrasubstituted imidazoles are carried out by four-component condensation of a 1,2-diketone / α-hydroxyketone with an aldehyde, primary amine, and ammonium acetate. It consist of condensing a dicarbonyl compound such as glyoxal, α-keto aldehyde or α-diketones with an aldehyde in the presence of ammonia, benzyl for instance, with benzaldehyde and two molecule of ammonia react to yield 2,4,5-triphenylimidazole. Formamide often proves a convenient substitute for ammonia.
2. Dehydrogenation of Imidzoline [9]

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 BaMnO$_4$ yield 2-substituted imidazoles.

3. From α-halo ketone [10]

This reaction involves an interaction between an imidine and alpha halo ketones. This method has been applied successfully for synthesis of 2, 4- or 2, 5- biphenyl imidazole phenacyl bromide and benzimidine according to this method affor 2,4-deiphenyl imidazole. Similarly, amidine reacts with acyloin or alpha halo ketones to yield imidazoles.

When N, N’-dimethyloxamide is treated with phosphorous pentachloride, a chlorine containing compound is obtained which on reduction with hydroiodic acid gives 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.

5. From aminonitrile and aldehyde
6. Markwald synthesis [14]

The preparation of 2-mercaptoimidazoles from α-amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulphur can readily be removed by a variety of oxidative method to give the desired imidazoles. The starting compounds, α-amino aldehyde or ketone are not readily available, and this is probably the chief limitation of the Markwald synthesis.

Some other methods by which imidazole can be synthesized are

7. Benimidazole 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 benimidazole.
The cyclization of N-haloamidines with sodium ethoxide forms benzimidazoles through a nitrene intermediate.

8. Imidazole can best be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinolone in presence of cooper [15].
9. Cyclization of $\alpha$-acylamino ketones [15]

$a$-acylaminoketones, also behave as 1, 4-diketo compounds.

![Diagram showing cyclization of $\alpha$-acylamino ketones]

2.2 Reactivity

Imidazole can be considered as having properties similar to both pyrrole and pyridine. The electrophilic reagent would attack the unshared electron pair on N-3, but not that on the ‘pyrrole’ nitrogen since it is the part of the aromatic sextet. While the imidazole ring is rather susceptible to electrophilic attack on an annular carbon, it is much less likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituents elsewhere in the ring. In the absence of such activation the position most prone to nucleophilic attack is C-2. The fused benzene ring in benzimidazoles provides sufficient electron withdrawal to allow a variety of nucleophilic substitution reaction at C-2.
The overall reactivity of imidazole and benzimidazole is referred from sets of resonance structure in which the dipolar contributors have finite importance these predict electrophilic attack in imidazole at N-3 or any ring carbon atom, nucleophilic attack at C-2 or C-1 and also the amphoteric nature of the molecule. In benzimidazole the nucleophilic attack is predicted at C-2. The reactivity of benzimidazole ion at the C-2 position with nucleophiles is enhanced compared with the neutral molecule [16].

Imidazoles shows a large value of dipole moment of 4.8 D in dioxane. It shows amphoteric properties and has pKa of 7.2 more than pyrazole and pyridine. Imidazoles are aromatic compound possessing a resonance value of 14.2 K cal/mol, which is almost half the value for pyrazole. The electrophilic substitution occurs frequently in imidazole
and nucleophillic substitution happens in the presence of electron withdrawing group in its nucleus. Imidazoles has M.pt. 90°C, it is a weak base and tautomeric substance, since position 4 and 5 are equivalent.

![Imidazole Tautomerism](image)

It’s spectroscopic paramaters are $\lambda_{\text{max}}$ of 207nm, I.R=1550, 1492, 1451(cm$^{-1}$) torque =2.30, 2.86, mass spectroscopy is studied for heterocyclic compounds containing one hetero-atom, in detail not in case containing two or more heteroatom [17].

**Recent literature**


Starting from 1,2-diketones and urotropine in the presence of ammonium acetate, a simple and efficient solventless microwave-assisted enabled the synthesis of 4,5-disubstitutedimidazoles.
A one-pot, four component synthesis of 1,2,4-trisubstituted 1H-imidazoles was achieved in very good yields by heating a mixture of a 2-bromoacetophenone, an aldehyde, a primary amine and ammonium acetate under the solvent-free conditions.

A simple and efficient approach allows the preparation of biologically active 2,4(5)- diarylimidazoles by parallel synthesis. The formation of 2-aryloxy-4(5)-arylimidazoles as side products strongly depends on the reaction conditions employed.
An improved and rapid one-pot synthesis of 2,4,5-triaryl imidazoles in a room temperature ionic liquid does not need any added catalyst. This one-pot methodology offers excellent isolated yields, simple work up procedures and efficient recovery and recycling of the ionic liquid.


The copper-catalyzed reaction between two different isocyanides produces imidazoles in good yields. The mechanism is discussed.

A rhodium (II)-catalyzed reaction of stable and readily available 1-sulfonyl triazoles with nitriles gives the corresponding imidazoles in good to excellent yields via rhodium iminocarbenoids intermediates.


\[
\text{NH}_2 \quad + \quad \text{R} \quad \text{N}^\equiv \quad \text{R}^\prime \\
\begin{array}{c}
\text{toluene} \\
115^\circ \text{C}, 18 \text{ h}
\end{array}
\xrightarrow{5 \text{ mol} \% \text{ catalyst}}
\text{R} \quad \text{R}' \\
\begin{array}{c}
\text{NH} \\
\text{R}^\prime
\end{array}
\]

Reactions of propargylamines with carbodiimides, in the presence of 5 mol% of the titanacarborance monoamide, \([\alpha;\eta]_5-(\text{OCH}_2)(\text{Me}_2\text{NCH}_2)\text{C}_2\text{B}_9\text{H}_9\text{Ti(NMe}_2\text{)}\) afford a new class of substituted 2-aminoimidazoles via [3+2] annulation in good to excellent yields. A possible reaction mechanism is proposed.

A one-pot procedure for the conversion of aromatic and heteroaromatic 2-nitroamines into bicyclic 2H-benzimidazoles employs formic acid, iron powder, and Nh4Cl as additive to reduce the nitro group and effect the imidazole cyclization with high-yielding conversions generally within one or two hours. The compatibility with a wide range of functional groups demonstrates the general utility of this procedure.


\[
\begin{align*}
R_1&\text{Ar}
\end{align*}
\]

A convenient method for the synthesis of 2-substituted benzimidazoles and benzothiazoles offers short reaction times, large-scale synthesis, easy and quick isolation of the products, excellent chemselectivity, and excellent yields as main advantages.


CuI/1-proline catalysed coupling of aqueous ammonia with 2-iodoacetanilides and 2-iodophenylcabamtes afford aryl amination products at room temperature, which undergo in situ additive cyclization under acidic conditions or heating to give substituted 1H-benzimiadazoles and 1,3-dihydrobenzimidazol-2-ones, respectively.
An experimentally simple, general, efficient and ligand-free synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles via intramolecular cyclization of a-bromoaryl derivatives is catalysed by copper(II) oxide nanoparticles in DMSO under air. The heterogeneous catalyst can be recovered and recycled without loss of activity.
A set of benzimidazoles, 3H-imidazo[4,5-b] pyridines, purines, xanthines and benzothiazoles was readily prepared from (hetero) aromatic ortho-diamines or ortho-aminothiophenol and aldehydes using chlorotrimethylsilane in DMF as a promoter and water-acceptor agent, followed by oxidation with air oxygen.
A highly efficient and versatile method for the synthesis of a series 2-substituted N-H, N-alkyl, and N-aryl benzimidazoles containing a wide range of functional groups was achieved in one step via the Na$_2$SO$_4$ reduction of o-nitro anilines in the presence of aldehydes.


![Chemical structure](image1)

A simple and efficient procedure for the synthesis of substituted benzimidazoles through a one pot condensation of o-phenylene diamines with aryl aldehydes in the presence of H$_2$O$_2$ and HCl in acetonitrile at room temperature features short reaction time, easy and quick isolation of the products, and excellent yields.


![Chemical structure](image2)
Various 2-arylbenzimidazoles were synthesized from phenylenediamines and aldehydes via one-step process using hypervalent iodine as oxidant. This method features mild conditions, short reaction times, high yields, and a simple procedure.


![Chemical structure](image)

Addition of oxone to a mixture of a 1, 2-phenylenediamine an aldehyde in DMF results in rapid formation of benzimidazoles under very mild conditions. Products are isolated in high purity in most cases by simple aqueous precipitation. The reaction is applicable to a wide range of substrates but does not allow the conversion of aldehydes that are sensitive to oxone under acidic reaction conditions.

Efficient and general cascade reactions of o-aminoanilines or naphthalene-1,8-diamine with terminal alkynes and p-tolysulfonyl azide allow a one-pot synthesis of functionalized benzimidazoles and 1H-pyrimidines in good yields.
A NaH-mediated reaction of carbonitriles and N-methyl-1, 2-phenylenediamine allows the formation of N-methylbenzimidazole and tolerates acid-labile acetal protective groups. Products were further converted in Suzuki, Sonogashira, Heck and Buchwald-Hartwig reactions.

A straightforward efficient and sustainable method for intramolecular N-arylation provides a library of benzimidazoles in high yields using Cu₂O as the catalyst, DMEDA as the ligand, and K₂CO₃ as the base. Remarkably the reaction was exclusively carried
out in water, rendering the methodology highly valuable from both environmental and economical points of view.


Various N-aryl-1H-indazoles and benzimidazoles were synthesized from common arylamino oximes in good to excellent yields depending upon the base in the reaction. Triethylamine promoted the formation of benzimidazoles, whereas 2-aminopyridine promoted the formation of N-arylindazoles.

An efficient Cu(I)-catalyzed cascade intermolecular addition/intramolecular C-N coupling process enables the synthesis of a side variety of 2-heterobenzimidazoles from O-haloarylcarbodiimides and N- or O- nucleophiles.


![Reaction Scheme](image)

2-Imidazolines were easily prepared in good yields from the reaction of aldehydes and ethylenediamine with iodine in the presence of potassium carbonate. The 2-imidazolines were smoothly oxidized to the corresponding imidazoles in good yields using (diacetoxyiodo) benzene at room temperature.


![Reaction Scheme](image)

A number of new reactions of IBX with heteroatom-containing substrates were discovered and their utility was demonstrated. IBX was used for the generation of imines.
from secondary amines in notably high yields, for the oxidative aromatization of nitrogen heterocycles and for the cleavage.


A versatile and modular one pot method allows the preparation of differently substituted symmetrical and unsymmetrical imidazolium salts from readily available formamidines and α-halo ketones. For many substitution patterns of the imidazolium salt products, this efficient strategy compares favourably with well-known processes in terms of yield, ease of synthesis, and robustness.
N-Phenacylpyridinium bromides, which were prepared in situ from the addition of pyridines to α-bromoketones, undergo nucleophilic addition of ammonium acetate under microwave irradiation and solvent-free conditions to afford the corresponding imidazo[1,2-a] pyridines in excellent yields.
1.2 References


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