Chapter One

Introduction

1.1. Imidazoles

Imidazole is an organic compound with the formula $C_3H_4N_2$. This aromatic heterocyclic is classified as an alkaloid. imidazole refers to the parent compound whereas imidazoles are a class of heterocycles with similar ring structure but varying substituents. The numbering system for the imidazoles is shown in[1] (Fig. 1.1).

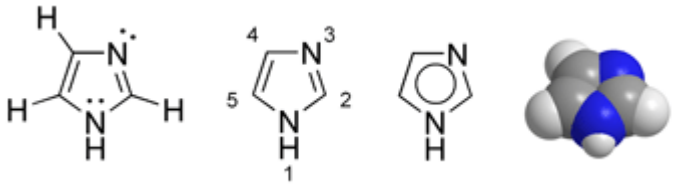
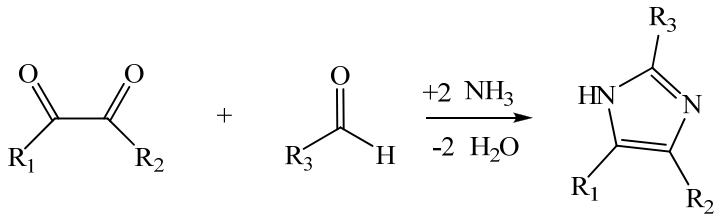


Figure 1.1

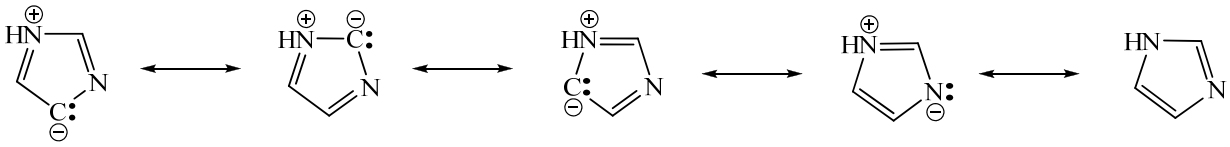
Imidazole was first synthesized by *Heinrich Debus* in 1858, but various imidazole derivatives had been discovered as early as the 1840s. His synthesis, as shown below, used glyoxal and formadehyde in ammonia to form imidazole. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles (Scheme1.1).



Scheme 1.1

Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents. 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-electron, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring.Some resonance structures of imidazole are shown below[2] (Scheme1.2).



Scheme 1.2

1.1.1. Amphotericity

Imidiazole is amphoteric, i.e. it can function as both an acid and as a base. As an acid, the pKa 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 pKa of the conjugate acid (cited above as $pKBH^{+}$ to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is N-3[3] (Fig 1.2).

1.1.2. Preparation

A ball-and-stick model of imidazole, showing carbon-carbon and a carbon-nitrogen double bonds. imidazole can be synthesized by numerous methods besides the *Debus* method. Many of these syntheses can also be applied to different substituted imidazoles and imidazole derivatives simply by varying the functional groups on the reactants. In literature, these methods are commonly categorized by which and how many bonds form to make the imidazole rings. For example, the *Debus* method forms the (1,2), (3,4), and (1,5) bonds in imidazole, using each reactant as a fragment of the ring, and thus this method would be a three-bond-forming synthesis. A small sampling of these methods is presented below [4](Fig 1.2).

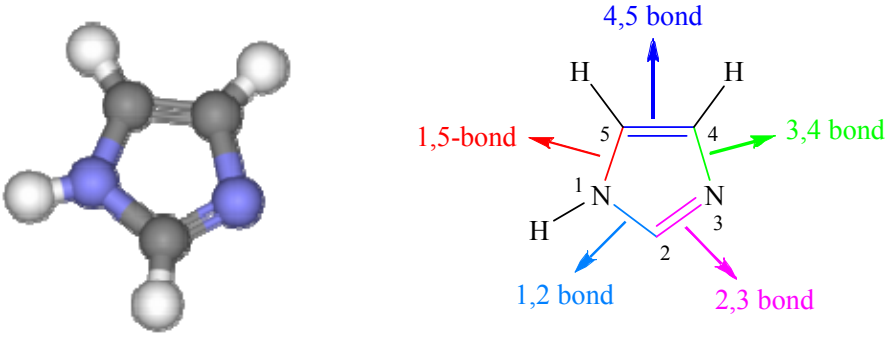
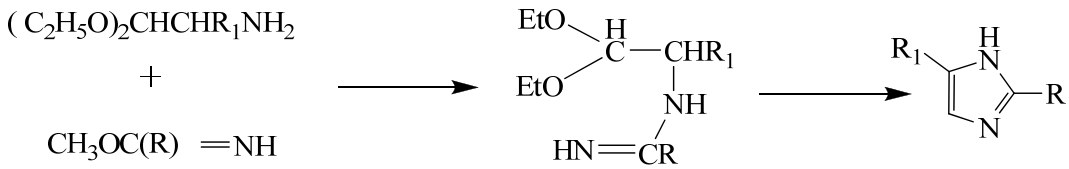


Figure 1.2

1.1.2.1. Formation of one bond

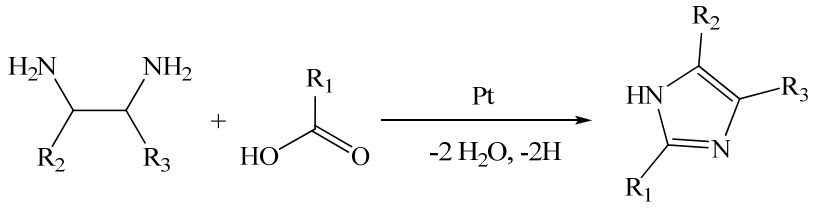
The (1,5) or (3,4) bond can be formed by the reaction of an imidate and an α-aminoaldehyde or α-aminoacetal, resulting in the cyclization of an amidine to imidazole. The example below applies to imidazole when R=R_1=Hydrogen (Scheme 1.3).



Scheme 1.3

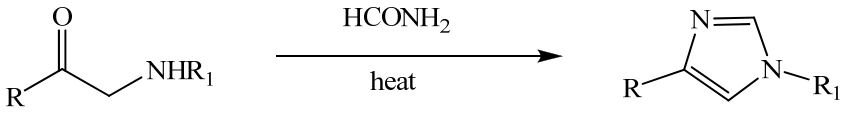
1.1.2.2. Formation of two bonds

The (1,2) and (2,3) bonds can be formed by treating a 1,2-diaminoalkane, at high temperatures, with an alcohol, aldehyde , or carboxylic acid. A dehydrogenating catalyst, such as platinum on alumina, is required (Scheme 1.4):



Scheme 1.4

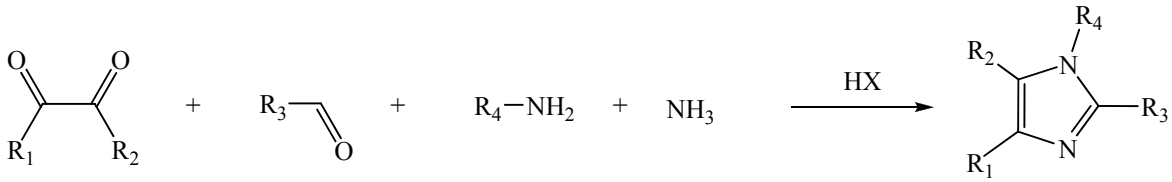
The (1,2) and (3,4) bonds can also be formed from N-substituted α-aminoketones and formamide and heat. The product will be a 1,4-disubstituted imidazole, but here since R=R_1=Hydrogen, imidazole itself is the product. The yield of this reaction is moderate, but it seems to be the most effective method of making the 1,4-substitution [5](Scheme 1.5).



Scheme 1.5

1.1.2.3. Formation of four bonds

This is a general method which is able to give good yields for substituted imidazoles. It is essentially an adaptation of the Debus method called the *Debus-Radziszewski imidazole synthesis*. The starting materials are substituted Glyoxal, aldehyde, amine, and ammonia or an ammonium salt [6] **(**Scheme 1.6).



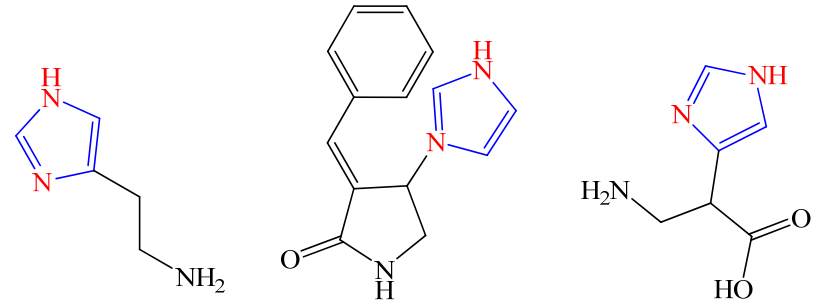
Scheme 1.6

Imidazole can also be formed in a vapor phase reaction. The reaction occurs with formamide, Ethylenediamine, and hydrogen over platinum on alumina, and it must take place between 340 and 480 °C. This forms a very pure imidazole product.

1.1.3. Biological active derivatives of imidazoles

1.1.3.1. Natural derivatives of imidazoles

Imidazole has several natural derivatives that are Histamine **(1)** Antamine **(2)** and Histidine **(3)**. Histamine and Antamine are the Alkaloid derivatives and Histidine is an amino acid. Histamine plays an important role in the regulation of several physiological processes. In the brain Histamine is synthesized in a restricted population of neurons located in the nucleus of the posterior hypothalamus. Histamine is considered as one of the most important mediators of allergy and inflammation. Naturally occurring substituted imidazoles, as well as synthetic derivatives therefore, exhibit wide ranges of biological activities,[7-10] making them attractive compounds for organic chemists (Fig. 1.3).



Histamine (1) **Antamine (2)** **Histidine (3)**

Figure 1.3

1.1.3.2. Antifungal derivatives of imidazole

Imidazole derivatives such as Metronidazole **(4)** Losartan **(5)**, Olmesartan **(6)**, Eprosartan **(7)** and Carnidazole **(8)** Trifenagrel **(9)** that belonged to the hydroxy and alkoxy imidazole class have antigungal properties[11] (Fig. 1.4).

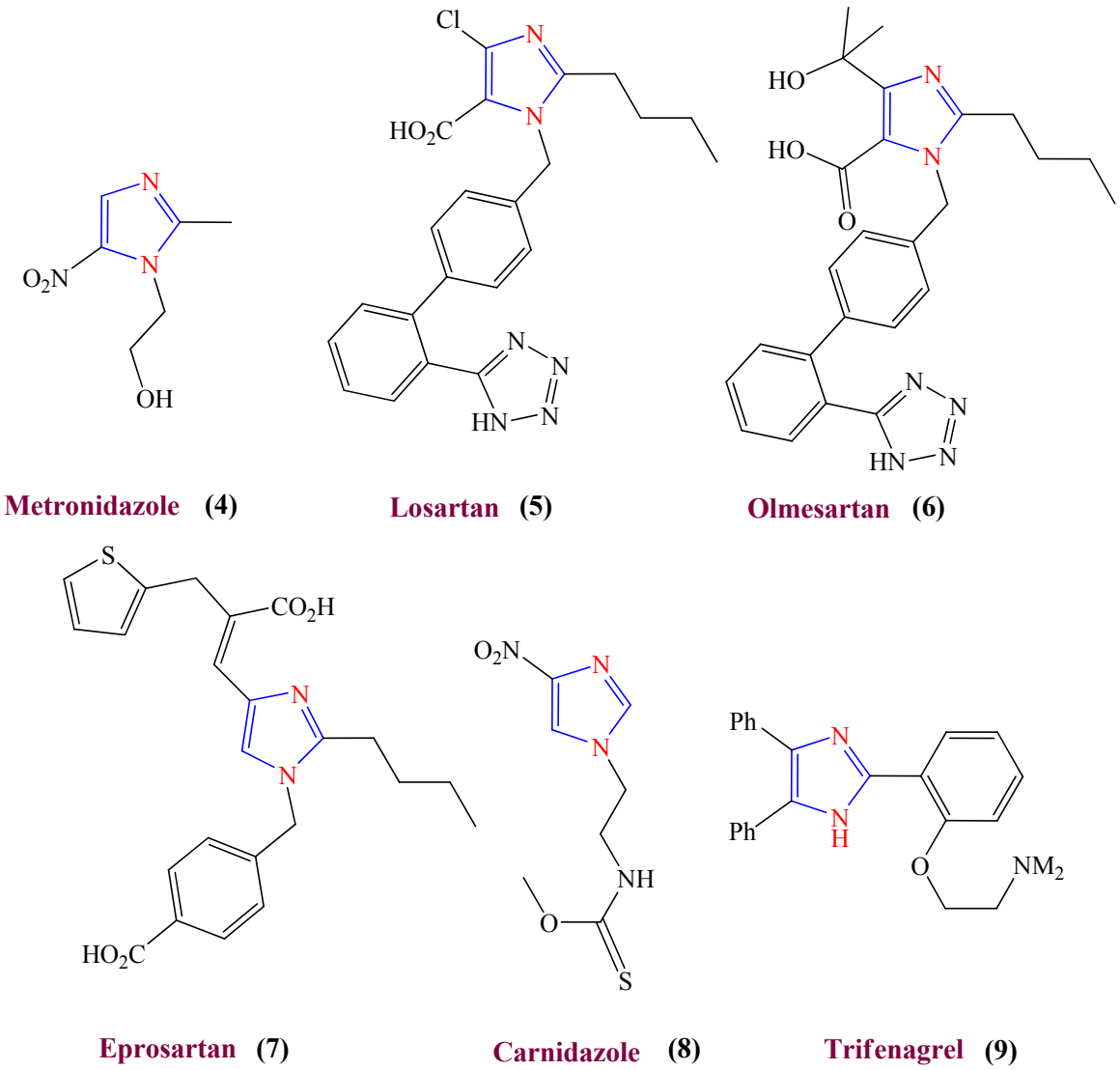


Figure 1.4

1.1.4. 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 thermo stable polybenzimidazole PBI contains imidazole fused to a 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.[12]

1.1.5. Salts of imidazole

Salts of imidazole where the imidazole ring is in the cation are known as imidazolium salts (for example, imidazolium chloride). These salts are formed from the protonation or substitution at nitrogen of imidazole. These salts have been used as ionic liquids and precursors to stable carbenes[6] (Fig. 1.5).

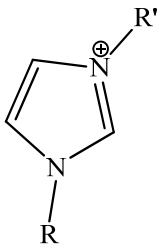
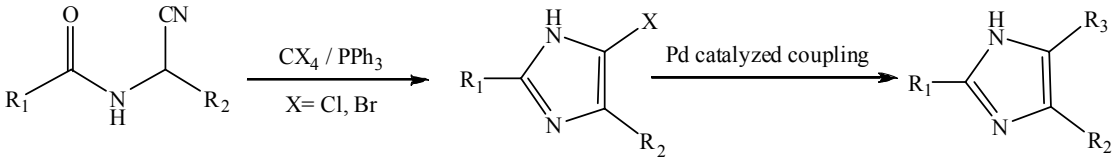


Figure 1.5

1.1.6. Synthesis of imidazoles

1.1.6.1. from N-acylated α-aminonitriles

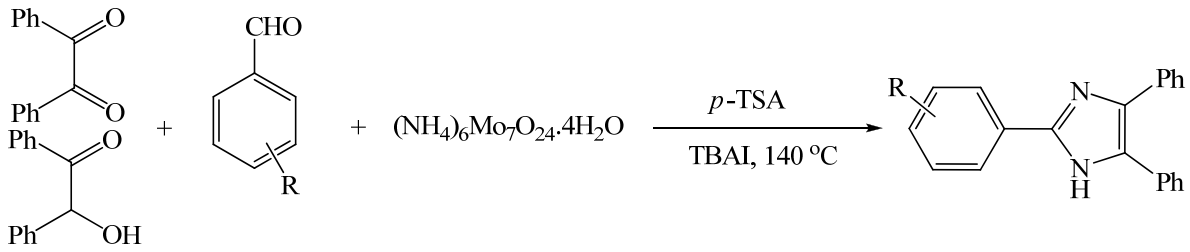
Yong-Li Zhong et al.[13] reported a general method for the synthesis of medicinally important diversely functionalized imidazoles from N-acylated α-aminonitriles has been developed. N-Acylated α-aminonitriles were reacted with triphenylphosphine and carbon tetrahalide to afford 2,4-disubstituted 5-halo-1*H* imidazoles. These haloimidazoles can be directly converted to 2,4,5-trisubstituted imidazoles through palladium-catalyzed coupling reactions (Scheme 1.7).



Scheme 1.7

1.1.6.2. *p*-TSA/TBAI

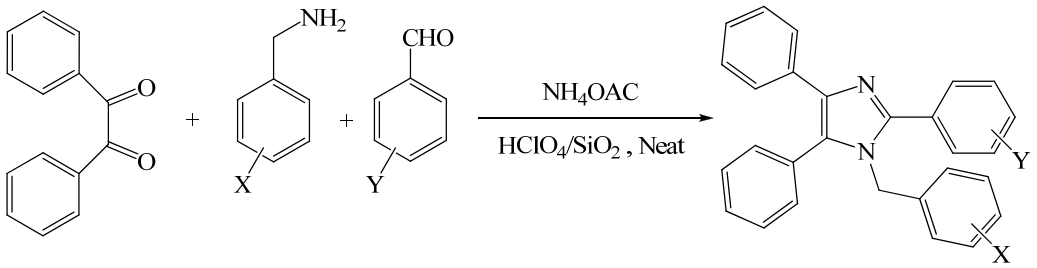
Khodaei et al.[14] showed a one-pot synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketone or α-hydroxy ketone, aldehyde and ammonium heptamolybdate tetrahydrate in an inexpensive and readily available ionic liquid, tetrabutylammonium iodide (TBAI) in molten state using catalytic amounts of *p*-TSA (Scheme 1.8).



Scheme 1.8

1.1.6.3. $HClO_4/SiO_2$

Srinivas K et al.[15] reported highly efficient, one-pot, four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles from the condensation of various aldehydes, benzil, aromatic primary amines and ammonium acetate under solvent free conditions using perchloric acid adsorbed on silica gel ($HClO_4/SiO_2$) as catalyst (Scheme 1.9).



X, Y=Cl, Br, NO_2

Scheme 1.9

1.2. Benzimidazoles

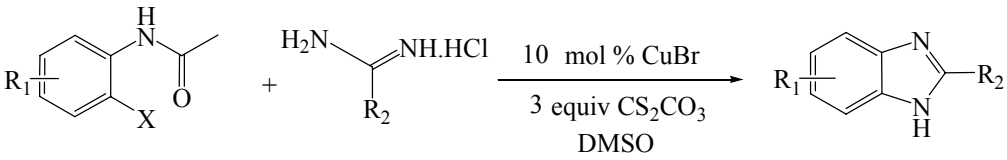
Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest.[16] benzimidazole and its derivatives are an important class of bioactive molecules in the field of drugs and pharmaceuticals[17] benzimidazole derivatives have found applications in diverse therapeutic areas including anti-ulcers, anti-hypertensives, anti-virals, anti-fungals, anti-cancers, and anti-histaminics. Moreover, these fused heterocycles have been studied as new non-nucleoside topoisomerase-I, poisons, human immunodeficiency virus-1 reverse transcriptase inhibitors, and/or potent DNA gyrase inhibitors.[18] They can act as ligands to transition metals for modeling biological systems.[19] In addition, benzimidazoles are very important intermediates in organic reactions.[20]

1.2.1. Synthesis of benzimidazoles

There are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids[21] or their derivatives (nitriles, imidates, or orthoesters).[22] The other way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of Schiff bases, which are often generated from the condensation of phenylenediamines and aldehydes.[23] Because of the availability of a vast number of aldehydes, the condensation of phenylenediamines and aldehydes has been extensively used. We present here a review of some current methods for obtaining of 2-substituted benzimidazoles.

1.2.1.1. CuBr/Cs_2CO_3

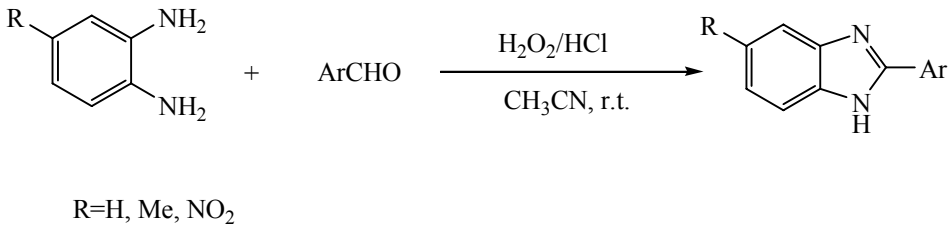
Daoshan Yang et al.[24] reported a method for the synthesis of benzimidazoles by reaction of *o*-haloacetoanilide derivatives with amidine hydrochlorides. CuBr as the catalyst, Cs_2CO_3 as the base, and DMSO as the solvent, and no ligand is required. The procedure proceeds *via* the sequential coupling of *o*-haloacetoanilide derivatives with amidines, hydrolysis of the intermediates (amides), and intramolecular cyclization with the loss of NH_3 to give 2-substituted 1*H*-benzimidazoles (Scheme 1.10).



Scheme 1.10

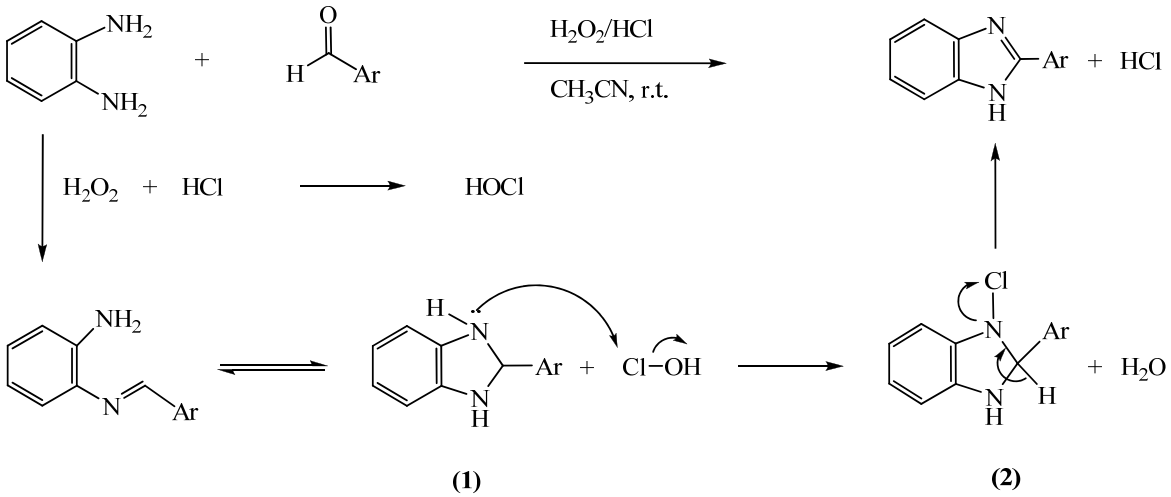
1.2.1.2. H_2O_2/HCl

Bahrami et al.[25] described H_2O_2/HCl as an efficient reagent system for the preparation of 2-substituted benzimidazoles by condensation of 1,2-phenylenediamines with aryl aldehydes (Scheme1.11).



Scheme 1.11

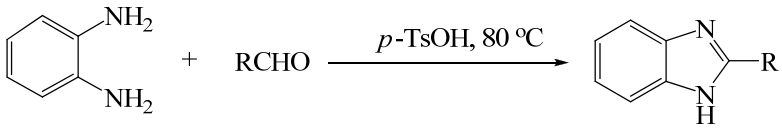
Regarding the mechanism of the oxidation step, the reaction probably involves the formation of hypochlorous acid by the reaction of aqueous hydrogen peroxide with hydrochloric acid, which then reacts with the cyclic hydrobenzimidazoles (**1**) to afford intermediate (**2**) followed by the elimination of hydrogen chloride to yield the corresponding benzimidazoles (Scheme1.12).



Scheme 1.12

1.2.1.3. *p*-TsOH

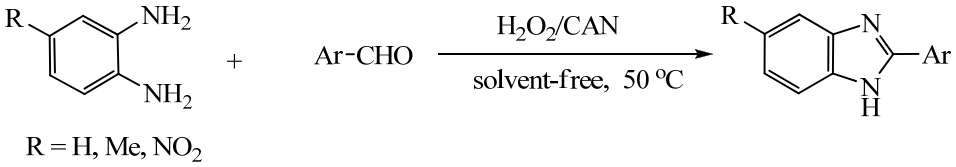
Han Xiangming et al.[26] tried to synthesize benzimidazoles using *p*-TsOH as organocatalyst for the condensation of aryl aldehydes with *o*-phenylenediamine. Simple and convenient procedure, easy purification and short reaction time are the advantageous features of this method (Scheme1.13).



Scheme 1.13

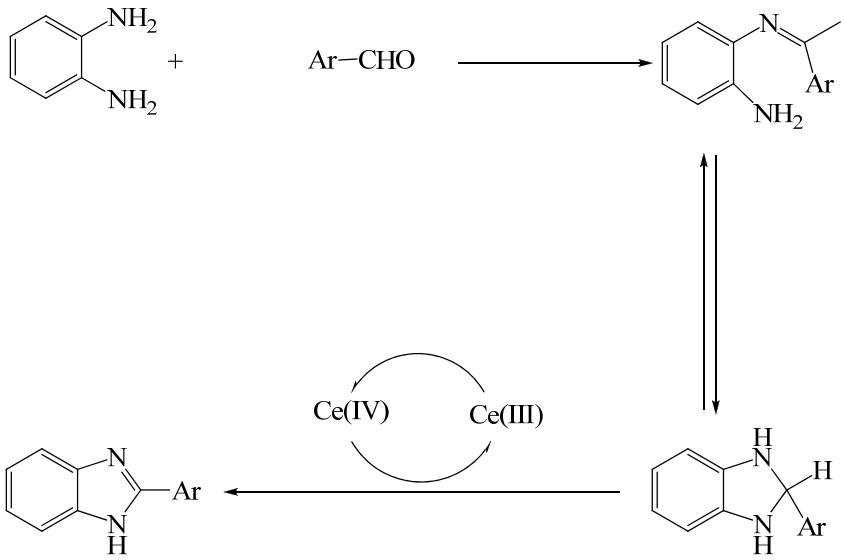
1.2.1.4. H_2O_2/CAN

Bahrami et al.[27] reported a new convenient method for the syntheses of 2-substituted benzimidazole. Short reaction time, large scale synthesis, easy and quick isolation of the product, excellent chemoselectivity, and excellent yields are the main advantages of this reaction (Scheme1.14).



Scheme 1.14

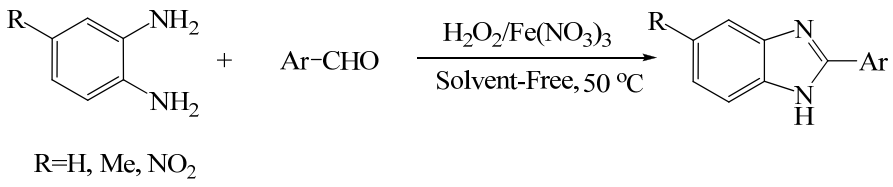
CAN could catalyze synthesis of 2-arylbenzimidazoles in the presence of H_2O_2. The proposed mechanism for the preparation of benzimidazole is show in (Scheme 1.15) that the actual oxidant is Ce(IV) and not H_2O_2 was conformed in control experiment, wherein the absent of Ce(IV) resulted in an extremely even after 10 h. In this case imine derivatives were obtained as only product. In contrast the addition of catalytic amount of Ce(IV) typically resulted in completion of reaction within 9-70 min rendering the procedure valuable for synthetic purposes.



Scheme 1.15

1.2.1.5. $H_2O_2/Fe(NO_3)_3.9H_2O$

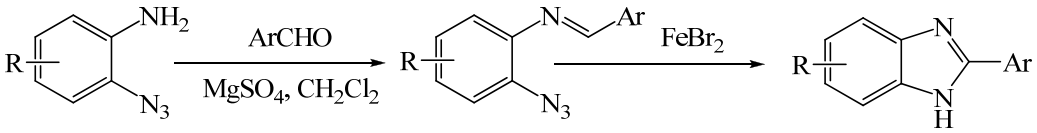
Bahrami et al.[28] reported the use of a catalytic redox cycling approach to the synthesis of various benzimidazole derivatives, based on (Fe**(III)**/Fe**(II)**)-redox-mediated oxidation of the Schiff base intermediates derived from differently substituted aromatic 1,2-phenylendiamines and a variety of aromatic aldehydes (Scheme 1.16).



Scheme 1.16

1.2.1.6. $FeBr_2$

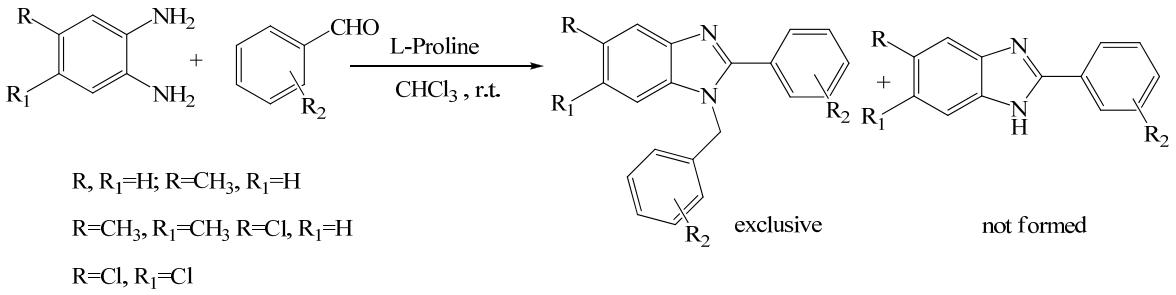
Tom et al.[29] showed that the identity of the ortho-substituent of an aryl azide influences its reactivity toward transition metals. Substitution of a vinyl group with an imine disables rhodium(II)-mediated C-H amination and triggers a Lewis acid mechanism catalyzed by iron(II) bromide to facilitate benzimidazole formation (Scheme1.17).



Scheme 1.17

1.2.1.7. L-Proline

Varala et al.[30] reported the efficacy of proline for the model reaction using *o*-phenylenediamine and benzaldehyde in chloroform with stirring at ambient temperature to afford the corresponding 1,2-disubstituted benzimidazolein (Scheme 1.18).

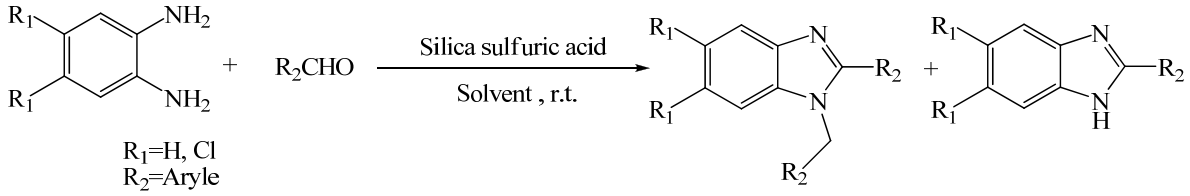


Scheme 1.18

1.2.1.8. Silica sulfuric acid

Salehi et al.[31] reported a synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles in ethanol and water. When *o*-phenylenediamine derivatives and aromaticaldehydes in the presence of silica sulfuric acid and different organic solvents, were allowed to react at

room temperature, both expected products were obtained whose ratios depended on the nature of the solvent (Scheme 1.19).



Scheme 1.19

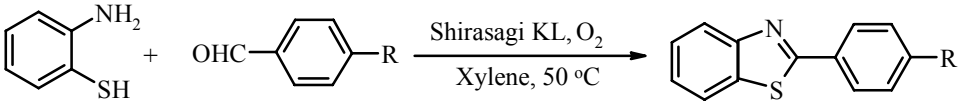
1.3. Benzothiazoles

The benzothiazole contain a phenyl ring fused to a thiazole ring, being a heterocyclic compound, benzothiazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Its aromaticity makes it relatively stable, although as a heterocyclic, it has reactive sites which allow for functionalization. Many dyes, such as thioflavin, and pharmaceutical drugs, such as riluzole, have benzothiazoles as a structural motif. We present here a review of some current methods for obtaining benzothiazole derivatives.

1.3.1. Synthesis of Benzothiazoles

1.3.1.1. Shirasagi KL/O_2

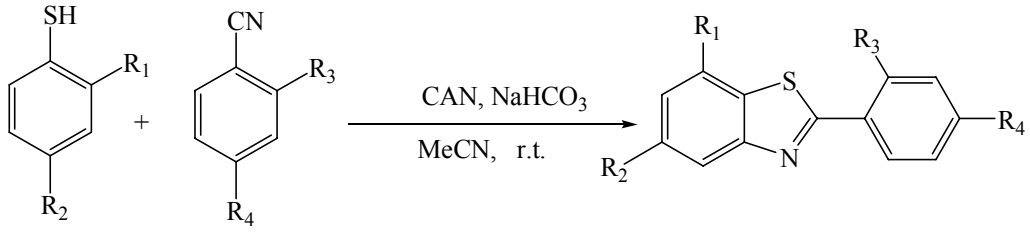
Yuka et al.[32] found that a variety of 4-substituted benzaldehydes reacted with 2-aminobenzenethiol to produce the corresponding 2-arylbenzothiazoles in the presence of activated carbon under oxygen atmosphere (Scheme1.20).



Scheme 1.20

1.3.1.2 CAN

Tale et al.[33] reported cyclization of the intermediate radical formed after initial oxidative coupling between thiophenols and aromatic nitriles leads to the synthesis of a wide range of 2-arylbenzothiazoles (Scheme1.21).

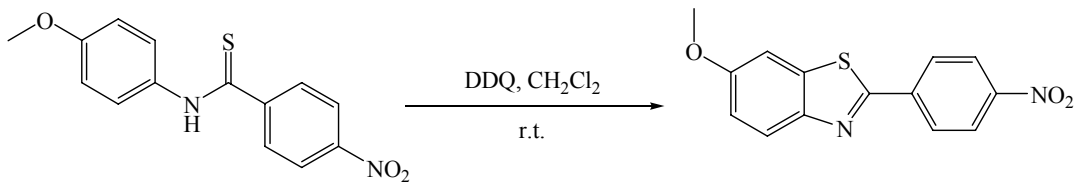


R_1, R_2, R_3, R_4=H, Cl, Br

Scheme 1.21

1.3.1.3. DDQ

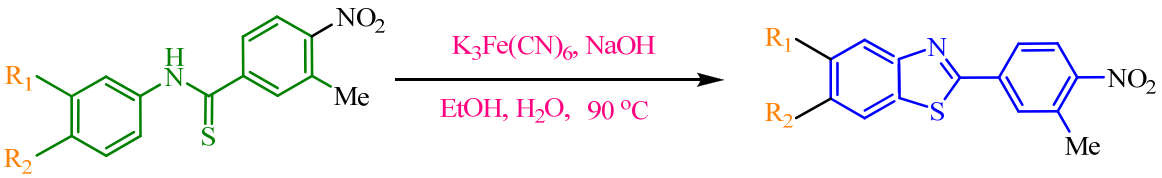
Bose et al.[34] reported a practical method for the synthesis of 2-substituted benzothiazoles *via* the intermolecular cyclization of thioformanilides using DDQ in CH_2Cl_2 at ambient temperature (Scheme1.22).



Scheme 1.22

1.3.1.4. $K_3Fe(CN)_6$

Westwell et al.[35] described the regiospecific synthesis of a range of antitumour 2-arylbenzothiazoles. In this procedure a bromine atom situated ortho to the anilido nitrogen is used to direct a regiospecific cyclisation where, in the absence of bromine, a mixture of regioisomers is produced. The chemistry described is applicable to the synthesis of 2-arylbenzothiazoles bearing both electron-withdrawing and electron-donating substituents on the aryl ring (Scheme 1.23).



R_1, R_2 = H, F

Scheme 1.23

1.4. Surfactant

1.4.1. Introduction

The term surfactant is a blend of "**surf**ace **act**ive **a**g**ent**". Surfactants find applications in almost every chemical industry, such as in detergents, paints, dyestuffs, paper coatings, inks, plastics and fibers, personal care and cosmetics, agrochemicals, pharmaceuticals, food processing, etc. In addition, they play a vital role in the oil industry, e.g. in enhanced and tertiary oil recovery, oil slick dispersion for environmental protection, among others.[36]

1.4.2. Surfactants are Amphiphilic

Surfactants are amphipathic molecules that consist of a non-polar hydrophobic portion, usually a straight or branched hydrocarbon or fluorocarbon chain containing 8–18 carbon atoms, which is attached to a polar or ionic portion (hydrophilic). The hydrocarbon chain interacts weakly with the water molecules in an aqueous environment, whereas the polar or ionic head group interacts strongly with water molecules *via* dipole or ion–dipole interactions[36] (Fig. 1.6).

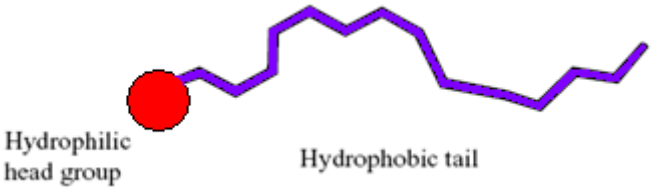


Figure 1.6

1.4.3. General Classification of Surfactants

A surfactant can be classified by the presence of formally charged groups in its head. A non-ionic surfactant has no charge groups in its head. The head of an ionic surfactant carries a net charge. If the charge is negative, the surfactant is more specifically called anionic; if the charge is positive, it is called cationic. If a surfactant contains a head with two oppositely charged groups, it is termed zwitterionic.[36]

1.4.3.1. Anionic Surfactants

These are the most widely used class of surfactants in industrial applications due to their relatively low cost of manufacture and they are used in practically every introduction type of detergent. The hydrophobic chain is a linear alkyl group with a chain length in the region of 12–16 carbon atoms. The most commonly used hydrophilic groups are carboxylates, sulphates, sulphonates and phosphates[36] (Fig 1.7).

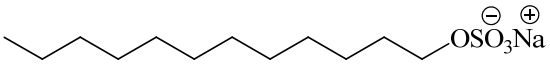


Figure 1.7

1.4.3.2. Cationic surfactants

The vast majority of cationic surfactants are based on the nitrogen atom carrying the cationic charge. Both amine and quaternary ammonium-based products are common. Fatty diamine salt a one type of cationic surfactant[36](Fig 1.8).

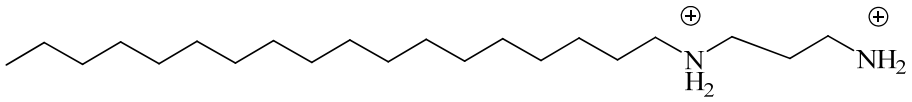


Figure 1.8

1.4.3.3. Zwitterionic surfactants

Zwitterionic surfactant contains two charged groups of different sign. Whereas the positive charge is almost invariably ammonium, the source of negative charge may vary, although carboxylat is by far the most common. *Betaine* is a type of zwitterionic surfactant [36](Fig 1.9).

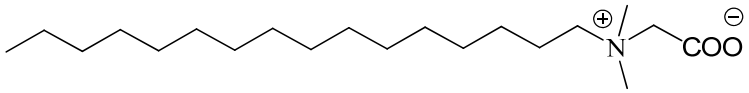


Figure 1.9

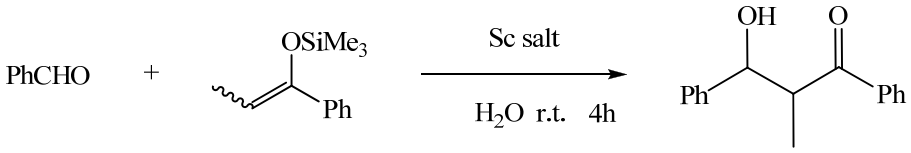
1.4.4. Surfactant-type catalysts in organic reactions

One of the biggest challenges in modern chemistry is to find environmentally friendly processes while carrying out already known chemical reactions. On the other hand, acid- and base catalysed reactions are by far the most numerous and best-studied reaction types, in which organic functional groups undergo an array of different transformations with nucleophilic reagents in the presence of acids or bases as catalysts. It is a widely accepted belief, however that Lewis acid-catalysed reactions must be carried out in the absence of water or even under strictly anhydrous conditions. Very frequently, the presence of even trace quantities of water stops the Lewis acid-catalysed reaction completely, because the most common Lewis acid catalysts react immediately with water and instantaneously or progressively decompose to form hydroxides or oxides, losing immediately or gradually their Lewis acid activity. The hydrolysis of anhydrous metal halides such as $AlCl_3$, $TiCl_4$, and BCl_3 is a paradigmatic example of the dramatic negative influence of the presence of water. Recently, various kinds of protonic and Lewis acids have been found to retain that catalytic activities in aqueous media and, in particular, many of them are not only compatible with water, but are also activated by water. Sodium dodecyl sulfate (SDS, a surfactant) acts both as a Lewis acid to catalyse the reaction and as a surfactant to solubilise organic substrates in water. An intriguing means of achieving aqueous solubility is by using surfactant. When the concentration of surfactant monomer exceeds a certain critical value (critical micelle concentration, CMC), micellization occurs. Micelles are spherical arrangements of surfactant monomers with a highly hydrophobic interior of the micelle, moderately polar locate themselves closer to the polar surface, while distinctly polar solutes will be found at the surface of the micelle. We present here a review of some application of surfactant in organic reaction.

1.4.4.1. $Sc(DS)_3$

Kobayashi et al.[39] reported $Sc(DS)_3$ as catalyst in aldol reaction. In this case, aldol reactions of silyl enol ethers with aldehyds proceeded smoothly in water without using any

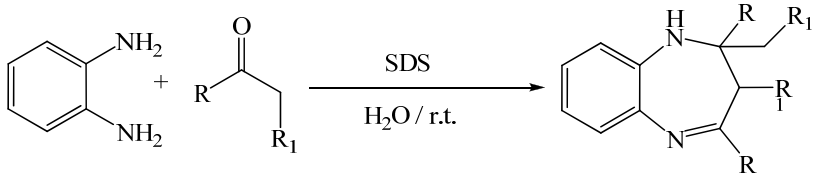
organic solvents. It was also found that $Sc(DS)_3$ worked well in water rather than in organic solvents (Scheme 1.24).



Scheme 1.24

1.4.4.2. SDS/H_2O

Sharma et al.[40] used SDS in water as a Brønsted acid catalyst in the condensation reaction of *o*-phenylenediamine with ketones having an α-hydrogen, leading to the product 1,5-benzodiazepines in a water medium at ambient temperature in high yields (Scheme 1.25).

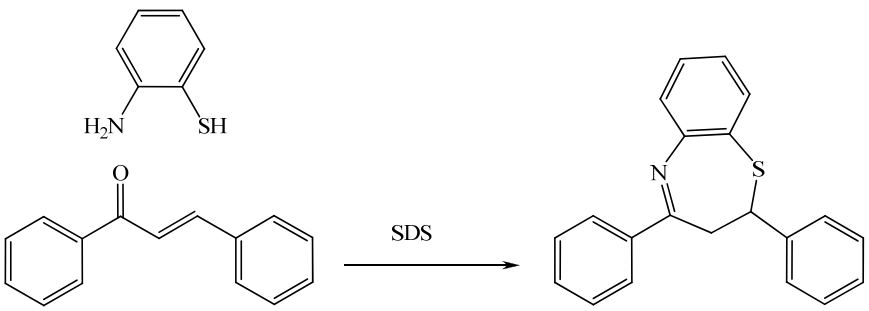


R, R_1= Alkyl, aryl, H

Scheme 1.25

1.4.4.3. SDS

Kumar et al.[41] reported a new synthesis of 1,3-diaryl-2,3-dihydro-1,5 benzothiazepines by the reaction of various 1,3-diaryl-2-propenones with 2-aminothiophenol in water under neutral conditions catalyzed by SDS (Scheme 1.26).



Scheme 1.26