PART I

CHAPTER III

“MICROWAVE MEDIATED SOLVENT FREE SYNTHESIS OF
2-ARYLIMIDAZOLINES AND 2-ARYLBENZIMIDAZOLES FROM
ALDEHYDES USING A SOLID BASE CATALYST”
Chapter III

MICROWAVE MEDIATED SOLVENT FREE SYNTHESIS OF 2-ARYLIMIDAZOLINES AND 2-ARYLBENZIMIDAZOLES FROM ALDEHYDES USING A SOLID BASE CATALYST

Introduction:

Heterocycles form by far the largest group of compounds in the classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocycles while countless of additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in a defined three dimensional representation.

The importance of imidazoline and benzimidazole units arises because they are found in many biologically active compounds. In organic synthesis, imidazoline units are also used as synthetic intermediates, chiral auxiliaries, chiral catalysis and ligands for asymmetric catalysis. In addition, the benzimidazole moiety is found in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including anti-ulcer, anti-tumor and anti-viral effects.

Biological and medicinal importance of Imidazolines and Benzimidazoles-

While imidazoline binding sites have only recently been discovered and their pharmacological role is still being elucidated, there is a growing body of evidence to suggest that they could be important therapeutic targets for a number of conditions.

Mammalian imidazoline binding sites can be divided into two main subtypes (I₁ and I₂), although evidence exists for a further two. It has been proposed that I₁ site mediates the antihypertensive effects of rilemenidine(Fig.III.1) and moxonidine(Fig.III.2).
It has also been found that certain β-carolines bind with high affinity and selectivity for the imidazoline sites\(^8\) e.g. β-caroline hormone was reported to produce hypotension in the rat, due to an effect attributed to activity at \(I_1\) sites\(^9\).

After the discovery of the antineoplastic properties of cis-dichloro diammine platinum(II), complexes like 2-aminomethyl benzimidazole(Fig.III.3), 2-(β-aminoethyl)benzimidazole(Fig.III.4) and 2-(α-aminoethyl) benzimidazole(Fig.III.5) with Pt(II) and Pd(II) have been prepared and were tested for antineoplastic activity both in cultures of neoplastic cells and in vivo in rodents bearing L-1210 leukemia\(^10\).

Many derivatives of imidazole and benzimidazole exhibited pharmacological properties, like 2-substituted benzimidazole drug Cytostasan(Fig.III.6) which showed considerable anti tumor activity\(^11\).
Chapter III

Compound [2-Di-(2-chloroethyl)aminomethyl] benzimidazole shows antitumor activity against Ehrlish, S 180, 755, and EO 771 tumor cells\textsuperscript{12} (Scheme III.7)

Similarly, compound with the following structure have potent antitumor activity against sarcoma-180 cells\textsuperscript{13} (Fig. III.8).

It has been found that chronic stimulation of sympathetic nervous activity contributes to the development and maintenance of hypertension, leading to left ventricular hypertrophy (LVH), arrhythmias and cardiac death. Moxonidine, the antihypertensive compound preferentially activates imidazoline receptors in brainstem rostroentrolateral medulla, suppresses sympathetic activation and reverse LVH\textsuperscript{14}. Again, Imidazoline $\alpha_2$-antagonist drugs such as efaroxan have been shown to increase the insulin secretory response to sulphonlureas from rat pancreatic $\beta$-cells\textsuperscript{15}. It has also been observed that gallium complexes, dichloro-(2-$\alpha$-oxybenzylidimazolato-N,O)gallium(III) and trans-dichlorotetras(benimidazole)gallium(III) chloride were active in the in vitro anti-HIV test\textsuperscript{16}.
Synthesis of Imidazolines and Benzimidazoles - a review:

Some methods of synthesis of 2-imidazolines include synthesis from nitriles\textsuperscript{17}, carboxylic acids\textsuperscript{18}, esters\textsuperscript{19}, ortho-esters\textsuperscript{20}, hydroxyamides\textsuperscript{21} and mono- or di- substituted chlorodicyanovinyl benzene\textsuperscript{22}. The microwave irradiation of benzonitriles, ethylenediamine and sulfur is also reported for the synthesis of 2-Imidazolines\textsuperscript{23}. Some special starting materials like azalactones\textsuperscript{24}, 2-aryl-1,1-dibromoethanes\textsuperscript{25} and amino amides\textsuperscript{26} has also been reported.

**Synthesis of Imidazolines:**

Although the most widely used methods of preparing 2-Imidazolines involve ring closure of 1,2-diamines or 1.2-diamine derivatives with carboxylic acids or derivatives of these acids, this heterocyclic ring system may be formed by several other synthetic approaches.

1. From 1, 2-diamines

(a) By reaction with monocarboxylic acids

A number of 1, 2-substituted-4,4-dimethyl-2-imidazolines have been prepared by heating 1,2-diamines containing one primary and one secondary amino group with organic acids in the presence of benzene(Scheme III.1). The mixtures were heated under conditions to remove water by azeotropic distillation\textsuperscript{27,28}.

\[ \text{NH}_2\text{C(CH}_3\text{)}_2\text{NHR} + \text{R'COOH} \xrightarrow{\text{benzene}} \text{H}_2\text{C-} \text{NR} + (\text{H}_3\text{C})_2\text{C-} \text{CR'} + 2\text{H}_2\text{O} \]

Scheme III.1

Aliphatic and aromatic carboxylic acids can be readily converted in one reaction step into their corresponding imidazolines by reaction with diamines in the presence of 3 equivalents each of triphenyl phosphine, triethylamine, diisopropylethylamine or DBU and excess CCl\textsubscript{4} in acetonitrile or better in acetonitrile-pyridine(1:1) at room temperature\textsuperscript{29}(Scheme III.2).
(b) By reaction with dicarboxylic acids

1,2-Diamines containing one primary and one secondary amino group have been found to react with dibasic acids containing four or more carbon atoms to give bisimidazolines and their molecular complexes with the dibasic acids (Scheme III.3).

Scheme III.3
Chawla \(^{31}\) reported that di- or polycarboxylic acids react at temperatures of about 280\(^\circ\)C with a mixture of 1,2-diamines and their salts in the presence of strong mineral acids to yield products containing more than one 2-imidazoline ring per molecule.

(c) By reaction with esters

2-Imidazolines may be prepared in 60-70 per cent yields by refluxing ethylenediamine with an ester and removing the alcohol and water formed by distillation\(^{32}\). Pachter and Riebsomer \(^{33}\) found that cyanoacetic ester reacts with N-(2-aminoisobutyl)isopropylamine to produce 2-cyanomethyl-2-imidazoline (Scheme III.4).
Chapter III

\[ C_2H_5OOCCH_2CN + NH_2C(CH_3)_2CH_2NHCH(CH_3)_2 \rightarrow H_2C-NCH(CH_3)_2 \]

\[ (H_3C)_2C-CCH_2CN + C_2H_5OH + H_2O \]

Scheme III.4

(d) By reaction with imino-ethers

The heating of iminoalkyl ethers or their hydrochlorides with 1,2-diamines is a satisfactory method of preparing 2-imidazolines\(^{34}\) (Scheme III.5).

\[ CR\text{NH.HCl} + CH_2NH_2 \rightarrow H_2C-NH \]

\[ + NH_3 + H_2O \]

\[ + NH_4Cl + R'OH \]

Scheme III.5

(e) By reaction with amides

Arylacetamides have been treated in the absence of mineral acids or condensing agents with an excess of anhydrous ethylenediamine at 150-200°C to yield 2-imidazolines\(^{35}\) (Scheme III.6).

\[ CH_2NH_2 + CH_2NH_2 \rightarrow H_2C-NH \]

\[ + NH_3 + H_2O \]

Scheme III.6

(f) By reaction with nitriles

It has been shown that 2-substituted-2-imidazolines may be prepared in excellent yields (often 90 per cent) by heating aromatic or aliphatic nitriles and the salts of 1,2-diamines at 140-250°C\(^{36}\) (Scheme III.7).
Chapter III

(g) By reaction with amidines and guanidines

It has been shown that N-substituted amidine salts may be heated with 1,2-diamines to yield 2-imidazolines and ammonia$^{37}$ (Scheme III.8). This is in accord with the suggestion that amidines may be intermediates in some of the reactions of nitriles and salts of 1,2-diamines to form 2-imidazolines$^{36}$.

![Scheme III.7]

2. From carbonyl-containing compounds and ammonia:

Aromatic aldehydes react with ammonia to yield hydroamides which may be cyclized on heating to 2,4,5-triaryl-2-imidazolines$^{36,39}$.

![Scheme III.8]

![Scheme III.9]
3. Miscellaneous syntheses:

Benzamidine hydrochloride has been reported to react in aqueous sodium acetate with glyoxals, such as dimethylglyoxal or phenylglyoxal, to yield 2-imidazoline derivatives (Scheme III.10). These compounds are precipitated as the hydrochlorides by adding an excess of hydrochloric acid.

\[
\text{COR'} + \text{NH}_2\text{HCl} \rightarrow \text{R'(HO)C} \equiv \text{NH. HCl}
\]

Scheme III.10

2-Imidazolines have been prepared in yields as high as 94 per cent by the monoacetyl derivatives of α-aminonitriles (Scheme III.11).

\[
\text{CN} \quad \text{R}(\text{R'})\text{C} \equiv \text{CCH}_3 \quad \text{H}_2 \quad \text{Raney nickel} \quad \text{H}_2\text{C} \equiv \text{NH} \quad \text{R}(\text{R'})\text{C} \equiv \text{CCH}_3
\]

Scheme III.11

Some recent methods of 2-Imidazolines synthesis:

In an efficient one pot synthesis of Imidazoline, the first condensation of aldehydes and diamines form aminals without any catalyst in CH\(_2\)Cl\(_2\). Next the addition of N-bromosuccinimide (NBS) oxidizes them to afford imidazolines in the one-pot operation (Scheme III.12).

\[
\text{RCHO} \quad \text{H}_2\text{N} \quad \text{NH}_2 \quad \text{CH}_2\text{Cl}_2 \quad \text{H}_2\text{N} \quad \text{NH}_2 \quad \text{R}\text{C} \equiv \text{N} \quad \text{R}\text{C} \equiv \text{N} \quad \text{R}\text{C} \equiv \text{N}
\]

Scheme III.12
In its modified version TBME has been used in place of CH$_2$Cl$_2$, a more environmentally friendly solvent (Scheme III.13).

\[
\text{Ph-CHO} \xrightarrow{H_2N \text{ NH}_2 \text{ (1.05 eq)}} \text{ then NBS (1.05 eq)} \xrightarrow{\text{ solvent (0.1 M), } 0^\circ \text{C-rt}} \]

**Scheme III.13**

This method could be applied to various aromatic and aliphatic aldehydes and N-nonsubstituted and N-monosubstituted 1,2-diamines (Scheme III.14).

\[
\text{R-CHO} \xrightarrow{H_2N \text{ NH}_2 \text{ (1.05 eq)}} \text{ then NBS (1.05 eq)} \xrightarrow{\text{ solvent (0.1 M), } 0^\circ \text{C-rt}} \]

**Scheme III.14**

Iodine has been used extensively as a synthetic reagent due to its inherent properties of low toxicity, electrophilicity and easy handling. Konwar et al found that the system I$_2$/KI/K$_2$CO$_3$/H$_2$O oxidizes carbon-nitrogen bonds for the synthesis of imidazolines and benzimidazoles from aldehydes and diamines under anaerobic conditions in water at 90°C with excellent yields (Scheme III.15).

\[
\text{R-CHO} \xrightarrow{\text{I}_2/\text{KI/K}_2\text{CO}_3/\text{H}_2\text{O}} \]

**Scheme III.15**
Pawar et al reported for the first time the microwave irradiation of different nitriles with ethylenediamine in presence of solvent carbon disulfide afforded the corresponding 2-Imidazolines\textsuperscript{47}(Scheme III.16). The yields of product obtained using this protocol is significantly high and the reaction time is reduced.

\[ \text{R-CN} \xrightarrow{\text{H}_2\text{N}-\text{CH}_2-\text{NH}_2, \text{CS}_2, \text{MW}} \text{N} \]

\textbf{Scheme III.16}

\( \alpha \)-aminohydrazone derivatives undergo a novel copper(I) promoted reaction to give 1-ureido-2-imidazolines\textsuperscript{48}. Those \( \alpha \)-aminohydrazone derivatives can be obtained by the 1,4-addition of sarcosine or glycine ethyl ester on 1,2-diaza-1,3-butadines.

\[ \text{R}^1\text{O} \xrightarrow{\text{THF, CuI, O}_2, \text{rt, 1h}} \text{N} \]

\textbf{Scheme III.17}

\textbf{Synthesis of Benzimidazoles:}

While many strategies are available for benzimidazole synthesis there are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids or their derivatives(nitriles, imidates, or orthoesters) which often requires strong acidic conditions, and sometimes combines with very high temperature or microwave irradiation. 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.
Chapter III

A. From Reactions of o-Aryl Diamines with Carbonyl-Containing Compounds, Imidates, and Miscellaneous Compounds

Synthetic methods leading to benzimidazoles from the reaction of o-aryl diamines with carboxylic acids or their derivatives are widely applicable. Phillips-type reactions can be effected by heating the diamine with the carboxylic acid in hydrochloric acid. Also polyphosphoric acid was found to be more suitable reaction medium. One problem concerning the Phillips reaction is that the diamine often competes successfully for the proton of the acid catalyst, hence inhibiting nucleophilic addition to the carbonyl group. This problem is alleviated by replacing the carbonyl group by the more basic imino group such as imino ethers (imidates).

A skeletal rearrangement is probably also involved in the reaction of o-phenylenediamine with 2-bromocyclobutanone which produces 2-cyclopropylbenzimidazole (Scheme III.18).

B. From o-Nitroarylamines and o-Dinitroarenes

The acid-catalyzed cyclization of N-(o-nitroanilino)-substituted aliphatic amines to N-aminobenzimidazoles gives fair yield under reflux conditions in aqueous hydrochloric acid (Scheme III.19).
Chapter III

C. From o-(N-Acylamino and -arylamino)arylamines and -Nitrobenzenes

Formation of the tricyclic derivatives from N-substituted heterocycles by heating in polyphosphoric acid is important\(^5\)(Scheme III.20). The best yields of benzimidazoles are obtained from piperidine derivatives and acetyl derivatives.

![Scheme III.20](image)

This type of reaction cannot be extended to other heterocycles such as morpholines and piperazines. The mechanism is thought to involve a Friedel-Crafts cyclization of an intermediate alkene.

D. From N-Benzylidene-2-nitro- and 2-Azidoanilines

N-Benzylidene-2-nitroaniline derivatives are converted into 2-phenyl benzimidazoles by reductive cyclization using triethyl phosphite with higher yields than obtained using the classical methods\(^4\)(Scheme III.21).

![Scheme III.21](image)

E. From Amidines and Related Compounds

The formation of benzimidazoles from N-arylamidines was first reported by Partridge and Turner\(^5\) who obtained them by allowing the hydroxy derivatives to react with benzenesulfonyl chloride in pyridine or triethylamine under anhydrous conditions(Scheme III.22).
F. From Heterocyclic Compounds

1. From Five-Membered Ring Heterocycles:

The formation of benzimidazoles by photolysis of tetrazoles was first noted by Moriarty and Kliegman\textsuperscript{57} who obtained 2-phenylbenzimidazole in 42\% yield by photolysis of 1,5-diphenyltetrazole(Scheme III.24).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {R=PhO};
\node (b) at (1,0) {\text{uv light}};
\node (c) at (2,0) {Ph\textsubscript{2}NPh} [draw, circle, inner sep=0pt, minimum size=0.5cm];
\node (d) at (4,0) {Ph\textsubscript{2}NPh} [draw, circle, inner sep=0pt, minimum size=0.5cm];
\node (e) at (5,0) {\text{OH}^{-}};
\node (f) at (6,0) {Ph\textsubscript{2}NPh} [draw, circle, inner sep=0pt, minimum size=0.5cm];
\node (g) at (7,0) {\text{Ph-Ph}};
\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (b) -- (d);
\draw[->] (b) -- (e);
\draw[->] (e) -- (f);
\draw[->] (f) -- (g);
\end{tikzpicture}
\end{center}

Scheme III.24

2. From Six-Membered Ring Heterocycles

2-(4-Thiazolyl) benzimidazoles are formed\textsuperscript{58} by reduction of the benzotriazine 1-oxides using a number of methods including zinc/acetic acid or platinum oxide in ethanol(Scheme III.25).
Some recent development in benzimidazole synthesis:

Cyclocondensation of N-(trifluoroacetamidoo)-o-arylenediamines leads to a series of 2-trifluoromethyl-aryl-imidazoles with good yields on montmorillonite K10 in dry media under microwave irradiation within 2 min\(^5\) (Scheme III.26)

Addition of oxone to a mixture of a 1,2-phenylenediamine and an aldehyde in wet DMF results in rapid formation of benzimidazoles under very mild conditions\(^6\) (Scheme III.27). Products were isolated with 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.

A simple and efficient procedure for the synthesis of substituted benzimidazoles through a one pot condensation of o-phenylenediamines with
aryl aldehydes in the presence of $\text{H}_2\text{O}_2$ and $\text{HCl}$ in acetonitrile at room temperature features short reaction time, easy and quick isolation of the products and excellent yields$^{61}$ (Scheme III.28).

$$\text{R NH}_2 + \text{HAr} \xrightarrow{7\text{eq H}_2\text{O}_2 (30\% \text{ in H}_2\text{O})} \text{MeCN, rt, 30-50 min} \xrightarrow{3.5\text{eq HCl (30\% in H}_2\text{O})} \text{R Ar}$$

Scheme III.28

Various 2-arylbenzimidazoles were synthesized from phenylenediamines and aldehydes via a one step process using hypervalent iodine as oxidant$^{62}$ (Scheme III.29). This method features mild condition, short reaction time, high yields and simple procedure.

$$\text{R NH}_2 + \text{HAr} \xrightarrow{1.5 \text{eq PhI(OAc)}_2} \text{dioxane, rt, 3-5 min} \xrightarrow{} \text{R Ar}$$

Scheme III.29

2-substituted benzimidazoles have been synthesized in excellent yields in a single pot by cyclodehydration of N-acyl-1,2-phenylene diamines prepared in situ from the corresponding 1,2-phenylenediamines and an acid chloride$^{63}$ (Scheme III.30). BF$_3$.Et$_2$O acts both as cyclodehydrating and deacylating agent.

$$\text{R}_1\text{NH}_2 + \text{R}_2\text{NH}_2 \xrightarrow{(i) \text{RCocl}} \xrightarrow{(ii) \text{BF}_3$.Et$_2$O} \text{R}_1\text{R}_2$$

Scheme III.30

Direct one step synthesis of various benzimidazoles from phenylenediamines and aldehydes is described by Lin et al$^{64}$ using air as the oxidant (Scheme III.31). The reaction is simple without any commercial oxidants
with easy purification. 2-alkenylbenzimidazoles can also be prepared by this method.

\[
\begin{align*}
\text{NH}_2 & + \text{H} & \xrightarrow{\text{air, solvent, reflux on 100°C}} & \text{N} \\
\text{NH}_2 & & & \text{N} \\
\end{align*}
\]

Scheme III.31

The novel solution phase synthesis of an array of biologically relevant benzimidazoles in a simple two step procedure is revealed by Hulme et al (Scheme III.32). The transformation was carried out in excellent yield by condensation of mono-Boc protected ortho-phenylenediamine and supporting Ugi reaction. Subsequent acid treatment and evaporation give high yields of benzimidazoles.

\[
\begin{align*}
\text{COOH} & + \text{NH}_2 & \xrightarrow{\text{MeOH}} & \text{N} \\
\text{AM} & + \text{COOH} & & \text{N} \\
\text{Boc} & & & \text{N} \\
\end{align*}
\]

Scheme III.32

Reaction of o-phenylenediamine and aldehydes (1: 1.1 ratio) in the presence of a catalytic amount (5mol%) of In(OTf)₃ at room temperature results 2-substituted benzimidazoles (Scheme III.33).

\[
\begin{align*}
\text{NH}_2 & + \xrightarrow{\text{In(OTf)₃}} \text{N} \\
\text{NH}_2 & & \text{R} \\
\end{align*}
\]

Scheme III.33
Ceric ammonium nitrate could also be used in the synthesis of both 2-imidazolines as well as 2-benzimidazoles\textsuperscript{67}. When aldehydes and 1,2-diamines were stirred in dichloromethane under reflux at 50°C for 15 min in presence of CAN, the corresponding imidazolines and benzimidazoles were obtained in good yields (Scheme III.34).

\[
\begin{align*}
\text{R-CHO} &\xrightarrow{\text{CAN(0.5 mol)}} \text{imidazoline} \\
\text{NH}_2 &\quad \text{NH}_2 \\
\text{NH}_2 &\quad \text{NH}_2
\end{align*}
\]

Scheme III.34

Wang et al\textsuperscript{68} reported the synthesis of 2-arylbenzimidazoles from aromatic carboxylic acids and o-phenylenediamine under MW irradiation (Scheme III.35). The reaction proceeded efficiently in the presence of catalytic amounts of hydrochloric acid and was complete within 10 min under solvent free and MW assisted condition.

\[
\begin{align*}
\text{R} &\xrightarrow{\text{MW, solvent free, Acid}} \text{benzimidazole} \\
\text{NH}_2 &\quad \text{NH}_2 \\
\text{HO} &\quad \text{CO}
\end{align*}
\]

Scheme III.35

Similarly, Niknam et al. have reported the synthesis of benzimidazoles by the reaction of 0-phenylenediamine and carboxylic acids in the presence of AMA under microwave irradiation\textsuperscript{69} (Scheme III.37). In addition, by this method some new bis-benzimidazoles from the direct reaction phenylenediamine and dicarboxylic acid under microwave irradiation in good to excellent yield is described.
Physical properties of 2-Imidazolines and 2-Benzimidazoles:

2-Imidazolines unsubstituted at the nitrogen of the 1-position show a greater solubility in polar solvents than the 1-alkyl or 1-aryl substituted derivatives. Again, the solubility of 2-substituted 2-Imidazolines in polar solvents decreases with increasing length of the 2-substituted alkyl group. 2-Imidazolines which are unsubstituted in the 1-position are solids or heavy viscous oils, while compounds substituted in this position are most frequently liquids. Ultraviolet absorption spectrum studies of 2-imidazolines shows the presence of the carbon-to-nitrogen double bond. Benzimidazoles with the imide nitrogen (i.e. hydrogen in the 1-position) are usually more soluble in polar solvents and less soluble in organic solvents. With the introduction of other non-polar substituents in various positions of the benzimidazole ring, the solubility in nonpolar solvents is increased. Benzimidazole, for example, is soluble in hot water whereas 2-methyl benzimidazole is easily soluble in ether. Benzimidazoles are weakly basic, in general soluble in dilute acids. They are also sufficiently acidic to be generally soluble in aqueous alkali and form N-metallic compounds. The IR and UV spectra indicate the presence of an amide linkage in these substances.

Solvent free synthesis of 2-arylimidazolines and 2-arylbenzimidazoles using solid base Al₂O₃-OK:

In the study, a simple and convenient procedure for the synthesis of 2-arylimidazolines and 2-arylbenzimidazoles from aromatic aldehydes under solvent free condition using microwave irradiation is described. The imidazolines were synthesized using the solid base Al₂O₃-OK, earlier reported by Li et al., and prepared by fusing a mixture of KNO₃ and Al₂O₃ at 600°C. When the loading of the KNO₃ is above the threshold, only about 7% of KNO₃ can be dispersed...
Chapter III

General procedure:

1. Preparation of the solid base: 26 g KNO₃ and 74 g Al₂O₃ were crushed in a mortar and then added appropriate (5-10 ml) deionised water which can be absorbed by Al₂O₃. After grounding, the mixture was dried at 110°C for 1hr and then activated at 600°C for 3hr.

2. Preparation of the 2-arylimidazolines and 2-arylbenzimidazoles under microwave: 1mmol of the aromatic aldehyde was mixed with 2 mmol (0.138 ml) of ethylene diamine/ o-phenylenediamine and 2 g of the solid base was thoroughly mixed and ground in a pestal grinder to a free flowing homogeneous powder. This mixture was exposed to microwave radiation at 750 W power for 2-3 minutes. The product was recovered by extraction with 10 ml of ethanol and the crude product was recovered by the reduced pressure distillation of the solvent in a rotavapor. The crude products were purified by column chromatography in silica gel column and 20% ethylacetate: petroleum ether (40-60) as the eluent.

The 2-arylimidazolines and Benzimidazoles thus obtained were identified by recording their melting points and by spectroscopic means. The physical characteristics are shown in table III.1 and table III.2.
through the interaction with Al₂O₃ supported and decomposed in a mild pre-treatment such as evacuation at room temperature, while a lot of undispersed KNO₃ located in the pores of Al₂O₃ forms a new phase such as K₂[Al(NO₃)₃]. Both the residual KNO₃ and K₂[Al(NO₃)₃] decompose during evacuation at 600°C and potassium ion migrate from the inner to the external surface of Al₂O₃. Consequently, several layers of base materials such as K₂O overlap on the Al₂O₃ resulting in the formation of some super basic sites. The Scanning Electron Micrograph (SEM) of the solid base Al₂O₃-OK is shown.

The experiments carried out are summarized as shown in the Scheme III.37 and results were summarized in table III.1 and table III.2.

![Scheme III.37](image)

Solid base have never been used as a catalyst for the synthesis of 2-Imidazolines and 2-Benzimidazoles. This method therefore appears to be an improvement over methods reported earlier.

**Experimental:**

The solid base was prepared according to the reported procedure. All chemicals used were procured from Merck Inc. (India). Melting points were determined in a melting point apparatus from scientific devices, India, Type MP-D in open capillaries and are uncorrected. ¹H NMR spectra were recorded on a Varian FT 400Mz spectrometer using TMS as the internal standard, IR spectra recorded on KBr pallets on Perkin Elmer 1600 FT IR spectrometer and UV spectra on Hitachi 3210 spectrometer. Microwave reactor used was procured from catalyst (India) Pvt. Ltd., Pune, India.
### Table III.1

Microwave mediated Solvent free synthesis of 2-arylimidazolines using solid base catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Mp (°C)</th>
<th>Exposure time (min)</th>
<th>Yield (%)</th>
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<td></td>
<td></td>
<td>obs</td>
<td>lit</td>
<td></td>
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<tr>
<td>1</td>
<td>NO₂</td>
<td>224</td>
<td>231</td>
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<tr>
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<td>CH₃</td>
<td>180</td>
<td>181-82</td>
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<tr>
<td>3</td>
<td>(CH₃)₂N</td>
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<td>258-260</td>
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<td>MeO</td>
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<td>110</td>
<td>108</td>
<td>2.5</td>
</tr>
<tr>
<td>11</td>
<td>O₂</td>
<td>165</td>
<td>161</td>
<td>2</td>
</tr>
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Microwave mediated Solvent free synthesis of 2-arylbenzimidazoles using solid base catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Mp (°C)</th>
<th>Exposure time (min)</th>
<th>Yield (%)</th>
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<td>obs</td>
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<tr>
<td>1</td>
<td>CH₃</td>
<td>261-263</td>
<td>270°⁰⁴</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>oil</td>
<td>234°⁰⁴</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
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<td>294°⁰⁶</td>
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<td>292°⁰⁶</td>
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<td>235-236°⁰⁵</td>
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<tr>
<td>6</td>
<td>Br</td>
<td>oil</td>
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<tr>
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<td>NO₂</td>
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<td>316°⁰⁶</td>
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<tr>
<td>8</td>
<td>(CH₃)₂N</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>O₂N</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>NO₂</td>
<td>-</td>
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Some spectral characteristics of the 2-imidazolines

Product 1: 2-(p-nitrophenyl)imidazoline: IR(KBr): $cm^{-1}$ 3185.9(NH), 1582.2(\(>\text{C}=\text{N}\))

$^1H$ NMR(400Mz, DMSO-$d_6$): $\delta$ 8.04(broad s, NH), 7.4(m, aromatic) 4.4(d, 2H), 3.6(d, 2H)

Elemental analysis

<table>
<thead>
<tr>
<th>M. F.</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_6$H$_9$N$_3$O$_2$ (191.19)</td>
<td>C 56.5</td>
<td>56.3</td>
</tr>
<tr>
<td></td>
<td>H 4.75</td>
<td>4.74</td>
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</table>

Product 2: 2-(p-tolyl)imidazoline: IR(KBr): $cm^{-1}$ 3310(N-H), 1645(\(>\text{C}=\text{N}\)), 1560, 1450,

$^1H$ NMR(400Mz, DMSO-$d_6$): $\delta$ 8.1(broad s, NH), 7.6(m, aromatic) 4.2(d, 2H), 3.8(d, 2H), 2.35(s, H)

Elemental analysis

<table>
<thead>
<tr>
<th>M. F.</th>
<th>Calculated</th>
<th>Found</th>
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</thead>
<tbody>
<tr>
<td>C$<em>{10}$H$</em>{12}$N$_2$ (160.210)</td>
<td>C 74.9</td>
<td>74.7</td>
</tr>
<tr>
<td></td>
<td>H 7.55</td>
<td>7.53</td>
</tr>
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</table>

Product 3: 2-(N,N'-dimethylaminophenyl)imidazoline: IR(KBr): $cm^{-1}$ 3489(N-H), 1606.3(\(>\text{C}=\text{N}\)),

$^1H$ NMR(400Mz, DMSO-$d_6$): $\delta$ 7.99(broad s, NH), 7.75(d, J=9.2 Hz, 2H), 7.56(d, J=9.2 Hz, 2H), 3.82(s, 6H), 2.99(d, J=4.4 Hz, 2H), 2.85(d, J=6 Hz, 2H)

Elemental analysis

<table>
<thead>
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<th>M. F.</th>
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<tbody>
<tr>
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<td>8.9</td>
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<tr>
<td></td>
<td>N 25.4</td>
<td>25.5</td>
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</table>

Product 4: 2-(3,4-dimethoxyphenyl)imidazoline: IR(KBr): $cm^{-1}$ 3310(N-H), 1665(\(>\text{C}=\text{N}\)),

$^1H$ NMR(400Mz, DMSO-$d_6$): $\delta$ 6.84-7.46(m, 3H), 3.93(s, 3H), 3.92(s, 3H), 3.78(s, 4H)
Chapter III

Product 5: 2-(4-bromophenyl)imidazoline: IR(KBr): cm^{-1} 3410(N-H), 1644(>C=N), 1553, 1440, \(^1\)H NMR(400Mz, DMSO-d$_6$): \(\delta\) 8.5(s, NH), 4.6(d,2H), 3.9 (d,2H), 7.3-7.6(m, aromatic,4H)

Product 6: 2-(p-methoxyphenyl)imidazoline: IR(KBr): cm^{-1} 3520(N-H), 1626(>C=N), 1535, 1410, \(^1\)H NMR(400Mz, DMSO-d$_6$): \(\delta\) 7.9(s, NH), 7.76(d, J=8.8 Hz, 2H), 6.92(d, J=8.8Hz, 2H), 3.8(s, 3H), 3.76(d, J= 3.2Hz, 2H), 3.72(d, J=3.2Hz, 2H)

Product 7: 2-(p-chlorophenyl)imidazoline: IR(KBr): cm^{-1} 3360(N-H), 1672(>C=N), 1585, 1440, \(^1\)H NMR(400Mz, DMSO-d$_6$): \(\delta\) 8.3(s, NH), 4.2(d,2H), 3.75 (d,2H), 7.5-7.8(m, aromatic,4H)

Elemental analysis

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
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</thead>
<tbody>
<tr>
<td>M. F.</td>
<td>C$_9$H$_9$N$_2$Cl</td>
<td></td>
</tr>
<tr>
<td>(180.685)</td>
<td></td>
<td>59.8</td>
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<td></td>
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<tr>
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<td>15.4</td>
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</tbody>
</table>

Product 8: 2-(o-chlorophenyl)imidazoline: IR(KBr): cm^{-1} 3350(N-H), 1672(>C=N), 1560, 1460, \(^1\)H NMR(400Mz, DMSO-d$_6$): \(\delta\) 8.3(s, NH), 4.1(d,2H), 3.8 (d,2H), 7.5-7.8(m, aromatic,4H)

Elemental analysis

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
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<tbody>
<tr>
<td>M. F.</td>
<td>C$_9$H$_9$N$_2$Cl</td>
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<td>(180.685)</td>
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<td>5.03</td>
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<tr>
<td></td>
<td>N</td>
<td>15.6</td>
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</table>

Product 9: 2-phenylimidazoline: IR(KBr): cm^{-1} 1635(>C=N), 1540, 1420 \(^1\)H NMR(400Mz, DMSO-d$_6$): \(\delta\) 8.4(s, NH), 3.8(d,2H), 3.5 (d,2H), 7.2-7.4(m, aromatic,5H)

Product 10: 2-(2,4-dichlorophenyl)imidazoline: IR(KBr): cm^{-1} 1658(>C=N), 1588, 1480, \(^1\)H NMR(400Mz, DMSO-d$_6$): \(\delta\) 8.1(s, NH), 4.2(d,2H), 3.8 (d,2H), 7.5-7.7(m, aromatic,3H)
Some spectral characteristics of the 2-Benzimidazoles:

Product 1: 2-(p-methylphenyl)benzimidazole: IR(KBr): cm\textsuperscript{-1} 3310(N-H), 1615(>C=N), \textsuperscript{1}H NMR(400Mz, DMSO-d\textsubscript{6}): \delta 8.3(broad s, NH), 7.8-7.9(m, aromatic 4H) 7.3-7.5(m, aromatic 4H), 2.38(s,3H)

Product 2: 2-(o-chlorophenyl)benzimidazole: IR(KBr): cm\textsuperscript{-1} 3310(N-H), 1609(>C=N), \textsuperscript{1}H NMR(400Mz, DMSO-d\textsubscript{6}): \delta 8.1(broad s, NH), 7.5-7.8(m, aromatic 4H) 7.1-7.3(m, aromatic 4H)

Product 3: 2-(p-chlorophenyl)benzimidazole: IR(KBr): cm\textsuperscript{-1} 3310(N-H), 1611(>C=N), \textsuperscript{1}H NMR(400Mz, DMSO-d\textsubscript{6}): \delta 8.3(broad s, NH), 7.5-7.8(m, aromatic 4H) 7.3-7.4(m, aromatic 4H)

Product 4: 2-phenylbenzimidazole: IR(KBr): cm\textsuperscript{-1} 3436.1 (N-H), 1595.3(>C=N) \textsuperscript{1}H NMR(400Mz, DMSO-d\textsubscript{6}): \delta 8.2 (broad s, NH), 8.04(s, 1H), 7.58( s,1H), 7.18-7.38(m, aromatic)

Product 5: 2-(p-methoxyphenyl)benzimidazole: IR(KBr): cm\textsuperscript{-1} 3310(N-H), 1608(>C=N), \textsuperscript{1}H NMR(400Mz, DMSO-d\textsubscript{6}): \delta 8.2(broad s, NH), 7.5-7.8(m, aromatic 4H) 7.1-7.3(m, aromatic 4H)

Product 6: 2-(p-bromophenyl)benzimidazole: IR(KBr): cm\textsuperscript{-1} 3283(N-H), 2962 and 2944.5(CH),1609(>C=N), \textsuperscript{1}H NMR(400Mz, DMSO-d\textsubscript{6}): \delta 8.1(broad s, NH), 7.7-7.9(m, aromatic 4H) 7.3-7.5(m, aromatic 4H)

Product 7: 2-(p-nitrophenyl)benzimidazole: \textsuperscript{1}H NMR(400Mz, DMSO-d\textsubscript{6}): \delta 7.7-7.9(m, aromatic 4H) 7-7.2(m, aromatic 4H)
Product 8: 2-(N,N'-dimethylaminophenyl)benzimidazole: IR(KBr): cm\(^{-1}\) 3310(N-H), 1609(>C=N), \(^1\)H NMR(400Mz, DMSO-\(d_6\)): \(\delta\) 8.2(s, NH), 7.7-7.9(m, aromatic 4H) 7.3-7.5(m, aromatic 4H), 3.1(s,6H)

Product 9: 2-(3-nitrophenyl)benzimidazole: IR(KBr): cm\(^{-1}\) 3278(N-H), 2962 and 2918(CH), 1615(>C=N), \(^1\)H NMR(400Mz, DMSO-\(d_6\)): \(\delta\) 8.1(s, NH), 7.9(s,1H),7.5-7.7(m, aromatic 3H) 6.8-7.2(m, aromatic 4H)

Product 10: 2-(2-nitrophenyl)benzimidazole: IR(KBr): cm\(^{-1}\) 3310(N-H), 1610(>C=N), \(^1\)H NMR(400Mz, DMSO-\(d_6\)): \(\delta\) 7.5-7.7(m, aromatic 4H) 7.2-7.3(m, aromatic 4H)

Conclusion:
The method used herein involves the solvent free synthesis of 2-arylimidazolines and 2-arylbenzimidazoles using microwave technique. The catalyst used for the transformations is the superbase AI\(_2\)O\(_3\)-OK which was prepared by fusing a mixture of AI\(_2\)O\(_3\) and KNO\(_3\) at 600°C. The method described here appears to be an improvement over other methods reported as the reaction time is short and the recovery of the product does not involve elaborate techniques. The yield has also been found to be high.
SEM IMAGE OF "Solid base Al$_2$O$_3$-OK"
IR SPECTRUM OF 2-(p-nitrophenyl)imidazoline
\( ^1H \text{ NMR SPECTRUM OF} "N,N'-\text{dimethylaminophenyl)imidazoline}" \)
$^1$H NMR SPECTRUM OF
"2-(N,N-dimethylaminophenylamino)imidazoline"
IR SPECTRUM OF "2-(p-methoxyphenyl)imidazole"
\textsuperscript{1}H NMR of \textit{2-(p-methoxyphenyl)imidazoline}
$^1$H NMR SPECTRUM OF
“2-(p-methoxyphenyl)imidazoline”
$^{1}$H NMR SPECTRUM OF "2-phenylbenzimidazole"
References:


(b) Levesque, G.; Gressier, J. C.; Proust, M. *Synthesis* **1981**, 963
31. Chwala, A.; German patent 704,410 (Feb. 27, 1941); *Chem. Abstracts 1942*, *36*, 2091; U. S. patent 2,194,419 (March 19, 1940)
32. Morrill, H. L.; U. S. patent 2,508,415 (1950); *Chem. Abstracts 1951*, *45*, 668
34. Sonn, A.: U. S. patent 2,161,938 (June 13, 1939); *Chem. Abstracts 1939*, *33*, 7316; German patent 615,227 (1935, October 17); *Chem. Abstracts 1936*, *30*, 487
37. Short, W. F.; Oxley, P.: British patent 612,693 (November 16, 1948); *Chem. Abstracts 1949*, *43*, 5049
41. Diels, O.; Schleich, K. *Ber.* **1917**, *49*, 1711