6.1 Introduction

Nitrogen containing heterocyclic compounds have maintained interest of researchers as their structures have led to several applications in various fields. The discovery of N-ribosyl-5,6-dimethylbenzimidazole,\(^1\) as an integral part of the chemical structure in vitamin B12 has generated considerable interest in the development of synthetic strategies for benzimidazole derivatives. The heterocyclic portion of the benzimidazole ring system has been referred as iminazole, imidazole, glyoxaline and 1,3-diazo. Historically, the first benzimidazole was synthesized by Hoebrecker in 1872 by the reduction of 2-nitro-4-methylacetanilide which yielded 2,5 (or 2,6)-dimethylbenzimidazole (6.01).

Later Ladenburg obtained the same compound by refluxing 3,4-diaminotoulene with acetic acid.

Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily undergo tautomerisation. This may be depicted as shown in Fig. 1. Because of this tautomerisation certain derivatives appear to be isomers, but in reality they are tautomers. Thus, 5-methylbenzimidazole is a tautomer of 6-methylbenzimidazole and both structures represent the same compound (Fig. 2).
Benzimidazoles have evolved as important scaffold in medicinal chemistry since from the past several years due to their diverse range of biological activities viz., antiviral, antimicrobial, antifungal, antitumor, antihistaminic, antihypertensive, anti-inflammatory, antiulcer and antitubercular. There are a number of benzimidazole derivatives which are proved to be potent drugs such as Mebendazole (antibiotic, 6.02), Thiabendazole (fungicide, 6.03), Albendazole (anthelmitnic, 6.04), Bendamustine (chronic lymphocytic leukemia and lymphomas, 6.05), Dovitinib (antineoplastic, 6.06).
6.2 Methods of preparation

Practically the synthesis of benzimidazoles start with benzene derivatives substituted with amine groups ortho to each other (6.07).

The most popular synthetic procedure for the synthesis of benzimidazoles generally involves condensation reaction of 1,2-phenylenediamine with carboxylic acids\cite{11} (Scheme 1, Phillips reaction) or with their derivatives (acid chlorides, nitriles, ortho esters or imidates).\cite{12} These procedures often employ use of strong acids [hydrochloric acid, polyphosphoric acid (PPA), boric acid or p-toluene sulphonlic acid (Scheme 2)] as catalyst, sometimes combined with high temperatures (i.e., PPA, 180°C).

Benzimidazole derivatives have also been generated using various catalytic reagents via oxidative cyclisation, cross-coupling reaction, condensation, C-N bond formation, Lewis acid assisted intramolecular cyclization and C-H functionalization.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme1.png}
\caption{Scheme 1}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme2.png}
\caption{Scheme 2}
\end{figure}
Lee et al\textsuperscript{13} developed a convenient protocol for the synthesis of benzimidazoles from \(o\)-phenylenediamines and aldehydes via aerobic oxidation in wet organic solvents (Scheme 3).

\[
\begin{align*}
\text{PhNH}_2 \underset{\text{PhCHO}}{\xrightarrow{\text{H}_2\text{O}}} \text{PhNH} \implies \text{PhN} \\
\text{DMF, } 80 \degree \text{C} \quad \text{open flask}
\end{align*}
\]

Scheme 3

Mahesh et al\textsuperscript{14} reported a novel one pot multi-component copper catalyzed imine chelated regioselective amination of \(N\)-aryl imines using trimethylsilyl azide (TMSN\(_3\)) in the presence of tert-butyl hydroperoxide (TBHP) at moderate temperature to afford 2-substituted benzimidazoles (Scheme 4).

\[
\begin{align*}
\text{PhNH}_2 \underset{\text{PhCHO}}{\xrightarrow{10 \text{ mol}\% \text{ CuI} \text{ TMSN}_3, \text{ TBHP}}} \text{PhNH} \implies \text{PhN} \\
\text{DMSO, } 60 \degree \text{C}
\end{align*}
\]

Scheme 4

Beckmann-type rearrangement of \(o\)-aminoaryl N-H ketimines has been developed by Zhang et al\textsuperscript{15} to prepare benzimidazoles using hypervalent iodine via an oxidative rearrangement. The catalyst (diacetoxyiodo)benzene was found to act as an efficient oxidant to trigger [1,2]-aryl migration towards the formation of the desired product. This strategy was applied to the synthesis of benzimidazole containing biorelevant target clemizole (Scheme 5).

\[
\begin{align*}
\text{PhN} \underset{\text{PhI(OAc)}_2}{\xrightarrow{\text{NH}_3 \text{ (i)} \quad \text{PhI(OAc)}_2 \text{ (ii)}}} \text{PhN} \implies \text{PhN} \\
\text{SO}_2\text{Ph} \quad \text{3 steps}
\end{align*}
\]

Scheme 5
Baars et al\textsuperscript{16} prepared benzimidazoles by intramolecular $N$-arylations of amidines mediated by potassium hydroxide in DMSO at 120°C (\textbf{Scheme 6}).

\begin{eqnarray*}
\text{Scheme 6}
\end{eqnarray*}

\textbf{Scheme 6} represents the synthesis of 1,2-disubstituted benzimidazoles (6.13) from 4-fluoro-3-nitro-benzoic acid through $N$-arylation via the formation of Meisenheimer adduct and reduction of intermediate using stannous chloride.\textsuperscript{17}

\begin{eqnarray*}
\text{Scheme 7}
\end{eqnarray*}

Kumar et al\textsuperscript{18} described a synthetic route for the synthesis of 2-substituted benzimidazoles (6.10) in presence of surfactant DBSA (dodecylbenzenesulfonic acid) as catalyst and molecular iodine as co-catalyst in aqueous media (\textbf{Scheme 8}).

\begin{eqnarray*}
\text{Scheme 8}
\end{eqnarray*}

Bommegouda \textit{et al}\textsuperscript{19} reported one pot synthesis of 2-substituted benzimidazoles through condensation followed by cyclization of Weinreb amide ($N$-methoxy-$N$-methylbenzamide) with $o$-phenylenediamine in presence of boron trifluoride etherate (\textbf{Scheme 9}).
The synthesis of $N$-substituted benzimidazoles (6.14) from $N$-($o$-halophenyl)imidoyl chlorides using palladium catalyst was successfully carried out by Sadig et al.

Scheme 10

Kim et al. synthesized benzimidazoles by copper-catalysed one pot, three component reaction of 2-haloanilines, aldehydes and sodium azide (Scheme 11).

Scheme 11

Various 2-substituted benzimidazoles were prepared by Eynde et al. using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant. The reaction proceeds with the formation of Schiff base and rearomatisation of the intermediate (Scheme 12).


\[
\begin{align*}
&\text{Scheme 12} \\
\text{Marri et al}^{23} &\text{ developed a protocol for one-pot synthesis of benzimidazoles from variety of aryl alcohols and 1,2,-diaminoarenes. This method employed alcohol under solvent free and catalyst free conditions (Scheme 13).}
\end{align*}
\]

\[
\begin{align*}
&\text{Scheme 13} \\
\text{Sluiter et al}^{24} &\text{ proposed sodium hydride mediated } N\text{-methylbenzimidazole using carbonitriles and } N\text{-methyl-1,2-phenylenediamine (Scheme 14).}
\end{align*}
\]

\[
\begin{align*}
&\text{Scheme 14} \\
\text{Lim et al}^{25} &\text{ demonstrated microwave assisted synthesis of benzimidazoles from resin bound esters (Scheme 15).}
\end{align*}
\]
Lin et al\textsuperscript{26} developed microwave assisted one-pot synthesis of benzimidazoles \textsuperscript{(6.15)} from aryldiamines and carboxylic acids using triphenoxy phosphine (\textbf{Scheme 16}).

\begin{center}
\textbf{Scheme 16}
\end{center}

\begin{center}
A wide variety of functionalized 2-aryl benzimidazoles was prepared by Nguyen et al\textsuperscript{27} through cobalt- or iron-catalyzed redox condensation of 2-nitroanilines and benzylamines. The cascade including benzylamine oxidation, nitro reduction, condensation and aromatisation occurred without any added reducing or oxidizing agent (\textbf{Scheme 17}).
\end{center}

\begin{center}
\textbf{Scheme 17}
\end{center}

\begin{center}
Wray et al\textsuperscript{28} reported synthesis of 1,2-disubstituted benzimidazoles \textsuperscript{(6.16)} from arylamino oximes using triethylamine and mesityl chloride (\textbf{Scheme 18}).
\end{center}

\begin{center}
\textbf{Scheme 18}
\end{center}
Benzimidazole derivatives have also been synthesized from the oxidative condensation of 1,2-arylene diamines with aldehydes using various oxidative and catalytic reagents which has been illustrated in Fig. 3.

**Figure 3**

Although the above mentioned reaction conditions often efficiently prompted, but most of them suffer from one or more disadvantages such as usage of high boiling solvents, costly catalyst, strong oxidising reagents, prolonged reaction times, laborious work up and purifications.


6.3 Present Work

The invention of simple, mild, practicable, cheap and eco-benign method for the synthesis of benzimidazoles have grabbed the attention of researchers. Microwave assisted organic synthesis has become rapid growing field in organic chemistry as this technique makes reaction time shorter and tolerate wide range of reactions which are best suited to the increased demands of industry.

In view of this, we have developed an efficient, rapid, facile and inexpensive method for the synthesis of benzimidazole derivatives using 1,2-arylenediamines and \(N,N\)-dimethylformamide (DMF) in acidic medium under thermal/microwave condition (Scheme 19). This reaction was further explored with various C-substituted amides to afford a library of 2-substituted benzimidazoles (Scheme 20). The advantage of the present synthetic method includes shorter reaction time, easy work up and excellent yields without using the catalysts.

\[
\text{NH}_2 \quad \text{NH}_2 \quad \text{H}_2 \text{N} \quad \text{O} \quad \Delta \quad 100^\circ\text{C}, 1 \text{ h} \quad \text{or} \quad \text{MWI, 150W, 150}^\circ\text{C, 2 min} \\
\text{R} \quad \text{N} \quad \text{H} \quad \text{R} \\
\text{1a} \quad + \quad \text{2a} \quad + \quad 70\% \text{HCl} \\
\rightarrow \\
\text{3a-g} \\
7 \text{ examples}
\]

Scheme 19

\[
\text{NH}_2 \quad \text{NH}_2 \quad \text{H}_2 \text{N} \quad \text{O} \quad \Delta \quad 100^\circ\text{C}, 1-24 \text{ h} \quad \text{or} \quad \text{MWI, 150W, 150}^\circ\text{C, 2-60 min} \\
\text{R'} \quad \text{N} \quad \text{H} \quad \text{R'} \\
\text{1a} \quad + \quad \text{4a-n} \quad + \quad 70\% \text{HCl} \\
\rightarrow \\
\text{3a, 5b-n} \\
14 \text{ examples}
\]

Scheme 20
6.4 Results and discussion

6.4.1 Chemistry

During the course of our investigation, we actually started with the direct one-pot conversion of aryl/alkyl nitriles to benzimidazoles using 1,2-phenylenediamine and dil.HCl in N,N-dimethylformamide (DMF) as solvent (Scheme 21). Initially, we were in the conclusion that, the nitrile (-CN) functional group would get converted into carboxylic acid (-COOH) in the presence of dil.HCl and thereafter it would condense with 1,2-phenylenediamine resulting in the formation of corresponding 2-substituted benzimidazole derivative.

\[
\text{RCN} + \text{NH}_2\text{NH}\text{NH}_2 \xrightarrow{70\% \text{HCl}} \text{RCOOH} + \text{NH}_2\text{NH}\text{NH}_2
\]

\[\text{R = alkyl, aryl, heterocycle}\]

Scheme 21

However, the TLC showed the presence of nitrile, while the spot corresponding to 1,2-phenylenediamine was missing. By this unusual observation, it was concluded that only 1,2-phenylenediamine was reacted instead of nitrile. Further, the product was isolated and analysed using NMR (\(^1\)H, \(^13\)C) and mass spectroscopic techniques. Surprisingly, the \(^1\)H and \(^13\)C NMR spectra were found to be identical to the earlier reports in the literature for benzimidazole. And also the mass spectral data showed the m/z value at 118 corresponding to the molecular mass of benzimidazole.

All these observations proved that an unusual reaction must have occurred between 1,2-phenylenediamine and DMF in presence of HCl that would lead to the formation of benzimidazole serendipitously. However, we could find reports for the synthesis of benzimidazoles from amides (not with
DMF) using ethylene glycol (high boiling) as solvent without significant details.\textsuperscript{29} In the present work we have successfully synthesized benzimidazoles using 1,2-arylenediamines and DMF (both as reagent and solvent) in acidic medium under thermal / microwave conditions. Also, we have used a good number of amides to exhibit the substrate scope and made a comparative study between conventional and microwave assisted reactions.

In order to establish the optimal reaction conditions, we opted 1,2-phenylenediamine (1a) and DMF (2a) as model substrates (Scheme 22).

\begin{center}
\begin{align*}
\text{1a} & \quad + \quad \text{2a} & \quad \text{Δ 100°C, 1 h} & \quad \text{or} & \quad \text{MWI, 150W, 150°C, 2 min} & \quad \text{3a} \\
\end{align*}
\end{center}

\textbf{Scheme 22}

Initially, we tried the reaction at room temperature by stirring 1,2-phenylenediamine and DMF in 70% HCl, however, the reaction couldn’t end up with complete conversion of the reactants into benzimidazole (3a) even after stirring for 24 h. Then, the same reaction was attempted under thermal conditions at 100°C. The reaction yielded benzimidazole with the complete conversion of the reactants in 1 h with 82% yield. Similarly, substituted benzimidazoles (3b-g) were prepared using various substituted 1,2-arylenediamines (1b-g) and DMF in 1 h with 80-82% yields.

Also, we have tried to achieve this reaction under microwave condition where the reaction was irradiated by 150W microwave radiations at 150°C. Interestingly, we observed completion of the reaction in 2 min with excellent yields (94-96%) for all 1,2-arylenediamines (1a-g, Table 1).
Table 1 Synthesis of benzimidazoles (3a-g) from 1,2-arylenediamines (1a-g) and DMF (2a) under optimized conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2-Arylenediamines (1a-g)</th>
<th>Products (3a-g)</th>
<th>Thermal</th>
<th>Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>( \text{NH}_2 \text{NH}_2 )</td>
<td>( \text{N} )</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>( \text{NH}_2 \text{NH}_2 )</td>
<td>( \text{N} )</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>( \text{NH}_2 \text{NH}_2 )</td>
<td>( \text{N} )</td>
<td>1</td>
<td>82</td>
</tr>
</tbody>
</table>
| 4     | \( \text{Cl}
\text{N} \text{H} \) | \( \text{Cl}
\text{N} \text{H} \) | 1       | 80        | 2          | 95        |
| 5     | \( \text{O}_2\text{N}
\text{NH}_2 \) | \( \text{O}_2\text{N}
\text{NH}_2 \) | 1       | 80        | 2          | 95        |
| 6     | \( \text{Br}
\text{N} \text{H}_2 \) | \( \text{Br}
\text{N} \text{H}_2 \) | 1       | 81        | 2          | 95        |
| 7     | \( \text{NH}_2 \) | \( \text{N} \) | 1       | 82        | 2          | 96        |

\(^a\) Isolated yield
We even obtained benzimidazole (3a, in 96% yield) in 2 min when the mixture of 1,2-phenylenediamine (1a) and formamide (4a) in 70% HCl was irradiated by 150W microwave radiations at 150°C. We have carried out the reactions between 1,2-phenylenediamine (1a) and various C-substituted amides (4b-n) in order to get the corresponding 2-substituted benzimidazoles (5b-n) by conventional method, but the reactions ended up with moderately good yields (40-78%) and time required for the completion of reactions was in the range from 1-12 h. However, it was surprising to observe that the same reactions progressed smoothly under microwave irradiation (150W) at 150°C for 40-60 min with 80-95% yields (Table 2).

Table 2 Synthesis of 2-substituted benzimidazoles (5b-n) from 1,2-phenylenediamine (1a) and C-substituted amides (4a-n)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amides (4a-n)</th>
<th>Products (5a-n)</th>
<th>Thermal</th>
<th>Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield(^a) (%)</td>
</tr>
<tr>
<td>1</td>
<td>H(_2)N-(\text{O})H (4a)</td>
<td>(\text{N} \text{N} \text{H} ) (3a)</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>H(_2)N-(\text{O}) (4b)</td>
<td>(\text{N} \text{H} ) (5b)</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>O(\text{NH})2 (4c)</td>
<td>(\text{N} \text{H} ) (5c)</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Cl(\text{O} \text{NH}_2) (4d)</td>
<td>(\text{N} \text{H} ) (5d)</td>
<td>4</td>
<td>72</td>
</tr>
</tbody>
</table>
Table 2 contd......

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amides (4a-n)</th>
<th>Products (5a-n)</th>
<th>Thermal</th>
<th>Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</td>
</tr>
<tr>
<td>5</td>
<td>(4e)</td>
<td>(5e)</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>(4f)</td>
<td>(5f)</td>
<td>5</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>(4g)</td>
<td>(5g)</td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>(4h)</td>
<td>(5h)</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>(4i)</td>
<td>(5i)</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>(4j)</td>
<td>(5j)</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>(4k)</td>
<td>(5k)</td>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>(4l)</td>
<td>(5l)</td>
<td>24</td>
<td>51</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield
The reaction of 1,2-arylenediamines (1a-g) with DMF (2a) are independent of wide range of functional groups leading to the formation of corresponding benzimidazole derivatives (3a-g) with excellent (94-96%) yields by microwave (150W) heating at 150°C for 2 min. The same reaction carried out by conventional heating at 150°C for 10 min afforded only a trace amounts and required 1 h at 100°C for completion of reaction with yield ranging from 80-82%. In the case of reaction carried out at 100°C by microwave heating, time required was 30 min to accomplish the reaction.

The formation of 2-substituted benzimidazoles (5b-n) from 1,2-phenylenediamine (1a) and C-substituted amides (4b-n) showed completion of reaction in the 1-12 h by conventional heating. When the reaction was carried out by microwave irradiation at 100°C for 1 h, only compounds 5b-d were formed in very low yields (40-50%), but the derivatives 5e-n were not formed. However, the same reaction when irradiated with 150W microwave radiation at 150°C for 40 min, corresponding 2-substituted benzimidazole derivatives (5b-k) were obtained with excellent yields (80-95%). It was interesting to note that, benzamides (4g-j) substituted with electron donating groups furnished reaction with moderate yields when compared to electron withdrawing groups which

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amides (4a-n)</th>
<th>Products (5a-n)</th>
<th>Thermal</th>
<th>Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>13</td>
<td>![Image]</td>
<td>![Image]</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>14</td>
<td>![Image]</td>
<td>![Image]</td>
<td>18</td>
<td>54</td>
</tr>
</tbody>
</table>

*Isolated yield
afforded lower yields and took more time for the completion by conventional heating. However, the same reaction by microwave (150W) heating at 150°C for 40 min proceeded with good yields. The formation of corresponding bis-benzimidazoles (5l-n) from oxalamide, malonamide and succinamide by conventional method was achieved by heating for a longer time (18-24 h) with lower yields (51-55%). But the same reaction was completed in 60 min with good yields (88-92%) by microwave irradiation (150W) at 150°C. As a result from the above observation it can be concluded that the reaction condition is independent on N-substituted amides, whereas, C-substituted amides influence the rate of reaction.

6.4.2 Plausible mechanism

![Scheme 23](image)

The reaction follows a simple concerted mechanism, wherein the use of HCl enhances the electrophilicity of the carbonyl carbon of amide thereby provoking the attack of lone pair of electrons on nitrogen atom of diamine resulting in the formation of \( N-(2\text{-aminophenyl})\text{formamide} \) (I) intermediate which then immediately undergo intramolecular cyclodehydration resulting in the formation of benzimidazole (3a, Scheme 23).
6.5 Experimental

6.5.1 Conventional method for the synthesis of benzimidazoles (3a-g)

1,2-Arylenediamine (1a-g, 4.62 mmol), DMF (1 ml, 13.87 mmol) and 70% HCl (10 ml) were heated in a round bottom flask at 100°C for 1 h. The completion of the reaction was monitored by TLC using hexane:ethylacetate (6:4) solvent mixture. The reaction mixture was cooled to room temperature and diluted with water (10 ml). The aqueous solution was neutralised by adding solid Na₂CO₃ till slightly basic pH (8-9) to get the precipitate. The solid separated was filtered, washed repeatedly with water, dried and recrystallized using ethanol to afford pure benzimidazole derivatives (3a-g).

Synthesis of benzimidazole (3a) from 1,2-phenylenediamine (1a) and formamide (4a) was carried out by similar procedure.

6.5.2 Conventional method for the synthesis of 2-substituted benzimidazoles (5b-n)

1,2-Phenylenediamine (1a, 4.62 mmol), substituted amide (4b-n, 4.62 mmol) and 70% HCl (10 ml) were heated in a round bottom flask at 100°C. The completion of the reaction was monitored by TLC using hexane:ethylacetate (6:4) solvent mixture. The reaction mixture was cooled to room temperature and diluted with water (10 ml). The aqueous solution was neutralised by adding solid Na₂CO₃ till slightly basic pH (8-9) to get the precipitate. The solid separated was filtered, washed repeatedly with water, dried and recrystallized using ethanol to afford 5b-n.

6.5.3 Microwave assisted procedure for the synthesis of benzimidazoles (3a-g)

1,2-Arylenediamine (1a-g, 0.92 mmol), DMF (1 ml, 2.78 mmol) and 70% HCl (5 ml) was introduced into a CEM microwave reaction vessel (10 ml) equipped with magnetic stirrer. The reaction vessel was sealed and the reaction mixture was pre-stirred for 1 min at room temperature. Then, the reaction mixture was irradiated by 150W microwave radiations for 2 min at 150°C. The completion of reaction was monitored by TLC using hexane:ethylacetate (6:4)
solvent mixture. The reaction mixture was cooled to room temperature and water (10 ml) was added. The reaction mixture was neutralised by solid Na₂CO₃ till slightly basic pH (8-9) to get the precipitate. The solid separated was filtered, washed repeatedly with water, dried and recrystallized using ethanol to afford **5b-n**.

Synthesis of benzimidazole **(3a)** from 1,2-phenylenediamine (1a) and formamide (4a) was carried out by similar procedure.

### 6.5.4 Microwave assisted procedure for the synthesis of 2-substituted benzimidazoles (5b-n)

1,2-Phenylenediamine (1a, 0.92 mmol), substituted amide (4b-n, 0.92 mmol) and 70% HCl was introduced into a 10 ml CEM microwave reaction vessel equipped with magnetic stirrer. The reaction vessel was sealed and the reaction mixture was pre-stirred for 1 min at room temperature. Further, the reaction mixture was irradiated by 150W microwave radiations for 40 min at 150°C for compounds **5b-k** and 60 min for compounds **5l-n**. The completion of reaction was monitored by TLC using hexane:ethylacetate (6:4) solvent mixture. The reaction mixture was cooled to room temperature and water (10 ml) was added. The aqueous solution was neutralised by adding solid Na₂CO₃ till slightly basic pH (8-9) to get the precipitate. The solid separated was filtered, washed repeatedly with water, dried and recrystallized using ethanol to afford **5b-n**.

The physical data (m.p, NMR) of all the known compounds were found to be identical with those reported earlier in the literature.
1H-Benz[d]imidazole (3a)

White solid; m.p: 169-171°C (lit.\(^30\): 172°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 1) 12.43 (s, 1H, NH), 8.19 (s, 1H, C\(_2\)H), 7.58-7.56 (dd, 2H, \(J = 7.2\) Hz, C\(_4\)H & C\(_7\)H), 7.19-7.15 (m, 2H, C\(_5\)H & C\(_6\)H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 2) 141.85, 138.08, 121.63, 115.44; MS (\(m/z\)): (Spectrum No. 3) 118 (M), 91, 78, 63.

5-Methyl-1H-benzo[d]imidazole (3b)

White solid; m.p: 114-116°C (lit.\(^30\): 116°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 4) 12.28 (s, 1H, NH), 8.01 (s, 1H, C\(_2\)H), 7.44 (d, 1H, \(J = 6.4\) Hz, C\(_7\)H), 7.34 (s, 1H, C\(_3\)H), 6.98 (d, 1H, \(J = 6.4\) Hz, C\(_6\)H), 2.39 (s, 3H, CH\(_3\));

\(^13\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 5) 141.49, 130.75, 123.08, 114.83, 21.17; MS (\(m/z\)): (Spectrum No. 6) 132 (M), 131, 78, 63.

4,6-Dimethyl-1H-benzo[d]imidazole (3c)

White solid; m.p: 142-144°C (lit.\(^31\): 146°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): 12.52 (s, 1H, NH), 8.14 (s, 1H, C\(_2\)H), 7.16 (s, 1H, C\(_7\)H), 6.81 (s, 1H, C\(_3\)H), 2.46 (s, 3H, CH\(_3\)), 2.35 (s, 3H, CH\(_3\));

\(^13\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): 140.73, 138.69, 135.51, 130.93, 124.74, 123.73, 111.77, 21.15, 16.60; MS (\(m/z\)): 146 (M), 145, 91, 78, 63.

5-Chloro-1H-benzo[d]imidazole (3d)

White solid; m.p: 121-123°C (lit.\(^30\): 125°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 7) 12.60 (s, 1H, NH), 8.26 (s, 1H, C\(_2\)H), 7.68 (s, 1H, C\(_4\)H), 7.62 (d, 1H, \(J = 15.6\) Hz, C\(_6\)H), 7.20 (d, 1H, \(J = 15.6\) Hz, C\(_7\)H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 8) 143.41, 121.96, 120.18, 118.48, 113.01, 111.55; MS (\(m/z\)): (Spectrum No. 9) 154 (M+2), 152 (M), 127, 125, 90, 78, 63.
5-Nitro-1H-benzo[d]imidazole (3e)

Pale yellow solid; m.p: 207-209°C (lit.\textsuperscript{30}:208°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): 13.01 (s, 1H, NH), 8.54 (s, 1H, C\(_2\)H), 8.51 (s, 1H, C\(_4\)H), 8.11 (d, 1H, \(J = 6.8\) Hz, C\(_6\)H), 7.77 (d, 1H, \(J = 6.8\) Hz, C\(_7\)H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): 146.72, 143.01, 142.58, 117.52, 114.96, 112.66; MS (\(m/z\)): 163 (M), 133, 117, 90, 78, 63.

6-Bromo-1H-imidazo[4,5-b]pyridine (3f)

Light brown solid; m.p: 222-224°C (lit.\textsuperscript{32}: 227°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 10) 13.14 (s, 1H, NH), 8.48 (s, 1H, C\(_2\)H), 8.42 (s, 1H, C\(_7\)H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 11) 150.02, 145.49, 143.99, 133.15, 126.25, 112.67; MS (\(m/z\)): (Spectrum No. 12) 199 (M+2), 197 (M), 172, 170, 118, 91, 78, 63.

1-Methyl-1H-benzo[d]imidazo (3g)

Brown semisolid; m.p: 59-62°C (lit.\textsuperscript{33}: 60°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 13) 7.82 (s, 1H, C\(_2\)H), 7.80 (d, 1H, C\(_4\)H), 7.36 (d, 1H, C\(_7\)H), 7.31-7.28 (m, 2H, C\(_5\)H & C\(_7\)H), 3.68 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 14) 143.81, 143.52, 134.58, 123.20, 122.02, 121.55, 112.65, 30.96; MS (\(m/z\)): (Spectrum No. 15) 132 (M), 131, 104, 90, 78, 63.

2-Methyl-1H-benzo[d]imidazole (5b)

White solid; m.p: 173-175°C (lit.\textsuperscript{30}: 177°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 16) 12.20 (s, 1H, NH), 7.48-7.42 (dd, 2H, C\(_4\)H & C\(_7\)H), 7.09-7.06 (m, 2H, C\(_3\)H & C\(_5\)H), 2.46 (s, 1H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 17) 151.15, 138.91, 130.90, 114.17, 14.54; MS (\(m/z\)): (Spectrum No. 18) 132 (M), 131, 104, 90, 78, 63.
2-Ethyl-1H-benzo[d]imidazole (5c)

White solid; m.p: 176-178°C (lit.\(^{30}\): 176°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 19) 12.13 (s, 1H, NH), 7.47-7.40 (dd, 2H, C_4H & C_7H), 7.07-7.09 (m, 2H, C_5H & C_6H), 2.83-2.78 (q, 2H, \(J = 6.0\) Hz, CH_2), 1.31-1.28 (t, 3H, \(J = 6.0\) Hz, CH_3); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 20) 156.05, 141.02, 120.94, 115.38, 21.89, 12.14; MS (m/z): (Spectrum No. 21) 146 (M), 145, 131, 118, 104, 92, 78, 63.

2-(Chloromethyl)-1H-benzo[d]imidazole (5d)

Yellow solid; m.p: 156-158°C (lit.\(^{34}\): 160°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): 12.50 (s, 1H, NH), 7.56-7.52 (dd, 2H, C_4H & C_7H), 7.22-7.11 (m, 2H, C_5H & C_7H), 4.91 (s, 2H, CH_2); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): 150.09, 141.59, 138.00, 124.10, 116.52, 42.06; MS (m/z): 168 (M+2), 166 (M), 131, 104, 77, 63.

2-Vinyl-1H-benzo[d]imidazole (5e)

White solid; m.p: 180-182°C (lit.\(^{35}\): 184°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): 12.27 (s, 1H, NH), 7.62-7.56 (dd, 2H, C_4H & C_7H), 7.12-7.10 (m, 2H, C_5H & C_6H), 6.77-6.73 (dd, 1H, \(J_{trans} = 16.8\) Hz, \(J_{cis} = 9.7\) Hz), 6.26 (dd, 1H, \(J_{trans} = 16.8\) Hz, \(J_{gem} = 1.8\) Hz), 5.66 (dd, 1H, \(J_{cis} = 9.7\) Hz, \(J_{gem} = 1.8\) Hz); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): 141.68, 138.79, 123.20, 122.02, 121.55, 112.65; MS (m/z): 144 (M), 143, 117, 104, 91, 63.

2-Phenyl-1H-benzo[d]imidazole (5f)

White solid; m.p: 294-296°C (lit.\(^{36}\): 292°C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 22) 12.95 (s, 1H, NH), 8.20-8.17 (dd, 2H, C_2H & C_6H), 7.63-7.48 (m, 5H, C_4H, C_7H, C_3H, C_4'H & C_5'H), 7.23-7.19 (m, 2H, C_3H & C_6H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\) ppm): (Spectrum No. 23)
151.14, 143.17, 130.10, 129.76, 128.86, 128.50, 127.36, 122.03; MS (m/z):

(Spectrum No. 24) 194 (M), 166, 104, 90, 78, 63.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (5g)

White solid; m.p: 222-224°C (lit.\textsuperscript{36}: 226°C);

\[^1\text{H} \text{NMR (400 MHz, DMSO-}d_6, \delta \text{ ppm): 12.86 (s, 1H, NH), 8.02-7.96 (d, 2H, C}_2\text{H & C}_6\text{H), 7.72-7.68 (dd, 2H, C}_4\text{H & C}_7\text{H), 7.20-7.14 (m, 2H, C}_5\text{H & C}_6\text{H), 6.86-6.84 (d, 2H, C}_3\text{H & C}_5\text{H), 3.75 (s, 3H, OCH}_3; \] ^13\text{C NMR (100 MHz, DMSO-}d_6, \delta \text{ ppm): 160.75, 153.02, 142.28, 130.86, 129.68, 128.72, 128.55, 122.59, 56.07; MS (m/z): 224 (M), 193, 117, 104, 91, 78, 63.

2-(4-Chlorophenyl)-1H-benzo[d]imidazole (5h)

White solid; m.p: 295-297°C (lit.\textsuperscript{36}: 294°C);

\[^1\text{H} \text{NMR (400 MHz, DMSO-}d_6, \delta \text{ ppm): 13.02 (s, 1H, NH), 8.18-8.14 (d, 2H, C}_2\text{H & C}_6\text{H), 7.82-7.78 (dd, 2H, C}_3\text{H & C}_7\text{H), 7.66-7.64 (d, 2H, C}_5\text{H & C}_5\text{H), 7.26-7.22 (m, 2H, C}_5\text{H & C}_6\text{H); \] ^13\text{C NMR (100 MHz, DMSO-}d_6, \delta \text{ ppm): 150.28, 143.63, 134.66, 129.88, 128.98, 128.27, 122.64, 118.59; MS (m/z): 230 (M+2), 228 (M), 193, 117, 104, 91, 78, 63.

2-(2-Chlorophenyl)-1H-benzo[d]imidazole (5i)

White solid; m.p: 236-238°C (lit.\textsuperscript{36}: 234°C);

\[^1\text{H} \text{NMR (400 MHz, DMSO-}d_6, \delta \text{ ppm): 13.11 (s, 1H, NH), 7.96-7.92 (d, 1H, C}_6\text{H), 7.74-7.72 (dd, 2H, C}_3\text{H & C}_7\text{H), 7.55-7.51 (m, 3H, C}_5\text{H, C}_8\text{H & C}_5\text{H), 7.27-7.18 (m, 2H, C}_2\text{H & C}_3\text{H); \] ^13\text{C NMR (100 MHz, DMSO-}d_6, \delta \text{ ppm): 151.09, 143.72, 139.47, 132.77, 130.58, 129.09, 128.97, 126.61, 123.59, 120.46, 118.74; MS (m/z): 230 (M+2), 228 (M), 117, 104, 91, 78, 63.
2-(4-Nitrophenyl)-1H-benzo[d]imidazole (5j)

Yellow solid; m.p: 312-314°C (lit.\textsuperscript{36}: 316°C);

\(^1\)H NMR (400 MHz, DMSO-\textit{d}_6, \delta \text{ ppm}): 13.02 (s, 1H, NH), 8.42-8.38 (d, 2H, C\textsubscript{3}'H \& C\textsubscript{5}'H), 7.78-7.76 (d, 2H, C\textsubscript{2}'H \& C\textsubscript{6}'H), 7.72-7.70 (dd, 2H, C\textsubscript{4}'H \& C\textsubscript{7}'H), 7.26-7.22 (m, 2H, C\textsubscript{5}H \& C\textsubscript{6}H); \(^13\)C NMR (100 MHz, DMSO-\textit{d}_6, \delta \text{ ppm}): 152.64, 148.37, 143.69, 135.64, 128.34, 122.72, 119.61; MS (\textit{m/z}): 239 (M), 193, 117, 104, 91, 78, 63.

2-Benzyl-1H-benzo[d]imidazole (5k)

White solid; m.p: 184-186°C (lit.\textsuperscript{34}: 187°C); \(^1\)H NMR (400 MHz, DMSO-\textit{d}_6, \delta \text{ ppm}): 12.26 (s, 1H, NH), 7.52-7.50 (dd, 2H, C\textsubscript{4}H \& C\textsubscript{7}H), 7.40-7.38 (dd, 2H, C\textsubscript{3}'H \& C\textsubscript{5}'H), 7.23-7.20 (m, 2H, C\textsubscript{2}'H \& C\textsubscript{6}'H), 7.12-7.07 (m, 2H, C\textsubscript{5}H \& C\textsubscript{6}H), 4.15 (s, 2H, CH\textsubscript{2}); \(^13\)C NMR (100 MHz, DMSO-\textit{d}_6, \delta \text{ ppm}): 153.43, 143.37, 137.61, 134.83, 134.38, 128.69, 128.40, 126.44, 121.53, 120.85, 118.19, 110.84, 34.88; MS (\textit{m/z}): 208 (M), 207, 131, 103, 91, 78, 63.

2-(1H-Benzo[d]imidazol-2-yl)-1H-benzo[d]imidazole (5l)

Pale yellow solid; m.p: >370°C (lit.\textsuperscript{29}: 400°C); \(^1\)H NMR (400 MHz, DMSO-\textit{d}_6, \delta \text{ ppm}): 12.27 (s, 2H, NH), 7.78-7.55 (dd, 4H, C\textsubscript{4}H \& C\textsubscript{7}H), 7.17-7.08 (m, 4H, C\textsubscript{5}H \& C\textsubscript{6}H); \(^13\)C NMR (100 MHz, DMSO-\textit{d}_6, \delta \text{ ppm}): 153.29, 141.59, 138.00, 124.89, 116.25; MS (\textit{m/z}): 234 (M), 162, 134, 118, 106, 91, 78, 63, 44.

Bis(1H-benzo[d]imidazol-2-yl)methane (5m)

White solid; m.p: >370°C (lit.\textsuperscript{29}: 389°C); \(^1\)H NMR (400 MHz, DMSO-\textit{d}_6, \delta \text{ ppm): (Spectrum No. 25) 12.07 (s, 2H, NH),
7.73-7.62 (dd, 4H, C₄H & C₇H), 7.21-7.11 (m, 4H, C₅H & C₆H), 3.79 (s, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): (Spectrum No. 26) 152.88, 143.82, 138.12, 124.20, 116.00, 39.00; MS (m/z): (Spectrum No. 27) 248 (M), 131, 118, 78, 63.

2-(2-(1H-Benzo[d]imidazol-2-yl)ethyl)-1H-benzo[d]imidazole (5n)

White solid; m.p: 316-318°C (lit. 37: 315°C); ¹H NMR (400 MHz, DMSO-d₆, δ ppm): (Spectrum No. 28) 12.15 (s, 2H, NH), 7.76-7.66 (dd, 4H, C₄H & C₇H), 7.29-7.21 (m, 4H, C₅H & C₆H), 2.84-2.76 (t, 4H, J = 15.6 Hz, CH₂); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): (Spectrum No. 29) 151.05, 142.95, 139.62, 123.59, 115.65, 33.03; MS (m/z): (Spectrum No. 30) 262 (M), 196, 132, 104, 90, 77, 63.
Spectrum No. 1: $^1$H NMR (DMSO-$d_6$) spectrum of compound 3a

Spectrum No. 2: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 3a
Chapter 6
Expeditious synthesis of benzimidazoles using amides

Spectrum No. 3: Mass spectrum of compound 3a

Spectrum No. 4: $^1$H NMR (DMSO-$d_6$) spectrum of compound 3b
Spectrum No. 5: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 3b

Spectrum No. 6: Mass spectrum of compound 3b
Spectrum No. 7: $^1$H NMR (DMSO-$d_6$) spectrum of compound 3d

Spectrum No. 8: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 3d
Spectrum No. 9: Mass spectrum of compound 3d

![Mass spectrum of compound 3d](image)

$m/z = 152$

$154 [M+2]$

Spectrum No. 10: $^1$H NMR (DMSO-$d_6$) spectrum of compound 3f

![$^1$H NMR spectrum of compound 3f](image)
Spectrum No. 11: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 3f

Spectrum No. 12: Mass spectrum of compound 3f
Spectrum No. 13: $^1$H NMR (DMSO-$d_6$) spectrum of compound 3g

Spectrum No. 14: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 3g
Spectrum No. 15: Mass spectrum of compound 3g

Spectrum No. 16: $^1$H NMR (DMSO-$d_6$) spectrum of compound 5b
Spectrum No. 17: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 5b

Spectrum No. 18: Mass spectrum of compound 5b
Spectrum No. 19: $^1$H NMR (DMSO-$d_6$) spectrum of compound 5c

Spectrum No. 20: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 5c
Spectrum No. 21: Mass spectrum of compound 5c

Spectrum No. 22: $^1$H NMR (DMSO-$d_6$) spectrum of compound 5f
Spectrum No. 23: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 5f

Spectrum No. 24: Mass spectrum of compound 5f
Spectrum No. 25: $^1$H NMR (DMSO-$d_6$) spectrum of compound 5m

Spectrum No. 26: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 5m
Spectrum No. 27: Mass spectrum of compound 5m

Spectrum No. 28: $^1$H NMR (DMSO-$d_6$) spectrum of compound 5n
Spectrum No. 29: $^{13}$C NMR (DMSO-$d_6$) spectrum of compound 5n

Spectrum No. 30: Mass spectrum of compound 5n
References


