Chapter 5
Synthetic studies on N-containing heterocycles
5.1 Importance of some synthetic studies on Nitrogen-containing heterocycles

In the last few decades, functionalization and derivatisation of simple N-containing heterocyclic compounds has gained considerable interest in synthetic community because of the potential medicinal and pharmaceutical applicability of these heterocyclic scaffolds. In this final chapter, I have studied three different reactions of nitrogen containing heterocycles. The heterocycles chosen were mainly azoles such as imidazoles, triazoles etc. Before proceeding into further details about these reactions, a brief review on the recent trends on the synthetic studies on N-containing heterocycles has been given below.

5.2 A brief review on the synthetic studies on selective N-containing heterocycles

J. E. Macor et al. demonstrated an expedient synthesis of functionalized imidazole derivatives arising from the direct nucleophilic displacement of hydroxide from hydroxymethylimidazoles.¹

\[
\text{HO} \rightarrow_{\text{base}}^{\text{OH}} \left[ \text{imidazole} \right] \rightarrow_{\text{NUC-H}}^{\text{CUN}} \]

\[
R^2, R^5 = H, CH_3
\]

Scheme 5.2.1

M. Adib and his coworkers demonstrated that 1-alkyl imidazoles reacted smoothly with dialkyl acetylenedicarboxylates in the presence of pyridine carboxaldehydes to produce 1,8a-dihydro-7H-imidazo[2,1-b][1,3]oxazine derivatives diastereoselectively in excellent yields.²

\[
[\text{imidazole}] + \text{RO}_2\text{C} \rightarrow_{\text{PyCHO}}^{\text{DCM}, \text{room temp, 1h}} \left[ \text{oxazine} \right]
\]

R = Me, nBu, R' = Me, Et

Scheme 5.2.2

A novel three-component annulation reaction involving N-alkylimidazoles, dimethyl acetylenedicarboxylate and in situ generated aryl methylketenes leading to the synthesis of 6-vinyl-1,3a-diazapentalene derivatives is reported by C. Ma et al.³
First examples of direct vinylolation of 1-substituted imidazoles at the 2-position of the imidazole nucleus was described by B. A. Trofimov and his co-workers.\(^4\)

N. Matsuyama et al. demonstrated the direct C-H alkynylation of azoles with alkynyl bromides to proceed efficiently in the presence of a nickel-based catalyst system. The reaction enabled the introduction of various alkynyl groups bearing aryl, alkenyl, alkyl and silyl substituents to the azole cores. In some cases, addition of a catalytic amount of Cul was observed to accelerate the direct coupling dramatically.\(^5\)

D. Monguchi et al. demonstrated that C-H, N-H coupling of azoles took place with several amines in the presence of a copper catalyst to undergo amination at the 2-position.\(^6\)
T. Kawano described the copper-mediated direct arylation of 1,3,4-oxadiazoles and 1,2,4-triazoles with aryl iodides in the presence of suitable ligands and bases. This method allowed the installation of a variety of aryl moieties bearing a functional group such as ketone, ester, or nitrile so as to enable the facile construction of various functionalized oxadiazole and triazole core π systems.

Scheme 5.2.6

A peripheral approach to construct C-C bonds at the 2-position of azoles via Cu(OAc)\(_2\)/air mediated oxidative homo- and cross-coupling reaction was reported by Y. Li et al.

Scheme 5.2.7

Azole derivatives were synthesized by iron-catalysed oxidative reactions of azoles and ethers in good to excellent yields by S. Pan. A wide variety of azoles and ethers were selectively transformed into the corresponding oxidative coupling products under neutral reaction conditions.

Scheme 5.2.8
B. Chattopadhyay et al. showed that various pyrido-, quinolino-, pyrazino-, and quinoxalinotetrazoles could be used efficiently as azide components in Cu-catalyzed click reaction with alkynes. This method allowed for efficient synthesis of a wide variety of N-heterocyclic derivatives of 1,2,3-triazoles.10

5.3 References

Chapter 5 (Section 5A)
N-Methylthiomethylation of imidazoles and benzimidazoles with DMSO and their chemoselective oxidation to sulfoxides
5A.1 Introduction

This section deals with N-Methylthiomethylation of imidazoles and benzimidazoles with DMSO and their chemoselective oxidation to sulfoxides using NaBiO₃ in acetic acid medium as the oxidizing agent.

5A.1.1 Importance of the N-methylthiomethylimidazoles and its sulfoxide derivatives

Several N-methylthiomethyl derivatives of imidazoles are endowed with useful anti-inflammatory, analgesic and antipyretic properties.¹ Also, organic sulfoxides are useful synthetic intermediates for the construction of chemically diverse and biologically active molecules. They often play significant role as therapeutic agents such as anti-ulcer (proton pump inhibitor),² anti-bacterial, anti-fungal, anti-atherosclerotic,³ anthelmintic,⁴ anti-hypertensive⁵ and cardiotonic agents⁶ as well as acting as psychotonic⁷ and vasodilators.⁸

5A.1.2 A brief review on methylthiomethylation

It was M. G. Burdon et al. who for the first time described the ortho-methylthiomethylation of phenols by the reaction of phenols with sulfoxides and carbodiimides.⁹

\[
\text{HO} \quad \text{Me₂SO} \quad \text{DCC} \quad \text{HO} \quad \text{CH₂SCH₃}
\]

Scheme 5A.1.2.1

Later, C. S. Foote and his coworkers reported the ortho-methylthiomethylation of anilines.¹⁰

\[
\text{NH₂} \quad \text{Me₂S, tBuCl} \quad \text{NaOMe, CH₂Cl₂} \quad \text{NH₂} \quad \text{CH₂SCH₃}
\]

Scheme 5A.1.2.2

P. G. Gassman et al. achieved the ortho-methylthiomethylation of phenols by the reaction of phenol and dimethylsulfide in presence of N-chlorosuccinimide (NCS) and triethylamine.¹¹
A. F. Janzen et al. reported that N-methylthiomethyl derivatives of imidazole, 2-methylimidazole, 4-methylimidazole, benzimidazole, pyrazole and 1,2,4-triazole can be obtained by the reaction of N-tert-butyldimethylsilyl or N-trimethylsilyl heterocycles with dimethylsulfoxide.\(^{12}\)

\[
\text{Het} = \text{imidazole, 2-methylimidazole, 4-methylimidazole, pyrazole, 1,2,4-triazole}
\]

N-Methylthiomethylimidazole (I) was prepared from Me\(_2\)SO and II or III (Scheme 5A.1.2.5) at elevated temperatures by Pummerer reaction by A. F. Janzen and his coworkers.\(^{13}\)

\[
\text{Het}
\]

**Scheme 5A.1.2.4**

This review is intended to survey the recent literature and to focus on new methods of sulfide oxidation to the corresponding sulfoxides.

N. J. Leonard et al. for the first time used sodium metaperiodate (NaIO\(_4\)) in ice-bath temperature as an efficient oxidizing agent for various organic sulfides to the corresponding sulfoxides.\(^{14}\)
C. G. Venier and his coworkers discovered that peroxytrifluoroacetic acid is an especially convenient reagent for the oxidation of sulfides to sulfoxides and sulfones.\textsuperscript{15} 

\[
\begin{array}{c}
\text{O} \\
\text{CF}_3\text{CO}_2\text{H} (1 \text{ eq.}) \\
\text{CF}_3\text{CO}_2\text{H} (2 \text{ eqv.}) \\
0 \degree \text{C} \\
30 \degree \text{C}
\end{array}
\]

\[\text{R}^1, \text{R}^2 = \text{alkyl or aryl}\]

Scheme 5A.1.3.2

R. S. Varma et al. selectively and expeditiously oxidized a variety of symmetrical and unsymmetrical sulfides to either sulfoxides or sulfones in good yields using wet silica-supported sodium periodate under microwave thermolysis conditions.\textsuperscript{16} 

\[
\begin{array}{c}
\text{O} \\
\text{20\% NaO}_4\text{-Silica} (3.0 \text{ eq.}) \\
\text{20\% NaO}_4\text{-Silica (1.7 eq.)} \\
\text{MW} \\
\text{R}^1, \text{R}^2 = \text{alkyl or aryl}
\end{array}
\]

Scheme 5A.1.3.3

Recently, the oxidation of sulfides to sulfoxides by hydrogen peroxide has proved to be one of the most attractive methods (Scheme 5A.1.3.4). Therefore, I have surveyed the recent literature related to the new methods of sulfide oxidation by hydrogen peroxide.

\[
\begin{array}{c}
\text{O} \\
\text{H}_2\text{O}_2 \\
\text{\textbf{H}_2\text{O}^+} \\
\text{R}^1, \text{R}^2 = \text{alkyl or aryl}
\end{array}
\]

Scheme 5A.1.3.4

M. Gazdar and S. Smiles initiated the oxidation of sulfides to the corresponding sulfoxides by the use of hydrogen peroxide. In their experiments, acetone and acetic acid were chosen as the solvents.\textsuperscript{17}
K. Bahrami reported that hydrogen peroxide (H$_2$O$_2$) in the presence of zirconium tetrachloride is a very efficient reagent for the oxidation of sulfides to sulfoxides and sulfones in methanol at room temperature.$^{18}$

K. Jeyakumar et al. achieved the selective oxidation of sulfides to sulfoxides and sulfones by H$_2$O$_2$ using MoO$_2$Cl$_2$ as the catalyst. Various substituted sulfides having functional groups such as methyl, methoxy, bromo, nitro, alkene, alkyne, alcohol, ester, aldehyde and remarkably an oxime were successfully and selectively oxidized without affecting the sensitive functionalities.$^{19}$

Several alkyl and aryl sulfides were oxidized to the corresponding sulfoxides or sulfones in excellent yields by A. Shaabani and his coworkers with aqueous hydrogen peroxide in the presence of silica sulfuric acid as an efficient solid acid catalyst.$^{20}$
M. Kirihara et al. demonstrated that the reaction of sulfides with 30% H$_2$O$_2$ catalysed by tantalum(V) chloride in acetonitrile, isopropanol, or t-butanol selectively provided the corresponding sulfoxides in high yields while the reaction of sulfides with 30% hydrogen peroxide catalysed by tantalum(V) chloride or tantalum(V) ethoxide in methanol effectively gave the sulfones.\textsuperscript{21}

![Scheme 5A.1.3.8]

A. Rostami and his coworkers reported boric acid as a highly efficient and eco-friendly catalyst for the selective oxidation of sulfides to sulfoxides or sulfones, in excellent yields under solvent-free conditions, using 30% H$_2$O$_2$ as an oxidant. Various sulfides, possessing functional groups such as alcohol, ester and aldehyde, were successfully and selectively oxidized without affecting the other sensitive functionalities.\textsuperscript{22}

![Scheme 5A.1.3.9]

![Scheme 5A.1.3.10]
5A.2 Results and Discussion

Here, a novel approach for the N-methylthiomethylation of imidazoles and benzimidazoles with DMSO has been reported and the chemoselective oxidation of these N-methylthiomethyl derivatives to the corresponding sulfoxides using NaBiO₃ in acetic acid medium as oxidizing agent has also been described (Scheme 5A.2.1).

![Scheme 5A.2.1 N-methylthiomethylation of benzimidazoles and their chemoselective oxidation to sulfoxides](image)

The reaction between 2-methylbenzimidazole and DMSO was selected as a model reaction to investigate the best reaction condition (Scheme 5A.2.2). After extensive studies with several bases, it was found that using N-methylpiperazine (2 equiv.) as a base at a moderate temperature (120 °C) produced the best yield of product after eight hours (Table 5A.2.1, entry 8). The complete optimization table is given below (Table 5A.2.1).

![Scheme 5A.2.2 Optimization for the N-methylthiomethylation of 2-methylbenzimidazole](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%) (isolated)</th>
</tr>
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<tbody>
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<td>-</td>
<td>160</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N (2)</td>
<td>90</td>
<td>24</td>
<td>25</td>
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<tr>
<td>3</td>
<td>K₂CO₃ (2)</td>
<td>160</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Cs₂CO₃ (2)</td>
<td>160</td>
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<td>35</td>
</tr>
<tr>
<td>5</td>
<td>DABCO (2)</td>
<td>160</td>
<td>24</td>
<td>40</td>
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<tr>
<td>6</td>
<td>NaH (2)</td>
<td>160</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>Piperidine (2)</td>
<td>110</td>
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<td>40</td>
</tr>
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<td>8</td>
<td>NMP (2)</td>
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<td>8</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>NMP (3)</td>
<td>120</td>
<td>8</td>
<td>65</td>
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</table>
Reaction conditions: 2-methylbenzimidazole (1 mmol), N-methylpiperazine (2 mmol) and DMSO (2 mL)

Having established the optimized reaction conditions, imidazole and a wide variety of 2-substituted benzimidazoles were investigated (Scheme 5A.2.3, Table 5A.2.2) for the same reaction methodology. As a result, a broad spectrum of N-methylthiomethylbenzimidazole(s) were obtained as shown in Table 5A.2.2.

Scheme 5A.2.3 N-Methylthiomethylation of imidazoles and benzimidazoles

Table 5A.2.2 N-Methylthiomethylation of imidazoles and benzimidazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product no.</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yields (%)</th>
</tr>
</thead>
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<td>1</td>
<td>5A.2.3a</td>
<td><img src="example.png" alt="Product 1" /></td>
<td>8</td>
<td>(65)\textsuperscript{12}</td>
</tr>
<tr>
<td>2</td>
<td>5A.2.3b</td>
<td><img src="example.png" alt="Product 2" /></td>
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<td>(60)\textsuperscript{12}</td>
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<td>62</td>
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<td>4</td>
<td>5A.2.3d</td>
<td><img src="example.png" alt="Product 4" /></td>
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<td>66</td>
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<td>5A.2.3e</td>
<td><img src="example.png" alt="Product 5" /></td>
<td>8.5</td>
<td>60</td>
</tr>
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<td>5A.2.3g</td>
<td>5A.2.3h</td>
<td>5A.2.3i</td>
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</tr>
<tr>
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<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>
Reaction conditions: benzimidazole (1 mmol), N-methylpiperazine (2 mmol) and DMSO (2 mL)

As an illustrative example, the structure of N-methylthiomethylation product of 2-phenylbenzimidazole (5A.2.3e, Table 5A.2.2, entry 5) was assessed by X-ray crystallography of its single crystal and is given below in Figure 5A.2.1.

Figure 5A.2.1 ORTEP diagram of compound 5A.2.3e (Table 5A.2.2, entry 5) with ellipsoids at 50 % probability (CCDC 780651).

A base catalysed mechanism for the N-methylthiomethylation of imidazole has been suggested below in which the valency of sulfur is reduced to 2 in the product from 4 (in DMSO).

Scheme 5A.2.4 Probable mechanism for the base catalysed N-methylthiomethylation of imidazole
The straightforward method for the synthesis of sulfoxides is the chemoselective oxidation of corresponding sulfide to sulfoxide. Therefore, once the N-methylthiomethylation of benzimidazoles was achieved, further chemoselective oxidation of these sulfides to sulfoxides came into my mind immediately.

The oxidation of sulfides to sulfoxides by \( \text{H}_2\text{O}_2 \) has proved to be one of the most attractive methods. Very recently, Amin Rostani et al.\(^{22}\) reported boric acid as a highly efficient and eco-friendly catalyst for the selective oxidation of sulfides to sulfoxides at room temperature under solvent-free condition using 30% \( \text{H}_2\text{O}_2 \) as an oxidant. I thought to test the oxidation of these sulfides under the same reaction condition. But unfortunately, even after 24 h of stirring at room temperature with 1.2 equivalent of \( \text{H}_2\text{O}_2 \) (30%), 0.1 mmol of boric acid using 1 mmol of prepared sulfide (5A.2.3b, Table 5A.2.2, entry 2) only 5% of sulfide was transformed into the desired product. Also, after 24 h of heating under reflux condition using the same proportion of \( \text{H}_2\text{O}_2 \), boric acid and sulfide, only 40% transformation of the sulfide to the desired sulfoxides were achieved. This unfortunate result forced me to search for a better oxidizing agent for the chemoselective oxidation of these sulfides to sulfoxides. After a thorough screening with the common oxidizing agents, NaBiO\(_3\) in acetic acid came out as the best choice for chemoselective oxidation of these sulfides to sulfoxides (Scheme 5A.2.5). The presence of acetic acid is extremely important as the reaction failed to produce the desired product in its absence. It has also been noticed that small amounts of acetone as co-solvent increased the yield of the reaction. Using this methodology a completely new class of organic sulfoxides was prepared (Scheme 5A.2.5, Table 5A.2.3)

![Scheme 5A.2.5 Chemoselective oxidation of sulfides to sulfoxides](image_url)
Table 5A.2.3 Chemoselective oxidation of sulfides to sulfoxides by NaBiO₃ in acetic acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product no.</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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</thead>
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<td>82</td>
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<tr>
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<td>5A.2.5b</td>
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<td>5A.2.5c</td>
<td><img src="image3" alt="Image" /></td>
<td>10</td>
<td>80</td>
</tr>
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<td>5A.2.5d</td>
<td><img src="image4" alt="Image" /></td>
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<td>82</td>
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<td>5</td>
<td>5A.2.5e</td>
<td><img src="image5" alt="Image" /></td>
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<td>78</td>
</tr>
<tr>
<td>6</td>
<td>5A.2.5f</td>
<td><img src="image6" alt="Image" /></td>
<td>16</td>
<td>70</td>
</tr>
</tbody>
</table>

Reaction conditions: sulfide (1mmol), NaBiO₃ (3 mmol), aqueous acetic acid (4 mL, 50% v/v) and acetone (4 mL)

The final structure of the sulfoxide was confirmed by the X-ray crystal structure of a single crystal of 5A.2.5c (Table 5A.2.3, entry 3) and is given below in Figure 5A.2.2.
The mechanism of the oxidation reaction by NaBiO\textsubscript{3} in acetic acid is not clear. Emil Kon and Edward McNelis predicted\textsuperscript{23} that the oxidation of phenol in acetic acid medium by NaBiO\textsubscript{3} involved a two electron oxidation and considering this reference it can also be predicted that the oxidation of sulfides to sulfoxides in this case may also proceed through two electron oxidation.

5A.3 Importance of the methodology

a) This is the first generalized approach for the rapid construction of N-methylthiomethylbenzimidazoles by a one step base catalysed reaction using DMSO both as a solvent and as a reagent.

b) Moderate reaction protocol, use of readily available reagents, good yields and simple work-up procedure are the main feature of this methodology.

c) NaBiO\textsubscript{3} in acetic acid has been used for the first time for the chemoselective oxidation of N-methylthiomethylbenzimidazoles to the corresponding sulfoxide analogues and thus yielding a completely new class of important sulfoxide derivatives.

5A.4 Conclusion: A straightforward method for the N-methylthiomethylation of benzimidazoles has been described under moderate reaction condition. Relatively mild reaction conditions, a wide range of substrate affordability and high yields are the major advantages of this methodology. Again, chemoselective oxidation of these N-
methylthiomethylimidazoles to sulfoxides has been achieved using NaBiO₃ in acetic acid medium as oxidizing agent. This is the first report of synthesis of this kind of sulfoxides.

This work has been recently communicated

"Unusual one-step N-methylthiomethylation of benzimidazoles with DMSO and their chemoselective oxidation to sulfoxides with NaBiO₃ under acidic conditions: a new approach" Chhanda Mukhopadhyay, Pradip Kumar Tapaswi, Swarbhanu Sarkar and Michael G. B. Drew, 2010 (communicated)

5A.5 Experimental

5A.5.1 Materials and instruments

General: All the chemicals were purchased from Aldrich Chemical Company and Spectrochem, Pvt. Ltd. (Mumbai, India). Silica Gel G with binder from Spectrochem, Pvt. Ltd. Mumbai, India was used for thin layer chromatography. ¹H and ¹³C NMR spectra were obtained on Bruker 300 MHz instrument at 300 and 75 MHz respectively. CDCl₃ was purchased from Aldrich Chemical Company and d₆-DMSO from CIL. Melting points were determined on an electrical melting point apparatus with an open capillary and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrophotometer RX / FT-IR system. The C-H-N analyses were carried out on a 2400 series II CHNS Analyzer, Perkin Elmer (USA).

5A.5.2 General experimental procedure

5A.5.2.1 General experimental procedure for the N-methylthiomethylation of imidazoles

In an Erlenmeyer flask, imidazole (1 mmol), N-methylpiperazine (2 mmol) and dry DMSO (99.9%) (2 mL) were mixed and heated in an oil-bath for the stipulated time (Table 5A.2.2). After the completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure in a rotary evaporator. The concentrated crude product was separated by column chromatography using silica gel (60-120 mesh) as column material and petroleum ether (60-80 °C) and ethyl acetate as eluants.

5A.5.2.2 General experimental procedure for the preparation of sulfoxides

In an Erlenmeyer flask, sulfide (1 mmol), NaBiO₃ (3 mmol), aqueous acetic acid (4 mL, 50% v/v) and acetone (4 mL) were mixed and refluxed for stipulated time (Table 5A.2.3). After the completion of the reaction (monitored by TLC), the reaction mixture was filtered
through a pad of celite and diluted with water (10 mL). The mixture was extracted with 
EtOAc (3 x 10 mL). The EtOAc extract was washed with sodium bicarbonate solution (3 x 
10 mL), brine (10 mL), dried over anhydrous sodium sulphate and concentrated under 
reduced pressure. The crude product was separated by column chromatography using silica 
gel (60–120 mesh) as column material and petroleum ether (60-80 °C) and ethyl acetate as 
eluants. The characteristic data of all the representative compounds are given below.

5A.5.3 Characteristic data of the representative compounds

1-Methylsulphanylmethyl-1H-imidazole\textsuperscript{12} (5A.2.3a, Table 5a.2.2, entry 1): Colourless oil; 
\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 2.03 (s, 3H), 4.93 (s, 2H), 7.08 (d, \( J = 7.2 \) Hz, 2H), 7.72(s, 
1H).

2-Methyl-1-methylsulphanylmethyl-1H-benzimidazole\textsuperscript{12} (5A.2.3b, Table 5a.2.2, entry 2): 
Colourless semisolid; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 1.98 (s, 3H), 2.59 (s, 3H), 5.04 (s, 2H), 
7.22 – 7.18 (m, 2H), 7.33 – 7.30 (m, 1H) 7.70 – 7.62 (m, 1H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): 
13.8, 14.2, 46.0, 109.4 (2C), 118.8 (2C), 122.2, 122.3, 134.6, 141.6, 151.3.

2,5-Dimethyl-1-methylsulphanylmethyl-1H-benzimidazole (5A.2.3c, Table 5a.2.2, entry 
3): (mixture of two tautomers), colorless semisolid; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 1.86 and
1.82 (two s, 3H), 2.31 and 2.28 (two s, 3H), 2.43 (s, 3H), 4.89 (s, 2H), 6.89 (d, J = 8.1 Hz, 1H), 6.98 (s, 0.47 H), 7.07 (d, J = 8.1 Hz, 0.56H), 7.30 (s, 0.53 H), 7.38 (d, J= 8.1 Hz, 0.44 H); 13C NMR (75 MHz, CDCl3): δ 13.8, 14.1, 21.3, 21.6, 45.8, 46.0, 108.9, 109.4, 118.4, 118.8, 123.6, 123.6, 131.8, 132.2, 132.9, 135.0, 140.1, 142.3, 150.8, 151.3; ESI-MS (m/z): 207.0 (M+1); IR (neat): 682, 852, 1090, 1276, 1380, 1463, 1532, 2376, 2909 cm⁻¹;
Elemental Analysis calculated for C11H14N2S: C 64.04, H 6.84, N 13.58% Found: C 63.94, H 6.90, N 13.62%.

1-Methylsulphanylmethyl-2,5,6-trimethyl-1H-benzimidazole (5A.2.3d, Table 5a.2.2, entry 4): colorless solid; mp 112–114 °C (EtOAc); 1H NMR (300 MHz, CDCl3): δ 2.02 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 2.59 (s, 3H), 5.05 (s, 2H), 7.12 (s, 1H), 7.42 (s, 1H); 13C NMR (75 MHz, CDCl3): δ 13.9, 14.1, 20.1, 20.4, 46.0, 109.8, 119.3, 130.9, 131.2, 133.4, 140.9, 150.5; ESI-MS (m/z): 221.1 (M⁺+1); HRMS (m/z) for C12H16N2S; calcd 220.1034, found 220.1032; IR (KBr): 675, 847, 990, 1291, 1389, 1453, 1521, 2372, 2919 cm⁻¹;
Elemental Analysis calculated for C12H16N2S: C 65.41, H 7.32, N 12.71% Found: C 65.29, H 7.40, N 12.75%.

1-Methylsulphanylmethyl-2-phenyl-1H-benzimidazole (5A.2.3e, Table 5a.2.2, entry 5): pale yellow solid; mp 156–158 °C (EtOAc); 1H NMR (300 MHz, CDCl3): δ 1.91 (s, 3H), 5.24 (s, 2H), 7.34 – 7.28 (m, 2H), 7.51-7.49 (m, 4H), 7.86-7.74 (m, 3H); 13C NMR (75 MHz, CDCl3): δ 14.6, 47.3, 110.8, 119.9, 122.9, 123.0, 128.7 (2C), 129.5 (2C), 129.7, 129.9, 134.9, 142.7, 153.7; ESI-MS (m/z): 255.0 (M⁺+1); HRMS (m/z) for C15H14N2S; calcd 254.0878, found 254.0876; IR (KBr): 750, 1000, 1077, 1151, 1277, 1365, 1447, 2374, 2920, 2993, 3047 cm⁻¹; Elemental Analysis calculated for C15H14N2S: C 70.83, H 5.55, N 11.01% Found: C 70.71, H 5.65, N 11.03%
5-Methyl-1-methylsulphonylmethyl-2-phenyl-1H-benzimidazole (5A.2.3f, Table 5a.2.2, entry 6): (mixture of two tautomers); yellow solid; mp 72-74 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): δ 1.91 (s, 3H), 2.52 and 2.49 (two s, 3H), 5.24 (s, 2H), 7.15 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 0.6 Hz, 0.44H), 7.40 (d, J = 8.2 Hz, 0.44H), 7.56-7.47 (m, 3H), 7.62 (d, J = 0.6 Hz, 0.56 H), 7.71 (d, J = 8.2 Hz, 0.56 H), 7.82-7.52 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 14.6, 21.5, 21.8, 47.2, 47.4, 110.4, 110.7, 119.4, 119.6, 124.6, 128.8, 129.5, 129.6, 129.7, 129.9, 128.0, 132.8, 133.0, 133.1, 135.1, 140.8, 142.9, 153.2, 153.6; ESI-MS (m/z): 269.2 (M$^+$+1); IR (KBr): 701, 780, 800, 1278, 1382, 1444, 1620, 2321, 1922, 3060 cm$^{-1}$; Elemental Analysis calculated for C$_{16}$H$_{16}$N$_2$S: C 71.61, H 6.01, N 10.44% Found: C 71.54, H 6.05, N 10.47%

5,6-Dimethyl-1-methylsulphonylmethyl-2-phenyl-1H-benzimidazole (5A.2.3g, Table 5a.2.2, entry 7): white crystalline solid; mp 82-84 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): δ 1.91 (s, 3H), 2.39 (s, 3H), 2.42 (s, 3H), 5.24 (s, 2H), 7.29 (s, 1H), 7.52-7.49 (m, 3H), 7.58 (s, 1H), 7.76-7.72 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 14.5, 20.2, 20.6, 47.3, 111.0, 120.0, 128.7 (2C), 129.5 (2C), 130.1, 131.8, 132.2, 133.5, 141.6, 153.1; ESI-MS (m/z): 283.1 (M$^+$+1); HRMS (m/z) for C$_{17}$H$_{18}$N$_2$S; calcd 282.1191, found 282.1201; IR (KBr): 701, 847, 999, 1072, 1177, 1280, 1383, 1461, 1627, 2330, 2923 cm$^{-1}$; Elemental Analysis calculated for C$_{17}$H$_{18}$N$_2$S: C 72.30, H 6.42, N 9.92% Found: C 7219, H 6.49, N 9.96%

2-(4'-Chlorophenyl)-1-methylsulphonylmethyl-1H-benzimidazole (5A.2.3h, Table 5a.2.2, entry 8): colorless crystalline solid; mp 100-102 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): δ 2.00 (s, 3H), 5.26 (s, 2H), 7.38 – 7.32 (m, 2H), 7.53 (td, J = 6.6 and 1.8 Hz, 3H),
7.77 (td, J = 8.4 and 2.0 Hz, 2H), 7.85 – 7.81 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 14.9, 47.4, 110.7, 120.1, 123.1, 123.3, 128.5, 129.2 (2C), 130.9 (2C), 135.3, 136.3, 143.0, 152.6; ESI-MS (m/z): 289.0 (M$^{+}$+1); HRMS (m/z) for C$_{15}$H$_{13}$N$_2$SCl: calc 288.0488, found 288.0482; IR (KBr): 740, 1049, 1089, 1182, 1242, 1346, 1529, 2374, 2866, 2922, 3090 cm$^{-1}$; Elemental Analysis calculated for C$_{15}$H$_{13}$N$_2$SCl: C 62.38, H 4.45, N 9.70%; Found: C 62.22, H 4.55, N 9.76%

1-MethyIsulphanyImethyl-2-(4'-nitrophenyl)-1H-benzimidazole (5A.2.3i, Table 5a.2.2, entry 9): yellow solid; mp 164 – 166 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.04 (s, 3H), 5.33 (s, 2H), 7.47 – 7.38 (m, 2H), 7.62 – 7.58 (m, 1H), 7.90 - 7.86 (m, 1H), 8.12 (d, J = 8.4 Hz, 2H), 8.41 (d, J = 8.4 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 15.1, 48.0, 111.1, 119.9, 124.2 (2C), 124.2, 124.6, 130.8 (2C), 134.8, 135.1, 141.4, 148.9, 150.5; ESI-MS (m/z): 300.0 (M$^{+}$+1); HRMS (m/z) for C$_{15}$H$_{13}$N$_2$S; calc 299.0728, found 299.0726; IR (KBr): 746, 855, 1281, 1340, 1452, 1521, 2923 cm$^{-1}$; Elemental Analysis calculated for C$_{15}$H$_{13}$N$_2$S: C 60.18, H 4.38, N 14.04%; Found: C 60.10, H 4.46, N 14.04%

2-(4'-N,N-dimethylaminophenyl)-1-methylsulphanyImethyl-1H-benzimidazole (5A.2.3j, Table 5a.2.2, entry 10): colorless crystalline solid; mp 150 – 152 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.98 (s, 3H), 3.03 (s, 6H), 5.29 (s, 2H), 6.79 (d, J = 9.0 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.51 - 7.46 (m, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.84 – 7.79 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 14.7, 40.1 (2C), 47.6, 110.6, 111.8 (2C), 115.8, 119.1, 122.6, 122.9, 130.6 (2C), 134.8, 141.9, 151.4, 154.4; ESI-MS (m/z): 298.0 (M$^{+}$+1); HRMS (m/z) for C$_{17}$H$_{19}$N$_3$S; calc 297.1300, found 297.1290; IR (KBr): 743, 816, 940, 1062, 1185, 1277, 1367, 1483, 1608, 2376, 2918 cm$^{-1}$; Elemental Analysis calculated for C$_{17}$H$_{19}$N$_3$S: C 68.65, H 6.44, N 14.13%; Found: C 68.57, H 6.46, N 14.19%
2-(3',4'-Dimethoxyphenyl)-1-methylsulphonylmethyl-1H-benzimidazole (5A.2.3k, Table 5a.2.2, entry 11): pale yellow solid; mp 94 – 96 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.98 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.28 (s, 2H), 6.93 (d, J = 8.1 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.35 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.50 – 7.46 (m, 1H), 7.78 – 7.75 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 15.0, 47.9, 56.0, 56.3, 110.9, 111.2, 112.8, 119.0, 120.4, 122.6, 123.6, 123.7, 134.5, 140.3, 149.4, 151.1, 153.0; ESI-MS (m/z): 315.1 (M$^{+}$+1); IR (KBr): 745, 1021, 1142, 1260, 1451, 1605, 2374, 2925 cm$^{-1}$; Elemental Analysis calculated for C$_{17}$H$_{18}$N$_2$O$_2$S: C 64.94, H 5.77 N 8.91% Found: C 64.83, H 5.85, N 8.94%

2-(3',4'-Dimethoxyphenyl)-5,6-dimethyl-1-methylsulphonylmethyl-1H-benzimidazole (5A.2.3l, Table 5a.2.2, entry 12): pale yellow solid; mp 96–98 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.02 (s, 3H), 2.38 (s, 3H), 2.42 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 5.24 (s, 2H), 6.98 (d, J = 8.2 Hz, 1H), 7.26 (s, 1H), 7.33 (dd, J = 8.2 and 1.8 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.56 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 14.8, 20.2, 20.7, 47.5, 56.0, 56.1, 110.8, 111.1, 112.7, 119.9, 122.3, 122.6, 131.8, 132.2, 133.8, 141.5, 149.2, 150.4, 153.1; ESI-MS (m/z): 343.1 (M$^{+}$+1); IR (KBr): 1020, 1141, 1261, 1379, 1475, 1508, 1602, 2372, 2853, 2924 cm$^{-1}$; Elemental Analysis calculated for C$_{19}$H$_{22}$N$_2$O$_2$S: C 66.64, H 6.48, N 8.18% Found: C 66.54, H 6.55, N 8.21%

5,6-Dimethyl-2-(4'-methoxyphenyl)-1-methylsulphonylmethyl-1H-benzimidazole (5A.2.3m, Table 5a.2.2, entry 13): pale yellow solid; mp 102 – 104 °C (EtOAc); $^1$H NMR
(300 MHz, CDCl₃): δ 1.94 (s, 3H), 2.39 (s, 3H), 2.42 (s, 3H), 3.88 (s, 3H), 5.23 (s, 2H), 7.03 (td, J = 8.7, and 2.3 Hz, 2H), 7.27 (s, 1H), 7.56 (s, 1H), 7.72 (td, J = 8.7 and 2.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 14.6, 20.2, 20.6, 47.3, 55.4, 110.9, 114.2 (2C), 119.9, 122.4, 131.0 (2C), 131.8, 132.0, 133.6, 141.5, 153.1, 160.8; ESI-MS (m/z): 313.1 (M⁺+1); IR (KBr): 847, 1030, 1175, 1457, 1606, 2850, 2923 cm⁻¹; Elemental Analysis calculated for C₁₈H₂₀N₂O₅S: C 69.20, H 6.45, N 8.97% Found: C 69.12, H 6.48, N 9.02%

2-(4'-Chlorophenyl)-5,6-dimethyl-1-methylsulphonylmethyl-1H-benzimidazole (5A.2.3n, Table 5a.2.2, entry 14): colorless crystalline solid; mp 178 – 180 °C (EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 1.95 (s, 3H), 2.38 (s, 3H), 2.43 (s, 3H), 5.26 (s, 2H), 7.31 (s, 1H), 7.50 (d, J =8.4 Hz, 2H), 7.57 (s, 1H), 7.77 (d, J = 8.4Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 14.7, 20.2, 20.7, 42.8, 111.2, 119.0, 126.7, 129.3 (2C), 130.5 (2C), 131.0, 132.9, 133.2, 133.5, 136.9, 150.7; ESI-MS (m/z): 317.0 (M⁺+1); HRMS (m/z) for C₁₇H₁₇N₂SCI; calcd 316.0801, found 316.0793; IR (KBr): 843, 1000, 1087, 1288, 1319, 1461, 2376, 2921 cm⁻¹; Elemental Analysis calculated for C₁₇H₁₇N₂SBr: C 64.44, H 5.41, N 8.84% Found: C 64.33, H 5.50, N 8.86%

2-(4'-Bromophenyl)-5,6-dimethyl-1-methylsulphonylmethyl-1H-benzimidazole (5A.2.3o, Table 5a.2.2, entry 15): colorless crystalline solid; mp 182 – 184 °C (EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 1.95 (s, 3H), 2.38 (s, 3H), 2.42 (s, 3H), 5.22 (s, 2H), 7.29 (s, 1H), 7.56 (s, 1H), 7.70-7.63 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ 14.8, 20.2, 20.7, 47.8, 111.3, 119.0, 125.3, 127.1, 131.1 (2C), 132.3 (2C), 132.9, 133.3, 133.6, 138.6, 150.8; ESI-MS (m/z): 361.0 (M⁺+1); HRMS (m/z) for C₁₇H₁₇N₂SBr; calcd 360.0296, found 360.0302; IR (KBr): 840, 1000, 1067, 1286, 1400, 1463, 1595, 2464, 2858, 2922 cm⁻¹; Elemental Analysis calculated for C₁₇H₁₇N₂SBr: C 56.51, H 4.74, N 7.75% Found: C 56.39, H 4.83, N 7.78%
5,6-Dimethyl-2-(4'-N,N-dimethylaminophenyl)-1-methylsulphanylmethyl-1H-benzimidazole (5A.2.3p, Table 5a.2.2, entry 16): pale yellow solid; mp 156 – 158 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.96 (s, 3H), 2.42 (s, 3H), 2.47 (s, 3H), 3.04 (s, 6H), 5.27 (s, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 7.26 (s, 1H), 7.58 (s, 1H), 7.68 (d, $J = 9.0$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 14.5, 20.2, 20.6, 40.1 (2C), 47.4, 110.9, 111.8 (2C), 116.4, 119.3, 130.5 (2C), 131.7 (2C), 133.4, 140.8, 151.2, 153.7; ESI-MS (m/z): 326.1 (M$^{+}+1$); IR (KBr): 740, 1049, 1089, 1182, 1242, 2922, 3090 cm$^{-1}$; Elemental Analysis calculated for C$_{19}$H$_{23}$N$_3$S: C 70.11, H 7.12, N 12.91% Found: C 69.99, H 7.21, N 12.94%

2-(1H-Benzimidazol-2-yl)-1-methylsulphanylmethyl-1H-benzimidazole (5A.2.3q, Table 5a.2.2, entry 17): white solid; mp 200 - 202 °C (EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.17 (s, 3H), 6.45 (s, 2H), 7.33 – 7.19 (m, 4H), 7.43 (t, $J = 7.8$ Hz, 1H), 7.68 (d, $J = 8.7$ Hz, 2H), 7.88 (d, $J = 7.8$ Hz, 1H), 14.30 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 14.5, 47.5, 111.7, 111.9, 119.6, 120.3, 122.7, 123.9, 124.3, 124.4, 134.0, 135.5, 142.0, 143.3, 143.5, 143.9; ESI-MS (m/z): 295.0 (M$^{+}+1$); IR (KBr): 767, 1034, 1241, 1356, 1453, 2356, 2907, 2990, 3040 cm$^{-1}$; Elemental Analysis calculated for C$_{16}$H$_{14}$N$_4$S: C 65.28, H 4.79, N 19.03% Found: C 65.21, H 4.86, N 19.04%

2-Methyl-1-methanesulphinylmethyl-1H-benzimidazole (5A.2.5a, Table 5a.2.3, entry 1): pale yellow solid; mp 186 – 188 °C (MeOH and EtOAc); $^1$H NMR (300 MHz, $d_6$-DMSO): $\delta$ 2.56 (s, 3H), 2.68 (s, 3H), 5.44 (d, $J = 13.8$ Hz, 1H), 5.59 (d, $J = 13.8$ Hz, 1H), 7.20 – 7.15
(m, 2H), 7.53 – 7.50 (m, 1H), 7.61 – 7.58 (m, 1H); \(^{13}\text{C}\) NMR (75 MHz, \(d_6\)-DMSO): \(\delta\) 14.0, 36.1, 62.5, 110.6, 118.5, 122.0, 122.1, 135.3, 142.3, 153.1; ESI-MS (m/z): 209.0 (M\(^{+1}\)); IR (KBr): 856, 1080, 1376, 1465, 1543, 2374, 2928, 2995 cm\(^{-1}\); Elemental Analysis calculated for \(\text{C}_{10}\text{H}_{12}\text{N}_2\text{OS}\): C 57.67, H 5.81, N 13.45% Found: C 57.58, H 5.88, N 13.47%

1-Methanesulphinylmethyl-2,5,6-trimethyl-1H-benzimidazole (5A.2.5b, Table 5a.2.3, entry 2): pale yellow solid; mp 72 – 74 °C (MeOH and EtOAc); \(^1\text{H}\) NMR (300 MHz, \(d_6\)-DMSO): \(\delta\) 2.24 (s, 3H), 2.26 (s, 3H), 2.51 (s, 3H), 2.71 (s, 3H), 5.36 (d, \(J = 14.1\) Hz, 1H), 5.52 (d, \(J = 14.1\) Hz, 1H), 7.28 (s, 1H), 7.37 (s, 1H); \(^{13}\text{C}\) NMR (75 MHz, \(d_6\)-DMSO): \(\delta\) 14.0, 19.9, 20.18, 36.1, 62.7, 110.8, 118.7, 130.3, 130.5, 133.8, 140.8, 152.1; ESI-MS (m/z): 237.0 (M\(^{+1}\)); HRMS (m/z) for \(\text{C}_{12}\text{H}_{16}\text{N}_2\text{OS}\); calcd 236.0983, found 236.0973; IR (KBr): 846, 1050, 1398, 1465, 1527, 2371, 2919, 2974 cm\(^{-1}\); Elemental Analysis calculated for \(\text{C}_{12}\text{H}_{16}\text{N}_2\text{OS}\): C 60.99, H 6.82, N 11.85% Found: C 60.87, H 6.91, N 11.88%

1-Methanesulphinylmethyl-2-phenyl-1H-benzimidazole (5A.2.5c, Table 5a.2.3, entry 3): Colorless crystalline solid; mp 68 – 70 °C (MeOH and EtOAc); \(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.42 (s, 3H), 5.08 (d, \(J = 13.5\) Hz, 1H), 5.19 (d, \(J = 13.5\) Hz, 1H), 7.31 – 7.22 (m, 2H), 7.50 – 7.47 (m, 4H), 7.77 – 7.69 (m, 3H); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)): \(\delta\) 36.6, 64.6, 110.6, 119.7, 123.3, 123.5, 128.7 (2C), 129.8 (2C), 130.1, 135.1 (2C), 142.3, 153.7; ESI-MS (m/z): 271.0 (M\(^{+1}\)); IR (KBr): 753, 1037, 1392, 1458, 2184, 3191 cm\(^{-1}\); Elemental Analysis calculated for \(\text{C}_{13}\text{H}_{14}\text{N}_2\text{OS}\): C 66.64, H 5.22, N 10.36% Found: C 66.56, H 5.26, N 10.40%

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5-Methyl-1-methanesulphinylmethyl-2-phenyl-1H-benzimidazole (5A.2.5d, Table 5a.2.3, entry 4): (mixture of two tautomers); pale yellow solid; mp 68 – 70 °C (MeOH and EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.46 (s, 1.18H), 2.49 (s, 1.82 H), 2.51 (s, 3H), 5.30 – 5.13 (m, 2H), 7.13 (d, J = 8.1 Hz, 1.21 H), 7.34 (s, 0.57 H), 7.52 – 7.40 (m, 3H), 7.53 (s, 0.43 H), 7.63 (d, J = 8.4 Hz, 0.79 H), 7.80 – 7.70 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 21.4, 21.8, 36.9, 64.9, 110.5, 110.7, 119.3, 119.3, 125.4, 125.5, 128.2, 128.5, 129.0, 129.0, 130.0, 130.0, 130.4, 130.6, 133.0, 133.9, 134.2, 135.3, 139.9, 141.7, 153.1, 153.5; ESI-MS (m/z): 285.0 (M$^{+1}$+1); IR (KBr): 774, 1082, 1397, 1478, 1522, 2284, 2996 cm$^{-1}$; Elemental Analysis calculated for C$_{16}$H$_{16}$N$_2$OS: C 67.58, H 5.67, N 9.85% Found: C 67.49, H 5.72, N 9.89%

2-(4'-Chlorophenyl)-1-methanesulphinylmethyl-1H-benzimidazole (5A.2.5e, Table 5a.2.3, entry 5): Colorless crystalline solid; mp 94 – 96 °C (MeOH and EtOAc); $^1$H NMR (300 MHz, CDCl$_3$ + three drops of d$_6$-DMSO): $\delta$ 2.49 (s, 3H), 5.04 (d, J = 13.5 Hz, 1H), 5.15 (d, J = 13.5 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.44 – 7.34 (m, 3H), 7.71 – 7.66 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$ + three drops of d$_6$-DMSO): $\delta$ 36.7, 64.6, 110.5, 119.7, 123.4, 123.5, 127.2, 128.8 (2C), 131.2 (2C), 135.0, 136.3, 142.2, 152.7; ESI-MS (m/z): 305.0 (M$^{+1}$+1); HRMS (m/z) for C$_{15}$H$_{13}$ClN$_2$OS; calcd 304.0437, found 304.0435; IR (KBr): 741, 1045, 1246, 1380, 1407, 1459, 1603, 2377, 2919, 2996, 3054 cm$^{-1}$; Elemental Analysis calculated for C$_{15}$H$_{13}$ClN$_2$OS: C 59.11, H 4.30, N 9.19% Found: C 59.02, H 4.37, N 9.21%

1-Methanesulphinylmethyl-2-(4'-nitrophenyl)-1H-benzimidazole (5A.2.5f, Table 5a.2.3, entry 6): Yellow solid; mp 212–214 °C (MeOH and EtOAc); $^1$H NMR (300 MHz, d$_6$-
DMSO): δ 2.72 (s, 3H), 5.50 (d, J = 14.1 Hz, 1H), 5.64 (d, J = 14.1 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 8.20 (d, J = 8.4 Hz, 2H), 8.35 (d, J = 8.4 Hz, 2H); 13C NMR (75 MHz, d6-DMSO): δ 36.3, 63.6, 112.1, 119.8, 123.4, 123.7, 123.8, 131.5 (2C), 135.5 (2C), 135.9, 142.5, 148.1, 152.0; ESI-MS (m/z): 316.3 (M+1); IR (KBr): 746, 857, 1052, 1343, 1512, 1599, 2448, 2922 cm⁻¹; Elemental Analysis calculated for C13H13N3O3S: C 57.13, H 4.16, N 13.33% Found: C 56.99, H 4.25, N 13.38%
5A.5.4 Few representative spectra of previously unknown products

a)

CHS DEPT or CHEMISTRY CD Bruker A.H 300 Supercon 300 System 5nmProbe
Sample no PET-128(A) 500 pCDCl3 Dr. Mukhopadhyay 17.06.08 Operator P. Ghose & S. Chatterjee

- 1H NMR and b) 13C NMR spectra of product [5A.2.3e] (Table 5A.2.2, entry 5)

Figure 5A.5.4.1 a) 1H NMR and b) 13C NMR spectra of product [5A.2.3e] (Table 5A.2.2, entry 5)
Figure 5A.5.4.2 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5A.2.3h] (Table 5A.2.2, entry 8)
Figure 5A.5.4.3  a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5A.2.3p] (Table 5A.2.2, entry 16)
Figure 5A.5.4.4 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5A.2.3q] (Table 5A.2.2, entry 17)
Figure 5A.5.5.5 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5A.2.5a] (Table 5A.2.3, entry 1)
Figure 5A.5.4.6 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5A.2.5c] (Table 5A.2.3, entry 3)
5A.5.5 Detailed analysis data of the two X-ray crystal structures (ORTEP diagrams given in Figure 5A.2.1 and 5A.2.2 respectively)

Compound 5A.2.3e (Table 5A.2.2, entry 5): C15H14N2S, M = 254.34, monoclinic, space group P2_1/c, Z = 4, a = 11.8986(7), b = 7.7364(3), c = 14.0305(8)Å, β = 95.129(6)°, V = 1286.37(12)Å³, ρ_calc = 1.313 gcm⁻³

Compound 5A.2.5c (Table 5A.2.3, entry 3): C30.5H37N4O6S2, M = 619.76, monoclinic, space group P2_1/n, Z = 4, a = 20.4771(9), b = 7.3488(2), c = 21.1873(17)Å, β = 108.114(6)°, V = 3030.3(3)Å³, ρ_calc = 1.358 gcm⁻³

3714, 8759 independent reflection data were collected with MoKα radiation at 150K using the Oxford Diffraction X-Calibur CCD System. The crystals were positioned at 50 mm from the CCD. 321 frames were measured with a counting time of 10s. Data analyses were carried out with the CrysAlis program. The structures were solved using direct methods with the Shelxs97 program. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. In compound 5A.2.5c, there were two water molecules refined with full occupancy. The hydrogen atoms were located in a difference Fourier map and refined with distance constraints. Three water molecules were also located with reduced occupancy (70, 30, 50% respectively) but their hydrogens could not be located. One methanol molecule was also located and refined with 50% occupancy.

The structures were refined on F² using Shelxl97 to R1 0.0400, 0.0788; wR2 0.0942, 0.2130 for 2544, 5921 data with I>2σ(I).

The structure of compound 5A.2.5c contains 2 molecules in the asymmetric unit together with five water molecules, three of which have reduced occupancy and one methanol, also with reduced occupancy. The two molecules in the asymmetric unit have similar geometries as is apparent from figure 5A.2.2.

In particular the angles around the N1-C and C-S11 bonds are 109.1(3) in A, -106.2(3) in B and -69.9(2) in A, 74.2(2)° in B respectively thus showing that the molecules are opposite enantiomers.

The phenyl rings in the two structures stack with the six C...C distances ranging from 3.54 to 3.75Å. The angle between the two phenyl ring planes is 2.3(1)°.
References


Chapter 5 (Section 5B)

A new three component aza-Friedel Crafts type reaction of imidazole towards 2-substituted imidazoles: scope and limitations
5B.1 Introduction
This section deals with a new three-component reaction involving imidazole, aromatic aldehydes and cyclic secondary amines to form diverse 2-substituted [(α-aryl-α'-amino)methyl]imidazoles.

5B.1.1 Importance of the substituted imidazoles
The imidazole nucleus is a common structural motif encountered in numerous biomolecules such as biotin, essential amino acid-histidine and the pilocarpin alkaloids. Some imidazole alkaloids manifest antimicrobial, antifungal and cytotoxic activities. Recent advancements in organometallic catalysis and green chemistry have extended the applicability of substituted imidazoles as ionic liquids, stable nucleophilic carbenes and organocatalysts. Therefore, reactions involving imidazoles to deliver versatile imidazole derivatives is a work of supreme importance. Before going into details about the three component aza-Friedel Crafts reaction of imidazole, I would like to present a brief review on some of the very recent work in this regard.

5B.1.2 A short review on the aza-Friedel-Crafts type reaction on nitrogen containing heterocycles

It was D. J. Hlasta and his coworkers who actually for the first time developed a new approach for the preparation of 2-substituted azole libraries using a polystyrene-carbamyl chloride resin in a traceless fashion.

Later, D. J. Hlasta modified the above methodology in order to meet even less reactive azoles like thiazoles. They described the synthesis of 2-substituted azoles by the reaction of an azolium ylide with reactive carbonyl compounds.
S. Shirakawa et al. described the carboxylic acid catalysed three-component aza-Friedel-Crafts reactions of aldehydes, primary amines and indoles in water. The aza-Friedel-Crafts products could be easily transformed to various 3-substituted indoles including biologically active compounds.\(^9\)

A novel and facile method for the direct construction of C–C–N bond with unsubstituted azoles under Mannich conditions has been developed for the first time by N. Srinivas et al. using L-proline as a catalyst.\(^10\)
A novel three-component reaction between 1-substituted imidazoles, aldehydes and electron-deficient acetylenes was developed by Boris A. Trofimov and his coworkers under mild conditions (20-25 °C, no catalyst and no solvent) to form an unknown family of C2-functionalized imidazoles.\textsuperscript{11}

\[
\begin{array}{c}
\text{R}^1 = \text{Me, Et, Feu, Bn, HC}==\text{CH}_2 \\
\text{R}^2 = \text{Me, Ph} \\
\text{R}^3 = \text{CO}_2\text{Et, CN} \\
\text{R}^4 = \text{Me, }^{\circ}\text{Pr, }^{\circ}\text{Bu, Ph}
\end{array}
\]

S. Ge'rand et al. developed a Ti(IV)/Et\textsubscript{3}N-promoted trimolecular condensation of aromatic heterocycles (furan, pyrrole, imidazole, indole) with aldehydes and active methylene compounds.\textsuperscript{12}

\[
\begin{array}{c}
\text{Het.} + \text{R}^1==\text{CHO} + \text{R}^3\text{O}_2\text{C}^+ \xrightarrow{\text{TiCl}_4 \text{ or TiCl}_2\text{(O'}\text{Pr)}_2} \text{R}^1\text{CO}_2\text{R}^3 \\
\text{Het.} = \text{indole, imidazole, pyrrole and furan} \\
\text{R}^1 = \text{alkyl, aryl}...... \quad \text{R}^2 = \text{Me, Et}...... \quad \text{R}^3 = \text{CO}_2\text{Et, COMe etc}
\end{array}
\]
5B.2 Results and Discussion

In this chapter, a novel three-component reaction between imidazole, aromatic aldehydes and cyclic secondary amines to form diverse 2-substituted [(α-aryl-α'-amino)methyl]imidazoles has been reported (Scheme 5B.2.1).

In order to standardize the multi-component reaction of imidazole with aromatic aldehydes and cyclic secondary amines, 4-chlorobenzaldehyde (2 mmol), imidazole (1 mmol) and piperidine (3 mmol) (Scheme 5B.2.2) were mixed and stirred initially at room temperature for 24 h which resulted in no appreciable conversion of imidazole into the desired product. Then, the reaction mixture was heated in an oil bath at 110 °C for 24 h which led to very poor conversion (Table 5B.2.1, entry 2). The same reaction was tried in different solvents in order to test whether there was any influence of the solvents in this reaction. After some screening with several polar and non-polar solvents, toluene came out as the best choice. Complete conversion of imidazole occurred after only 6 h of reflux in toluene. Bases such as K$_2$CO$_3$, Cs$_2$CO$_3$, Et$_3$N, Pr$_3$N, DABCO had no additional influence in this reaction suggesting excess amine (3 equivalents) itself providing the basic condition required. With lesser equivalents of the starting secondary amine, the reaction did not go to completion. The complete optimization is given in Table 5B.2.1.

Scheme 5B.2.1 Three component reaction between imidazole, aromatic aldehydes and cyclic secondary amines

In order to standardize the multi-component reaction of imidazole with aromatic aldehydes and cyclic secondary amines, 4-chlorobenzaldehyde (2 mmol), imidazole (1 mmol) and piperidine (3 mmol) (Scheme 5B.2.2) were mixed and stirred initially at room temperature for 24 h which resulted in no appreciable conversion of imidazole into the desired product. Then, the reaction mixture was heated in an oil bath at 110 °C for 24 h which led to very poor conversion (Table 5B.2.1, entry 2). The same reaction was tried in different solvents in order to test whether there was any influence of the solvents in this reaction. After some screening with several polar and non-polar solvents, toluene came out as the best choice. Complete conversion of imidazole occurred after only 6 h of reflux in toluene. Bases such as K$_2$CO$_3$, Cs$_2$CO$_3$, Et$_3$N, Pr$_3$N, DABCO had no additional influence in this reaction suggesting excess amine (3 equivalents) itself providing the basic condition required. With lesser equivalents of the starting secondary amine, the reaction did not go to completion. The complete optimization is given in Table 5B.2.1.
Scheme 5B.2.2 Three component reaction of imidazole, piperidine and 4-chlorobenzaldehyde

Table 5B.2.1 Optimization of the three component reaction of imidazole, piperidine and 4-chlorobenzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%) (isolated)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>-</td>
<td>Room temperature</td>
<td>24</td>
<td>nil</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>100</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>45</td>
<td>24</td>
<td>10</td>
</tr>
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<td>65</td>
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<td>8</td>
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<td>100</td>
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</tr>
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<td>9</td>
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<td>110</td>
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</tr>
<tr>
<td>10</td>
<td>Toluene</td>
<td>110</td>
<td>6</td>
<td>88</td>
</tr>
</tbody>
</table>

Reaction conditions: 4-chlorobenzaldehyde (2 mmol), imidazole (1 mmol) and piperidine (3 mmol)

After standardizing the reaction conditions, the reaction was tested with different aromatic aldehydes possessing both electron-donating and electron-withdrawing groups along with cyclic secondary amines. The yields were excellent in almost all cases (Table 5B.2.2). Unfortunately, I was not able to isolate the product of the reaction of N-methylimidazole with secondary amines and aromatic aldehydes. Other substituted imidazoles e.g., 2-methylimidazole, 4,5-diphenylimidazoles and different substituted benzimidazoles did not react at all with secondary amines and aldehydes under the present reaction condition. I, therefore thought that the basicity \([pK_{BH}^{+}(MeNO_2) = 14.64]^{13}\) and hence corresponding nucleophilicity of the starting imidazole is a very important factor in this reaction. Thus, imidazole is quite a strong base in nitromethane, whereas, the \(pK_{BH}^{+}\) of benzimidazole is 1.7 units lower due to the anneleted benzene ring. One of the most interesting facts about this reaction is that only 2-substituted imidazoles were formed in this reaction condition and no 1 or 4 or 5 substituted imidazoles were obtained. Thus, the
position of attack and hence the product was highly selective in this case. Another point that needs to be mentioned is that this methodology worked out well only with cyclic secondary amines. A probable explanation that can be given for this is that, since the reaction goes via the formation of iminium ion (as suggested in the mechanism, Scheme 5B.2.3), the interaction of the NCH₂ protons with those of the aromatic aldehyde nucleus is probably lower for cyclic amines compared to acyclic ones.

Table 5B.2.2 Three component reaction between imidazole, aromatic aldehydes and cyclic secondary amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product no.</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tr>
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<td>6.5</td>
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</tr>
<tr>
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<td>84</td>
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</tr>
<tr>
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<td></td>
<td>8</td>
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</tr>
<tr>
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<td>81</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5B.2.1h</td>
<td></td>
<td>8</td>
<td>80</td>
</tr>
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<td>80</td>
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</tr>
<tr>
<td>9</td>
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<td>6</td>
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</tr>
<tr>
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<tr>
<td>10</td>
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</tr>
</tbody>
</table>
Reaction conditions: aldehyde (2 mmol), imidazole (1 mmol) and cyclic secondary amine (3 mmol)

The final structure of the product has been confirmed by the X-ray diffraction of a single crystal of the product 5B.2.1a (Table 5B.2.2, entry 1) and is shown below in Figure 5B.2.1.

![Figure 5B.2.1 ORTEP diagram of a single crystal of product 5B.2.1a (Table 5B.2.2, entry 1) showing the crystallographic numbering (CCDC 777835)](image)

Imidazole and N-methylimidazole are well-known to acylate at 2-position by the reaction with acid chloride in the presence of a base and the reaction of an imidazole with benzoyl chloride is reported initially to form an imidazolium ylide as an intermediate. The ylide is proposed to react with a second benzoyl chloride in a bimolecular fashion to form a 2-benzoylimidazole. The exclusive formation of 2-substituted imidazole in our case, is a strong evidence in favor of the involvement of the imidazolium ylide as an intermediate in the mechanistic pathway because if it went through the normal base catalysed Mannich-type
reaction pathway, 4 or 5-substituted imidazoles should have formed preferably than 2-substituted imidazoles. The details of the mechanism is given below (Scheme 5B.2.3) in which imidazolium ylide [B] formed in the reaction of imidazole and iminium ion [A], reacts with another molecule of iminium ion at 2-position of the imidazole to give the final product [C] after the elimination of one molecule of iminium ion from the 3-position of imidazole.

Scheme 5B.2.3 Plausible mechanism of the three-component reaction of imidazole, secondary amines and aromatic aldehydes.

5B.3 Importance of the work
a) This is the first report on the catalyst-free, one-pot, three-component reaction of imidazole, aromatic aldehydes and cyclic secondary amines for the synthesis of 2-substituted [(α-arylene)-α'-amino)methyl] imidazoles.
b) 2-Substituted [(α-arylene)-α'-amino)methyl]imidazoles are formed exclusively and thus the reaction is highly regioselective in nature.

5B.4 Scope and limitation
Although the present methodology works well with unsubstituted imidazoles, several aromatic aldehydes and cyclic secondary amines, the reaction fails to produce the desired products in case of substituted imidazoles, and other azoles such as 1,2,3-triazole and benzimidazoles. Again, the reaction also fails to produce the desire products in case of secondary amines other than cyclic secondary amines. Thus the reaction works well only with imidazole and cyclic secondary amines.

5B.5 Conclusion: In summary, a new three-component reaction involving imidazole, aromatic aldehydes and secondary amines to form diverse 2-substituted [(α-arylene)-α'
amino)methyl]imidazoles has been developed for the first time. Catalyst-free condition, exclusive formation of the 2-substituted imidazoles, moderate reaction condition and simple work-up procedure are the major features of this methodology.

This work has been accepted for publication.


5B.6 Experimental

5B.6.1 Materials and instruments

**General:** All the chemicals were purchased from Aldrich Chemical Company and Spectrochem Pvt. Ltd. (Mumbai, India). Silica Gel G with binder from Spectrochem Pvt. Ltd. Mumbai, India was used for thin layer chromatography. $^1$H and $^{13}$C NMR spectra were obtained on Bruker 300 MHz instrument at 300 and 75 MHz respectively. CDCl$_3$ was purchased from Aldrich Chemical Company and d$_6$-DMSO from CIL. Melting points were determined on an electrical melting point apparatus with an open capillary and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrophotometer RX / FT-IR system. The C-H-N analyses were carried out on a 2400 series II CHNS Analyzer, Perkin Elmer (USA).

5B.6.2 General experimental procedure: Aromatic aldehyde (2 mmol), imidazole (1 mmol), secondary amine (3 mmol) and toluene (5 mL) were mixed together in a 25 mL Erlenmeyer flask. It was refluxed in an oil bath at 110 °C for the stipulated time (Table 5B.2.2). After the completion of the reaction (monitored by TLC), toluene was removed under reduced pressure in a rotary evaporator and the residue was dissolved in EtOAc (5 mL). The compound was then purified by column chromatography in basic alumina using petroleum ether (60-80 °C) and EtOAc as eluant. The characteristic data of all the representative compounds are given below.

5B.6.3 Characteristic data of the representative compounds

For majority of compounds (except 5B.2.1b, 5B.2.1e, 5B.2.1i and 5B.2.1l), the total number of $^{13}$C peaks are lower compared to the actual number of carbons. In most of the cases, the imidazole CH carbons either do not appear or appear as very small broad peaks. Increasing the delay times for these compounds did not improve the situation. The actual structures of
the final products were confirmed from the very clean $^1$H NMR of all the products and from
the X-ray crystallographic data of 5B.2.1a.

1-[(4-Chlorophenyl)-(1H-imidazol-2-yl)-methyl]-piperidine (5B.2.1a, Table 5B.2.2, entry 1): White solid, mp 168-170 °C (EtOAc); IR (KBr): 2934, 2798, 2376, 1449, 1095 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ: 9.72 (s, 1H), 7.33–7.26 (m, 4H), 6.97 (s, 2H), 4.67 (s, 1H), 2.40–2.00 (m, 4H), 1.90–1.30 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 148.4, 136.7, 133.4, 129.9 (2C), 128.6 (2C), 69.4, 52.5 (2C), 26.2 (2C), 24.3; Anal. calcd. for C$_{15}$H$_{18}$N$_3$Cl; C: 65.33, H: 6.58, N: 15.24% Found: C: 65.22, H: 6.63, N: 15.30%.

1-[(2-Chlorophenyl)-(1H-imidazol-2-yl)-methyl]-piperidine (5B.2.1b, Table 5B.2.2, entry 2): White crystalline solid, mp 188-190 °C (MeOH); IR (KBr): 2936, 2804, 2378, 1566, 1452, 1108 cm$^{-1}$; $^1$H NMR (300 MHz, d$_6$-DMSO) δ: 12.42 (s, 1H), 8.39 (d, J = 7.5 Hz, 1H), 7.86 – 7.75 (m, 2H), 7.73 – 7.65 (m, 1H), 7.45 (s, 1H), 7.25 (s, 1H), 5.43 (s, 1H), 2.90 – 2.50 (m, 4H), 1.91 (br. s, 4H), 1.83 (br. s, 2H); $^{13}$C NMR (75 MHz, d$_6$-DMSO) δ: 146.2, 137.7, 133.1, 130.4, 129.2, 128.6, 127.5, 127.1, 116.3, 64.4, 52.1 (2C), 25.6 (2C), 24.2; Anal. calcd. for C$_{15}$H$_{18}$N$_3$Cl; C: 65.33, H: 6.58, N: 15.24% Found: C: 65.24, H: 6.62, N: 15.29%.

1-[(1H-Imidazol-2-yl)-phenyl-methyl]-piperidine (5B.2.1c, Table 5B.2.2, entry 3): White solid, mp 188-190 °C (EtOAc); IR (KBr): 2936, 2862, 2794, 1831, 1533, 1446, 1096, 735 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$ + three drops of d$_6$-DMSO) δ: 9.70 (s, 1H), 7.39 (d, J =
6.6 Hz, 2H), 7.34–7.20 (m, 3H), 6.96 (s, 2H), 4.60 (s, 1H), 2.50 – 2.20 (m, 4H), 1.70 – 1.30 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$ + three drops of d$_6$-DMSO) δ: 148.4, 139.0, 128.2 (3C), 127.1 (2C), 70.0, 52.5 (2C), 25.9 (2C), 24.1; Anal. calcd. for C$_{13}$H$_{19}$N$_3$: C: 74.65, H: 7.94, N: 17.41% Found: C: 74.51, H: 8.02, N: 17.47%.

1-[(1H-Imidazol-2-yl)-(4-methylphenyl)-methyl]-piperidine (5B.2.1d, Table 5B.2.2, entry 4): White solid, mp 174-176 °C (EtOAc); IR (KBr): 3051, 2929, 2801, 2371, 1560, 1441, 1288, 1090 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$ + three drops of d$_6$-DMSO) δ: 7.30 (d, $J = 8.1$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H), 6.93 (s, 2H), 4.55 (s, 1H), 2.41 – 2.25 (m, 7H), 1.59 – 1.41 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$ + three drops of d$_6$-DMSO) δ: 148.7, 136.7, 135.9, 128.8 (2C), 128.1 (2C), 69.7, 52.5 (2C), 25.9 (2C), 24.2, 20.8; Anal. calcd. for C$_{16}$H$_{21}$N$_3$: C: 75.26, H: 8.29, N: 16.46% Found: C: 75.20, H: 8.30, N: 16.51%.

1-[(1H-Imidazol-2-yl)-(3-nitrophenyl)-methyl]-piperidine (5B.2.1e, Table 5B.2.2, entry 5): White solid, mp 184-186 °C (EtOAc); IR (KBr): 3033, 2988, 2880, 1891, 1572, 1408, 1206 cm$^{-1}$; $^1$H NMR (300 MHz, d$_6$-DMSO) δ: 12.01 (s, 1H), 8.30 (s, 1H), 8.06 (d, $J = 7.8$ Hz, 1H), 7.83 (d, $J = 7.8$ Hz, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 6.92 (br. s, 2H), 4.70 (s, 1H), 2.27 – 2.13 (m, 4H), 1.43 (br. d, $J = 5.1$ Hz, 4H), 1.29 (br. d, $J = 4.2$ Hz, 2H); $^{13}$C NMR (75 MHz, d$_6$-DMSO) δ: 147.8, 146.1, 142.3, 135.2, 129.6, 122.9, 122.2, 117.8, 116.6, 67.7, 51.7 (2C), 25.7 (2C), 24.1; Anal. Calcd. for C$_{15}$H$_{18}$N$_4$O$_2$: C: 62.92, H: 6.34, N: 19.57% Found: C: 62.80, H: 6.40, N: 19.63%.

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1-[(1H-Imidazol-2-yl)-(4-pyridyl)-methyl]-piperidine (5B.2.1f, Table 5B.2.2, entry 6): Off-white solid, mp 170-172 °C (EtOAc); IR (KBr): 3035, 2964, 2808, 2325, 1898, 1564, 1441, 1088 cm⁻¹; ¹H NMR (300 MHz, d₆-DMSO) δ: 11.89 (s, 1H), 8.46 (d, J = 4.5 Hz, 2H), 7.39 (d, J = 4.5 Hz, 2H), 7.00 (s, 1H), 6.77 (s, 1H), 4.53 (s, 1H), 2.25 – 2.12 (m, 4H), 1.45 (br. d, J = 5.1 Hz, 4H), 1.31 (br. d, J = 4.5 Hz, 2H); ¹³C NMR (75 MHz, d₆-DMSO) δ: 149.6 (2C), 148.8, 145.9, 123.5 (2C), 67.9, 51.9 (2C), 25.6 (2C), 24.1; Anal. calcd. for C₁₄H₁₈N₄; C: 69.39, H: 7.49, N: 23.12% Found: C: 69.29, H: 7.55, N: 23.17%.

1-[(1H-Imidazol-2-yl)-(4-methoxyphenyl)-methyl]-piperidine (5B.2.1g, Table 5B.2.2, entry 7): Pale yellow solid, mp 180-182 °C (EtOAc); IR (KBr): 2998, 2929, 2880, 2372, 1450, 1296, 1108 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 9.59 (s, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.96 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.59 (s, 1H), 3.80 (s, 3H), 2.43 – 2.37 (m, 2H), 2.27 – 2.24 (m, 2H), 1.60 – 1.53 (m, 4H), 1.46 – 1.42 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ: 159.0, 148.7, 130.3, 129.6 (2C), 113.9 (2C), 69.4, 55.2, 52.6 (2C), 26.2 (2C), 24.3; Anal. calcd. for C₁₆H₂₁N₃O; C: 70.82, H: 7.80, N: 15.49% Found: C: 70.69, H: 7.88, N: 15.54%.

2-[(4-Bromophenyl)-(1-pyrrolidinyl)-methyl]imidazole (5B.2.1h, Table 5B.2.2, entry 8): Pale yellow solid, mp 176-178 °C (EtOAc); IR (KBr): 3039, 2964, 2800, 1898, 1570, 1483,
4-[(4-Chlorophenyl)-(1H-imidazol-2-yl)-methyl]-morphtoline (5B.2.1i, Table 5B.2.2, entry 9): White solid, mp 172-174 °C (EtOAc); IR (KBr): 2959, 2857, 2813, 1935, 1820, 1565, 1485, 1452, 1289, 1107 cm⁻¹; ¹H NMR (300 MHz, d₆-DMSO) δ: 8.25 (s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.19 (s, 2H), 5.22 (s, 1H), 3.90 - 3.70 (m, 4H), 2.70 - 2.30 (m, 4H); ¹³C NMR (75 MHz, d₆-DMSO) δ: 146.4, 138.4, 131.9, 130.0, 129.7, 128.9, 127.1, 67.0, 51.6 (2C); Anal. calcd. for C₁₄H₁₆N₅ClO; C: 60.54, H: 5.81, N: 15.13% Found: C: 60.41, H: 5.88, N: 15.19%.

4-[(2-Chlorophenyl)-(1H-imidazol-2-yl)-methyl]-morphtoline (5B.2.1j, Table 5B.2.2, entry 10): Pale white solid, mp 170-172 °C (EtOAc); IR (KBr): 3027, 2957, 2860, 2813, 1935, 1820, 1561, 1451, 1278, 1111 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.71 (dd, J = 7.5 and 1.8 Hz, 1H), 7.35 (dd, J = 7.8 and 1.5 Hz, 1H), 7.30 - 7.15 (m, 2H), 7.00 (s, 2H), 5.22 (s, 1H), 3.90 - 3.70 (m, 4H), 2.70 - 2.30 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ: 146.5, 135.6, 134.4, 130.0, 129.7, 128.9, 127.1, 67.0 (2C), 64.8, 51.9 (2C); Anal. calcd. for C₁₄H₁₆N₅ClO; C: 60.54, H: 5.81, N: 15.13% Found: C: 60.44, H: 5.87, N: 15.17%.
4-[(1H-Imidazol-2-yl)-(4-methylphenyl)-methyl]-morpholine (5B.2.1k, Table 5B.2.2, entry 11): White solid, mp 172-174 °C (EtOAc); IR (KBr): 2963, 2856, 2804, 1852, 1566, 1372, 1290 and 1109 cm⁻¹; ¹H NMR (300 MHz, 4-DMSO) δ: 11.91 (s, 1H), 7.33 (d, J = 7.5 Hz, 2H), 7.07 (d, J = 7.2 Hz, 2H), 6.86 (s, 2H), 4.39 (s, 1H), 2.28 – 2.24 (m, 4H), 2.21 (s, 3H), 2.14 – 2.10 (m, 4H); ¹³C NMR (75 MHz, 4-DMSO) δ: 147.7, 136.9, 136.9, 129.3 (2C), 128.8 (2C), 69.5, 66.7 (2C), 55.2 (2C), 21.1; Anal. calcd. for C₁₅H₁₉N₃O; C: 70.01, H: 7.44, N: 16.33% Found: C: 69.88, H: 7.49, N: 16.41%.

1-[(1H-Imidazol-2-yl)-(4-methylphenyl)-methyl]-4-methyl-piperazine (5B.2.11, Table 5B.2.2, entry 12): White solid, mp 186-188 °C (EtOAc); IR (KBr): 2938, 2880, 2799, 1890, 1511, 1456, 1292, 1153, 1097 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.30 (d, J = 7.8 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 6.95 (s, 2H), 4.56 (s, 1H), 2.41 (br. s, 8H), 2.28 (s, 3H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 148.4, 137.1, 135.7, 129.2 (2C), 128.1 (2C), 121.8 (2C), 69.2, 55.1 (2C), 51.4 (2C), 45.8, 20.9; Anal. calcd. for C₁₆H₂₂N₄; C: 71.08, H: 8.20, N: 20.72% Found: C: 70.97, H: 8.27, N: 20.76%
5B.6.4 Few representative spectra of previously unknown products

a)

Figure 5B.6.4.1 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5B.2.1a] (Table 5B.2.2, entry 1)
Figure 5B.6.4.2 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5B.2.1b] (Table 5B.2.2, entry 2)
Figure 5B.6.4.3 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5B.2.1e] (Table 5B.2.2, entry 5)
Figure 5B.6.4.4 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5B.2.1h] (Table 5B.2.2, entry 8)
Figure 5B.6.4.5 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5B.2.1i] (Table 5B.2.2, entry 9)
5B.6.5 Detailed analysis data of the X-ray crystal structure (ORTEP diagram given in Figure 5B.2.1)

Compound 5B.2.1a: Empirical formula C15 H18 Cl N3, M = 275.77, colorless crystal, Crystal size 0.650 x 0.310 x 0.150 mm³, a = 9.6625(4) Å, b = 15.0959(6) Å, c = 9.8446(3) Å, Crystal system Monoclinic, α = 90° β = 97.633(2)° γ = 90°, Volume = 1423.25(9) Å³, \( \rho_{calc} = 1.287 \text{ Mg/m}^3 \), \( \mu = 0.259 \text{ mm}^{-1} \), Z = 4, Space group P 21/c, \( \lambda = 0.71073 \text{ Å} \), T = 173(2) K, Reflections collected 38518, Independent reflections 5312 [R(int) = 0.0497], F(000) = 584, Theta range for data collection 2.49 to 33.24°, Index ranges -14<=h<=14, -23<=k<=23, -14<=l<=15, Completeness to theta = 25.00° 100 %, Absorption correction Semi-empirical from equivalents, Max. and min. transmission 5312 / 0 / 172, Refinement method: Full-matrix least-squares on F², Data / restraints / parameters 4945 / 0 / 172, Goodness-of-fit on F² 1.026, Final R indices [I>2sigma(I)] R1 = 0.0467, wR2 = 0.1184, R indices (all data) R1 = 0.0710, wR2 = 0.1311, Largest diff. peak and hole 0.659 and -0.541 e.Å⁻³, CCDC 777835 contains the crystallographic data of compound 5B.2.1a.
5B.7 References


Chapter 5 (Section 5C)

N-arylation of nitrogen-containing heterocycles such as imidazoles, triazoles, indole, pyrrole and pyrazole catalysed by Cu(OH)$_2$.CuCO$_3$ in aqueous medium
5C.1 Introduction
This section deals with the N-arylation of nitrogen-containing heterocycles such as imidazoles, benzimidazoles, triazoles, benzotriazoles, pyrrole, indole and pyrazole using basic copper carbonate as a catalyst in water.

5C.1.1 Importance of the copper catalysed N-arylation of nitrogen-containing heterocycles
N-arylazoles are important compounds that find extensive applications in the biochemical, pharmaceutical and material fields. Traditionally, these moieties were prepared by the nucleophilic aromatic substitution of azoles with activated aryl halides or the classical Ullmann-type coupling reactions. In both cases, the reaction suffered from several shortcomings such as high reaction temperature, use of stoichiometric copper reagents, moderate yields and poor substrate generality thereby limiting their applications. The development of a mild, eco-friendly and highly efficient protocol for the synthesis of N-arylazoles over the classical Ullmann-type or nucleophilic aromatic substitution reactions has recently gained considerable interest in both academia and in industries. Due to the economic attractiveness of copper and using N,N- and N,O-bidentate compounds as ligands, many Cul catalysed C-N, C-O, C-S and C-C bond formation reactions have instigated a growing interest in carbon-heteroatom coupling reactions which seem to possess more and more importance. Before going into details about the N-arylation of aza-heterocycles, I would like to present a brief review on the N-arylation of N-containing heterocycles.

5C.1.2 Review on the N-arylation of nitrogen-containing heterocycles
Traditionally, N-arylazoles were prepared by nucleophilic aromatic substitution of azoles with activated aryl halides and following this strategy J. Ohmori et al. described the synthesis of 3-imidazolylaniline.

\[
\begin{align*}
\text{X} &= \text{Cl, F} \\
\text{1. RNH}_2 & \rightarrow \\
\text{2. imidazole, KOH} & \\
\text{DMSO/imidazole, DMF} & \\
\text{120 °C, 2h} & \\
\end{align*}
\]

Scheme 5C.1.2.1
N-arylazoles were prepared by the classical Ullmann-type coupling of azoles with aryl halides, which has a broader substrate scope with respect to aryl halides. S. L. Buchwald et al. used this method for the copper-catalysed N-arylation of imidazoles. They found that the coupling proceeds fairly mildly in the presence of 1,10-phenanthroline (phen) and trans,trans-dibenzylideneacetone (dba) as additives, with (CuOTf)$_2$ as the copper source and Cs$_2$CO$_3$ as the base, in xylene at 110-125 °C.

![Scheme 5C.1.2.2](image)

P. S. Y. Lam et al. described an interesting copper-mediated C-N bond cross-coupling reaction using hypervalent aryl or vinyl siloxanes. This was the first example of room temperature N-arylation with aryl iodide in the absence of strong base.

![Scheme 5C.1.2.3](image)

J. P. Collman et al. developed a copper-catalysed N-arylation of azoles using aryl boronic acids, akin to a modified Ullmann reaction.

![Scheme 5C.1.2.4](image)

Complete regiocontrol (N-1 versus N-3) was obtained in the arylation of substituted imidazoles with arylead(IV) reagents by G. I. Elliott et al. under catalysis by copper(II) acetate. The mildness of the reaction conditions (room temperature, no added base) allowed for the first synthesis of the histidine-tyrosine side chain coupled dipeptide found in the active site of cytochrome c oxidase.
R. A. Altman et al. found that 4,7-Dimethoxy-1,10-phenanthroline behaves as an efficient ligand for the copper-catalysed N-arylation of imidazoles and benzimidazoles with both aryl iodides and bromides under mild conditions.17

![Scheme 5C.1.2.5](image)

R. A. Altman et al. found that 4,7-Dimethoxy-1,10-phenanthroline behaves as an efficient ligand for the copper-catalysed N-arylation of imidazoles and benzimidazoles with both aryl iodides and bromides under mild conditions.17

L. Liang et al. described the N-arylation of imidazoles with aryl halides catalysed by a combination of copper(II) sulfate and 1,2-bis(2-pyridyl)-ethane-N,N'-dioxide in water.18

![Scheme 5C.1.2.6](image)

L. Liang et al. described the N-arylation of imidazoles with aryl halides catalysed by a combination of copper(II) sulfate and 1,2-bis(2-pyridyl)-ethane-N,N'-dioxide in water.18

Efficient, regioselective, N-2 arylation of triazole was developed by Y. Liu et al. from C-4, C-5 disubstituted-1,2,3-NH-triazoles.19
K. Swapna et al. developed an efficient and ligand-free C-N cross-coupling of aryl halides with various heterocycles using Fe/C₈ (graphite supported iron(III) acetylacetonate) as a recyclable catalyst.¹⁰

$$\begin{align*}
\text{Ar--F / Ar--Cl, base} \\
\text{R} \\
\text{R'}=^{\text{.N-H}} \text{N} \\
\text{R, R' = H, Ph, PhCH}_2 \text{ etc.}
\end{align*}$$

**Scheme 5C.1.2.8**

L. Zhu et al. developed a copper-catalysed process for the N-arylation reaction under very mild conditions in the absence of additional ligand. This protocol could not only tolerate an array of thermally sensitive functional groups, but also achieve high chemoselectivity.²¹

$$\begin{align*}
\text{X}=\text{I, Br} \\
\text{NuH = imidazole, pyrazole, benzimidazole, indole etc.}
\end{align*}$$

**Scheme 5C.1.2.9**
5C.2 Results and Discussion

In this chapter, a simple, efficient and eco-friendly approach for the N-arylation of azoles with aryl halides catalysed by readily available Cu(OH)$_2$.CuCO$_3$ with N-heterocyclic ligands in water has been reported (Scheme 5C.2.1).

Scheme 5C.2.1 N-arylation of nitrogen containing heterocycles in water

Despite significant progress in the copper catalysed N/O-arylation with aryl halides, few reports are available describing N-arylation of azoles in aqueous medium.$^{18}$ Therefore, enough room for exploration of an efficient ligand-assisted catalytic system in the aqueous medium still remained quite open.

In general, almost all the organic solvent mediated synthesis of organic compounds has the inherent problems of pollution. In recent years, water mediated organic synthesis without using organic solvents has become one of the most important aspects in present day organic chemistry in order to meet the environmental demands.$^{22}$ Carrying out organic synthesis in water is extremely challenging both from synthetic view point and also from the impact of environmental pollution. The additional problems of N-arylation of azoles in aqueous medium are the water tolerance for the catalyst and solubility of the substrates and ligands in aqueous phase. In this regard, the development of less expensive and more sustainable catalysts in water proved a demanding and attractive goal in modern synthetic organic chemistry.

As this thesis concentrates only on N-containing heterocycles, three N-containing heterocyclic compounds, namely [bis(3,5-dimethyl-1H-pyrazol-1-yl)methane] (L$_1$), [bis(1,2,4-triazol-1-yl)methane] (L$_2$) and [2-(2-pyridyl)benzimidazole] (L$_3$) which have long been recognized as ligands in coordination chemistry$^{23-25}$ (Figure 5C.2.1), but not so far been applied for copper catalysed N-arylation of aza-heterocycles, have been chosen as the
ligands for the initial optimization of N-arylation of aza-heterocycles in water. Imidazole and iodobenzene were chosen as model substrates (Scheme 5C.2.2) in order to optimize the reaction conditions, such as amount of ligands, base, copper source and reaction temperature. Imidazole (1 mmol), iodobenzene (1.2 mmol), base (2 mmol), Cu source (15 mol%) and ligand (20 mol%) in water were taken for the initial optimization and after thorough screening with several combinations, the best result was obtained after 12 h of reflux using \([\text{bis(3,5-dimethyl-1H-pyrazol-1-yl)methane}]\) \((L_1)\) as ligand and \(\text{Cu(OH)}_2\cdot\text{CuCO}_3\) as copper source in aqueous medium.

![Figure 5C.2.1 Proposed ligands for the N-arylation of nitrogen containing heterocycles in water](image)

It should be mentioned here that using \(\text{Cu(OH)}_2\cdot\text{CuCO}_3\) (1.2 equivalents) both as source of metal and as base almost complete conversion of imidazole to 1-phenylimidazole occurred after 16 h of reflux under aqueous conditions. The isolated yield was however poor (50%) which may be due to the partial conversion of imidazole to corresponding Cu(ii) complex of imidazole. Then, I thought of using \(\text{Cu(OH)}_2\cdot\text{CuCO}_3\) only as the metal source not also as base. Under this condition, the product yield was higher than before. The arylation reaction was highly sensitive to reaction temperature and time. The rate of conversion of imidazole to 1-arylimidazole decreased sharply with lowering of temperature (below 90 °C) and of reaction time (below 12 h). Among the three ligands used, \(L_1\) was more beneficial for the catalysis than the other two ligands \((L_2\) and \(L_3)\) (Table 5C.2.1, entries 4-6). The higher basicity of the coordinating nitrogen atoms in \(L_1\) and \(L_2\) compared to \(L_3\) is the probable reason behind the higher catalytic efficiency of the former two than the latter. Among \(L_1\) and \(L_2\), basicity of the coordinating nitrogen atoms is higher in case of \(L_1\) than that of \(L_2\) probably because of the presence of two methyl groups in \(L_1\) at 3 and 5 position (ortho-to coordinating nitrogen atoms). Again, relatively higher solubility of \(L_1\) and \(L_2\) in the aqueous medium than \(L_3\) might also contribute to the higher catalytic efficiency of \(L_1\) and \(L_2\).
than that of L3. Therefore, the optimized conditions for the N-arylation of imidazole in water consisted of the combination of [Cu(OH)2.CuCO3] (15 mol%), L1 (20 mol%) and K2CO3 (2 mmol) at 100 °C for 12 h in air (Table 5C.2.1, entry 4). The results are listed below (Table 5C.2.1).

![Scheme 5C.2.2 Optimization of N-arylation of imidazole with iodobenzene in water](image)

**Table 5C.2.1 Optimization of reaction condition for the N-arylation of imidazole in water using imidazole (1 mmol) and iodobenzene (1.2 mmol)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper source</th>
<th>Ligand</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yields (%) (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>K2CO3</td>
<td>24</td>
<td>nil</td>
</tr>
<tr>
<td>2</td>
<td>CuCO3.Cu(OH)2</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>nil</td>
</tr>
<tr>
<td>3</td>
<td>CuCO3.Cu(OH)2</td>
<td>-</td>
<td>K2CO3</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>CuCO3.Cu(OH)2</td>
<td>L1</td>
<td>K2CO3</td>
<td>12</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>CuCO3.Cu(OH)2</td>
<td>L2</td>
<td>K2CO3</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>CuCO3.Cu(OH)2</td>
<td>L3</td>
<td>K2CO3</td>
<td>12</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>CuCO3.Cu(OH)2</td>
<td>L1</td>
<td>Cs2CO3</td>
<td>12</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>CuCO3.Cu(OH)2</td>
<td>L1</td>
<td>K3PO4</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>CuCO3.Cu(OH)2</td>
<td>L1</td>
<td>DABCO</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OH)2</td>
<td>L1</td>
<td>K2CO3</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>CuSO4</td>
<td>L1</td>
<td>K2CO3</td>
<td>12</td>
<td>65</td>
</tr>
<tr>
<td>12</td>
<td>CuI</td>
<td>L1</td>
<td>K2CO3</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OAc)2</td>
<td>L1</td>
<td>K2CO3</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>14</td>
<td>CuCl2</td>
<td>L1</td>
<td>K2CO3</td>
<td>12</td>
<td>55</td>
</tr>
</tbody>
</table>

After optimizing the reaction condition, the procedure was tested with different aza-heterocycles. The scope of this coupling reaction was further expanded to diverse aryl bromides and it was observed that the overall yields were slightly lower with aryl bromides than the aryl iodides. The results clearly indicated that this methodology is quite general and applicable for the reaction of a wide variety of imidazoles, benzimidazoles, triazole, benzotriazoles, indole, pyrole and pyrazole. Substrate possessing electron rich groups such as 4-bromotoluene, 3,4-dimethyliodobenze, 2,5-dichloriodobenzene afforded coupling products in good yields but with larger reaction time than 3-nitroiodobenzene. The reaction
was also less sensitive to steric factors and gave good yields as is evident in case of the reaction of 2,5-dichloroiodobenzene with 2-methylimidazole. This methodology also provided good results in case of the reaction of sterically hindered 5,6-dimethylbenzimidazole and benzotriazoles. The complete results are shown in Table 5C.2.2.

Table 5C.2.2 N-arylation of nitrogen containing heterocycles in water

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Product no</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yields (%)&lt;sup&gt;ref&lt;/sup&gt;</th>
</tr>
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To our delight, most of the imidazole and triazole derivatives afforded the corresponding arylated products in good yields. Notably, 2-methylimidazole, 2-methylbenzimidazole and even more bulky, 2-dichloromethylbenzimidazole gave satisfactory yields under the present reaction conditions.

A probable mechanism for the basic copper carbonate catalysed N-arylation of nitrogen containing heterocycles has been proposed below (Scheme 5C.2.3), in which the first step is the rapid coordination of copper hydroxide and the ligand (L$\textsubscript{1}$) with the N-containing heterocycles such as imidazole to form a four coordinated copper (ii) complex [A]. The second step involves the oxidative addition of the aryl halide to form the five coordinated complex (intermediate B). Complex [B] subsequently undergoes the reductive elimination to form the N-aryl product [C].
Scheme 5C.2.3 Probable mechanism for N-arylation of nitrogen containing heterocycles (imidazole) with basic copper carbonate

5C.3 Importance of the present methodology

a) The reaction has been carried out in water thereby trying to maintain a "green" reaction medium.

b) Cu(OH)$_2$.CuCO$_3$ (15 mol%), for the first time has been used as an efficient catalyst for the N-arylation of nitrogen containing heterocycles.

c) [Bis(3,5-dimethyl-1/-pyrazol-1-yl)methane] (L$_1$) has been for the first time used as a ligand in the N-arylation of nitrogen containing heterocycles.

d) The methodology works well with many sterically-hindered imidazoles and triazoles.

e) The reaction dose not require any inert condition which is a common requisite with most of the previous works.

5C.4 Conclusion: In summary, I have utilized a cheap and commercially available Cu(OH)$_2$.CuCO$_3$ as an efficient catalyst for the N-arylation of nitrogen containing heterocycles with a wide range of aryl iodosides and aryl bromides in aqueous medium using [bis(3,5-dimethyl-1/-pyrazol-1-yl)methane] (L$_1$) as the ligand. This methodology avoids the use of hazardous, toxic organic solvents and inert atmosphere which are common requisites with most of the earlier works. Therefore, this methodology is rather very simple and highly efficient for N-arylation reaction of nitrogen containing heterocycles.
This work has been recently communicated
“A highly efficient and simple catalytic system for the N-arylation of some hindered aza-
heterocycles in water”, Chhanda, Mukhopadhyay and Pradip Kumar Tapaswi, 2010
(communicated)

5C.5 Experimental
5C.5.1 Materials and instruments
General: All the chemicals were purchased from Aldrich Chemical Company and
Ltd. Mumbai, India was used for thin layer chromatography. \(^1\)H and \(^{13}\)C NMR spectra were
obtained on Bruker 300 MHz instrument at 300 and 75 MHz respectively. CDCl\(_3\) was
purchased from Aldrich Chemical Company and \(d_6\)-DMSO from CIL. Melting points were
determined on an electrical melting point apparatus with an open capillary and are
uncorrected. IR spectra were recorded on a Perkin Elmer Spectrophotometer RX / FT-IR
system. The C-H-N analyses were carried out on a 2400 series II CHNS Analyzer, Perkin
Elmer (USA).

5C.5.2 General experimental procedure for N-arylation of nitrogen containing
heterocycles in water: In an Erlenmeyer flask (10 mL) fitted with a reflux condenser, azole
(1 mmol), aryl halide (1.2 mmol), Cu(OH)\(_2\).CuCO\(_3\) (15 mol%), ligand (L\(_1\)) (20 mol%),
K\(_2\)CO\(_3\) (2 mmol) and water (2 mL) were mixed and refluxed in an oil bath for the stipulated
period of time. After the completion of the reaction (monitored by TLC), 20 mL of EtOAc
was added to the reaction mixture after transferring to a beaker (50 mL) and stirred for
several minutes. It was then filtered through a bed of celite and the organic layer was
separated in a separating funnel which was washed successively with water (2 x 10 mL) and
brine (2 x 10 mL). The organic layer was then dried over anhydrous Na\(_2\)SO\(_4\) and
concentrated under reduced pressure in a rotary evaporator. Finally, the products were
purified by column chromatography using neutral alumina as the column material and
EtOAc and petroleum ether (60-80 °C) as eluant. The characteristic data of all the
representative compounds are given below. For compounds 5C.2.1l, 5C.2.1m and 5C.2.1n
(Table 5C.2.2, entries 13-15) the characteristics data are not included here as these have
already been given in chapter 4 (section 4.4.4).
5C.5.3 Characteristic data of the representative compounds

1-Phenyl-1H-imidazole\textsuperscript{26} (5C.2.1a, Table 5C.2.2, entry 1): Yellowish oil; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.89 (s, 1H), 7.49 - 7.45 (m, 2H), 7.40 - 7.34 (s, 3H), 7.25 - 7.19 (m, 2H).

1-(3,4-Dimethylphenyl)-2-methyl-1H-imidazole\textsuperscript{26} (5C.2.1b, Table 5C.2.2, entry 3): Yellowish semisolid; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.65 (d, J = 7.8 Hz, 1H), 7.21 (d, J= 7.8 Hz, 1H), 7.08-6.98 (m, 3H), 2.38 (s, 3H), 2.26 (s, 6H).

1-(2,5-Dichlorophenyl)-2-methyl-1H-imidazole (5C.2.1c, Table 5C.2.2, entry 4): White crystalline solid; mp 60-62 °C (EtOAc); IR (KBr): 3052, 2980, 2926, 2213, 1609, 1517, 1448, 1392, 1279 and 744 cm\(^{-1}\); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.29 (dd, J=9.0 and 3.6 Hz, 1H), 7.22-7.15 (m, 2H), 6.87 (s, 1H), 6.70 (s, 1H), 2.06 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\):145.4, 136.1, 133.4, 131.4, 130.7, 130.5, 129.1, 127.3, 120.5, 12.9; Anal. Calcd. for C\textsubscript{10}H\textsubscript{8}N\textsubscript{2}Cl\textsubscript{2}; C: 52.89, H: 3.55, N: 12.34%. Found: C: 52.76, H: 3.65, N: 12.37%.

1-(3,4-Dimethylphenyl)-1H-benzimidazole (5C.2.1d, Table 5C.2.2, entry 5): Pale yellow low melting solid; IR (KBr): 3042, 2923, 1605, 1504, 1452, 1293, 1210 and 736 cm\(^{-1}\); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 8.02 (s, 1H), 7.88-7.82 (m, 1H), 7.48-7.43 (m, 1H), 7.29-7.23 (m, 2H), 7.20 (d, J = 7.7 Hz, 2H), 7.14 (d, J= 7.7 Hz, 1H), 2.24 (s, 6H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 143.6, 141.9, 138.1, 136.2, 133.5, 133.4, 130.5, 124.6, 123.0, 122.1, 120.8, 120.0,
110.1, 19.4, 19.0; Anal. Calcd. for C_{13}H_{14}N_{2}; C: 81.05, H: 6.35, N: 12.60%. Found: C: 80.92, H: 6.44, N: 12.64%.

2-Methyl-1-phenyl-1H-benzimidazole (5C.2.1e, Table 5C.2.2, entry 6): White solid; mp 68 °C (EtOAc) [lit.\textsuperscript{27} 69-70 °C]; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.75 (d, \(J = 7.8\) Hz, 1H), 7.60-7.46 (m, 3H), 7.54 (d, \(J = 7.8\) Hz, 2H), 7.26 (t, \(J = 7.8\) Hz, 1H), 7.18 (t, \(J = 7.8\) Hz, 1H), 7.12 (d, \(J = 7.8\) Hz, 1H), 2.51 (s, 3H).

1-Phenyl-2,5,6-trimethyl-1H-benzimidazole\textsuperscript{27} (5C.2.1f, Table 5C.2.2, entry 7): Yellowish oil; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.57-7.48 (m, 3H), 7.34-7.31 (m, 2H), 6.88 (s, 1H), 6.72 (s, 1H), 2.63 (s, 3H), 2.48 (s, 3H), 2.35 (s, 3H).

1-(3,4-Dimethylphenyl)-2-methyl-1H-benzimidazole (5C.2.1g, Table 5C.2.2, entry 8): Pale yellow solid; mp 84-86 °C (EtOAc); IR (KBr): 3029, 2934, 1598, 1466, 1289, 1225 and 744 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 7.68 (d, \(J = 7.8\) Hz, 1H), 7.25 (d, \(J = 7.8\) Hz, 1H), 7.12 (t, \(J = 7.8\) Hz, 1H), 7.08-6.98 (m, 3H), 2.39 (s, 3H), 2.30 (s, 3H), 2.19 (t, \(J = 7.8\) Hz, 1H), 2.12 (t, \(J = 7.8\) Hz, 1H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 151.5, 141.4, 138.5, 137.7, 136.3, 133.2, 130.9, 127.8, 124.2, 122.5, 118.5, 110.1, 19.8, 19.5, 14.1; Anal. Calcd. for C\textsubscript{16}H\textsubscript{16}N\textsubscript{2}; C: 81.32, H: 6.82, N: 11.85%. Found: C: 81.19, H: 6.93, N: 11.87%.

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2-Dichloromethyl-1-phenyl-1H-benzimidazole (5C.2.1h, Table 5C.2.2, entry 9): Oil; IR (neat): 2935, 1577, 1499, 1381, 1278 and 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 8.12 (s, 1H), 7.90-7.87 (m, 1H), 7.59-7.42 (m, 6H), 7.36-7.25 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ: 142.2, 136.3 (2C), 130.0 (2C), 128.0, 124.0 (3C), 123.6, 122.7, 120.5, 118.1, 110.4; Anal. Calcd. for C₁₄H₁₀N₂Cl₂; C: 60.67, H: 3.64, N: 10.11%. Found: C: 60.58, H: 3.70, N: 10.14%.

2-Dichloromethyl-1-(4-methylphenyl)-1H-benzimidazole (5C.2.1i, Table 5C.2.2, entry 10): Oil; IR (neat): 3033, 2928, 1601, 1467, 1288, 1221 and 754 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 8.01 (s, 1H), 7.80-7.77 (m, 1H), 7.42-7.39 (m, 1H), 7.29-7.16 (m, 6H), 2.35 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 143.5, 142.1, 138.0 (2C), 133.7, 133.5, 130.4 (2C), 123.8 (2C), 123.5, 122.6, 120.2, 110.4, 20.9; Anal. Calcd. for C₁₅H₁₂N₂Cl₂; C: 61.87, H: 4.15, N: 9.62%. Found: C: 61.79, H: 4.22, N: 9.63%.

1-(3,4-Dimethylphenyl)-1H-[1,2,4]triazole (5C.2.1j, Table 5C.2.2, entry 11): pale white solid; mp 52-54 °C (MeOH); IR (KBr): 3095, 2936, 2369, 1587, 1477, 1139, 1021 and 798 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 8.45 (s, 1H), 8.01 (s, 1H), 7.38 (s, 1H), 7.31-7.25 (m, 1H), 7.15 (d, J=8.1 Hz, 1H), 2.25 (s, 3H), 2.22 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 152.1, 140.6, 133.2, 136.7, 134.7, 130.4, 121.1, 117.2, 19.7, 19.2; Anal. Calcd. for C₁₀H₁₁N₃; C: 69.34, H: 6.40, N: 24.26 %. Found: C: 69.25, H: 6.47, N: 24.28%.
1-(2,5-Dichlorophenyl)-1H-1,2,4-triazole (5C.2.1k, Table 5C.2.2, entry 12): White crystalline solid, mp 102-104 °C (EtOAc); IR (KBr): 3099, 2927, 2374, 1581, 1513, 1477, 1141, 1091, 1029 and 820 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 8.66 (s, 1H), 8.16 (s, 1H), 7.65 (d, J=2.1 Hz, 1H), 7.50 (d, J=8.7 Hz, 1H), 7.39 (dd, J=8.7 Hz and 2.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ: 152.4, 144.4, 135.5, 133.7, 131.6, 130.1, 127.4, 126.3; Anal. Calcd. for C₈H₅N₃C₁₂: C: 44.89, H: 2.35, N: 19.63%. Found: C: 44.77, H: 2.44, N: 19.66%.

5,6-Dimethyl-1-phenyl-1H-benzotriazole (5C.2.1o, Table 5C.2.2, entry 16): Pale yellow crystalline solid; mp 88-90 °C (EtOAc); IR (KBr): 3046, 2965, 2373, 1590, 1498, 1455, 1063 and 760 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.82 (s, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.56 (t, J= 8.7 Hz, 2H), 7.46-7.41 (m, 2H), 2.39 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ: 145.6, 138.5, 137.2, 134.0, 131.1, 129.6 (2C), 128.7, 122.5 (2C), 119.1, 109.7, 20.8, 20.2; Anal. Calcd. for C₁₄H₁₄N₃: C: 75.31, H: 5.87, N: 18.82%. Found: C: 75.22, H: 5.94, N: 18.84%.

5,6-Dimethyl-1-(4-methylphenyl)-1H-benzotriazole (5C.2.1p, Table 5C.2.2, entry 17): Pale yellow crystalline solid; mp 132-134 °C (EtOAc); IR (KBr): 2950, 2372, 1512, 1457, 1058, 996 and 817 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.71 (s, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.33 (s, 1H), 7.25 (d, J= 7.8 Hz, 2H), 2.32 (s, 3H), 2.28 (s, 6H); ¹³C NMR (75 MHz,
3,4-Dimethylphenyl-1H-indole (5C.2.1q, Table 5C.2.2, entry 18): Oil; IR (neat): 2954, 2934, 1487, 1243, 1190 and 845 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.91 (d, \(J = 7.8\) Hz, 1H), 7.77 (d, \(J = 7.8\) Hz, 1H), 7.48-7.35 (m, 6H), 6.86 (br. d, \(J = 3.0\) Hz, 1H), 2.49 (s, 6H); \(^13\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\): 137.9, 136.9, 135.2, 134.6, 130.5, 128.9, 128.4, 124.8, 122.1, 121.1, 120.9, 120.0, 110.3, 103.0, 19.4, 18.9; Anal. Caled. for C\(_{16}\)H\(_{15}\)N; C: 86.84, H: 6.83, N: 6.33%. Found: C: 86.72, H: 6.92, N: 6.36%.

1-(3,4-Dimethylphenyl)-1H-pyrrole-2-carbaldehyde (5C.2.1r, Table 5C.2.2, entry 19): Dark brown semisolid; IR (KBr): 2923, 2853, 2376, 1657, 1383, 1040 and 750 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 9.54 (s, 1H), 7.21 (d, \(J = 7.9\) Hz, 1H), 7.16-7.10 (m, 2H), 7.07 (d, \(J = 7.9\) Hz, 1H), 7.03 (s, 1H), 6.37 (t, \(J = 3.0\) Hz, 1H), 2.30 (s, 6H); \(^13\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\): 178.7, 137.2, 136.2, 136.1, 132.0, 131.6, 129.8, 126.7, 123.1, 121.5, 110.6, 19.2, 18.9; Anal. Caled. for C\(_{16}\)H\(_{13}\)NO; C: 78.36, H: 6.58, N: 7.03%. Found: C: 78.24, H: 6.67, N: 7.06%.
3,5-Dimethyl-1-phenyl-1H-pyrazole\textsuperscript{29} (5C.2.1s, Table 5C.2.2, entry 20): Colourless oil; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textdelta: 7.51-7.39 (m, 4H), 7.34 (dd, \textit{J} = 10.4 and 4.2 Hz, 1H), 5.99 (s, 1H), 2.30 (s, 6H).
5C.5.4 Few representative spectra of previously unknown products

a)

Figure 5C.5.4.1 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5C.2.1d] (Table 5C.2.2, entry 4)
Figure 5C.5.4.2 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5C.2.1j] (Table 5C.2.2, entry 10)
Figure 5C.5.4.3 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5C.2.1q] (Table 5C.2.2, entry 17)
Figure 5C.5.4.4  a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5C.2.1r] (Table 5C.2.2, entry 18)
Figure 5C.5.4.5 a) $^1$H NMR and b) $^{13}$C NMR spectra of product [5C.2.1s] (Table 5C.2.2, entry 19)
5C.6 References


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