Development of Convenient and Greener Routes for Some Organic Transformations
Cesium Fluoride Catalyzed Aza-Michael Addition Reaction in Aqueous Medium
2.1.1. Introduction

Conjugate addition (Michael addition) of nucleophiles to $\alpha,\beta$-unsaturated compounds is one of the most important new bond forming strategies in synthetic organic chemistry.\textsuperscript{1,2} The versatility of the conjugate addition is due to the large variety of nucleophiles (organometallic reagents, other carbanions, heteroatoms, Michael donors) and acceptors ($\alpha,\beta$-unsaturated carbonyl compounds, esters, nitriles, and nitroalkenes) that can be used.\textsuperscript{3-6}

Among these variety of synthetic transformations, development of new methods for an efficient conjugate addition reaction with wide range of heteroatom nucleophiles has attracted special attention.\textsuperscript{7-9} In particular, the conjugate addition of nitrogen nucleophiles to $\alpha,\beta$-enones (Aza-Michael reaction) is noteworthy as a widely used method for carbon-nitrogen bond formation. The products of Aza-Michael additions, $\beta$-amino carbonyl compounds and derivatives, can be used in peptide analogues or as precursors to optically active amino acids, amino alcohols, diamines, and lactams, many of which serve as powerful antibiotics or other drugs.\textsuperscript{10,11}

Organic synthesis in aqueous medium is rapidly gaining importance in view of the fact that the use of many toxic and volatile organic solvents contributes to pollution. Since the pioneering studies by Breslow\textsuperscript{12} on Diels-Alder reactions, there has been a profound research activity in the development of organic reactions in aqueous media offering key advantages such as rate enhancement and insolubility of the final products, which facilitates their isolation by simple filtration. Also, in the context of green chemistry, aqueous media is acting as a stepping stone in the greener synthesis of bioactive heterocyclic compounds. In this respect, the development of water-tolerant catalysts has rapidly become an area of intense research.\textsuperscript{13}

For many chemical processes, a major adverse effect to the environment is the consumption of energy for heating and cooling. To overcome such problems, it is highly desirable to develop efficient methods that utilize alternative energy sources such as ultrasound and microwave irradiation to facilitate chemical reaction. Ultrasound technique has increasingly been used in organic synthesis in the recent years. Ultrasonic irradiation enhances the chemical reaction \textit{via} the process of acoustic cavitation. The assistance of ultrasonic irradiation efficiently shortens the reaction time. Simple experimental procedure, very high yields, increased selectivity, and clean reaction of many ultrasound induced organic transformations offer
additional convenience in the field of synthetic organic chemistry.\textsuperscript{14-17} The chemical effects resulting from the irradiation of aqueous solutions with ultrasound were first time introduced by Loomis et al.\textsuperscript{18}

2.1.2. Literature Review

Among the methods for generating $\beta$-amino carbonyl compounds, Lewis acid and base catalyzed conjugate addition of $N$-containing nucleophiles to $\alpha,\beta$-unsaturated carbonyl compounds is one of the most simple and effective methods (Scheme 2.1.1).\textsuperscript{19,20}

A number of alternative procedures have been developed over the past few years for Aza-Michael addition reaction. Various metal catalysts, such as Yb(OTf)$_3$, InCl$_3$, CeCl$_3$.7H$_2$O/NaI, Bi(NO)$_3$, Bi(OTf)$_3$, Cu(OTf)$_2$, transition metal salts, LiClO$_4$, heterogeneous solid acids, ionic liquids, quaternary ammonium salts, and Cu(acac)$_2$ immobilized in ionic liquids efficiently catalyze the Aza-Michael reaction\textsuperscript{21-35}. However, many of these procedures are associated with one or more drawbacks. Hence the search continues to develop better synthetic protocols for the Aza-Michael reaction in terms of operational simplicity, economic viability and ecofriendly reaction conditions.

![Scheme 2.1.1. General scheme for Aza-Michael addition reaction.](image)

2.1.3. Objectives

Literature revealed that, most of the reported protocols for Aza-Michael addition reaction requires large excess of reagents, long reaction time, drastic reaction conditions and particularly, volatile organic solvents.

In this regard, water could be the best surrogate to the volatile organic solvents being used as a reaction medium. In spite of this, there are only few reports on the conjugate addition of nitrogen nucleophiles to $\alpha,\beta$-unsaturated carbonyl compounds in aqueous reaction medium.\textsuperscript{21,25,26,30} These findings promoted us to investigate the Aza-Michael reaction in aqueous medium.

Cesium fluoride (CsF) is a useful base in organic chemistry due to the fact that fluoride ion is largely unreactive as a nucleophile.\textsuperscript{36} Removal of silicon groups
(desilylation) is one of the major applications of CsF in the laboratory, as its anhydrous nature allows clean formation of water-sensitive intermediates.\textsuperscript{37} It is exploited as an efficient catalyst for the synthesis of carboxylic esters,\textsuperscript{38} trans-$\alpha$-trifluoromethyl allylic alcohols,\textsuperscript{39} $\gamma$-lactones,\textsuperscript{40} aromatic esters and ethers,\textsuperscript{41} thioesters and thioethers,\textsuperscript{42} and 3,4-dihydropyrimidine-2-(1H)-ones.\textsuperscript{43} In addition, it has been used for N-alkylation of anilines, carboxamides, and nitrogen heterocyclic compounds,\textsuperscript{44} and regio- and chemoselective ring opening of epoxides with thiols.\textsuperscript{45}

Aforementioned discussed aspects necessitated us to utilize water as a unique reaction medium in combination with cesium fluoride as a basic catalyst.

### 2.1.4. Present Work

As a part of our ongoing project\textsuperscript{46} we wish to report cesium fluoride catalyzed convenient synthesis of $\beta$-amino carbonyl compounds via Aza-Michael addition reaction in aqueous medium at ambient temperature by conventional and ultrasonication method. (Scheme 2.1.2).

![Scheme 2.1.2. Synthesis of $\beta$-amino carbonyl compounds via Aza-Michael addition.](image-url)
2.1.5. Results and Discussion

In search for the best experimental reaction conditions, Cesium fluoride the Aza-Michael addition reaction between piperidine 1a and methyl acrylate 2a in the presence of CsF at ambient temperature was considered as a standard model reaction. (Scheme 2.1.3)

![Scheme 2.1.3. Standard model reaction.](image)

In an order to evaluate the effect of solvent various solvents such as acetonitrile (MeCN), tetrahydrofuran (THF), methanol (MeOH), ethanol (EtOH), chloroform (CHCl₃), dichloromethane (DCM), water (H₂O) as well as mixtures of solvents, viz. CH₃CN/H₂O, MeOH/H₂O, and EtOH/H₂O, have been used for the model reaction (Table 2.1.1). The use of different solvents like MeCN, THF, MeOH, EtOH, CHCl₃, and DCM afforded the desired product in very low yields 35-55%, (Table 2.1.1, entries 1-6). However, the addition of water to MeCN, MeOH, and EtOH gave the product in slightly higher yields (66-75%, Table 2.1.1, entries 7-9).

Table 2.1.1. Screening of solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>CHCl₃</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>MeCN/H₂O (1:1)</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>MeOH/H₂O (1:1)</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>EtOH/H₂O (1:1)</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>H₂O</td>
<td>2</td>
<td>92</td>
</tr>
</tbody>
</table>

*aStandard conditions: 1a (1 mmol), 2a (1.1 mmol), CsF (10 mol%) in solvent (10 mL) at RT; *bIsolated yields.
Whereas, use of neat water brought the reaction to completion efficiently to obtain the corresponding 3-(piperidin-1-yl)-propionic acid methyl ester in excellent 92% yield. The reaction proceeds smoothly at ambient temperature with 10 mol% of CsF and completes within 2 h (Table 2.1.1, entry 10). This is due to the fact that water has a profound effect on the basic behavior of fluoride anion.47

The model reaction was further investigated under ultrasound irradiation in the presence of CsF with a view to explore whether (i) the reaction could be expedited, and (ii) the product yield could be enhanced. In this case, no significant improvement in the product yield (94%) was observed, but the reaction time enormously reduced to 20 min as compared to conventional method (2 h).

It is a well established fact that fluoride ion is capable of forming strong hydrogen bonding with a variety of hydrogen bond acceptor compounds.48 On the basis of that, it is proposed that CsF forms hydrogen bond between fluoride anion and amine (Figure 2.1.1), which results in the transfer of electron density from fluoride anion to amine, and ultimately enhances the nucleophilicity of amine, while at the same time it reduces the nucleophilicity of the fluoride.49 This accelerates the rate of reaction enormously and affords the desired product in shorter reaction time.

![Figure 2.1.1. Proposed mechanism for CsF catalyzed Aza-Michael addition reaction.](image)

For assessing the generality of the optimized reaction conditions various primary and secondary amines such as piperidine, morpholine, dimethylamine, diethylamine, methylamine, 2-methoxyethanamine, n-butylamine and anilines with respect to acrylonitrile and α,β-unsaturated esters such as methyl acrylate and ethyl acrylate were subjected for Aza-Michael addition reaction in the presence of CsF.
(Table 2.1.2). It was observed that secondary amines react faster than primary amines, providing excellent yield of product 90-92% (Table 2.1.2, entries 1-12). In comparison with these results, primary aliphatic amines required longer reaction time and formed the corresponding monoadduct in 76-85% yields (Table 2.1.2, entries 13-16). Whereas utilization of 2.2 equivalents of ethyl acrylate with respect to primary aliphatic amine resulted in the formation of bisadduct in good yields (78-81%, Table 2.1.2, entries 17-18). Unfortunately, when anilines were subjected to undergo this addition reaction, starting materials were recovered even after prolonged reaction time by both conventional and non-conventional methods. Ultrasound irradiation technique was also established to be compatible with all these substrates and products were obtained in excellent yield (81-94%) within only 20-40 min (Table 2.1.2). Formation of the product was confirmed with the help of $^1$H NMR, $^{13}$C NMR and mass spectroscopic data.

2.1.6. Conclusion

In conclusion, CsF has been proved to be an efficient catalyst for the synthesis of β-amino esters/nitriles via Aza-Michael reaction in water at ambient temperature by conventional and ultrasonication methods. This method offers remarkable advantages such as simple experimental procedure, mild reaction conditions, lower reaction time, and higher product yields, avoiding hazardous organic solvents.
**Table 2.1.2.** Synthesis of β-amino carbonyl compounds via Aza-Michael addition\(^a\)

\[
\begin{align*}
\text{Amines} & = \text{NH}_2(1a), \text{NH}(1b), \text{NH}(1c), \\
& \quad \text{NH}_2(1d), \text{NH}_2(1e), \\
& \quad \text{NH}_2(1f), \\
\text{Olefins} (R_1) & = \xrightarrow{\text{COOMe}} (2a), \xrightarrow{\text{COOH}} (2b), \xrightarrow{\text{CN}} (2c)
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine 1</th>
<th>Olefin 2</th>
<th>Product 3</th>
<th>Conventional</th>
<th>Ultrasonication</th>
</tr>
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<td></td>
<td></td>
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<td>Time (h)</td>
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<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a</td>
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<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td>3b</td>
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<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2c</td>
<td>3c</td>
<td>2.0</td>
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<td>1c</td>
<td>2c</td>
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<td>16</td>
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<td>17</td>
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<tr>
<td>18</td>
<td>1g</td>
<td>2b</td>
<td>3r</td>
<td>4.0</td>
<td>78(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 1 (1 mmol), 2 (1.1 mmol) and CsF (10 mol\%) in water (10 mL) at RT; \(^b\)Isolated yields. \(^c\)2.2 equiv ethyl acrylate was added. \(^d\)All compounds were oils at RT.\(^2\)
2.1.7. Experimental

*General experimental procedure for the synthesis of β-amino carbonyl compounds via Aza-Michael addition 3(a-r)*

(A) *Conventional method:* Corresponding amine 1 (1 mmol) and α,β-unsaturated compound 2 (1.1 mmol) were added to a 25 mL round bottom flask (RBF) containing 10 mL water. To the reaction mixture then added CsF (0.1 mmol). The reaction mixture was stirred at room temperature for appropriate time given in Table 2.1.2. Progress of the reaction was monitored using TLC (methanol:chloroform = 1:19). After particular time, the reaction mixture was extracted with ethyl acetate (10 mL x 2) and the organic layer was dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under vacuum to afford desired compound 3.

(B) *Ultrasound method:* Corresponding amine 1 (1 mmol) and α,β-unsaturated compound 2 (1.1 mmol) were added to a 25 mL round bottom flask (RBF) containing 10 mL water. To the reaction mixture then added CsF (0.1 mmol). The reaction mixture was subjected to ultrasonication bath for specified time in Table 2.1.2. The progress of the reaction was monitored using TLC (methanol:chloroform = 1:19). After particular time, the reaction mixture was extracted with ethyl acetate (10 mL x 2) and the organic layer was dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under vacuum to afford desired compound 3.

**Spectral data for representative compound**

3-((piperidin-1-yl)propanenitrile (3c)

<table>
<thead>
<tr>
<th><strong>1H NMR (400 MHz, DMSO-d6)</strong></th>
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</thead>
<tbody>
<tr>
<td>δ 1.35-1.39 (m, 2H), 1.49-1.54 (qnt, 4H, J = 5.6 Hz), 2.35-2.38 (t, 4H, J = 5.2 Hz), 2.42-2.45 (t, 2H, J = 7.2 Hz), 2.58-2.62 (t, 2H, J = 7.2 Hz).</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>13C NMR (100 MHz, DMSO-d6)</strong></th>
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<tbody>
<tr>
<td>δ 15.6, 24.6, 26.1, 54.0, 54.2, 120.7.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mass (ES-MS)**

m/z 138.8 (M+).
Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (A)

\[ ^1H \text{NMR} (400 \text{MHz}, \text{DMSO-d}_6) \]

\[ \text{(3c)} \]

\[ ^13C \text{NMR} (100 \text{MHz}, \text{DMSO-d}_6) \]

\[ \text{(3c)} \]

Vilas B. Labade
Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (A)

Mass Spectrum

Vilas B. Labade

35
2.1.8. References


Citric Acid: An Efficient and Biodegradable Catalyst for the Convenient Synthesis of 1,5-Benzodiazepines in Water
2.2.1. Introduction

Benzodiazepines constitute an important class of biodynamic heterocycles and synthesis of these compounds has been receiving great attention in the field of medicinal and pharmaceutical chemistry owing to their broad spectrum of biological/pharmacological activities\(^1\) and their often use as analgesic, sedative, hypnotic, anti-consultant, anti-anxiety, anti-depressive, and anti-inflammatory agents.\(^2\) In addition, 1,5-Benzodiazepines are valuable synthetic intermediates for the preparation of other heterocyclic compounds such as triazolo-, oxadiazolo-, oxazino-, furano-, and quinazolino-benzodiazepines.\(^3\)

Furthermore, 1,5-benzodiazepines (1,5-BDZs) based on their potential structural diversity represent such a class of medicinally significant compounds, libraries of which demonstrate activity against a wide range of biological target families, which include cholecystokinin receptors,\(^4\)-\(^6\) interleukin converting enzymes\(^7\),\(^8\) and ion channels.\(^9\),\(^10\) Their activity against cancer, HIV and central nervous system disorder\(^11\) has attracted strong interest of medicinal chemists.

The neurotransmitter dopamine plays an important role in the development of several neurological and psychiatric disorders such as schizophrenia,\(^12\),\(^13\) Huntington’s disease, and Parkinson’s disease.\(^14\) Thus, the investigation of the dopaminergic system has become an important target in research in order to understand the etiology of these diseases and to find efficient drugs for their treatment. Making use of modern molecular biological techniques, five dopamine receptor subtypes (D1–D5) were characterized and divided into two main families, the D1-like (including the D1 and D5 subtype) and the D2-like (D2, D3, and D4).\(^15\),\(^16\)

Clozapine, having 1,5-benzodiazepine moiety (3.1), is a significant neuroleptic agent, which blocks preferentially the D4 receptor with typical selectivity versus the D2 subtypes. The 1,5-benzodiazepine-2-one core is also a “privileged scaffold” found in compounds active against numerous targets such as protease inhibitors, 7-TM receptors, etc. (Examples are 3.2-3.4).\(^17\)-\(^19\)
2.2.2. Literature Review

Cyclo-condensation of 1,2-diamines with carbonyl compounds having methylene (-CH₂-) group α- to carbonyl is one of the well established synthetic methods for the construction of 1,5-benzodiazepine derivatives²⁰ (Scheme 2.2.1).

![Scheme 2.2.1. Cyclocondensation of 1,2-diamines with carbonyl compounds.](image)

Literature reveals that presence of acid catalyst favors the reaction in the desired path. Hence for this purpose, wide range of catalysts, like BF₃·OEt₂,²¹ polyphosphoric acid,²² CeCl₃·NaI/SiO₂,²³ I₂,²⁴ ZnCl₂,²⁵ SmI₂,²⁶ YbCl₃,²⁷ MgO/POCl₃,²⁸ Amberlyst-15,²⁹ Yb(OTf)₃,³⁰ Ga(OTf)₃,³¹ Al₂O₃/P₂O₅,³² AcOH/MW,³³ sulfated zirconia,³⁴ NBS,³⁵ ceric ammonium nitrate (CAN),³⁶ montmorillonite K10,³⁷
Ag₃PW₁₂O₄₀,³⁸ InBr₅/InCl₃,³⁹ and ionic liquids,⁴⁰ have been utilized for this transformation, along with their own merits and demerits. In this regard, few eco-friendly routes involving the use of ultrasound irradiations in halogenated solvents⁴¹a and dodecyl sulfonic acid in water⁴¹b have also been reported in literature.

Additionally, use of magnesium bromide (MgBr₂)⁴²a and (±) camphor sulphonic acid⁴²b as a catalyst for the synthesis of 1,5-benzodiazepines has been reported by our group.

2.2.3. Objectives

Benzodiazepines hold a special place among pharmaceutically significant natural products and synthetic compounds. The remarkable ability of this nucleus to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. Owing to such significance of benzodiazepine based molecules, work was planned to search improved method for their synthesis in terms of mild reaction conditions, cleaner reaction medium, easily available and biodegradable catalytic system, simple work up procedure, shorter reaction times and higher yields of the product.

Utilization of naturally as well as easily available and biodegradable catalyst for organic transformation is achieving enormous significance in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of these reactions meet the standards of established organic reactions. In this regard, Citric acid keeps the potential of performing the role of ideal catalyst. It is a relatively mild organic acid. Citric acid and its salts are widely used because they are nontoxic, relatively non-corrosive, safe to handle, and easily biodegraded. Additionally, there is a single report on the use of citric acid as a catalyst for organic synthesis.⁴³ Therefore, in continuation our interest towards the development of novel synthetic methodologies for the synthesis of 1,5-benzodiazepines,⁴² attempt has been made to carry out this organic transformation using citric acid as a catalyst.
2.2.4. Present Work

In the present study, efficient synthesis of 1,5-benzodiazepines using o-phenylenediamines 1 and carbonyl compounds 2 under milder reaction conditions in aqueous medium is described. Successful utilization of citric acid in water as a novel catalytic system is demonstrated. (Scheme 2.2.2)

Scheme 2.2.2. Synthesis of 1,5-benzodiazepine derivatives.

2.2.5. Results and Discussion

For our initial study, reaction of o-phenylenediamine 1a with acetophenone 2a using water as a solvent was considered as a standard model reaction (Scheme 2.2.3). Model reaction in the absence of catalyst did not led to the formation of desired product. It means intervention of catalyst is necessary for initiation of the reaction.

Scheme 2.2.3. Standard model reaction.

To obtain best reaction conditions, different water-soluble acid catalysts were screened for the model reaction viz. boric acid, oxalic acid, p-TSA, EDTA·2Na salt and citric acid. With the use of EDTA·2Na salt the product was formed in poor yield, 39% (Table 2.2.1, entry 4). In contrast, boric acid, oxalic acid, and p-TSA afforded the product good yields (Table 2.2.1, entries 1-3). In comparison with these, citric acid proved to be most efficient catalyst which delivered the desired product in higher yield, 84% within 60 min (Table 2.2.1, entry 5).

The model reaction was further investigated using different solvent systems in a view, whether, the reaction rate could be accelerated and, the product yield could be enhanced. During this study, model reaction was tested under solvent-free conditions
and using solvents like ethanol, aqueous ethanol, methanol and water. But, use of water proved to be most suitable for the model reaction.

**Table 2.2.1.** Screening of reaction medium

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst Conc. (mol%)</th>
<th>Time (min)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boric acid</td>
<td>10</td>
<td>60</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>Oxalic acid</td>
<td>10</td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>p-TSA</td>
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<td>79</td>
</tr>
<tr>
<td>4</td>
<td>EDTA:2Na</td>
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<td>39</td>
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<tr>
<td>5</td>
<td>Citric acid</td>
<td>10</td>
<td>60</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>Citric acid(^c)</td>
<td>10</td>
<td>60</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>Citric acid(^d)</td>
<td>2.5, 5, 10, 15</td>
<td>60</td>
<td>41, 62, 91, 90</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 1a (1 mmol) and 2a (2 mmol) in water (10 mL) at RT;\(^b\)Isolated yields; \(^c\)at 50 °C; \(^d\)Consider respective yields.

To determine the exact requirement of catalyst for the reaction, we investigated the model reaction using different concentrations of citric acid such as 2.5, 5, 10 and 15 mol%. During this study, formation of the product was observed in 41, 62, 91 and 90% yield respectively (Table 2.2.1, entry 7). This indicated that 10 mol% of citric acid was sufficient to carry out the reaction smoothly.

To evaluate the temperature effect on reaction rate model reaction was performed at different temperatures such as room temperature, 50 °C, 60 °C, 80 °C and reflux temperature. Surprisingly, temperature of 50 °C proved to be efficient for carrying out model reaction smoothly. Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 50 °C did slow down the reaction rate.

Success of Citric acid as a catalyst in the presence of water as a solvent could be attributed to the following points – (i) Citric acid is a slightly stronger acid than typical carboxylic acids because the anion can be stabilized by intramolecular hydrogen-bonding from other protic groups on citric acid. (ii) One more aspect that could be helpful for bringing the reaction in favor of water is hydrophobic interactions which induce favorable aggregation of organic substrates in water.

A possible mechanism involved in citric acid catalyzed cyclo-condensation reaction for the synthesis of 1,5-benzodiazepines can be outlined as follows: o-phenylenediamine (1) reacts with two molecules of ketone (2) in the presence of citric
acid as a catalyst to form schiff base (A), which undergoes 1,3-H shift and get converted into intermediate (B). Thus formed intermediate (B) via subsequent cyclization affords the final product (3), i.e. 1,5-benzodiazepine. Diagrammatic representation of the mechanism is rationalized in Figure 2.2.1.

![Diagram](image)

**Figure 2.2.1.** Plausible mechanism involved in the synthesis of 1,5-benzodiazepine.

Having established the optimum experimental conditions for obtaining the best yields of 1,5-benzodiazepine derivatives, different o-phenylenediamines with respect to various ketones were examined against standard reaction conditions. Remarkably, all the substrates were found to be compatible under the optimized reaction condition delivering the product in good to excellent yields. All the results are summarized in Table 2.2.2. Formation of the desired product was confirmed by on the basis of $^1$H NMR and mass spectroscopic data.
Table 2.2.2. Synthesis of 1,5-Benzodiazepine Derivatives 3(a-l)\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comp.</th>
<th>R</th>
<th>R(_1)</th>
<th>R(_2)</th>
<th>Time (min)</th>
<th>Yield(^b) (%)</th>
<th>M.P.(^c) (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>60</td>
<td>91</td>
<td>151-153</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>120</td>
<td>89</td>
<td>135-136</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>90</td>
<td>86</td>
<td>140-141</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>H</td>
<td>Et</td>
<td>Me</td>
<td>150</td>
<td>89</td>
<td>144-146</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>H</td>
<td>i-Butyl</td>
<td>H</td>
<td>120</td>
<td>85</td>
<td>117-119</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>H</td>
<td>Cyclohexanone</td>
<td>120</td>
<td>88</td>
<td>136-138</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>60</td>
<td>85</td>
<td>93-94</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>60</td>
<td>91</td>
<td>126-127</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>120</td>
<td>87</td>
<td>115-117</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>Me</td>
<td>i-Butyl</td>
<td>H</td>
<td>120</td>
<td>86</td>
<td>124-126</td>
</tr>
<tr>
<td>11</td>
<td>3k</td>
<td>NO(_2)</td>
<td>Ph</td>
<td>H</td>
<td>90</td>
<td>83</td>
<td>137-139</td>
</tr>
<tr>
<td>12</td>
<td>3l</td>
<td>NO(_2)</td>
<td>Me</td>
<td>H</td>
<td>90</td>
<td>87</td>
<td>112-113</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 1 (1 mmol), 2 (2 mmol) and citric acid (10 mol%) in water (10 mL) at RT; \(^b\)Isolated yields; \(^c\)Melting points matches with literature values.

2.2.6. Conclusion

In summary, an efficient, mild and clean synthetic protocol for 1,5-benzodiazepines has been developed. In this method, attempt has been made for exploitation of the catalytic activity of citric acid in organic transformation. Water is not only inexpensive and environmentally benign solvent but also plays a distinguished role in reactivity and selectivity. Citric acid catalyzed the reaction efficiently without using any harmful organic reagents/ solvents.
2.2.7. Experimental

General experimental procedure for the Synthesis of 1,5-Benzodiazepines 3(a-l)

A mixture of o-phenylenediamine 1 (1 mmol), carbonyl compound 2 (2 mmol), citric acid (0.1 mmol) and water (10 mL) in a closed round bottom flask of capacity 25 mL was allowed to stir vigorously at 50 °C. Reaction progress was monitored by TLC (ethyl acetate/n-hexane, 2:8). After completion of the reaction, reaction mixture was poured on ice-cold water and stirred well. Thus obtained yellow coloured solid product was collected by simple filtration, washed with water and dried. This crude product (3) was then recrystallized from aqueous ethanol (30%) to get pure product.

Spectral data for representative compounds

2,2,4-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (3b)

<table>
<thead>
<tr>
<th>$^1$H NMR (400 MHz, DMSO-$d_6$)</th>
<th><img src="image" alt="Structure of 3b" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>δ 1.33 (s, 6H), 2.19 (s, 2H), 2.35 (s, 3H), 2.90 (brs, 1H, -NH), 6.70-6.73 (m, 1H, Ar-H), 6.95-6.99 (m, 2H, Ar-H), 7.10-7.13 (m, 1H, Ar-H).</td>
<td>m/z 189.1 (M$^+$).</td>
</tr>
</tbody>
</table>
Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (B)

\[ ^{1}H \text{NMR} \ (400 \text{ MHz, DMSO-d}_6) \]

(3b)

Mass Spectrum 189.1 Peak #1

(3b)
2.2.8. References


Citric Acid Catalyzed Synthesis of Benzothiazole and Benzimidazole Derivatives in Aqueous Medium
2.3.1. Introduction

A number of heterocyclic derivatives containing nitrogen and sulphur atoms serve as a unique and versatile scaffolds for experimental drug design. Benzothiazole is a heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. It consists of thiazole ring fused with benzene ring and possesses multiple applications. The survey of literature related to benzothiazoles reveals the presence of this bicyclic ring system in various amine or terrestrial natural compounds, which have useful biological properties. In recent years, heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. Benzothiazole is one of the most important heterocycles that has received overwhelming response owing to its diversified molecular design and remarkable optical and electronic properties.

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry. These structures represent a class of molecules capable of binding to multiple receptors with high affinity. The exploitation of these molecules enables the medicinal chemist to rapidly discover biologically active compounds across a wide range of therapeutic areas on a reasonable time scale. 2-Arylbenzothiazole is such an important class of bicyclic privileged substructures owing to their potent utility as imaging agents for α-amyloid, antitumor agents, calcium channel antagonists, antituberculosis, antiparasitics, chemiluminescent agents, and also as photosensitizers.

Benzothiazoles are precursors of natural products, pharmaceutical agents and other compounds that exhibit a wide spectrum of biological activity such as immunosuppressive, immunomodulatory and antiviral properties. For example, polyhydroxylated 2-phenylbenzothiazoles showed potent in vitro cytotoxicities against varieties of human tumor cell lines.

Benzothiazoles are widely found in bioorganic and medicinal chemistry with applications in drug discovery and have a very intensive antitumor, antiviral, anti-HIV, and microbiological activity. Benzothiazoles are used for treatment of autoimmune and inflammatory diseases, in the prevention of solid organ transplant rejection, epilepsy, amyotrophic lateral sclerosis, and analgesia. Further industrial applications as antioxidants, vulcanization accelerators, and a dopant in light emitting organic electroluminescent devices have also been reported.
Among the well known wide variety of heterocyclic systems known till date, the nitrogen heterocycles are of great importance and benzimidazole is one such important nitrogen heterocyclic species because of its synthetic utility, number of commercial products and broad spectrum of pharmacological activity.\textsuperscript{17,18} Most significantly, the benzimidazole ring system has been found to be an integral part of Vitamin-B\textsubscript{12} in the form of 5,6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole.

Some benzimidazole derivatives with different pharmacological properties such as human & veterinary anthelmintic,\textsuperscript{19} anti-ulcer,\textsuperscript{20} cardiotonic,\textsuperscript{21} antihypertensive\textsuperscript{22} etc. have already been reported. The literature precedence revealed that the substitutions at 1, 2 and 5 positions of the benzimidazole moiety is crucial for the compounds to exhibit wide range of pharmacological activities. A wide range of benzimidazoles and their derivatives find use in pharmaceuticals and veterinary drugs showing varied therapeutic activities. Some of the commercially important benzimidazole derivatives are presented in following Figure 2.3.1.

**Figure 2.3.1.** Some commercially important benzimidazole derivatives.

Since, above discussed heterocycles has tremendous significance in various areas, they offer challenge to organic chemists to develop an environmentally benevolent methods for the synthesis of these biodynamic heterocycles. Our interest
in all these heterocycles stems from their aforementioned bioactivities. In this regard, development of novel synthetic strategies for such heterocycles is becoming one of the most important and attractive topics of research among the synthetic organic chemists.

2.3.2. Literature Review

Numerous methods have been reported in the literature for the synthesis of benzothiazoles. A range of methods currently available for the synthesis of 2-substituted benzothiazoles includes condensation-dehydration of 2-aminothiophenol with carboxylic acids,\textsuperscript{23} aldehydes,\textsuperscript{24} alcohols,\textsuperscript{25} acid chlorides\textsuperscript{26} and esters.\textsuperscript{27} Another well known approach for obtaining benzothiazole derivatives is Jacobson’s cyclization of thiobenzanilides.\textsuperscript{28}

Literature survey reveals that, among the existing routes, the most useful approach for the preparation of benzothiazoles is cyclo-condensation of aldehydes and 2-aminothiophenol in the presence of catalysts\textsuperscript{24} such as [PMIM][Br], Iodine, ZrOCl\textsubscript{2}.8H\textsubscript{2}O, TMSCl, PCC, CAN etc. (Scheme 2.3.1). Most of the reported methodologies are generally efficient, but, they require long reaction times, harsh reaction conditions including the use of corrosive acids (e.g. polyphosphoric acid) and heating in high boiling point solvents, and are associated with the generation of hazardous wastes, low functional group tolerance, and tedious work-up procedures thus leaving room for further upgradation.

![Scheme 2.3.1.](image)

**Scheme 2.3.1.** Most Common approach for the preparation of benzothiazoles.

Earlier synthetic strategies for the synthesis of benzimidazoles\textsuperscript{29} involved the use of variety of starting materials such as- (i) \(\alpha\)-phenylenediamines, (ii) \(\alpha\)-(\(N\)-acylamino and -arylamino)arylamines and nitroarenes, (iii) \(\alpha\)-nitroarylamines and \(\alpha\)-dinitroarenes, (iv) \(\alpha\)-substituted-\(N\)-benzylideneanilines, (v) amidines and other heterocyclic compounds.

Among the well known methods for the synthesis of benzimidazoles, cyclo-condensation reaction of aldehydes and \(\alpha\)-phenylene diamines is the most common, efficient and easily accessible (Scheme 2.3.2). Ample of catalysts have been disclosed
for achieving this transformation. Some of them are hypervalent iodine as oxidant,\textsuperscript{30} oxalic acid,\textsuperscript{31} H$_2$O$_2$/$\text{HCl}$,\textsuperscript{32} TiCl$_4$,\textsuperscript{33} PPA,\textsuperscript{34} SOCl$_2$/SiO$_2$,\textsuperscript{35} silica-sulfuric acid,\textsuperscript{36} L-proline,\textsuperscript{37} sulphanic acid,\textsuperscript{38} zeolite\textsuperscript{39} and CuCl/TMEDA.\textsuperscript{40}

![Scheme 2.3.2](image)

**Scheme 2.3.2.** General route for the synthesis of benzimidazole derivatives.

Despite of the above discussed synthetic protocols, in an era, where green methods are warranted many of these methods does not hold satisfactory, due to one or more drawbacks such as, use of halogenated solvents, low yields, longer reaction times, higher catalyst loading, drastic reaction conditions and tedious work-up procedure.

### 2.3.3. Objectives

Considering the increasing environmental pollution and its drastic impact on living systems, emerging area of green chemistry demands eco-friendly organic chemical processes that utilize biocompatible, inexpensive and readily available catalysts. In this regard, implementation of biodegradable organic catalysts like citric acid is playing very attractive role to build up eco-friendly routes for the construction of various heterocyclic molecules.

Therefore, it was thought worthwhile to develop a new, greener and efficient method for such type of cyclo-condensation reactions by means of easily available and biodegradable catalyst.

Considering the significance of all above discussed aspects and with our successful implementation of citric acid as a catalyst for previous reaction, it was planned to explore the catalytic activity of citric acid as a catalyst for the greener and expeditious synthesis of benzo-thiazole as well as benzimidazole derivatives in aqueous medium.
2.3.4 Present Work

In the present work, successful implementation of citric acid as a catalyst for greener and expeditious synthesis of benzothiazoles as well as an attempt for the synthesis of benzimidazole derivatives in aqueous medium is described (Scheme 2.3.3 and Scheme 2.3.4).

![Scheme 2.3.3. Synthesis of benzothiazoles.](image)

2.3.5 Results and Discussion

Our preliminary study was focused on the utilization of citric acid for the synthesis of benzothiazoles. For this purpose reaction of 2-aminothiophenol 1 and 4-nitro benzaldehyde 2a was considered as a standard model reaction (Scheme 2.3.5).

![Scheme 2.3.5. Standard model reaction.](image)

To effect the model reaction, various attempts were made using citric acid in combination with several solvent systems such as water, ethanol, methanol, acetonitrile and 1,4-dioxane.

When 1,4-dioxane and acetonitrile were employed as solvent, reaction did not proceed effectively (Table 2.3.1, entries 1-2). Furthermore, use of methanol and ethanol resulted in poor and moderate yield respectively (Table 2.3.1, entries 3-4),
whereas, utilization of water as reaction medium proved to be beneficial and desired compound was delivered in good yield 76% (Table 2.3.1, entry 5). When, model reaction was carried out in the presence of aqueous ethanol (1:1) fascinating result with higher yield 88% was achieved (Table 2.3.1, entry 6), which may be due to the appropriate homogeneity and proper concentration of reaction mixture.

Table 2.3.1. Screening of Solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,4,-Dioxane</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Water</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Water:Ethanol (1:1)</td>
<td>88</td>
</tr>
</tbody>
</table>

aReaction conditions: 1 (1 mmol), 2a (1 mmol), citric acid (10 mol%) for 30 min at 70 °C; bIsolated yield.

Encouraged by this, model reaction was further tried under variable temperature conditions (Table 2.3.2). Reaction at room temperature delivered the product in poor yield (Table 2.3.2, entry 1), whereas at 40 and 55 °C formation of the product was observed in 42 and 70% respectively (Table 2.3.2, entries 2-3). In comparison, model reaction at 70 °C completed efficiently yielding 88% of desired product (Table 2.3.2, entry 4). Reactions at higher temperature than 70 °C were not found to be fruitful in terms of both reaction time and product yield.

Table 2.3.2. Screening of Temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RT</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

aReaction conditions: 1 (1 mmol), 2a (1 mmol), citric acid (10 mol%) in Aq. ethanol (10 mL) for 30 min; bIsolated yield.
To determine the exact requirement of catalyst for the reaction, model reaction was performed using different concentrations of citric acid such as 5, 10, 15, 20 and 25 mol%. During this, formation of the product was observed in 85, 88, 98, 89 and 89% yield respectively (Table 2.3.3). This indicated that 15 mol% of citric acid is sufficient to carry out the reaction smoothly.

Table 2.3.3. Screening of Catalyst Conc.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Citric acid (mol%)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>89</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1 (1 mmol), 2a (1 mmol) in Aq. ethanol (10 mL) for 30 min at 70 °C; $^b$Isolated yields.

In accordance with the literature, plausible mechanistic path leading to the formation of benzothiazole is outlined in the following figure (Figure 2.3.2) – Initially nucleophilic addition of 2-aminothiophenol (1) to aldehyde (2) leads to corresponding schiff base (B). Subsequent cyclization of (B) gives intermediate (C) which on air affords the final product (3).

Figure 2.3.2. Plausible mechanism involved in the synthesis of benzothiazoles.
To further establish the scope of optimized reaction conditions and in order to generalize the synthetic procedure, variety of electronically divergent aryl aldehydes were treated with 2-aminothiophenol, and all these substrates were found to be equally amenable to these conditions. Interestingly, some heteryl aldehydes also underwent the reaction efficiently. All the results are summarized in Table 2.3.4 Formation of the synthesized compounds was confirmed on the basis of $^1$H NMR and mass spectroscopic data.

### Table 2.3.4. Synthesis of benzothiazole derivatives$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comp.</th>
<th>Aldehyde</th>
<th>Time (min)</th>
<th>Yield$^b$ (%)</th>
<th>M.P.$^c$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>4-NO$_2$-Ph</td>
<td>18</td>
<td>98</td>
<td>228-230</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Ph</td>
<td>25</td>
<td>93</td>
<td>114-115</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>3-NO$_2$-Ph</td>
<td>20</td>
<td>95</td>
<td>185-186</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>4-OMe-Ph</td>
<td>30</td>
<td>88</td>
<td>118-120</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>4-Br-Ph</td>
<td>30</td>
<td>83</td>
<td>131-133</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>2-OH-Ph</td>
<td>18</td>
<td>85</td>
<td>128-130</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>2-Cl-Ph</td>
<td>20</td>
<td>91</td>
<td>74-75</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>4-F-Ph</td>
<td>12</td>
<td>85</td>
<td>97-99</td>
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<td>9</td>
<td>3i</td>
<td>4-Cl-Ph</td>
<td>20</td>
<td>94</td>
<td>114-115</td>
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<tr>
<td>10</td>
<td>3j</td>
<td>4-N(Me)$_2$-Ph</td>
<td>15</td>
<td>85</td>
<td>175-177</td>
</tr>
<tr>
<td>11</td>
<td>3k</td>
<td>Piperonyl</td>
<td>20</td>
<td>88</td>
<td>120-122</td>
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<tr>
<td>12</td>
<td>3l</td>
<td>Thiophen-2-yl</td>
<td>15</td>
<td>82</td>
<td>100-101</td>
</tr>
<tr>
<td>13</td>
<td>3m</td>
<td>Furfuryl</td>
<td>20</td>
<td>86</td>
<td>101-103</td>
</tr>
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<td>14</td>
<td>3n</td>
<td>Pyridin-3-yl</td>
<td>15</td>
<td>89</td>
<td>138-140</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1 (1 mmol), 2 (1 mmol) and citric acid (15 mol%) in Aq. ethanol (10 mL) at 70 °C $^b$Isolated yields; $^c$Melting points matches with the literature values.
In view of the ever-growing significance of benzimidazole derivatives, our work was extended for the exploitation of catalytic activity of citric acid for preparation of these compounds.

For our initial experiments, reaction of 4-methoxy benzaldehyde 2a and o-phenylene diamine 4a was considered as a standard reaction (Scheme 2.3.6).

Scheme 2.3.6. Standard model reaction

This typical reaction was performed following optimized reaction conditions achieved for benzothiazoles and it was observed that under these conditions product was isolated in 78% yield.

In further attempts, our attention was turned over the temperature factor to ensure whether product yield could be enhanced. During the study, reaction was carried out using different reaction temperature, i.e. RT, 40, 55 and 70 °C. While going through all these experiments, it was proved that increase in temperature beyond 55 °C leads to decrease in the product yield (Table 2.3.5).

Table 2.3.5. Screening of Temperaturea

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RT</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>78</td>
</tr>
</tbody>
</table>

aReaction conditions: 1 (1 mmol), 2a (1 mmol), citric acid (15 mol%) for 30 min at 70 °C; bIsolated yield.

Though benzimidazole compounds were getting good yields, to our observation, we came to know that whatever product was obtained, it was the mixture of benzimidazole (5) and 1,2-disubstituted benzimidazole (6). This conclusion is drawn based upon various techniques like mass spectrum, 1H NMR data and TLC technique. Some attempts were made to obtain the pure benzimidazole derivative of either 5 or 6 using citric acid in the presence of different solvents and by varying
concentration of citric acid. But, all the experiments failed and formation of pure benzimidazole compound (either 5 or 6) did not take place.

Later on, it was decided to find out and fix the strategy for obtaining the pure compounds 5 and 6 from the reaction mixture. After performing several experiments, it was finalized that the purification of the isolated product (mixture of 5 & 6) can be carried out by using absolute ethanol. In an order to isolate mixture of compounds 5 and 6, after completion of the reaction, reaction mixture was cooled to RT to get mixture of mono- and 1,2-disubstituted benzimidazoles. This mixture was separated by crystallization using absolute ethanol. During crystallization, crystals of 1,2-disubstituted compound 6 were precipitated at RT and it was collected by simple filtration. Whereas, monosubstituted benzimidazole compound 5 was obtained by concentration and evaporation of the filtrate.

Plausible mechanism involved in the synthesis of benzimidazole derivatives shown with the help following figure (Figure 2.3.3).

**Figure 2.3.3.** Plausible mechanism for the synthesis of benzimidazole derivatives.
Various derivatives of benzimidazole were synthesized by utilizing different aromatic aldehydes as well as o-phenylene diamines. In each and every reaction, product was obtained as a mixture of mono-substituted benzimidazole and 1,2-disubstituted benzimidazole derivatives. All the results are compiled in the form of Table 2.3.6. Formation of the synthesized compounds was confirmed on the basis of $^1$H NMR, $^{13}$C NMR and mass spectroscopic data.

**Table 2.3.6. Synthesis of benzimidazole derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R$_1$</th>
<th>Aldehyde</th>
<th>Time (min)</th>
<th>Yield$^b$ (%)</th>
<th>Total Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>4-OMe-Ph</td>
<td>35</td>
<td>34</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>H</td>
<td>Ph</td>
<td>25</td>
<td>37</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>H</td>
<td>4-F-Ph</td>
<td>15</td>
<td>34</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>H</td>
<td>4-OH-Ph</td>
<td>15</td>
<td>34</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>H</td>
<td>2-NO$_2$-Ph</td>
<td>10</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>H</td>
<td>3,4,5-OMe-Ph</td>
<td>40</td>
<td>32</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>H</td>
<td>4-OH-3-OMe-Ph</td>
<td>25</td>
<td>37</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>H</td>
<td>Piperyonyl</td>
<td>20</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>H</td>
<td>Indol-3-yl</td>
<td>15</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>H</td>
<td>2-Cl-Ph</td>
<td>15</td>
<td>36</td>
<td>57</td>
</tr>
<tr>
<td>11</td>
<td>k</td>
<td></td>
<td>4-NO$_2$-Ph</td>
<td>20</td>
<td>33</td>
<td>48</td>
</tr>
<tr>
<td>12</td>
<td>l</td>
<td></td>
<td>2-Cl-Ph</td>
<td>20</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td></td>
<td>Indol-3-yl</td>
<td>15</td>
<td>36</td>
<td>41</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1 (1 mmol), 2 (1 mmol) and citric acid (15 mol\%) in Aq. ethanol (10 mL) at 55 °C $^b$Isolated yields; *Total yield as well as respective yields of 5 & 6 is calculated based on the molecular weight of mono-substituted benzimidazole derivative (5); $^\#$Actual yield of 1,2-disubstituted benzimidazole (6) is half of the given isolated yield for compound 6, i.e. [$\frac{1}{2}$ x (value provided under heading 6$^\#$)].
2.3.6. Conclusion

In summary, an efficient, greener and expeditious synthetic protocol for benzothiazoles has been developed. After the successful implementation of citric acid for preparing benzothiazole derivatives, the same was applied for the synthesis of benzimidazoles. Remarkable advantages of this synthetic strategy over others are- (i) use of biodegradable, non-toxic, readily available and inexpensive catalyst, (ii) reduced reaction times, (iii) utilization of water as a solvent, (iv) ambient reaction temperature, (vi) simplified work-up procedure, and (v) use of common catalyst i.e. citric acid for the synthesis of benzothiazole and benzimidazole derivatives.
2.3.7 Experimental

General experimental procedure for the synthesis of 2-(4-aryl)benzo[d]thiazole 3(a-n)

A mixture of 2-aminothiophenol 1 (1 mmol), aryl aldehyde 2 (1 mmol) and citric acid (0.15 mmol) in aq. ethanol (10 mL) was stirred well at 70 °C. Progress of the reaction was monitored by TLC (ethyl acetate:n-hexane, 2:8). After completion of the reaction, reaction mixture was cooled to RT to get product 3. Then it was collected by simple filtration. Thus obtained product was crystallized with aq. ethanol to afford pure product without need of any further purification.

General experimental procedure for the synthesis of 2-(4-aryl)-1H-benzo[d]imidazole 5(a-m) and 1-(aryl)-2-(4-aryl)-1H-benzo[d]imidazole 6(a-m)

A mixture of o-phenelenediamine 4 (1 mmol), aryl aldehyde 2 (1 mmol) and citric acid (0.15 mmol) in aq. ethanol (10 mL) was stirred well at 55 °C. Progress of the reaction was monitored by TLC (ethyl acetate:n-hexane, 2:8). After completion of the reaction, reaction mixture was cooled to RT to get mixture of mono- and disubstituted benzimidazoles 5 and 6. This mixture was separated by crystallization using absolute ethanol. During crystallization, crystals of 1,2-disubstituted compound 6 were precipitated at RT and it was collected by simple filtration. Whereas, benzimidazole compound 5 was obtained by concentration in crude form and it was further purified by column chromatography (eluent, EtOAc:n-hexane=1:5).
Spectral Data of Representative Compounds

2-(4-nitrophenyl)benzo[d]thiazole (3a)

<table>
<thead>
<tr>
<th><strong>1H NMR (400 MHz, DMSO-d$_6$)</strong></th>
<th><img src="image" alt="3a" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>δ 7.33-7.37 (t, 1H, J = 8.0 Hz, Ar-H), 7.46-7.48 (d, 1H, J = 7.6 Hz, Ar-H), 7.79-7.83 (m, 2H, Ar-H), 8.23-8.28 (m, 1H, Ar-H), 8.32-8.38 (m, 1H, Ar-H), 8.42-8.44 (d, 1H, J = 6.8 Hz, Ar-H), 8.82-8.84 (d, 1H, J = 6.8 Hz, Ar-H).</td>
<td></td>
</tr>
<tr>
<td><strong>Mass (ES-MS)</strong></td>
<td>m/z 257.2 (M$^+$).</td>
</tr>
</tbody>
</table>

2-(4-methoxyphenyl)-1H-benzo[d]imidazole (5a)

<table>
<thead>
<tr>
<th><strong>1H NMR (400 MHz, DMSO-d$_6$)</strong></th>
<th><img src="image" alt="5a" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>δ 3.81 (s, 3H), 7.08-7.11 (t, 2H, J = 2.4 and 9.2 Hz, Ar-H), 7.16-7.18 (m, 2H, Ar-H), 7.54-7.56 (m, 2H, Ar-H), 8.09-8.11 (d, 2H, J = 8.8 Hz, Ar-H), 12.98 (brs, 1H, -NH).</td>
<td></td>
</tr>
<tr>
<td><strong>Mass (ES-MS)</strong></td>
<td>m/z 225.1 (M$^+$).</td>
</tr>
</tbody>
</table>

1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (6a)

<table>
<thead>
<tr>
<th><strong>1H NMR (400 MHz, DMSO-d$_6$)</strong></th>
<th><img src="image" alt="6a" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>δ 3.68 (s, 3H), 3.82 (s, 3H), 5.49 (s, 2H), 6.83-6.85 (d, 2H, J = 8.8 Hz, Ar-H), 6.93-6.95 (d, 2H, J = 8.8 Hz, Ar-H), 7.07-7.09 (d, 2H, J = 8.8 Hz, Ar-H), 7.19-7.23 (m, 2H, Ar-H), 7.43-7.45 (d, 1H, J = 8.8 Hz, Ar-H), 7.67-7.69 (d, 3H, J = 8.8 Hz, Ar-H).</td>
<td></td>
</tr>
<tr>
<td><strong>13C NMR (100 MHz, DMSO-d$_6$)</strong></td>
<td>δ 46.9, 54.9, 55.3, 110.9, 114.1, 114.2, 118.9, 122.0, 122.3, 122.4, 127.4, 128.8, 130.5, 135.8, 142.7, 153.2, 158.5, 160.4.</td>
</tr>
<tr>
<td><strong>Mass (ES-MS)</strong></td>
<td>m/z 345.3 (M$^+$).</td>
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</tbody>
</table>
Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (C)

\^{1}H\ \text{NMR} \ (400\ \text{MHz}, \text{DMSO-d}_6)

Mass Spectrum

Vilas B. Labade
Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (C)

Vilas B. Labade

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Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (C)

\[ ^1H \text{NMR (400 MHz, DMSO-}d_6) \]

\[ ^13\text{C NMR (100 MHz, DMSO-}d_6) \]
Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (C)

Vilas B. Labade
2.3.8. References


Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (C)


Triethyl Ammonium Sulphate Mediated Synthesis of Benzoxazole Derivatives
2.4.1. Introduction

The small and simple benzoxazole nucleus is present in many compounds involved in research aimed at evaluating new products that possess interesting biological activities. Being a heterocyclic compound, benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Benzoxazoles can be considered as structural isosters of the naturally occurring nucleic bases adenine and guanine, which allow them to interact easily with polymers of living systems.¹

Benzoxazoles are an important class of heterocycles that are encountered in a number of natural products and are used in drug and agrochemical discovery programs, as well as for a variety of other purposes. These compounds are widely found in bioorganic and medicinal chemistry with applications in drug discovery such as antitumour, anticonvulsant, and antiviral applications.²⁻⁴ Moreover, benzoxazole core is a part of numerous molecules that are encountered in a number of natural products and are used in drug and agrochemical discovery programs, as well as for a variety of other purposes. For example, the benzoxazole core structure is found in a variety of cytotoxic natural products, such as the antimycobacterial pseudopteroxazole,⁵ UK-1,⁶ AJI9561,⁷ and salvianen.⁸

Recent medicinal chemistry applications of benzoxazoles include the cathepsin S inhibitor,⁹ 5-HT3 receptor agonist,¹⁰ HIV reverse transcriptase inhibitor L-697,661,¹¹ estrogen receptor- agonist ERB-041,¹² selective peroxisome proliferator-activated receptor γ antagonist JTP-426467,¹³ anticancer agent NSC-693638,¹⁴ and orexin-1 receptor antagonist SB-334867.¹⁵ Benzoxazole derivatives have also been characterized as melatonin receptor agonists,¹⁶ amyloidogenesis inhibitors,¹⁷ Rho kinase inhibitors,¹⁸ and antitumor agents.¹⁹

In addition to their use in medicinal chemistry, benzoxazoles are recognized as an important scaffold in fluorescent probes such as anion and metal cation sensors.²⁰ Other applications of benzoxazoles include their use as herbicides, such as Fenoxaprop, and as fluorescent whitening agent dyes such as bisbenzoxazolyl ethylenes and arenes.²¹ They have also found applications in industry as antioxidants, vulcanization accelerators, and as a dopant in a light-emitting organic electroluminescent device.²²
Aforementioned bioactivities of such a class of oxygenated heterocycles reveal that there is tremendous significance for the development of environmentally benevolent methods for the synthesis of these biodynamic heterocycles.

Currently, Ionic liquids (ILs) are receiving widespread attention as medium for variety of organic reactions. Ionic liquids as new reaction media and catalysts have been experimentally and theoretically recognized and accepted. They are environmentally friendly and “greener” alternatives to organic solvents because they have very low vapor pressure and are non-explosive and thermally stable over a wide temperature range. They can be employed as solvents for a number of chemical processes, such as separation, reactions, two-phase catalysis, extractions and polymerizations. The application of ionic liquids as novel media may provide convenient solutions to both the solvent emission and catalyst reuse problem.

2.4.2. Literature Review

Among the methods for generation of benzoxazole compounds, well established protocols include the cyclo-condensation of 2-amino phenols with carboxylic acids, acid chlorides, aldehydes, etc. (Scheme 2.4.1)

![Scheme 2.4.1. General route for the synthesis of benzoxazoles.](image)

A number of alternative procedures have been developed over the past few years for the synthesis benzoxazole derivatives. Various catalysts, such as SnCl₂, Lawesson's reagent, Propylphosphonic anhydride (T3P), PS-PPh₃ resin have been reported for the synthesis of benzoxazoles from 2-aminophenol and carboxylic acids. Moreover, activated carbon, chromium-manganese complex, glycerol, phenylboronic acid in combination with KCN have also been proved to be efficient for generation of benzoxazole derivatives utilizing 2-amino phenol and aldehydes as starting material.

Additionally, Bonnamour and Bolm reported intramolecular O-arylation reaction and its application in the synthesis of benzoxazole derivatives, starting from the readily available 2-haloanilines in the presence of FeCl₃ and 2,2,6,6-tetramethyl-
3,5-heptanedione (TMHD) as the catalyst system.\textsuperscript{36} Oxidative condensation of primary and secondary amines with 2-aminophenols under hydrogen transfer catalysis is reported by Blacker \textit{et al.}\textsuperscript{37} A facile route to benzoxazoles has been developed by Pottorf \& co-workers which involves condensation of 2-amino phenol and acid chloride using microwave-assisted dielectric heating.\textsuperscript{38} Direct coupling of 1,1-dibromoethenes with 2-aminophenols have been reported by Tao \textit{et al} to form corresponding benzoxazoles under mildly basic reaction conditions.\textsuperscript{39}

However, many of these procedures found to be associated with one or more drawbacks thus leaving room for further upgradation in the synthesis of benzoxazoles following greener synthetic strategies. Most prominent route for the synthesis of benzoxazole derivatives among the current researchers is the simple cyclocondensation of 2-amino phenol and aldehyde (\textbf{Scheme 2.4.2}). Hence, attention was diverted for the development of better synthetic protocol for such molecule of interest by condensation of 2-amino phenol and aromatic aldehydes.

\begin{center}
\textbf{Scheme 2.4.2.} Most prominent route for the synthesis of benzoxazoles.
\end{center}

\subsection{2.4.3. Objectives}

Literature reveals that, evolution of clean and environmentally benign chemical processes using less hazardous catalysts has become a primary goal in synthetic organic chemistry.

Ionic liquids have attracted considerable interest as greener surrogates of conventional molecular organic solvents as well as catalysts and hence now a days ionic liquids have been used as environmentally benign solvents or catalysts for a number of chemical processes. Inspired by such significant applications of ionic liquids in organic synthesis and increasing reports on the application of IL, triethyl ammonium sulphate \([\text{Et}_3\text{NH}]\text{HSO}_4\) for organic transformations, it was decided to focus on utilization of \([\text{Et}_3\text{NH}]\text{HSO}_4\) for our studies towards the synthesis of benzoxazole derivatives.
2.4.4. Present Work

In continuation of our work on the applications of ionic liquids for organic synthesis, we wish to report the triethyl ammonium sulphate catalyzed convenient synthesis of 2,3-dihydro benzoxazole derivatives using 2-amino phenol 1 and various aromatic aldehydes 2. (Scheme 2.4.3)

![Scheme 2.4.3. Synthesis of 2,3-dihydro benzoxazoles.](image)

2.4.5. Results and Discussion

In search for the best experimental reaction conditions, reaction between 2-amino phenol 1 and anisaldehyde 2a in the presence of ionic liquid, i.e. [Et$_3$NH][HSO$_4$] was considered as a model reaction. (Scheme 2.4.4)

![Scheme 2.4.4. Standard model reaction.](image)

In an order to evaluate the effect of solvent on model reaction, some polar protic solvents such as water, MeOH and EtOH were used for the model reaction (Table 2.4.1). Use of almost all solvents afforded the product in moderate yields (51-64%) (Table 2.4.1, entries 2-4). Additionally, even when neat reaction was performed, i.e. in the absence of any solvent, formation of product was observed in 54% yield (Table 2.4.1, entry 1). To further improve the product yield, some experiments in mixed solvent systems like ethanol-water and methanol-water were carried out. As expected, ethanol-water system delivered the product in good 74% yield (Table 2.4.1, entry 6), whereas, methanol-water system failed to afford the product with improved yields (Table 2.4.1, entry 5). Based on this study, ethanol-water solvent system was finalized for our subsequent studies.
Table 2.4.1. Screening of solvents\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>[Et\textsubscript{3}NH][HSO\textsubscript{4}] (mol%)</th>
<th>Yield\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neat</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>15</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>H\textsubscript{2}O</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>MeOH/H\textsubscript{2}O (1:1)</td>
<td>15</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>EtOH/H\textsubscript{2}O (1:1)</td>
<td>15</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>EtOH/H\textsubscript{2}O (1:1)</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>EtOH/H\textsubscript{2}O (1:1)</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>EtOH/H\textsubscript{2}O (1:1)</td>
<td>10</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>EtOH/H\textsubscript{2}O (1:1)</td>
<td>20</td>
<td>74</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 1 (1 mmol) and 2a (1 mmol) in solvent (5 mL) at RT for 45 min.; \textsuperscript{b}Isolated yields.

To determine the appropriate concentration of [Et\textsubscript{3}NH][HSO\textsubscript{4}], model reaction was investigated at different concentrations of [Et\textsubscript{3}NH][HSO\textsubscript{4}] such as 0, 5, 10, 15 and 20 mol %. The product was formed in trace, 48\%, 73\%, 74\%, and 74\% yield, respectively (Table 2.4.1, entries 6-10). This indicates that 10 mol % of [Et\textsubscript{3}NH][HSO\textsubscript{4}] is sufficient to carry out the reaction smoothly.

For evaluation of temperature effect, model reaction using [Et\textsubscript{3}NH][HSO\textsubscript{4}] in ethanol-water solvent system was performed at room temperature, 45 ºC, 60 ºC and 75 ºC (Table 2.4.2, entries 1-4). Reaction at room temperature and 45 ºC afforded product in 73 & 81 % yields (Table 2.4.2, entries 1-2), while at 60 ºC product was obtained in excellent 92 % yield (Table 2.4.2, entry 3). Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 60 ºC did slow down the reaction rate. Hence, temperature of 60 ºC was considered as standard for remaining experimental studies.

The reaction completes within 45 min, at 60 ºC with 10 mol% of [Et\textsubscript{3}NH][HSO\textsubscript{4}]. This fact may be attributed to profound effect of ethanol-water system on the catalytic behavior of triethyl ammonium sulphate based on their highly polar nature and good miscibility of IL as well as substrates with the aqueous ethanol.
Table 2.4.2. Screening of Temperature$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RT</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>87</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1 (1 mmol), 2a (1 mmol) and [Et$_3$NH][HSO$_4$] (10 mol%) in EtOH/H$_2$O (1:1) (5 mL) for 45 min.; $^b$Isolated yields.

Plausible mechanism involved in [Et$_3$NH][HSO$_4$] catalyzed synthesis of 2,3-dihydro benzoxazoles is rationalized with the help of Figure 2.4.1.

![Plausible mechanism](image)

**Figure 2.4.1.** Proposed mechanism for [Et$_3$NH][HSO$_4$] catalyzed synthesis of 2,3-dihydro benzoxazoles.

For assessing the generality of the optimized reaction conditions 2-aminophenol was subjected to various aromatic aldehydes bearing electron donating as well as electron withdrawing substituents. Moreover, some heterocyclic aldehydes were also found to be compatible with optimized reaction conditions (Table 2.4.3). Formation of the product was confirmed by $^1$H NMR, $^{13}$C NMR, and mass spectroscopic data.
Table 2.4.3. Synthesis of 2,3-dihydrobenzoxazoles 3(a-n)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Entry</th>
<th>Aldehyde</th>
<th>Time (min)</th>
<th>Yield\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>4-OMe</td>
<td>45</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>2-NO\textsubscript{2}</td>
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<td>93</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>2-Cl</td>
<td>20</td>
<td>86</td>
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<td>4</td>
<td>3d</td>
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<td>6</td>
<td>3f</td>
<td>4-OH</td>
<td>60</td>
<td>87</td>
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<td>7</td>
<td>3g</td>
<td>2-OH</td>
<td>65</td>
<td>84</td>
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<td>8</td>
<td>3h</td>
<td>2-CF\textsubscript{3}</td>
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<td>90</td>
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<tr>
<td>9</td>
<td>3i</td>
<td>4-Cl</td>
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<td>84</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>4-OH-3-OMe</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>3k</td>
<td>Piperonyl</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>3l</td>
<td>Furfuryl</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>3m</td>
<td>Indol-3-yl</td>
<td>20</td>
<td>88</td>
</tr>
<tr>
<td>14</td>
<td>3n</td>
<td>Thiophen-2-yl</td>
<td>60</td>
<td>88</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 1 (1 mmol), 2 (1 mmol) and [Et\textsubscript{3}NH][HSO\textsubscript{4}] (10 mol\%) in EtOH/H\textsubscript{2}O (1:1) (5 mL) at 60 °C; \textsuperscript{b}Isolated Yields.

2.4.6. Conclusion

In conclusion, triethyl ammonium sulphate has been proved to be an efficient reaction medium for the synthesis of 2,3-dihydrobenzoxazoles at ambient temperature. This method offers remarkable advantages such as simple experimental procedure, mild reaction conditions, lower reaction time, and higher product yields, avoiding hazardous organic solvents.
2.4.7. Experimental

**General experimental procedure for the synthesis of 2-(aryl)-2,3-dihydrobenzo[d]oxazole 3(a-n)**

2-Amino phenol 1 (1 mmol) and aldehyde 2 (1 mmol) were added to a 25 mL RBF containing 5 mL ethanol:water (1:1) and [Et₃NH][HSO₄] (10 mol%). The reaction mixture was stirred at 60 °C for appropriate time. Progress of the reaction was monitored using TLC (methanol:chloroform, 1:9). After time specified in Table 2.4.3, reaction mass was cooled down to RT. Thus obtained solid was filtered, washed with ethanol (10 mL) and recrystallized from ethanol.

**Spectral data for representative compound**

2-(4-methoxyphenyl)-2,3-dihydrobenzo[d]oxazole (3a)

<table>
<thead>
<tr>
<th>¹H NMR (400 MHz, DMSO-d₆)</th>
<th>¹³C NMR (100 MHz, DMSO-d₆)</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ 3.84 (s, 3H, -OCH₃), 6.79-6.84 (dt, 1H, J = 1.2 and 6.8 Hz, Ar-H), 6.86-6.88 (dd, 1H, J = 1.2 and 8.0 Hz, Ar-H), 7.02-7.03 (d, 1H, J = 1.2 Hz, Ar-H), 7.05-7.07 (d, 2H, J = 8.8 Hz, Ar-H), 7.15-7.18 (dd, 1H, J = 1.2 and 8.0 Hz, Ar-H), 7.96-7.98 (d, 2H, J = 8.8 Hz, Ar-H), 8.61 (s, 1H, -CH), 8.85 (s, 1H, -NH).</td>
<td>δ 55.4, 114.1, 115.8, 118.8, 119.4, 126.8, 129.3, 130.6, 138.1, 151.0, 158.5, 161.7.</td>
</tr>
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<td></td>
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</tbody>
</table>
Conventional and Non-conventional Organic Synthesis by Some Novel Methods

Part II (D)

Vilas B. Labade
2.4.8. References


