Chapter- 2
Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans
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2.1 Introduction

Tetrahydrobenzo[b]pyrans have recently attracted attention as an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals. These compounds are widely used as anti-coagulant, diuretic, spasmolytic, anticancer and anti-anaphylactin agents [1-5]. In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative disease, including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS associated dementia and Down’s syndrome as well as for the treatment of schizophrenia and myoclonus [6]. Pyrans and benzocondensed derivatives constitute a structural unit of a series of natural products (Fig 2.1) (a) 2-amino-5-oxo-5H, 10bH-pyran [3,4-c] chromene-1-carbonitrile; (b) 2-amino-4-methyl-1, 4-dihydro phenanthrene-3-carbonitrile; (c) 2-Oxo-2H-chromene-3-carboxylic acid phenylamide; (d) 2-Oxo-2H-chromene-3-carboxylic acid benzylamide) [7, 8]. They are often used in cosmetics, pigments and used as potential biodegradable agrochemicals [9-11]. Some 2-amino-tetrahydrobenzo[b]pyrans can be employed as photoactive materials [12]. Synthesis of tetrahydrobenzo[b]pyrans was traditionally promoted by bases, acids or high temperature in the presence of volatile organic solvents [13-20].

![Fig 2.1: Examples of natural products](image-url)
2.2 Recent reports on synthesis of tetrahydrobenzo[b]pyran derivatives

The dramatic influence of catalyst in multicomponent method over multistep synthesis is to achieve the corresponding adducts with maximum simplicity and in high percentage of yield. Coupling of aldehyde and active methylene compounds like malononitrile, ethylcynoacetate complimented with electron rich compound like phenol, resorcinol and β naphthol justifies the most reliable route for synthesis of tetrahydrobenzo[b]pyrans.

Jiang, et al demonstrates the synthesis of tetrahydrobenzo[b]pyrans via three-component coupling reactions of aldehydes, dimedone and malononitrile at room temperature in ionic liquids (RTILs) without any catalyst. The reuse of ionic liquids and the effect of different ionic liquids as solvent on the reaction have also been investigated. The reactions were completed in 2 - 6 h (Scheme 2.1) [21].

![Scheme 2.1](image)

Chen et al [22] have reported three-component process for the synthesis of tetrahydrobenzo[b]pyran derivatives using ionic liquid N, N-dimethylaminoethyl-benzyldimethyl ammonium chloride ([PhCH₂Me₂N⁺CH₂CH₂NMe₂] Cl⁻) as an efficient catalyst under solvent-free condition. Author has investigated the condensation reaction of aromatic aldehydes with malononitrile and 5, 5-dimethylcyclohexane-1, 3-dione (dimedone) in the presence of N, N-dimethylaminoethylbenzyldimethyl ammonium chloride at 60°C to afford the desired products (Scheme 2.2).
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Scheme 2.2

D. M. Pore et al. [23] presented the efficient, rapid, one-pot synthesis of tetrahydrobenzo[b]pyran via a three-component reaction of aldehydes, 1,3-diketone, malononitrile in 20% ethanol using anhydrous potassium phosphate as a catalyst at room temperature (Scheme 2.3).

Scheme 2.3

Basic nature of oxides of alkaline earth metals eg. MgO promote the synthesis of benzo[b]pyran. Mohammad Sietiof et al. used MgO with high surface area [24] whereas N. Lingaiah et al. employed strong basic Mg/ La mixed oxide [25] catalyst for polyfunctionalized pyrans (Scheme 2.4).

Scheme 2.4

Ahmad shaabani and co-workers [26] performed three component condensation of aldehyde, malononitrile and 4- hydroxyl-coumarine in TMGT as a solvent. An excellent yield of pyran derivatives had been isolated from the reaction (Scheme 2.5).
Scheme 2.5

Diversion to use of chemical base as a catalyst to synthesize tetrahydrobenzo[b]pyran is reported by electrochemical conditions [27] and by grindstone technique in the presence of D, L-Proline and MgO as a catalyst for the synthesis of pyran derivatives [28, 29].

Each method mentioning above has its own merit but it have some limitations like longer reaction times, harsh reaction conditions, tedious work up procedure, commercially unavailable catalysts, lack of reusability of the catalyst, excess use of solvent. Thus there is need to develop a sustainable and greener protocol for the synthesis of tetrahydrobenzo[b]pyran.

Ionic liquids (ILs) offer the potential for ground-breaking changes to synthesis routes and unit operations in the research as well as chemical industry. Although ILs was initially introduced as an alternative green reaction medium, today it has marched far beyond showing its significant role in controlling the reaction as catalyst. The large number of cations and anions allow a wide range of physical and chemical characteristics to be achieved, including volatile and nonvolatile systems, and thus the terms “designer” and “task-specific” ILs have been developed [30-33]. The prospects of ionic liquid uses are very vast. A number of ionic liquids with unique properties have been developed and applied to catalyze many types of reactions. Recently, basic ionic liquids have aroused unprecedented interest because they showed more advantages such as catalytic efficiency and recycling of the ionic liquid than the combination of inorganic base and ionic liquid.
for some base-catalyzed processes. Some of the recent interesting examples carried out in basic ionic liquids are tabulated in Table 1.1.

**Table 1.1** Synthetic transformations carried out using basic ionic liquids

<table>
<thead>
<tr>
<th>Starting Materials</th>
<th>Reagents and conditions</th>
<th>Products</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Ar - CHO} + \text{R}^1\text{CO}_2\text{R}^2$</td>
<td>$[\text{Bmim}]\text{OH, water, 86%-95%}$</td>
<td>$\text{O} \quad \text{R}^1\text{R}^2\text{Ar}$</td>
<td>34</td>
</tr>
<tr>
<td>$\text{R - NH}_2 + \text{CO}_2$</td>
<td>$[\text{Bmim}]\text{OH, 78-85%}$</td>
<td>$\text{O} \quad \text{R} \text{NH}_2 \text{N} \text{R}$</td>
<td>35</td>
</tr>
<tr>
<td>$\text{R}^1\text{Cl} + \text{NH}_2\text{OH}$</td>
<td>$[\text{Bmim}]\text{OH, water, 83-96%}$</td>
<td>$\text{H} \quad \text{H} \quad \text{R}^1 \text{R}^2 \text{CO}_2\text{R}^3 \text{CO}_2\text{R}^3$</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>$[\text{Bmim}]\text{OH, Cul, R. T., 90-95%}$</td>
<td>$\text{R} \quad \text{R}$</td>
<td>37</td>
</tr>
<tr>
<td>$\text{R}^1\text{CHO} + \text{R}^2\text{NO}_2$</td>
<td>$[\text{Bmim}]\text{OH, 85-92%}$</td>
<td>$\text{OH} \quad \text{R}^1 \text{R}^2 \text{NO}_2$</td>
<td>38</td>
</tr>
<tr>
<td>$\text{Ar - CHO} + \text{CN}$</td>
<td>$[\text{Bmim}]\text{OH, ethanol, 93-98%}$</td>
<td>$\text{Ar} \quad \text{CN} \quad \text{NH}_2$</td>
<td>39</td>
</tr>
<tr>
<td>$\text{Ar - CHO} + \text{S}$</td>
<td>$[\text{Bmim}]\text{OH, 60 \degree C, 89% to 96%}$</td>
<td>$\text{Ar} \quad \text{H} \quad \text{S}$</td>
<td>40</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;CHO + [CN]</td>
<td>[Bmim]OH, 85% to 98%</td>
<td>![image]</td>
<td>41</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>-----</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt; + [CN]X</td>
<td>[Bmim]OH, 89% to 96%</td>
<td>![image]</td>
<td>42</td>
</tr>
<tr>
<td>Ar - CHO + RSH</td>
<td>[Bmim]OH, ethanol, 63-98%</td>
<td>![image]</td>
<td>43</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt; + R&lt;sup&gt;3&lt;/sup&gt; - X</td>
<td>[Bmim]OH, 91-98%</td>
<td>![image]</td>
<td>44</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;, R&lt;sup&gt;2&lt;/sup&gt; = CO&lt;sub&gt;2&lt;/sub&gt;Me, CN, NO&lt;sub&gt;2&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt; = alkyl, benzyl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;H + R&lt;sup&gt;3&lt;/sup&gt; - CHO</td>
<td>[Bmim]OH, R. T., 85%-95%</td>
<td>![image]</td>
<td>45</td>
</tr>
<tr>
<td>R - X + Ar</td>
<td>[Bmim]OH, 60 °C, 75-85%</td>
<td>![image]</td>
<td>46</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt; + [CN]</td>
<td>[Bmim]OH, neat, R. T. 10-30 min, 88-93%</td>
<td>![image]</td>
<td>47</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;, R&lt;sup&gt;2&lt;/sup&gt; = CO&lt;sub&gt;2&lt;/sub&gt;Me, CN, NO&lt;sub&gt;2&lt;/sub&gt;, R&lt;sup&gt;3&lt;/sup&gt;, R&lt;sup&gt;4&lt;/sup&gt; = alkyl, benzyl, phenyl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2.3 Present work

Organic reactions in ionic liquids have recently attracted much attention, not only because of the unique reactivity observed but also because an ionic liquid is usually a safe and recyclable substitute for
conventional organic solvents. Thus, development of atom-economical reactions in ionic liquids is a desirable goal in synthetic chemistry.

We have developed 4-amino-1-(2, 3-dihydroxy propyl) pyridinium hydroxide \([\text{ADPPY}[\text{OH}]]\) ionic liquid as novel catalyst for multicomponent synthesis.

2.3.1 Preparation of [ADPPY][OH]

4-amino-1-(2, 3-dihydroxy propyl) pyridinium, hydroxide; [ADPPY][OH] has been prepared by two different routes i.e. (a) by synthetic route and (b) by anion exchange chromatography route.

(a) Synthetic route

The synthetic route have two simple steps.

In the first step, 4-amino-1-(2, 3-dihydroxy propyl) pyridinium, chloride \([\text{ADPPY}[\text{Cl}]]\) salt was prepared by modification of a reported procedure (scheme 2.6) [44]. A mixture of 4-amino pyridine (4.7 g, 50 mmol) and 3-Chloro-1, 2-propanediol (4.15 mL, 50 mmol) was charged into a 150 mL round bottom flask. The mixture was stirred at 65-70°C for 48 h in presence of absolute alcohol to get viscous liquid i.e. [ADPPY][Cl]. The solvent is removed from the resulting viscous product under reduced pressure. The viscous product was washed with diethyl ether (3 x 10 mL). Here, the viscous product get solidify. Finally, the white solid product washed with ethyl acetate (3 x 10 mL) to remove polar impurities and dried in vacuum desiccator at reduced pressure to remove the volatile solvents.

![Scheme 2.6](image)
In the second step, 4-amino-1-(2, 3-dihydroxy propyl) pyridinium, hydroxide ([ADPPY][OH]) salt was prepared by modification of a reported procedure (Scheme 2.7) [47]. The [ADPPY][OH] was prepared by introducing solid potassium hydroxide (1.12 g, 20 mmol) and [ADPPY][Cl] (6.08 g, 20 mmol) in anhydrous methylene chloride (20 mL). Then, the mixture was stirred vigorously at room temperature for 10 h. The precipitated KCl was filtered off, and the filtrate was evaporated to leave the crude [ADPPY][OH] as yellow viscous liquid (Fig 2.2) that was washed with ether (3 x 10 mL) and dried in vacuum desiccator at reduced pressure to remove the volatile solvents.

![Scheme 2.7](image)

**Scheme 2.7**

![Fig 2.2](image)

**Fig 2.2** Images of [ADPPY][Cl] and [ADPPY][OH].
(b) **Anion exchange chromatographic route**

This method was explored in our earlier accepted paper [48]. For this method [ADPPY][Cl] was synthesized by similar method given as above. To synthesize [ADPPY][OH], the Amberlite IRA 400 Cl resin was kept in 0.1 M NaOH for 24 h. The socked resin was loaded on the column and washed it with distilled water till it became free from excess of NaOH (checked by litmus). Then the aqueous solution of [ADPPY][Cl] was slowly passed through the column. The obtained aqueous layer was checked by AgNO$_3$ test. The [ADPPY][OH] was then separated from aqueous layer by using rotary evaporator.

Newly synthesized [ADPPY][OH] was utilized to catalyze multicomponent reaction (MCR) between aldehydes (1), malononitrile (2) and 1, 3-di ketone (3) as an environmentally benign and clean protocol (Scheme 2.8).

\[
\text{Ar-CHO + } \begin{array}{c}
\text{CN} \\
\text{CN} \\
\end{array} + R_1 \xrightarrow{\text{Ionic Liquid}} R_2 \xrightarrow{\text{R.T.}} \begin{array}{c}
\text{CN} \\
\text{NH}_2 \\
\end{array}
\]

**Scheme 2.8**

### 2.4 Results and discussion

#### 2.4.1 Screening of different ILs

We have compared the reaction conditions and yield for synthesis of the tetrahydrobenzo[b]pyrans by the newly synthesized amino functionalized ionic liquid in compare with other ILs (Table 2.2).
Table 2.2 Optimization of reaction conditions for the synthesis of tetrahydrobenzo[b]pyran in presence of different ILs as a catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic Liquids</th>
<th>Solventb</th>
<th>Mol%</th>
<th>Time (min.)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Bmim][BF4]</td>
<td>H2O</td>
<td>40</td>
<td>480</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>[Bmim][OH]</td>
<td>H2O</td>
<td>40</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>[Bmim][PF6]</td>
<td>H2O+C2H5OH(70:30)</td>
<td>40</td>
<td>120</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>[BPyr][BF4]</td>
<td>H2O</td>
<td>40</td>
<td>240</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>[BPyr][PF6]</td>
<td>H2O+C2H5OH(70:30)</td>
<td>40</td>
<td>180</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>[Oimim][BF4]</td>
<td>H2O</td>
<td>40</td>
<td>180</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>[Oimim][PF6]</td>
<td>H2O+C2H5OH(70:30)</td>
<td>40</td>
<td>180</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>[ADPPY][OH]</td>
<td>H2O+C2H5OH(90:10)</td>
<td>10</td>
<td>15</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>[ADPPY][OH]</td>
<td>H2O</td>
<td>05</td>
<td>25</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>[ADPPY][OH]</td>
<td>H2O</td>
<td>10</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>[ADPPY][OH]</td>
<td>H2O</td>
<td>15</td>
<td>15</td>
<td>92</td>
</tr>
<tr>
<td>12</td>
<td>[ADPPY][OH]</td>
<td>H2O</td>
<td>30</td>
<td>15</td>
<td>91</td>
</tr>
<tr>
<td>13</td>
<td>[ADPPY][OH]</td>
<td>H2O</td>
<td>45</td>
<td>15</td>
<td>91</td>
</tr>
</tbody>
</table>

aAll reactions were carried out of benzaldehyde : malononitrile : dimedone 1:1:1 (molar ratio) at room temperature in ionic liquids; yield refer to pure isolated products.
bEntries in bracket indicate the ratio of H2O to C2H5OH on volume basis.

As shown in Table 2.1, molar ratio of ILs and reaction time all have significant effects on the reaction. It could be seen that with the increase in the molar ratio of IL/substrate from 5 mol% to 10 mol%, reaction yield was significantly improved. Upon examining it was found that 10 mol% of IL was sufficient to promote the reaction. However, in the presence of lower amounts, the yield dropped dramatically, even if longer reaction times were used (Entry 9). When the amount of IL was increased over 10 mol% equivalent, neither the yield nor the reaction time was improved (Entry 11-13). Experiments have shown that the catalytic performance of [ADPPY][OH], [Bmim][OH] could be much
better than other ILs under the same reaction conditions. It is evident that the yields of the desired product in the ionic liquids containing hydroxyl anion are higher than those in the ionic liquids containing tetrafluoroborate as well as hexafluorophosphate. Among the solvent system screened H₂O + C₂H₅OH (70:30, 90:10) lack in effectiveness as compared to aqueous solvent system. The best reaction profile was observed for H₂O only.

Furthermore, it has been observed that the conversion for reaction with [ADPPY][OH] as catalysts was better than [Bmim][OH]. These results suggest that the performance of the IL is dependent upon the character of the side chain of the cation and the N-heterocyclic ring. [ADPPY][OH] exhibited the most excellent catalytic performance with high conversion under the same reaction conditions (Entry 10).

Encouraged by this result, we planned to diversify the methodology by using various aromatic aldehydes carrying either electron donating or withdrawing substituents gives high yield of the product with good purity. The reaction was then extended towards heterocyclic aldehydes viz. Pyridine-3-carboxaldehyde and thiophene-2-carboxaldehyde to get expected product. All the products have characterized by spectroscopic methods. The physical data of the result is shown in Table 2.3.
Table 2.3 [ADPPY][OH] catalyzed synthesis of tetrahydrobenzo[b]pyran derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (min.)</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>m. p., °C</th>
<th>Obtained</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>15</td>
<td>94</td>
<td>209-211</td>
<td>209-211</td>
<td>[8]</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>20</td>
<td>90</td>
<td>199-201</td>
<td>199-201</td>
<td>[14]</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>15</td>
<td>95</td>
<td>228-230</td>
<td>228-230</td>
<td>[8]</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>25</td>
<td>89</td>
<td>238-240</td>
<td>240-242</td>
<td>[36]</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>15</td>
<td>84</td>
<td>184-186</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>20</td>
<td>92</td>
<td>204-205</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>
G

H

I

J

K

L

\[ \text{a All products showed satisfactory spectroscopic data (IR, } ^1\text{H and } ^{13}\text{C NMR)} \]

\[ \text{b Yields refer to pure, isolated products.} \]
2.4.2 Probable mechanism for the formation of tetrahydrobenzo[b]pyran

The probable mechanism for the present transformation is described in 

\textbf{Scheme 2.9.} Hydroxyl ion from ionic liquid abstracts the active methylinic proton of malononitrile generating carbanion (1). This carbanion attacks on carbonyl carbon (2) to give Knoevenagel product (3). In second step Michael attack of stable enol form of 1, 3-diketone takes place on Knoevenagel product. Finally subsequent cyclization and stabilization achieved via generation of six membered pyran ring.

\begin{center}
\includegraphics[width=\textwidth]{scheme29.png}
\end{center}

\textbf{Scheme 2.9}

2.4.3 Reusability of [ADPPY][OH]

One of the main aims of our study was to investigate the reuse and recycling of the catalyst. The reusability investigation of [ADPPY] [OH] has been demonstrated (Fig 2.3). As the product is insoluble in water it was collected by simple filtration, while the ionic liquid is completely soluble in water. The IL could be recovered easily by using
rotary evaporator and further employed for subsequent runs. As shown in Fig 2.3, no noticeable changes were observed on the recovered catalyst and yield of the product. After five runs IL is still stable enough to act as effective catalyst for the present transformation.

![Figure 2.3 Reusability of [ADPPY] [OH]](image)

**2.5 Experimental**

**2.5.1 Materials and methods**

The chemicals, 4-amino pyridine, 3-chloro-1, 2-propanediol, potassium hydroxide, malononitrile, 1, 3-di ketone and all aldehydes were purchased from Sigma Aldrich. While, dichloromethane, absolute ethanol were purchased from Runa, India and used without further purification.

**2.5.2 Instrumental details and their operational conditions**

**NMR analysis**

NMR analysis was performed using Brucker 300 MHz, NMR spectrophotometer. For $^1$H NMR and $^{13}$C NMR, CDCl$_3$ and DMSO were used as the solvent; the chemical shifts are reported in ppm using TMS as an internal standard.
IR analysis

IR analysis was done on Perkin–Elmer, FTIR-1600 spectrophotometer. KBr was used for the preparation of pellets for spectral recordings.

LC-MS analysis

LC-MS analysis was performed using LC-MS – 2010 equipped with electro spray ionization interface (Shimadzu Corporation, Kyoto, Japan).

2.5.3 General procedure for the preparation of tetrahydrobenzo[b]pyran

To demonstrate the utility of [ADPPY][OH] in multicomponent reaction, we began with a mixture of aldehyde (1 mmol), malononitrile (1mmol) and 1, 3-di ketone (1 mmol) as a model. Unfortunately, as the ionic liquid is very viscous, water (3 ml) was used as sequester. The reaction was carried out at room temperature with constant stirring for just 10 min. to get a single product in excellent yield (95%). The formation of the product was further confirmed by IR, $^1$H NMR and $^{13}$C NMR spectroscopy. It is worthy to mention that no by-product was detected. A variety of aldehydes and 1, 3-diketone also underwent to afford the corresponding tetrahydrobenzo[b]pyrans in moderate to high yields. Aromatic aldehydes with either electron donating or electron withdrawing groups underwent the reaction smoothly. Having obtained favorable results with aromatic aldehydes we, then examined heterocyclic aldehydes such as pyridine-3-carboxylaldehyde and thiophene-2-carboxyldehyde. The results are summarized in Table 2.2.
2.6 Spectroscopic data

2.6.1 Spectroscopic data of TSILs

2.6.1.1 4-amino-1-(2, 3-dihydroxy propyl) pyridinium chloride, [ADPPY] [Cl]. (White color powder)

![Chemical structure of 4-amino-1-(2, 3-dihydroxy propyl) pyridinium chloride](attachment:structure.png)

$^1$H NMR of 4-amino-1-(2, 3-dihydroxy propyl) pyridinium chloride shows (Fig 2.03) a pair of multiplets at δ 3.17 – 3.64 for two distereotopic methylene protons attached to –OH group. A multiplet exhibited at δ 3.72 – 4.02 for two distereotopic methylene protons attached to –N. Doublet of doublet observed at δ 4.23 for one methine proton attached to –OH group. Triplet at δ 5.06 exhibited a primary hydroxyl proton. A doublet observed at δ 5.42 for hydroxyl proton attached to secondary carbon atom. A doublet at δ 6.85 exhibited two aromatic protons, which is ortho to amino group with coupling constant of 7.2 Hz. A doublet at δ 8.09 exhibited two protons which is meta to amino group with coupling constant of 7.2 Hz. A broad singlet exhibited at δ 8.31 for aromatic amino group.

$^{13}$C spectrum of same compound exhibited (Fig 2.04) peak at δ 60.24 for methylene carbon attached to terminal –OH group. Another methylene carbon attached to –N of pyridine ring observed at δ 63.07. The methine carbon attached to –OH group observed at δ 70.78. The aromatic carbons observed at δ 109.24 and 144.03, while the methine carbon of aromatic ring observed at δ 159.15.
2.6.1.2 4-amino-1-(2, 3-dihydroxy propyl) pyridinium hydroxide, [ADPPY][OH]. (Brown color viscous liquid)

\[
\text{H}_2\text{N}-\text{N}^+\text{OH} \quad \text{OH} \quad \text{OH}
\]

\(^1\text{H}\) NMR of 4-amino-1-(2, 3-dihydroxy propyl) pyridinium hydroxide, [ADPPY][OH] exhibited (Fig 2.05) a multiplet at \(\delta 3.20 - 3.64\) for two distereotopic methylene protons attached to –OH group. Multiplets exhibited at \(\delta 3.72 - 4.02\) for two distereotopic methylene protons attached to –N group. Doublet of doublet observed at \(\delta 4.23\) for one methine proton attached –OH group. A sharp singlet appeared at \(\delta 4.81\) indicated the presence of –OH group. Triplet at \(\delta 5.06\) exhibited a primary hydroxyl proton. A doublet observed at \(\delta 5.42\) for hydroxyl proton attached to secondary carbon atom. Aromatic region: Doublet exhibited at \(\delta 6.85\) indicated two aromatic protons, which is ortho to amino group with coupling constant of 7.2 Hz. A doublet at \(\delta 8.09\) exhibited two protons which are meta to amino group with coupling constant of 7.2 Hz. A broad singlet exhibited at \(\delta 8.31\) for aromatic amino group.

\(^{13}\text{C}\) spectrum of same compound exhibited (Fig 2.06); peak at \(\delta 60.24\) is of methylene carbon attached to terminal –OH group. Another methylene carbon attached to –N of pyridine ring observed at \(\delta 63.14\). The methine carbon attached to –OH group observed at \(\delta 70.86\). The aromatic carbons observed at \(\delta 109.49\) and 143.56, while the methine carbon of aromatic ring observed at \(\delta 159.54\).
2.6.2 Spectroscopic data of unknown compounds

The purified products obtained by silica gel column chromatography were characterized by IR, NMR and Mass spectroscopy. The characterization data was found to be consistent with the earlier reports and proposed structure. For the selected compounds the characterization data is presented below:

2.6.2.1 Table 2.3; entry E: 2-amino-7, 7-dimethyl-5-oxo-4-(pyridin-3-yl)-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile. (White colored solid compound. mp 184 – 186°C)

IR spectrum of 2-amino-7, 7-dimethyl-5-oxo-4-(pyridin-3-yl)-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile exhibited (Fig 2.07) primary amino group stretching frequencies at 3377 and 3315 cm\(^{-1}\). A strong band at 2184 cm\(^{-1}\) confirms the presence of cyano group in the compound.

\(^1\)H NMR of same compound exhibited (Fig 2.08) two singlets for methyl groups of dimedone moiety at δ 1.01 and 1.10. The two methylene protons of dimedone ring appear as two separate singlets at δ 2.20 and 2.46. The presence of benzylic methine proton exhibited singlet at δ 4.43. The exchangeable proton of amino group appears as broad singlet at δ 4.99. The four protons of pyridine ring occupied the region from δ 7.24 – 8.50 in the form of multiplet, doublet and multiplet. More specifically, the multiplet from δ 7.24 – 7.28 contribute for meta
proton to –N atom. The doublet at δ 7.64 with coupling constant 7.8 Hz indicated the para proton to –N came as multiplet at δ 8.44 – 8.50.

The $^{13}$C spectrum of same compound exhibited (Fig 2.09) peaks at δ 27.71 and 28.74 for –CH$_3$ group of dimerdone ring and methylene group at δ 32.21 and 33.65. The benzylic methane group i.e. –CH peak observed at 50.54, 61.57, 113.08, 118.38, 123.61, 136.06, 139.12, 147.75, 148.71, 158.08, 162.17 while carbonyl carbon at 195.79.

Mass spectrum of the same compound (Fig 2.10) has also supports the expected structure by showing m/z 296 (M$^+$).

2.6.2.2 Table 2.3; entry F: 2-amino-5-oxo-4-(pyridin-3-yl)-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile. (Pale yellow colored solid compound. mp 204 – 205°C)

IR spectrum of the 2-amino-5-oxo-4-(pyridin-3-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile exhibited (Fig 2.11) the peaks at 3360 and 3330 cm$^{-1}$ confirm the presence of –NH$_2$ group. The –CN group is confirmed by the presence of 2192 cm$^{-1}$. The peak at 1665 cm$^{-1}$ is for α, β – unsaturated carbonyl group. The aromatic C = C bond is confirmed by the presence of peak at 1612 cm$^{-1}$.

$^1$H NMR of the same compound exhibited (Fig 2.12) the three methylene protons of cyclohexanone ring appears separately as multiplet at δ 1.96, 2.25, 2.52. The benzylic methine proton exhibited a sharp singlet at δ 4.30. The amine protons appear as a singlet at δ 6.29
ppm. The aromatic protons of the pyridine ring appeared in the range of δ 7.21 – 8.41. The multiplet proton of the ring corresponding to the –N of the pyridine appears at δ 7.21 – 7.24 ppm. The doublet at δ 7.57 ppm with coupling constant 7.8 Hz indicates the para proton of the pyridine ring showing a multiplet at δ 8.34 – 8.41 ppm.

The $^{13}$C NMR spectrum of the same compound exhibited (Fig 2.13) peaks at δ 20.06, 27.05, 33.74, 36.64 for methylene carbons. The peak at δ 58.49 exhibited for methine carbon. The remaining carbon atom shows the peaks at δ 113.81, 119.38, 123.85, 136.30, 140.23, 147.03, 148.25, 158.91, 164.48. The peak at δ 195.92 confirmed the presence of carbonyl carbon.

Mass spectrum of the same compound (Fig 2.14) also supports the expected structure by showing m/z 268 ($M^+$).

**2.6.2.3 Table 2.3; entry H:** 2-amino-4-(3, 4-dimethylphenyl)-7, 7-dimethyl-5-oxo-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile. (White colored solid compound. *mp 201 – 202°C*)

![Chemical Structure](image)

IR spectrum of the 2-amino-4-(3, 4-dimethylphenyl)-7, 7-dimethyl-5-oxo-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile exhibited (Fig 2.15) the presence of weak stretching frequencies at 3451 and 3329 cm$^{-1}$ indicates the primary amino group. The stretching frequencies of aliphatic group and cyano group are observed at 2964 and 2193 cm$^{-1}$ respectively. A decrease in frequency at 1670 cm$^{-1}$ rather
than normal ketonic group indicates that the compound contains α, β – unsaturated carbonyl group. A sharp band at 1600 cm\(^{-1}\) exhibited C = C stretching.

\(^1\)H NMR spectrum of same compound exhibited (Fig 2.16) peaks at δ 1.06 and 1.11 as singlet which confirms the presence of protons of two different methyl groups of dimedone ring. The methylene protons of dimedone ring appeared at δ 2.22 and 2.45, while the two aromatic methyl groups exhibited singlet at δ 2.22. The benzylic methine proton and amine protons exhibited singlet and broad singlet at δ 4.32 and 4.57. Three aromatic protons exhibited as multiplet from δ 6.92 – 7.05.

The \(^13\)C NMR spectrum of same compound exhibited (Fig 2.17) four separate peaks at δ 19.41, 19.91, 27.72 and 28.89 for two methyl carbons of dimedone ring and aromatic ring. The methylene carbons of dimedone ring exhibited at δ 32.21 and 33.09. The benzylic methine carbon exhibited at δ 40.68 while, the remaining carbon exhibited peaks at δ 50.69, 63.76, 114.10, 118.83, 124.76, 128.77, 129.87, 135.35, 136.61, 140.71, 157.35 and 161.46. The carbonyl carbon appeared at δ 196.00.

Mass spectrum of the same compound (Fig 2.18) also supports the expected structure by showing m/z 323 (M\(^+\)).

2.6.2.4 Table 2.3; entry I: 2-amino-4-(3, 4-dimethylphenyl)-5-oxo-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile. (White colored solid compound. mp 198 – 200°C)
IR spectrum of the 2-amino-4-(3, 4-dimethylphenyl)-5-oxo-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile exhibited (Fig 2.19) stretching frequencies at 3396 cm\(^{-1}\) indicated the presence of –\(\text{NH}_2\) group. The presence of –CN group is confirmed by the presence of peak at 2892 cm\(^{-1}\). The decrease in the stretching carbonyl frequencies at 1690 cm\(^{-1}\) indicated the presence of \(\alpha, \beta\) – unsaturated carbonyl group. The stretching frequencies at 1606 cm\(^{-1}\) indicated the presence of aromatic C = C bonds.

\(^1\)H NMR of same compound exhibited (Fig 2.20) the methylene protons of the cyclohexanone ring appeared separately as a multiplet at \(\delta\) 1.90, 2.26 and 2.56. The two methyl groups from aromatic ring exhibited as a singlet at \(\delta\) 2.15 and 2.12. The benzylic methine proton appeared as a singlet at \(\delta\) 4.11. The exchangeable protons of amine group appeared as a broad peak at \(\delta\) 6.57. A multiplet at \(\delta\) 6.81 – 6.96 exhibited the three aromatic protons.

\(^{13}\)C spectrum of same compound exhibited (Fig 2.21) peaks for methylene carbons of the cyclohexanone ring at \(\delta\) 19.39, 19.16, 20.23, 27.05, 35.37 and 36.84. The methine carbon atom exhibited peak at \(\delta\) 58.49. The remaining carbon atoms exhibited peaks at \(\delta\) 114.81, 120.11, 124.94, 128.70, 129.65, 134.66, 136.12, 142.31, 158.72 and 163.98. The peak at \(\delta\) 195.90 exhibited carbonyl carbon.
Mass spectrum of the same compound (Fig. 2.22) also supports the expected structure by showing m/z 317 (M⁺ + Na).

2.7 Conclusion

In conclusion, we have developed a new amino-functionalized ionic liquid, [ADPPY] [OH] and demonstrated it as a mild and highly efficient catalyst for three component synthesis of tetrahydrobenzo[b]pyrans. The heterocycles synthesized in this study were obtained in high regioselectivity, good yields, shorter reaction times and simple work-up procedure with greener touch. The study of this TSIL is going on for further applications.
2.8 References


Chapter- 2: Synthesis of Novel Amino Functionalized Ionic Liquid - \([\text{ADPPY}]\text{[OH]}\) and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Fig 2.03

Fig 2.04
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

![IR Spectrum Image]

Fig 2.07

Wave number (cm$^{-1}$)

T%
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Fig 2.08

Fig 2.09
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Method: LCMS_METHOD (5 min)
Column: YMC, C18, 50 X 4.6 mm, 3 µ,
Column ID: E-AC-3/08/COL/006
Mobile Phase: A. 10mM Ammonium Formate in water + 0.1% Formic Acid
   B. Acetonitrile + 5% Solvent A + 0.1% Formic Acid
Inj Volume: 5.0µL, Flow Rate: 1.20 mL/minute
Gradient program:
5% B to 100% B in 3.5 minute, Hold till 0.50 min, At 4.010 min B conc is 5 % up to 5.0min

Chromatogram

Fig 2.10

MS Chromatogram

MS Spectrum Graph

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PDA Ch1 210nm - 400nm 4nm

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Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Fig 2.11
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Fig 2.12

Fig 2.13
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Method: LCMS_METHOD (5 min)
Column: YMC, C18, 50 X 4.6 mm, 3 μ,
Column ID: E-AC-3/08/COL/006
Mobile Phase: A. 10mM Ammonium Formate in water + 0.1% Formic Acid
B. Acetonitrile + 5% Solvent A + 0.1% Formic Acid
Inj Volume: 5.0μL, Flow Rate: 1.20 mL/minute
Gradient program:
5% B to 100% B in 3.5 minute, Hold till 0.500 min, At 4.010 min B conc is 5% up to 5.0min

Chromatogram
E:\AC-3\LCMS-2\Data\2011\Jan\19\Sample\073.lcd

MS Chromatogram
E:\AC-3\LCMS-2\Data\2011\Jan\19\Sample\073.lcd
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0.00
Min

MS Spectrum Graph
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BG Mode: Averaged 1.633-1.641 (99.99)
Mass Peaks: 388 Base Peak: 423.30 (317714) Polarity: Pos Segment1 - Event1

PeakTable
PDA Ch1 210nm - 400nm 4nm

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Fig 2.14
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid \([\text{ADPPY}][\text{OH}]\) and its Application in the Synthesis of Tetrahydrobenzo[\text{b}]pyrans

![Figure 2.15](image-url)

**Fig 2.15**
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Fig 2.16

Fig 2.17
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Method: LCMS_METHOD (5 min)
Column: YMC, C18, 50 x 4.6 mm, 3 μ
Column ID: E-AC-3/08/COL/006
Mobile Phase: A. 10mM Ammonium Formate in water + 0.1% Formic Acid
B. Acetonitrile + 5% Solvent A + 0.1% Formic Acid
Inj Volume: 5.0μL, Flow Rate: 1.20 mL/minute
Gradient program:
5% B to 100% B in 3.5 minute, Hold till 0.50 min, At 4.010 min B conc is 5 % up to 5.0min

Chromatogram
E: \AC-3\LCMS-2\Data\2011\Jan\19\Sample\074.lcd

**Fig 2.18**
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Fig 2.19
Chapter 2: Synthesis of Novel Amino Functionalized Ionic Liquid - [ADPPY][OH] and its Application in the Synthesis of Tetrahydrobenzo[b]pyrans

Fig 2.20

Fig 2.21
Method: LCMS_METHOD (5 min)
Column: YMC, C18, 50 X 4.6 mm, 3 μ,
Column ID: E-AC-3/08/COL/006
Mobile Phase: A, 10mM Ammonium Formate in water + 0.1% Formic Acid
B, Acetonitrile + 5% Solvent A + 0.1% Formic Acid
Inj Volume: 5.0μL, Flow Rate: 1.20. mL/minute
Gradient program:
5% B to 100% B in 3.5 minute, Hold till 5.00 min, At 4.010 min B conc is 5 % up to 5.0min

Chromatogram

E:\AC-3\LCMS-2\Data\2011\Jan\19\Sample\075.lcd

**Fig 2.22**

**MS Chromatogram**

E:\AC-3\LCMS-2\Data\2011\Jan\19\Sample\075.lcd

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MS Spectrum Graph

Ret. Time : 3.067 min
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PeakTable
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