SYNTHESIS OF 1-ALKYL TRIAZOLIUM TRIFLATE AND PHENYLSULFONATE IONIC LIQUIDS AND THEIR CATALYTIC STUDIES IN MULTICOMPONENT BIGINELLI REACTION

Abstract

In this chapter, six Brønsted acidic ionic liquids 1-ethyl-1,2,4-triazolium triflate, 1-propyl-1,2,4-triazolium triflate, 1-butyl-1,2,4-triazolium triflate, 1-ethyl-1,2,4-triazolium phenylsulfonate, 1-propyl-1,2,4-triazolium phenylsulfonate, 1-butyl-1,2,4-triazolium phenylsulfonate have been synthesized and characterized. A comparative study done between room temperature ionic liquids like 1-alkyl-1,2,4-triazolium triflate and ionic liquids like 1-alkyl-1,2,4-triazolium phenylsulfonate as a catalyst for one pot synthesis of derivatives of 3,4-dihydropyrimidin-2(1H)-ones/thiones have been employed and the results were discussed in detail.

3.1: Introduction

Multicomponent reactions (MCRs) are one-pot synthesis methodology has given new pathway to form three or more carbon-carbon bond formation (Cioc C R et al., 2014). The biginelli reaction is one of the examples of multicomponent reactions (MCRs) (Puripat M et al., 2015). The synthesis of dihydropyrimidinones was
reported by Biginelli in 1893 using hydrochloric acid as catalyst (Biginelli P, 1893). Mainly, the DHPMs have employed as calcium channel blockers, antiviral, antimitotic, anticarcinogenic and antihypertensive agents (Kappe O. C, 2000). The derivatives of dihydropyrimidinones/thiones (DHPMs) are essential substructure in many biologically active natural products (Fig 3.11) (Murata H et al., 2010). Many marine alkaloids with dihydropyrimidinones/thiones skeleton have significance in biological properties (Patil et al., 1995). These important derivatives of DHPMs can be synthesized by three component condensation of an aldehyde, urea and β-keto ester under acidic condition in ethanol as solvent (scheme 3.11) (Panda S. S et al., 2012).

\[
\begin{align*}
\text{Scheme 3.11: Biginelli reaction for the synthesis of DHPMs}
\end{align*}
\]

Numerous examples of catalysts were used to improve the quality and quantity of DHPMs in the past one century. The DHPMs synthesis in environmental benign route is an outstanding research (Suresh J. S, 2012). The green chemistry is suitable for the above mentioned route and many green catalysts were used to synthesis DHPMs and the Ionic liquids (ILs) is one of them (Ramos L. M et al., 2013).
In Biginelli reaction, chemists used number of catalyst like metal salts such as LiBr (Rudrawa S, 2005), FeCl₃/Si (OEt)₄ (Cepanec I et al., 2005), Cu(OTf)₂ (Paraskar A, S., 2003), CeCl₃ (Bose D, S et al., 2003), ZrCl₄ (Reddy C, V, 2002), InCl₃ (Ranu B. C et al., 2000), Bi(OTf)₃ (Antoniotti S, 2003), YbCl₃ (Zhang et al., 2009), LaCl₃ (Lannou M et al., 2008), Alum-SiO₂ (Azizian J et al., 2006), SnCl₂ (Singh M. O and Devi N. S, 2009), Mn(OAc)₃ (Kumar A K et al., 2001), TiO₂ (Safari J and Gandomi-Ravandi S, 2014), nanomaterials of Fe₃O₄ (Zamani F and Izadi E, 2013). Several zeolite catalyzed (Mistry S. R et al., 2011; Rani R. V et al., 2001) and non-metal acid catalyzed (Narahari S. R et al., 2012; Rajack A et al., 2013; Kolvari E et al., 2014) have been reported for the syntheses of dihydropyrimidinones/thiones. However, the above catalyst used in Biginelli reaction protocols are associated with certain limitations such as less biodegradability of the catalyst, expensive reagents for the synthesis of catalyst, drastic reaction conditions and generation of chemical wastages. On the other hand, employing metal catalysts also resulted with over oxidized product and substantial amount of metal-waste to the environment, which is a major problem towards a sustainable process. Therefore, the development of a new protocol toward this direction is an active area of research (Hallett J. P and Welton T, 2011). The synthesis of organic, inorganic and any materials employed by green technology is a leading and challenging task in any field of research. Therefore, the
development of a new protocol toward this direction is an active area of research. In this context, several new reagents have been developed employing various ionic liquids as catalyst to carry out Biginelli reaction (Yuan C et al., 2012; Safari J and Zarnegar Z, 2014; Alvim H G O et al, 2013).

Particularly, ionic liquids such as cmmim \([\text{BF}_4]\) (Dadhania A N et al., 2012), TMGT (Shaabani A and Rahmati A, 2005), tri-(2-hydroxyethylammoniumacetate) (Chavan S S et al., 2009), [Gly]NO\(_3\) (Sharma N et al., 2012), Hmim[HSO\(_4\)] (Hajipour A R et al., 2011), bmim[MeSO\(_4\)] (Siddiqui I R et al., 2014) and BMIM[OH] (Roy S R et al., 2011) have been known to achieve this one-pot transformation. The interest to synthesis a new class of ionic liquids and development of eco-friendly and reusable catalytic transformations. (Elango K, et al., 2007).

In this chapter six Brønsted acidic ionic liquids, 1-ethyl-1,2,4-triazolium triflate (3a), 1-propyl-1,2,4-triazolium triflate (3b), 1-butyl-1,2,4-triazolium triflate (3c), 1-ethyl-1,2,4-triazolium phenylsulfonate (3d), 1-propyl-1,2,4-triazolium phenylsulfonate (3e), 1-butyl-1,2,4-triazolium phenylsulfonate (3f) have been used as a catalyst for one pot synthesis of dihydropyrimidinones/thiones by biginelli reaction.

3.2. Experimental

3.2.1. Materials and methods

\(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on a Brucker Avance 400 and 300 MHz. Elemental analyses of the compounds were obtained from thermoquest CE instruments CHNS-O, EA/110 model. Electrospray ionization mass spectrometry (ESI-MS) spectra were recorded on a Waters Q-TOF Premier mass spectrometer. LC-MS analyses were done on an Agilent MSD mass spectrometer. Method info
A: HCOOH in H_2O, B: 0.04% HCOOH in CH_3CN; flow rate: 2.0mL/min; Column: Chromolith RP-18e, 100-3mm, +ve mode. Melting Points were measured in DALAL melting point apparatus, India and corrected.

Solvents were freshly distilled prior to use and glassware was dried in oven at 120 °C overnight. Chemical such as trifluromethanesulfonic and phenyl sulfonic acid were purchased from sigma aldrich and 1,2,4-triazole, ethyl bromide, and n-butyl bromide were purchased from SD fine chemicals, India. starting materials such as urea, thiourea, ethylacetoacetate, methylacetoacetate, benzaldehyde, 4-isopropylbenzaldehyde, 4-methoxybenzaldehyde, 4-bromobenzaldehyde, 4-flurobenzaldehyde, 4-chloro benzaldehyde,3-hydroxybenzaldehyde and 4-methyl benzaldehyde, were purchased from SRL, India. All chemicals were used without further purification.

3.3. Synthesis

Common procedure for the synthesis of ionic liquids (3a-f):

To a solution of 1-alkyl-1, 2, 4-triazoles (10 mmole) (alkyl = Et, Pr and Bu) in toluene (10 ml) trifluromethanesulfonic acid or phenyl sulfonic acid (10 mmole) was added drop wise. This reaction mixture was then heated to 80 °C for 12 h (Scheme 3.12). After completion of the reaction, flask was cooled to room temperature and excess of toluene was removed under reduced pressure. The resulting residue was thoroughly washed with hexane (20 mL x 2) and further dried over vacuum to afford pure catalyst (3a-f) (Figure 3.12).
Scheme 3.12: Synthesis of 1-alkyl-1,2,4-triazolium based Brønsted acidic ionic liquids

\[
\begin{align*}
\text{N} & \text{N} \\
\text{R} & \xrightarrow{\text{XH}} \\
\text{N} & \text{N} \\
\text{H} & \xrightarrow{\text{toluene, 80 °C}} \\
\text{R} & \text{N} \\
\text{N} & \text{H} \\
\text{X} & \end{align*}
\]

Where, \( X = \text{CF}_3\text{SO}_3, \text{C}_6\text{H}_5\text{SO}_3 \)

Figure 3.12: 1-alkyl-1,2,4-triazolium based Brønsted acidic ionic liquids

General Procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-ones/thiones:

Scheme 3.13: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones in 3a-c

Catalyst 3a-f (10 mol %) was added to a solution of aldehyde (1.0 mmole), \( \beta \)-ketoester (1.5 mmole) and urea or thiourea (2.0 mmole) in ethanol (0.5 mL). The
reaction mixture was heated at 80 °C using oil bath for the specified time (0-5 h) (Scheme 3.13). The progress of the reaction was monitored by TLC. After completion of the reaction checked by TLC (Ethyl acetate: Hexane- 4:1), the reaction mixture was cooled to room temperature. Subsequently, quenched with mixture of water:ethanol (5:0.5 mL). The corresponding solid product was filtered, and washed with n-hexane (5 mL x 2), which afforded pure 3,4-dihydropyrimidin-2(1H)-Ones or 3,4-dihydropyrimidin-2(1H)-thiones in the pure form.

**Spectral data for Brønsted acidic room temperature ionic liquids (3a-f)**

1-ethyl-1,2,4-triazolium triflate (3a)

Colorless Liquid, (2.1g, 85 %), Anal. Calcd. For C₅H₈F₃N₃O₃S (247.02): C, 24.29; H, 3.26; N, 17.00; Found: C, 24.15; H, 3.12; N, 16.95. ¹H NMR (CDCl₃, 400 MHz): δ 11.9 (s, 1H, 4-NH ), 9.6 (s, 1H, 5-CH), 8.6 (s, 1H, 3-CH ) 4.5 (q, 2H ), 1.5 (t, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 143.3 (C-5), 140.5 (C-3), 124.8,121.6, 118.4,115.3 (CF₃-SO₃ ) 47.4, 13.7; ES-MS m/z: 98.0711 [M- CF₃-SO₃]⁺.

1-Propyl 1,2,4-triazolium triflate (3b)

Colorless Liquid, ( 2.46g, 94%), Anal. Calcd. for C₆H₁₀F₃N₃O₃S (261.04): C, 27.59; H, 3.86; N, 16.09; Found: C, 27.49; H, 3.79; N, 15.99 ¹H NMR (CDCl₃, 300 MHz): δ 11.9 (s, 1H, NH), 9.6 (s, 1H, 5-CH), 8.5 (s, 1H, 3-CH), 4.3 (t, 2H), 1.9 (m, 2H), 0.9 (t, 3H), ¹³C NMR (CDCl₃, 75 MHz): δ 143.6 (C-5), 141.1 (C-3), 122.3, 118.0 (CF₃-SO₃ ) 53.6, 22.3, 10.4; ES-MS m/z: 112.0869. [M- CF₃-SO₃]⁺.

1-butyl-1,2,4-triazolium triflate (3c)

Colorless liquid, (2.6g, 95 %), Anal. Calcd. For C₇H₁₂N₃F₃O₃S (275.06): C, 30.55; H, 4.39; N15.27 Found: 30.45; H, 4.36; N, 15.09. ¹H NMR (CDCl₃ ,400 MHz): δ 11.7 (s, 1H, 4-NH ), 9.5 (s, 1H, 5-CH ), 8.6 (s, 1H, 3-CH ) 4.4 (t ,2H ) 1.9 (m, 2H)
1.4 (m, 2H) 1.3 (t, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 144.0 (C-5), 144.1 (C-3), 124.8, 121.7, 118.5, 115.3 (CF$_3$-SO$_3$), 51.5, 30.7, 19.1, 13.0; ES-MS m/z: 126.0963 [M- CF$_3$-SO$_3$]$^+$. 

1-ethyl-1,2,4-triazolium phenylsulfonate (3d)

Colorless solid, (2.31g, yield 90%), Anal. Calcd. For C$_{11}$H$_{15}$N$_3$O$_3$S (269.08): C, 49.06; H, 5.61; N, 15.60. Found: C, 49.01; H, 5.54; N, 15.51. $^1$H NMR (DMSO-d$_6$, 400 MHz): 9.77 (s, 1H, 5-CH), 8.90 (s, 1H, 3-CH), 8.57 (s, 1H, NH) 7.66 (dd, 2H, aromatic CH), 7.35 (m, 3H, aromatic, CH) 4.33 (t, 2H, N-CH$_2$-), 1.4 (t, 3H, CH$_3$). $^{13}$C NMR (DMSO-d$_6$, 100 MHz): 147.50 (C-quaternery), 145.03 (C-5), 141.66 (C-3), 129.20, 128.57, 125.69 (C$_6$H$_5$SO$_3$), 46.30 (N-CH$_2$), 14.25 (-CH$_3$). ES-MS m/z: 98.13[M- C$_6$H$_5$SO$_3$]$^+$. 

1-propyl-1,2,4-triazolium phenylsulfonate (3e)

Colorless solid, (2.4g, yield 90%), Anal. Calcd. For C$_{11}$H$_{15}$N$_3$O$_3$S (269.08) C, 49.06; H, 5.61; N, 15.60. Found: C, 48.98; H, 5.51; N, 15.53. $^1$H NMR (CDCl$_3$, 300 MHz): 12.32 (bs, 1H, NH), 10.23 (s, 1H, 5-CH), 8.54 (s, 1H, 3-CH), 7.88 (d, 2H, aromatic CH), 7.39 (m, 3H, aromatic CH) 4.33 (t, 2H, N-CH$_2$-), 1.91 (m, 2H, -CH$_2$-CH$_3$), 0.87 (t, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): 144.44 (C-quaternery), 142.98 (C-5), 141.75 (C-3), 130.41, 128.43, 125.87 (C$_6$H$_5$SO$_3$), 53.55 (N-CH$_2$), 22.38 (-CH$_2$-CH$_3$), 10.53 (-CH$_3$). ES-MS m/z: 112.16[M- C$_6$H$_5$SO$_3$]$^+$. 

1-butyl-1,2,4-triazolium phenylsulfonate (3f)

Colorless solid, (2.5 g, yield 91%) , Anal. Calcd. For C$_{12}$H$_{17}$N$_3$O$_3$S (283.10) C, 50.87; H, 6.05; N, 14.83. Found: C, 50.77; H, 5.94; N, 14.74. $^1$H NMR (DMSO-d$_6$, 400 MHz): 9.63 (s, 1H, 5-CH), 8.80 (s, 1H, 3-CH), 7.64 (m, 2H, aromatic CH), 7.46 (bs, 1H, NH) 7.34 (m, 3H, aromatic CH) 4.31 (t, 2H, -CH$_2$-CH$_2$-CH$_2$-CH$_3$)
1.79 (m, 2H, CH₂-CH₂-CH₂-CH₃) 1.27 (m, 2H, CH₂-CH₂-CH₂-CH₃). 0.87(t, 2H, CH₂-CH₂-CH₂-CH₃). ¹³C NMR (DMSO-d₆, 400 MHz): 147.75 (C-quaternary), 145.76 (C-5), 142.19 (C-3), 128.88, 127.91, 125.60 (C₆H₅SO₃), 50.17 (CH₂-CH₂-CH₂-CH₃), 30.56 (CH₂-CH₂-CH₂-CH₃), 18.92 (CH₂-CH₂-CH₂-CH₃), 13.34 (CH₂-CH₂-CH₂-CH₃). ES-MS m/z: 126.19 [M- C₆H₅SO₃]⁺

Spectral data of 3,4-dihydropyrimidin-2(1H)-Ones/thiones:

**Methyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate** (Table 3.15, entry 1) Colorless solid, 95% yield. ¹HNMR (400 MHz, CDCl₃): δ 8.3 (s, 1H), 7.3 (m, 5H), 5.9 (s, 1H), 5.3 (d, J = 4.0 Hz, 1H), 3.6 (s, 3H), 2.3 (s, 3H); ¹³CNMR (CDCl₃, 100 MHz): δ 166.1, 153.5, 146.6, 143.6, 128.7, 127.9, 126.5, 101.1, 55.5, 51.1, 18.7.

**Methyl-4-(4-isopropylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate** (Table 3.15, entry 3) Colorless solid, 88% yield. ¹HNMR (CDCl₃, 400 MHz): δ 8.4 (s, 1H), 7.2 (m, 4H), 5.9 (s, 1H), 5.3 (d, J = 4.0 Hz, 1H), 3.6 (s, 3H), 2.9 (m, 1H), 2.3 (s, 3H), 1.2 (d, J = 8.0 Hz, 6H); ¹³CNMR (CDCl₃, 400 MHz): δ 166.2, 153.7, 148.5, 146.5, 141.0, 126.8, 126.4, 101.3, 55.2, 51.16, 33.7, 23.9, 18.6.

**Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate** (Table 3.15, entry 16) pale brown solid 74 %. ¹HNMR (400 MHz, DMSO-d₆): δ 9.3 (s, 1H), 9.1 (d, J = 1.6 Hz, 1H), 7.6 (m, 1H) 7.0 (t, J = 8.0 Hz, 1H), 6.6 (m, 2H), 6.6 (m, 1H), 5.0 (s, 1H), 3.9 (q, 2H), 2.4 (m, 3H), 1.0 (t, J = 7.2 Hz, 3H); ¹³CNMR (100 MHz, DMSO-d₆): δ 165.4, 157.3, 152.2, 148.1, 146.2, 129.3, 116.9, 114.19, 113.1, 99.4, 59.2, 53.8, 17.7, 14.1.

**Methyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate** (Table 3.15, entry 17) Colorless solid 91% yield. ¹HNMR (CDCl₃, 400 MHz): δ 8.4 (s, 1H), 7.4 (d, J = 2.0 Hz, 1H), 7.3 (d, J = 2.0 Hz, 1H), 6.9 (d, J = 2.0 Hz, 1H), 6.8 (m, 1H), 5.0 (s, 1H), 3.9 (q, 2H), 2.4 (m, 3H), 1.0 (t, J = 7.2 Hz, 3H); ¹³CNMR (100 MHz, DMSO-d₆): δ 165.4, 157.3, 152.2, 148.1, 146.2, 129.3, 116.9, 114.19, 113.1, 99.4, 59.2, 53.8, 17.7, 14.1.
MHz): δ 8.5 (s, 1H), 7.2 (m, 3H), 7.0 (m, 2H), 6.1 (s, 1H), 5.3 (d, J = 4.0 Hz, 1H), 3.6 (s, 3H), 2.3 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 166.0, 163.5, 161.1, 153.6, 146.7, 139.5, 139.5, 128.2, 128.1, 115.7, 115.5, 101.1, 54.8, 51.2, 18.6.

**Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate** (Table 3.15, entry 32) Pale brown solid 72% $^1$HNMR (DMSO-d$_6$, 400 MHz): δ 10.2 (s, 1H), 9.5 (d, 1H), 9.4 (s, 1H), 7.1 (m, 1H), 6.6 (d, 3H), 5.0 (d, 1H), 4.0 (q, 2H), 2.2 (s, 3H), 1.1 (t, J = 7.2 Hz); $^{13}$CNMR (100 MHz, DMSO-d$_6$): δ 174.1, 165.1, 157.4, 144.8, 144.7, 129.4, 117.0, 114.6, 113.2, 100.7, 59.5, 53.9, 17.1, 14.0.

**3.4. Results and discussion.**

The ILs, 3a-f were synthesized by adopting reported procedure (Elango K et al., 2007) and characterized by $^1$H NMR, $^{13}$C NMR, ESI-MS and elemental analysis. In $^1$H-NMR, the 5-CH and 3-CH protons of 3a-f fall in the range of 9.5 to 10.2 ppm and 8.9 to 8.5 ppm respectively. In addition positive ion ESI-MS$^+$ gave the corresponding cationic ([M-X]$^+$) peak for 3a-f. All ILs 3a-f (5 mmole) were dissolved in triply distilled water (10 mL) for pH measurement.

**Table 3.11** pH of Brønsted acidic ILs

<table>
<thead>
<tr>
<th>No</th>
<th>Ionic Liquids</th>
<th>State</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Liquid</td>
<td>2.21</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Liquid</td>
<td>2.27</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>Liquid</td>
<td>2.45</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>Solid</td>
<td>3.58</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>Solid</td>
<td>3.65</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>Solid</td>
<td>3.81</td>
</tr>
</tbody>
</table>
The synthesized Brønsted acidic ILs based on 1-alkyl 1,2,4-triazolium triflate (3a-c) exists in liquid state, while in the case of Brønsted acidic ILs based on 1-alkyl 1,2,4-triazolium phenylsulfonate (3d-f) exist in solid state.

**Table 3.12: Solvent studies in Biginelli reaction**

<table>
<thead>
<tr>
<th>No</th>
<th>solvent</th>
<th>(3a)</th>
<th>(3b)</th>
<th>(3c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>time (h)</td>
<td>yield (%)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>time (h)</td>
<td>yield (%)&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>neat</td>
<td>1.0</td>
<td>81</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>water</td>
<td>1.0</td>
<td>54</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>methanol</td>
<td>1.0</td>
<td>60</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>ethanol</td>
<td>0.45</td>
<td>93</td>
<td>0:30</td>
</tr>
<tr>
<td>5</td>
<td>dichloromethane</td>
<td>1.0</td>
<td>45</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>1.0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>tetrahydrofuran</td>
<td>1.0</td>
<td>34</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>acetonitrile</td>
<td>1.0</td>
<td>55</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: benzaldehyde (1.0 mmole), ethyl acetoacetate (1.5 mmole), urea (2.0 mmole) and RTILs (10 mol%);<sup>b</sup> isolated yield;<sup>c</sup> products were characterized by mp, <sup>1</sup>H and <sup>13</sup>C-NMR.

It was observed that without six triazolium based Brønsted acidic ionic liquids (3a-c) the reaction failed to give any product (Table 3.13 and 3.14, entry 1). Initially, all the six triazolium based Brønsted acidic ionic liquids (3a-f) are tested as a catalyst and solvent to promote one-pot Biginelli reaction using benzaldehyde, ethyl acetoacetates and urea as a model reaction. It is found that, in the absence of solvent (neat) dihydropyrimidinone obtained is 80-85% yield in 3a-c as a solvent and catalyst (Table 3.12, entry 1).
Scheme 3.14: Solvent studies for Biginelli reaction

In order to determine the suitable solvents for the synthesis of dihydropyrimidinones (scheme 3.14) in different solvent systems were used and their results are presented in Table 3.12. Among all the solvents screened it was found that ethanol was found the most suitable solvent for this reaction. However, in non-polar solvents such as toluene, tetrahydrofuran, and dichloromethane the reaction resulted with moderate yield, this is due to the low solubility of starting materials.

While the reaction was performed in the presence of 5 mol% ILs (3a-c) and (3a-f), the desired product DHPMs was obtained in 74-79% and 70-89% yields respectively (Table 3.2.2, entry 2 and Table 3.2.3, entry 2). Indeed the yield of dihydropyrimidinone was increased to 85-95%, using 10 mol% ILs (3a-f), with full conversion in a relatively shorter time of 20 min with 3c (Table 3.13 and 3.14, entry 3). While increasing the catalyst loading the yield of DHPMs was decreased, which did not significantly improved the reaction. Because the ionic liquids are acidic and high catalyst loading leads to the formation of side products. After extensive screening of different reaction parameters, the optimized reaction conditions involved aldehyde (1.0 mmol), β-ketoesters (1.5 mmol), urea or thiourea (2.0 mmol) and ionic liquids (10 mol %) (3a-c) in ethanol as solvent at 80 °C to provide desired product DHPMs in excellent yields. This catalyst was directly subjected to Biginelli reaction using model reaction between
benzaldehyde, ethyl acetoacetate and urea with our optimized reaction condition. It is important to note that the recycled catalysts (3a-c) produced excellent yields of dihydropyrimidinones/thiones in 89-95%, respectively (Table 3.15, entries 1-4). It was observed that the yields were consistent without the significant loss in its catalytic activity. With these optimized conditions in Biginelli reactions, the scope of this methodology in synthesizing various derivatives of DHPMs. The Biginelli products obtained by varying different substituent in aldehyde and the results are summarized in Table 3.15 and 3.16.

**Scheme 3.15:** Optimization of reaction condition for the synthesis of 3,4-dihydropyrimidinones in 3a-c as catalyst

**Scheme 3.16:** Optimization of reaction condition for the synthesis of 3,4-dihydropyrimidinones in 3d-f as catalyst
Table 3.13: Optimization of reaction conditions in Biginelli reaction using 3a-c

<table>
<thead>
<tr>
<th>No</th>
<th>RTILS mole (%)</th>
<th>(3a)</th>
<th>(3b)</th>
<th>(3c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>time (hh:mm)</td>
<td>Yield(^{b,c}) (%)</td>
<td>time (hh:mm)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1:00</td>
<td>0</td>
<td>1:00</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>1:0</td>
<td>74</td>
<td>1:0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0:45</td>
<td>93</td>
<td>0:30</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>0:35</td>
<td>90</td>
<td>0:30</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>0:25</td>
<td>84</td>
<td>0:25</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: benzaldehyde (1.0 mmole), ethyl acetoacetate (1.5 mmole), urea (2.0 mmole) and RTILs (10 mol%); \(^{b}\) isolated yield; \(^{c}\) products were characterized by mp, \(^{1}\)H and \(^{13}\)C-NMR.

Table 3.14: Optimization of reaction conditions in Biginelli reaction using 3d-f

<table>
<thead>
<tr>
<th>No</th>
<th>ILS mole (%)</th>
<th>3d</th>
<th>3e</th>
<th>3f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>time (hh:mm)</td>
<td>Yield(^{b,c}) (%)</td>
<td>time (hh:mm)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1.00</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>1:00</td>
<td>70</td>
<td>1:00</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>1:00</td>
<td>87</td>
<td>1:00</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>0:45</td>
<td>81</td>
<td>0:50</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>0:25</td>
<td>77</td>
<td>0:25</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: benzaldehyde (1.0 mmole), urea (2.0 mmole) ethyl acetoacetate (1.5 mmole), and ILS (10 mol%); \(^{b}\) isolated yield; \(^{c}\) products were characterized by mp, \(^{1}\)H and \(^{13}\)C-NMR.
Scheme 3.3.4: Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones in 3a-c as a catalyst

Table 3.1.5: Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones and thiones in 3a-c using Biginelli reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>X</th>
<th>RTILs</th>
<th>mp (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>01.00</td>
<td>93</td>
<td>208-209 Ma Y et al., 2000</td>
</tr>
<tr>
<td>2</td>
<td>4-CH₃</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>01.30</td>
<td>84</td>
<td>211-212 Ramalingan C and Kwak Y W, 2008</td>
</tr>
<tr>
<td>3</td>
<td>4-i-Pr</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>02.00</td>
<td>86</td>
<td>178-179 -</td>
</tr>
<tr>
<td>4</td>
<td>4-OCH₃</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>03.00</td>
<td>88</td>
<td>190-191 Ma Y et al., 2000</td>
</tr>
<tr>
<td>5</td>
<td>4-F</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>03.30</td>
<td>76</td>
<td>191-192 Ma Y et al., 2000</td>
</tr>
<tr>
<td>6</td>
<td>4-Cl</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>04.00</td>
<td>88</td>
<td>204-205 Lu and Bai, 2002</td>
</tr>
<tr>
<td>7</td>
<td>4-Br</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>03.30</td>
<td>80</td>
<td>218-219 Aridoss G and Jeong T Y, 2010</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>3-OH</td>
<td>H</td>
<td>O</td>
<td>01.00</td>
<td>75</td>
<td>221-222 Li W et al, 2011</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>O</td>
<td>00.45</td>
<td>93</td>
<td>201-202 Lu and Bai, 2002</td>
</tr>
<tr>
<td>10</td>
<td>4-CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>O</td>
<td>02.00</td>
<td>87</td>
<td>212-214 Heravi M. M et al., 2005</td>
</tr>
<tr>
<td>11</td>
<td>4-i-Pr</td>
<td>H</td>
<td>CH₃</td>
<td>O</td>
<td>04.00</td>
<td>85</td>
<td>154-155 Pore D. M et al., 2007</td>
</tr>
<tr>
<td></td>
<td>Reactant 1</td>
<td>Reactant 2</td>
<td>Reactant 3</td>
<td>Time</td>
<td>Yield</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>------</td>
<td>-------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4-OCH₃</td>
<td>H</td>
<td>CH₃</td>
<td>03:00</td>
<td>90</td>
<td>02.30</td>
<td>93</td>
</tr>
<tr>
<td>13</td>
<td>4-F</td>
<td>H</td>
<td>CH₃</td>
<td>04:00</td>
<td>77</td>
<td>04:00</td>
<td>75</td>
</tr>
<tr>
<td>14</td>
<td>4-Cl</td>
<td>H</td>
<td>CH₃</td>
<td>02:00</td>
<td>80</td>
<td>03:30</td>
<td>84</td>
</tr>
<tr>
<td>15</td>
<td>4-Br</td>
<td>H</td>
<td>CH₃</td>
<td>03:00</td>
<td>72</td>
<td>03:00</td>
<td>75</td>
</tr>
<tr>
<td>16</td>
<td>H</td>
<td>3-OH</td>
<td>CH₃</td>
<td>01:00</td>
<td>70</td>
<td>00:45</td>
<td>70</td>
</tr>
<tr>
<td>17</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>01:30</td>
<td>90</td>
<td>01:00</td>
<td>90</td>
</tr>
<tr>
<td>18</td>
<td>4-CH₃</td>
<td>H</td>
<td>H</td>
<td>02:00</td>
<td>85</td>
<td>02:00</td>
<td>88</td>
</tr>
<tr>
<td>19</td>
<td>4-iPr</td>
<td>H</td>
<td>H</td>
<td>03:00</td>
<td>86</td>
<td>03:00</td>
<td>86</td>
</tr>
<tr>
<td>20</td>
<td>4-OCH₃</td>
<td>H</td>
<td>H</td>
<td>02:30</td>
<td>83</td>
<td>02:30</td>
<td>80</td>
</tr>
<tr>
<td>21</td>
<td>4-F</td>
<td>H</td>
<td>H</td>
<td>03:30</td>
<td>76</td>
<td>03:00</td>
<td>75</td>
</tr>
<tr>
<td>22</td>
<td>4-Cl</td>
<td>H</td>
<td>H</td>
<td>05:00</td>
<td>84</td>
<td>04:30</td>
<td>87</td>
</tr>
<tr>
<td>23</td>
<td>4-Br</td>
<td>H</td>
<td>H</td>
<td>04:00</td>
<td>76</td>
<td>04:00</td>
<td>75</td>
</tr>
<tr>
<td>24</td>
<td>H</td>
<td>3-OH</td>
<td>H</td>
<td>03:30</td>
<td>72</td>
<td>03:00</td>
<td>70</td>
</tr>
<tr>
<td>25</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>02:00</td>
<td>84</td>
<td>02:00</td>
<td>87</td>
</tr>
<tr>
<td>26</td>
<td>4-CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>03:30</td>
<td>83</td>
<td>03:30</td>
<td>83</td>
</tr>
<tr>
<td>27</td>
<td>4-iPr</td>
<td>H</td>
<td>CH₃</td>
<td>03:30</td>
<td>87</td>
<td>03:00</td>
<td>89</td>
</tr>
<tr>
<td>28</td>
<td>4-OCH₃</td>
<td>H</td>
<td>CH₃</td>
<td>03:00</td>
<td>90</td>
<td>03:00</td>
<td>92</td>
</tr>
<tr>
<td>29</td>
<td>4-F</td>
<td>H</td>
<td>CH₃</td>
<td>04:30</td>
<td>69</td>
<td>04:30</td>
<td>74</td>
</tr>
<tr>
<td>30</td>
<td>4-Cl</td>
<td>H</td>
<td>CH₃</td>
<td>02:30</td>
<td>79</td>
<td>02:30</td>
<td>82</td>
</tr>
<tr>
<td>31</td>
<td>4-Br</td>
<td>H</td>
<td>CH₃</td>
<td>03:00</td>
<td>70</td>
<td>02:30</td>
<td>73</td>
</tr>
<tr>
<td>32</td>
<td>H</td>
<td>3-OH</td>
<td>CH₃</td>
<td>01:30</td>
<td>69</td>
<td>01:30</td>
<td>70</td>
</tr>
</tbody>
</table>

*Reaction conditions: benzaldehyde (1.0 mmole), ethyl acetoacetate (1.5 mmole), urea (2.0 mmole) and RTILs (10 mol%); bisolated yield; cproducts were characterized by mp, H and C-NMR
Scheme 3.3.5: Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones in 3d-f as a catalyst

Table 3.1.6: Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones and thiones in 3d-f using Biginelli reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>X</th>
<th>ILs</th>
<th>mp (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>3d</td>
<td>94</td>
<td>Ma Y et al., 2000</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>3e</td>
<td>84</td>
<td>Ramalingan C and Kwak Y W, 2008</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>3f</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>3-OH</td>
<td>H</td>
<td>O</td>
<td>3d</td>
<td>72</td>
<td>Lu and Bai, 2002</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3e</td>
<td>89</td>
<td>Aridoss G and Jeong T Y, 2010</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>3f</td>
<td>90</td>
<td>Li W et al., 2011</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>3d</td>
<td>88</td>
<td>Lu and Bai, 2002</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3f</td>
<td>90</td>
<td>Heravi M M et al., 2005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3d</td>
<td>88</td>
<td>Pore D M et al., 2007</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3f</td>
<td>90</td>
<td>Lu and Bai, 2002</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3d</td>
<td>88</td>
<td>Aridoss G and Jeong T Y, 2010</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3f</td>
<td>90</td>
<td>Li W et al., 2011</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3d</td>
<td>88</td>
<td>Lu and Bai, 2002</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3f</td>
<td>90</td>
<td>Heravi M M et al., 2005</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3d</td>
<td>88</td>
<td>Pore D M et al., 2007</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3f</td>
<td>90</td>
<td>Lu and Bai, 2002</td>
</tr>
<tr>
<td></td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O</td>
<td>3d</td>
<td>88</td>
<td>Aridoss G and Jeong T Y, 2010</td>
</tr>
<tr>
<td></td>
<td>4-Cl</td>
<td>H</td>
<td>CH₃</td>
<td>O</td>
<td>04:00</td>
<td>81</td>
<td>04:00</td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>15</td>
<td>4-Br</td>
<td>H</td>
<td>CH₃</td>
<td>O</td>
<td>04:00</td>
<td>74</td>
<td>03:30</td>
</tr>
<tr>
<td>16</td>
<td>H</td>
<td>3-OH</td>
<td>CH₃</td>
<td>O</td>
<td>04:00</td>
<td>65</td>
<td>04:00</td>
</tr>
<tr>
<td>17</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>S</td>
<td>02:00</td>
<td>90</td>
<td>01:30</td>
</tr>
<tr>
<td>18</td>
<td>4-CH₃</td>
<td>H</td>
<td>H</td>
<td>S</td>
<td>02:30</td>
<td>83</td>
<td>02:00</td>
</tr>
<tr>
<td>19</td>
<td>4-iPr</td>
<td>H</td>
<td>H</td>
<td>S</td>
<td>04:30</td>
<td>84</td>
<td>04:00</td>
</tr>
<tr>
<td>20</td>
<td>4-OCH₃</td>
<td>H</td>
<td>H</td>
<td>S</td>
<td>03:30</td>
<td>91</td>
<td>02:30</td>
</tr>
<tr>
<td>21</td>
<td>4-F</td>
<td>H</td>
<td>H</td>
<td>S</td>
<td>04:30</td>
<td>77</td>
<td>03:30</td>
</tr>
<tr>
<td>22</td>
<td>4-Cl</td>
<td>H</td>
<td>H</td>
<td>S</td>
<td>02:30</td>
<td>76</td>
<td>02:00</td>
</tr>
<tr>
<td>23</td>
<td>4-Br</td>
<td>H</td>
<td>H</td>
<td>S</td>
<td>04:00</td>
<td>75</td>
<td>02:30</td>
</tr>
<tr>
<td>24</td>
<td>H</td>
<td>3-OH</td>
<td>H</td>
<td>S</td>
<td>01:45</td>
<td>69</td>
<td>01:00</td>
</tr>
<tr>
<td>25</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>02:30</td>
<td>81</td>
<td>02:30</td>
</tr>
<tr>
<td>26</td>
<td>4-CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>03:00</td>
<td>82</td>
<td>03:00</td>
</tr>
<tr>
<td>27</td>
<td>4-iPr</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>04:30</td>
<td>89</td>
<td>04:30</td>
</tr>
<tr>
<td>28</td>
<td>4-OCH₃</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>03:00</td>
<td>86</td>
<td>02:00</td>
</tr>
<tr>
<td>29</td>
<td>4-F</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>04:00</td>
<td>69</td>
<td>03:00</td>
</tr>
<tr>
<td>30</td>
<td>4-Cl</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>03:30</td>
<td>72</td>
<td>02:00</td>
</tr>
<tr>
<td>31</td>
<td>4-Br</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>04:00</td>
<td>70</td>
<td>03:45</td>
</tr>
<tr>
<td>32</td>
<td>H</td>
<td>3-OH</td>
<td>CH₃</td>
<td>S</td>
<td>02:30</td>
<td>64</td>
<td>02:30</td>
</tr>
</tbody>
</table>

*aReaction conditions: benzaldehyde (1.0 mmole), ethyl acetoacetate (1.5 mmole), urea (2.0 mmole) and ILs (10 mol%); bisolated yield; cproducts were characterized by mp, ¹H and ¹³C-NMR*
The reaction of 4-methyl benzaldehyde proceeded to give the desired products methyl substituted 3, 4-dihydropyrimidin-2-ones (Table 3.1.5, entry 2) and 3,4-dihydropyrimidin-2-thiones (Table 3.15, entry 18) in excellent isolated yields. The effect of several substituents on benzaldehyde, such as alkyl, alkoxy and halides were investigated, which smoothly resulted to the formation of products DHPMs in excellent yields.

Similarly, the β-keto ester substituted with methyl- or ethyl-acetoacetate did not alter the yield of Biginelli product (Table 3.15, entries 1 to 7 and 25 to 30). Interestingly, it was found that the Biginelli reaction in ionic liquid 3c shows better results when compared to the all other ionic liquids such as reaction time and yield wise.

Probably, the alkyl substituent’s in ionic liquids have significant steric effects, which impact the rate of Biginelli reaction. Moreover, the 1-alkyl-1,2,4-triazolium triflate based BrØnsted acidic room temperature ionic liquids shows better results in the synthesis of dihydropyrimidones/thiones (Table 3.15) derivatives than the 1-alkyl-1,2,4-triazolium phenylsulfonate based BrØnsted acidic ionic liquids (Table 3.16).

3.5. Reusability study

Scheme 3.17: Reusability studies in Biginelli reaction
Table 3.17: Catalyst reusability (3a-c) study in Biginelli reactions

<table>
<thead>
<tr>
<th>No</th>
<th>cycle</th>
<th>3a</th>
<th>3b</th>
<th>3c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>time (h)</td>
<td>yield (%)</td>
<td>time (h)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0:45</td>
<td>93</td>
<td>0:30</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1:0</td>
<td>90</td>
<td>0:45</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1:0</td>
<td>89</td>
<td>1:0</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1:0</td>
<td>89</td>
<td>1:0</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: benzaldehyde (1.0 mmole), ethyl acetoacetate (1.5 mmole), urea (2.0 mmole) and RTILs (10 mol%), EtOH (1 mL), 80 °C.

Table 3.18: Catalyst reusability (3d-f) study in Biginelli reactions

<table>
<thead>
<tr>
<th>entry</th>
<th>cycle</th>
<th>3d</th>
<th>3e</th>
<th>3f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>time (h)</td>
<td>yield (%)</td>
<td>time (h)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1:00</td>
<td>87</td>
<td>1:0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1:15</td>
<td>85</td>
<td>1:0</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1:15</td>
<td>84</td>
<td>1:0</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1:15</td>
<td>82</td>
<td>1:0</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: benzaldehyde (1.0 mmole), ethyl acetoacetate (1.5 mmole), urea (2.0 mmole) and ILs (10 mol%), EtOH (1 mL), 80 °C.

The reusability of the catalyst 3a-f performed in benzaldehyde, ethylacetoacetate and urea, recovered from the reaction mixture without significant the results are described in Table 3.17 (3a-c) and Table 3.18 (3d-f). The catalyst was recovered from the reaction mixture by using simple filtration technique. The filtrate was
evaporated to remove the excess of ethanol. Then the crude residue was washed with mixture of solvents, hexane: ethyl acetate (4:1), subsequently dried over vacuum for one hour

3.7. Summary

In this chapter, a convenient and reusable protocol for the multicomponent Biginelli reaction with 1,2,4-triazolium triflate and phenylsulfonate based Brønsted acidic ionic liquid as catalyst. The Biginelli products 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones has been obtained in excellent isolated yields. The product was isolated by simple filtration technique, thus free from chromatographic purification. It is important to note that the catalysts were recovered and reused without loss of its catalytic activity.
$^1$H NMR SPECTRUM OF 3a

$^{13}$C NMR SPECTRUM OF 3a
$^{19}$F NMR SPECTRUM 3a

ESI-MASS SPECTRUM OF 3a
$^1$H NMR SPECTRUM OF 3b

$^{13}$C NMR SPECTRUM OF 3b
$^{19}$F NMR SPECTRUM OF 3b

ESI-MASS SPECTRUM OF 3b
$^1$H NMR SPECTRUM OF $3c$

$^{13}C$ NMR SPECTRUM OF $3c$
$^{19}$F NMR SPECTRUM OF 3c

ESI-MASS SPECTRUM OF 3c
$^1$H NMR SPECTRUM OF 3d

$^{13}$C NMR SPECTRUM OF 3d
ESI-MASS SPECTRUM OF 3d

1H NMR SPECTRUM OF 3e
$^{13}$C NMR SPECTRUM OF 3e

![NMR spectrum of 3e](image)

ESI-MASS SPECTRUM OF 3e

![Mass spectrum of 3e](image)
$^1$H NMR SPECTRUM OF 3f

$^{13}$CNMR SPECTRUM OF 3f
ESI-Mass SPECTRUM OF 3f
$^1$H NMR SPECTRUM OF ENTRY 1 IN TABLE 3.15

$^{13}$C NMR SPECTRUM OF ENTRY 1 IN TABLE 3.15
$^1$H NMR SPECTRUM OF ENTRY 3 IN TABLE 3.15

$^{13}$C NMR SPECTRUM OF ENTRY 3 IN TABLE 3.15
LC-MASS SPECTRUM OF ENTRY 3 IN TABLE 3.15

[Image of mass spectrometry graphs and tables]

Peak | RT (min) | Area | Area %
--- | ------- | ---- | ----
1   | 12.416  | 1.980 | 0.0010.016
2   | 12.458  | 1.433 | 0.0010.210
3   | 12.590  | 1.117 | 0.000196.467
4   | 12.724  | 1.104 | 0.0011.817
5   | 12.750  | 1.936 | 0.00010.513
6   | 12.866  | 1.420 | 0.00010.408
7   | 13.222  | 1.741 | 0.0010.084
8   | 13.401  | 1.614 | 0.00010.485

Mass Spectrum: [Image of mass spectrum graphs]
$^{1}H$ NMR SPECTRUM OF ENTRY 16 IN TABLE 3.15

$^{13}C$ NMR SPECTRUM OF ENTRY 16 IN TABLE 3.15
$^1$H NMR SPECTRUM OF ENTRY 17 IN TABLE 3.15

$^{13}$C NMR SPECTRUM OF ENTRY 17 IN TABLE 3.15
$^1$H NMR SPECTRUM OF ENTRY 32 IN TABLE 3.15

$^{13}$C NMR SPECTRUM OF ENTRY 32 IN TABLE 3.15