

# Synthesis of 1-alkyl triazolium triflate room temperature ionic liquids and their catalytic studies in multi-component Biginelli reaction

SANKARANARAYANAN NAGARAJAN, TANVEER M SHAIKH and ELANGO KANDASAMY\*

Department of Chemistry, Vel Tech University, Chennai 600 062, India  
e-mail: elangoomc@gmail.com

MS received 24 January 2015; revised 25 April 2015; accepted 25 May 2015

**Abstract.** Synthesis of three Brønsted acid-based ionic liquids, namely, 1-ethyl-1,2,4-triazolium triflate (1a), 1-propyl-1,2,4-triazolium triflate (1b) and 1-butyl-1,2,4-triazolium triflate (1c), is described. These ionic liquids have been employed as catalysts for convenient and high-yielding one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones, which are Biginelli reaction products. Advantages of the methodology are operational convenience, short reaction times, avoidance of chromatographic purification and non-production of toxic waste. Further, the catalysts are easily recovered and reused without any noticeable diminution in their catalytic activity.

**Keywords.** Brønsted acid; ionic liquid; 1,2,4-Triazolium triflate; Biginelli reaction; Pyrimidones.

## 1. Introduction

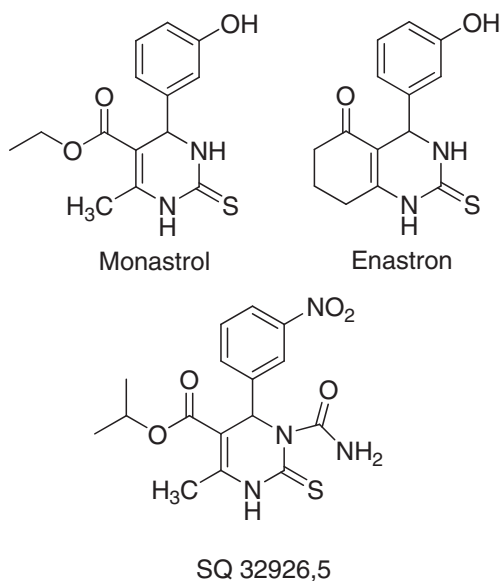
The construction of C-C bond *via* multicomponent one-pot reaction has given new pathway to a large variety of important compounds.<sup>1</sup> Particularly, the Biginelli reaction is an example of such multicomponent bond forming reactions.<sup>2</sup> Although this reaction was originally reported<sup>3</sup> in 1893 using hydrochloric acid as catalyst,<sup>4</sup> later several modifications have been reported in literature. Moreover, the Biginelli product, dihydropyrimidinone (DHPM) derivatives (figure 1) are associated with important bioactive properties, such as anti-cancer, anti-HIV, anti-hypertensive, anti-viral, calcium channel blockers,  $\alpha$ -1-antagonists and neuropeptide Y (NPY) antagonists, etc.<sup>5</sup>

In view of these useful properties, development of an environmentally benign and clean method is a concern both academia and industries. Since the discovery of this reaction, a variety of homogeneous and heterogeneous catalysts has been developed, which are effective in this one-pot transformation. Those methods involved use of a number of metal salts, such as Li,<sup>6</sup> Fe,<sup>7–10</sup> Cu,<sup>11,12</sup> Ce,<sup>13</sup> Zr,<sup>14</sup> In,<sup>16</sup> Bi,<sup>17</sup> Yb,<sup>18</sup> La,<sup>19</sup> Al,<sup>20,21</sup> Sn,<sup>22</sup> Mn,<sup>23</sup> Ti<sup>24</sup> and nanomaterials of Fe<sub>3</sub>O<sub>4</sub>.<sup>25</sup> Several zeolite catalyzed<sup>26–28</sup> and non-metal acid catalyzed<sup>29–32</sup> syntheses of dihydropyrimidinone have also been reported. However, some of these

procedures are associated with certain limitations such as use of metal catalysts, expensive reagents, and drastic reaction conditions, use of microwave or ultrasonication which often resulted in unsatisfactory yields of product. On the other hand, employing metal catalysts also resulted in over-oxidized product and substantial amount of metal-waste, which are major problems towards a sustainable process. 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.<sup>33–37</sup> Particularly, ionic liquids such as [cmmim][BF<sub>4</sub>],<sup>38</sup> TMGT,<sup>39</sup> tri-(2-hydroxyethylammoniumacetate),<sup>40</sup> [Gly]NO<sub>3</sub>,<sup>41</sup> Hmim[H<sub>2</sub>SO<sub>4</sub>]<sup>42</sup> Si-[SbSipim][PF<sub>6</sub>],<sup>43</sup> [bmim][Meso<sub>4</sub>]<sup>44</sup> and [BMIM]OH<sup>45</sup> have been known to achieve this one-pot transformation.

We are interested in syntheses of a new class of ionic liquids and development of eco-friendly and reusable catalytic transformations.<sup>46</sup> Recently, we have demonstrated Brønsted acid-based ionic liquids, 1,2,4-triazolium methanesulfonate (figure 2) as catalyst in multicomponent Mannich reaction.<sup>47</sup> In continuation of our efforts towards the development of sustainable process, we herein disclose an efficient and reusable protocol using 1,2,4-triazolium triflate Brønsted acid-based ionic liquids for the one-pot preparation of 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones.

\*For correspondence



**Figure 1.** Dihydropyrimidinone derivatives.

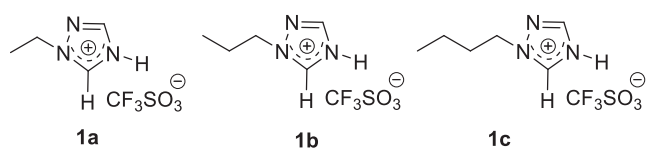
## 2. Experimental

### 2.1 Instruments

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance 400 MHz. Electrospray ionization mass spectrometry (ESI-MS) spectra were obtained with a Waters Q-TOF premier mass spectrometer.

### 2.2 Materials

Solvents were freshly distilled prior to use and glassware was dried in oven at  $120^\circ\text{C}$  overnight. Trifluoromethanesulfonic acid was purchased from Sigma Aldrich. 1,2,4-triazole, ethyl bromide, propyl bromide and *n*-butyl bromide were purchased from SD fine chemicals, India. Starting materials such as urea, thiourea, ethylacetoacetate, methylacetoacetate, benzaldehyde, 4-methyl benzaldehyde, 4-isopropylbenzaldehyde, 4-fluorobenzaldehyde, 4-bromobenzaldehyde, 4-chloro benzaldehyde, 3-hydroxybenzaldehyde were obtained from SRL, India. All the chemicals were used without further purification.



**Figure 2.** Bronsted acid-based ionic liquids: 1,2,4-triazolium triflates.

### 2.3 Synthesis of 1-alkyl-1,2,4-triazolium triflate based RTILs (scheme 1)

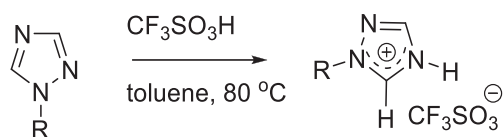
**2.3a Common procedure for the synthesis of ionic liquids 1a-c:** 1-Ethyl-1,2,4-triazolium triflate (**1a**), 1-Propyl-1,2,4-triazolium triflate (**1b**) and 1-butyl-1,2,4-triazolium triflate (**1c**). To a solution of 1-alkyl-1, 2, 4-triazoles (10 mmol) (alkyl = Et, Pr and Bu) in toluene (10 mL) trifluoromethanesulfonic acid (10 mmol) was added drop wise. This reaction mixture was then heated to  $80^\circ\text{C}$  for 12 h. After completion of the reaction, the flask was cooled to room temperature ( $25^\circ\text{C}$ ) and excess of toluene was removed under reduced pressure. The resulting residue was thoroughly washed with hexane ( $20\text{ mL} \times 2$ ) and further dried over vacuum to afford pure catalyst **1a-c**.

### 2.4 General Procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-Ones/thiones

Catalyst **1a-c** (10 mol%) was added to a solution of aldehyde (1.0 mmol),  $\beta$ -ketoester (1.5 mmol) and urea or thiourea (2.0 mmol) in ethanol (0.5 mL). The reaction mixture was heated at  $80^\circ\text{C}$  using oil bath for the specified time (0–5 h). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and subsequently quenched with a mixture of water:ethanol (5:0.5 mL). The solid product was filtered and washed with *n*-hexane ( $5\text{ mL} \times 2$ ), which afforded pure 3,4-dihydropyrimidin-2(1H)-ones or 3,4-dihydropyrimidin-2(1H)-thiones in pure form.

### 2.5 Catalyst recycling study

The catalyst was separated from the reaction mixture by simple filtration technique. Then the filtrate was concentrated under reduced pressure to remove excess ethanol and water. Then the residue was washed with 5 mL of hexane:ethyl acetate (4:1) and dried over vacuum for 1 h, which was directly used in reusability studies.



**Scheme 1.** Synthesis of 1-alkyl-1,2,4-triazolium triflate based RTILs.

## 2.6 Spectral data for selected compounds

2.6a *1-ethyl-1,2,4-triazolium triflate (1a)*: Colorless liquid; yield 85%;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  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);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  143.3 (C-5), 140.5 (C-3), 124.8, 121.6, 118.4, 115.3 ( $\text{CF}_3\text{-SO}_3$ ) 47.4, 13.7;  $^{19}\text{F NMR}$  ( $\text{DMSO-d}_6$ ):  $-78.42$  ppm; ES-MS  $m/z$ : 98.0711 [ $\text{M- CF}_3\text{-SO}_3$ ] $^+$ .

2.6b *1-Propyl 1,2,4-triazolium triflate (1b)*: Colorless liquid, yield 94%;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  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);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  143.6 (C-5), 141.1 (C-3), 122.3, 118.0 ( $\text{CF}_3\text{-SO}_3$ ) 53.6, 22.3, 10.4;  $^{19}\text{F NMR}$  ( $\text{CDCl}_3$ ):  $-78.95$  ppm; ES-MS  $m/z$ : 112.0869. [ $\text{M- CF}_3\text{-SO}_3$ ] $^+$ .

2.6c *1-butyl-1,2,4-triazolium triflate (1c)*: Colorless liquid; yield 95%;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  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);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  144.0 (C-5), 144.1 (C-3), 124.8, 121.7, 118.5, 115.3 ( $\text{CF}_3\text{-SO}_3$ ), 51.5, 30.7, 19.1, 13.0;  $^{19}\text{F NMR}$  ( $\text{DMSO-d}_6$ ):  $-77.91$ ; ES-MS  $m/z$ : 126.0963 [ $\text{M- CF}_3\text{-SO}_3$ ] $^+$ .

2.6d *5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one*: (table 4, entry 1)  $^1\text{HNMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  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);  $^{13}\text{CNMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  166.1, 153.5, 146.6, 143.6, 128.7, 127.9, 126.5, 101.1, 55.5, 51.1, 18.7.

2.6e *5-methoxycarbonyl-4(4-isopropylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one*: (table 4, entry 3): M.p.: 178–179°C;  $^1\text{HNMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.4 (s, 1H), 7.2 (m, 4H), 5.8 (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);  $^{13}\text{CNMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  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; (LC-Mass,  $m/z$ ) = 289 ( $\text{M}^+ + 1$ ).

2.6f *5-Ethoxycarbonyl-4(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one*: (table 4, entry 16)  $^1\text{HNMR}$  ( $\text{DMSO-d}_6$ , 400 MHz):  $\delta$  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);  $^{13}\text{CNMR}$  ( $\text{DMSO-d}_6$ , 100 MHz):  $\delta$  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.

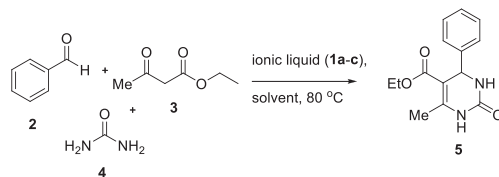
2.6g *5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione*: (table 4, entry 17)  $^1\text{HNMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.5 (s, 1H), 7.2 (m, 3H), 7.0 (m, 2H), 6.1 (s, 1H), 5.3 (d,  $J = 4.0$  Hz, 1H), 3.6 (s, 3H), 2.3 (s, 3H);  $^{13}\text{CNMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  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.

2.6h *5-ethoxycarbonyl-4(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione*: (table 4, entry 32)  $^1\text{HNMR}$  ( $\text{DMSO-d}_6$ , 400 MHz):  $\delta$  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);  $^{13}\text{CNMR}$  ( $\text{DMSO-d}_6$ , 100 MHz):  $\delta$  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. Results and Discussion

Initially, we studied the suitable reaction conditions employing ionic liquids **1a–c** as the catalyst to promote one-pot Biginelli reaction using benzaldehyde, ethyl acetoacetate and urea with altered catalyst loading, and the results are summarized in table 1. It was observed that without catalyst the reaction failed to give any product (table 1, entry 1). While the reaction was performed in the presence of 5 mol% ILs **1a–c**, the desired product **5** was obtained in 74–79% yield, respectively (entry 2). Indeed the yield of dihydropyrimidinone increased to 93–95%, using 10 mol% ILs **1a–c**, with full conversion in a relatively shorter time of 20 min (entry 3). While increasing the catalyst loading the yield of **5** decreased. The reaction did not significantly improve because the ionic liquids are acidic and high catalyst loading leads to the formation of side products.

In order to determine the effect of solvents, we investigated the Biginelli reaction in different solvent systems and the results are presented in table 2. It was observed that in the absence of solvent (neat) dihydropyrimidinone was obtained in 75% yield (table 2, entry 1). Among all the solvents screened, it was found that ethanol is the most suitable solvent for this reaction. However, in non-polar solvents such as toluene, tetrahydrofuran, acetonitrile and dichloromethane the reaction resulted in moderate yield, which might be due to poor solubility of starting materials. After extensive

**Table 1.** Optimization of reaction conditions: role of catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-one<sup>a</sup>.

entry	RTILs mole (%)	TrEtHTA ( <b>1a</b> )		TrPrHTA ( <b>1b</b> )		TrBuHTA ( <b>1c</b> )	
		time (h)	yield <sup>b,c</sup> (%)	time (h)	yield <sup>b,c</sup> (%)	time (h)	yield <sup>b,c</sup> (%)
1	0	1.0	0	1.0	0	1.0	0
2	5	1:0	74	1:0	75	1:0	79
3	10	0:45	93	0:30	93	0:20	95
4	15	0:35	90	0:30	90	0:30	90
5	20	0:25	84	0:25	84	0:20	85

<sup>a</sup>Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.5 mmol), urea (2.0 mmol) and RTILs (10 mol%);

<sup>b</sup>isolated yield;

<sup>c</sup>products were characterized by M.p., <sup>1</sup>H and <sup>13</sup>C-NMR

**Table 2.** Optimization of reaction conditions: solvent study for the synthesis of 3,4-dihydropyrimidin-2(1H)-one<sup>a</sup>.

entry	solvent	TrEtHTA ( <b>1a</b> )		TrPrHTA ( <b>1b</b> )		TrBuHTA ( <b>1c</b> )	
		time (h)	yield (%) <sup>b,c</sup>	time (h)	yield (%) <sup>b,c</sup>	time (h)	yield (%) <sup>b,c</sup>
1	neat	1.0	81	1.0	82	1.0	75
2	water	1.0	54	1.0	54	1.0	65
3	methanol	1.0	60	1.0	60	1.0	62
4	ethanol	0.45	93	0:30	93	0.20	95
5	dichloromethane	1.0	45	1.0	50	1.0	51
6	toluene	1.0	0	1.0	0	1.0	0
7	tetrahydrofuran	1.0	34	1.0	45	1.0	50
8	acetonitrille	1.0	55	1.0	56	1.0	56

<sup>a</sup>Reaction conditions: the reaction conditions are similar to table 1 except the mol% of catalyst.

**Table 3.** Catalyst reusability study in three component Biginelli reaction<sup>a</sup>.

entry	cycle	TrEtHTA ( <b>1a</b> )		TrPrHTA ( <b>1b</b> )		TrBuHTA ( <b>1c</b> )	
		time (h)	yield (%)	time (h)	yield (%)	time (h)	yield (%)
1	0	0:45	93	0:30	93	0:20	95
2	1	1:0	90	0:45	91	0:30	92
3	2	1:0	89	1:0	91	0:30	90
4	3	1:0	89	1:0	90	0:45	90

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

screening of different reaction parameters, the optimized reaction conditions involved aldehyde (1.0 mmol),  $\beta$ -ketoesters (1.5 mmol), urea or thiourea (2.0 mmol) and ionic liquids **1a** or **1b** or **1c** (10 mol%) in ethanol as

solvent at 80°C to provide the desired product **5** in excellent yield.

We also investigated the reusability of the catalyst **1a-c** and the results are described in table 3.

**Table 4.** Substrate scope for the Biginelli reaction for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones and thiones<sup>a</sup>.

entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	RTILs						M.p. <sup>(c)</sup>
					1a		1b		1c		
					time (h)	yield <sup>b</sup> (%)	time (h)	yield <sup>b</sup> (%)	time (h)	yield <sup>b</sup> (%)	
1	H	H	H	O	1.0	93	0:40	94	0.30	95	209–210 <sup>48</sup>
2	4-CH <sub>3</sub>	H	H	O	1.30	84	1:30	83	1.0	87	207–208 <sup>49</sup>
3	4- <sup>i</sup> Pr	H	H	O	2.0	86	2:0	88	1.3	89	178–179
4	4-OCH <sub>3</sub>	H	H	O	3.0	88	1:30	91	1.0	91	190–191 <sup>48</sup>
5	4-F	H	H	O	3.30	76	3:30	70	3.0	75	191–192 <sup>50</sup>
6	4-Cl	H	H	O	4.0	88	3:30	87	3.0	89	204–205 <sup>48</sup>
7	4-Br	H	H	O	3.30	80	3:30	82	3.3	81	218–219 <sup>56</sup>
8	H	3-OH	H	O	1.0	75	0:50	75	0.4	77	221–222 <sup>52</sup>
9	H	H	CH <sub>3</sub>	O	0.45	93	0:30	93	0.2	95	200–201 <sup>48</sup>
10	4-CH <sub>3</sub>	H	CH <sub>3</sub>	O	2.0	87	2:0	87	2.0	89	212–214 <sup>50</sup>
11	4- <sup>i</sup> Pr	H	CH <sub>3</sub>	O	4.0	85	4:0	86	3.3	89	140–141 <sup>51</sup>
12	4-OCH <sub>3</sub>	H	CH <sub>3</sub>	O	3.0	90	3:0	90	2.3	93	200–201 <sup>48</sup>
13	4-F	H	CH <sub>3</sub>	O	4.0	77	4:0	75	3.0	78	173–174 <sup>42</sup>
14	4-Cl	H	CH <sub>3</sub>	O	2.0	80	3:30	84	3:0	87	215–216 <sup>48</sup>
15	4-Br	H	CH <sub>3</sub>	O	3.0	72	3:0	75	2.3	76	214–215 <sup>50</sup>
16	H	3-OH	CH <sub>3</sub>	O	1.0	70	0:45	70	0.30	74	164–165 <sup>51</sup>
17	H	H	H	S	1.30	90	1:0	90	0.45	91	220–222 <sup>48</sup>
18	4-CH <sub>3</sub>	H	H	S	2.0	85	2:0	88	2.0	89	154–155 <sup>49</sup>
19	4- <sup>i</sup> Pr	H	H	S	3.0	86	3:0	86	2.30	88	169–171 <sup>55</sup>
20	4-OCH <sub>3</sub>	H	H	S	2.30	83	2:30	80	3.0	81	177–178 <sup>48</sup>
21	4-F	H	H	S	3.30	76	3:0	75	3.0	76	183–184 <sup>48</sup>
22	4-Cl	H	H	S	5.0	84	4:30	87	4.0	88	152–153 <sup>48</sup>
23	4-Br	H	H	S	4.0	76	4:0	75	3.30	78	178–179 <sup>48</sup>
24	H	3-OH	H	S	3.30	72	3:0	70	3.0	74	207–209 <sup>53</sup>
25	H	H	CH <sub>3</sub>	S	2.0	84	2:0	87	1.30	89	204–209 <sup>48</sup>
26	4-CH <sub>3</sub>	H	CH <sub>3</sub>	S	3.30	83	3:30	83	3.0	83	191–193 <sup>49</sup>
27	4- <sup>i</sup> Pr	H	CH <sub>3</sub>	S	3.30	87	3:0	89	2.30	90	138–140 <sup>54</sup>
28	4-OCH <sub>3</sub>	H	CH <sub>3</sub>	S	3.0	90	3:0	92	2.0	94	154–155 <sup>48</sup>
29	4-F	H	CH <sub>3</sub>	S	4.30	69	4:30	74	3.0	75	186–187 <sup>48</sup>
30	4-Cl	H	CH <sub>3</sub>	S	2.30	79	2:30	82	2.0	84	192–193 <sup>48</sup>
31	4-Br	H	CH <sub>3</sub>	S	3.0	70	2:30	73	3.0	75	190–191 <sup>48</sup>
32	H	3-OH	CH <sub>3</sub>	S	1.30	69	1:30	70	1.0	72	182–184 <sup>51</sup>

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

The catalyst was recovered from the reaction mixture by using simple filtration technique. The filtrate was dried over vacuum to remove excess ethanol. Then the crude residue was washed with mixture of solvents, hexane:ethyl acetate (4:1), subsequently dried over vacuum for 30 min. This catalyst was directly subjected to Biginelli reaction using the model reaction between

benzaldehyde, methyl acetoacetate and urea with our optimized reaction conditions. It is important to note that the recycled catalysts (**1a–c**) produced excellent yields of dihydropyrimidinone (**5**) in 90–95%, respectively (table 3, entries 1–4). It was observed that the yields were consistent without significant loss in its catalytic activity.



With these optimized conditions in hand, we extended the scope of this methodology in synthesizing various 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones, Biginelli products and the results are summarized in table 4. The reaction of 4-methyl benzaldehyde proceeded to give the desired products methyl substituted 3,4-dihydropyrimidin-2-ones (table 4, entry 2) and 3,4-dihydropyrimidin-2-thiones (table 4, entry 18) in excellent isolated yields. The effect of several substituents on benzaldehyde, such as alkyl, alkoxy, halides, F, Cl and Br were investigated, which smoothly resulted to the formation of products **5** in excellent yields. Similarly, the  $\beta$ -keto ester substituted with methyl- or ethyl-acetoacetate did not alter the yield of Biginelli product (entries 1 to 7 and 25 to 30). Interestingly, it was found that the reaction in ionic liquid **1c** was faster compared with ionic liquids **1a** and **1b**. Probably, the substituents in ionic liquids have significant steric effects which impact on the rate of the reaction.

#### 4. Conclusions

In summary, we have developed a convenient, sustainable and reusable protocol for the multicomponent Biginelli reaction, using 1,2,4-triazolium triflate based ionic liquids as catalyst. The Biginelli products 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones have been obtained in excellent isolated yields. The product was isolated by simple filtration technique without chromatographic purification. It is important to note that the catalysts were recovered and reused without loss of its catalytic activity. This protocol involves inexpensive reagents and reusable catalyst which may be suitable for large-scale preparation of important heterocycles in academia and industries.

#### Supplementary Information

Complete experimental procedure for synthesis of ionic liquids **1a-c** and the corresponding scanned spectra,  $^1\text{H}$ -,  $^{13}\text{C}$ -,  $^{19}\text{F}$ -NMR, ESI-MS, LC-MS are given in Supplementary Information as figures S2 to S13, respectively. Also, synthetic procedure to the preparation of 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones along with some selected scanned spectra of compounds in table 4, entries 1,3,16,17 and 32 are also given (figure S14 to S24). Supplementary Information is available at [www.ias.ac.in/chemsci](http://www.ias.ac.in/chemsci).

#### Acknowledgements

The authors thank the Department of Science and Technology, Science and Engineering Research Board (DST-SERB, SR/FT/CS-60/2011), India for providing research fund. Also the authors thank Dr. G. Anantharaman Department of Chemistry, India Institute of Technology Kanpur for NMR and ESI-MS measurements.

#### References

1. Posner G H 1986 *Chem. Rev.* **86** 831
2. Safari J and Ravandi S G 2014 *J. Mol. Struct.* **1065** 241
3. Biginelli P 1893 *Gazz. Chim. Ital.* **23** 360
4. Alvim H G O, Lima T B, Oliveira A L, Oliveira H C B, Silva F M, Gozzo F C, Souza R Y, Silva W A and Neto B A D 2014 *J. Org. Chem.* **79** 3383
5. Murata H, Ishitani H and Iwamoto M 2010 *Org. Biomol. Chem.* **8** 1202 and the references cited therein
6. Rudrawa S 2005 *Synlett.* **7** 1197
7. Cepanec I, Litvic M, Bartolincic A and Lovric M 2005 *Tetrahedron* **61** 4275
8. Adibi H, Samimi H A and Beygzadeh M 2007 *Catal. Commun.* **8** 2119
9. Mondal J, Sen T and Bhaumik A 2012 *Dalton Trans.* **41** 6173
10. Seyedi N 2013 *Transition. Met. Chem.* **38** 93
11. Paraskar A S, Dewkar G K and Sudalai A 2003 *Tetrahedron Lett.* **44** 3305
12. Reddy V Y, Kurva S and Tammishetti S 2004 *Catal. Commun.* **5** 511
13. Bose D S, Fatima L and Mereyala M H B 2003 *J. Org. Chem.* **68** 587
14. Khaleghi S, Heravi M M, Khosroshahi M, Behbahani F K and Daroogheha Z 2008 *Green Chem. Lett. Rev.* **2** 133
15. Reddy C V, Mahesh M, Raju P V K, Babu T R and Reddy V V N 2002 *Tetrahedron Lett.* **43** 2657
16. Ranu B C, Hajra A and Jana U 2000 *J. Org. Chem.* **65** 6270
17. Antoniotti S 2003 *Synlett* **10** 1566
18. Zhang H, Zhou Z, Yao Z, Xu F and Shen Q 2009 *Tetrahedron Lett.* **50** 1622
19. Lannou M I, Helion F and Namy J L 2008 *Synlett* **1** 105
20. Azizian J, Mohammadi A A, Karimi A R and Mohammadzadeh M R 2006 *Applied Catal. A* **300** 85
21. Hashem S 2009 *Synth. Commun.* **39** 958
22. Singh M O and Devi N S 2009 *J. Org. Chem.* **74** 3141
23. Kumar K A, Kasthuraiah M, Reddy C S and Reddy C D 2001 *Tetrahedron Lett.* **42** 7873
24. Safari J and Gandomi-Ravandi S 2014 *New J. Chem.* **38** 3514
25. Zamani F and Izadi E 2013 *Catal. Commun.* **42** 104
26. Mistry S R, Joshi R S, Sahoo S K and Maheria K C 2011 *Catal. Lett.* **141** 1541
27. Rani V R, Srinivas N, Kishan M R, Kulkarni S J and Raghavan K V 2001 *Green Chem.* **3** 305
28. Kang L, Jin D and Cai Y 2013 *Synth. Commun.* **43** 1896
29. Narahari S R, Reguri B R, Gudaparthi O and Mukkanti K 2012 *Tetrahedron Lett.* **53** 1543

30. Rajack A, Yuvaraju K, Praveen C and Murthy Y L N 2013 *J. Mol. Catal. A* **370** 197
31. Ahmed N and Siddiqui Z N 2014 *J. Mol. Catal. A* **387** 45
32. Kolvari E, Koukabi N and Armandpour O 2014 *Tetrahedron* **70** 1383
33. Yuan C, Huang Z and Chen J 2012 *Catal. Commun.* **24** 56
34. Safari J and Zarnegar Z 2014 *New J. Chem.* **38** 358
35. Srivastava R 2010 *Catal. Lett.* **139** 17
36. Hallett J P and Welton T 2011 *Chem. Rev.* **111** 3508
37. Alvim H G O, de Lima T B, de Oliveira H C B, Gozzo F C, de Macedo J L, Abdelnur P V, Silva W A and Neto B A D 2013 *ACS Catal.* **3** 1420
38. Dadhania A N, Patel V K and Raval D K 2012 *J. Chem. Sci.* **124** 921
39. Shaabani A and Rahmati A 2005 *Catal. Lett.* **100** 177
40. Chavan S S, Sharma Y O and Degani M S 2009 *Green Chem. Lett. Rev.* **2** 175
41. Sharma N, Sharma U K, Kumar R and Richa Sinha A K 2012 *RSC Adv.* **2** 10648
42. Hajipour A R, Khazdooz L and Zarei A 2011 *Synth. Commun.* **41** 2200
43. Daily L A and Miller K M 2013 *J. Org. Chem.* **78** 4196
44. Siddiqui I R, Srivastava A, Shamim S, Srivastava A, Waseem M A, Rahila S, Abumhdi A H, Srivastava A and Rai P 2014 *J. Mol. Catal. A* **382** 126
45. Roy S R, Jadhavar P S, Seth K, Sharma K K and Chakraborti A K 2011 *Synthesis* **14** 2261
46. Elango K, Srirambalaji R and Anantharaman G 2007 *Tetrahedron Lett.* **48** 9059
47. Nagarajan S and Elango K 2014 *Catal. Lett.* **144** 1507
48. Liu Q, Pan N, Xu J, Zhang W and Kong F 2013 *Synth. Commun.* **43** 139
49. Ramalingan C and Kwak Y 2008 *Tetrahedron* **64** 5023
50. Heravi M M, Derikvand F and Bamoharram F F 2005 *J. Mol. Catal. A* **242** 173
51. Litvic M, Vecenaj I, Ladisic Z M, Lovric M, Vinkovic V and Litvic M F 2010 *Tetrahedron* **66** 3463
52. Wanmei L 2011 *Heterocycles* **83** 2067
53. Mukhopadhyay C and Datta A 2010 *J. Heterocycl. Chem.* **47** 136
54. Pore M D 2007 *Aust. J. Chem.* **60** 435
55. Misra A K, Agnihotri G and Madhusudan S K 2004 *Indian J. Chem. B* **43** 2018
56. Aridoss G and Jeong Y T 2010 *Bull Korean Chem. Soc.* **31** 863