



# A new dual basic ionic liquid promoted synthesis of spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile

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## Abstract

An efficient new dual basic task specific ionic liquid, 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide has been synthesized and explored as a catalyst for an eco-friendly synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile at ambient temperature. A broad variety of functional groups are tolerated without much affecting the yield of the product. Rapid, ecobenign reaction condition with high yields, operable under ambient temperature condition, greener ethanol:water (1:1) solvent system, easy work-up procedure, as well as isolation of product, excellent catalyst recyclability, high atom economy are the advantages of the present transformation.

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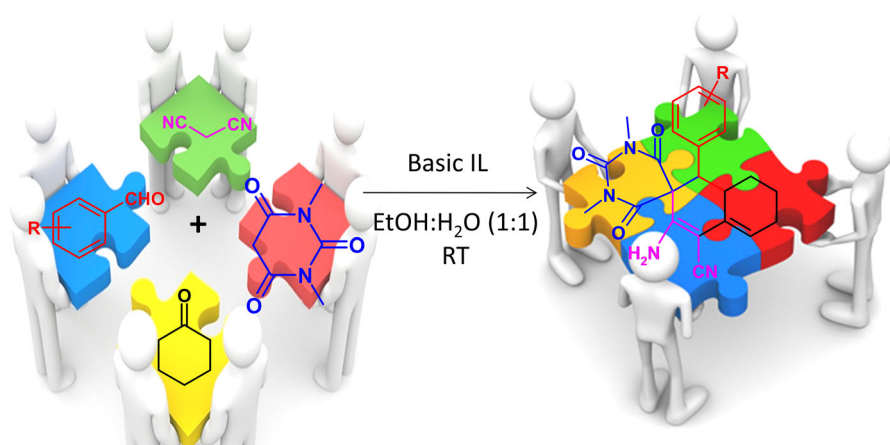
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## Graphical abstract



**Keywords** Lewis base · Bronsted base · Task specific · Reusability · Green chemistry

## Introduction

Ionic liquids (ILs) are emerging as a promising alternative to the existing volatile organic solvents because they have high thermal stability and very low volatility, which improve their reusability along with unique selectivity and reactivity [1–4]. Generally, ILs are used as a solvent, as they have a melting point below 100 °C, but today the use of ILs has changed beyond that. Almost every field of organic synthesis has used ILs. Also, ILs have been found to be extremely useful in various fields of analytical applications, physical study and in inorganic metal complex synthesis [5–8]. So, overall, research in ILs and research publications on ILs has increased exponentially. During the last couple of decades, there is a growing awareness regarding environmental problems, which arose due to use of harmful and hazardous organic matter, especially solvents, catalysts and reagents in view of the 12 Principles of Green Chemistry [9]. One of the best alternatives to this is the use of ILs for carrying out organic transformations.

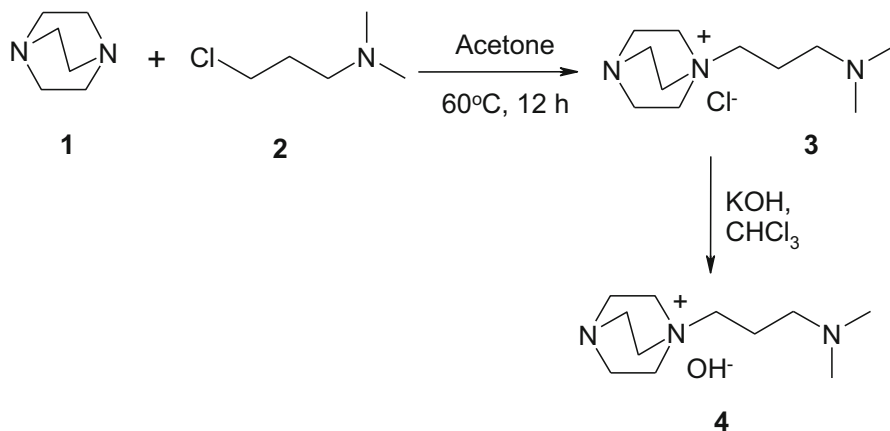
Recently, the concept of task-specific ionic liquids (TSILs) has become popular in synthetic organic chemistry. ILs equipped with specific functional groups either as cations or anions have been designed so that one of these can serve as a catalyst for the reaction [10–14]. Hence, an IL can be useful if the cations or anions of the IL act as a catalyst, catalyst activator, or cocatalyst for a reaction [15, 16]. In some of the literature it is found that the IL is deliberately prepared so that one of the ions serves as the catalyst for the reaction. Especially, the basic ILs along with any

functionality have attracted much more attention of young researchers on account of their strong catalytic activity, as well as ability to promote reactions in all media including protic and aprotic [17–19].

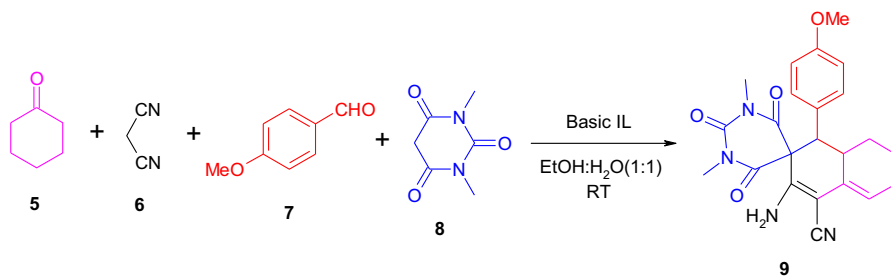
In light of this, we synthesized a new IL 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide comprising a Lewis basic cation and Bronsted basic anion. The synthesis of IL is depicted in Scheme 1. The synthesized IL was characterized by techniques such as  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR analysis (See Supporting information).

One-pot synthesis, sometimes also called multicomponent reaction (MCR), in organic synthesis is becoming a popular strategy for the preparation of structurally diverse chemical libraries of heterocyclic compounds [20–22]. This is because of its simplicity in terms of avoiding the separation of chemical intermediates, thus saving time and resources while trying to increase the reaction yield. Earlier, Khurana and his group [23, 24] synthesized the Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile derivatives by the use of catalyst DBU and ethylene glycol, which have their own merits and drawbacks. So we took this challenge, and with our earlier interest in MCRs and spiroheterocycles, [25, 26] herein we report the synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile derivatives by using synthesized dual basic IL as a catalyst.

The catalytic activity of IL 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide was investigated for the model reaction between cyclohexanone (1 mmol), malononitrile (1 mmol), anisaldehyde (1 mmol), and 1,3-dimethyl barbituric acid (1 mmol) at room temperature (Scheme 2). Initially, we began in different organic solvents such as toluene, 1,4-dioxane, DCM, Acetonitrile, DMF, DMSO, methanol and ethanol, as well as in aqueous medium. The results are summarized in Table 1. Either no formation or only a trace amount of the desired product was observed in toluene, 1,4-dioxane, DCM, acetonitrile, DMF, DMSO and water (Table 1, entries 1–6 and 9). However, in the case of methanol and ethanol the desired product was obtained in 80 and 95% yields (Table 1, entries 7–8). In



**Scheme 1** Synthesis of dual basic IL



**Scheme 2** Model reaction with anisaldehyde

**Table 1** Screening of solvent for synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile

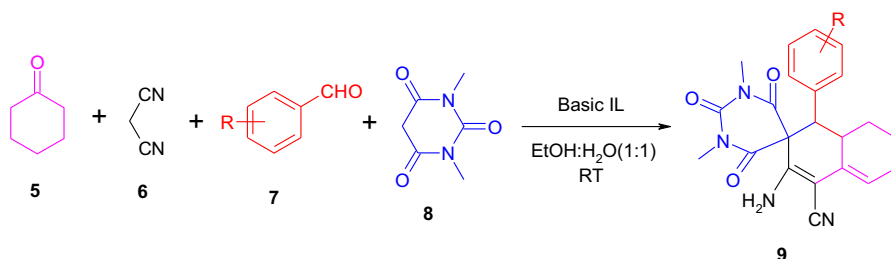
Entry	Solvent	Time in h	Yield <sup>a</sup>
1	Toluene	4	–
2	1,4-dioxane	5	–
3	DCM	4	30
4	Acetonitrile	5	34
5	DMF	6	trace
6	DMSO	4	55
7	Methanol	3	80
8	Ethanol	2.5	95
9	Water	6	40
10	Ethanol:water (1:1)	2.5	95
11	Ethanol:water (1:2)	3	60

Reaction condition: cyclohexanone (1 mmol), malononitrile (1 mmol), anisaldehyde (1 mmol), 1,3-dimethyl barbituric acid, IL (20 mol%), solvent (10 mL), at room temperature

<sup>a</sup>Isolated yield

addition to this reaction was also carried out using an ethanol and water, mixed solvent system. To check the output of the reaction we performed reaction in a 1:1 ethanol:water system and surprisingly we found an excellent result (Table 1, entry 10). But increasing the percentage of water did not improve the yield of the reaction. These results indicate the detrimental effect of the solvents on this transformation. For this study the synthesized IL was used as a catalyst (Scheme 3).

Different ILs were also examined for the model reaction (Table 2, entries 2–7). Only trace or a small amount of product was observed in the presence of IL 1, IL 2, IL 3 and IL 4 (Table 2, entries 2–5), whereas a moderate yield of product was found when IL 5 and some other traditional catalysts were employed (Table 2, entries 6, 10–14). Pleasingly, in the presence of a catalytic amount of IL 6, 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide, the reaction proceeded smoothly and furnished the desired product in 95% yield within 1 h (Table 2, entry 7). To examine the impact of catalyst loading on the model reaction,



**Scheme 3** General reaction for synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile

**Table 2** Screening of catalyst for synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile

Entry	Catalyst (mol%)	Time in h	Yield <sup>a</sup>
1	–	12	Trace
2	IL 1 (20)	5	50
3	IL 2 (20)	5	20
4	IL 3 (20)	5	25
5	IL 4 (20)	5	60
6	IL 5 (20)	3	80
7	<b>IL 6 (20)</b>	<b>1</b>	<b>95</b>
8	<b>IL 7 (20)</b>	<b>2</b>	<b>70</b>
9	IL 6 (10)	3	79
10	IL 6 (30)	1	95
11	K <sub>3</sub> PO <sub>4</sub> (20)	5	65
12	K <sub>2</sub> CO <sub>3</sub> (20)	6	40
13	TEA (20)	2.5	72
14	Morpholine (20)	4	65
15	Piperidine (20)	4	69

Reaction condition: cyclohexanone (1 mmol), malononitrile (1 mmol), anisaldehyde (1 mmol), 1,3-dimethyl barbituric acid (1 mmol), ethanol:water (1:1) (10 mL), at room temperature

<sup>a</sup>Isolated yield

an amount of IL 6 was varied from 10 to 30 mol% (Table 2, entries 9, 10). We also used IL 7 and got 70% of the reaction product (Table 2, entries 8). From Table 2, it can be concluded that 20 mol% of IL 6 was sufficient to catalyze the present transformation, yielding the desired product in 95%. No significant progress in the yield was observed even though 30 mol% was employed, whereas 10 mol% catalyst loading resulted into comparatively lower yield of product. The product formed precipitated from the reaction mixture. The work-up procedure involves simple filtration followed by washing with cold ethanol for purification. The structure of isolated products was confirmed by spectral techniques viz. IR, <sup>1</sup>H and <sup>13</sup>C NMR analysis. Thus, IL 6 was found to be the catalyst of choice for the present transformation with respect to yield and reaction time.

Thus, with the optimized reaction condition in hand obtained from Tables 1 and 2, further exploration for the scope of substrate and functional group tolerance was explored. The electron donating group aldehyde furnished the corresponding product in excellent yield, while the electron withdrawing group containing aldehyde take more time with little low yield. The reaction does not work well with aliphatic aldehydes, so no formation of desired product was observed. All the results are summarized in Table 3.

The plausible mechanism for the IL assisted formation of product 9 is proposed in Scheme 4. The basic IL favors formation of carbanion 11 which subsequently attacks on Knoevenagel product of aldehyde and 1,3-dimethyl barbituric acid to give intermediate 13. The reaction follows vinylogous Michael addition pathway. The intermediate 13 on intramolecular nucleophilic reaction to give 14, which isomerizes to give targeted compound 9 (Fig. 1).

### Green metric calculations

The effectiveness of the present protocol was cross checked in terms of green metrics calculations. These calculations were carried out using the procedures reported in the literature [27, 28] and their formulae are given in the following:

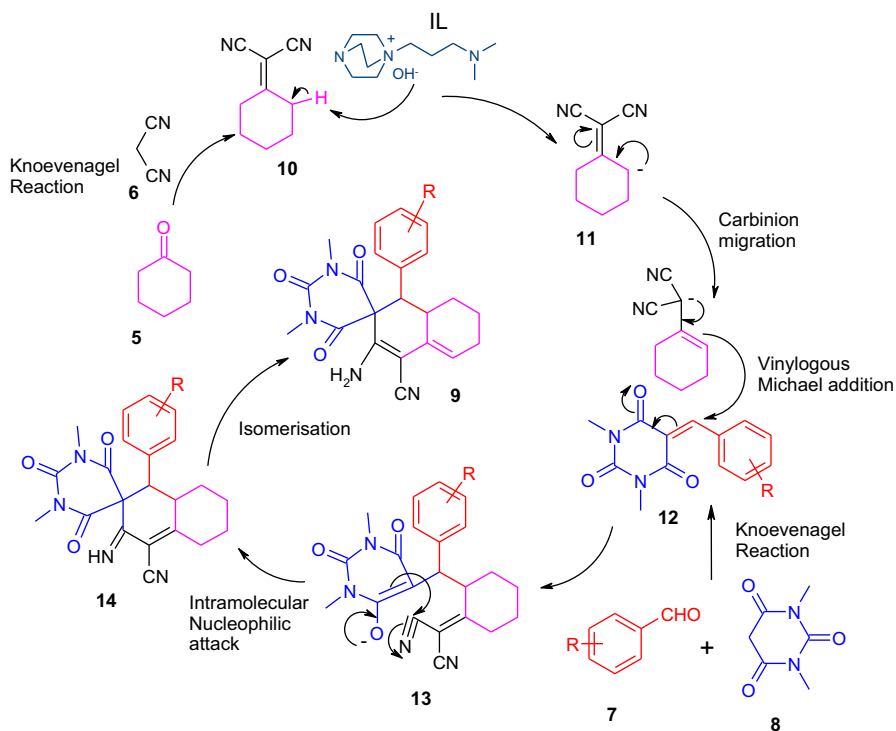
Mass intensity (MI) = Total mass used in a process or process step (g)/mass of product (g); reaction mass efficiency (RME) = ( $\sum$  mass of products/ $\sum$  mass of

**Table 3** Substrate screening

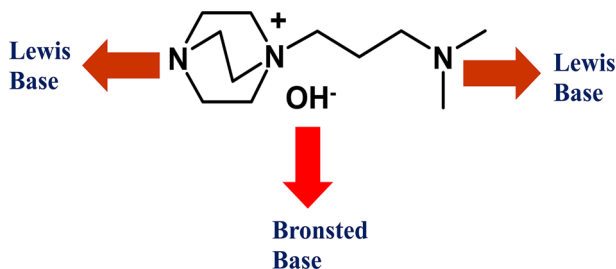
Entry	Aldehyde R	Time in h	Yield <sup>a</sup> %	M.P. [Lit.]
1	4-OMe	1	95	252–254 °C <sup>24</sup>
2	3,4-Cl	1.5	92	230–232 °C
3	4-NO <sub>2</sub>	4	88	249–251 °C <sup>24</sup>
4	4-N(CH <sub>3</sub> ) <sub>2</sub>	2	90	273–275 °C <sup>24</sup>
5	2-thiophene	3	87	236–238 °C <sup>24</sup>
6	4-OEt	1.5	93	279 °C
7	1-Naphthaldehyde	3	90	268–270 °C <sup>24</sup>
8	3-I, 4-OH, 5-OMe	2	91	255 °C
9	3-OCH <sub>2</sub> Ph	5	83	95 °C
10	4-CN	2	89	270–272 °C <sup>23</sup>
11	3,4-OMe	1.5	93	280 °C
12	4-Cl	3	87	284–286 °C <sup>24</sup>
13	4-Br	3	88	280–282 °C <sup>24</sup>
14	Cyclohexane carbaldehyde	6	–	–
15	Butaraldehyde	6	–	–

Reaction condition: cyclohexanone (1 mmol), malononitrile (1 mmol), aldehyde (1 mmol), 1,3-dimethyl barbituric acid (1 mmol), IL 6 (20 mol%), ethanol:water (1:1) (10 mL), at room temperature

<sup>a</sup>Isolated yield

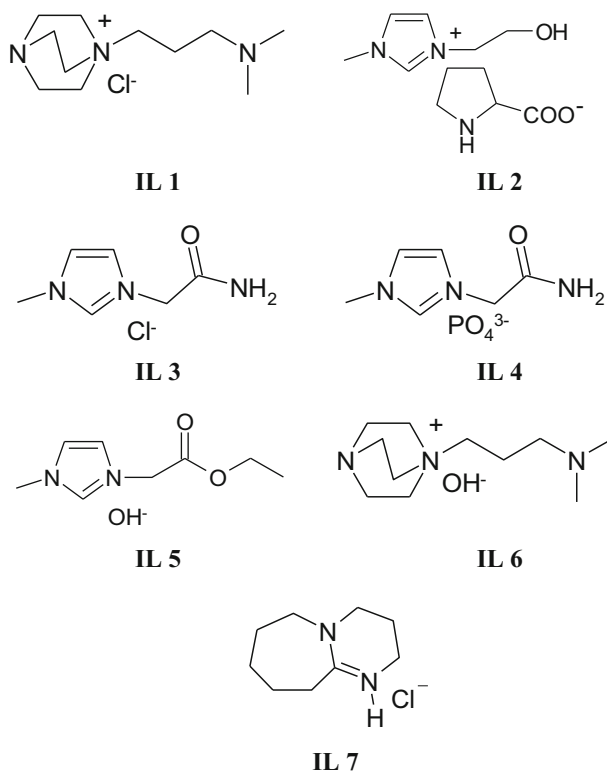


**Scheme 4** Plausible mechanism for Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile



**Fig. 1** Characteristic of dual basic ionic liquid

reactants)  $\times 100$ ; carbon efficiency (CE) = [(No. of moles of product  $\times$  No. of carbons in product) /  $\sum$  (No. of moles of reactant  $\times$  No. of carbons in reactant)]  $\times 100$ ; atom economy (AE) = [molecular weight of product /  $\sum$  molecular weight of reactant]  $\times 100$ . TON = mole of product/IL mole; TOF = TON/time in h. All the results are summarized in Fig. 2. The present procedure is highly efficient in terms of its carbon efficiency (CE), atom economy (AE) and reaction mass efficiency (RME). All these calculation reveals that method is near to ideal



**Fig. 2** Different ionic liquids (ILs) studied

condition in terms of green chemistry. Along with this we also calculated the turn over number (TON) and turn over frequency (TOF) of the used catalyst (for exact values please see supporting information) (Fig. 3).

**Fig. 3** Green metrics calculations

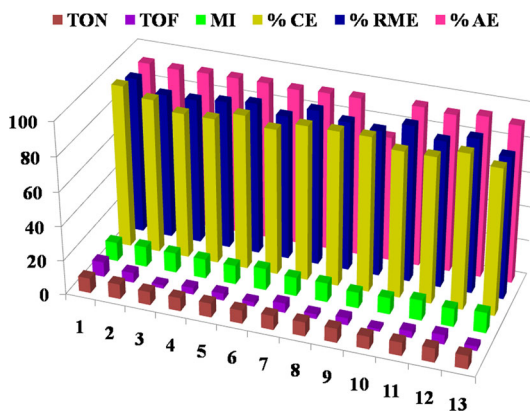
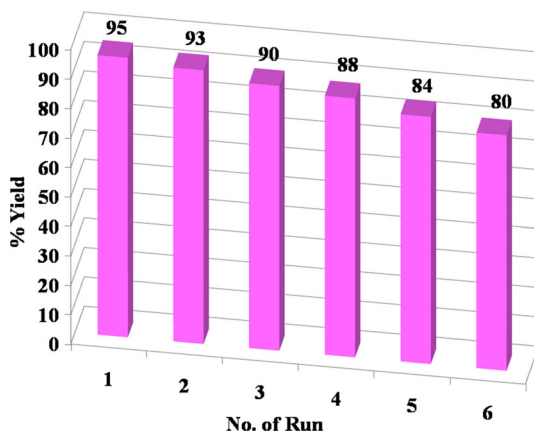




Fig. 4 Reusability study



### Reusability of ionic liquid

It is the main advantage of the present work that IL used can be recycled. After completion of the reaction as monitored by TLC, the solid product formed was filtered from the reaction mixture. The remaining filtrate was evaporated and washed with ethyl acetate to get the IL back. The recovered IL was dried at 60 °C and used for subsequent reaction, and it was found that IL can be used effectively at least six times without any significant loss in yield of the product. The drop in yield during reusability study might be due to a leaching effect, as earlier experiments reported [29, 30] (Fig. 4).

### Conclusion

In conclusion, we have synthesized a new dual basic IL utilized as a catalyst for the synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile from aldehydes, malononitrile, cyclohexanone and *N*-methyl barbituric acid using ethanol:water (1:1) system at ambient temperature. This reaction covers a enormous range of substrates with excellent yields of within short time span. The protocol also provides a sustainable route for the synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile. Advantages of this procedure are its simplicity, shorter reaction time, high yield, reusability of catalyst with high atom economy and it does not involve any purification technique such as column chromatography.

### Experimental

Melting points were measured by open capillary method and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrometer. NMR spectra were recorded on a BrukerAC-400 spectrometer in DMSO- $d_6$  using trimethylsilane as internal standard.

### Procedure for synthesis of IL 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide

3-chloro-*N,N*-dimethylpropan-1-amine (11 mmol) was slowly added to a vigorously stirred solution of bicyclo[2.2.2]octane, i.e. DABCO (10 mmol) in toluene (25 mL), at room temperature, and quarternisation was carried out at 80 °C for 24 h, after which it was cooled to room temperature for 1 h. Toluene was decanted and the remaining viscous oil was repeatedly washed with diethyl ether to yield a white viscous ionic liquid, which was dried in vacuum furnished 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium chloride.

1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (10 mmol) was then dissolved in dichloromethane and cooled to 0 °C followed by addition of potassium hydroxide (11 mmol) and stirred for 24 h at room temperature. The suspension was filtered to remove the precipitated potassium chloride salt and the solvent was evaporated under reduced pressure furnished 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide.

### Typical procedure for synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile

A mixture of cyclohexanone (1 mmol), malononitrile (1 mmol), aldehyde (1 mmol), *N*-methyl barbituric acid (1 mmol) and IL (20 mol%) in ethanol:H<sub>2</sub>O (1:1) (10 mL) was stirred at room temperature till the completion of reaction as monitored by TLC (Table 3). Then the solid formed after finishing the reaction was filtered and washed with cold ethanol to get the pure compound.

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