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[bmim(SO_3H)][OTf]/[bmim][X] and $Zn(NTf_2)_2$/[bmim][X] (X = PF_6 and BF_4); efficient catalytic systems for the synthesis of tetrahydropyrimidin-ones (-thiones) via the Biginelli reaction

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ABSTRACT

A facile, high yielding, and simple method for the synthesis of a library of dihydropyrimidinones (and -thiones) via the one-pot Biginelli reaction of aldehydes is reported. The method employs the Brønsted acidic IL [bmim(SO_3H)][OTf] or $Zn(NTf_2)_2$ as catalyst along with the readily available imidazolium-ILs as solvent, and exhibits good potential for the recycling and reuse of the IL solvent.

Due to their wide spectrum of biological activity and unique properties dihydropyrimidinones (DHPMs) have been the subject of intense research activity. These bioactive compounds can be synthesized via a multicomponent reaction (MCR)[1–3] by reacting β-ketoesters with aldehydes and urea or thiourea (for the corresponding thiones).[4,5] Over the years this classical method known as the Biginelli reaction has undergone many modifications and tweaking, employing numerous catalysts and conditions. The mechanism of this transformation (iminium, enamine, or Knoevenagel) has been debated, and can vary depending on the reaction conditions and substrate ratios. The keto-enol tautomerization equilibrium of the 1,3-dicarbonyl compound has been recognized as an important factor for the success of this reaction.[6]

In the past several years a large number of studies have utilized ionic liquids (ILs) in the Biginelli reaction. These included the use of Brønsted acid ILs bearing various counterions, under homogeneous, heterogeneous, solvent-free, and catalyst-free conditions, in some cases assisted by sonication or microwave irradiation.[7–18] Among various classes of Brønsted acidic ILs that have been used, triazolium, benzimidazolium, 1-sulfopyridinium, pyridinium, and *N*, *N*-diethyl-*N*-sulfoethanaminium ILs are not readily available, and their synthesis in many instances require harsh and corrosive reagents.[7–11] Most other classes of ILs that were employed, such as [Hbim], [Hmim], and [Et_3NH],[12–14] are prepared by protonation of the cationic core. Tethered sulfonic acid ILs were also utilized.[15] Other workers focused on designing heterogeneous systems in which the IL was embedded in mesoporous silica or in some other support material,[16,17] or by combinatorial protocol in which one of the Biginelli reaction components is bound to the IL.[18] The Lewis acid-catalyzed version of Biginelli reaction (using conventional solvents) have also been extensively studied over the years, with B(C_6F_5)$_3$ and Li(glycine)(OTf) as notable recent examples.[19,20]

Whereas these and other studies have led to many publications and demonstrated the versatility of this MCR process, it is unclear if they brought about major developments or a paradigm shift. These issues have been critically examined by Neto and associates[21–23] who extensively studied this transformation under a variety of condition using different ILs, and performed kinetic, mechanistic, and computational studies to clarify the facts, myths, and presumptions about this important reaction, focusing specially on solvent–free and catalyst-free studies. Their computational studies underscored the interaction of the cationic intermediates with the IL anion, and pointed to spontaneous formation of supramolecular aggregates. They also examined the Lewis-acid catalyzed version of this reaction in ILs and identified several metal-complexed

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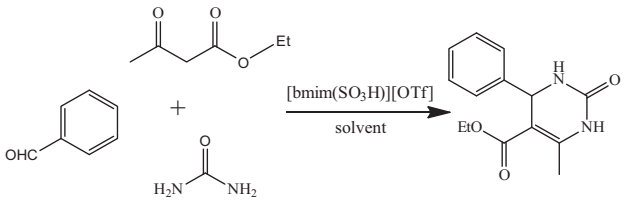
0040-4039/

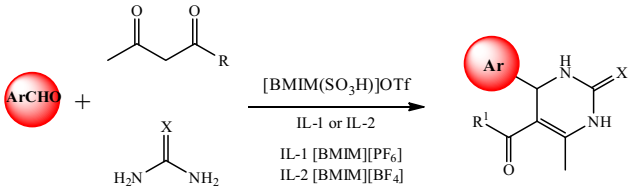
Table 1
Optimization of the reaction conditions with Brønsted-acidic IL as catalyst[a]



Entry	solvent	Catalyst load[b]	Time (h)	Temp (°C)[c]	Yield (%)[d]
1	[bmim(SO_3H)][OTf]	5 equiv	2	50	89
2	MeOH	15 mol %	4	60	58
3	EtOH	15 mol %	5	80	62
4	DCM	15 mol %	8	65	60
5	DCE	15 mol %	6	70	66
6	**[bmim][PF_6]**	**10 mol %**	**4**	**60**	**80**
7	[bmim][PF_6]	15 mol %	5	60	86[e]
8	**[bmim][PF_6]**	**15 mol %**	**8**	**60**	**88** [f]
9	[bmim][PF_6]	15 mol %	6	60	78 [f]
10	**[bmim][BF_4]**	**15 mol %**	**5**	**65**	**85**[e]
11	[bmim][BF_4]	15 mol %	6	65	76[f]
12	[bmim][BF_4]	15 mol %	6	65	68 [f]
13	[bmim][PF_6]	4 mol %	8	65	NR
14	[bmim][BF_4]	4 mol %	8	65	NR

[a] Benzaldehyde (1.0 mmol), ethylacetoacetate (1.1 mmol), urea (1.0 mmol), IL solvent (6–8 mL).
[b] Catalyst: [bmim(SO_3H)][OTf] for all entries.
[c] Oil bath temperature.
[d] Isolated yield of pure product.
[e] Yield using recycled IL (2nd cycle).
[f] Yield using recycled IL (3rd cycle); NR—no reaction.

Table 2
Substrate scope for the Biginelli reaction catalyzed by [bmim(SO_3H)][OTf] in IL-1 or IL-2[a]



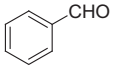
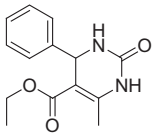
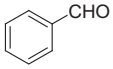
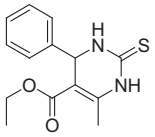
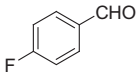
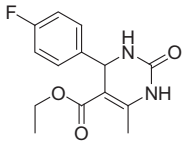
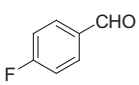
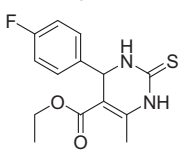
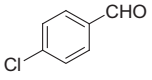
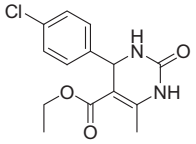
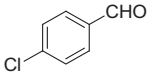
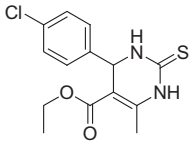
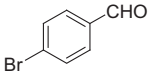
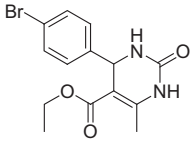
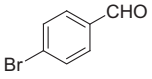
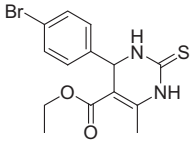
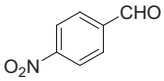
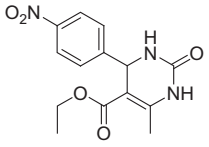
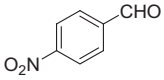
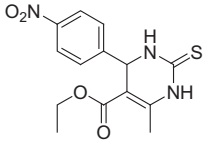
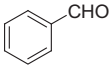
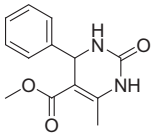
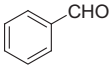
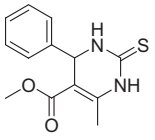
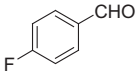
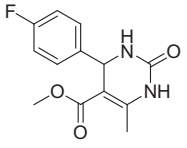
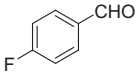
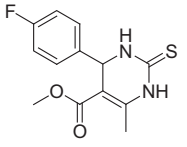
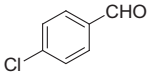
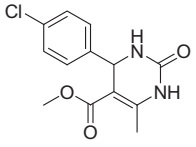
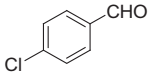
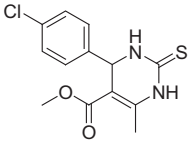
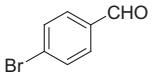
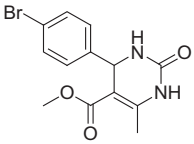
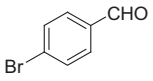
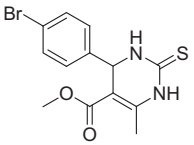
Entry	Aldehyde	R group	X	Product	Time (h)	IL	Yield (%)[b]
1		OEt	O		4	IL-1	86
2		OEt	S		4	IL-1	80
3		OEt	O		5	IL-1	74[c]
4		OEt	S		6	IL-1	68[d]

Table 2 (*continued*)

Entry	Aldehyde	R group	X	Product	Time (h)	IL	Yield (%)[b]
5		OEt	O		3	IL-2	92
6		OEt	S		4	IL-2	88
7		OEt	O		3	IL-2	80
8		OEt	S		4	IL-1	72
9		OEt	O		4	IL-1	72[c]
10		OEt	S		5	IL-1	70[d]
11		OMe	O		5	IL-1	87[c]
12		OMe	S		6	IL-1	80[d]
13		OMe	O		6	IL-2	86
14		OMe	S		6	IL-2	90
15		OMe	O		7	IL-2	80

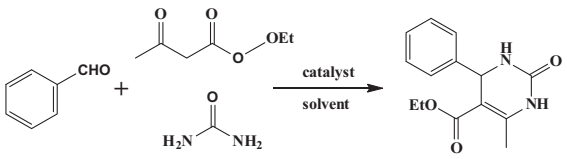
(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	R group	X	Product	Time (h)	IL	Yield (%)[b]
16		OMe	S		7	IL-1	84
17		OMe	O		6	IL-1	80[c]
18		OMe	S		6	IL-1	72[d]

[a] Aldehyde(1.0 mmol), β-ketoester (1.1 mmol), urea or thiourea (1 mmol), Brønsted acidic IL (15 mol %); IL solvent (6–8 mL).
[b] Isolated yield after purification.
[c] Isolated yield using recycled IL (2nd cycle).
[d] Isolated yield using recycled IL (3rd cycle); oil-bath temperature 60–65 °C.

Table 3
Optimization of the reaction conditions with $Zn(NTf_2)_2$ as catalyst and comparison with $Sc(NTf_2)_3$ in different IL solvents[a]



Entry	Catalyst[b]	IL	Temp[c] (°C)	Time (h)	Yield[d] (%)
1	$Zn(NTf_2)_2$	[bmim][Cl]	60	4	88
2	**$Zn(NTf_2)_2$**	**[bmim][PF_6]**	**60**	**3**	**92**
3	$Zn(NTf_2)_2$	[bmim][Cl]	80	6	76
4	**$Zn(NTf_2)_2$**	**[bmim][BF_4]**	**45**	**3**	**96**
5	$Zn(NTf_2)_2$	[bmim][BF_4]	50	4	88[e]
6	$Sc(NTf_2)_3$	[bmim][BF_4]	60	4	80
7	**$Sc(NTf_2)_3$**	**[bmim][PF_6]**	**60**	**6**	**86**
8	$Sc(NTf_2)_3$	[bmim][Cl]	80	6	67
9	$Sc(NTf_2)_3$	[bmim][BF_4]	50	4	84
10	$Sc(NTf_2)_3$	[bmim][BF_4]	50	3	77[e]
11	None	[bmim][BF_4]	50	6	43

[a] Benzaldehyde (1.0 mmol); ethylacetoacetate (1.1 mmol); urea (1.0 mmol); IL (6–8 mL).
[b] 10 mol % catalyst.
[c] Oil-bath temperature.
[d] Isolated yield of pure product.
[e] Isolated yield using recycled IL (2nd cycle).

adducts.[24] Taken together, these findings highlighted the importance of the iminium ion mechanism and the significance of the IL effect. It was suggested that the Lewis-acid is likely acting as pre-catalyst leading to in situ formation of the actual catalytic species.[24] An important function of the Lewis acid is to stabilize the enol form of the β-ketoester by coordination. The enol form is additionally stabilized by the IL, a stabilizing feature that would be lacking in the 'solvent-free' version of this reaction.

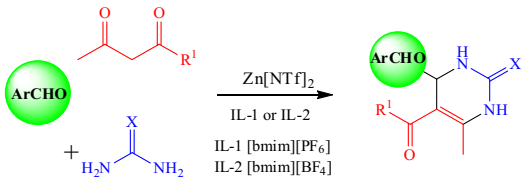
Our continuing interest in the application of ILs as catalyst and solvent in electrophilic and onium ion chemistry,[25–28] prompted the present investigation in which readily available, shelf-stable, imidazolium ILs were used as solvent along with catalytic amounts of Brønsted acidic IL, while catalytic amounts of $Zn(NTf_2)_2$ was employed in the Lewis acid-catalyzed version of this MCR. Both reactions were amenable to recycling and reuse of the IL solvent, and meet the positive improvement criteria proposed by Neto et al.[23] in terms of reactant ratios, catalyst amounts, reaction times, and yields.[29,30]

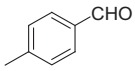
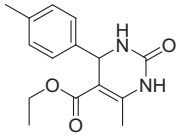
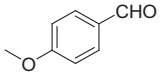
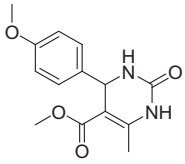
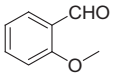
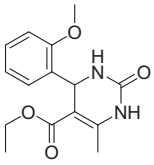
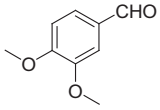
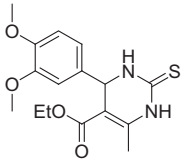
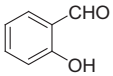
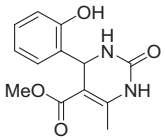
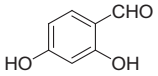
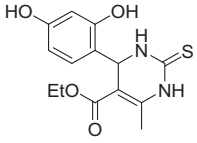
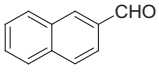
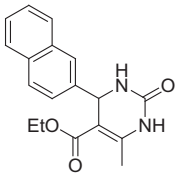
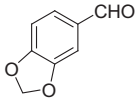
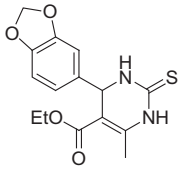
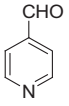
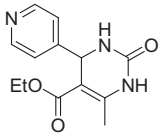
Table 1 shows the optimization study employing [bmim(SO_3H)][OTf] alone (entry 1) or in organic solvents (entries 2–5), and in [bmim][X] (entries 6–14) with 10% and 15% catalysts, reaching the highest conversions (entries 6, 8, and 10) under very mild temperatures, and with short reaction times.

The optimized conditions were subsequently applied to the study of the scope of the reaction by using various substituted ArCHO, employing both urea and thiourea (Table 2), with isolated yields ranging from 70% (*p*-NO_2) to 92% (for *p*-Cl).

In the next phase, optimization studies were performed for the Lewis acid-catalyzed version of this reaction using $Zn(NTf_2)_2$ as catalyst with [bmim][PF_6] and [bmim][BF_4] as solvent, and

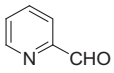
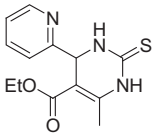
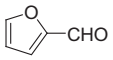
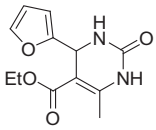
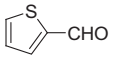
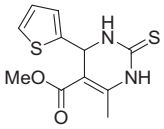
Table 4
Substrate scope for the Biginelli reaction catalyzed by $Zn(NTf_2)_2$ in IL-1 or IL-2[a]



Entry	Substrate R	Substrate R^1	Substrate X	Product	Time (h)	IL	Isolated yield[b] (%)
1		OEt	O		4	IL-1	94
2		OMe	O		4	IL-1	89
3		OEt	O		5	IL-1	82[c]
4		OEt	S		5	IL-1	78[d]
5		OMe	O		4	IL-2	90
6		OEt	S		4	IL-2	92
7		OEt	O		5	IL-2	88[c]
8		OEt	S		6	IL-2	80[c]
9		OEt	O		6	IL-1	76[d]

(*continued on next page*)

Table 4 (*continued*)

Entry	Substrate R	Substrate R^1	Substrate X	Product	Time (h)	IL	Isolated yield[b] (%)
10		OEt	S		5	IL-1	87
11		OEt	O		5	IL-1	86
12		Me	S		6	IL-1	80[c]

[a] ArCHO (1.0 mmol), β-ketoester (1.1 mmol), urea(1 mmol), 10 mol % $Zn(NTf)_2$; 6–8 mL of the IL at 55–65 °C.
[b] Isolated yield of pure product.
[c] Yield using recycled IL (2nd cycle).
[d] Yield using recycled IL (3rd cycle).

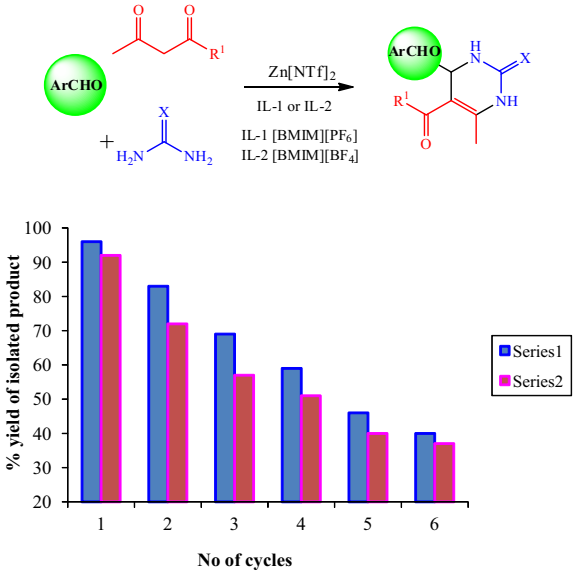


Figure 1. Recycling and reuse of the IL for a representative reaction. Series 1, [bmim][BF_4]; Series 2, [bmim][PF_6]. Reaction conditions: ArCHO (1.0 mmol), β-ketoester (1.1 mmol), urea (1 mmol), $Zn(NTf)_2$ (10 mol %); [BMIM][X] (6 mL); temp. 60–65 °C.

comparison was also made with $Sc(NTf_2)_3$ (Table 3). Both catalysts proved efficient but better yields were obtained with $Zn(NTf_2)_2$ at lower temperatures with shorter reaction times (see entry 4 in Table 3). Although [bmim][BF_4] performed better than [bmim][PF_6] (compare entries 2 and 4 in Table 3) the fact that this IL is somewhat soluble in Et_2O leads to a gradual loss of the IL during work-up, therefore [bmim][PF_6] was selected for study of the scope of the reaction (Table 4). Apart from various substituted benzaldehyde derivatives the study included a number of bicyclic and heterocyclic analogs, with isolated yields ranging from 76% to 94%.

The recycled/re-used IL was reemployed in a number of runs that are embedded in the tabulated data (Tables 3 and 4). In addition, this feature was separately tested for a representative reaction using $Zn(NTf_2)_2$ as catalyst. The results are shown in graphical format in Figure 1.

Summary

The present study has reinforced that this fundamental multicomponent reaction can be conveniently carried out in readily available, shelf-stable, ILs in combination with easy to prepare Brønsted acidic ILs or by Lewis acid activation using $Zn(NTf_2)_2$. The results are comparable and in many instances superior to those reported in less common/less-stable ILs whose synthesis require the use of corrosive and harsh reagents, or in other Lewis-acids, and the conditions are milder. We echo the comments by Neto et al.[23] that further studies of this useful MCR is warranted only if 'real' practical advantages can be demonstrated in systems that meet the improvement criteria listed in Ref. 23.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.103.

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29. *Synthesis of dihydropyrimidinones (or -thiones) catalyzed by Brønsted acidic IL or by Zn(NTf$_2$)$_2$* (Tables 2 and 4). The IL solvent (6–8 mL) was charged into a dry Schlenk tube and the aldehyde (1.0 mmol), β-ketoester (1.1 mmol), urea or thiourea (1 mmol) were added and the mixture was stirred at rt for 15–20 min. To the reaction mixture was then added [bmim(SO$_3$H)][OTf] (15 mol %) or Zn(NTf$_2$)$_2$ (10 mol %) and the mixture was gently heated at 60–65 °C or 55–65 °C respectively for the specified time (see Tables). The progress of the reaction was monitored by TLC and by GC–MS. After completion of reaction, the reaction mass was cooled to rt and the products were extracted with dry diethyl ether (4 times). Removal of solvent under vacuum furnished the crude products which were chromatographed with hexane/ethyl acetate (80:20) or DCM/MeOH (95:5) mixtures to afford the pure compounds. The purity of the isolated products was checked by TLC and GC, and they were subsequently characterized by ^{1}H and ^{13}C NMR, IR, GC–MS, and by elemental analysis.
30. *Recycling and re-use of the IL solvent*. The light brown-colored IL was dried overnight under vacuum at 60 °C and reused directly in subsequent runs, after which it was set aside for recovery and recycling as follows: the combined brown-colored IL recovered from several runs were dissolved in dry acetonitrile and filtered through Celite to remove insoluble brown particles. After removal of solvent from the filtrate under vacuum, the recycled IL was dried overnight under vacuum at 60 °C and reused in subsequent runs