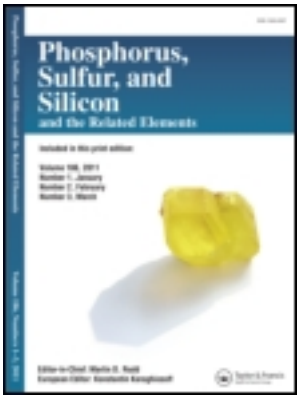

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BrØnsted Reusable Acidic Ionic Liquids Catalyzed Biginelli Reaction under Solvent-Free Conditions

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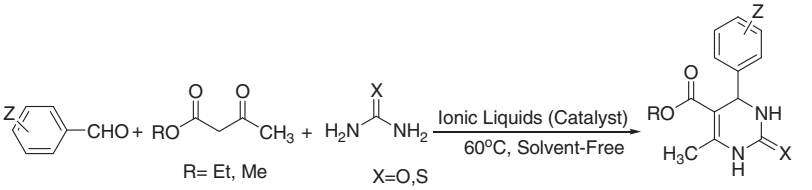
GRAPHICAL ABSTRACT



Z = H, Cl, Br, OH, NO_2, MeO, Me, $(Me)_2N$

Ionic Liquids = [Hnhp][HSO_4], [NMP][HSO_4], and [NMP][H_2PO_4]

Abstract *2-Pyrrolidonium hydrogensulfate,* N-*methyl-2-pyrrolidonium hydrogensulfate, and* N-*methyl-2-pyrrolidonium dihydrogenphosphate as Brønsted reusable acidic ionic liquids (ILs) catalyzed the preparation of 3,4-dihydropyrimidin-2(1*H*)-one (thione) derivatives from ethyl/methyl acetoacetate, urea/thiourea, and aromatic aldehydes under thermal solvent-free conditions.*

Keywords Biginelli reaction; ionic liquid; catalyst; solvent-free; aldehyde

INTRODUCTION

The Biginelli reaction was developed by Pietro Biginelli in 1891.[1] It is a multiple-component chemical reaction that creates 3,4-dihydropyrimidine-2-(1*H*)-ones (DHPMs) from ethyl acetoacetate, urea, and aryl aldehyde.[1] The reaction can be catalyzed by Brønsted acids and/or by Lewis acids.[2] DHPMs are pharmacologically important compounds because of the promising biological activities including antiviral, antibacterial, antitumor, and antihypertensive agents.[3,4] Furthermore, these compounds have emerged as the integral backbones of several calcium channel blockers.[3–5]

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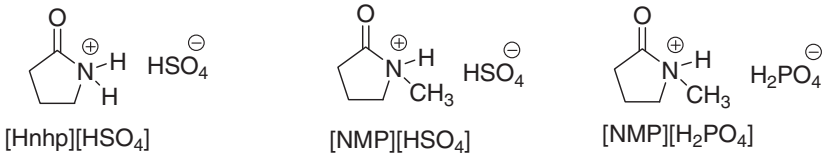
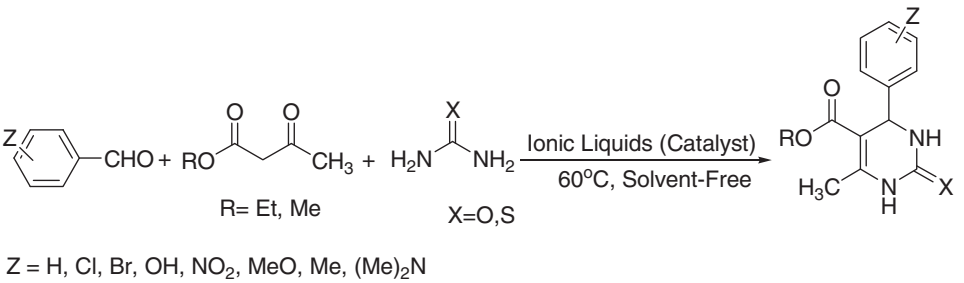


Figure 1 The structure of [Hnhp][HSO_4], [NMP][HSO_4], and [NMP][H_2PO_4].

Ionic liquids (ILs) are emerging as effective promoters and solvents for green chemical reactions.[6] One of the most important advantages of ILs is the behavior of solvophobic interactions that generate an internal pressure, which promotes the association of the chemical reactants and reagents and also shows an acceleration of MCRs in comparison to conventional solvents.[7] Brønsted acidic ILs (BAILs) have been deemed promising alternatives for acid-catalyzed reactions and play a dual solvent–catalyst role in a variety of reactions.[7,8]

Dihydropyrimidines have been synthesized using various ILs as catalyst such as [Hmim]HSO_4-$NaNO_3$,[9] [C_4mim][HSO_4],[10] tri-(2-hydroxyethyl) ammonium acetate,[11] BMImSac,[12] and [bmim][$FeCl_4$].[13] In continuation of our research on new synthetic methods in organic synthesis,[14,15] we developed the Biginelli reaction with three BAILs such as 2-pyrrolidonium hydrogensulfate ([Hnhp][HSO_4]), *N*-methyl-2-pyrrolidonium hydrogensulfate ([NMP][HSO_4]), and *N*-methyl-2-pyrrolidonium dihydrogenphosphate ([NMP][H_2PO_4]) (Figure 1) as catalysts (Scheme 1).



Scheme 1 The preparation of 3,4-dihydropyrimidin-2(1*H*)-one (thione) derivatives.

RESULTS AND DISCUSSION

In order to carry out the Biginelli condensation in a more efficient way, the reaction of ethyl acetoacetate (1.5 mmol), urea (1.1 mmol), and benzaldehyde (1.0 mmol) was selected as a model system under thermal solvent-free conditions to find optimization conditions. The preparation of 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one was studied at different reaction temperatures (25, 60, 80, and 100 °C) and different amounts of acidic ILs as catalyst (5, 10, 15, 20, 25, and 30 mol%) (Table 1). The

Table 1 Optimization of the amount of the acidic ILs, 2-pyrrolidonium hydrogensulfate (IL_1), *N*-methyl-2-pyrrolidonium hydrogensulfate (IL_2), and *N*-methyl-2-pyrrolidonium dihydrogenphosphate (IL_3), as catalysts at different temperatures in the reaction of ethyl acetoacetate (1.5 mmol), urea (1.1 mmol), and benzaldehyde (1 mmol) under solvent-free conditions

Entry	Catalyst (mol%)	Temperature (°C)	Time (min)			Yield (%)[a]		
			IL_1	IL_2	IL_3	IL_1	IL_2	IL_3
1	–	100	60	60	60	–	–	–
2	5	100	9	10	13	85	78	78
3	10	100	7	9	12	87	84	80
4	15	100	6	8	11	89	88	83
5	20	100	5	6	13	90	88	86
6	25	100	7	8	12	90	92	89
7	30	100	10	9	8	93	92	91
8	5	25	48	42	58	18	15	25
9	5	60	12	8	11	83	85	80
10	5	80	11	10	9	79	85	83

[a]Yields refer to isolated pure products.

best result was obtained by using 5 mol% of [Hnhp][HSO_4], 5 mol% of [NMP][HSO_4], and 5 mol% of [NMP][H_2PO_4] at 60 °C (Table 1).

Using these optimized reaction conditions, the scope and efficiency of the procedure was explored for the synthesis of a wide variety of substituted 3,4-dihydropyrimidin-2(1*H*)-ones (thiones). As shown in Table 2, aromatic aldehydes with both electron-withdrawing and electron-donating substituents reacted efficiently with urea (thiourea) and methyl/ethyl acetoacetate in the presence of a catalytic amount of [Hnhp][HSO_4] (5 mol%) or [NMP][HSO_4] (5 mol%) or [NMP][H_2PO_4] (5 mol%), forming the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones (thiones) without the formation of any side products, in good to high yields. We also used aliphatic aldehydes such as *n*-heptanal and *n*-octanal instead of benzaldehydes in the mentioned reactions. Experimental observation showed us that all the starting reactants were intact after 12 h without formation of any desired products and also byproducts (Table 2, Entries 22 and 23).

The suggested mechanism was presented according to the proposed mechanism in the literature.[9,10,15] The ILs catalyzed this transformation. In the cyclic catalytic mechanism (Scheme 2), the first step is the condensation between the aldehyde (1) and urea/thiourea (2), with some similarities to Mannich condensation and formation of acyl imine. The acyl imine (3) was activated with protonation in the presence of acidic ILs and afforded the intermediate (4). Then, the intermediate (4) reacted with CH acid of methyl/ethyl acetoacetate (5) and produced the intermediate (6). Subsequently, the ketone functional group undergoes condensation with the NH_2 of urea (thiourea) to give the cyclized Biginelli product.

We also compared the results of the present ILs with other catalysts reported in the literature such as [Hmim]HSO_4-$NaNO_3$,[9] [C_4mim][HSO_4],[10] tri-(2-hydroxyethyl) ammonium acetate,[11] $Al(HSO_4)_3$,[14] and Al_2O_3-SO_3H,[14] for synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones (Table 3). Table 3 clearly demonstrates that 2-pyrrolidonium hydrogensulfate, *N*-methyl-2-pyrrolidonium hydrogensulfate, and *N*-methyl-2-pyrrolidonium dihydrogenphosphate are effective catalysts in terms of reaction time and yield of obtained product relative to other reported catalysts.

Table 2 Preparation of 3,4-dihydropyrimidine-2-(1*H*)-ones (thiones)

				Time (min)			Yield (%)[a]			
Entry	Aldehyde	R	X	IL_1	IL_2	IL_3	IL_1	IL_2	IL_3	M.p. (°C)/Lit.M.p.[ref]
1	C_6H_5CHO	Et	O	12	8	11	83	85	80	201–203/[203–205][14]
2	$4\text{-}O_2NC_6H_4CHO$	Et	O	6	7	7	83	86	82	207–209 /[206–208][9]
3	$4\text{-}CH_3OC_6H_4CHO$	Et	O	39	27	43	75	80	76	207–208/[207–208][9]
4	$4\text{-}ClC_6H_4CHO$	Et	O	7	8	8	89	91	85	214–216/[214–215][9]
5	$4\text{-}HOC_6H_4CHO$	Et	O	12	15	18	66	72	75	227–230/[227–229][11]
6	$4\text{-}CH_3C_6H_4CHO$	Et	O	14	12	30	84	82	75	215/[214–217] [9]
7	$3\text{-}O_2NC_6H_4CHO$	Et	O	8	9	9	86	88	90	228–230/[230–232][9]
8	$3,4\text{-}(CH_3O)_2C_6H_3CHO$	Me	O	26	23	38	80	76	78	237/[238–240][10]
9	$4\text{-}O_2NC_6H_4CHO$	Me	O	6	5	7	86	88	84	235–236/[236–238] [9]
10	C_6H_5CHO	Me	O	10	9	12	65	84	79	210–212/[211–212][10]
11	$4\text{-}BrC_6H_4CHO$	Me	O	8	9	10	89	92	86	210/[210–212][10]
12	$2\text{-}BrC_6H_4CHO$	Me	O	6	9	8	83	85	87	220/[220–222][10]
13	$4\text{-}ClC_6H_4CHO$	Me	O	7	8	8	82	87	85	206–207/[206–208][10]
14	C_6H_5CHO	Et	S	120	120	120	55	58	62	204/[205–207] [14]
15	$4\text{-}O_2NC_6H_4CHO$	Et	S	58	40	63	78	72	81	108/[108–110] [14]
16	$4\text{-}HOC_6H_4CHO$	Et	S	95	78	112	89	92	90	194–195/[194–196] [14]
17	$3\text{-}CH_3OC_6H_4CHO$	Et	S	55	59	73	85	82	87	153–154/[150–152][14]
18	C_6H_5CHO	Me	S	120	120	120	58	61	60	219–220/[221–223][14]
19	$3\text{-}O_2NC_6H_4CHO$	Me	S	46	43	52	80	82	86	234–236/[237–239][14]
20	$4\text{-}HOC_6H_4CHO$	Me	S	72	67	62	90	85	88	226/[226–228][14]
21	$4\text{-}(Me_2N)C_6H_4CHO$	Me	S	58	49	42	78	79	76	150–152/[152–154][14]
22	*n*-Heptanal	Et	O	720	720	720				No reaction
23	*n*-Octanal	Et	O	720	720	720				No reaction

[a]Yield refers to isolated pure product. The molar ration of the starting reactants was chosen as: methyl/ethyl acetoacetate (1.5 mmol), urea/thiourea (1.1 mmol), and benzaldehyde (1 mmol); the reaction was carried out in an oil bath at 60 °C. All known products have been reported in the literature and they were characterized by comparing their melting point and IR and NMR spectra with authentic samples.[9-11,14]

In green organic synthesis, the recovery of the catalysts is more important. Thus, the reusability of the ILs as catalysts was studied. After the completion of the reaction, the mixture was cooled to r.t. and water (5 mL) was added to the reaction mixture. The IL was dissolved in water, and filtered for separation of the crude product. The separated product was washed twice with water (2 × 5 mL). To recover the ILs, water-containing ILs was evaporated, and the remaining viscous liquid was washed with CH_2Cl_2 (5 mL) and dried under reduced pressure. The recovered ILs were tested for studying their catalytic activity in the subsequent run without adding the fresh catalyst. The ILs were tested for 5 runs. It was seen that the ILs, as catalysts, displayed very good reusability without any considerable loss of their activities.

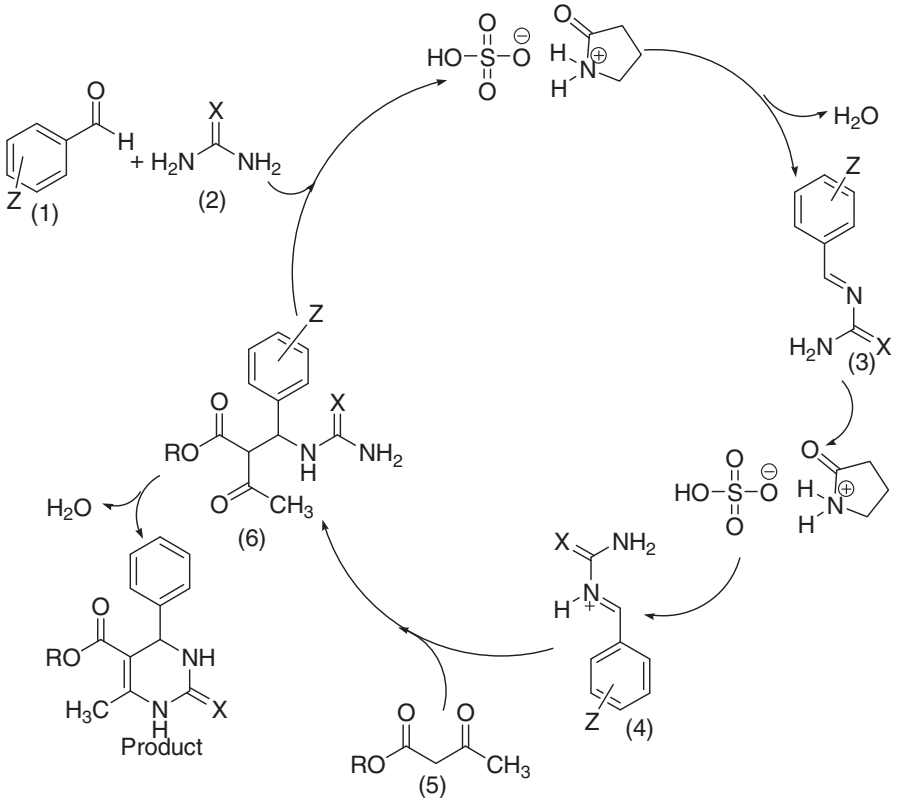
EXPERIMENTAL

All reagents were purchased from Merck (Darmstadt, Germany) and Aldrich (St. Louis, MO) and used without further purification. All yields refer to isolated products after purification. 2-Pyrrolidonium hydrogensulfate,[16] *N*-methyl-2-pyrrolidonium hydrogensulfate,[17] and *N*-methyl-2-pyrrolidonium dihydrogenphosphate[18] were prepared according to the literature procedure. The NMR spectra were recorded on a Bruker Avance DPX

Table 3 Comparison of the results of 2-pyrrolidonium hydrogensulfate, *N*-methyl-2-pyrrolidonium hydrogensulfate, and *N*-methyl-2-pyrrolidonium dihydrogenphosphate with other catalysts reported in the literature for synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones

Entry	Catalyst	Conditions	Time (min)	Yield (%)[a]	Ref
1	$[Hmim]HSO_4$-$NaNO_3$ (40 mol%)	80 °C	180	94	9
2	$[C_4mim][HSO_4]$ (10 mol%)	Microwave irradiation (150 W)/140 °C	5	80	10
3	Tri-(2-hydroxyethyl)-ammonium acetate, (62 mol%)	90 °C	360	88	11
		Microwave irradiation (200 W)/90 °C	4	90	
5	$Al(HSO_4)_3$ (10 mol%)	100 °C	35	79	14
6	Al_2O_3-SO_3H (15 mol%)	120 °C	126	88	14
7	$[Hnhp][HSO_4]$ (5 mol%)	Solvent-Free, 60 °C	12	83	This work
8	$[NMP][HSO_4]$ (5 mol%)	Solvent-Free, 60 °C	8	85	This work
9	$[NMP][H_2PO_4]$ (5 mol%)	Solvent-Free, 60 °C	11	80	This work

[a]Based on the reaction of ethyl acetoacetate, urea, and benzaldehyde.



Scheme 2 The proposed mechanism for 2-pyrrolidonium hydrogensulfate as selected ILs that catalyzed the preparation of 3,4-dihydropyrimidin-2(1*H*)-one (thione) derivatives.

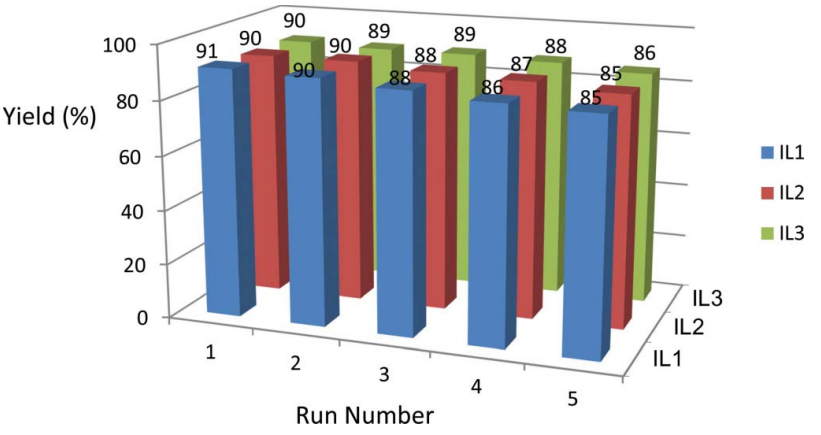


Figure 2 Reusability of ILs as catalysts. (Color figure available online).

300 MHz instrument (Germany). The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica-gel Poly Gram SIL G/UV 254 plates.

General Procedure for the Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (thione)

A stirred mixture of ethyl/methyl acetoacetate (1.5 mmol), aromatic aldehyde (1 mmol), and urea (thiourea) (1.1 mmol) and 2-pyrrolidonium hydrogensulfate (0.009 g, 5 mol%, 0.05 mmol) or *N*-methyl-2-pyrrolidonium hydrogensulfate (0.0098 g, 5 mol%, 0.05 mmol) or *N*-methyl-2-pyrrolidonium dihydrogenphosphate (0.0098 g, 5 mol%, 0.05 mmol) was reacted in an oil bath at 60 °C for the appropriate time (Table 2). After completion of the reaction, it was cooled to r.t. Then, water (5 mL) was added to the mixture. The IL was dissolved in water, and filtered for separation of the crude product. The separated product was washed twice with water (2 × 5 mL). The solid product was purified by recrystallization procedure in ethanol. To recover the ILs, after the isolation of insoluble products, water-containing IL was evaporated, and the remaining viscous liquid was washed with CH_2Cl_2 (5 mL) and dried under reduced pressure.

All known products have been reported in the literature and they were characterized by comparing their mp, IR, and NMR spectra with authentic samples.[9–11,14]

CONCLUSIONS

We have described a rapid and highly efficient method for the green synthesis of multisubstituted 3,4-dihydropyrimidine-2-(1*H*)-ones (thiones) using Brønsted reusable acidic ILs as catalysts under homogeneous catalysis and also thermal solvent-free reaction conditions. With such successful results, this convenient and efficient protocol should provide a superior alternative to the existing methods because of its fast and clean reactions and high yields. Furthermore, its simple workup procedure will make the present method useful and important for Biginelli synthesis.

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