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Brønsted Acidic Ionic Liquid: An Efficient and Reusable Catalyst for the Multi-Component Synthesis of Dihydropyrimidinones under Solvent-Free Conditions

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Abstract: An efficient and convenient procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones by condensation of 1,3-dicarbonyl compounds, Aromatic and aliphatic aldehydes, and urea or thiourea in the presence of catalytic amount of Brønsted acidic ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} under thermal solvent-free conditions reacted easily to afford the corresponding 3,4-dihydropyrimidin-2(1H)-ones and thiones. Straightforward and clean workup, short reaction time, good to excellent yields and reusability of the catalyst are the advantages of this method.

Keywords: Dihydropyrimidinone, Ionic liquid, Brønsted acidic, reusable catalyst, thiourea

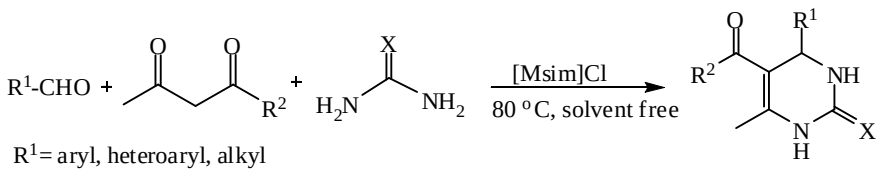
Introduction

Multi-component reactions (MCRs) are important synthetic tools that can be useful in the preparation of biologically and pharmacologically active compounds [1].

The Biginelli reaction is a well-known, simple and straightforward procedure for synthesis of 3,4-dihydropyrimidinones (3,4-DHPMs). 3,4-DHPMs are the most important class of multi-component reactions. These heterocyclic compounds have wide range of biological and pharmacological properties such as antiviral, antibacterial, anticancer, antitumor, and anti-inflammatory activities [2]. For example, they have been employed as calcium channel blocker [3], antihypertensive agents selective α_{1A} receptor antagonists [4] and neuro peptide Y(NPY) antagonists [5]. Moreover, several alkaloids containing the DHPM core unit have been isolated

from marine sources, which also exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD_4 inhibitors [6]. One of the most important methods for the synthesis of these compounds is three-component condensation of an aliphatic or aromatic aldehyde, β-ketoester and urea. The original reaction was first reported by Pietro Biginelli [7] in 1893 and was catalyzed by mineral acids. During the last few years, numerous catalytic methods and reaction conditions have been developed in order to improve the reaction yield, including the use of Lewis acids, milder protic acids or metal-based catalysts such as $NiCl_2.6H_2O$, $LaCl_3$ $.7H_2O$, $BF_3.OEt_2$, $InBr_3$, $LiClO_4$, $FeCl_3$, $InCl_3$ [8-10], I_2 [11], p-TsOH [12], microwave and ultrasound irradiation [13], solid-phase reaction [14], ionic liquids [15], and metal triflates [16].

Recently ionic liquids (ILs) have been widely used for various organic reactions. They have received considerable interest as eco-friendly solvents, catalysts and reagents in green synthesis because of their unique properties, such as low volatility, high thermal stability, negliable vapor pressure and ability to dissolve a wide range of materials [17-19]. Imidazolium salts having a Brønsted acidic group are important catalysts in organic synthesis. Herein, we report the synthesis of 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl an inexpensive, green, and efficient Brønsted acidic ionic liquid for the one-pot condensation of aldehydes with β-carbonyl (ethylacetoacetate or acetylacetone) and urea or thiourea for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones under solvent-free conditions (Scheme). The preparation of acidic IL 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl was developed on the basis of the previous report [20].



R^1= aryl, heteroaryl, alkyl
R^2 =CH_3, OCH_2CH_3
X= O, S

Experimental

General Information: All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Products were

characterized by comparison with authentic samples and by spectroscopy data (FTIR, ^{1}H-NMR and ^{13}C-NMR spectra, melting point). ^{1}H NMR spectra were recorded on a Bruker DRX-400 AVANCE spectrometer in $CDCl_3$ or DMSO as solvent. Melting points were determined on a thermo scientific IA9200 and are uncorrected and were uncorrected.

Typical procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones or thiones Under solvent-free conditions

A mixture of the aldehyde (1 mmol), β- carbonyl (ethylacetoacetate or acetylacetone (1.1 mmol), urea or thiourea (1.3 mmol), and 7 mol% of 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl (0.014g, 0.07 mmol) was heated in an oil bath at 80ºC for the specified time. The reaction was followed by thin-layer chromatography (TLC; EtOAc–Cyclohexane, (30:70). After completion of the reaction, the solidified mixture was cooled to room temperature and 5 ml cool water was added. The mixture was stirred for 5 min, and the product was filtered off. The products were purified by recrystallization from aqueous ethanol.

Result and Discussion

Initially, to optimize the reaction conditions, we studied the reaction of benzaldehyde (1 mmol), ethylacetoacetate (1.1 mmol) and urea (1.3 mmol) as a simple model substrate under different conditions (Table 1). We found that the best result was obtained when the reaction was carried out at 80ºC by using 7 mol% of ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl under solvent-free conditions (Table 1, entry 9). Using the same reaction conditions without ion liquid, the reaction gave trace products even after 180 min (Table 1, entry 13). According to these results, [Msim]Cl is necessary for this purpose. Reaction in different solvents was not suitable, and solvent-free conditions gave the best results, as demonstrated in Table 1, entries 1–3.

After optimizing the reaction conditions, the generality of these conditions to other substrates was studied by employing the reaction of various aromatic and aliphatic aldehydes with ethylacetoacetate or acetylacetone and urea or thiourea to produce the corresponding 3,4-dihydropyrimidin-2-(1H)-ones or thiones (Table 2). The aromatic aldehydes with electron-donating groups as well as electron-withdrawing ones gave the desired products in excellent yields within very short time (Table 2, entries 2-20). Also, the steric effects did not show any significant effect on the yields and reaction times (Table 2, entries 2, 5, 8, 11 and 13).

Table 1. Reaction of benzaldehyde, ethylacetoacetate, and urea in the presence of [Msim]Cl under different conditions [a]

Entry	Solvent	Catalyst (mol %)	Conditions (°C)	Time (min)	Yield (%)
1	Ethanol	7	Reflux	180	20
2	Ethyl acetate	7	Reflux	180	60
3	H_2O	7	Reflux	180	Trace
4	Solvent-free	7	RT	180	20
5	Solvent-free	5	60	60	60
6	Solvent-free	5	80	30	90
7	Solvent free	5	100	25	90
8	Solvent-free	7	60	80	95
9	Solvent-free	7	80	15	97
10	Solvent-free	7	100	30	90
11	Solvent-free	10	80	20	95
12	Solvent-free	10	100	30	90
13	Solvent-free	0	80	180	Trace

[a] benzaldehyde: ethylacetoacetate :urea, 1:1.1:1.3

However, when aliphatic aldehyde was used as the starting materials, the yield dropped significantly because of the lower activity of the carbonyl group in aliphatic aldehyde (Table 2, entry 25).

We also studied the reaction between terephthaldialdehyde (1 mmol) and excess amounts of ethylacetoacetate (2.2 mmol) and urea (2.6 mmol), and we observed that both formyl groups on the aromatic ring of terephthaldialdehyde were reacted and the corresponding product was obtained in good yield (Table 2, entry 26).

Table 2. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones catalyzed by [Msim]Cl

						Melting point (°C)		
Entry	R^1	R^2	X	Time(min)	Yield(%)[a]	Found	Reported	Ref.
1	C_6H_5-	OC_2H_5	O	15	97	204-206	204-206	[21]
2	2-ClC_6H_4-	OC_2H_5	O	20	95	212-213	213-214	[22]
3	3-ClC_6H_4-	OC_2H_5	O	35	90	191-192	190-193	[23]
4	4-ClC_6H_4-	OC_2H_5	O	30	87	212-213	213-214	[24]
5	2-BrC_6H_4-	OC_2H_5	O	20	84	207-208	206-208	[25]
6	3-BrC_6H_4-	OC_2H_5	O	35	90	190-192	190-192	[26]
7	4-BrC_6H_4-	OC_2H_5	O	30	85	219-222	219-221	[27]
8	2-$CH_3OC_6H_4$-	OC_2H_5	O	35	92	253-255	253-256	[27]
9	3-$CH_3OC_6H_4$-	OC_2H_5	O	25	93	217-220	216-219	[27]
10	4-$CH_3OC_6H_4$-	OC_2H_5	O	40	90	204-206	202-204	[28]
11	2-$NO_2C_6H_4$-	OC_2H_5	O	40	76	220	220	[29]
12	4-$NO_2C_6H_4$-	OC_2H_5	O	30	90	207-209	207-209	[30]
13	2-HOC_6H_4-	OC_2H_5	O	20	85	200-201	198-200	[31]
14	4-HOC_6H_4-	OC_2H_5	O	30	94	229-231	227-228	[32]

15	4-$CH_3C_6H_4$-	OC_2H_5	O	40	86	215-217	210-213	[33]
16	4-FC_6H_4-	OC_2H_5	O	20	92	181-183	179-180	[34]
17	4-$N(Me)_2C_6H_4$-	OC_2H_5	O	20	89	249-251	249-250	[27]
18	PhCH=CH-	OC_2H_5	O	35	85	226-228	230-231	[27]
19	2,4-di $CH_3C_6H_3$-	OC_2H_5	O	30	95	234-236	-	
20	4-HO-3-CH_3O-C_6H_3 -	OC_2H_5	O	20	95	233-235	232-233	[7]
21	1-Naphthyl-	OC_2H_5	O	40	80	252-253	253-254	[12]
22	2-Naphthyl-	OC_2H_5	O	35	85	206-208	210-212	[22]
23	2-Thienyl-	OC_2H_5	O	20	90	210-212	207-208	[23]
24	Terephthyl-	OC_2H_5	O	15	70	>300	>300	[19]
25	$(CH3)_2CH$-	OC_2H_5	O	45	60	197-198	195-197	[19]
26	C_6H_5-	OC_2H_5	S	35	85	204-206	206-207	[18]
27	4-ClC_6H_4-	OC_2H_5	S	30	90	183-186	184-185	[24]
28	4-$CH_3OC_6H_4$-	OC_2H_5	S	35	89	152-153	150-151	[19]
29	4-$CH_3C_6H_4$-	OC_2H_5	S	25	85	190-192	192-194	[25]
30	C_6H_5-	CH_3	O	20	90	233-235	236-237	[18]
31	4-$CH_3OC_6H_4$-	CH_3	O	35	95	160-162	169-170	[25]
32	4-$CH_3C_6H_4$-	CH_3	O	30	85	254-256	253-255	[26]
33	C_6H_5-	CH_3	S	20	89	199-201	210-212	[26]
34	4-$CH_3OC_6H_4$-	CH_3	S	25	92	171-173	168-170	[17]

[a] Reaction conditions: benzaldehyde: ethylacetoacetate :urea, 1:1.1:1.3 [Msim] Cl (7mol %) at 80 ^oC under solvent-free conditions

[b] The yields refer to the isolated pure products

The reusability of the [Msim]Cl was also determined. After each run, water was added to the reaction mixture and the product was filtered and the containing ionic liquid was extracted with CH_2Cl_2 (3 × 10 ml) to remove non-ionic organic impurities. Then the water was evaporated and the catalyst was dried at room temperature under reduced pressure for 2 h and reused in the reaction of benzaldehyde, ethylacetoacetate and urea (Table 3). The results show that the catalyst can be employed four times, although the activity of the catalyst gradually decreased. This indicates that the Brønsted acidic ionic liquid [Msim]Cl as a catalyst for the preparation of 3,4-dihydropyrimidin-2(1H)-ones and thiones is recyclable.

Table 3. The reusability of the catalyst

Run No.	1	2	3	4
Time (min)	15	15	20	20
Yield (%)[a]	97	97	95	95

[a] The yields refer to isolated products

Conclusion

We have developed a reusable catalyst for an efficient one-pot three-component synthesis of 3, 4-dihydropyrimidinones. The salient features of the present procedure are easy work-up, recyclability of the catalyst, short reaction time, solvent-free conditions and good to excellent yields.

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