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Bronsted acidic ionic liquid $[C_3SO_3HDoim]HSO_4$ catalyzed one-pot three-component Biginelli-type reaction: An efficient and solvent-free synthesis of pyrimidinone derivatives and its mechanistic study

Zhi-Lei Zhou, Peng-Cheng Wang, Ming Lu *

School of Chemical Engineer, Nanjing University of Science & Technology, Nanjing 210094, China

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ABSTRACT

A series of Bronsted acidic ionic liquids (ILs) were prepared and used for Biginelli-type condensation reaction among aromatic aldehydes, urea or thiourea and cyclopentanone. Through this reaction, the synthesis of various pyrimidinones could be achieved. Of interest, it was found that the reaction was efficiently catalyzed by a novel, eco-friendly functionalized IL $[C_3SO_3HDoim]HSO_4$, which could be reused for at least 7 times without significantly loss of catalytic activity. The reaction proceeded efficiently at 80 °C to afford the desired products in good yield (up to 96%). In addition, a possible mechanism that accounted for the IL $[C_3SO_3HDoim]HSO_4$-catalyzed reaction was proposed.

1. Introduction

The pyrimidinone skeleton has received considerable attention in recent years because of its existence in many natural or synthetic biologically active materials, and its derivatives have been applied to various pharmaceutical and biochemical fields [1,2]. It is of great interest that, specifically functionalized pyrimidinone may possess specific biological properties, such as antihypertensive, antiviral, antifungal and anticancer activities [3,4]. This has led to the development of various methods for the synthesis of pyrimidinone and its derivatives in the last few years.

Biginelli [5] reported that in concentrated hydrochloric acid, 3,4-dihydropyrimidine-2(*H*)-ketones were generated through a ring condensation reaction of ethyl acetoacetate, aromatic aldehydes and urea, which was now widely known as the Biginelli-type reaction. Its operation is simple, but the yield is low (20%–50%). In 2005, Pan [6] first described an efficient method for the synthesis of pyrimidinones by a three-component condensation with aromatic aldehydes, cyclopentanone, and urea or thiourea as starting materials. Although the reaction could proceed smoothly, the use of stoichiometric amount of TMSCl as an additional reagent and mixed CH_3CN/DMF as a reaction solvent were necessary to obtain the targets. In recent years, various synthetic methods for pyrimidine ketones have been developed, which can be roughly categorized as catalytic synthesis [7–10], solid synthesis [11], microwave-promoted synthesis [12] and so on. However, these methods mainly related to the study of classical Biginelli reaction, and the synthesis of pyrimidine ketone and its derivatives were seldom reported [13].

Metal-catalyzed reactions [14] are recognized as attractive and environmentally benign methods in synthetic organic chemistry. In this area, remarkable progress has been made in the applications of lanthanide reagents as catalysts in organic synthesis recently [15]. Zhang [16] described a method for the synthesis of pyrimidinones using a three-component condensation with aromatic aldehydes, cyclopentanone, and urea catalyzed by ytterbium chloride. But the costly metal catalysts are not readily available and they cannot be recycled and reused. In addition, reagent wasting and long reaction time make this method less appealing.

Considering the characteristics mentioned above, the room temperature ionic liquids have been described as one of the most promising new reaction mediums [17] because of their relatively benign characters, low volatility, thermal stability, efficiency as a catalyst and promoter, and reusability [18]. Bronsted acid ionic liquids (ILs) containing acidic protons that are adjustable to exhibit

* Corresponding author.
E-mail address: luming@mail.njust.edu.cn (M. Lu).

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desired catalytic activity. On the basis of previous pioneering work, a novel environment-friendly ionic liquid $[C_3SO_3HDoim]HSO_4$ was designed to catalyze the Biginelli-type condensation reaction, which exhibited dramatically efficiency in the course of the reaction with its sulfonic functional groups and long carbon chain. In addition, $[C_3SO_3HDoim]HSO_4$ can be successfully recovered and reused for several times.

2. Experimental

All reagents were of analytical grade and were purchased from commercial sources and used without any further purification. Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. ^1H NMR (500 MHz) was recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra was recorded on an Agilent technologies 6110 quadrupole LC/MS equipped with an electrospray ionization (ESI) probe operating in the positive ion mode. Yields refer to the isolated yields of the products after purification. All starting chemicals were commercially available. [HMim]X (X = HSO_4, HNO_3), [TEPSA]HSO_4 and $[C_3SO_3HMim]HSO_4$ were prepared according to literature procedures [19–21].

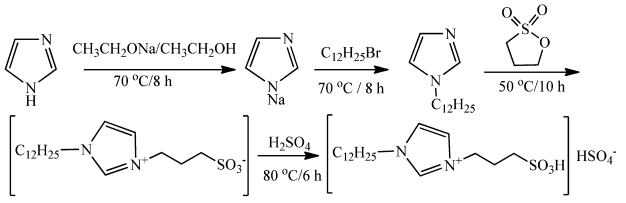
2.1. Preparation of $[C_3SO_3HDoim]HSO_4$

The synthetic process of $[C_3SO_3HDoim]HSO_4$ was shown in Scheme 1. First, imidazole (6.8 g, 0.1 mol) was dissolved in 100 mL of ethanol sodium ethoxide. The mixture was heated to 70 °C and kept at this temperature with stirring for 8 h under reflux [22]. Then an equal mole of 1-bromododecane was added and the system was allowed to stir for 8 h under reflux. The white precipitate was filtered off and the filtrate was extracted three times by diethyl ether followed by vacuum distillation to remove organic solvents to obtain *N*-dodecyl imidazole, a yellow viscous liquid at room temperature. *N*-Dodecyl imidazole was characterized by LC/MS.

Second, an equal mole of 1,3-propanesultone was added dropwise over a period of 10 min under stirring in an ice bath [23], after which the mixture was heated to 70 °C and kept at this temperature with stirring for 10 h, followed by the addition of an equal mole of sulfur acid (98%) with stirring. The mixture was then warmed to 90 °C and kept at this temperature for 2 h [21]. After that, diethyl ether was added and 1-dodecyl-3-(3-sulfopropyl)-imidazolium hydrogen sulfate ($[C_3SO_3HDoim]HSO_4$) was precipitated as a highly viscous and pale-yellow oily liquid. The product was dried under vacuum at 50 °C for 6 h giving a yield of 98%–99%. $[C_3SO_3HDoim]HSO_4$ was characterized by IR, ^1H NMR, ^{13}C NMR and LC/MS.

2.2. Typical procedure for the synthesis of pyrimidinones

A mixture of aromatic aldehydes (50 mmol), cyclopentanone (2.1 g, 25 mmol), urea or thiourea (25 mmol) and $[C_3SO_3H$-Doim]HSO_4 (5 mmol) was well stirred at 80 °C for a given time. After that, the system was cooled to room temperature. The pure



Scheme 1. The synthesis of 1-dodecyl-3-(3-sulfopropyl)-imidazolium hydrogen sulfate.

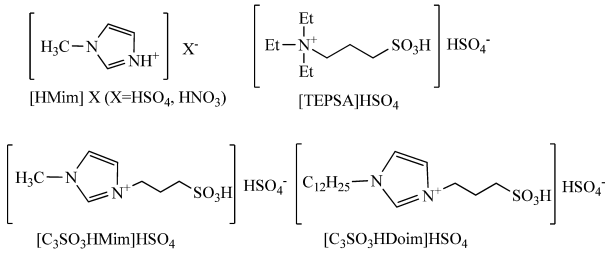


Fig. 1. Four kinds of ionic liquids.

product was isolated by filtering through a Büchner funnel and washed with water, diethyl ether and acetone, followed by crystallization from ethanol, and then dried to give the crystalline or powdered products [6].

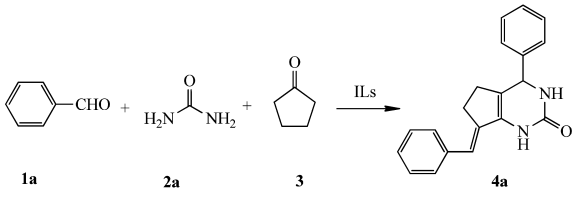
The spectral data of known compounds characterized by ^1H NMR were found to be identical with those reported in the literature [16,24].

3. Results and discussion

The experimental process could be easily achieved with simple operation under solvent-free conditions. Four ILs were prepared and used as catalysts for the Biginelli-type reaction, including $[HMim]HSO_4$, [TEPSA]HSO_4, $[C_3SO_3HMim]HSO_4$, $[C_3SO_3HDoim]HSO_4$. The structures were shown in Fig. 1.

The catalytic performance of different ILs was summarized in Table 1. During the experimental process, a mixture of three reagents, benzaldehyde, cyclopentanone, and urea was stirred at a suitable temperature in air in the presence of IL, which acted as a model reaction to optimize reaction conditions. As can be seen,

Table 1
Optimization of the reaction conditions.[a]



1a 2a 3 4a

Entry	ILs	Loading (mmol)	T (°C)	Time (h)	**1a:2a:3**	Yield (%)[b]
1	None[c]	0	80	1	2:1:1	49
2	$[HMim]HSO_4$	5	80	1	2:1:1	65
3	$[HMim]NO_3$	5	80	1	2:1:1	65
4	[TEPSA]HSO_4	5	80	1	2:1:1	74
5	$[C_3SO_3HMim]HSO_4$	5	80	1	2:1:1	75
6	$[C_3SO_3HDoim]HSO_4$	5	80	1	2:1:1	80
7	$[C_3SO_3HDoim]HSO_4$	2	80	1	2:1:1	75
8	$[C_3SO_3HDoim]HSO_4$	8	80	1	2:1:1	80
9	$[C_3SO_3HDoim]HSO_4$	10	80	1	2:1:1	79
10	$[C_3SO_3HDoim]HSO_4$	5	50	1	2:1:1	73
11	$[C_3SO_3HDoim]HSO_4$	5	100	1	2:1:1	78
12	$[C_3SO_3HDoim]HSO_4$	5	120	1	2:1:1	77
13	$[C_3SO_3HDoim]HSO_4$	5	80	0.5	2:1:1	72
14	$[C_3SO_3HDoim]HSO_4$	5	80	1.5	2:1:1	78
15	$[C_3SO_3HDoim]HSO_4$	5	80	2	2:1:1	75
16	$[C_3SO_3HDoim]HSO_4$	5	80	1	2:1:2	80
17	$[C_3SO_3HDoim]HSO_4$	5	80	1	2:2:1	79
18	$[C_3SO_3HDoim]HSO_4$	5	80	1	2:2:2	79
19	$[C_3SO_3HDoim]HSO_4$	5	80	1	2:3:2	78

[a] Reaction conditions: benzaldehyde/urea/cyclopentanone = 2:1:1, 80 °C, 1 h, $[C_3SO_3HDoim]HSO_4$ 5 mmol relative to aromatic aldehyde, solvent-free.
[b] Yields refer to those of purified isolated products.
[c] 98% H_2SO_4 (5 mL) was added in the reaction.

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$[C_3SO_3HDoMim]HSO_4$ was the most efficient one, giving the highest yield.

As shown in Table 1 (entries 1–6), in the absence of IL, the yield was only 49% using sulfuric acid as catalyst. The IL, $[C_3SO_3H$-Doim$]HSO_4$, was found to give the best result at 80 °C compared with other imidazolium salt-based ILs such as $[HMim]HSO_4$ and $[C_3SO_3HMim]HSO_4$, or hyamine-based ILs. The possible reason for this was that $[C_3SO_3HDoim]HSO_4$ with a distinct sulfonic functional group and long carbon chain could make it soluble in organic phase, which was beneficial for the interactions between catalyst and substrates. On the other hand, imidazole cation could form coordination bonds with the carbonyl oxygen, which performed better than the hyamine ion. With $[C_3SO_3HDoim]HSO_4$ as a model catalyst, the screening of catalyst loading was then carried out. The result revealed that 5 mmol% was the most suitable proportion, more loading or less could not enhance the product yield (entries 6–9). Reaction temperature significantly affected the reaction. The rise of the temperature from 50 °C to 80 °C led to an increased yield from 73% to 80% (entries 6 and 10), while a decreased yield was obtained when the temperature was over 100 °C (entries 11 and 12). Then the impact of reaction time on yield (entries 6 and 13–15) was investigated and the highest yield was obtained after 1 h. These results indicated that lower temperature and shorter reaction time may result in incomplete reaction while overheating and prolonged time led to complicated side reactions.

The ratio of benzaldehyde, urea and cyclopentanone should be 2:1:1 to produce pyrimidinones in theory. To explore the influence of the ratio on this reaction, we attempted to modify the ratio in various ways. Corresponding control reactions were performed and the results indicated that even when the amount of cyclopentanone or urea was doubled, there is almost no increase in yield (entries 6 and 16–19). In other words, excessively used cyclopentanone and urea barely enhanced the yield with the participation of $[C_3SO_3HDoim]HSO_4$, which is contrasted to the research of Zhang [16].

In addition, using $[C_3SO_3HDoim]HSO_4$ as a catalyst, the effect of gas and solvent on the reaction was also investigated, as shown in Table 2. N_2 was used as a protection gas to screen the reaction conditions compared with air (entries 1 and 2). The results showed that N_2 protection could increase the yield. In other words, materials in air containing CO_2, O_2, H_2O, *etc*. did not have an influence on the Biginelli-type reaction. Besides, four common organic reagents, such as toluene, benzene, *n*-hexane, *n*-heptane, were chosen as solvents in this reaction (entries 3–6). It was found that solvent-free condition under atmosphere gave the best result with a yield of 80% after 1 h. A probable reason would be that solvation effect hindered the catalytic effect of IL. So N_2 protection and organic solvent could be avoided to afford a simple and green process. Thus the reaction worked well while being exposed to air under solvent-free conditions.

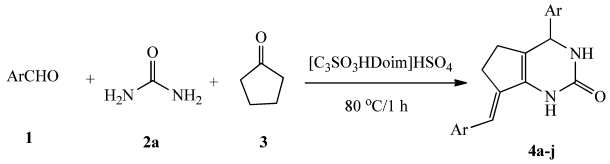
In order to examine the scope and generality of this procedure, we extended the methodology to different aromatic aldehydes.

Table 2
The effect of solvent and gas on the reaction.[a]

Entry	Solvent[b]	Gas	Yield (%)[c]
1	–	–	80
2	–	N_2	80
3	Toluene	N_2	77
4	Benzene	N_2	77
5	*n*-Hexane	N_2	78
6	*n*-Heptane	N_2	78

[a] Reaction conditions: benzaldehyde/urea/cyclopentanone = 2:1:1, 80 °C/1 h, the loading of ILs $[C_3SO_3HDoim]HSO_4$ (5 mmol) relative to benzaldehyde.
[b] The volume of added solvent was 50 mL.
[c] Yields refer to those of purified isolated products.

Table 3
Synthesis of pyrimidinones **4(a–j)** from aromatic aldehydes, cyclopentanone and urea.[a]



Entry	Ar	Time (h)	Yield (%)[b]	Product
1	Ph	1	80	**4a**
2	*p*-$CH(CH_3)_2$Ph	2	59(54)[c]	**4b**
3	*p*-CH_3OPh	2	75(70)[c]	**4c**
4	*o*-CH_3OPh	2	77	**4d**
5	*m*-CH_3OPh	2	66	**4e**
6	*o*-ClPh	1	76	**4f**
7	*m*-ClPh	1	82	**4g**
8	*p*-ClPh	1	85	**4h**
9	*m*-NO_2Ph	1	89	**4i**
10	*p*-NO_2Ph	1	96	**4j**

[a] Reaction conditions: aldehyde/urea/cyclopentanone = 2:1:1, 5 mmol $[C_3SO_3H$-Doim$]HSO_4$ relative to aromatic aldehyde, 80 °C.
[b] Yields refer to those of purified isolated products characterized by spectroscopic data (^{1}H NMR).
[c] The reaction time was run for 1 h.

Several substituted aromatic aldehydes were applied to this condensation reaction with cyclopentanone and urea to produce corresponding pyrimidinones. The results were summarized in Table 3. Aromatic aldehydes with both electron donating (entries 2–5) and electron withdrawing groups (entries 6–10) could participate this reaction effectively. Aldehydes with electron withdrawing groups reacted with cyclopentanone and urea smoothly to give the corresponding products in higher yields compared with the ones with electron donating groups. So we attempted to prolong the reaction time moderately for aldehydes with electron donating groups to increase the yields as much as possible (entries 2–5). In addition, the high stereo-hindrance effect was another vital reason for the relatively low yield as seen in the case of *para*-isopropylbenzaldehyde. We found that the nature and position of substitution on the aryl ring did have an influence on reactivity. Apparently, substrates with strong electron-withdrawing group (entries 9 and 10) gave evidently increased yields, compared with the weak ones (entries 6–8). In addition, the para-substituted aldehyde could afford a higher yield than the *meta*- and *ortho*-substituted ones. So it was proposed that as for the attack of carbon in aldehyde group by nucleophilic species, benzaldehyde with electron-withdrawing substituent group was easier than that with the electron-donating one.

Considering the widespread use of sulfur-containing intermediates in the medical fields [24], thiourea was used in place of urea in this reaction. Under the optimized conditions, the synthesis of pyrimidinones with aromatic aldehydes, cyclopentanone and thiourea was achieved, as shown in Table 4. In view of electronic effect, sulfur exhibited stronger electron-donating ability than oxygen. Thus, unlike urea, reactions of thiourea proceeded smoothly to give targeted products in yields ranging from 66% to 90% with high purity. But reaction time would be prolonged to achieve a higher yield. We believed that expanding the reaction from urea to thiourea would be meaningful to synthesize biologically active pyrimidinone scaffolds.

On the basis of our experimental results and literature reports about the synthesis of pyrimidinones [16,25], and previous studies of ILs-catalyzed condensation reactions [26,27], a possible mechanism for the synthesis of pyrimidinones catalyzed by $[C_3SO_3HDoim]HSO_4$ was proposed as shown in Scheme 2.

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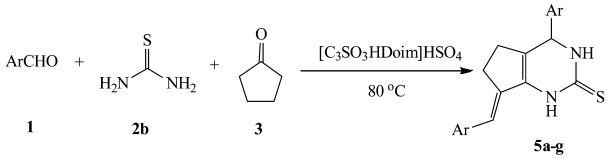
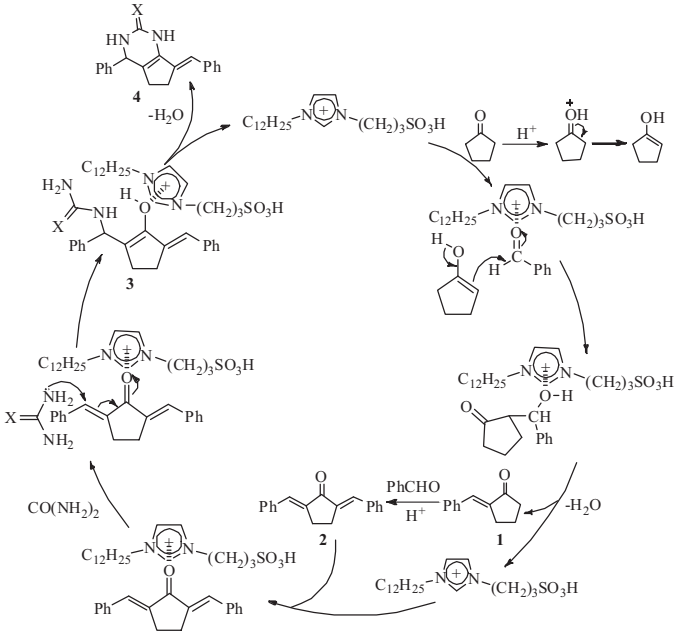
Table 4
Synthesis of pyrimidinones **5(a–g)** from aromatic aldehydes, cyclopentanone and thiourea.[a]



Entry	Ar	Time (h)	Yield %)[b]	Product
1	Ph	2	81	**5a**
2	*p*-CH(CH$_3$)$_2$Ph	3	66	**5b**
3	*p*-CH$_3$OPh	3	75	**5c**
4	*o*-CH$_3$OPh	3	78	**5d**
5	*m*-CH$_3$OPh	3	65	**5e**
6	*o*-ClPh	4	83	**5f**
7	*p*-NO$_2$Ph	4	90	**5g**

[a] Reaction conditions: aldehyde/thiourea/cyclopentanone = 2:1:1, 5 mmol [C$_3$SO$_3$HDoim]HSO$_4$ relative to aromatic aldehyde, 80 °C.
[b] Yields refer to those of purified isolated products characterized by spectroscopic data (^{1}H NMR).

[C$_3$SO$_3$HDoim]HSO$_4$ showed remarkable reactivity as an organic-phase catalyst, which considerably accelerated the reactions. It was probably due to its long chain with twelve carbons that allowed it to dissolve in the organic phase more easily compared with [C$_3$SO$_3$HMim]HSO$_4$ containing only one methyl. Thus, a hydrogen proton from [C$_3$SO$_3$HDoim]HSO$_4$ combined with ketonic oxygen in cyclopentanone to produce an enol form. Then the cross-aldol condensation of benzaldehyde with the enol form took place to generate keto-aldehyde **1** with the assistance of [C$_3$SO$_3$H-Doim]HSO$_4$, which was similar to the Yb(OTf)$_3$-catalyzed process reported by Wang [28]. Afterwards, keto-aldehyde **1** further reacted with another benzaldehyde resulting in the formation of keto-aldehyde **2** in the same way. Then compound **3** was generated through a Michael addition of urea or thiourea with keto-aldehyde **2**, followed by the removing a H$_2$O molecule and cyclizing to form the targeted compound **4**. When one round of condensation



Scheme 2. The possible mechanism for the synthesis of pyrimidinones catalyzed by [C$_3$SO$_3$HDoim]HSO$_4$ (X = O, S).

Table 5
Recyclability of recovered [C$_3$SO$_3$HDoim]HSO$_4$.[a]

Entry	Run	Yield (%)[b]
1	Fresh	80
2	1	81
3	2	80
4	3	79
5	4	78
6	5	78
7	6	77

[a] Reaction conditions: aldehyde/urea/cyclopentanone = 2:1:1, 5 mmol [C$_3$SO$_3$H-Doim]HSO$_4$ relative to aromatic aldehyde, 80 °C/1 h.
[b] Yields refer to those of purified isolated products characterized by spectroscopic data (^{1}H NMR).

reaction was finished, [C$_3$SO$_3$HDoim]HSO$_4$ was recovered and catalyzed the reaction over and over.

At last, the recycling performance of [C$_3$SO$_3$HDoim]HSO$_4$ was also investigated using the model reaction. After the separation of the products, the solvents in the filtrate were moved through rotary evaporation to recover [C$_3$SO$_3$HDoim]HSO$_4$, which could be reused without further purification. The data listed in Table 5 showed that the [C$_3$SO$_3$HDoim]HSO$_4$ could be reused at least 7 times without obvious reduction of the catalytic activity. Compared with the traditional catalysts, the easy recycling performance is also an attractive property of the [C$_3$SO$_3$H-Doim]HSO$_4$ for the environmental protection and economic reasons. The reason for the minimal loss in yield could be that the ILs run off with filtration and purification of the products. Upon our research, it can be seen that this ILs-catalyzed condensation reaction for the synthesis of pyrimidinones constituted an efficient, convenient, eco-friendly and most importantly recyclable system. Firstly, no poisonous auxiliary solvents were injected into the reaction, and the purification of the products was just performed through filtration, washing and crystallization. Second, the reaction worked well while being exposed to the air, so the steps of drying and protecting were avoided. In addition, reusability of ILs led to an economical and environmental benign process.

4. Conclusion

In conclusion, the present procedure using a novel functionalized IL [C$_3$SO$_3$HDoim]HSO$_4$ as catalyst, provides a very simple and efficient methodology for the synthesis of pyrimidinone and its derivatives through the condensation of aromatic aldehydes, cyclopentanone and urea or thiourea. In addition to short reaction time, low energy consumption, high yields, and reusability of ILs, no hazardous organic solvents are used in the entire processes including workup and purification. These eco-friendly features provide an attractive method to synthesize pyrimidinones.

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