Green Process Synth 2019; 8: 568–576 **DE GRUYTER**

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Deep eutectic solvents (DESs) as powerful and recyclable catalysts and solvents for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones

https://doi.org/10.1515/gps-2019-0026
Received August 11, 2018; accepted March 26, 2019.

Abstract: Deep eutectic solvents (DESs) are successfully used as powerful and recyclable catalysts and solvents for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (DHPMs). The acidity of DESs is the main factor that determines catalytic activity. DESs, based on *p*-toluene sulfonic acid (PTSA) and choline chloride (ChCl), exhibits the highest catalytic activity. ChCl/2PTSA is suitable for a vast variety of aromatic aldehydes with electron-donating and electron-withdrawing groups, different β-diketonates, and urea or thiourea to obtain the corresponding DHPMs. Furthermore, DESs can be recycled easily after synthesis. The reused DESs achieve catalytic efficiency six times without significant changes. This study will provide a new green catalyst and efficient process for the synthesis of DHPMs.

Keywords: deep eutectic solvents; 3,4-dihydropyrimidin-2(1*H*)-one/thiones; Biginelli reaction; green catalyst

1 Introduction

In recent years, green synthesis processes actively seeks new solvents to replace common organic solvents that present inherent toxicity and have high volatility. Deep eutectic solvents (DESs), as ionic liquids analogues, have attracted considerable attention from researchers because of their environment performance. They do not only posses the advantages of ionic liquids, such as designability, chemical stability, and low vapor pressure, they also pose many other advantages, such as diversity, low-cost and easily sourced raw materials, and green and simple synthesis without using other organic solvents [1-3]. Therefore, DESs are good alternatives to volatile organic solvents as green solvents. In recent years, DESs have been widely used in organic reactions [4-6], materials preparation [7], electrochemistry [8,9], separation process [10,11], and so on. Moreover, as novel reaction media or catalysts, DESs have been widely used in traditional organic synthesis reactions. For example, choline chloride-zinc chloride ($[ChCl][ZnCl_2]_2$) based DESs could be used for catalyzing Friedel-Crafts alkylation of electron-rich arenes with aldehydes [12]; Imperato et al. reported the use of carbohydrates, sugar alcohols or citric acid, with urea and inorganic salts based DESs as reaction media for Diels-Alder reaction [13]; The Knoevenagel condensation proceeded smoothly in reusable and cheap DESs (choline chloride/urea) [14]; The enzyme-catalyzed Henry reaction was realized using choline chloride-based DESs as reaction medium [15]; Choline chloride and urea based DESs provided an efficient and convenient method for Perkin reaction [16]; Urea or glycerol with choline chloride were effective solvents/catalysts for Paal-Knorr reactions [17].

3,4-Dihydropyrimidin-2(1*H*)-ones/thiones (DHPMs) have high pharmacological and therapeutic activities, such as antibacterial, antiviral, antitumor, calcium antagonistic and antihypertensive [18-20]. Thus, synthesizing DHPMs has attracted considerable attention in the area of synthetic chemistry by using the multicomponent reactions (MCRs) [21]. Generally, DHPMs can be synthesized by reacting β-ketoesters with aldehydes and urea or thiourea [22]. However, the low yield of the Biginelli reaction has limited its applications in substituted aromatic and aliphatic aldehydes. Selecting suitable catalysts has become the key point in solving this limitation. Brønsted acids or Lewis acids, such as HBF_4 [23], $H_3PW_{12}O_{40}$ [24], $InBr_3$ [25], $ZrCl_4$ [26], $Fe(OTs)_3{\cdot}6H_2O$ [27], and $Ce(NO_3)_3{\cdot}6H_2O$ [28], have been traditionally used as catalysts. In recent years, some novel catalysts, including organocatalysts [29,30], biocatalysts [31], immobilized

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urease [32], PS-PEG-SO_3H [33], Ti-graftedpolyamidoamine dendritic silica hybrid catalyst [34], halogenated macroporous sulfonic resins [35], polyaniline-supported $FeCl_3$ [36], cobalt supported on alumina catalyst [37], and ionic liquid [38-41] have attracted great attention for use in the Biginelli reaction. These catalysts, for their uses in accomplishing the Biginelli reaction, have produced varying degrees of success. However, some of these catalysts are harmful to the environment and have other disadvantages, such as sensitive reaction conditions, complex preparation process, and use of hazardous reagents. Recently, the use of environmentally suitable, economically viable, and green catalysts for organic synthesis has gathered interest. Therefore, developing new green catalytic processes with increased efficiency and selectivity is necessary.

Our group designed, synthesized, and applied DESs in previous research. The results showed that the concise control of the acidity of DESs can be modified by changing the hydrogen bond donors (HBDs) and hydrogen bond acceptors (HBAs). Biginelli reaction was occurred under acidic conditions. This finding inspired us to design new acid DESs for the synthesis of DHPMs. The synthesis of DHPMs using DESs have been reported in the literature [42-45], however, the types of DESs is limited and catalytic activities need to be further improved. Therefore, the development of new types of DESs catalysts with high efficiency is an important subject in the field of synthesis of DHPMs.

In this work, some novel DESs with different acidities were designed, synthesized and applied as powerful and recyclable catalysts and solvents for synthesizing DHPMs. The reaction system based on DESs benefits from the benign reaction conditions, high catalytic activity, easy work-up procedures, feasible reusability and wide substrates tolerance. The specific synthesis was successful and obtained a variety of DHPMs with reduced reaction time and increased yields. Choline chloride (ChCl), tetrabutylammonium bromide (TBAB), tetrabutyl ammonium chloride (TBAC), tetrabutyl ammonium acetate (TBAA), tetraethylammonium chloride (TEAC), and tetraethylammonium bromide (TEAB) were chosen as typical HBAs; and *p*-toluenesulfonic acid (PTSA), trichloroacetic acid (TCA), monochloroacetic acid (MCA), propionic acid (PA), and ethylene glycol (EG) were chosen as HBDs to control the acidity of DESs, through which different DESs with acidity gradients were synthesized. The above DESs were used as catalysts and solvents for the Biginelli reaction of benzaldehyde, ethyl acetoacetate and urea; moreover, this was selected as the model reaction to optimize the synthesis conditions. Some important parameters, such as system temperature, reaction time, and amount of DESs, as well as the different kinds of aromatic aldehyde, were investigated. Furthermore, the possible catalytic mechanisms were studied.

2 Experimental

2.1 Chemicals and instruments

Chemicals were purchased from Aladdin Reagent Co., Ltd. (Shanghai) and J&K Scientific LTD. ^1H and ^{13}C NMR spectra were recorded on a Bruker Ascend 500 spectrometer. FT-IR analyses were carried out on a Nicolet IS-10 using a single reflection ATR cell.

2.2 Synthesis of DESs

Purified HBAs and HBDs were mixed at a certain molar ratio (mostly 1:2 in this research). DESs were prepared by using different processes to meet the requirements from the final products. ChCl and TCA (or MCA) were grinded with a mortar and pestle at room temperature until a homogeneous liquid was formed [46]. ChCl and PA was stirred at room temperature until a homogeneous liquid was formed. The above methods were applied to prevent the formation of ester impurities between ChCl and the acid. The other DESs were synthetized by heating, in which the systems were stirred vigorously with a magnetic stirrer at 80°C for 4h to obtain pure DESs. The details of the synthesis were reported in our previous literature [47]. The properties of the synthesized DESs, which can be of great significance for future industrial applications, were investigated [48]. The FTIR and ^1H NMR spectra of DESs were shown in Figures S1-S5 of the Supplementary material.

2.3 General procedure for the synthesis of DHPMs

The mixture of aromatic aldehyde (2.0 mmol), methyl (or ethyl) acetoacetate (2.0 mmol), urea (or thiourea) (3.0 mmol), and DESs were stirred at 70°C for a certain time. Completion of the reaction was monitored by thin layer chromatography. After the completion of the above reaction, the mixtures were cooled to room temperature (25°C). Water was added into the mixtures to separate the DESs and final products. It is worth mentioning that the products were easily separated with high yield and DESs were easily recovered and reused. After adding water to the reaction system, the DESs was dissolved in water, and the final product was separated by filtration due to its insolubility in water. Then the filter cake washed with water repeatedly, and recrystallized in ethanol to obtain the pure products. The DESs contained in filtrate were recovered by evaporating the water and drying under reduced pressure. All the experiments in this study were performed in triplicate to determine its reproducibility, and the experimental errors were within 3%. All the synthesized products were characterized based on their spectra (^{1}H and ^{13}C NMR).

3 Results and discussion

3.1 Selection of DESs

Generally, Biginelli reaction is carried out in acidic conditions. However, the acidity of the reaction process is difficult to control precisely. Fortunately, one of the advantages of DESs is the simple control of its acidity, which can be achieved by selecting the appropriate HBDs. Thus, the selection of HBD is important for the Biginelli reaction process. With the above considerations, a series of DESs was designed and synthesized according to the acidity of the HBDs. In this way, the acidity of DESs can be controlled precisely. ChCl was chosen as the HBA, and PTSA, TCA, MCA, PA, and EG were chosen as HBDs. A series of DESs was prepared and applied as catalysts and solvents for the Biginelli reaction. The selection of DESs was probed, and the results are shown in Figure 1. The HBDs referring to organic acids or alcohols showed greater influence on the reaction process. The catalytic capabilities decreased with reducing acidity of HBDs. ChCl/2PTSA exhibited the highest yield of DHPM product and reached 88% with DESs of 0.4 mmol. Thus, PTSA was more preferred as HBD than the other acids for the specific reaction. Afterward, the influences of different molar ratios of ChCl and PTSA on the yield were discussed. When the molar ratios of ChCl and PTSA were 1:0.5, 1:1, and 1:2, the DHPM yields were 63%, 74%, and 88%, respectively. Thus, the HBA to HBD at a molar ratio of 1:2 was preferable. Moreover, HBAs were observed to have little influence. DESs based on quaternary ammonium salts had the same catalytic activities with those of the ChCl-based DESs. Compared with quaternary ammonium salts, ChCl was cheaper, greener, and easier to biodegrade. Thus, ChCl/2PTSA was chosen as the typical catalyst and solvent in the following experiments.

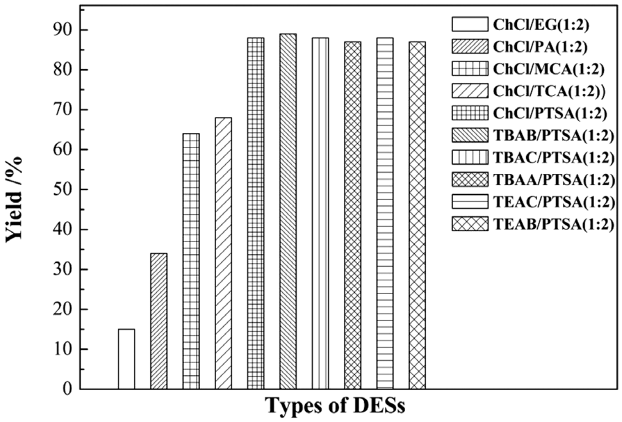


Figure 1: Effect of DESs types on reaction yield.
Reaction conditions: benzaldehyde (2.0 mmol), ethyl acetoacetate (2.0 mmol), urea (3.0 mmol), ChCl/2PTSA (0.4 mmol), 70°C, 40 min.

Biginelli reaction can also be catalyzed by PTSA; thus, a comparative study on PTSA and ChCl/2PTSA was conducted. The results demonstrated that the yield of DHPM was 64% with PTSA catalyst under solvent-free condition, which was lower than that of ChCl/2PTSA (88%). Jin et al. reported the use of Biginelli reaction with PTSA as a catalyst in refluxing ethanol [49]. However, the use of the organic solvent in Jin's study did not meet the requirements of green chemistry. Moreover, DESs can act as solvent and catalyst with high catalytic activity, are environmentally benign, and are easily recycled, which are in accordance with the requirements of green chemistry.

3.2 Optimization of the reaction parameters

The reaction of benzaldehyde and ethyl acetoacetate with urea catalyzed by ChCl/2PTSA was chosen for the synthesis of DHPM. Many factors, such as reaction temperature, DESs dosage, and reaction time, affect the reaction process. Therefore, the above parameters were investigated in detail to optimize the reaction process (Table 1).

Reaction temperature is important in organic reactions. Moreover, our results showed that high temperature within a certain range (50°C to 70°C) benefitted the organic reaction. When the reaction temperature exceeded 70°C, the yield of DHPM remained unchanged (Table 1, entries 1-5). Thus, 70°C was chosen as the reaction temperature throughout the research.

Table 1: Optimization of the reaction conditions with ChCl/2PTAS as catalyst and solvent.[a]

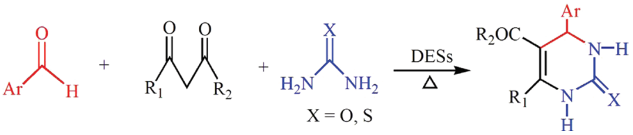
Entry	DESs (mmol)	Temp. (°C)	Time (min)	Yield[b] (%)
1	0.4	50	40	72
2	0.4	60	40	78
3	0.4	70	40	88
4	0.4	80	40	87
5	0.4	90	40	86
6	0.1	70	40	77
7	0.2	70	40	81
8	0.5	70	40	90
9	0.6	70	40	92
10	0.7	70	40	89
11	0.8	70	40	81
12	1.0	70	40	68
13	0.6	70	30	82
14	0.6	70	50	88
15	0.6	70	60	86

[a] Reaction conditions: benzaldehyde (2.0 mmol), ethyl acetoacetate (2.0 mmol), urea (3.0 mmol). [b] Isolated yield.

DES dosage is another factor that influences the reaction process. Table 1 shows that an increase of up to 0.6 mmol strengthened and increased the yield of DHPM. However, when DES dosage continued to increase, the yield decreased gradually and the color of the final product deepened (Table 1, entries 6-12). This finding can be attributed to the fact that very strong acidity is not favorable for the specific reaction. To improve the selectivity of the final product, suitable acidity is necessary. Thus, 0.6 mmol of DES was chosen as the optimal quantity in the following experiments.

Reaction time is an important parameter for the reaction; thus, to determine the reaction more precisely, the effect of reaction time was investigated. Thin layer chromatography was used to monitor the reaction endpoint. At less than 40 min, the yield of DHPM increased tremendously with increasing time. The reaction equillibrium can be achieved in 40 min with an increased yield of up to 92%. The suitable acidity and increased catalytic capability of DESs accounted for the reduced reaction time.

Table 2: Substrate scope for the Biginelli reaction in presence of ChCl/2PTAS.[a]



Entry	Ar	R_1	R_2	X	Product	Yield[b] (%)
1	C_6H_5	CH_3	OEt	O	3a	92
2	4-$CH_3C_6H_4$	CH_3	OEt	O	3b	91
3	4-$OCH_3C_6H_4$	CH_3	OEt	O	3c	88
4	4-FC_6H_4	CH_3	OEt	O	3d	91
5	4-ClC_6H_4	CH_3	OEt	O	3e	92
6	4-BrC_6H_4	CH_3	OEt	O	3f	88
7	4-$NO_2C_6H_4$	CH_3	OEt	O	3g	88
8	4-OHC_6H_4	CH_3	OEt	O	3h	90
9	3-ClC_6H_4	CH_3	OEt	O	3i	80
10	2-ClC_6H_4	CH_3	OEt	O	3j	78
11	3-BrC_6H_4	CH_3	OEt	O	3k	92
12	3-$NO_2C_6H_4$	CH_3	OEt	O	3l	80
13	2-OH-3-$OCH_3C_6H_3$	CH_3	OEt	O	3m	58
14	C_6H_5	CH_3	OEt	S	3n	80
15	C_6H_5	CH_3	OMe	O	3o	90
16	4-$OCH_3C_6H_4$	CH_3	OMe	O	3p	88
17	4-BrC_6H_4	CH_3	OMe	O	3q	90
18	4-$NO_2C_6H_4$	CH_3	OMe	O	3r	88
19	C_6H_5	CH_3	OMe	S	3s	80
20	C_6H_5	CH_3	CH_3	O	3t	85
21	4-$NO_2C_6H_4$	CH_3	CH_3	O	3u	84
22	C_6H_5	C_6H_5	OEt	O	3v	–

[a] Reaction conditions: aldehyde (2.0 mmol), β-ketoesters (2.0mmol), urea or thiourea (3.0 mmol), ChCl/2PTSA (0.6 mmol), 70°C, 40 min. [b] Isolated yield.

3.3 Biginelli reaction of substituted aldehydes

To widen the scope of the reactions, various substituted aldehydes, β-diketonates, were chosen as raw materials. The reaction was carried out under optimized conditions, i.e. DES loading of 0.6 mmol at 70°C for the synthesis of the corresponding DHPMs. Results are shown in Table 2. The melting points, ^1H NMR, and ^{13}C NMR of the products were characterized (see the Supplementary material). As indicated in Table 2, the Biginelli reaction catalyzed by ChCl/2PTSA was suitable for a vast variety of aromatic aldehydes with both electron-donating and electron-withdrawing groups, different β-diketonates, and urea or thiourea to obtain the corresponding DHPMs. Moreover, methyl acetoacetate exhibited the same reactivity as that of ethyl acetoacetate (Table 2, entries 1 and 15; entries 3 and 16; entries 6 and 17; and entries 7 and 18). Furthermore, acetylacetone also had increased reactivity (Table 2, entries 20 and 21). However, the activity of ethyl benzoyl acetate were relatively lower (Table 2, entries 22), and no product was formed in 40 min. Extending the reaction time was favorable in yielding 5-ethoxycarbonyl-4-(2-phenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3v), which was 42% in 4 h. The steric hindrance of the benzene ring was the main reason for the low reactivity. In addition,

Table 3: Synthesis of DHPMs using different DESs

[a]Entry	DES	DES dosage	Time	Yield (%)	Reference
1	L-(+)-tartaric acid-dimethylurea	1.5 g	8-48 h	70-99	[42]
2	ChCl/$ClCH_2CO_2H$	10 mmol	5-75 min	70-95	[43]
3	ZnCl/Urea	urea:$ZnCl_2$ (3.5:1mmol)	5-60 min	76-96	[44]
4	ChCl/Urea	3 mL	7.5 h	20	[45]
5	ChCl/2PTSA	0.6 mmol	40 min	78-92[b]	This work

[a] Entry 1-3: substrate aldehyde 1 mmol; Entry 4-5: substrate aldehyde 2 mmol. [b] The reaction yield of 2-hydroxy-3-methoxybenzaldehyde is 58%, but this compound has not been reported in other reference.

the reactivity of urea was higher than that of thiourea (Table 2, entries 1 and 14; and entries 15 and 19). Meanwhile, the Biginelli reaction of aliphatic aldehyde was achieved with *n*-butylaldehyde, ethyl acetoacetate, and urea as substrates, and yielded up to 52% in 40 min; the product yield for the reaction of hexaldehyde was 48%. So most aldehydes are suitable for the Biginelli reaction catalyzed by ChCl/2PTSA. Further work on the extension of substrates, such as heterocyclic aldehydes, aliphatic aldehydes, and β-diketonates, is on going.

To show the merit of the present work in comparison with previously reported results in the literature, we summarized some results for the synthesis of DHPMs in Table 3. As shown in Table 3, ChCl/2PTSA has high catalytic activity with the yields of DHPMs are over 78%. Compared with other DESs, the main advantage of ChCl/2PTSA lies in less dosage, thus saving resources and lowering the production cost.

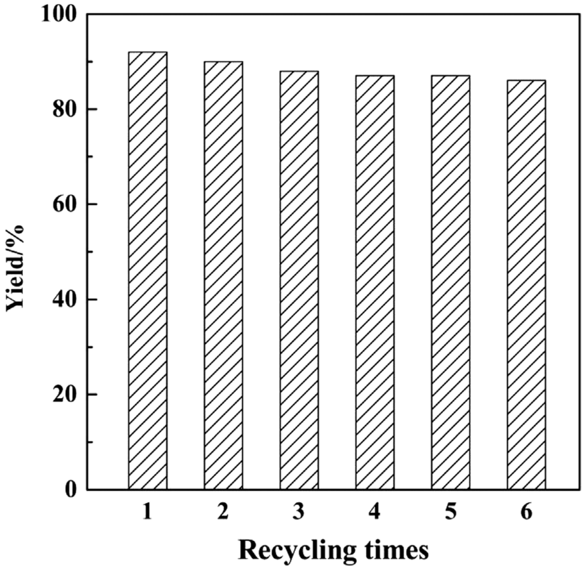


Figure 2: Reuse of ChCl/2PTSA for Biginelli reaction.

3.4 Recycling and reuse of DESs

Synthesizing DESs is low-cost; however, recycling and reusing DESs are also necessary to consider for economic and environmental considerations. Reuse of DESs was carried out by using ChCl/2PTSA to catalyze the model reactions of benzaldehyde, ethyl acetoacetate, and urea at 70°C. Fortunately, DESs was recycled by simply adding water into the reaction mixture after the completion of the reaction. Afterward, by simple filtration, the target compound was obtained. The DESs were obtained by evaporating the water. The recycled DESs was then reused for another cycle. In the next run, the reaction using a mixture of benzaldehyde, ethyl acetoacetate, and urea at stoichiometric ratio was carried out under the same conditions. The results are summarized in Figure 2. The yields were highly stable after six recycling cycles, indicating the potential of DESs for facile recycling.

3.5 Reaction mechanism catalyzed by ChCl/2PTSA

The reaction mechanism, which is important for revealing the specific process, was investigated systematically based on the previous mechanism proposed by Kappe [50]. The mechanism for the specific Biginelli reaction with ChCl/2PTSA as catalyst and solvent is shown in Figure 3. The rate-limiting reaction of benzaldehyde and urea catalyzed by ChCl/2PTSA was monitored. The IR spectra of the mixtures with heating treatment were compared with the initial ones. The IR spectra of benzaldehyde, urea, and ChCl/2PTSA significantly changed after heating (Figure 4). The C–H

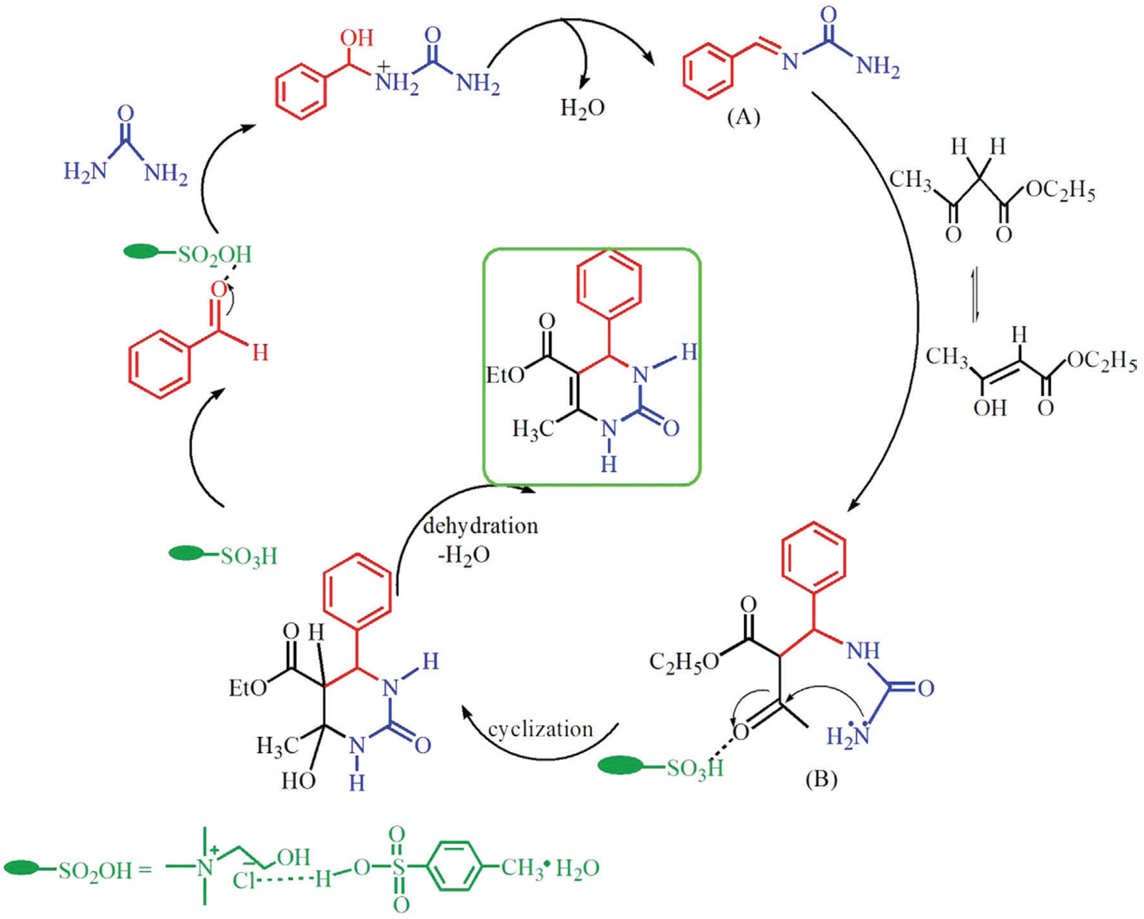


Figure 3: Mechanism of Biginelli reaction in the presence of ChCl/2PTSA.

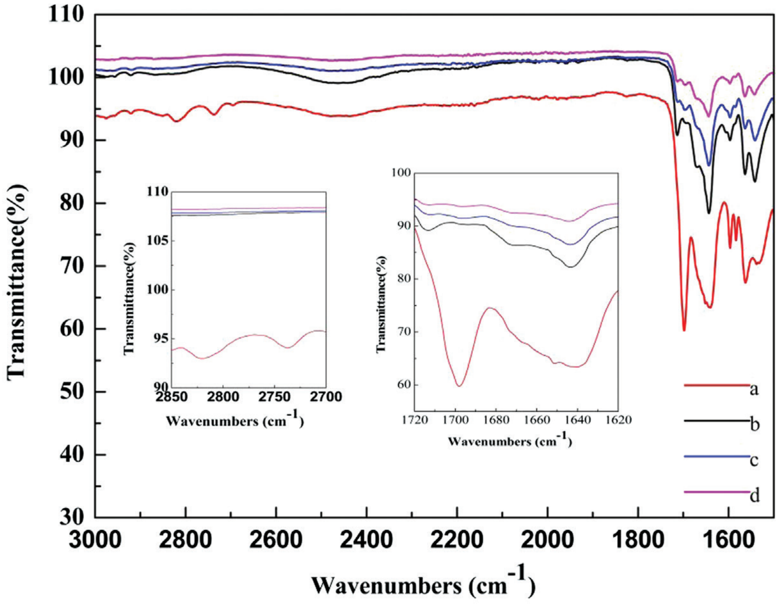


Figure 4: IR spectra of benzaldehyde, urea and ChCl/2PTSA.
Reaction condition: aldehyde (2.0 mmol), urea (3.0 mmol), ChCl/2PTSA (0.6 mmol), 70°C; a: initial mixtures, b: heating for 10 min, c: heating for 20 min, d: heating for 30 min.

bond stretching vibration peak (2817.9 and 2735.0 cm^{-1}) of benzaldehyde disappeared after heating. Meanwhile, the C=O stretching vibration peak of benzaldehyde (1695.4 cm^{-1}) disappeared gradually by heating, whereas the peak at 1644.2 cm^{-1} widened. Thus, benzaldehyde can react with urea catalyzed by ChCl/2PTSA to obtain the N-acyl imine intermediate (A). Based on the experiment phenomena, wherein ethyl acetoacetate was added in the benzaldehyde, urea, and ChCl/2PTSA heating mixtures, the final product 3,4-dihydropyrimidin-2(1*H*)-ones can be obtained immediately, and we speculated that intermediate (B) can be obtained through the reaction of intermediate (A) and the enolized ethyl acetoacetate. Finally, intermediate (B) under went consecutive cyclization and dehydration under the catalytic effect to quickly obtainthe targeted product. From the above investigations, the proposed mechanism obeyed the following scheme (Figure 3).

4 Conclusions

Biginelli reactions of β-ketoesters with aldehydes and urea or thiourea were achieved in the presence of low-cost and green DESs. Notably, the catalytic performance of DESs was greatly enhanced, which is important from the green chemistry perspective. Under optimal conditions, high yields of DHPMs were obtained. Furthermore, DESs can be recycled and reused by washing with water, indicating a green and simple process. Importantly, the yields did not change after six recycling cycles, thereby demonstrating the potential of DESs for future industrial applications. The reaction systems can be a good alternative to green synthesis of the Biginelli reaction product in mild and solvent free conditions. This specific process provides a green method for the synthesis of DHPMs.

Supplementary material: Supplementary material available: The FTIR and ^{1}H NMR spectra of DESs and ^{1}H and ^{13}C NMR spectra for synthetic compounds.

Acknowledgments: Sincere gratitude is extended to National Natural Science Foundation of China (NSFC Grant No. 21546007 and 21133055), Natural Science Foundation of Liaoning Provice of China (Grant No. 20180550078), Dalian Outstanding Scholar Project (Grant No. 2016RJ11), and Dalian Technology Star Project (Grant No. 2016RQ079) for the financial support.

Conflict of interest statement: The authors declare to have no conflicts of interest regarding this article.

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