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### Original Research article

## Eutectic Mixture Choline Chloride–Chloroacetic acid: a New and Efficient Catalyst for Synthesis of 3,4-Dihydropyrimidin-2-ones

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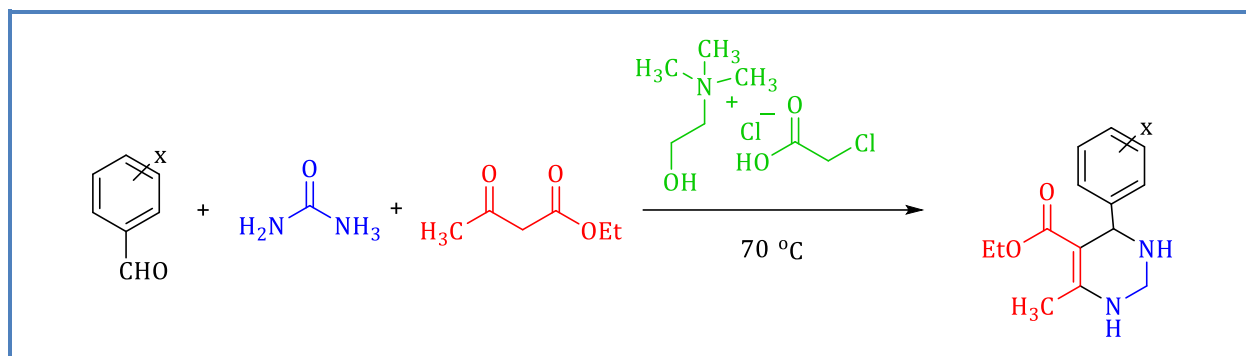
#### ABSTRACT

Deep Eutectic Solvents (DES) with the properties of an ionic liquid can be formed between choline chloride and chloroacetic acid in a 1:1 molar ratio. In this paper, we discuss our success in synthesizing dihydropyrimidinones employing choline chloride: chloroacetic acid as catalyst. The advantage of using DES is in its ability to act as a solvent and catalyst simultaneously for the synthesis of dihydropyrimidinones via one-pot multi-component reaction of ethyl acetoacetate, aldehyde and urea. The results showed that choline chloride: chloroacetic acid based DES is the best catalyst and is successfully applicable to a wide range of aldehydes with high yields (70–95%) and short reaction times (5–75 min). The deep eutectic solvent can be easily recycled and reused.

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## Graphical Abstract



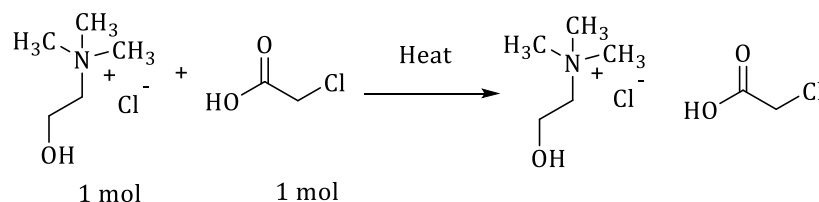
## Introduction

Dihydropyrimidinones (DHPMs) are an important class of biologically active heterocycles. The DHPMs have shown to possess a diverse range of biological activities like antibacterial, antiviral and antitumor activities. The dihydropyrimidinone skeleton is common in many calcium channel blocker agents [1-4]. For the first time, Biginelli has reported, in 1893, the synthesis of DHPMs by one-pot cyclocondensation reaction of benzaldehyde, ethyl acetoacetate and urea under Brønsted acid catalysis [5]. The harsh conditions, high reaction times and often low yields of this reaction caused numerous methods for improvement of the synthesis of DHPMs [6-8].

Recently, ionic liquids (ILs) have been successfully employed in Biginelli reaction [9-18]. The replacement of solid acids and acidic homogeneous catalyst with ILs have received considerable interest because of their unique properties, such as low volatility, non-flammability, high thermal stability, negligible vapor pressure and ability to dissolve a wide range of materials [19-23]. However, there are limitations to the widespread use of ionic liquids, such as high cost, high purity requirement and environmental toxicity. The toxicity of many ionic liquids is similar to or higher than that of organic solvents [24-27]. Recently, deep eutectic solvents (DES) which were developed by Abbott and co-workers, were considered as attractive alternatives to room temperature ionic liquids.

DES which is similar to ILs forms a eutectic by mixing two components with a melting point lower than to either of the individual components. DES possesses properties similar to ILs such as low vapor pressure and low flammability. In addition, DES is biodegradable, non-toxic, and inexpensive. The simple procedure for the synthesis of DES is its mixing of an ammonium salt mostly choline chloride (ChCl) and a hydrogen-bond donor compound such as urea, acids, amines and salts [28-33].

It has recently been shown that DES can be formed by using carboxylic acids with choline chloride [34]. Herein, we report the synthesis of DHPMs using acidic deep eutectic solvent, prepared from choline chloride and chloroacetic acid which plays a dual role as a solvent and as efficient catalyst (scheme 1).



**Scheme 1.** Preparation of deep eutectic mixture

## Materials and methods

All starting materials and choline chloride are commercially available and were purchased from Aldrich and Merck and used without further purification. The reactions were monitored by TLC with F<sub>254</sub> silica gel precoated plates, which were visualized with UV light.

### *General procedure for the synthesis of dihydropyrimidin-2-ones in the deep eutectic solvent*

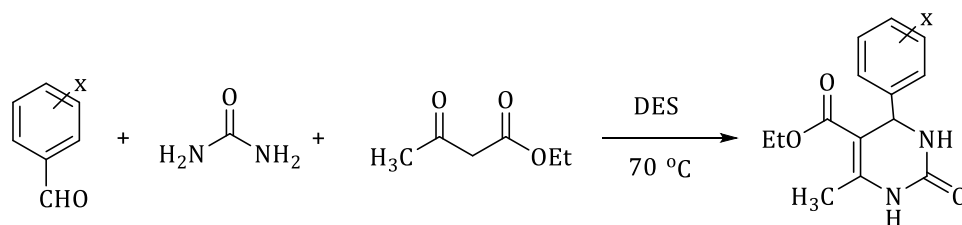
Choline chloride (10 mmol, 1.4 g) was mixed with chloroacetic acid (10 mmol, 0.95 g) into a test tube and heated with stirring to 70°C in an oil bath until a clear colorless liquid began to form. To this homogenous colorless liquid, 1 mmol of aldehyde and 1 mmol of ethyl acetoacetate and 1 mmol of urea were added at 70 °C. The progress of reaction was monitored by thin layer chromatography. After the reaction was completed, water was added and the filtered mixture. The crude product was purified by recrystallization from ethanol. The deep eutectic solvent was recovered and re-used by removing the water using rotary evaporator. All compounds were known and were characterized on the basis of their spectroscopic data (IR, NMR) and melting point by comparing with those reported in the literature.

## Results and discussion

We started the work to test a number of DESs as solvents and catalysts for the synthesis of DHPMs, including ChCl/SnCl<sub>2</sub> (1:2), ChCl/ascorbic acid (1:1), ChCl/urea (1:2), ChCl/CrCl<sub>3</sub>·6H<sub>2</sub>O (1:2) and ChCl/ClCH<sub>2</sub>CO<sub>2</sub>H (1:1). The results indicate that except ChCl/ClCH<sub>2</sub>CO<sub>2</sub>H, other catalysts were not efficient in producing DHPMs. It was found that the reaction proceeded smoothly in ChCl/CrCl<sub>3</sub>·6H<sub>2</sub>O to afford the DHPM in 70% yield after 3 h heating. Unfortunately, on prolong heating, the colour of the liquid is changed from green to purple indicating that the coordination sphere around the chromium centre has been changed [35], and the mixture became solid. The reaction was

repeated with  $\text{ChCl}/\text{CrCl}_3$  in ethanol at reflux conditions and, as a result, a lower yield of product around 10% was obtained after 6h heating.  $\text{ChCl}/\text{ascorbic acid}$  was not active in the synthesis of DHPMs and the reaction mixture was sticky liquid at 100 °C due to the high melting point of ascorbic acid (190 °C). Recently, Sangram Gore et al. reported the synthesis of DHPM derivatives in L-(+)-tartaric acid–dimethylurea and L-(+)-tartaric acid–urea [36]. It is worth mentioning that Urea is one of the components of DHPMs. In this sense, when  $\text{ChCl}/\text{urea}$  was employed as solvent under similar reaction, poor yields of DHPMs were observed.

We found that the mixture of 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1 mmol) in  $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$  as DES gave corresponding of 3,4-dihydropyrimidin-2-ones in 95% yield after 5 minutes (scheme 2).



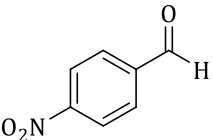
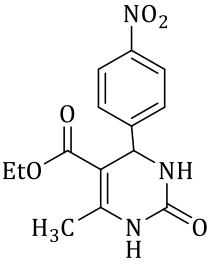
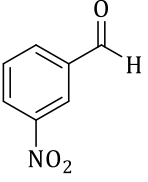
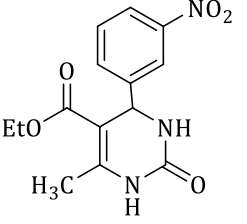
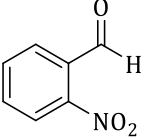
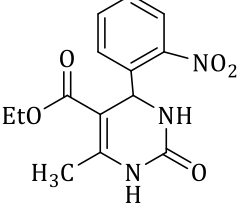
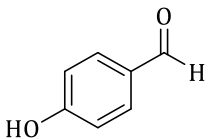
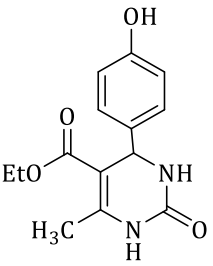
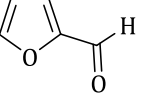
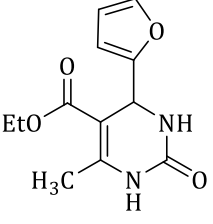
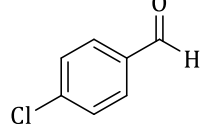
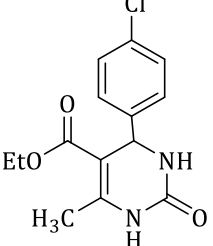
**Scheme 2.** Synthesis of dihydropyrimidinones in DES.

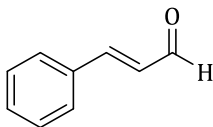
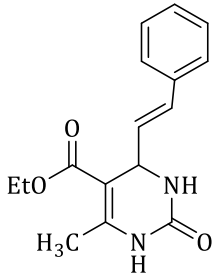
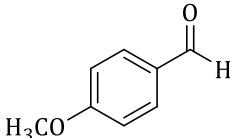
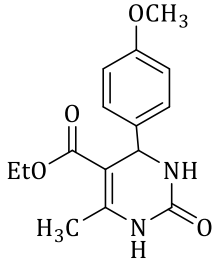
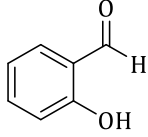
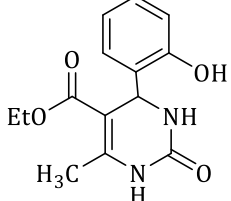
To investigate the efficiency and generality of this catalytic system, we examined the reaction of a range of other aromatic aldehydes containing either electron-releasing or electron-withdrawing substitutes under optimized conditions.

The results are summarized in Table 1. Aromatic aldehydes carrying electron- withdrawing groups gave the products in shorter periods as compared to those of aromatic aldehydes with electron-releasing substitutes. Acid sensitive aldehydes such as furfural and cinnamaldehyde were efficiently converted into the corresponding 3,4-dihydropyrimidin-2-ones. In all cases, the reactions are affording high yields of products. In the case of aliphatic aldehydes, reactions were not performed under solvent-free conditions because of the low boiling point of the aldehydes.

**Table 1.** Synthesis of 3,4-dihydropyrimidin-2-ones using  $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$

Entry	Aldehyde	Product	Time (min)	Yield (%) <sup>a</sup>
1			15	90

2			5	95
3			5	90
4			5	90
5			30	75
6			75	85
7			10	85

8			60	70
9			40	90
10			45	80

<sup>a</sup>Isolated yield

The reaction of 4-nitrobenzaldehyde with ethyl acetoacetate and urea was selected as a standard reaction for the recycling purposes. The recycled  $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$  was re-used up to four runs and a decrease in yield was observed after the third cycle as shown in Table 2.

**Table 2.** Recycling of deep eutectic solvent ( $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$ ) in synthesis of DHPMs

Recycle of DES	Yield (%) <sup>a,b</sup>
Fresh (non-recycled)	95
First	90
Second	90
Third	85
Fourth	73

<sup>a</sup>4-Nitrobenzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.0 mmol), DES (10 mmol) at 70 °C.

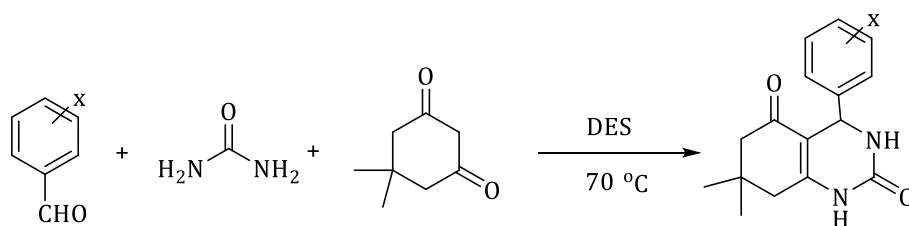
<sup>b</sup>Isolated yield

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 derivatives in Table 3. As shown in Table 3,  $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$  can act as effective catalyst with respect to reaction times and yields.

**Table 3.** Comparison results of  $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$  with some of other catalysts reported in the literature for the synthesis of DHPMs derivatives.

Entry	Conditions	Catalyst	Time	Yield (%)	Reference
1	Ethanol/Reflux	$\text{ZrCl}_4$	4- 6 h	80- 98	[37]
2	Solvent free/80 °C	$\text{Et}_3\text{N}$	2- 6 h	52- 89	[38]
3	HOAc/100 °C	HTMA	4- 5 h	75- 80	[39]
4	-/ 80 °C	$[\text{Cbim}]\text{Cl}$	60- 90 min	69- 91	[40]
5	Ethanol/MW	$\text{GlyNO}_3$	10 min	75- 92	[41]
6	Solvent free/70 °C	$\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$	5- 75 min	70- 95	This work

Next, we investigated the effect of 5,5-dimethyl-1,3-cyclohexanedione as a cyclic 1,3-dicarbonyl compound for the synthesis of DHPMs derivatives (Scheme 3). Aromatic aldehydes react with dimedone and urea in the presence of  $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$  to afford the corresponding DHPMs derivatives in excellent yields. These results are shown in Table 4.

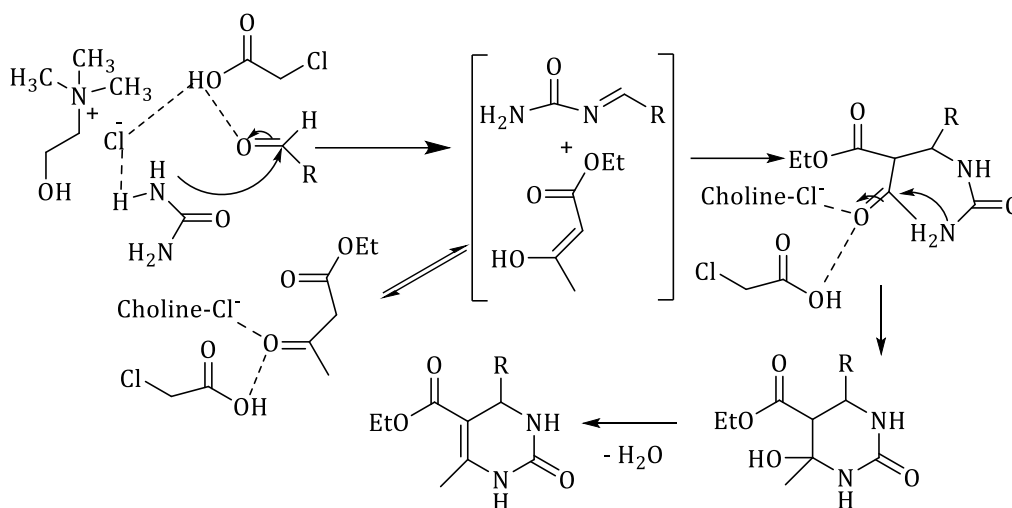
**Scheme 3.** Synthesis of DHPM from cyclic 1,3-dicarbonyl compound in DES

Scheme 4 shows a plausible mechanism for the present reaction. It is well-known that the electrophilicity of carbonyl group of the aldehyde is increased by hydrogen bonding with acidic hydrogen of chloroacetic acid. Moreover, DES might help in the improving reactivity of urea and finally in promoting cyclization to form the dihydropyrimidinone core. Finally, acid catalyzed dehydration occurs by the exit of  $\text{H}_2\text{O}$  and as a result, the final product is created.

**Table 4.**  $\text{ChCl}/\text{ClCH}_2\text{CO}_2\text{H}$  catalyzed synthesis of DHPM using cyclic 1,3-dicarbonyl compounds in DES<sup>a</sup>

Entry	Aldehyde	Time (min)	Yield <sup>b</sup> (%)	M.P (°C)
1	4- $\text{NO}_2$ - $\text{C}_6\text{H}_4\text{CHO}$	5	89	295-297
2	4- $\text{CH}_3\text{O}$ - $\text{C}_6\text{H}_4\text{CHO}$	10	92	>300

<sup>a</sup>The reaction was carried out in presence of aldehyde (1 mmol), urea (1 mmol), dimedone (1 mmol), DES (10 mmol) at 70 °C. <sup>b</sup>Isolated yield



**Scheme 4.** Proposed reaction mechanism in synthesis of dihydropyrimidinone derivatives using acidic DES as catalyst.

## Conclusion

In conclusion, we have demonstrated that the deep eutectic mixture formed from choline chloride and chloroacetic acid in 1:1 ratio is a novel and efficient medium for the Biginelli reaction. The suitable reaction time, easy work-up procedure, high yields, recyclability and easy preparation of the catalyst are the main advantages of this method. With these properties, the DES may be suitably applied for more chemical transformations and processes.

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