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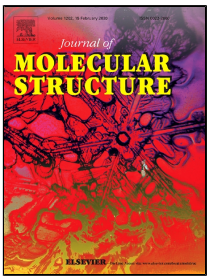

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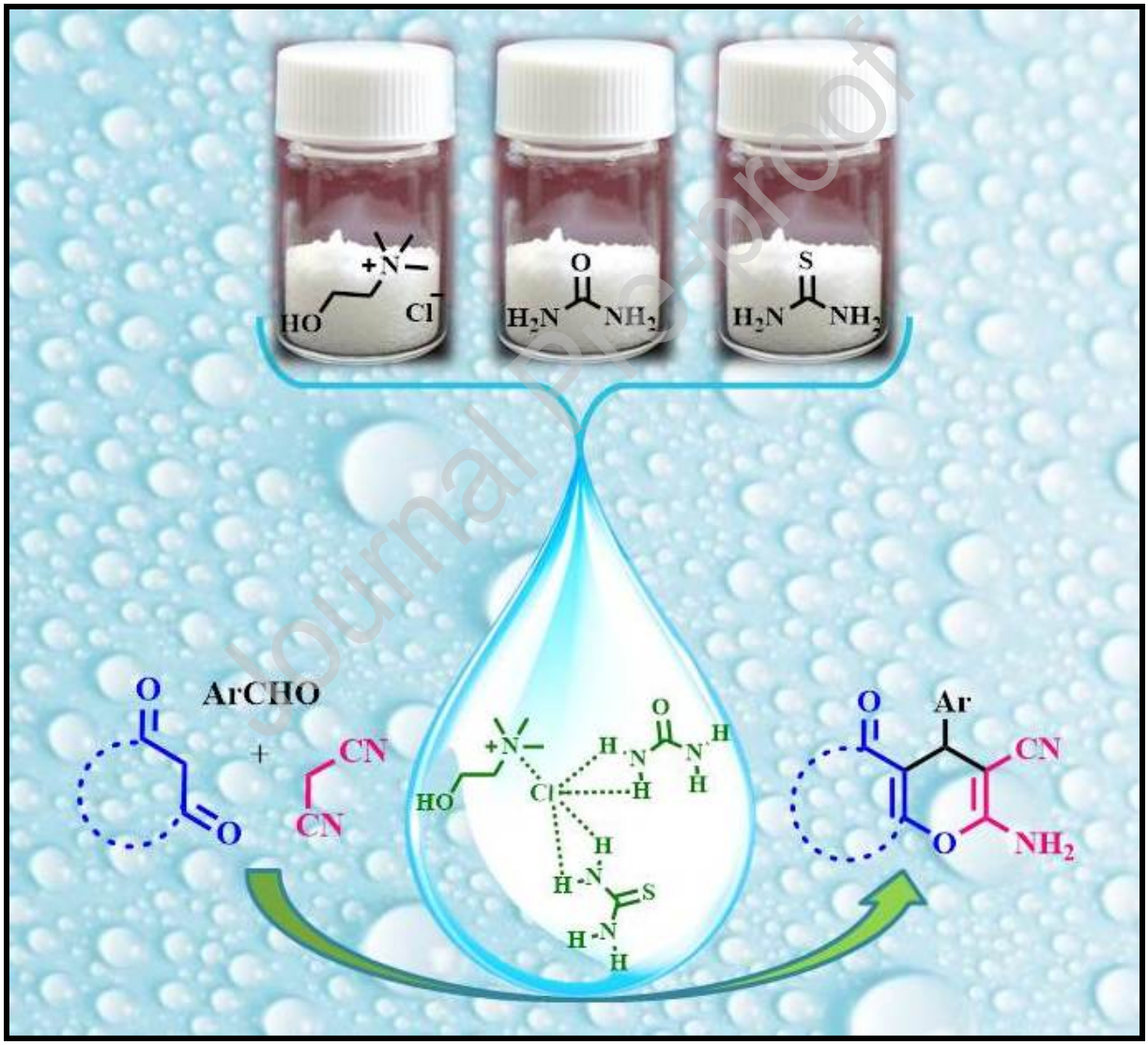

A choline chloride-based deep eutectic solvent promoted three-component synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*] pyrimidinone (thione) derivatives

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Abstract— An efficient one-pot method for the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone (thione) derivatives through a three-component reaction between aldehydes, malononitrile and enolizable C–H activated acidic compounds using a new deep eutectic solvent made of choline chloride, urea and thiourea as an environmentally benign catalyst has been reported. The structure of the catalyst was characterized using FT-IR, ^{1}H NMR, and ^{13}C NMR. The present method exhibits some notable advantages such as ease of the preparation and handling of the catalyst, low cost, green reaction conditions, short reaction times, high yields, and simple work-up. Also, the catalyst could be recovered easily and recycled up to four times without significant loss of catalytic activity.

Keywords: Choline chloride, deep eutectic solvent, multicomponent reactions, tetrahydrobenzo[*b*]pyran, pyrano[2,3-*d*]pyrimidinone.

1. Introduction

Recently, research on deep eutectic solvents (DESs) as a new generation of eco-friendly and sustainable solvent/catalyst systems have attracted strong interest in organic synthesis. The concept of DES was first described by Abbott and co-workers in 2003 [1]. DESs are eutectic mixtures of two or more hydrogen-bond acceptors (HBA) (e.g. quaternary ammonium or phosphonium-based salts) and hydrogen-bond donors (HBD) (e.g. alcohols, amines, acids or carbohydrates) in a certain molar ratio which combine *via* hydrogen bond interactions with each other. The resulting DESs are characterized by their melting points, which are significantly lower than that the melting point of the raw materials (HBD) and (HBA), separately [2-4]. The synthesis of DESs is often straightforward, does not require further purification steps, and no by-products are formed. DESs have similar physicochemical properties to conventional ionic liquids (ILs) such as thermal stability, low flammability, nonvolatility, and recyclability. Also, these compounds exhibit bio-degradability, bio-compatibility, non-toxicity, and water-compatibility and can be prepared with 100 % atom economy from easily accessible chemical materials [4-7]. Among the numerous DES components, choline chloride (ChCl) (used as HBA) is the most frequently used salt. ChCl is non-toxic, bio-degradable, and cheap salt which can be synthesized from fossil reserves or extracted from biomass [4, 8]. This compound is considered as an essential nutrient and is often regarded as a part of the B complex vitamins [9]. In recent years, ChCl-based DESs have been extensively used in chemistry and chemical technology, namely biotransformations, nanoscience, biodiesel preparation, polymer synthesis, and catalysis [10].

4*H*-pyran-based heterocyclic scaffolds have been attracted considerable attention because of their various useful biological and pharmacological activities such as anti-diabetic [11], anti-microbial [12], anti-oxidant [13], anti-fungal [14], anti-HIV [15], cytotoxic [16], and anti-cancer [17] properties. In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative disease, including Parkinson's disease, Huntington's disease, Alzheimer's disease, and Down's syndrome as well as for the treatment of schizophrenia [18]. These compounds also are present in a variety of important natural compounds including alkaloids, antibiotics, iridoids, and pheromones [19]. Figure 1 shows some of the 4*H*-pyran derivatives which display strong pharmacological activities [20, 21]. Hence, design and development of novel synthetic methods to the synthesis of the libraries of these compounds is an important field for many organic chemists. Among the known procedures for the synthesis of 4*H*-pyran frameworks such as tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone (thione) derivatives, the most straightforward method involves a multi-component reaction of aldehydes, malononitrile and diverse enolizable C–H activated acidic compounds. Multi-component reactions (MCRs) have a major role in synthetic organic chemistry and pharmaceutical industry due to their advantages such as high yields compared with multi-step reactions, minimization of time, cost, energy, and waste generation, better selectivity, and simple performance [22]. Based on this, a large number of catalysts were introduced for the three-component synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]-pyrimidinone (thione) derivatives under various conditions namely: NaN_3 [23], Fe_3O_4@SiO_2@BenzIm-Fc[Cl]/$NiCl_2$ nanoparticle [24], Fe_3O_4@MCM-41@Zr-piperazine-MNPs [25], 2,2,2-trifluoroethanol [26], MNP-DMAP [27], Urea [28], SO_4^{2-}/MCM-41[29], DABCO [30], nano ZnO [31], [H_2-DABCO][H_2PO_4]$_2$ [32], Fe_2O_3@SiO_2@VB_1 [33], RHPrBPCl [34], Glutamic acid [35], [DABCO-PDO][CH_3COO] [36], Al-HMS-20 [37], $CaHPO_4$ [38], Choline chloride.$ZnCl_2$ [39], CuO/ZnO nanocatalyst [40], diammonium hydrogen phosphate [41], *L*-Proline [42], Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 [43], and Fe_3O_4@SiO_2@$(CH_2)_3$-Urea-SO_3H/HCl [44].

Considering the merit of all the above-mentioned catalysts and their methodologies, most of them suffer from several drawbacks such as difficulties in the preparation of the catalyst, expensiveness of the reagent, long reaction times, need to use of excess amounts of reagent or catalyst, moderate yields, and tedious work-up procedure. Thus, further efforts are needed to introduce more efficient and cleaner methods using scalable low-cost materials for the synthesis of the aforementioned important target molecules.

As a part of our continuing interest on designing environmentally benign methods for various chemical transformations [25, 45-47], herein we have described an efficient and more practical route for the synthesis 4*H*-pyran frameworks such as tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone (thione) derivatives using a new deep eutectic solvent made of ChCl, urea, and thiourea as a green catalyst.

2. Experimental

2.1. Materials

All chemicals used in this study were purchased from Merck (Munich) and Sigma-Aldrich (Mumbai) Chemical Companies and were used without further purification. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates. Yields refer to the isolated products. Products were characterized by their physical constants, comparison with authentic samples, FT-IR and NMR spectroscopy.

2.2. Characterization techniques

Melting points were determined by electro-thermal IA9100 melting point apparatus in capillary tubes. The melting point range was input manually through keyboard and the material changes were visually monitored. FT-IR spectra were recorded on a PerkinElmer spectrum BX series with KBr plates for solid samples. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 500 MHz using TMS as internal standard and DMSO-d6 as solvent.

2.3. Synthesis of ChCl/urea/thiourea DES

A mixture of ChCl, urea, and thiourea in the ratio of 1:1:1 was heated in a round-bottomed flask (10 mL) at 80 ^{o}C under constant stirring for 5 min until a clear and homogeneous liquid appeared. Then, the reaction was stopped and the prepared DES was collected without any further purification. The characterization of the obtained DES was determined using FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques.

Spectral data for ChCl/urea/thiourea DES:

^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.13 (s, 9H); 3.42 (t, 2H), 3.81 (td, J = 5 Hz, 2H), 5.52 (t, OH), 5.58 (brs, NH), 7.25 (s, NH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.6, 54.5, 66.3, 159.3, 183.2 ppm. FT-IR (KBr, cm^{-1}) υ = 3333, 3188, 1665, 1616, 1471, 1399, 1082, 954, 587, 483 cm^{-1}.

2.4. General procedure for the synthesis of tetrahydrobenzo[b]pyran derivatives

In a round-bottomed flask (10 mL) a mixture of aldehyde (1 mmol), malanonitrile (1 mmol), dimedone (1 mmol), and DES (0.1 g, 36 mol%) was stirred and heated in an oil-bath at 100 ^{o}C for an appropriate period of time. The reaction progress was followed by TLC (eluent: EtOAc : *n*-hexane). After completion of the reaction, water was added and the mixture was stirred for 10 min at 100 ^{o}C. Then, the precipitated product was filtered, dried, and subsequently recrystallized from ethanol if necessary.

2.5. General procedure for the synthesis of pyrano[2,3-d]pyrimidinone (thione) derivatives

A mixture of aldehyde (1 mmol), malanonitrile (1 mmol), barbituric or thiobarbituric acid (1 mmol), and DES (0.1 g, 36 mol%) was stirred in refluxing water (2 mL) for an appropriate period of time. The reaction progress was followed by TLC (eluent: EtOAc : *n*-hexane). After completion of the reaction, the mixture was diluted with water (4 mL) and filtered off. Finally, the solid product was recrystallized from warm ethanol if necessary.

2.6. Spectroscopic data of the selected previously introduced and new compounds

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (Table 2, entry 2, **1b**). yield 95%; m.p. 210-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.22 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.18 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.05 (s, 2H), 4.31 (s, 1H), 2.43-2.50 (m, 2H), 2.23 (d, $^2J_{HH}$ = 16 Hz, 1H), 2.15 (d, $^2J_{HH}$ = 16 Hz, 1H), 1.09 (s, 3H), 1.01 (s, 3H); FT-IR (KBr, cm^{-1}) υ = 3380, 3324, 2189, 1678, 1218 cm^{-1}.

2-Amino-4-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*chromene-3-carbonitrile (Table 2, entry 14, **1n**). yield 96%; m.p. 202-204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.95 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 6.82 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 6.90 (s, 2H), 4.15 (s, 1H), 2.90 (s, 6H), 2.46-2.52 (m, 2H), 2.25 (d, $^2J_{HH}$ = 16.2 Hz, 1H), 2.09 (d, $^2J_{HH}$ = 16.2 Hz, 1H), 1.08 (s, 3H), 0.97 (s, 3H); FT-IR (KBr, cm^{-1}) υ = 3374, 3235, 2196, 1671, 1609, 1216 cm^{-1}.

7-Amino-5-(2-nitrophenyl)-4-oxo-2-thioxo1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (Table 2, entry 29, **2o**). yield 89%; m.p. 241-244 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 5.06 (s, 1H), 7.34 (s, 2H),7.48 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.54 (dd, J_1 = 8Hz, J_2 = 1.2 Hz, 1H), 7.67 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.86 (dd, J_1 = 8Hz, J_2 = 1.2 Hz, 1H), 12.43 (NH, s, 1H), 13.67 (NH, s, 1H); FT-IR (KBr, cm^{-1}) υ = 3426, 3062, 2197, 1675, 1573, 1518, 1349 cm^{-1}.

7-Amino-5-(4-hydroxy-3-methoxy-5-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (Table 2, entry 25, **2k**, **new compound**). yield 93%; m.p. 240-243 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 3.86 (s, 3H), 4.30 (s, 1H), 7.16 (s, 2H), 7.18 (s, 1H), 7.25 (s, 1H), 10.29 (s, NH), 11.07 (s, NH), 12.06 (s, OH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) = 34.64, 56.14, 57.48, 87.05, 113.63, 115.26, 118.51, 134.38, 136.33, 140.76, 148.59, 148.97, 151.88, 157.17, 162.03 ppm. FT-IR (KBr, cm^{-1}) υ = 3429, 3332, 3196, 3116, 3023, 2197, 1711, 1661, 1550, 1521, 1398, 1271 cm^{-1}.

3. Results and Discussion

The most famous employed example of ChCl-based DESs is the blend of ChCl and urea in a 1:2 molar ratio which is also the first reported DES [1]. To date, ChCl/urea DES has been applied as an efficacious reaction medium or catalyst in many organic transformations [48-51]. Nevertheless, despite the promising performance of this eutectic mixture, we have found its efficiency could be significantly modified by adding thiourea as HBD.

3.1. Synthesis of ChCl/urea/thiourea DES and the characterization

As we have mentioned previously in continuation of our studies on the design, preparation and use of efficient and eco-friendly catalytic systems, ChCl/urea/thiourea DES was prepared as an inexpensive and biodegradable eutectic mixture by mixing ChCl, urea and thiourea using the heating method (Figure 2). For being certain about the purity of the product, it was checked by FT-IR, ^{1}H NMR and ^{13}C NMR.

The FT-IR spectra of choline chloride (a), urea (b), thiourea (c) and the prepared DES (d) are presented in Figure 3. At first look, it can be noted that the absorption bands related to the stretching modes of -NH_2 (ν_{as} NH_2 and νs NH_2) in b and c moved towards the lower wave number region and changed to broader bands in d. This maybe results from the forming of more hydrogen bonds between choline chloride, urea and thiourea. In addition, the bands associated to ChCl, such as the rocking vibrations of CH_3 (1471 cm^{-1}), and CH_2 groups (1082 cm^{-1}), and the asymmetric stretching vibrations of CCO (954 cm^{-1}) appeared in d which reveal that the structure of Ch^+ was not destroyed in the ChCl/urea/thiourea DES.

^{1}H NMR and ^{13}C NMR spectra of ChCl/urea/thiourea DES are presented in Figures 4 and 5. In the ^{1}H NMR spectrum of ChCl/urea/thiourea DES, six peaks related to six types of hydrogens are observed. The peaks at 3.13, 3.42, 3.81, and 5.52 ppm are related to CH_3, CH_2 and OH associated to ChCl, respectively. Two singlet peaks at 5.58 and 7.25 ppm are related to NH_2 groups of thiourea and urea. Also the ^{13}C NMR of the prepared DES properly showed five types of carbons.

3.2. Catalytic activity

The obtained data pointed out that ChCl/urea/thiourea DES was successfully synthesized, so in the next step, the catalytic efficacy of this new DES was investigated. For this reason, this reagent was utilized as a catalyst in the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone (thione) derivatives. The catalytic study commenced with the optimization of the three-component reaction of 4-chlorobenzaldehyde (1 mmol), malononitrile (1mmol) and dimedone (1 mmol) as a model reaction (Table 1, entries 1-20). Preliminary trials revealed only a trace amount of the desired product was obtained when aprotic solvents like acetonitrile and dichloromethane were used at room temperature and under reflux conditions. Next, the reaction was tested in green solvents, such as water and EtOH. No significant product was observed when the mixture of the reaction was refluxed in EtOH. In contrast, when water was used as a solvent, the product formation enhanced rapidly with 90% conversion in a short reaction time of 15 min, but the reaction was not completed even after a prolonged reaction time of 120 min. Surprisingly, when the reaction was carried out under solvent-free conditions, both reaction time and the yield were drastically improved. Finally, the best result was obtained using 36 mol % of DES under solvent-free conditions at 100 ^{o}C (Table 1, entry 17) (Scheme 1). Any further increase in the catalyst amounts did not improve the reaction time and yield. To demonstrate the scope and generality of this protocol, a number of aromatic aldehydes having substituents such as halogens, hydroxy, methoxy, nitro, and methyl, and aliphatic aldehydes such as butaraldehyde and isobutaraldehyde were reacted with malononitrile and dimedone under the optimized reaction conditions to obtain various tetrahydrobenzo[*b*]pyran derivatives. All reactions were proceeded smoothly with aromatic aldehydes, whereas using aliphatic aldehydes led to a mixture of products. As a result, this procedure cannot be convenient for these substrates. The results are depicted in Table 2.

Next, the efficiency of the prepared DES for promoting the synthesis of pyrano[2,3-*d*]pyrimidinone (thione) derivatives was investigated. Like above-mentioned model reaction, a one-pot, three-component system was designed containing 4-chlorobenzaldehyde (1 mmol), malononitrile (1mmol) and barbituric acid (1 mmol). Control experiments on the model reaction showed that the reaction was not completed under solvent-free conditions. Then, the reaction was studied in water. The progress of the reaction at room temperature in water was slow, and became even slower as it proceeded; however, by carrying out the reaction under reflux temperature the rate of it increased drastically. Finally, The best result was obtained using 36 mol % of DES in water and under reflux conditions (Table 2, entry 24) (Scheme 2). Subsequently, to reveal the generality of this method, different derivatives of pyrano[2,3-*d*]pyrimidinone (thione) were prepared and the results were summarized in Table 2. It should be mentioned that although the conversion yields in all of the above-mentioned reactions were 100 %, a small amounts of the products wasted through the work-up procedure and the percentage yields got less than conversion yields.

The possibility of the recycling of ChCl/urea/thiourea DES was examined for the synthesis of product **1b** (2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile) under the optimized conditions. For this purpose, after the completion of the reaction, (Monitored by TLC), water was added and the mixture was stirred for 10 min at 100 ^{o}C. The resulting precipitates of the crude solid product was filtered and the filtrate was evaporated under the reduced pressure. The DES remained after evaporation of water was collected and used in the next cycles of the same synthesis. As Figure 6 shows, the recovered catalyst could be reused at least for four runs without significant decrease in catalytic efficiency.

The postulated mechanism for the synthesis of pyran derivatives in the presence of ChCl/urea/thiourea DES is explained in Scheme 3 based on previous literatures [32, 45, 52]. According to this mechanism, initially, the aldehyde, malononitrile and *β*-dicarbonyl could be activated by DES. Then the process could occur from two routes (routes 1 and 2). The activated aldehyde could be attacked by the activated malononitrile (route 1) or *β*-dicarbonyl (route 2) through a Knoevenagel condensation reaction to generate the intermediate **a** or the intermediate **b**. Both routes associated together in intermediate **c** which followed by intramolecular cyclization produces the 4*H*-pyran derivatives.

The comparison of the catalytic activity of ChCl/urea/thiourea DES with other reported catalysts in the literature especially other ChCl-based catalysts such as ChCl/urea DES (Table 3, entry 9) and ChCl/$ZnCl_2$ (Table 3, entry 11) for the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone (thione) derivatives of 4-chlorobenzaldehyde is depicted in Table 3. It is clear that ChCl/urea/thiourea DES promoted the reaction in less time and more yield than other mentioned catalytic systems. Moreover, the preparation of ChCl/urea/thiourea DES takes less time compared to ChCl/urea DES (Scheme 4) [53].

4. Conclusion

In summary, the eutectic mixture of ChCl, urea and thiourea was found to be an efficacious and eco-friendly catalyst for the synthesis of tetrahydrobenzo[*b*]pyran and pyrano[2,3,*d*] pyrimidinone (thione) derivatives *via* one-pot three-component reaction of aldehyde, malononitrile, and dimedone or (thio)barbituric acid. The simple and green experimental procedure both for preparation of the catalyst and products, use of readily available, inexpensive, and biocompatible reagents for the synthesis of the catalyst, short reaction times, easy work-up procedure needing no special separation methods, simple recovery of the catalyst from the reaction mixture, high purity and high yields of the desired products are the considerable advantages of this protocol. Further studies are currently on-going in our laboratories to identify additional transformations that can be mediated by this eutectic mixture.

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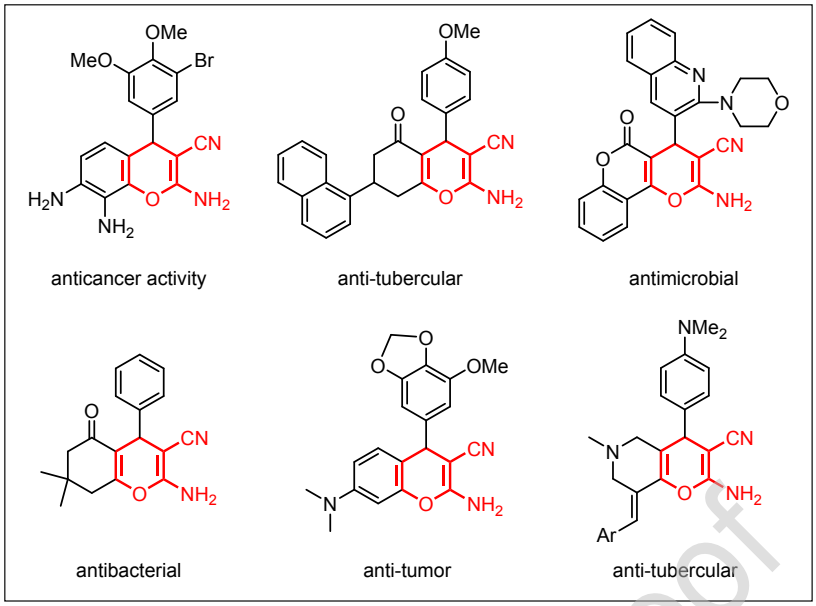


Fig. 1. Selected examples of 4*H*-pyran-based biologically active molecules

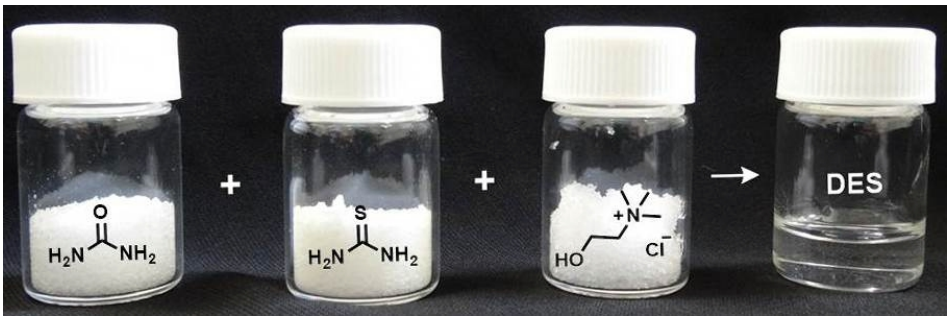


Fig. 2. Deep eutectic solvent preparation from choline chloride, urea and thiourea at 80 °C.

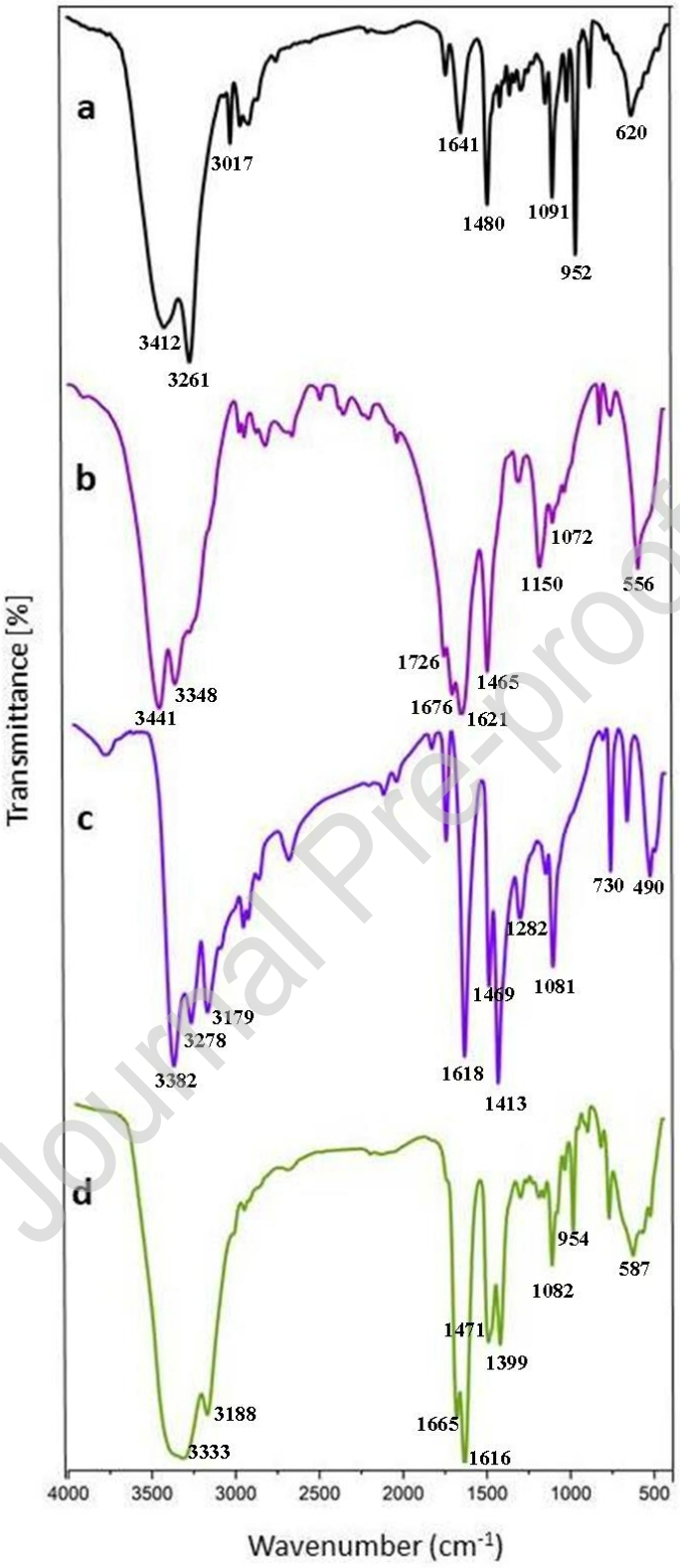


Fig. 3. FT-IR spectra of ChCl (a), urea (b), thiourea (c), and prepared DES (d).

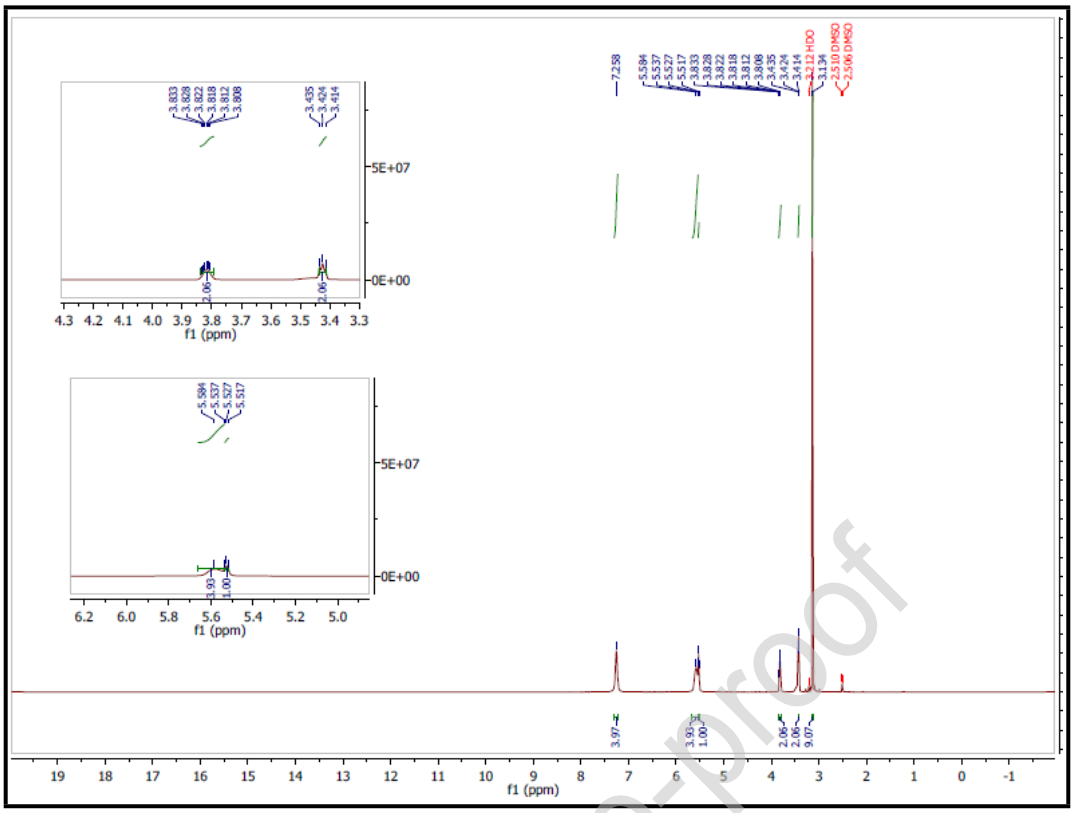


Fig. 4. The ^{1}H NMR spectrum of ChCl/urea/thiourea DES.

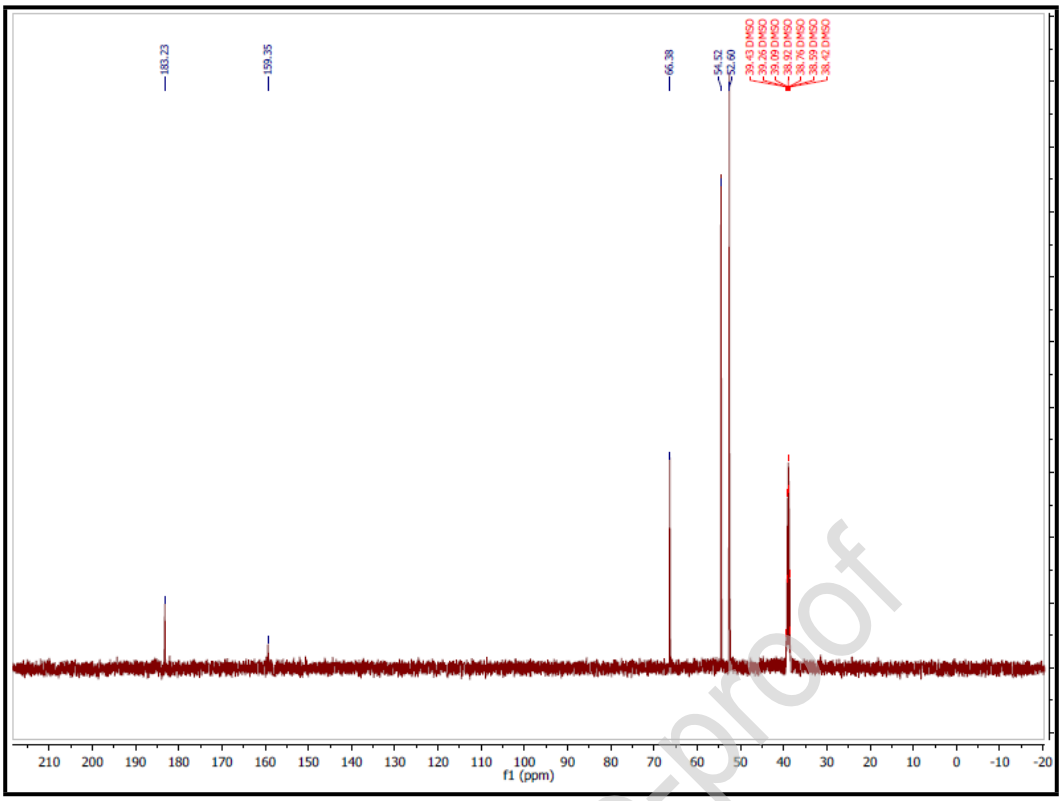


Fig. 5. The ^{13}C NMR spectrum of ChCl/urea/thiourea DES.

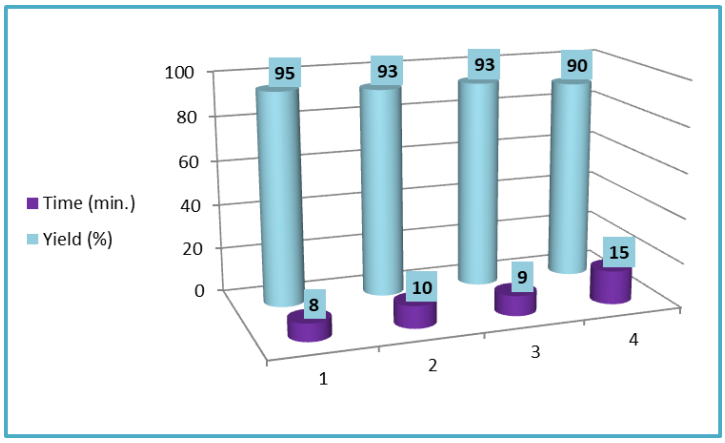
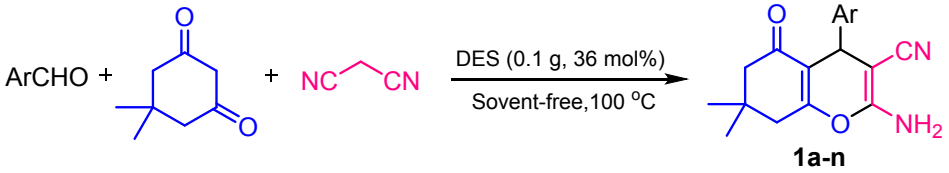
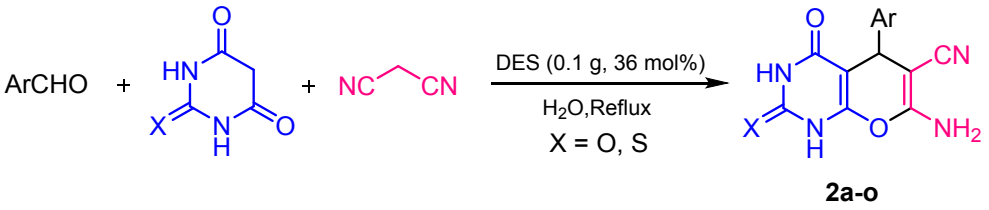


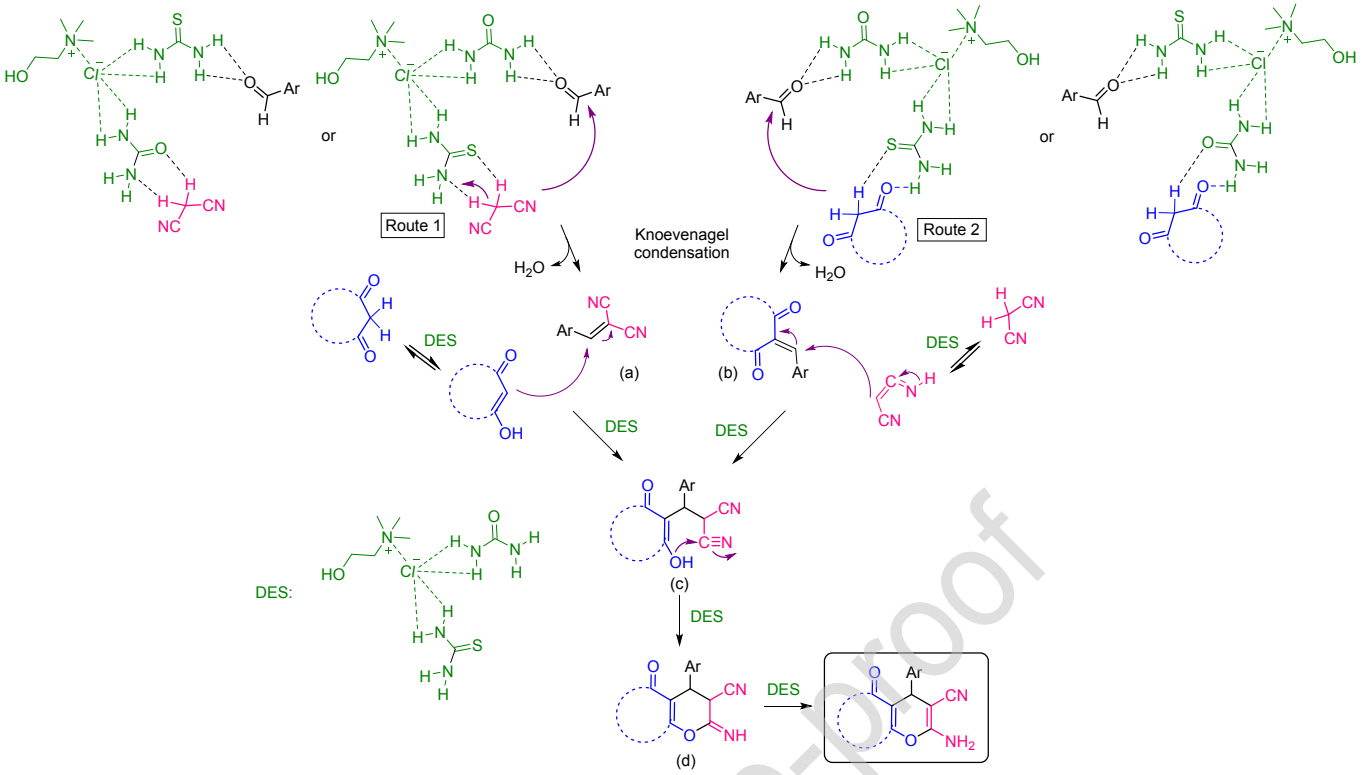
Fig. 6. Recyclability of ChCl/urea/thiourea DES on the synthesis of **1b**.



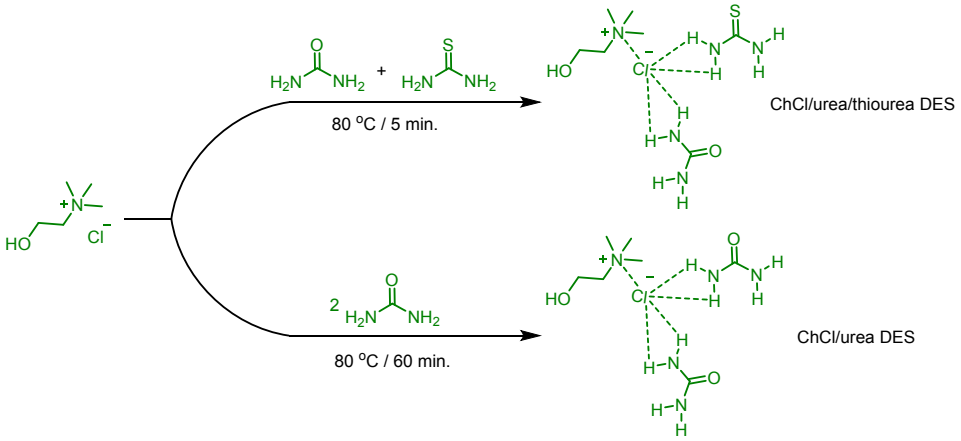
Scheme 1. Synthesis of tetrahydrobenzo[*b*]pyran derivatives catalyzed by ChCl/urea/thiourea DES.



Scheme 2. Synthesis of pyrano[2,3-*d*]pyrimidinone (thione) derivatives catalyzed by ChCl/urea/thiourea DES.



Scheme 3. Plausible mechanism for the synthesis of pyran derivatives.



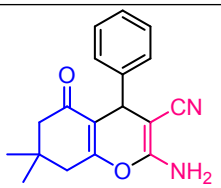
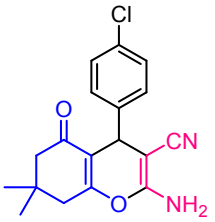
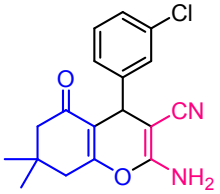
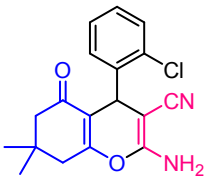
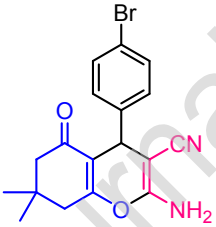
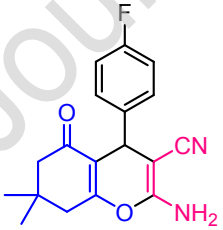
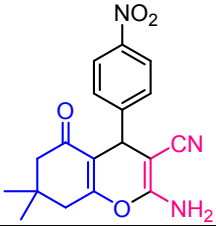
Scheme 4. Synthesis of ChCl/urea/thiourea DES and ChCl/urea DES.

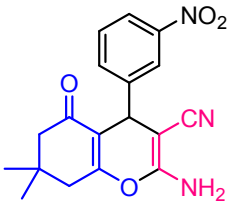
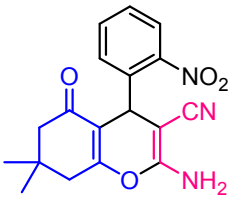
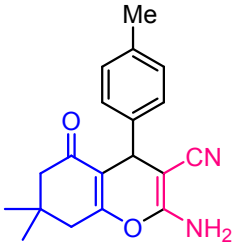
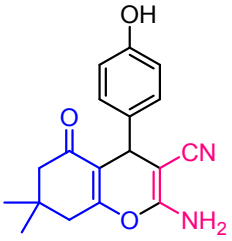
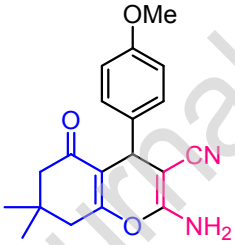
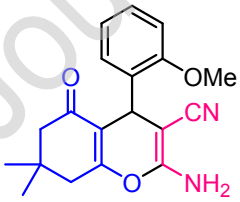
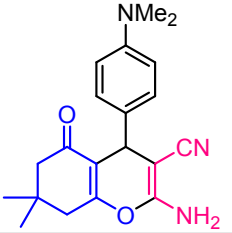
Table 1. Optimization of the amounts of the catalyst, temperature and solvent in the synthesis of tetrahydrobenzo[*b*]pyran (entries 1-20) and pyrano[2,3-*d*]pyrimidinone (thione) (entries 21-26) derivatives of 4-chlorobenzaldehyde.

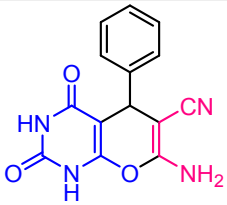
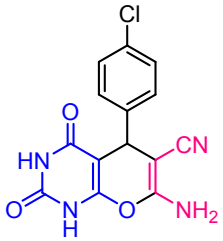
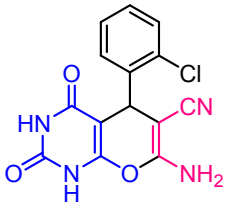
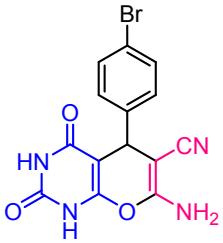
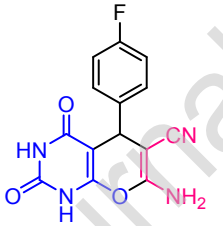
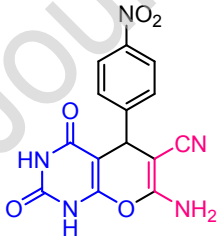
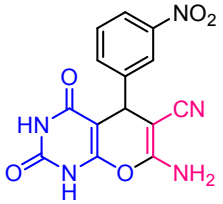
Entry	Amount of the catalyst (mol %)	Solvent	Temp. (°C)	Time (min.)	Conversion yield (%)
1	---	---	r.t.	120	Trace
2	---	---	100	120	Trace
3	18	CH_3CN	r.t.	120	Trace
4	18	CH_3CN	Reflux	120	Trace
5	72	CH_3CN	Reflux	120	Trace
6	36	CH_2Cl_2	r.t.	120	Trace
7	36	CH_2Cl_2	Reflux	120	Trace
8	72	CH_2Cl_2	Reflux	120	Trace
9	---	C_2H_5OH	Reflux	120	Trace
10	36	C_2H_5OH	r.t.	120	Trace
11	72	C_2H_5OH	Reflux	120	Trace
13	36	H_2O	r.t.	120	Not completed
14	36	H_2O	Reflux	120	Not completed
15	72	H_2O	Reflux	120	Not completed
16	36	---	r.t.	120	Not completed
17	36	---	100	8	100 (95)[a]
18	18	---	100	120	Not completed
19	36	---	70	120	Not completed
20	72	---	100	7	100 (93)[a]
21	36	---	100	120	Not completed
22	72	---	100	120	Not completed
23	36	H_2O	r.t.	120	Not completed
24	36	H_2O	Reflux	17	100 (93)[a]
25	72	H_2O	Reflux	15	100 (91)[a]
26	36	H_2O	70	120	Not completed

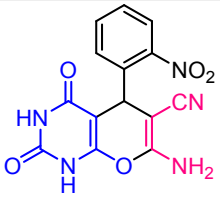
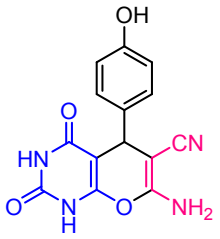
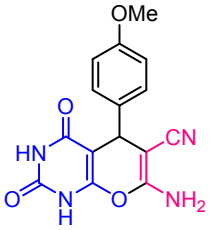
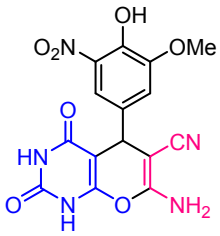
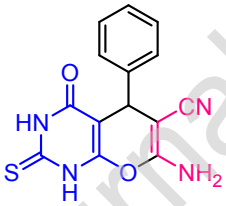
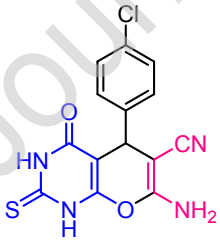
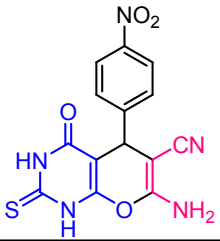
[a] Isolated yields

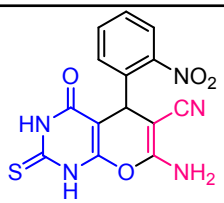
Table 2. Preparation of tetrahydrobenzo[*b*]pyran (entries 1-14) and pyrano[2,3-*d*]pyrimidinone (thione) (entries 15-29) derivatives using ChCl/urea/thiourea DES as the catalyst.

Entry	Aldehyde	Product		Time (min.)	Yield (%)[a]	M. P. (°C)		Ref.
						Found	Rep.	
1	C_6H_5CHO		1a	12	90	226-228	227-229	[46]
2	4-ClC_6H_4CHO		1b	8	95	210-212	208-210	[32]
3	3-ClC_6H_4CHO		1c	11	91	230-232	229-232	[25]
4	2-ClC_6H_4CHO		1d	14	93	215-217	216-218	[25]
5	4-BrC_6H_4CHO		1e	13	94	203-205	204-206	[46]
6	4-FC_6H_4CHO		1f	14	91	175-177	171-174	[32]
7	4-$NO_2C_6H_4CHO$		1g	17	90	179-181	178-179	[25]

8	3-$NO_2C_6H_4CHO$		1h	15	89	212-214	211-213	[46]
9	2-$NO_2C_6H_4CHO$		1i	18	89	214-216	218-219	[25]
10	4-MeC_6H_4CHO		1j	21	91	215-217	211-214	[32]
11	4-OHC_6H_4CHO		1k	23	93	205-207	208-210	[25]
12	4-$OMeC_6H_4CHO$		1l	21	91	200-202	200-203	[46]
13	2-$MeOC_6H_4CHO$		1m	27	90	200-202	198-203	[32]
14	4-$NMe_2C_6H_4CHO$		1n	19	96	202-204	199-203	[46]

15	C_6H_5CHO		2a	21	91	220-223	219-222	[32]
16	$4\text{-}ClC_6H_4CHO$		2b	17	93	241-243	238-240	[46]
17	$2\text{-}ClC_6H_4CHO$		2c	21	91	211-215	209-214	[32]
18	$4\text{-}BrC_6H_4CHO$		2d	19	95	225-227	225-227	[25]
19	$4\text{-}FC_6H_5CHO$		2e	21	91	263-265	264-266	[46]
20	$4\text{-}NO_2C_6H_4CHO$		2f	25	91	236-238	237-239	[32]
21	$3\text{-}NO_2C_6H_4CHO$		2g	23	90	268-270	268-270	[46]

22	2-$NO_2C_6H_4CHO$		2h	25	88	254-256	249-251	[32]
23	4-HOC_6H_4CHO		2i	23	91	>300	>300	[32]
24	4-$MeOC_6H_4CHO$		2j	27	90	277-279	276-279	[32]
25	4-OH-3-MeO-5-NO_2-C_6H_2CHO		2k	15	93	240-243	---	New
26	C_6H_5CHO		2l	22	90	223-226	220-224	[46]
27	4-ClC_6H_4CHO		2m	19	94	>300	>300	[32]
28	4-$NO_2C_6H_4CHO$		2n	21	92	235-237	233-235	[32]

29	2-$NO_2C_6H_4CHO$		2o	25	89	241-244	242-245	[46]

[a] Isolated yields

Table 3. Comparison of catalytic activity of ChCl/urea/thiourea DES with some reported catalysts in the synthesis of 4-chlorophenyl derivatives of tetrahydrobenzo[*b*]pyran (entrise 1-10) and pyrano[2,3,*d*] pyrimidinone (entries 11-18).

Entry	Catalyst	Amount	Conditions	Time (min.)	Yield (%)[a]	Ref.
1	SO_4^{2-}/MCM-41	25 mg	EtOH /reflux	60	80	[29]
2	$CaHPO_4$	10 mol%	H_2O/EtOH(4:1)/80 °C	120	92	[38]
3	DABCO	10 mol%	H_2O/reflux	120	94	[30]
4	2,2,2-Trifluoroethanol	2 mL	reflux	300	95	[26]
5	Fe_3O_4@MCM-41@Zr-Piperazine	30 mg	H_2O/EtOH(7:3)/reflux	10	90	[25]
6	Glutamic acid	20 mol%	EtOH/reflux	40	91	[35]
7	Fructose	20 mol%	H_2O/EtOH(2:1)/40 °C	80	78	[54]
8	Urea	10 mol%	EtOH:H_2O(1:1)/r.t.	180	87	[28]
9	ChCl/urea	1 mL	80 °C	60	92	[55]
10	ChCl/urea/thiourea	36 mol%	Solvent-free/100 °C	8	95	This Work
11	$ChCl/ZnCl_2$	50 mol%	EtOH/75 °C	2	82	[39]
12	Urea	10 mol%	EtOH:H_2O(1:1)/r.t.	840	86	[28]
13	$CaHPO_4$	10 mol%	H_2O/EtOH(4:1)/80 °C	120	92	[38]
14	Al-HMS-20	30 mg	EtOH/r.t.	720	92	[37]
15	Nano-titania Sulfuric Acid	20 mg	EtOH:H_2O(19:1)/ reflux	60	89	[56]
16	Fe_3O_4@SiO_2-Propyl-Pip-$SO_3H.HSO_4$	30 mg	H_2O/80 °C	20	95	[43]
17	boric acid	10 mol%	THF:H_2O(8:2)/ reflux	110	85	[56]
18	ChCl/urea/thiourea	36 mol%	H_2O/reflux	17	93	This Work

Dear Chief in Editor

I am interested in having this article published in Journal of molecular Structure.

Best Regards

F. Shirini

The present research is the result of our activities carried out on the use of DES compounds, as novel and attractive compounds, in the acceleration of some organic reactions .This research area is a novel field in the catalysis studies.

Highlights

- The eutectic mixture of choline chloride, urea and thiourea was successfully synthesized.
- The prepared DES introduced as an efficacious and eco-friendly catalyst for the synthesis of pyran derivatives.
- Simple and green experimental procedure both for preparation of the catalyst and products.
- Easy separation and recyclability of the catalyst.
- The catalyst exhibited high stability.