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Efficient deep eutectic solvents catalyzed synthesis of pyran and benzopyran derivatives

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ABSTRACT

An ecofriendly one-pot multicomponent reaction of 1,3-dicarbonyl compounds, aldehydes, and malononitrile was carried out in a different deep eutectic solvent (DES) based on choline chloride, to synthesize highly functionalized benzopyran and pyran derivatives under catalyst-free conditions. The results showed that urea:choline chloride based DES is the best solvent and is successfully applicable to a wide range of aldehydes, active methylene compounds with high yields (75–95%) and short reaction times (1–4 h).

1. Introduction

The development of environmentally benign, atom economic and sustainable methods in the synthesis of highly functionalized and diversified molecules in combinatorial chemistry from simple starting materials remain a significant challenge in synthetic chemistry and chemical industry. In this context, one-pot multicomponent reactions (MCRs) in green reaction media such as water and ionic liquid may be competent to come close to reaching this ideal goal [1–3]. Ionic liquids (ILs) also called molten salts, are important green solvents in chemical industry and laboratory, because of their unique properties such as negligible vapor pressure, recyclability, stability and non-flammability. Main disadvantages of ionic liquids such as high cost, difficult preparation and some toxic properties enforced scientists to discover environmentally friendly reaction media. New sustainable alternatives to traditional solvents and ILs are deep eutectic solvents (DESs). DES forms by mixtures of quaternary ammonium salt and a simple hydrogen bond donor (HDB) such as urea, carboxylic acid, sugar and amide. DESs exhibit some properties similar to ionic liquids such as non-volatility, biodegradability, low cost, thermal stability, and ready availability from bulk renewable resources without any further modification [4–12].

Since the discovery of cromakalim as a typical ATP-sensitive potassium channel opener, the synthesis of benzo[b]pyran and their derivatives has attracted great interest. A considerable number of benzopyran derivatives have shown the significant rule in possessing potent relaxant activity on blood vessels, cardiac muscle and other smooth muscles. The pyran is an important pharmacophore which shows antitumor, antibiotic, antibacterial, antiallergic, hypolipidemic and immunomodulating activities [13–15]. Furthermore, substituting of a pyran's hydrogen atom with amino or cyano makes these compounds as synthons of natural compounds [16–18]. The conventional reported syntheses of 4H-benzo[b]pyrans was in organic solvents such as DMF, DMSO, diethyl ether, acetonitrile and acetonitrile with water [19–25]. Recently, numerous clean procedures for synthesis of benzo[b]pyran derivatives have been practiced in water, ethanol, mixture of water and ethanol and ionic liquid with or without a solvent [26–30], in the presence of a catalyst. The existing green methods are not well suited for the catalyst-free one-pot multi-component condensations of 1,3-dicarbonyl compounds, aldehyde and malononitrile under green reaction media. Herein, we report the synthesis of highly functionalized benzopyran and pyran derivatives by one-pot three-component reaction of 1,3-dicarbonyl compounds, aldehydes, and malononitrile in deep eutectic solvent as a catalyst and reaction media.

2. Experimental section

2.1. Materials and equipment's

^{1}H NMR spectra were recorded on 500 MHz NMR spectrometer using $CDCl_3$ or DMSO, as solvent, chemical shifts have been expressed in (ppm) downfield from TMS. All starting materials such as aldehydes, 1,3-dicarbonyl compounds, malononitrile, choline chloride and all deep eutectic solvent component were commercially available and were

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purchased from Merck. Solvents were distilled before use. All the reactions are monitored by thin layer chromatography (TLC) with UV light as detecting agent. Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

2.2. Preparation of deep eutectic solvents (DESs) based choline chloride

Deep eutectic solvent based choline chloride was prepared according to the literature [6], choline chloride and the second component were mixed on the basis of reported relationships (reported in Table 1), and heated until a clear liquid appeared. The obtained DES was used without any further purification (Fig. 1).

2.3. General procedure for the synthesis of benzopyran and pyran derivatives

In the test tube with a magnetic stirrer benzaldehyde (0.5 mmol), malononitrile (0.5 mmol), dimedone (0.5 mmol), and deep eutectic solvent (1 mL) were added and the mixture was heated at 80 °C for 60–240 min. After completion of the reaction, water (5 mL) was added. The DES being soluble in water comes in the water layer. The solid was separated by filtration and was washed with ethanol–water. The crude products were obtained in high purity after purification by recrystallization from ethanol.

Selected data:

4i: m.p = 240–242 °C, ^{1}H NMR (500 MHz, DMSO-d6) δ = 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.12 (d, J = 16Hz, 1H, C^8–H), 2.27 (d, J = 16Hz, 1H, C^8–H), 2.54 (m, 2H, C^6–H_2), 4.20 (s, 1H, C^4–H), 7.06 (s, 2H, NH_2), 7.18 (d, J = 8.33Hz, 2H, ArH), 7.36 (d, J = 8.33Hz, 2H, ArH), ^{13}C NMR (125 MHz, DMSO-d6): δ 20.1, 26.6, 27.9, 31.2, 34.3, 49.7, 112.7, 114.0, 114.3, 118.7, 128.3, 139.2, 157.7, 159.0, 161.1, 162.2, 195.0;

4p: m.p = 195–199 °C, ^{1}H NMR (500 MHz, DMSO-d6), δ = 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.11 (d, J = 16 Hz, 1H, C^8–H), 2.26 (d, J = 16 Hz, 1H, C^8–H), 2.51 (m, 2H, C^6–H_2), 3.71 (s, 3H, OMe), 4.13 (s, 1H, C^4–H), 6.85 (d, J = 8.5 Hz, 2H, ArH), 6.94 (s, 2H, NH_2), 7.06 (d, J = 8.49 Hz, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d6): δ 26.8, 28.1, 31.3, 34.2, 49.9, 54.4, 60.2, 113.1, 118.9, 127.8, 135.6, 157.6, 160.9, 195.2.

2.4. Recycling of DES

The combination of an atom economic, one-pot, multicomponent reaction and the ease of preparation recovery and reuse of DES as novel reaction media and catalyst are expected to contribute to the development of a novel protocol for the simple and fast preparation of benzopyran and pyran derivatives. The recycling of DES was examined using the reaction of benzaldehyde, malononitrile and dimedone in urea–choline chloride under optimized conditions. After reaction was completed, water (5 mL) was added to the reaction mixture, shacked vigorously and solid was separated by filtration to recover reaction mixture from DES. Finally, DES was recovered by evaporating the water at 80 °C under vacuum and was reused for the next batch and recycled again. The color and FT-IR spectra of recycled DES were similar to the original DES.

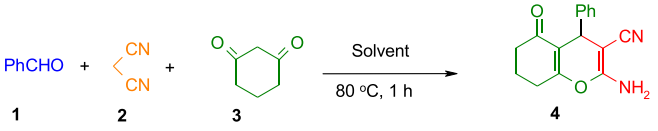
2.5. Reaction mechanism

The role of the DES as a catalyst is still not clear. Hydrogen bonding and Brønsted basicity of urea are the main factors that influence the reactivity and selectivity of the process. We tentatively propose the mechanism of the present reaction to proceed in a manner similar to that described in the analogous urea catalyzed reactions outlined in Fig. 2. The reversible hydrogen bonding between urea and carbonyl groups giving substrate–solvent complex and activated aldehydes are depicted in Fig. 2. The initial condensation of carbonyl groups with activated malononitrile with urea in the DES leads to the formation of arylidene malononitrile with the loss of a water molecule. Then nucleophilic addition of the enolizable ethylacetoacetate to arylidene malononitrile followed by intramolecular cyclization of the resulting species produces the 4H-pyran derivatives.

3. Results and discussion

As part of our continuing interest in developing the environmental benign synthetic methodologies by using water and deep eutectic solvent as the reaction medium [31–33]. herein, we wish to report the first catalyst-free three component reactions of 1,3-dicarbonyl compound's, aldehydes, and malononitrile to synthesize highly functionalized benzopyran and pyran derivatives in deep eutectic solvents based

Table 1
Optimization of reaction condition in model reaction.



1 2 3 4

Entry	Solvent (1 mL)	Temp. [°C]	Yields [%][a]
1	Urea:ChCl (2:1)	25	50
2	Urea:ChCl (2:1)	40	50
3	Urea:ChCl (2:1)	60	50
4	Urea:ChCl (2:1)	80	95
5	Malonic acid:ChCl (1:1)	80	82
6	Citric acid:ChCl (1:1)	80	60
7	Tartaric acid:ChCl (0.5:1)	80	68
8	Glycerine:ChCl (2:1)	80	45
9	$LaCl_3$:ChCl(2:1)	80	62
10	Water	80	55
11	CH_3CN	80	30
12	EtOH	80	60
13	MeC_6H_5	80	50
14	EtOAc	80	45
15	DMF	80	78

[a] Isolated yields ChCl:choline chloride.

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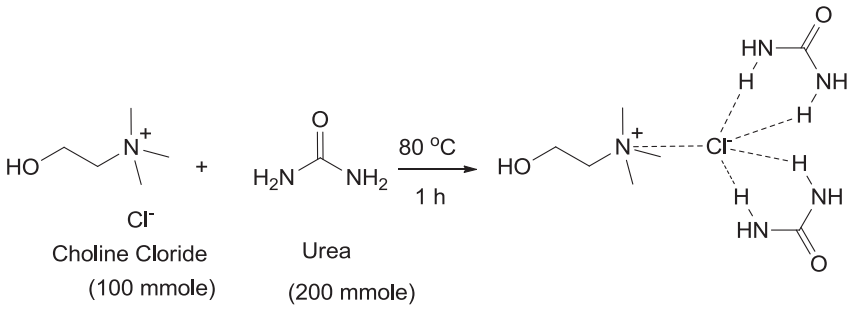

Fig. 1. Deep eutectic solvent preparation.

on choline chloride. In a typical experiment, benzaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol) and six different deep eutectic solvent (1 mL) were selected as the model reaction to examine various reaction conditions (Table 1). After screening a different temperature, we are pleased to find that the heating equivalent mixture of the starting material in DES (1 mL) at 80 °C within 60 min, the starting material was consumed, and the corresponding product was formed and isolated in 95% after a simple workup. The model reaction was also carried out in several conventional solvents such as ethyl acetate, ethanol, acetonitrile, toluene, water and five other types of DES such as malonic acid:choline chloride (2:1), glycine:choline chloride (2:1), $LaCl_3.6H_2O$:choline chloride (2:1), tartaric acid:choline chloride (0.5:1),

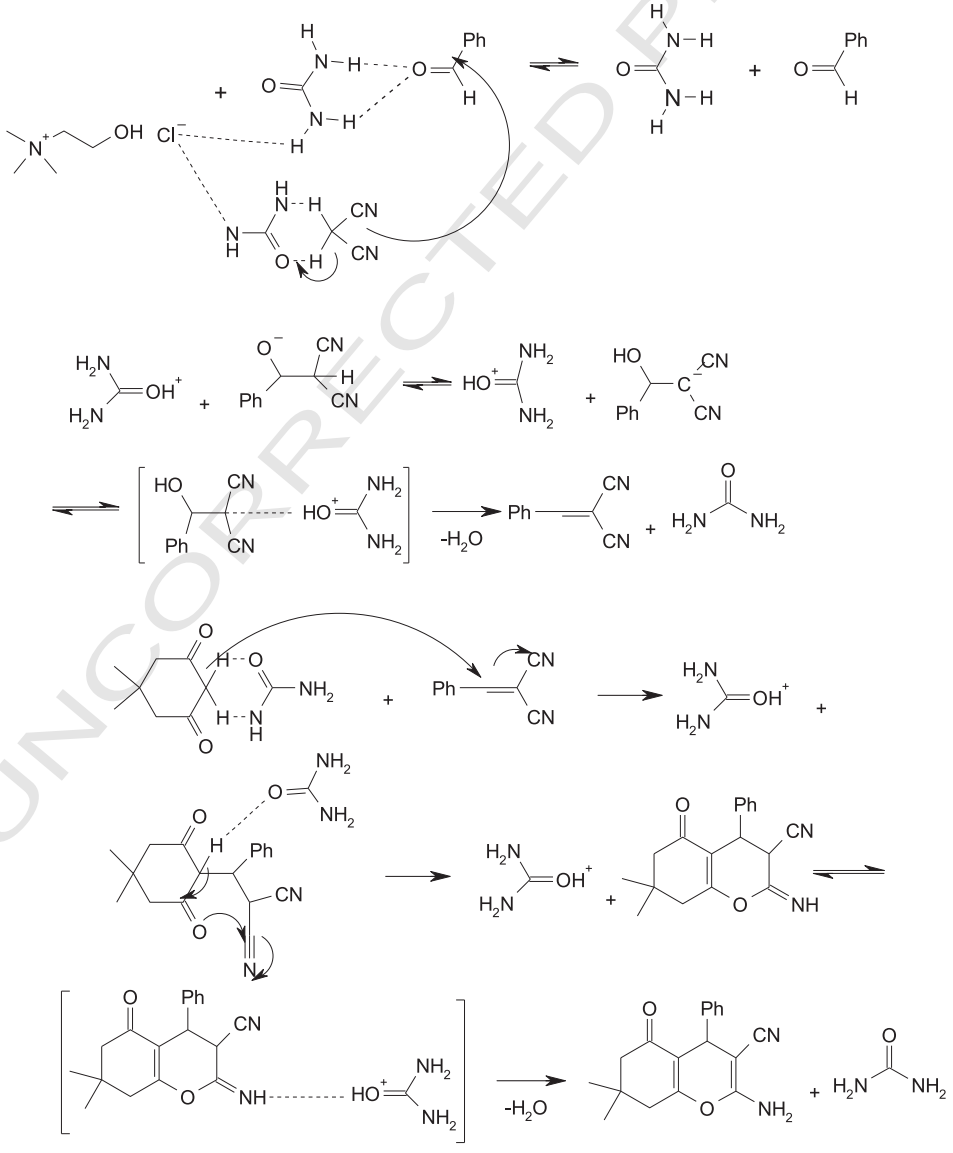

Fig. 2. Proposed mechanism of the reaction in DES.

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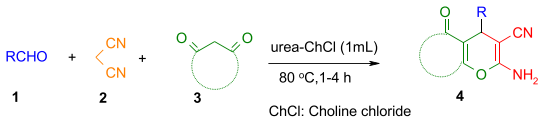
Table 2
Green syntheses of pyran and benzopyran derivatives in DES.



Entry	RCHO (**1**)	1,3-dicarbonyl compounds (**3**)	Product	Yield [%][a]	m.p [°C] Found	Reported
1	C_6H_5CHO	Acetyl acetone	4a	82	154-dec.	164[28]
2	4-OMe-C_6H_4CHO	Acetyl acetone	4b	75	139	156[28]
3	C_6H_5CHO	Ethyl acetoacetate	4c	80	182–186	192[28]
4	4-$OMeC_6H_4CHO$	Ethyl acetoacetate	4d	78	134–136	136[27]
5	4-ClC_6H_4CHO	Ethyl acetoacetate	4e	82	173	170[27]
6	C_6H_5CHO	Methyl acetoacetate	4f	78	176	178[20]
7	4-$OMeC_6H_4CHO$	Methyl acetoacetate	4g	84	149	153[20]
8	C_6H_5CHO	Dimedone	4h	95	233	232[28]
9	4-ClC_6H_4CHO	Dimedone	4i	92	214–217	213–215[22]
10	3-$NO_2C_6H_4CHO$	Dimedone	4j	95	212	210[28]
11	4-OHC_6H_4CHO	Dimedone	4k	95	203–205	205–207[27]
12	4-MeC_6H_4CHO	Dimedone	4l	95	216	212[25]
13	Furaldehyde	Dimedone	4m	84	225	224[28]
14	4-FC_6H_4CHO	Dimedone	4n	94	117	192[27]
15	4-$NO_2C_6H_4CHO$	Dimedone	4o	94	180–182	176[27]
16	4-$OMeC_6H_4CHO$	Dimedone	4p	85	195–199	200[27]
17	2,4-$OMeC_6H_3CHO$	Dimedone	4q	75	180–182	181–183[30]

[a] Isolated yields.

and citric acid:choline chloride (1:1) for comparison. After considering all examined reaction media urea:choline chloride was selected as the best media due to obtained results (Table 1).

Under optimized reaction condition, a wide range of commercially available substituted aromatic as well as hetero aromatic aldehydes underwent this three-component condensation with malononitrile and dimedone by this procedure to produce 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes with good to excellent yields. The results were summarized in Table 2. The electronic effects of substrates had not impacted on the reaction yields and time. Aromatic aldehydes bearing electron-withdrawing groups as well as those possessing electron-donating groups in the reactions synthesized benzopyran derivatives in 80–95% yields. Several functionalities on the aromatic ring such as Cl, F, NO_2, OH, and OMe were found to be compatible with the reaction conditions. Moreover, under a mild reaction condition, acid-sensitive aldehydes such as 2-furfural participated under this protocol and give good yields without formation of any side products.

The scope of deep eutectic solvent as catalyst and reaction medium further investigated with other 1,3-dicarbonyl compounds such as acetylacetone, ethyl acetoacetate and methyl acetoacetate using aromatic aldehyde and malononitrile under similar reaction condition and the results were summarized in Table 2. The reactions of commercially available 1,3-dicarbonyl compounds with either electron-withdrawing or electron-donating substituents on the aromatic ring of the aldehyde proceeded well and synthesized benzopyran and pyran derivatives in good to moderate yields. The use of DES as a recyclable solvent and catalyst has the advantages of being economically viable and green for multicomponent reactions in the future. The reaction system can be successfully applied to a variety of aryl aldehydes as well as 1,3-dicarbonyl compounds to synthesize a wide variety of biologically active heterocycles in good to excellent yields. All prepared compounds were secured by spectroscopy data (^{1}HNMR), and by the comparison of the melting points with the literature values.

In addition, the DES can be recycled by a simple protocol. After the completion of the reaction, water was added to the reaction mixture, and participate was filtered. The obtained participate was recrystalized from ethanol to synthesize pure products. The water was evaporated and recovered DES was reused for second and third consecutive cycles without any significant loss in catalytic activity (95%, 90% and 86%), respectively, for the three consecutive cycles in the synthesis of **4 h**.

The procedure described here appears to be highly efficient and competitive with other methods reported in the literature for the synthesis of benzopyran and pyran derivatives. The ring-opening reaction of styrene oxide in the presence of different catalyst is compared in Table 3.

4. Conclusion

In summary, we have demonstrated a rapid, efficient and inexpensive one-pot synthesis of pyran and benzopyran in six different types of choline chloride based deep eutectic solvents under mild reaction condition. Urea:choline chloride showed the best results for the synthesis of pyran and benzopyrans as important pharmacophore in medicinal chemistry. The present method offers the advantages of catalyst-free reaction, easy purification, short reaction time, and high yield. Further studies in our laboratory are underway to develop new multicomponent reactions in this green reaction media.

Table 3
Comparing of previous reports on the benzopyran synthesis in the literature.

Entry	Catalyst	Solvent	Time [h]	Yield [%]	Ref.
1	Nano ZnO	H_2O	3.5	99	[28]
2	DAHP	H_2O	4	97	[23]
3	1,4-diaza-bicyclo[2.2.2]octane	H_2O	2	93	[24]
4	Hydrogen hexafluorosilicate	H_2O	0.5	32	[23]
5	Ionic liquid	H_2O	1	89	[23]
6	Ammonium acetate	EtOH	0.5	96	[26]
7	Silica nanoparticles	EtOH	0.4	94	[27]
8	$N(Et)_4ClO_4$	H_2O/MeCN	5	96	[22]
9	I_2	DMSO	3	92	[19]
10	$CeCl_3.7H_2O$	EtOH/H_2O	1.5	90	[29]
11	PEG 1000 based dicationic	Toluene	1	89	[28]
12	$MeCO_2H$	MeCN	2	81	[21]
13	Thiourea derivatives	Et_2O	4	65	[20]
14	—	DES	1	95	This work

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