ORIGINAL PAPER



Choline chloride/pentaerythritol: a deep eutectic solvent for the synthesis of pyran and chromene derivatives

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Received: 11 July 2020 / Accepted: 19 October 2020 © Iranian Chemical Society 2020

Abstract

A novel deep eutectic solvent system was prepared by mixing choline chloride as a hydrogen-bond acceptor with 2,2-bis(hydroxymethyl)propane-1,3-diol (pentaerythritol) as a hydrogen-bond donor. This green solvent was used for the one-pot synthesis of pyran and chromene derivatives from aromatic aldehydes, 1,3-dicarbonyl compounds, and malononitrile. The solvent was readily recycled and can be reused three times without significant loss of activity or mass. This procedure offers advantages such as environmental friendliness, shorter reaction times, and higher yields.

Graphical abstract



Keywords Deep eutectic solvent · Choline chloride · Pentaerythritol · Pyran · Chromene · Green chemistry

Introduction

The design of innovative organic and green solvents plays a significant role in synthetic organic chemistry [1-3]. Deep eutectic solvents (DESs) are a new class of green organic solvents introduced by Abbott [4] and continuously have

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13738-020-02108-5) contains supplementary material, which is available to authorized users.

Published online: 21 November 2020

been investigated in academic and applied research for more than a decade. In general, a DES is defined as simple mixture of two or three components forming a eutectic with lower melting point than each of the pure components. This liquid system, composed of a network of hydrogen-bond acceptor and hydrogen-bond donor molecules, provides suitable polarity owing to the abundance of hydrogen bond [5–9]. These solvents are less toxic, biodegradable, cheap, easy to prepare, with low vapor pressure and melting points, and often good thermal stability [10, 11].

The combination of choline chloride (ChCl) and urea as a deep eutectic solvent has been applied to the synthesis of benzo-fused seven-membered heterocycles via a one-pot, three-component reaction [12]. Recently, sustainable synthesis and application of natural DES systems based on malic acid, citric acid, xylitol, and water were

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reported [13]. The effect of water on the physicochemical properties and on the structural features of three DESs formed by ChCl and glycols with a different number of oxyethylene units has been evaluated [14]. A series of ternary DES systems have been prepared using a mixture of microorganism-derived (R)-3-hydroxynonanoic and (R)-3-hydroxyheptanoic acids as hydrogen-bond donors and selected quaternary ammonium salts as hydrogen-bond acceptors [15].

Pyrans are attractive heterocyclic compounds with various biological and pharmacological activities such as antimicrobial [16], antioxidant [17], antibacterial [18], anticancer [19], and antiproliferative [20] properties. Various approaches have been employed for the synthesis of pyrans, some of them suffered from disadvantages including the use of toxic and volatile organic solvents and expensive catalysts, high temperatures, laborious and complex procedures. Following the increasing environmental and economic considerations, the search for enviro-economic synthetic methods for organic reactions has received overwhelming attention. In this regard, efforts are being made to replace the expensive and hazardous solvents and catalysts with environmentally benign biodegradable materials. Herein, we describe the preparation and characterization of choline chloride/pentaerythritol (ChCl/PE) DES system and its application as dual solvent and organocatalyst in the one-pot synthesis of pyran and chromene derivatives from aromatic aldehydes, malononitrile, and 1,3-dicarbonyl compounds.

Experimental

Materials and methods

All starting materials and DES components were purchased from Merck and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. FT-IR spectra were recorded on a Shimadzu IR-460 instrument using the KBr self-supported pellet technique. ¹H and ¹³C NMR spectra: Bruker DRX-300 Avance instrument at 300 and 75 MHz, resp.; δ in ppm, *J* in Hz (Scheme 1).

Preparation and characterization of ChCI/PE DES system

ChCl/PE DES was prepared by mixing choline chloride (ChCl) and pentaerythritol (PE) with 1:1 molar ratio and heating the mixture at 75–80 °C for a period of 1 h until a clear solution was obtained (see Scheme 2). The reaction mixture was dissolved in water, and the insoluble crude ChCl/PE DES was filtered off. Colorless solid; M.p.: 75–80 °C. IR (KBr): (ν_{max} , cm⁻¹) = 3327 (O–H), 2954 (C–H), 2886 (C–H), 1481, 1409, 1276, 1129, 1016, 955; ¹H



Scheme 2. Proposed mechanism of the reaction in ChCl/PE DES system

NMR (300 MHz, DMSO- d_6): 3.12 (9 H, s, Me₃N), 3.26 (8 H, d, ³ J = 5.7 Hz, 4 CH₂O), 3.41 (2 H, t, ³ J = 5.0 Hz, CH₂N), 3.77–3.79 (2 H, m, CH₂O), 4.34 (2 H, t, ³ J = 5.7 Hz, 4 OH), 5.40 (1 H, t, ³ J = 5.0 Hz, OH) ppm; ¹³C NMR (75 MHz, DMSO- d_6): 46.0 (Me₃N), 53.3 (CH₂O), 55.3 (CH₂N), 60.6 (4 CH₂O), 67.1 (C) ppm.

The viscosity of the ChCl/PE DES was measured in a temperature range of 99–119 °C, using a Fungilab Expert



Fig.1 Viscosity (η) profiles of ChCl/PE DES in the temperature range between 99 and 119 °C

L viscometer, fitted with a thermostatic jacket and a temperature probe. The viscometer jacket was connected to an external thermostated bath. The viscosity measurements were carried out using a spindle attachment. The profiles of viscosity versus T (in °C) are shown in Fig. 1. The viscosity of ChCl/PE DES follows an Arrhenius-like behavior as it decreases with increase in temperature.

General procedure for the synthesis of pyran derivatives 4 and 6

A mixture of aldehyde 1 (1 mmol), nitrile 2 (1 mmol), 1,3-dicarbonyl compound 3 or hydroxyl compounds 5 (1 mmol), and ChCl/PE DES (2 mL) was heated at 75–80 °C for 1 h. After reaction completion (monitored by TLC), about 5 mL water was added to the mixture. In cases of precipitate formation, the solid was filtered. When a viscose liquid was separated after water addition, EtOAc was added to extract the product from the organic layer. The products 4 or 6 were purified by recrystallization from EtOH. All products were known and were characterized by comparison of their melting points (see Tables 2, 3) and spectroscopic data with those described in the literature [16, 21–24, 26–30].

Results and discussion

To examine the viability of this protocol, the three-component reaction of benzaldehyde (1a), malononitrile (2a), and dimedone (3a) was selected as a model reaction. As shown in Table 1, the reaction proceeds in common solvents such as H_2O , EtOH, and DMF at 80 °C and affords

Table 1 Synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a) in various solvents



Entry	Solvent	Temp (°C)	Yield (%) ^b
1	H ₂ O	80	60
2	EtOH	80	65
3	DMF	80	75
4	ChCl/urea (1:2)	80	80
5	ChCl/malonic acid (1:1)	80	78
6	ChCl/PE (1:1)	80	96
7	ChCl/PE (1:1)	60	70

^aReaction condition: 1a (1 mmol), 2a (1 mmol), 3a (1 mmol), in solvent (2 mL) for 1 h

^bIsolated yield

 Table 2
 Three-component synthesis of tetrahydro-4H-chromene derivatives 4



Entry	Ar	Е	3	Product yield (%)	M.p. (°C) found {reported}
1	Ph	CN			228–230 {232 [21]}
2	<i>p</i> -Me-C ₆ H ₄	CN		Ar CN Ar CN NH ₂ 4b (87%)	213–215 {212 [21]}
3	<i>p</i> -Cl-C ₆ H ₄	CN		$\begin{array}{c} O \\ H_{1} \\ H_{2} \\ H_{$	212–214 {213–215 [16]}
4	<i>p</i> -O ₂ N-C ₆ H ₄	CN	3a O O	40 (50 %)	173–175 {176 [21]}
5	<i>p</i> -Me ₂ N-C ₆ H ₄	CN	3a O O	4e (87%)	209–211 {208–210 [24]}
6	2-Furyl	CN	3a O J Ja	O 2-Furyl CN NH ₂	224–224 {224 [21]}
7	Ph	CN	O O J OEt 3b	$\begin{array}{c} O \\ EtO \\ O \\ O \\ O \\ O \\ NH_2 \\ 4g (92\%) \end{array}$	189–191 {192 [21]}
8	<i>p</i> -Me-C ₆ H ₄	CN	O O OEt 3b	$\begin{array}{c} \begin{array}{c} & \\ & \\ \\ & \\ \\ \\ & \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	155–157 {158 [21]}
9	<i>p</i> -O ₂ N-C ₆ H ₄	CN	O O J OEt 3b	$\begin{array}{c} 0 & \text{Ar} \\ \text{Eto} & & \text{CN} \\ & & 0 & \text{NH}_2 \end{array}$	180–182 {183 [21]}
10	p-Cl-C ₆ H ₄	CN			262–263 {263–264 [21]}
11	<i>p</i> -Me-C ₆ H ₄	CN	JC Me N N N N O N O N O N O	Me N + CN + CN + Me N + CN + Me	202–204 {203 [25]}

Table 2 (continued)

Entry	Ar	Е	3	Product yield (%)	M.p. (°C) found {reported}
12	p-Cl-C ₆ H ₄	CO ₂ Et		O Ar CO ₂ Et 41 (85%)	257–259 {256–259 [22]}
13	<i>p</i> -O ₂ N-C ₆ H ₄	CO ₂ Et	o J Ja	O Ar CO ₂ Et (NH ₂ 4m (80%)	180–182 {181–183 [23]}
14	<i>m</i> -O ₂ N-C ₆ H ₄	CO ₂ Et		Ar CO ₂ Et O NH ₂ 4n (83%)	183–185 {182–184 [23]}
15	<i>p</i> -O ₂ N-C ₆ H ₄	CO ₂ Et	O O O OEt OEt	Eto 40 (92%)	153–155 {152–155 [28]}
16	<i>p</i> -MeO-C ₆ H ₄	CO ₂ Et	O O OEt 3b	$\begin{array}{c} O & Ar \\ EtO & & CO_2Et \\ O & & NH_2 \\ 4p (92\%) \end{array}$	166–168 {167–169 [28]}

^aReaction condition: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), in ChCl/PE DES (2 mL) at 80 °C for 1 h ^bIsolated yield

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4a**) in moderate to good yields (Table 1, entries 1–3). Using ChCl/urea and ChCl/malonic acid DES systems, the yield of **4a** was increased to 80% and 78%, respectively. When the reaction was carried out in ChCl/PE DES solvent, product **4a** could be obtained in 96% yield (Table 1, entry 6). Increasing the reaction temperature to 90 °C did not improve the yield of **4a**, but decreasing the temperature to 60 °C reduced the yield to 70% (Table 1, entry 7). Thus, the optimal reaction conditions for preparation of **4a** is equimolar amounts of **1a**, **2a**, and **3a** in ChCl/ PE DES system at 80 °C.

Using the optimal reaction conditions, we extended the scope of the process using a broad range of aromatic aldehydes containing electron-withdrawing or electron-donating groups 1 and cyano components 2 in the presence of cyclic and open-chain 1,3-dicarbonyl compounds 3, which led to the formation of products 4 in good yields (Table 2).

Hydrogen bonding and basicity of ChCl/PE DES are important factors that influence the reactivity and selectivity of these reactions. A proposed mechanism for the formation of product **4a** is outlined in Scheme 2. The reaction proceeds by initial formation of aldehyde-malononitrile condensation adduct **7a**. This intermediate reacts with the active methylene compound **3a** to afford intermediate **8a**. Subsequently, intramolecular cyclization of **8a** gives imine **9a**, which is converted to product **4a** by imine–enamine tautomerization. ChCl/PE DES system can play a dual role in this reaction: (a) as a solvent and (b) as an organocatalyst which activates the carbonyl and nitrile functional groups via extensive hydrogen bond formation.

To further explore the potential of this one-pot reaction for synthesis of chromene derivatives, we investigated the reaction of benzaldehydes 1 and malononitrile (2a) in the presence of 1-naphthole (5a), 2-naphthole (5b), and 4-hydroxycumarin (5c) (see Table 2). As shown in Table 3, highly functionalized chromene derivatives 6a-6 g are obtained in good to excellent yields.

The stability of ChCl/PE DES was tested on the reaction of benzaldehyde, malononitrile, and 1-naphthol. The reaction mixture was dissolved in water, and the insoluble crude product **6a** was filtered off. The DES was readily recycled from the aqueous layer resulted from work up, dried at 80 °C for 2 h, and reused three times with 1-3% loss of activity or mass (see Table 4).

 Table 3
 Three-component reaction of benzaldehydes, malononitrile, naphthols, and 4-hydroxycoumarin in ChCl/PE DES



Entry	Ar	5	Product 6	M.p. (°C)	
				Found	Reported
1	C ₆ H ₅	OH C 5a	Ph CN NH2 Ba (04%)	215–217	216–217 [29]
2	<i>p</i> -MeO-C ₆ H ₄	OH C 5a	Ar CN 6b (91%)	196–197	195–196 [29]
3	p-Cl-C ₆ H ₄	OH C 5a	Ar CN NH ₂ 6c (88%)	242–244	243–244 [26]
4	p-O ₂ N-C ₆ H ₄	OH 5a	Ar CN 0 NH ₂ 6d (85%)	235–237	236 [27]
5	p-O ₂ N-C ₆ H ₄	Sb OH	O ₂ N CN NH ₂	188–190	187 [27]
6	Ph	OH C Sc	$ \begin{array}{c} be\left(cS_{\mathcal{H}}\right) \\ NH_{2} \\ CN \\ CN \\ CN \\ ff\left(R_{\mathcal{H}}\right) \\ ff\left(R_{\mathcal{H}}\right) \end{array} $	255–257	256–258 [30]
7	p-Cl-C ₆ H ₄	OH C 5c	G (20 %)	265–266	264–266 [26]

^aReaction condition: **1** (1 mmol), **2** (1 mmol), **5** (1 mmol), in ChCl/PE DES (2 mL) at 80 $^{\circ}$ C for 1 h ^bIsolated yield

Table 4 Recycling of ChCl/PE	Cycle
DES for synthesis of product	Cycle
6a by condensation reaction	1
benzaldehyde, malononitrile,	2
and 1-naphthol	2
	3

Yield (%		
94		
93		
91		

Conclusions

In summary, we have described the preparation of a new deep eutectic solvent system by mixing choline chloride (ChCl) as a hydrogen bond acceptor with 2,2-bis(hydroxymethyl) propane-1,3-diol (pentaerythritol, PE) as a hydrogen bond donor. This DES was used for the one-pot synthesis of pyran derivatives from aromatic aldehydes, 1,3-dicarbonyl compounds, and malononitrile. Highly functionalized chromene was also prepared using benzaldehydes and malononitrile in the presence of 1-naphthole, 2-naphthole, and 4-hydroxycumarin. The easy preparation, short reaction time, high yield, and simple work-up procedures are significant advantages of this method.

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