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Choline chloride based eutectic solvent: an efficient and reusable solvent system for the synthesis of primary amides from aldehydes and from nitriles[†]

Choline chloride: a 2ZnCl₂ based deep eutectic solvent was found to be a simple, green, efficient and new

solvent system for the preparation of primary amides from aldehydes. The same catalytic system is also

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applicable for the preparation of amides from nitriles. Good to excellent yields of primary amides were obtained in both these transformations.

Organic functional groups play a key role in synthetic chemistry and among them, amides are the most significant and productive. These groups are present in detergents, lubricants, biologically active molecules, agrochemicals, pharmaceuticals and polymers. Also, amides are the most important functional group necessary to maintain biological systems.¹

Amides are important building blocks of peptides, many natural products and synthetic materials.^{2,3} Various methodologies have been developed for the preparation of amides due to their importance as intermediates in organic syntheses.⁴ Aldehydes and nitriles are the attractive starting materials for syntheses of amides as they are inexpensive and easily available. Generally, amides are prepared by reacting amines with either acyl chlorides, or acid anhydrides or esters or coupling reagents such as carbodiimides.5 They are also obtained via the metalmediated hydrolysis of organonitriles.6 These reactions produce lot of waste and toxic materials. Various catalytic methods have been reported for the synthesis of amides from aldehydes and nitriles,⁷⁻¹⁴ owing to their non-toxic character. However it is very difficult to separate the catalyst and product from the reaction mixture in these transformations. In the case of air sensitive metal catalysts, an inert atmosphere is required. Some metal catalysts such as rhodium, ruthenium, iridium, and palladium are very costly. Some of the metals like nickel, indium, and zinc reduce the selectivity of the product when used as a catalyst.15

Hence the preparation of amides from aldehydes as well as from nitriles under ecofriendly conditions has been a great challenge. The other objective of this research work was to develop an atom efficient and greener route for the synthesis of amides and thereby to reduce the waste and toxic material. Herein we report a method for the synthesis of amides from aldehydes and from nitriles by using a choline chloride based deep eutectic solvent (ionic liquid) as the catalyst (Fig. 1). Table 1 summarizes some of the catalysts used for the synthesis of benzamide from an aldehyde and from a nitrile. The catalysts used in these reported methods are expensive or toxic. Our catalyst (choline chloride: 2 zinc chloride) gave a better yield than the reported catalysts (Table 1 entry 1–13). It is clear from Table 1 that the reported catalysts are used only for one transformation. Whereas the choline chloride: 2 zinc chloride solvent can used for both of the transformations to form amides from aldehydes as well as from nitriles (Table 1 entry 12, 13).

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Deep eutectic solvents (DESs) have attracted a lot of attention as green solvents for many organic transformations. The properties of DES are similar to those of ionic liquids. Negligible vapor pressure, nonflammability, a non-toxic and biodegradable nature, low cost and thermal stability are the important properties of DESs. Some of the eutectic mixtures used are, choline chloride with MCl_2 (M = Zn or Sn)¹⁶ and substituted alkyl imidazolium–chloroaluminates.¹⁷ A choline chloride–zinc chloride based ionic liquid has been effectively used for the Diels–Alder reaction,¹⁸ Fischer-indole synthesis,¹⁹ O-acetylation



Fig. 1 Greener routes for the synthesis of amides from aldehydes and nitriles by using $ChCl \cdot 2ZnCl_2$ based DES.

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Table 1 Catalytic performance of different catalysts and solvents for the synthesis of an amide from aldehyde and from nitrile

Entry	Starting material	Catalyst/base	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ref.
1	Aldehyde (1a)	Fecl ₃ /Cs ₂ CO ₃	H ₂ O	100	20	95	7a
2	Aldehvde (1a)	OMS-2	1,4 Dioxane	130	3	89	7 <i>b</i>
3	Aldehyde (1a)	Ru(II) carbonyl complexes	Acetonitrile	78	18	89	9 <i>c</i>
4	Aldehyde (1a)	$Cu(OAc)_2$	H_2O	100	48	91	9 <i>e</i>
5	Aldehyde (1a)	$Pd(OAc)_2/Cs_2CO_3$	DMSO	100	15	98	14b
6	Aldehyde (1a)	Ru(complex)/NaHCO ₃	H_2O	100	7-24	50-92	7 <i>c</i>
7	Nitrile (4a)	NiNPs	H ₂ O	120	10	85	10b
8	Nitrile (4a)	$Ru(OH)x/Al_2O_3$	H_2O	140	6	99	11 <i>e</i>
9	Nitrile (4a)	Ru(complex)	H ₂ O	100	2	86	11f
10	Nitrile (4a)	Ag/SiO ₂	H_2O	140	48	85	11 <i>c</i>
11	Nitrile (4a)	Incl ₃	Toluene	Reflux	3	98	11 <i>d</i>
12	Aldehyde (1a)	DES	_	100	15	94	This work
13	Nitrile (4a)	DES	H_2O	100	12	98	This work

of cellulose and monosaccharide,²⁰ protection of carbonyl groups,²¹ Kabachnik–Fields reaction,²² synthesis of oxazoles,²³ coumarin synthesis²⁴ and for the preparation of polymers.²⁵

We have developed a greener route for the synthesis of an amide by using a DES. Initially the DES was prepared by a simple procedure. A mixture of choline chloride (1 mmol) and zinc chloride (2 mmol) was heated at 100 $^{\circ}$ C for 30 min. The obtained clear homogeneous liquid was then cooled slowly at room temperature.

The reaction was carried out by using 0.106 g of benzaldehyde (1 mmol) and 0.069 g of hydroxyl amine hydrochloride (1 mmol) in the presence of a choline chloride-zinc chloride deep eutectic solvent (4 g). The mixture was stirred for 15 h at a temperature of 100 °C. Benzamide was obtained with a 94% isolated yield (Scheme 1). We have also shown that the path of formation of benzamide from benzaldehyde is *via* benzaldoxime (**5a**) formation during the course of reaction (Fig. 2). This was confirmed by GC-MS and ¹H NMR.

To generalise this protocol, various aromatic and aliphatic substrates were used (Table 2). This catalytic system was found to be applicable for aromatic, aliphatic and conjugated substrates. The aromatic aldehydes having electron donating or withdrawing groups gave excellent product yields (Table 2, entries 1–6). α , β -Unsaturated derivatives also gave excellent product yields (Table 2, entries 7 and 9). An interesting case is the preparation of phthalimide from phthalic anhydride. An excellent yield was obtained under the same reaction conditions (Table 2, entry 8).

We also developed a simple and efficient route for the synthesis of amides from nitriles by using the choline chloride: 2 zinc chloride based ionic liquid. The hydration of benzonitrile was carried out at a temperature of 100 $^{\circ}$ C for 12 h. It was



Scheme 1 Preparation of amide from aldehyde.

observed that a small quantity of water increased the product yield to 98% in this reaction (Scheme 2).

The applicability of the protocol was verified by preparing different types of amides from various nitriles (Table 3). The amidation of a nitrile, bearing electron-donating or electronwithdrawing groups, gave excellent product yields (Table 3 entry



Fig. 2 Possible reaction path for the choline chloride: 2 zinc chloride catalyzed amidation of primary aldehydes to primary amides.

Table 2 Conversion of aldehydes and anhydride to amides by using DES^a

Entry	Substrate	Product	Time (h)	Yield ^b
1	СНО	CONH ₂	15	94
	Ia CHO	3a CONH ₂		
2	CH ₃	CH ₃ 3b	16	86
	СНО			
3	OCH ₃	OCH ₃	17	89
		CONH ₂ OCH ₃		90
4	ld	3d	19	
5			15	93
6	CHO CI	CONH ₂ CI 3f	18	87
	сно	CONH ₂		
7		39	14	92
8		O NH	12	93
	O 1h	3h		
9	СНО	CONH ₂	15 ^c	91
	1i	3i		

 a Reaction Conditions: aldehyde (1 mmol), hydroxyl amine hydrochloride (1 mmol), DES (4 g) at a temperature of 100 °C. b Isolated yield. c At 80 °C.

1–10). The nitriles with electron donating groups at the *orthopara* positions gave excellent product yields. More time was required for *ortho* substituted groups (Table 3 entries 2–4),

which may be due to steric hindrance. The cases with electron withdrawing groups also gave excellent product yields (Table 2 entries 6 and 7). The strong withdrawing group required the maximum time for this transformation (Table 3 entry 5). While aliphatic nitriles and vinyl nitrile also gave maximum product yields (Table 3 entries 8–10).

Reusability of the deep eutectic solvent was also one of the most important advantages of these transformations. Reusability of the DES was examined for the preparation of benzamide from benzaldehyde and from benzonitrile under optimized reaction parameters. The product was extracted in ethyl acetate and the DES was dried at 90 °C under vacuum. It was found that the deep eutectic solvent can be recycled for three times but with decrease in the product yield (Table 4).

Conclusions

(%)

In conclusion, we have developed a simple, greener and efficient catalytic system using a deep eutectic mixture for the synthesis of amides from aldehydes and from nitriles. DES was an ecofriendly, biodegradable, safe, cheap, and recyclable solvent system. The deep eutectic solvent (choline chloride: 2 zinc chloride) also represents a high-quality substitute over conventional ionic liquids due to its easy preparation.

Experimental

Preparation of the deep eutectic solvent (choline chloride: zinc chloride)

Choline chloride (1 mmol) and zinc chloride (2 mmol) were taken in a round bottom flask and heated up to 100 $^{\circ}$ C for 30 min to give a colourless transparent liquid. This was used as the eutectic solvent after cooling.

General process for the synthesis of amides from aldehydes

Aldehyde 0.106 g (1 mmol), hydroxyl amine hydrochloride 0.069 g (1 mmol) and choline chloride: 2 zinc chloride based DES (4 g) were added to a 50 ml round bottom flask and the reaction mixture was stirred at 100 °C. The progress of the reaction was monitored by TLC. The product was extracted in ethyl acetate. The solid product was obtained after evaporation of ethyl acetate. The obtained solid was purified by column chromatography over silica (ethyl acetate–*n*-hexane, 1 : 2). The pure product was characterized by GC-MS, ¹H NMR and ¹³C NMR.

Table 3 Conversion of nitriles to amides using DES^a

Table 3 (Contd.)

Entry	Substrate	Product	Time (h)	Yield ^b (%)	
10	CH ₂ CN	CH ₂ CONH ₂	10	87	

 a Reaction Conditions: nitrile (1 mmol), water (1 ml), DES (4 g) at 100 $^\circ \rm C$ temperature. b Isolated yield.

Table 4 Reusability study

Run	1	2	3	4	5
Yield ^a (%) Yield ^b (%)	94 98	90 96	82 93	78 89	70 82

 a Isolated yield of a mide prepared from aldehyde. b Isolated yield of a mide after hydration of nitrile.

General process for the synthesis of amides from nitriles

Nitriles 0.103 g (1 mmol), water (1 ml) and the choline chloride: zinc chloride based DES (4 g) were added to a 50 ml round bottom flask and the reaction mixture was stirred at 100 °C temperatures. The progress of the reaction was monitored by TLC. The product was extracted in ethyl acetate. The solid product was obtained after evaporation of ethyl acetate. The obtained solid was purified by column chromatography over silica (ethyl acetate–*n*-hexane, 1 : 2). The pure product was characterized by GC-MS, ¹H NMR and ¹³C NMR.

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