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Microwave Irradiated Deep Eutectic Solvent Catalysed Green, Rapid and Efficient Synthesis of Primary Amides

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Abstract: *Primary amides from aldehydes and nitriles were synthesized by using simple, greener and efficient Choline chloride: 2ZnCl2 based deep eutectic solvent (DES) as catalyst under microwave irradiation. Good to excellent yields of primary amides were obtained in this transformation. Deep eutectic solvent can be reused upto three cycles as a catalyst for amide synthesis without much loss in activity.*
Keywords: *Greener solvent, Deep eutectic solvent, Ionic liquid, Microwave irradiation, Primary amides, Recyclable catalyst*

I. INTRODUCTION

Primary amides are the most important functional groups in synthetic organic chemistry. These groups are present in natural products, detergents, lubricants, biologically active molecules, agrochemicals, pharmaceutical, polymers, and also in peptides as building blocks [1, 2]. Various methods are reported in the literature for the synthesis of amides [3], since it is the basic reaction in organic chemistry [4]. Generally amides are prepared by reacting amines with either acyl chlorides, or acid anhydrides or esters [5]. These reactions produce lot of waste and toxic materials during the synthesis of amide. Various catalytic methods are also reported for the synthesis of amides from aldehydes and nitriles [6-13]. However; it is very difficult to separate the catalyst and product from reaction mixture in these transformations. Most of the metal catalysts such as rhodium, ruthenium, iridium, and palladium are very costly as well as reduces the selectivity of product [14, 15] The present research work is the continuation of our earlier reported work [16]. Aldehydes and nitriles are inexpensive and easily available. We have synthesized amides from aldehydes and nitriles by conventional method using Choline chloride: $2ZnCl_2$ based deep eutectic solvent (DES) as catalyst as well as solvent. The objective of this research work was to make the protocol more efficient by reducing the amount of DES and also the reaction time. The microwave irradiated synthesis of primary amides from aldehydes as well as from nitriles can be the better alternative to the conventional method. It is the greener, atom economical and very rapid synthetic route. Choline chloride: 2ZnCl2 based deep eutectic solvent (ionic liquid) is used as the catalyst (Fig. 1).

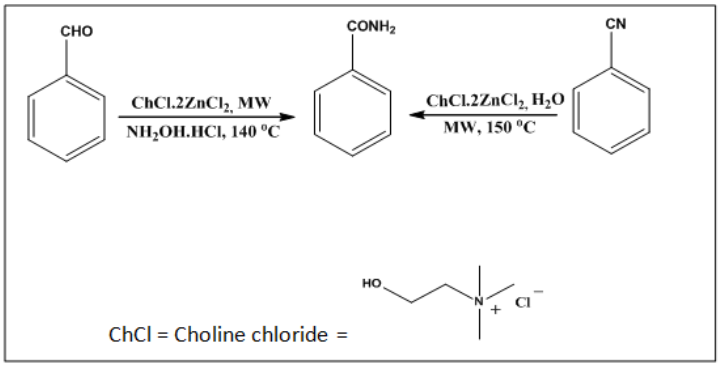


Fig 1. synthesis of primary amide by using choline chloride: $2zncl_2$ based des as catalyst under microwave irradiation

The DES is attracting lot of attention since it can be used as'green catalyst' in various organic reactions. The properties of DES are similar to that of ionic liquid. They possess negligible vapour pressure. They are thermally stable, nonflammable, non-toxic and biodegradable in nature. Abbott et. al has extensively studied the applications of DES [16]. Choline chloride: 2ZnCl2 based DES has been efficiently used for many organic transformations [17]. The DES was prepared by heating the mixture of choline chloride (1 mmol) and zinc chloride (2 mmol) at 100 °C for 30 min [18].

II. EXPERIMENTAL

2.1 Materials

Hydroxyl amine hydrochloride (99%), Choline chloride (99%), Benzonitrile (99%) obtained from Sigma-Aldrich. zinc chloride and aldehydes procured from S. D. Fine chemicals, Mumbai. 2.2 Preparation of 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 ºC, for 30 min. to give colourless transparent liquid. This was used as a eutectic solvent after cooling.

2.3 General process for the microwave irradiated synthesis of primary amides from aldehydes

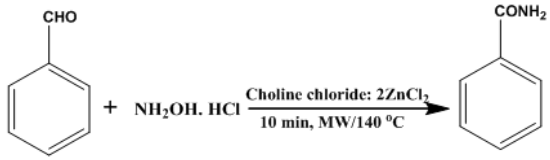
A mixture of aldehyde 0.106 gm. (1 mmol), hydroxyl amine hydrochloride 0.069 gm. (1 mmol) and choline chloride: 2 zinc chloride based DES (2 gm) were added in vial and the reaction mixture was stirred at 140 ºC temperature for 10 min under microwave irradiation. The product was extracted in ethyl acetate. The solid product was obtained after evaporation of ethyl acetate. The obtained solid was purified by column chromatography over silica. The pure product was characterized by GC-MS and 1H NMR.

2.4 General process for the microwave irradiated synthesis of primary amides from nitriles:

Nitriles 0.103 gm. (1 mmol), Water (1 ml) and choline chloride: 2 zinc chloride based DES (2 gm) were added in vial and the reaction mixture was stirred at 150 ºC temperature for 10 min under microwave irradiation. 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. The pure product was characterized by GC-MS and 1H NMR.

III. RESULTS AND DISCUSSION

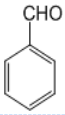
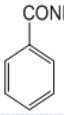
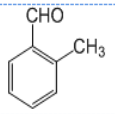
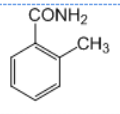
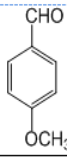
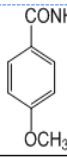
The synthesis of benzamide under microwave irradiation was carried out at 150 °C temperature for 10 min. by using 0.106 gm of benzaldehyde (1 mmol) and 0.069 gm of hydroxyl amine hydrochloride (1 mmol) in the presence of choline chloride/zinc chloride deep eutectic solvent (2 gm). 97 % benzamide was obtained (scheme 1).This is a very encouraging result as it shows 50% reduction in the amount of DES as compared to the conventional method.

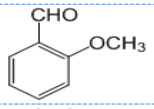
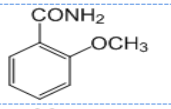
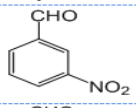
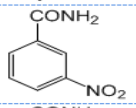
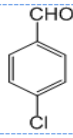
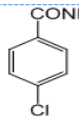
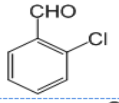
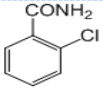
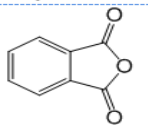
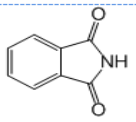
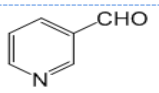
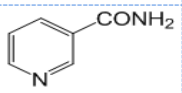


Scheme 1. Preparation of primary amide from aldehyde

The applicability of this protocol for the synthesis of various substituted benzamides under microwave irradiation was investigated and it was found that benzaldehyde can be transformed into the desired amides with good to excellent yield by using DES as the catalyst as well as solvent (Table 1). The yields of the desired products obtained under microwave irradiation are higher and that too in short time than the conventional method [16]. The benzaldehyde having electron donating or electron withdrawing groups gave good to excellent yield of products (Table 1).

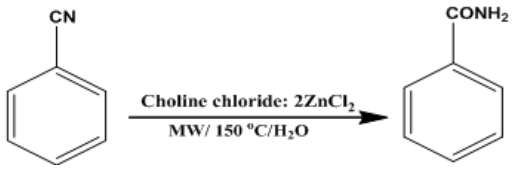
Table 1. Preparation of primary amides from aldehydes under microwave irradiation by using DES[a]

Entry	Substrate	Product	Yield[b] (%)
1			97
2			90
3			92

4			94
5			94
6			97
7			92
8			92
9			90

[a]Reaction Conditions: aldehyde (1 mmol), hydroxyl amine hydrochloride (1 mmol), DES (2 gm) at 140 °C temperature for 10 min under MW irradiation.
[b]Isolated yield of product.

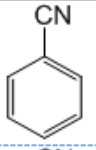
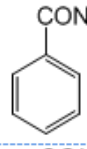
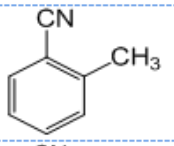
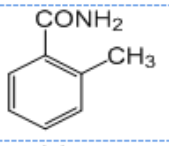
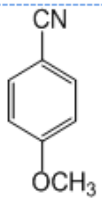
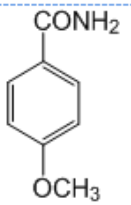
We have also carried out microwave irradiated synthesis of amide from nitrile by using Choline chloride: 2ZnCl2 based ionic liquid. The hydration of benzonitrile under microwave irradiation was carried out at 140 °C temperature for 10 min. The product yield was 99 % (Scheme 2).

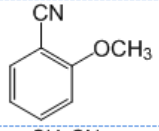
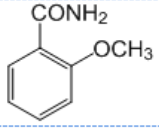
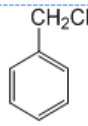
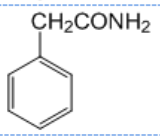
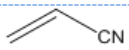


Scheme 2 Preparation of primary amide from nitrile

Furthermore we have investigated the applicability of the present method for various nitriles and obtained excellent yields of corresponding amides (Table 2 entries 2-6). The substituted and unsubstituted nitriles provided good to excellent yield of products (Table 2 entries 1-6)

Table 2. Preparation of primary amides from nitriles under microwave irradiation by using DES[a]

Entry	Substrate	Product	Yield [b](%)
1			99
2			93
3			98

4			96
5			98
6			90

[a]Reaction Conditions: nitrile (1 mmol), water (1 ml), DES (2 gm) at 140 °C temperature for 10 min under MW irradiation.
[b]Isolated yield.

Reusability of the DES was one of the important advantages of this protocol. Reusability of the DES was examined for the preparation of benzamide from benzaldehyde and also from benzonitrile under same reaction conditions. Product was extracted in ethyl acetate and DES was dried at 90°C under vacuum. It was found that deep eutectic solvent can be recycled upto three times with marginal decrease in product yield (Table 3).

Table 3 Reusability study

Run	1	2	3	4	5
Yield [a] (%)	97	92	84	79	72
Yield [b] (%)	99	95	91	87	79

[a]Isolated yield of amide prepared from aldehyde.
[b]Isolated yield of amide after hydration of nitrile

IV. CONCLUSION

In conclusion, we have developed environmentally benign one-pot synthesis of primary amides from aldehydes and also from nitriles under microwave irradiation. Short reaction time, high yield and a simple, greener and efficient catalytic system are the major advantages of the reported method. Choline chloride: 2ZnCl2 is eco-friendly, biodegradable, safe, cheap, and recyclable solvent system. It also gives high product yield as compared to conventional ionic liquids.

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