

Deep eutectic solvent catalyzed green, rapid and efficient synthesis of secondary amides from ketones

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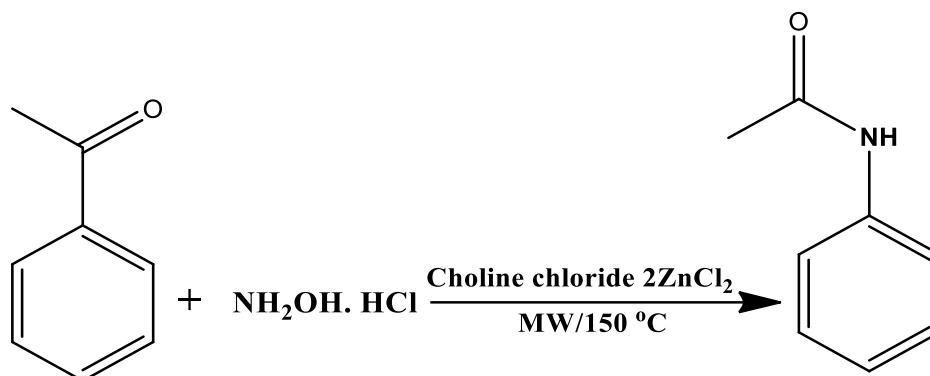
ABSTRACT

Synthesis of secondary amides from ketones by conventional microwave irradiation methods. The simple, greener and efficient Choline chloride: 2ZnCl₂ based deep eutectic solvent is used as catalyst. Good to excellent yields of secondary amides were obtained in this transformation.

KEYWORDS

Secondary amides, deep eutectic solvent, ketones, hydroxyl amine hydrochloride, microwave

GRAPHICAL ABSTRACT



I. INTRODUCTION

Amides are the most important functional group in synthetic chemistry. These groups are present in peptides as building blocks [1] in natural product, detergents, [2] lubricants, biologically active molecules, agrochemicals, pharmaceutical and polymers. They also sustain the life system. [3] Amide formation is a fundamental reaction in organic synthesis [4].

Numerous methods for the preparation of amide are reported in the literature [5]. Ketones are inexpensive and easily available starting materials for synthesis of amides. The synthesis of secondary amides through rearrangement of ketoximes is known as Beckmann reaction and it is an important reaction in organic chemistry [6]. In this rearrangement reaction, the synthesis of amides from ketones requires harsh conditions such as a large amount of a strong acid and high reaction temperature and time. Various methods are reported to avoid the harsh reaction conditions. Reaction carried out in liquid phase, [7] in vapour phase, [8] in supercritical water, [9] ionic liquids [10] and one-pot Beckmann rearrangement of ketones under microwave irradiation reported earlier [11].

Also amides are prepared by reacting amines with either acyl chlorides, or acid anhydrides or esters or coupling reagents such as carbodiimides. [12] These reactions produce lot of waste and toxic materials. Many of these catalytic methods are also reported for the synthesis of primary amides from aldehydes and nitriles [13], [14], [15], [16], [17], [18], [19], [20]. Owing to their non-toxic character. However, difficulties in separation of catalyst and product from reaction mixture as well as inert atmosphere for air sensitive metal catalysts are main drawbacks of these transformations. Some metal catalysts such as rhodium, ruthenium, iridium, and palladium are very costly. Hence the synthesis of amides from ketones through Beckmann rearrangement under

environmentally friendly conditions was the challenge. The important objective of this research work was to increase atom economy and develop a greener route for the synthesis of amides by reducing the waste and toxic material.

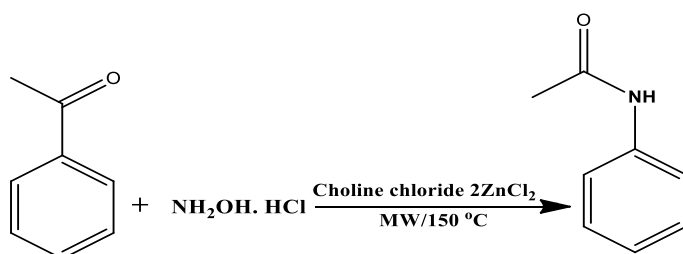
The important properties of Deep eutectic solvent (DES) are negligible vapour pressure, no flammability; non-toxic, biodegradable nature, low cost and thermal stability. The properties of DES are similar to that of ionic liquid. The DES is gaining lot of attention as green catalyst in organic synthesis. Abbott et. al has extensively studied the applications of DES [21]. Choline chloride: 2 zinc chloride based ionic liquid have been efficiently used for many organic transformations. [22]

II. RESULTS AND DISCUSSION

Herein we report Microwave irradiated synthesis of amides from ketones by using choline chloride based deep eutectic solvent (ionic liquid) as the catalyst (Scheme 1).

Choline chloride: 2 ZnCl₂ gave the maximum yield of desired products. The DES was prepared by simple reported method. The mixture of choline chloride (1 mmol) and zinc chloride (2 mmol) was heated at 100 °C for 30 min.

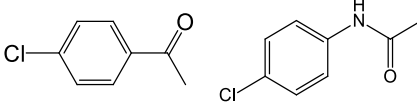
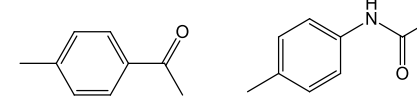
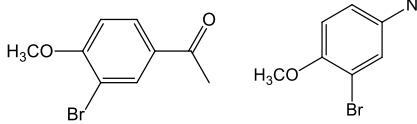
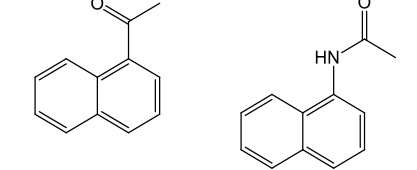
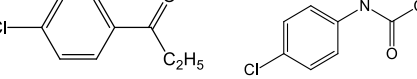
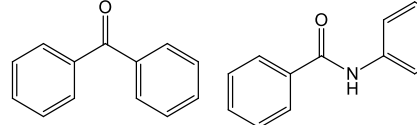
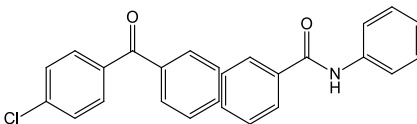
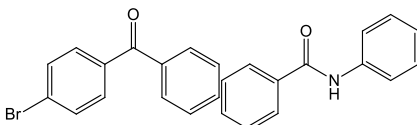
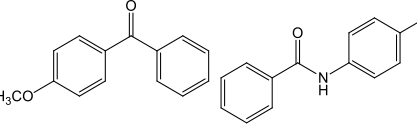
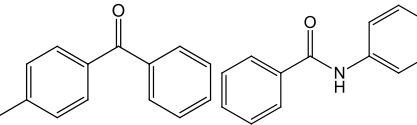
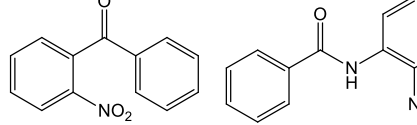
Mixture of 0.120 gm of ketone (1mmol) and 0.069 gm of hydroxyl amine hydrochloride (1mmol) in the presence of choline chloride/zinc chloride deep eutectic solvent (2 gm) was heated at 150 °C for 10 min. 90 % product yield was obtained. The formation of secondary amides from corresponding ketoxime through Backmann rearrangement is shown in Scheme 1.



Scheme 1 Preparation of secondary amide from ketone by using choline chloride: 2 ZnCl₂ based deep eutectic solvent (DES).

Table 1 Synthesis of amides from various ketones by using choline chloride: zinc chloride based DES^a

Entry	Substrate	Product	Time		Yield ^b (%)	
			Conventional (h)	M.W. Irradiation ^c (min)	Conventional	M.W. Irradiation
1			12	10	87	90
2			12	10	85	88
3			12	10	70	77

4		12	10	80	85
5		12	10	87	91
6		12	10	77	80
7		12	10	84	89
8		12	10	60	66
9		12	10	87	92
10		12	10	79	83
11		12	10	82	83
12		12	10	80	82
13		12	10	83	85
14		12	10	65	70

^aReaction Conditions: ketone (1 mmol), hydroxyl amine hydrochloride (1 mmol), DES (2 gm) at 150 °C temperature.

^bIsolated yield of product.

The applicability of this rearrangement was verified by preparing different types of secondary amides from various ketones by using DES as the catalyst as well as solvent for reaction (Table 1). The DES can be used for the preparation of secondary amide under microwave irradiation as well as under conventional methods. The yields of the products obtained by microwave irradiation are higher than the conventional method. The corresponding amides are obtained in high yields for electron-donating as well as electron-withdrawing groups (Table 1).

Table 2 Reusability study of catalyst^a

Entry	No. of cycle	Yield ^b (%)
1	1	90
2	2	87
3	3	85
4	4	79
5	5	72

^aReaction Conditions: ketone (1 mmol), hydroxyl amine hydrochloride (1 mmol), catalyst (2 gm), at 150°C temperature for 10 min. under M.W. irradiation.

^bIsolated yield of product

Reusability of the deep eutectic solvent was also one of the most important advantage of these transformations. Reusability of the DES was examined for the preparation of N-phenylacetamide from acetophenone. After completion of reaction, the product was extracted in ethyl acetate. The DES was dried at 90°C under vacuum. It was found that deep eutectic solvent can be recycled for three times but with marginal decrease in product yield (Table 2).

III. CONCLUSION

We have developed environmentally benign one-pot synthesis of amides from ketones by using environmentally friendly deep eutectic solvent. The DES can be efficiently used for these transformations for synthesis of nitriles under microwave irradiation and conventional methods. Microwave irradiation is extremely efficient as compared to conventional method with respect to time. The developed protocol has advantages of high yield and a simple, greener and efficient catalytic system. The DES has advantages such as eco-friendly nature, biodegradable, safe, cheap, and recyclable solvent system. The deep eutectic solvent (choline chloride: 2zinc chloride) also gives high-quality substitute over conventional ionic liquids due to its easy preparation.

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 °C, for 30 min. to give colourless transparent liquid. This was used as a eutectic solvent after cooling.

General process for the synthesis of secondary amides from ketones:

Conventional method: A mixture of Ketone 0.120 gm. (1 mmol), hydroxyl amine hydrochloride 0.069 gm. (1 mmol) and choline chloride: 2 zinc chloride based DES (2 gm) was taken in a 25 ml round bottom flask and heated at 120 °C temperature for 12 h. under vigorous stirring. After completion of the reaction, the reaction mass was cooled to room temperature. 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.

Microwave Irradiation: A mixture of Ketone 0.120 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 150 °C temperatures 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.

Characterization data of the compounds

Acetanilide (Table 1, entry 1):

M.P. 113 °C ¹H NMR (300 MHz, CDCl₃) δ 2.15 (s, 3H), δ 7.09 (t, 1H), δ 2.72-2.32 (m, 2H), δ 7.50 (br, 1H), δ 7.52 (m, 2H), GC-MS (m/z): 135.0 (M⁺)

N-Phenylbenzamide (Table 1, entry 9):

M.P. 113 °C ¹H NMR (300 MHz, CDCl₃) δ 7.98 (s, 1H), 7.90-7.82 (m, 2H), 7.60-7.53 (m, 2H), 7.55-7.50 (m, 1H), 7.50-7.45 (m, 2H), 7.40-7.34 (m, 2H), 7.18-7.08 (m, 1H), GC-MS (m/z): 197.0 (M⁺)

N-(4-chlorophenyl) benzamide (Table 1, entry 10):

M.P. 113 °C ¹H NMR (300 MHz, CDCl₃) δ 9.70 (s, 1H), 8.08-8.00 (m, 2H), 7.80-7.75 (m, 2H), 7.71-7.30 (m, 4H), 7.20-6.90 (m, 1H), GC-MS (m/z): 231.0 (M⁺)

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