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Deep Eutectic Solvent as a Recyclable Catalyst for Three-Component Synthesis of β-Amino Carbonyls

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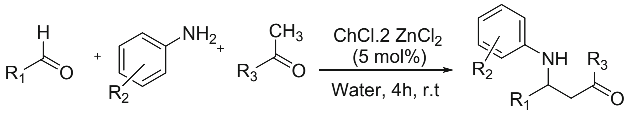
Abstract We have reported one-pot, three-component Mannich type reaction of aldehyde, amines and ketone (acetone and acetophenones), catalyzed by deep eutectic solvent (choline chloride/zinc chloride) at room temperature to give β-amino carbonyls in good yields. The catalyst could be recycled at least four times without remarkable decrease in its catalytic activity. The general method is easy, fast and environmental friendly.

Graphical Abstract



Keywords Choline chloride · Mannich · Green · Eutectic solvent · β-Amino carbonyl

1 Introduction

Multicomponent reactions are one of the most important class of reactions in organic synthesis, which have been used for the synthesis of various structures [1]. The first reaction of this class is three-component synthesis of β-amino carbonyl, discovered by Carl Mannich [2], which presents a simple method consisted of carbon–carbon bond formation. The Mannich reaction uses aldehyde, ketone and amine in the presence of catalyst [3] to prepare desired product. Since the first report of Mannich reaction, several studies have published to optimize the reaction conditions and present new and efficient catalysts for this reaction. In this line, using microwave [4, 5] and ultrasound irradiation [6], Lewis acids [7–10], Lewis bases [11] and metal salts [12] have reported as catalyst for this reaction. Although a large number of methods have been reported for the Mannich reaction, some of these methods have a series of limitations. To overcome these problems, ionic liquids (ILs) have introduced as new and green media for the Mannich reaction as well as their applications in many organic reactions [13–16]. ILs have desired properties such as thermal stability (some of them), wide range solubility for chemical (both organic and inorganic) compounds and low vapor pressure. However, using ILs has been restricted by some unfavorable properties such as high cost, degradation and toxicity [17]. Therefore, a new category of ILs, known as deep eutectic solvents (DESs), have presented. DESs were first described by Abbot et al. which consisted of the composition of two salts using simple procedure to prepare the mixture with low meting point [18]. In this line, choline chlorides (ChCl) have been extensively used as a green, biodegradable and non-toxic structure in DESs [17–24] in composition with many organic and inorganic molecules.

Therefore, In the course of our previous efforts in multicomponent synthesis [25–27] it seems to be useful to use ChCl in combination of a Lewis acid (i.e. zinc chloride) in a multicomponent Mannich reaction. This mixture have been successfully used as a green media in many organic reactions. In this paper, we report the three-component Mannich reaction using $ChCl{\cdot}2ZnCl_2$ as both catalyst and solvent to prepare β-amino carbonyls. The employed methodology and results obtained in this research will be discussed in the next sections.

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2 Experimental

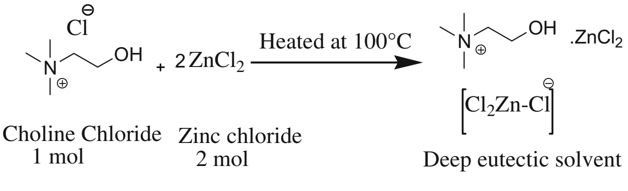
All chemical compounds have purchased from Sigma-Aldrich and Merck companies and used without further purifications. Melting points were determined using Gallen Kamp melting point apparatus. Thin layer chromatography was used to monitor the reaction and check purities. IR spectra (KBr) were recorded by JASCO FT-IR and ^{1}HNMR spectra and ^{13}CNMR spectra were recorded by Brucker Ultrashield 400 MHz. NMR chemical shifts were expressed in ppm versus the chemical shift of tetramethylsilane (TMS) as internal reference.

2.1 Preparation of Deep Eutectic Solvent

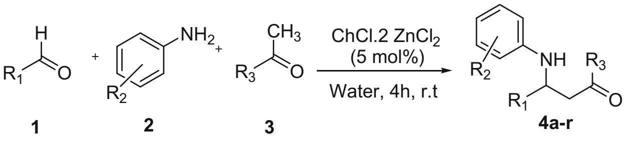
The employed DES (ChCl·2ZnCl$_2$) have synthesized according to the reported method [28]. The preparation method involved reaction of ChCl (1 mol) with ZnCl$_2$ (2 mol) at 100 °C (Scheme 1) to obtain a clear solution that will be used without further purification.

2.2 General Procedure for Preparation of β-Amino Carbonyls

In a round bottom flask, to a mixture ChCl·2ZnCl$_2$ (5 mol%) in 1 ml water (to reduce the viscosity and provide proton source), aldehyde (2 mmol), amine (2 mmol), and ketone (2 mmol) were added. The mixture was stirred at room temperature for a certain time (Scheme 2). After completion (confirmed by TLC), the precipitated crude product was collected by filtration and recrystallized from ethanol to obtain the pure product. The filtrate, containing catalyst, was recycled and directly used in the next run without further purification. The structures of all the products were determined by comparison of their melting points, elemental analysis, FT-IR, ^{1}HNMR and ^{13}CNMR spectra data with those of authentic samples [29–37].



Scheme 1 Preparation of deep eutectic solvent



Scheme 2 Mannich-type reaction catalyzed by the ChCl-2ZnCl$_2$

2.3 Selected Spectral Data

Choline chloride·2ZnCl$_2$: IR (KBr, cm^{-1}): 3,550, 3,500, 1,609, 1,473, 1,081, 952, 866. Elemental Anal. for (C, 14.75; H, 3.42; N, 3.4) Found: (C, 14.54; H, 4.037; N, 3.48).

4a: White solid, mp 169–170 °C, IR (KBr, cm^{-1}): 3,383, 3,020, 1,669, 1,598, 1,510, 1,298, 1,219, 1,073, 1,026, 997, 859, 710, 510. ^{1}HNMR (400 MHz, CDCl$_3$): 7.93 (d, 2H, J = 8.6 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.47 (m, 4H), 7.35 (m, 2H), 7.28 (m, 1H), 7.11 (m, 2H), 6.68 (t, 1H, J = 7.6 Hz), 6.58 (d, 2H, J = 7.6 Hz), 5.03 (dd, 1H, J = 5.2, 7.6 Hz), 4.58 (s, 1H), 3.53 (dd, 1H, J = 5.2, 15.4 Hz), 3.44 (dd, 1H, J = 7.6, 15.4 Hz).^{13}CNMR (100 MHz, CDCl$_3$): 45.3, 54.8, 113.8, 117.8, 126.4, 127.4, 128.2, 128.7, 128.8, 129.1, 133.4, 135.4, 136.7, 142.9, 144.7, 146.9, 198.2. Elemental Anal. for $C_{21}H_{19}NO$ (C, 83.72; H, 6.31; N, 4.65) Found: C, 84.05; H, 6.07; N, 4.72.

4e: Colorless solid, mp 149–151 °C, IR (KBr, cm^{-1}): 3,381, 1,674, 160, 1,509, 1,259, 1174,835, 510. ^{1}HNMR (400 MHz, CDCl$_3$): 7.97 (d, 2H, J = 7.6 Hz), 7.90 (d, 2H, J = 8.8 Hz), 7.47 (d, 2H, J = 7.6 Hz), 7.34 (t, 2H, J = 7.2 Hz), 7.10 (t, 2H, J = 7.6 Hz), 6.95 (t, 2H, J = 9.2 Hz), 6.67 (t, 1H, J = 7.2 Hz), 6.58 (d, 2H, J = 7.6 Hz), 4.97 (dd, 1H, J = 5.2, 7.6 Hz), 3.89 (s, 3H), 3.45 (dd, 2H, J = 5.2, 15.8 Hz).^{13}CNMR (100 MHz, CDCl$_3$):45.9, 55.06, 55.49, 113.7, 117.67, 126.35, 127.27, 127.47, 128.35, 128.55, 128.78, 128.93, 129.05, 130.31, 130.45, 130.55, 130.82, 143.19, 147.11, 163.5, 163.76, 196.74; Elemental Anal. for $C_{22}H_{21}NO_2$ (C, 79.76; H, 6.34; N, 4.23) Found: C, 80.14; H, 6.65; N, 4.12.

3 Results and Discussion

The reaction of benzaldehyde, aniline and acetophenone (model reaction) to prepare *β*-amino carbonyl was examined first without using ChCl·2ZnCl$_2$ (eutectic solvent) that any product has not been observed after 20 h. Therefore all reactions should be performed using ChCl·2ZnCl$_2$. To obtain the best reaction conditions, several experiments, based on the model reaction have designed using 5, 10, 15 and 20 % of ChCl·2ZnCl$_2$ in different times and temperatures. The results of optimization processes were listed in Table 1.

The data listed in Table 1 show that using 5 mol% of the catalyst (ChCl·2ZnCl$_2$) give the highest yield for the reaction. When the amount of catalyst increased to more than 5 mol%, the yield was decreased. Moreover, the best time for the model reaction is 4 h. To optimize the

Table 1 The effects of reaction time, temperature and catalyst loading on the reaction yield for the reaction of benzaldehyde, aniline and acetophenone

Entry	Catalyst (mol%)	Temp.	Time (h)	Yield
1	–	r.t.	20	0
2	5	r.t.	1	30
3	5	r.t.	4	96
4	5	r.t.	10	96
5	5	r.t.	20	96
6	10	r.t.	4	83
7	15	r.t.	4	75
8	20	r.t.	4	62
9	10	80	4	<50

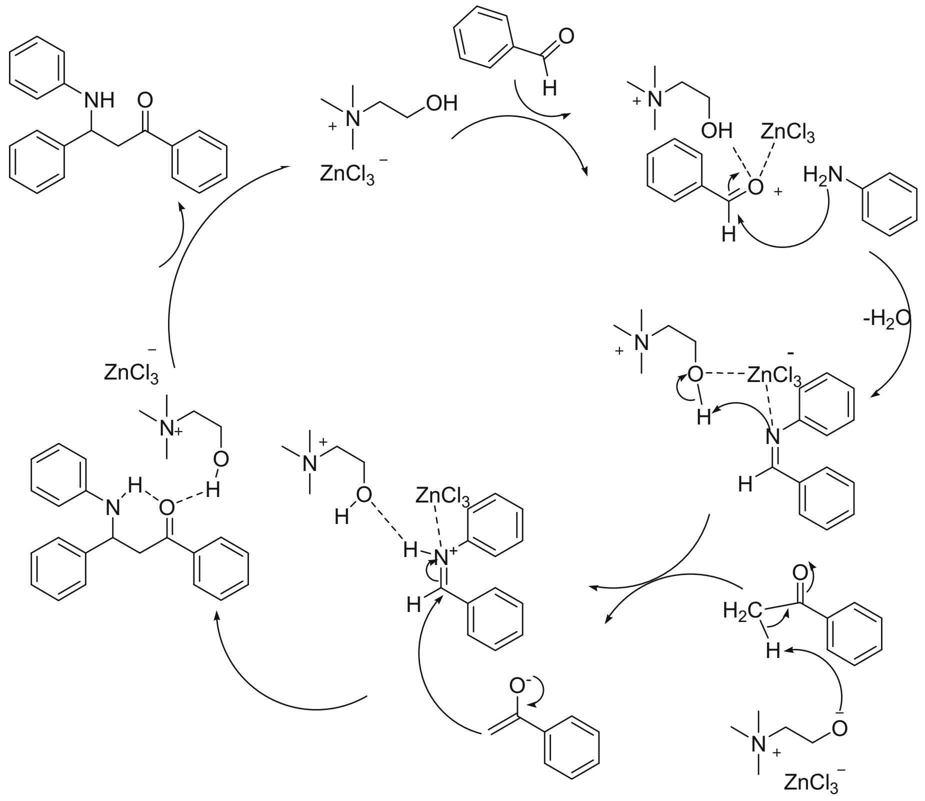
temperature, the model reaction has examined at various temperatures (one case was added to the end of Table 1). It was observed that with the increasing of reaction temperature, side reactions would be increased and the yield was decreased. Therefore, room temperature was obtained as best temperature for the reaction. All of these optimized conditions were used in next experiments for the synthesis of other β-amino carbonyls (Scheme 2) from the Mannich reaction.

To examine the versatility of the reaction and showing its ability to prepare various β-amino carbonyls, different substituted benzaldehyde were used with aniline or 4-nitroanilines (as amine sources) and acetone, acetophenone and 4-methoxy acetophenone as ketone sources at the optimized conditions (presented in previous paragraph) and the results obtained in these reactions were listed in Table 2. These experiments prove that ChCl·2ZnCl$_2$ could be employed as a general, green and effective catalyst for three-component Mannich synthesis of various β-amino carbonyl. The reaction proceeded effectively to give products with acceptable yields in the range of 52–98 %. The data listed in Table 2 show that aldehydes with an electron-donor substituent give higher yield than the others. Therefore, 4-nitrobenzaldehyde has the least yield and 4-hydroxy benzaldehyde has the highest yield in this reaction (entries **4b** and **4f** of the Table). Moreover, the yields of reactions using acetone are nearly the same with those values for acetophenone or 4-hydroxy acetophenone (comparing **4a**, **4h** and **4o**). Therefore, substituents on ketone have not important effect on the reaction yield. In some reactions, an amine with electron-withdrawing substituent (4-nitroaniline) was also investigated that a little smaller yields were observed in these reactions, involved with electron deficient amines. Mannich reactions were carried out for several aliphatic aldehydes (such as butanal, propanal and 2-methyl propanal) and because they are enolizable (they have α hydrogen), several products were observed that showed this reaction could not performed using aliphatic aldehydes.

This should be noticed that by previous reports, acceptable yields were obtained when the Mannich type was using neat ZnCl$_2$ as catalyst. However, neat ZnCl$_2$ is sometimes non-recoverable, corrosive and this process should use toxic solvents that do not represent green protocols [38, 39]. Therefore, we employed ChCl·2ZnCl$_2$ instead of neat ZnCl$_2$ as both catalyst and green solvent to

Table 2 Three component reaction of various aldehydes, anilines, and ketones catalyzed by ChCl·2ZnCl$_2$ at the optimized conditions (5 mol% eutectic solvent, 4 h and r.t)

Structure	R1	R2	R3	Yield %	Ref
4a	Ph	H	Ph	96	[29]
4b	4-NO$_2$-C$_6$H$_5$	H	Ph	52	[30]
4c	4-Cl-C$_6$H$_5$	H	Ph	73	[30]
4d	2-Naphthyl	H	Ph	98	[30]
4e	4-OMe-C$_6$H$_5$	H	Ph	91	[30]
4f	4-OH-C$_6$H$_5$	H	Ph	98	[31]
4g	H	H	Ph	64	[32]
4h	Ph	H	4-OCH$_3$-C$_6$H$_5$	98	[33]
4i	Ph	4-NO$_2$	4-OCH$_3$-C$_6$H$_5$	70	[34]
4j	Ph	4-NO$_2$	Ph	52	[35]
4k	4-Cl-C$_6$H$_5$	4-NO$_2$	Ph	64	[34]
4l	4-OCH$_3$-C$_6$H$_5$	4-NO$_2$	Ph	60	[36]
4m	3,4-OCH$_3$-C$_6$H$_5$	4-NO$_2$	Ph	98	[36]
4n	4-(Me)$_2$N-C$_6$H$_5$	4-NO$_2$	Ph	82	[36]
4o	Ph	H	CH$_3$	96	[37]
4p	4-OCH$_3$-C$_6$H$_5$	H	CH$_3$	95	[37]
4q	4-OH-C$_6$H$_5$	H	CH$_3$	84	[37]
4r	4-Cl-C$_6$H$_5$	H	CH$_3$	75	[37]



Scheme 3 Proposed mechanism for the synthesis of β-amino carbonyls

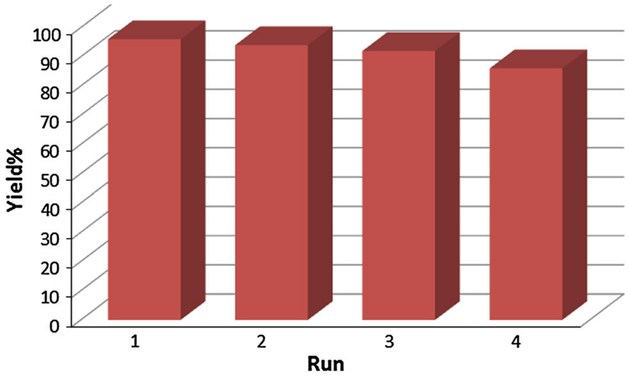


Fig. 1 Reusability of the catalyst

overcome these problems. The important role of ChCl·$2ZnCl_2$ in multicomponent reactions have been described previously [28, 40]. It was reported that the presence of choline chloride enhance the catalytic properties of zinc chloride. Abbott showed that the actual species presented in ChCl·$2ZnCl_2$, could be $[ZnCl_3]^-$, $[ZnCl_5]^-$, $[ZnCl_7]^-$. $[ZnCl_3]^-$. These species may act as Lewis base to adsorb a proton of acetophenone to give anionic species. Moreover, ChCl·$2ZnCl_2$ can form an acceptor–donor complex with the aldehyde and the imine in the first stage. Therefore, addition of the enol (or enolate) form of acetophenone could be facilitated. On the basis of these assumptions, the experimental results and reported studies, possible mechanism for the formation of β-amino carbonyl using ChCl·$2ZnCl_2$ was proposed in Scheme 3.

To complete this work, the recovering ability of ChCl·$2ZnCl_2$ in the model reaction using optimized conditions was examined and the results were shown in Fig. 1. After each run, the eutectic solvent (ChCl·$2ZnCl_2$) was isolated from the product and used without further purification in the next run. As shown in Fig. 1, ChCl·$2ZnCl_2$ could be reused at least four runs without remarkable loss of its activity.

4 Conclusions

In summary, an effective, green, and simple procedure have presented for the synthesis of β-amino carbonyl reaction using deep eutectic solvents (ChCl·$2ZnCl_2$) as both catalyst and solvent. The advantages of this method are simplicity, easy separation, recoverability of catalyst and high yields. In addition, the employed deep eutectic solvent is cheap, green (biodegradable and non-toxic) and could be easily prepared.

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