

Basic Functionalized Ionic Liquid Catalyzed One-pot *Mannich*-type Reaction: Three Component Synthesis of β -Amino Carbonyl Compounds

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Summary. Three-component *Mannich*-type reaction of cyclohexanone, aromatic aldehydes, and aromatic amines was catalyzed by a basic functionalized ionic liquid, 1-butyl-3-methylimidazolium hydroxide ([*bmim*][OH]), at room temperature to give various β -amino carbonyl compounds in high yields. The ionic liquid, which is environmentally friendly, can be recycled at least 5 times without significant loss of activity.

Keywords. *Mannich*-type reaction; Ionic liquid; Catalyst; One-pot reaction.

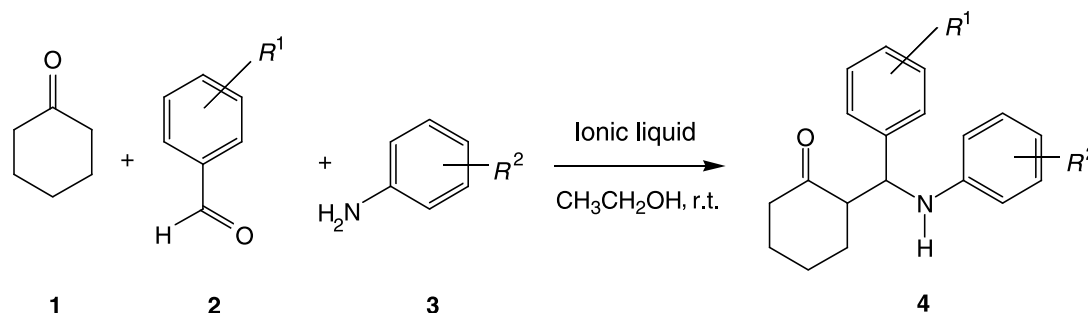
Introduction

The *Mannich*-type reactions are very important carbon–carbon bond-forming reactions in organic synthesis and have been one of the most basic and useful methods for the preparation of β -amino carbonyl compounds for its use in various pharmaceuticals, natural products, and versatile synthetic intermediates [1]. *Mannich* reactions have gained popularity in synthetic chemistry over the past decades. The most frequently used promoters like *Lewis* acid catalysts [2], *Brønsted* acid catalysts [3], *Lewis* base catalysts [4], rare metal salt catalysts [5], and organo catalysts [6] have been reported to catalyze the *Mannich* reaction. Most of these methods suffer from severe drawbacks including the use of large amount of catalysts, expensive reagents or catalysts, harsh reaction conditions and difficulty in

product separation, sometimes long reaction time, and low yield, *etc.* Hence, there is high interest in developing new convenient methods for the synthesis of β -amino carbonyl compounds.

Fortunately, ionic liquids have recently attracted increasing interest in the context of green synthesis nowadays, of which functionalized ionic liquids have been one of the hottest topics [7]. Basic functionalized ionic liquids have aroused unprecedented interest because they showed more advantages, such as convenient recycling and high catalytic efficiency than the mixture of inorganic base and ionic liquid for some base-catalyzed processes [8]. A basic functionalized ionic liquid [*bmim*][OH] has been successfully applied to catalyze the *Michael* addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles [9], the *Markonikov* addition of *N*-heterocycles to vinyl esters [10], and the three-component condensation reaction of aromatic aldehydes, malononitrile, and α - or β -naphthol for the synthesis of 2-amino-2-chromenes [11]. The versatility of this ionic liquid encouraged us to study its utility for three-component *Mannich*-type reaction. To the best of our knowledge in the open literature, one-pot *Mannich*-type reactions catalyzed by the basic ionic liquid [*bmim*][OH] have not yet been reported. Herein, we have discovered that this basic functionalized ionic liquid effectively promoted *Mannich*-type reaction of cyclohexanone, aromatic aldehydes, and aromatic amines under relatively mild conditions (Scheme 1).

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Scheme 1

Results and Discussion

In the initial experiments, we screened different basic functionalized ionic liquids for their ability to catalyze three-component *Mannich*-type reactions. Herein the reaction of cyclohexanone, benzaldehyde, and aniline was selected as model. The results are summarized in Table 1. No products were observed in the absence of ionic liquids (Table 1, entry 1). Among the basic functionalized ionic liquids, such as $[H_3NCH_2CH_2OH][CH_3COO]$, $[H_2N(CH_2CH_2OH)_2][CH_3COO]$, $[HN(CH_2CH_2OH)_3][CH_3COO]$, $[emim][OH]$, and $[bmim][OH]$ studied for this reaction, $[bmim][OH]$ was found to be the most effective catalyst for this conversion since it resulted in the highest conversion to the desired product (Table 1, entry 7). We also observed that 10 mol% of $[bmim][OH]$ (based on cyclohexanone) could most effectively catalyze the reaction (Table 1, entry 7), and increasing the amount of $[bmim][OH]$ to 20 mol% showed no substantial improvement in the yield (Table 1, entry 8). In conclusion, $[bmim][OH]$

Table 1. The *Mannich* reaction catalyzed by different basic functionalized ionic liquids^a

Entry	Ionic liquids (mmol)	Yield/% ^b
1	–	0
2	$[H_3NCH_2CH_2OH][CH_3COO]$ (1)	59
3	$[H_2N(CH_2CH_2OH)_2][CH_3COO]$ (1)	55
4	$[HN(CH_2CH_2OH)_3][CH_3COO]$ (1)	50
5	$[emim][OH]$ (1)	76
6	$[bmim][OH]$ (0.5)	55
7	$[bmim][OH]$ (1)	85
8	$[bmim][OH]$ (2)	81

^a Reaction conditions: cyclohexanone (10 mmol), benzaldehyde (10 mmol), aniline (10 mmol), *EtOH* (5 cm³), r.t., 10 h

^b Isolated yield

Table 2. The *Mannich* reaction catalyzed by $[bmim][OH]$ in different solvents^a

Entry	Solvents	Yield/% ^b
1	Water	52
2	<i>EtOH</i>	85
3	CH_3CN	81
4	CH_2Cl_2	60
5	None	61

^a Reaction conditions: cyclohexanone (10 mmol), benzaldehyde (10 mmol), aniline (10 mmol), $[bmim][OH]$ (1 mmol) as catalyst, solvent (5 cm³), r.t., 10 h

^b Isolated yield

is an effective catalyst for the *Mannich*-type reaction of cyclohexanone, benzaldehyde, and aniline.

Similarly, the model reaction of cyclohexanone, benzaldehyde, and aniline catalyzed by $[bmim][OH]$ at room temperature was chosen for investigating the effect of solvents. The effect of solvents on the yield of β -amino carbonyl compounds is given in Table 2. The model reaction proceeded smoothly in polar organic solvents, such as ethanol and acetonitrile (Table 2, entries 2, 3), which afforded better yields than others (Table 2, entries 1, 4, 5), and ethanol was found to be the most effective solvent.

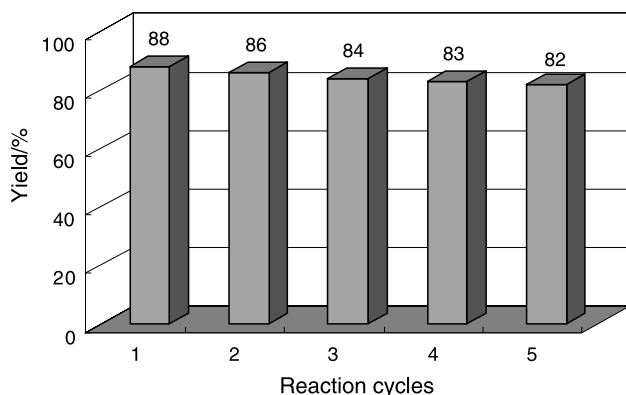
Next, we examined the scope of the reaction by using various aromatic aldehydes and aromatic amines. The results are summarized in Table 3. In general, the three-component *Mannich*-type reaction proceeded in presence of 10 mol% of $[bmim][OH]$ smoothly to give the corresponding products in high yields at room temperature in ethanol for 10 h. It should be noted that benzaldehydes and anilines carrying either electron-donating or electron-withdrawing substituents all reacted well. Particularly, aryl

Table 3. Three-component *Mannich*-type reaction of cyclohexanone, aromatic aldehydes, and aromatic amines catalyzed by $[bmim][OH]^a$

Entry	R^1	R^2	Product	Yield/% ^b	m.p./°C	m.p./°C Ref.
1	H	H	4a	85	116–117	115–116 [2c]
2	H	4-CH ₃	4b	91	117–118	116–118 [5b]
3	H	4-Cl	4c	83	137–138	137–138 [5b]
4	H	4-Br	4d	86	97–98	98–99 [2c]
5	4-CH ₃ O	4-Cl	4e	78	122–123	122–123 [2c]
6	4-CH ₃ O	4-Br	4f	75	130–131	131–132 [2c]
7	4-Cl	H	4g	88	133–134	135–136 [2c]
8	4-Cl	4-Cl	4h	91	98–99	96–97 [2c]
9	4-Cl	4-Br	4i	90	135–136	134–135 [2c]
10	3-NO ₂	4-Cl	4j	95	127–128	125–126 [2c]
11	4-NO ₂	4-CH ₃	4k	92	137–138	137–138 [2c]

^a Reaction conditions: cyclohexanone (10 mmol), aromatic aldehydes (10 mmol), aromatic amines (10 mmol), $[bmim][OH]$ (1 mmol), *EtOH* (5 cm³), r.t., 10 h

^b Isolated yield

**Fig. 1.** Reusability of $[bmim][OH]/EtOH$

aldehydes bearing an electron-withdrawing group are favorable for the transformation while anilines with electron-donating groups are beneficial for these reactions.

The recycling of the ionic liquid was also investigated. In the model reaction among cyclohexanone, benzaldehyde, and aniline, the products were isolated from ethanol media by filtration. The filtrate was reused in the next run without further purification. As shown in Fig. 1, the catalyst can be recycled up to 5 times without significant decrease in catalytic activity, the yields ranged from 88 to 82%.

In conclusion, we developed a simple, green, and efficient protocol for the three-component *Mannich*-type reactions catalyzed by the basic functionalized ionic liquid, $[bmim][OH]$. The most attractive part of this work is that $[bmim][OH]$ is easily recycled and can be reused without obvious loss of the cata-

lytic activity. This approach could make a valuable contribution on the synthesis of β -amino carbonyl compounds.

Experimental

Melting points were determined in open capillaries. ¹H NMR spectra were obtained from solution in CDCl₃ with *TMS* as internal standard using a Bruker DRX 300 (300 MHz) spectrometer. IR spectra were recorded on a Nicolette spectrometer using KBr discs.

The functionalized ionic liquids, $[bmim][OH]$ and $[emim][OH]$ (1-ethyl-3-methyl-imidazolium hydroxide), $[H_3NCH_2CH_2OH][CH_3COO]$, $[H_2N(CH_2CH_2OH)_2][CH_3COO]$, and $[HN(CH_2CH_2OH)_3][CH_3COO]$ were prepared by the procedures given in Refs. [9, 12]. All other chemicals and reagents were of analytical grade and used as obtained.

General Procedure for the Synthesis of β -Amino Carbonyl Compounds

To a mixture of 0.98 g cyclohexanone (10 mmol), 10 mmol aromatic aldehyde, 10 mmol aniline derivative, and 5 cm³ ethanol as the solvent, 1 mmol ionic liquid $[bmim][OH]$ was added and stirred at room temperature for the appropriate time. When the reaction was completed as indicated by TLC, the products were filtered off to get crude products, which were then purified by recrystallization from ethanol to give the corresponding compounds. The ionic liquid is remaining in the ethanol and could be reused in the next run without further purification.

2-(Phenyl(phenylamino)methyl)cyclohexanone (**4a**, C₁₉H₂₁NO)

White solid; mp 116–117°C; ¹H NMR (300 MHz, CDCl₃): δ = 7.37–7.33 (m, 2H), 7.31–7.26 (m, 2H), 7.24–7.19 (m, 1H), 7.05–7.02 (m, 2H), 6.60 (m, 1H), 6.54–6.51 (m, 2H),

4.80–4.78 (d, 1H), 4.61–4.61 (d, 1H), 2.75–2.73 (m, 1H), 2.42–2.31 (m, 2H), 1.90–1.84 (m, 4H), 1.72–1.57 (m, 2H) ppm; IR (KBr): $\bar{\nu}$ = 3330, 1705, 1600, 1498 cm^{-1} .

Acknowledgements

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