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Mannich reaction catalyzed by carboxyl-functionalized ionic liquid in aqueous media

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Three-component Mannich reactions of aromatic aldehydes, anilines and acetophenone were efficiently catalyzed by a recyclable carboxyl-functionalized ionic liquid ([cmmim][BF_4]) in aqueous [bmim][BF_4] under mild conditions. Twelve β-aminoketones were successfully synthesized in high yields and the catalyst can be recycled at least 6 times without significant loss of activity.

KEY WORDS: Mannich reaction; functional ionic liquid; catalyst; aqueous media.

1. Introduction

Heterogeneous catalysts are widely preferred in chemical industry due to the well-known advantages of easier product-catalyst separation and recovery of the catalyst [1]. But in terms of selectivity and efficiency, homogeneous catalysts usually provide better results [2]. Homogeneous catalysts can offer high molar catalytic efficiencies and reaction rates under mild conditions, tolerance to many types of organic functionality, and high selectivity in reactions that allow formation of a specific desired product [3]. Unfortunately, the recovery of homogeneous catalysts is difficult than their heterogeneous counterparts.

An ideal catalyst would possess the beneficial aspects of both homogeneous and heterogeneous systems. The fixation of known homogeneous catalysts on room temperature ionic liquids [4] is an ideal combination in order to achieve the advantages of both heterogeneous and homogeneous catalysis [5]. Some efforts have been expended in attempts to develop a homogeneous catalyst that is grafted to an ionic liquid to form a functionalized ionic liquid. Such special homogeneous catalysts are benign to environment and easy to be recycled. Several functionalized ionic liquids have been proofed to be excellent catalysts to some organic reactions such as ring-closing olefin metathesis [6], acetalization [7], Michael reaction [8].

As we all know, β-aminoketones are important building blocks for the synthesis of biologically attractive compounds [9]. Generally, β-aminoketones are synthesized from aromatic aldehydes, anilines and acetophenone through Mannich reaction catalyzed by inorganic acids [10], praline [11], or hydrophobic polystyrene supported sulfonic acids (PS-SO_3H) [12]. Zhao and co-workers [13] reported several anion-functional acidic ionic liquids (e.g. 1-methylimidazolium trifluoroacetic acid, [Hmim][Tfa]) as catalytically active solvents for three-component Mannich reactions of aldehydes, amines and ketones at 25 °C. However, it needs the tedious and energy-consuming vacuum distillation for the recovery of catalytically active ionic liquids.

Herein we report our primary results on the Mannich reaction catalyzed by a cation-functionalized acidic ionic liquid, 1-carboxymethy1-3-methylimidazolium tetrafluoroborate (abbreviated as [cmmim][BF_4] below) in the mixture of water and 1-buty1-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) (Scheme 1). Twelve β-aminoketones were synthesized successfully in aqueous [bmim][BF_4] with satisfactory to excellent yields, and the catalyst-containing aqueous media can be recycled at least 6 times with similar activity. In our procedure, the recovered catalyst-containing aqueous media could be reused directly (straightforwardly) without other manipulation such as distillation and dehydration.

2. Experimental

2.1. *Preparation of carboxyl-functionalized ionic liquid [cmmim][BF_4]*

The catalyst was prepared from 1-methylimidazole and chloroacetic acid (Scheme 2). Chloroacetic acid (9.4 g, 0.10 mol) was added to 1-methyl-imidazole (8.2 g, 0.10 mol) in portion within an hour, and then the mixture was heated at 70°C for 3.5 h. The solid thus obtained was cooled to room temperature, washed with acetonitrile, and dried under vacuum. The intermediate, 1-carboxymethy1-3-methylimidazolium chloride, was obtained as a white solid in 92% yield (mp 172–174°C). The [cmmim][Cl] (17.6 g, 0.10 mol) and $NaBF_4$ (10.9 g,

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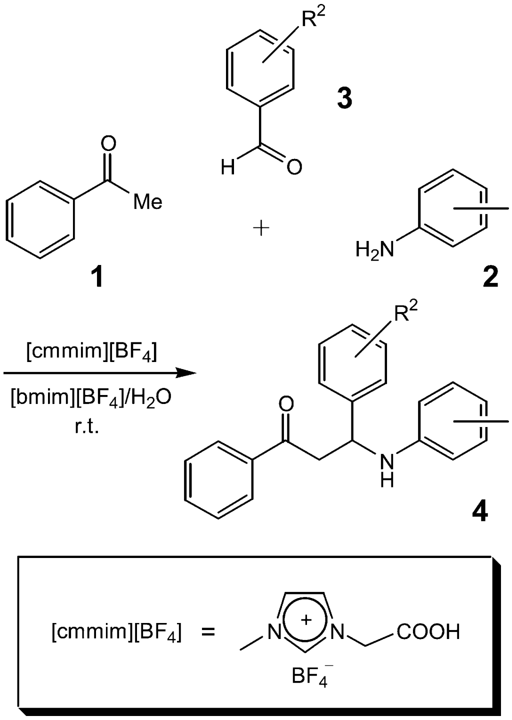
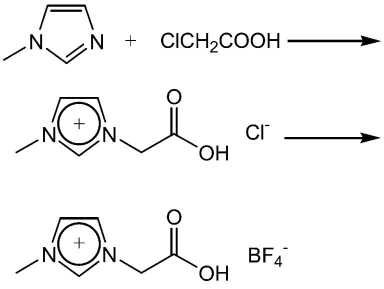


Scheme 1.

0.10 mol) were dissolved in H_2O and refluxed for 5 h, after the removal of water and dried under vacuum, [cmmim][BF_4] was obtained in 93% yield as a yellowish oil. ^{1}H NMR (500 MHz, D_2O): δ_H: 8.58 (1 H, s, CH = N), 7.35–7.36 (2 H, d, J = 5.23 Hz, CH = CH), 4.98 (2 H, s, CH_2), 3.81 (3 H, s, CH_3). IR (KBr): ν 3112, 3089, 2898, 1732, 1581, 1437, 1395, 1055 cm^{-1}.



Scheme 2.

2.2. *General procedure for the synthesis of β-aminoketones* **4a–l**

To a flask charged with aniline (0.93 g, 10 mmol), acetophenone (1.20 g, 10 mmol), aromatic aldehyde (10 mmol) and 10 ml of aqueous [bmim][BF_4] (v/v = 1 : 2) was added [cmmim][BF_4] (0.114 g, 0.5 mmol) under stirring. The mixture was then stirred for 10–15 h at room temperature. On completion (monitored by TLC), the precipitated crude product was collected by filtration and recrystallized from acetone/ethanol (v/v = 1 : 1) to afford pure β-aminoketone **4**. The filtrate ([cmmim][BF_4] + [bmim][BF_4] + H_2O) could be reused in the next run without further purification.

2.3. *Selected characterization data*

1,3-diphenyl-3-(phenylamino)-1-Propanone (**4a**): Mp 172–174 °C, IR (KBr): ν 3385, 1669, 1601, 1509, 1228, 744 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ_H 8.02 (2H, d, J = 7.51 Hz, ArH), 7.64 (1H, t, J = 7.36 Hz, ArH), 7.55 (2H, t, J = 7.80 Hz, ArH), 7.54 (2H, d, J = 7.64 Hz, ArH), 7.33 (2H, t, J = 7.61 Hz, ArH), 7.22 (1H, t, J = 7.35 Hz, ArH), 6.62 (2 H, d, J = 8.02 Hz, ArH), 6.53 (1 H, t, J = 7.27 Hz, ArH), 5.13 (1H, dd, J = 5.05, 5.13 Hz, NCH), 3.67 (1H, dd, J = 8.48, 8.43 Hz, $COCH_2$), 3.45 (1H, dd, J = 4.76, 4.76 Hz, $COCH_2$).

3-(4-chlorophenyl)-3-((4-methylphenyl)amino)-1-phenyl-1-Propanone (**4f**): Mp 118–119°C; IR (KBr): ν 3358, 1683, 1624, 1283, 805 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.92 (2H, d, J = 7.50 Hz, ArH), 7.60 (1H, t, J = 7.40 Hz, ArH), 7.46 (4H, m, ArH), 7.25 (2H, d, J = 7.91 Hz, ArH), 6.85 (2H, d, J = 8.19 Hz, ArH), 6.60 (2H, d, J = 5.77 Hz, ArH), 4.95 (1H, t, J = 6.42 Hz, NCH), 3.60 (2H, m, $COCH_2$), 2.18 (3H, s, CH_3).

3-((3-chlorophenyl)amino)-1,3-diphenyl-1-Propanone (**4h**): Mp 139–140°C, IR (KBr): ν 3363, 1683, 1606, 1288, 708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.95 (2H, d, J = 7.31 Hz, ArH), 7.60 (1H, t, J = 7.51 Hz, ArH), 7.48 (2H, t, J = 7.72 Hz, ArH), 7.46 (2H, d, J = 7.53 Hz, ArH), 7.25 (1H, d, J = 6.52 Hz, ArH), 6.98 (1H, t, J = 8.20 Hz, ArH), 6.60 (1H, t, J = 2.01 Hz, ArH), 6.65 (1H, dd, J = 1.28, 1.19 Hz, ArH), 6.48 (1H, dd, J = 1.83, 1.93 Hz, ArH), 4.98 (1H, dd, J = 5.13, 5.09 Hz, NCH), 4.70 (1H, s, NH), 3.55 (1H, dd, J = 4.91, 4.91 Hz, $COCH_2$), 3.48 (1H, dd, J = 7.79, 7.67 Hz, $COCH_2$).

3-(4-chlorophenyl)-3-((3-chlorophenyl) amino)-1-phenyl-1-Propanone (**4i**): Mp 128–130°C, IR (KBr): ν 3392, 1680, 1596, 1298, 769 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.90 (1H, d, J = 7.26 Hz, ArH), 7.60 (1H, t, J = 7.49 Hz, ArH), 7.48 (2H, t, J = 7.71 Hz, ArH), 7.35 (2H, d, J = 8.45 Hz, ArH), 7.30 (2H, d, J = 8.47 Hz, ArH), 6.90 (1H, d, J = 8.04 Hz, ArH), 6.65 (1H,d, J = 7.59 Hz, ArH), 6.45 (1H, dd, J = 1.67, 1.78 Hz, ArH), 4.98 (1H, t, J = 6.23 Hz, NCH), 3.49 (2H, m, $COCH_2$).

4-((3-oxo-1,3-diphenyl) propylamino)-benzoic acid (**4l**): Mp 190–192°C, IR (KBr): ν 3368, 2947, 1669, 1608, 1273, 708 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 11.90 (1H, s, COOH), 7.95 (2H, d, J = 7.46 Hz, ArH), 7.62 (1H, t, J = 7.36 Hz, ArH), 7.58 (2H, d, J = 8.79 Hz, ArH), 7.50 (2H, t, J = 7.72 Hz, ArH), 7.42 (2H, d, J = 7.43 Hz, ArH), 7.30 (2H, t, J = 7.61 Hz, ArH), 7.19 (1H, t, J = 7.33 Hz, ArH), 6.90 (1H, d, J = 7.36 Hz, ArH), 6.50 (2H, t, J = 8.73 Hz, ArH), 5.55 (1H, m, NCH), 3.62 (1H, m, $COCH_2$), 3.58 (1H, m, $COCH_2$).

3. Results and discussions

With carboxyl-functionalized ionic liquid [cmmim][BF_4] in hand, the suitable solvent was initially screened in model reaction (benzaldehyde, acetophenone and aniline) in the mixture of [bmim][BF_4] and water (Table 1). Unfortunately, when using water as the sole solvent, the reaction system was heterogeneous and no expected product was obtained. When the voluminal ratio of [bmim][BF_4] to water was increased, a ramp in the yields of β-aminoketone was observed. The optimal ratio of [bmim][BF_4] to water is determined as 1 : 2(v/v).

The effect of substrate to catalyst molar ratio on the reaction was next investigated using the same model reaction. It was found that the use of 1% mol of catalyst gave a low yield even after longer reaction duration (Table 2). In comparison, 5% mol of catalyst led to a 90% yield of product. Increasing in the amount of catalyst couldn't bring much better results. Hence, the molar ratio of catalyst to substrates was chosen as 5% in the reaction.

Based on the investigation described above, the effects of other catalysts and solvents on the synthesis of β-aminoketones were studied. The results reported in the literatures were also compared (Table 3, entries 1, 7, 8 and 9). When using acetic acid as catalyst (Table 3, entries 5 and 6), only a few **4a** was obtained even after longer reaction duration, and the main products were imine and chalcone as determined by GC-MS. The solvents also affect the yields of Mannich reaction catalyzed by [cmmim][BF_4]. In the cases investigated, higher yields was obtained in aqueous [bmim][BF_4] than those in ethanol solution and in sole [bmim][BF_4] (Table 3), perhaps due to the higher solubility of products in ethanol and [bmim][BF_4].

To generalize our protocol, a serial of β-aminoketones were prepared under optimized reaction conditions described above. As shown in Table 4, the reactions proceeded smoothly at room temperature in aqueous [bmim][BF_4] ([bmim][BF_4]/ H_2O = 1 : 2 v/v) to afford the desired products in good yields. The substituents of anilines and aromatic aldehydes affect the yields of β-aminoketones to a large extent. Electron-donating substituents of aniline and aromatic aldehydes are disadvantageous to Mannich reaction, the yields of 4-methy-aniline (**4d**, **4e**, **4f**) were lower than those of other aromatic amines. Moreover, no β-aminoketones were obtained when using 4-aminoanisole as an amine component.

Compared with traditional solvents, it is easy for ionic liquids to be reused, which is prior to the conventional solvents and catalysts [14]. Hence, we decide to study the catalytic activity of recycled carboxyl-functionalized ionic liquid in the synthesis of **4a**. After the separation of products, the catalyst-containing

Table 1
The effects of the ration between [bmim][BF_4] and water on the synthesis of **4a**[a]

Entry	[bmim]BF_4/ H_2O (v/v)	Yield (%)[b]
1	0	0
2	1 : 3	78
3	1 : 2	90
4	1 : 1	85
5	2 : 1	83

[a] 5% mol catalyst. [b] Isolated yields.

Table 2
The effects of ration between [cmmim][BF_4] and **1** on the synthesis of **4a**[a]

Entry	[cmmim][BF_4] /**1** (mol/mol)	Time (h)	Yield (%)[b]
1	1%	18	35
2	2%	12	50
3	5%	12	90
4	10%	12	91
5	20%	12	88

[a] The aqueous [bmim]BF_4 (v/v = 1 : 2). [b] Isolated yields.

Table 3
The effects of different solvents and catalysts on the synthesis of **4a** at room temperature

Entry	Solvent	Catalyst	Time (h)	Yield (%) [a]
1	Ethanol	conc. HCl (37%)	10	81 [10]
2	Ethanol	[cmmim][BF_4]	12	85
3	[bmim]BF_4	[cmmim][BF_4]	12	87
4	[bmim]BF_4/H_2O (v/v = 1 : 2)	[cmmim][BF_4]	12	90
5	solvent free	CH_3COOH	55	25
6	Ethanol	CH_3COOH	48	20
7	H_2O	PS-SO_3H	24	83 [12]
8	Ethanol	[Hmim][Tfa]	12	68 [13]
9	[Hmim][Tfa]	[Hmim][Tfa]	12	83 [13]

[a] Isolated yields.

Table 4
Three-component Mannich reaction of aromatic aldehydes, anilines and acetophenone catalyzed by [cmmim][BF_4]

Product	R_1	R_2	Time (h)	Yield (%)[a]
4a	H	H	12	90
4b	H	4-CH_3O	15	88
4c	H	4-Cl	15	92
4d	4-CH_3	H	15	90
4e	4-CH_3	4-CH_3O	15	77
4f	4-CH_3	4-Cl	15	85
4g	3-Cl	4-CH_3O	15	86
4h	3-Cl	H	12	91
4i	3-Cl	4-Cl	12	93
4j	4-COOH	4-CH_3O	12	87
4k	4-COOH	4-Cl	12	92
4l	4-COOH	H	12	90

[a] Isolated yields.

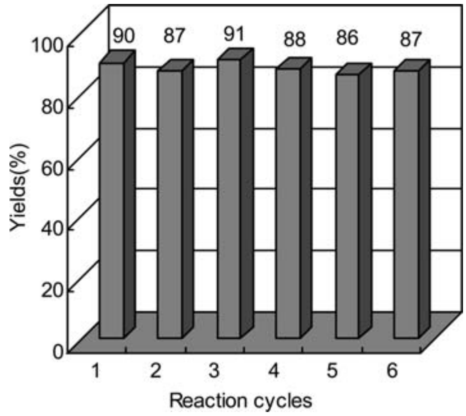


Figure 1. Reusability of [cmmim][BF_4]/[bmim][BF_4]/H_2O.

aqueous media was reused in the next run without further purification. As shown in Figure 1, the catalyst and the solvent can be recycled at least 6 times without significant decrease of the yields, the yields ranged from 90% to 87%.

4. Conclusions

In summary, a stable acidic ionic liquid, [cmmim][BF_4], was synthesized in high yield. This ionic liquid was found to be an efficient catalyst for Mannich reaction of aromatic aldehydes, amines and acetophenone in aqueous [bmim][BF_4]. The method described herein compares favorably with heretofore-reported methodologies, especially in terms of environmentally friendly procedure, improved yields, easier work-up and simple recycling of the catalyst.

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