

Highly efficient aza-Michael reactions of aromatic amines and *N*-heterocycles catalyzed by a basic ionic liquid under solvent-free conditions

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Abstract—A task-specific basic ionic liquid, [Bmim]OH, has been introduced as a catalyst for the aza-Michael addition of aromatic amines and *N*-heterocycles to cyclic or acyclic ketones under neat conditions. The catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency.
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Due to their prevalence and wide utility in organic synthesis, the development of novel synthetic methods leading to β -amino ketones or their derivatives has attracted much attention in recent years, and the approach based on conjugate addition of amines to α,β -unsaturated carbonyl compounds is one of the most widely used methods for preparing β -amino carbonyl compounds due to its atom economy and simplicity.^{1–3}

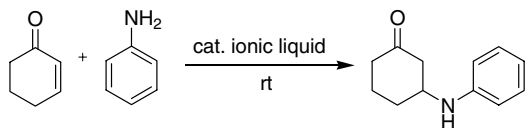
Different methods to be carried out in the conjugate addition of amines to α,β -unsaturated carbonyl compounds are described, and in particular, various Lewis acid induced reactions have been reported.⁴ Reagents like heterogeneous solid acid, ionic liquid, elevated temperature without solvents have also been utilized to promote this reaction.⁵ Recently, there were also some reports of this reaction conducted in Cu(acac)₂/ionic liquid,⁶ boric acid in water,⁷ β -CD in water,⁸ ZrOCl₂·8H₂O on montmorillonite K10 under solvent-free conditions,⁹ [HP(HNCH₂CH₂)₃N]NO₃ in CH₃CN¹⁰ and intramolecular aza-Michael addition catalyzed by InBr₃ or Silica gel supported TaBr₅.¹¹ Unfortunately, many of these procedures often require an excess of reagents,

long reaction times, using expensive heavy metal salts and drastic reaction conditions in CH₃CN or CH₂Cl₂, which are toxic organic solvents. Additionally, *most of the reported methods are only successful with aliphatic amines and failed to work with aromatic amines.*^{6–12,27} So the development of a simpler, greener and more efficient catalyst for the aza-Michael reaction of aromatic amines and *N*-heterocycles to α,β -unsaturated carbonyl compounds is highly desirable.

Recently, there has been considerable interest in the use of ionic liquids as an environmentally benign reaction media due to its unique properties such as a wide liquid range, good solvating ability, tunable polarity, high thermal stability, negligible vapor pressure, and ease of recyclability.¹³ Numerous chemical reactions, such as polymerization,¹⁴ hydrogenation,¹⁵ regioselective alkylation,¹⁶ Friedel–Crafts reactions,¹⁷ dimerization of alkenes,¹⁸ Diels–Alder reactions,¹⁹ Michael reactions,²⁰ cross-coupling reactions²¹ and some enzymic reactions²² can be carried out in ionic liquids. Basic ionic liquids have also aroused unprecedented interest because they showed more advantages such as the catalytic efficiency and recycling of the ionic liquid than the combination of inorganic base and ionic liquid for some base-catalyzed processes.²³ A basic ionic liquid [Bmim]OH has been successfully applied to catalyze the Michael addition of active methylene compounds to α,β -unsaturated ketones, esters and nitriles.²⁴ And [Bmim]OH has also

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Scheme 1.

Table 1. Aza-Michael reaction of aniline catalyzed by imidazolium salt-based basic ILs

Entry ^a	Catalyst	Time (h)	Yield ^b (%)
1	[Emim]OH ^c	9	63
2	[Emim]OH	9	68
3	[Emim]OH ^d	9	65
4	[Emim]OH	26	90
8	K ₂ CO ₃	24	9
9	KOH	24	NR
10	KF/Al ₂ O ₃	24	11
11	NaOH/[Bmim]BF ₄ (1:1)	24	NR
12	PPh ₃	24	62
13	DMAP	24	42
14	— ^e	36	70

^a All reactions were carried out (except entry 14) catalyst (30 mol %), cyclohexenone 1.5 mmol, aniline 1.0 mmol, rt.

^b GC yield.

^c Using 10 mol % of catalyst.

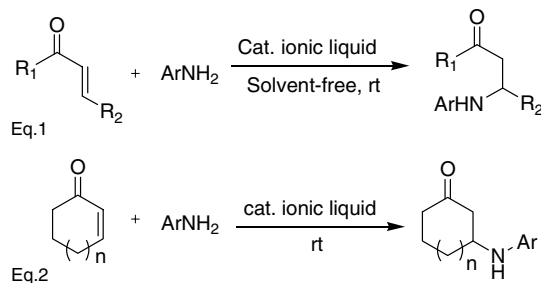
^d Using 50 mol % of catalyst.

^e No addition of catalyst.

been introduced as a catalyst and reaction medium for the Markovnikov addition of *N*-heterocycles to vinyl es-

ters under mild conditions.²⁵ However, the ability of an ionic liquid as a clean catalyst and reagent has not been explored to any great extent although it is of much importance in the context of the green synthesis.²⁶ In our search for an economical, environmentally friendly route to β -amino carbonyl compounds,²⁷ and with our continuous research in the organic transformation using ionic liquid as both a catalyst and green solvent,²⁸ herein we first reported a simple and environmentally benign methodology for the conjugate addition of aromatic amines and *N*-heterocycles to α,β -unsaturated ketones using ionic liquid as catalyst with neat conditions.

In a model reaction, cyclohexanone (1.5 mmol) was used as a representative of α,β -unsaturated ketones. This was treated with aniline (1 mmol) in the presence of various organic or inorganic bases under neat conditions with stirring (Scheme 1). A summary of the results obtained is provided in Table 1. As shown in Table 1, the base catalyst has a significant effect on the yield of the reaction, and no desired or trace aza-Michael adduct was obtained in the presence of KOH, K₂CO₃, or the combination of NaOH and [Bmim]BF₄. Using KF/Al₂O₃ which is highly efficient in the conjugate addition between oxazolidinone and α,β -unsaturated compounds as catalyst,^{27a} only a low yield of aza-Michael product was obtained. An organic base such as DMAP or PPh₃ gave a moderate yield for a long time of 24 h. Surprisingly, however, when we used the basic ionic liquid [Emim]OH²⁹ (10 mol %) as catalyst, a 63% yield was obtained only for 9 h. Increasing the amount of the cat-

Table 2. Aza-Michael reactions of various aromatic amines to α,β -unsaturated compounds catalyzed by [Bmim]OH at room temperature³⁰

Entry ^a	Amines	R ₁	R ₂	Time (h)	Yield ^b (%)
1	PhNH ₂	CH ₃	CH ₃	8	96(90 ^c)
2	PhNH ₂	Et	H	8	98
3	PhNH ₂	<i>n</i> = 0	<i>n</i> = 0	24	72
4	<i>p</i> -Cl-C ₆ H ₄ NH ₂	<i>n</i> = 0	<i>n</i> = 0	24	84
5	<i>p</i> -Cl-C ₆ H ₄ NH ₂	CH ₃	CH ₃	10	91
6	<i>p</i> -Cl-C ₆ H ₄ NH ₂	Et	H	8	97
7	<i>p</i> -CH ₃ -C ₆ H ₄ NH ₂	<i>n</i> = 1	<i>n</i> = 1	24	71
8	<i>p</i> -CH ₃ -C ₆ H ₄ NH ₂	<i>n</i> = 0	<i>n</i> = 0	24	68
9	<i>p</i> -CH ₃ -C ₆ H ₄ NH ₂	Et	H	8	98
10	<i>p</i> -OCH ₃ -C ₆ H ₄ NH ₂	<i>n</i> = 1	<i>n</i> = 1	24	67
11	PhNHCH ₃	CH ₃	CH ₃	10	20
12	PhNHCH ₃	Et	H	8	96
13	PhNH ₂	OEt	H	24	42
14	HN(<i>n</i> -Pr) ₂	<i>n</i> = 1	<i>n</i> = 1	6	86
15	PhCH ₂ NH ₂	<i>n</i> = 1	<i>n</i> = 1	6	84

^a All reactions were carried out using a catalytic basic ionic liquid, [Bmim]OH (30 mol %), acceptors (1.5 mmol), amines (1.0 mmol), rt.

^b GC yield using an initial standard.

^c Isolated yield.

alyst to 30 mol %, the yield of the adduct could be increased to 68% within the same time. 90% yield of the adduct was obtained after a long reaction time (26 h). From the above, the amount of the catalyst (30 mol %) was the best choice.

The catalysis was then applied to various α,β -unsaturated compounds and aromatic amines as summarized in Table 2. All the reactions were able to undergo the corresponding conjugate addition well within 6–24 h and the yields of the desired Michael adducts were good to excellent. The acyclic enones reacted smoothly; however, as cyclohexanone and cyclopentanone showed, cyclic enones decreased the reactivity and required a longer reaction time. The corresponding amine also has an effect on the reaction: whereas 1° aromatic amines reacted smoothly in these conditions, *N*-methyl aniline (2° amine) formed the corresponding product in lower yields. We could get a moderate yield with methyl acrylate as an acceptor. Excellent yields were also obtained when using aliphatic amines as nitrogen sources within a short reaction time. Unfortunately, no desired compound was found when chalcone was used as a substrate under our reaction conditions.




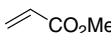




We also attempted to study the addition of aromatic *N*-heterocycles (imidazole or pyrazole) to α,β -unsaturated

compounds (Table 3). Fortunately, moderate to good yields of the Michael adducts were obtained in a short reaction time. In other words, this catalyst system was also a good choice for the addition of *N*-heterocycles to α,β -unsaturated compounds.

Next, we also investigated the reusability and the recycling of the basic ionic liquid [Bmim]OH, and found that the catalyst could be easily recovered after completion of the reaction and reused in subsequent reactions. The reaction of 3-penten-2-one with aniline at room temperature as a model reaction was again studied. When the reaction was completed, the reaction mixture was extracted with ethyl acetate–ether = 1:1, the ionic liquid left in the reaction vessel was rinsed with ether and dried under vacuum at 90 °C for 8 h to eliminate any water trapped from moisture and reused for subsequent reactions. The activity of the catalyst did not show any significant decrease after 3 runs (Table 4).

In conclusion, a highly efficient [Bmim]OH catalyzed the aza-Michael reaction of aromatic amines and *N*-heterocycles to α,β -unsaturated cyclic and acyclic ketones under solvent-free conditions to produce the desired Michael adducts smoothly. The process was simple and generated a diverse range of aromatic amino carbonyl derivatives in excellent yields. Furthermore, it is remarkable that the use of an easily accessible and recyclable basic ionic liquid makes this procedure quite simple, more convenient and environmentally benign.

Table 3. Aza-Michael reactions of aromatic *N*-heterocycles to α,β -unsaturated compounds catalyzed by [Bmim]OH

Entry ^a	Substrate	Acceptor	Time (h)	Yield ^b (%)
1			6	90
2			6	96
3			6	80
4			6	84

^a All reactions were carried out using a catalytic basic ionic liquid, [Bmim]OH (30 mol %), acceptor (1.5 mmol), substrate (1.0 mmol), rt.
^b GC yield using an initial standard.

Table 4. Recycling and reusability of the catalyst [Bmim]OH

Run ^a	Time (h)	Yield ^b (%)	Time (h)	Yield ^b (%)
1	8	96	8	96
2	8	92	12	94
3	8	91	13	95

^a All reactions were carried out using a catalytic basic ionic liquid, [Bmim]OH (30 mol %), α,β -enones (1.5 mmol), amines (1.0 mmol), rt.
^b GC yield using an initial standard.

Acknowledgements

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29. The synthesis of [Bmim]OH was carried out as in Ref. 24: The basic ionic liquid [Bmim]OH was prepared by anion change of [Bmim]Cl using 1 mol equivalent KOH. The ionic liquid was dried under vacuum for 24 h and stored in a desiccator.
30. General procedure for the aza-Michael additions: α,β -unsaturated compounds (1.5 mmol) were added to a well stirred mixture of aromatic amines (1 mmol) and catalyst, and the reaction mixture was stirred for given times. After completion of the reaction, the reaction mixture was extracted with ethyl acetate-ethyl ether = 1:1, the extract was washed with brine, dried (Na_2SO_4), evaporated and purified by using column chromatography to obtain the pure product. All the known compounds were fully characterized by GC-MS (Agilent 6890N GC/5973N MS, DM-5MS) and the usual spectral methods (NMR and IR).