Cu(acac)$_2$ Immobilized in Ionic Liquids: A Recoverable and Reusable Catalytic System for Aza-Michael Reactions

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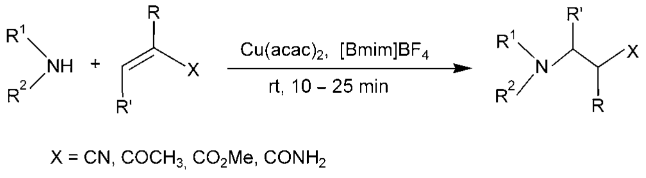
Abstract: Copper(II) acetylacetonate immobilized in ionic liquids efficiently catalyzes the aza-Michael reaction of amines with α,β-unsaturated carbonyl compounds to produce the corresponding β-amino carbonyl compounds with great alacrity in excellent yields. The reactions are far more facile than those reported earlier. The recovered ionic liquid phase containing the copper catalyst can be reused for several cycles with consistent activity.

Keywords: amides; amines; β-amino ketones; aza-Michael reaction; copper(II) acetylacetonate; esters; ionic liquids; α,β-unsaturated carbonyl compounds

The aza-Michael reaction is one of the important reactions in organic chemistry especially for the synthesis of C–N heterocycles[1,2] containing the β-amino carbonyl functionality. Such a functionality[3] not only constitutes a component of biologically active natural products but also serves as an essential intermediate in the synthesis of β-amino ketones, β-amino acids and β-lactam antibiotics, in addition to its use in the fine chemicals and pharmaceutical sectors.[4] Because of the intrinsic importance of β-amino carbonyl compounds, they have attracted sustained attention in organic synthesis, and the methods of construction of the functionality have undergone a metamorphosis from the classic Mannich-type reactions to the more widely used conjugated addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds[5] which is commonly known as the aza-Michael reaction. The classical Mannich-type reactions are certainly very powerful but need quite severe reaction conditions and are rather sluggish thereby limiting their use in practice.[6] The conjugated addition reactions are, in the contrast, atom economic and quite easy to operate. However, these reactions require either basic conditions[7] or acidic catalysts[8] which seem to be detrimental to the desired synthesis. In order to overcome some of the disadvantages, a good number of alternative procedures have been reported over the past few years using Yb(OTf)$_3$,[9] InCl$_3$,[10] CeCl$_3\cdot$7 H$_2$O,[11] Bi(NO)$_3$,[12a] Bi(OTf)$_3$,[12b] Cu(OTf)$_2$,[13] FeCl$_3\cdot$7 H$_2$O/Co(OAc)$_2$,[14] LiClO$_4$[15] and heterogeneous solid acids,[16] but the need for an environmentally benign and facile protocol still exists. Room temperature ionic liquids are acknowledged as eco-benevolent alternatives to volatile organic solvents and have also other useful properties like very low vapor pressure, wide liquid range, high thermal stability and possess highly conductive solvation ability for a variety of organic substrates and catalysts including Lewis acids and enzymes.[17,18] Recently, ionic liquids[19] and quaternary ammonium salts in water[19b] have been reported to efficiently catalyze the aza-Michael reaction. Considering all these, it was thought that a combination of a suitable catalyst immobilized in an ionic liquid would enable facile conjugate additions, as desired. Incidentally, our attention was drawn to this problem at a juncture when we were engaged[20] in the aziridination of olefins catalyzed by Cu(acac)$_2$ immobilized in ionic liquids. To the best of our knowledge, aza-Michael reactions involving a combination of the chosen catalyst and an ionic liquid are unprecedented. Herein, we report the aza-Michael reaction of amines with α,β-unsaturated carbonyl compounds and nitriles to produce the corresponding β-amino ketones and nitriles in very high yields under mild reaction conditions (Scheme 1) using a recyclable catalytic system, Cu(acac)$_2$ immobilized in ionic liquids.

BmimBF$_4$ and bmimPF$_6$ were synthesized according to the procedures reported in the literature.[21] First,



Scheme 1.

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Table 1. Aza-Michael reaction between piperidine and methyl acrylate under different reaction conditions.[a]

Entry	Catalyst	Solvent	Isolated Yield [%]
1	$Cu(acac)_2$	IL	98[b]
2	$CuCl_2$	IL	95[b]
3	–	IL	60[b]
4	$Cu(acac)_2$	CH_3CN	30
5	$Cu(acac)_2$	H_2O	46
6	$CuCl_2$	H_2O	40
7	$Cu(acac)_2$	H_2O+IL	54[c]
8	–	H_2O+IL	32[c]

[a] Reaction conditions: piperidine (1 mmol), methyl acrylate (1.2 mmol), Cu catalyst (2 mol %) at room temperature for 10 min.

[b] Using 1 mL of the ionic liquid (IL).

[c] Using 1 mL of H_2O and 10 mol % of ionic liquid.

we demonstrated the catalytic effect of $Cu(acac)_2/CuCl_2$ for the conjugate addition of piperidine with methyl acrylate and the results are summarized in Table 1. In order to investigate if $CuCl_2$ would catalyze similar aza-Michael reactions, an independent experiment was carried out using $CuCl_2$ in lieu of $Cu(acac)_2$ (Table 1, entry 2). The result was quite interesting showing that $CuCl_2$ is equally effective as an aza-Michael catalyst in ionic liquids. Furthermore, in recognition of the fact that an ionic liquid alone is capable of catalyzing both Michael[22] as well as aza-Michael[19b] reactions, an experiment was conducted without any metal catalyst but using only either $bmimBF_4$ or $bmimPF_6$ with other conditions being similar to those maintained in the $Cu(acac)_2$-catalyzed reactions (Table 1, entry 3). It was observed that the yield of product was far lower but was, however, improved to some extent by prolonging the reaction time. Thus, the importance of the metal catalysts in the present methodology is quite clear. To ascertain the superior performance of ionic liquids over other solvents, several experiments were conducted using $Cu(acac)_2$ or $CuCl_2$ as the catalyst separately in acetonitrile (Table 1, entry 4), water (entries 5 and 6), and a mixture of water and ionic liquid with and without a metal catalyst (entries 7 and 8). The conjugate addition took place in each case albeit with low yields.

A variety of α,β-unsaturated carbonyl compounds or nitriles such as methyl acrylate, acrylonitrile, methyl vinyl ketone, and cyclohexenone underwent 1,4-addition with a wide range of aliphatic amines in the presence of 2 mol % of $Cu(acac)_2$ in 1 mL ionic liquid at room temperature to give the corresponding β-amino compounds or nitriles in high yields in a very short time. The results are summarized in Table 2. In general, secondary amines gave higher yields than the primary amines. Cyclic α,β-unsaturated ketone such as cyclohexenone reacted readily with benzylamine and piperidine to give the corresponding 1,4-adducts in high yields (entries 4 and 8). In the case of primary amines, 8–15% of the bis-adducts were also formed (entries 7 and 12). Sterically hindered amines were found to be less active and gave the corresponding 1,4-adducts in moderate yields after 2 h (entries 13 and 14). Both $bmimBF_4$ and $bmimPF_6$ showed almost similar activities in the aza-Michael reaction of amines with α,β-unsaturated carbonyl compounds (entry 1). When benzylamine and cyclohexylamine were reacted with an excess of methyl acrylate, bis-addition products were observed.

In order to extend the scope of this methodology, α,β-substituted Michael acceptors like methyl methacrylate, and methyl *trans*-cinnamate were tested under the same reaction conditions (Table 2). It was found that methyl methacrylate reacted readily with piperidine to give the corresponding 1,4-adduct in a very high yield (entry 15) where as methyl *trans*-cinnamate reacted rather sluggishly to give the 1,4-adduct in a relatively low yield (entry 16). Some other electron-deficient olefins like ω-nitrostyrene and cinnamaldehyde, for instance, failed to react with piperidine, although acrylamide afforded the corresponding 1,4-adduct in good yield (entry 17). Furthermore, with a view to demonstrate the scope of practical applicability of this methodology, the aza-Michael reaction was carried out on a larger scale (20 mmol) using IL-$Cu(acac)_2$. The reaction was complete in 15 min affording the 1,4-adduct in 96% yield (Table 2, entry 1) leading credence to the contention that the method can be scaled up.

Finally, upon completion of the reaction, the ionic liquid phase containing $bmimBF_4$ and $Cu(acac)_2$ was almost quantitatively recovered by simple extraction of the product with Et_2O. The recovered ionic liquid phase containing the catalyst was reused for several cycles with consistent activity (Table 2, entry 1).

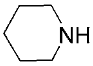
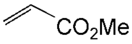
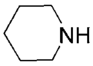
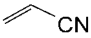
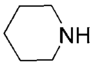
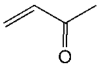
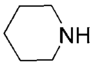
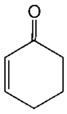
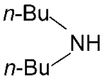
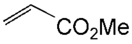
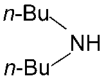
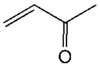
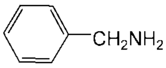
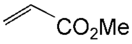
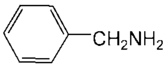
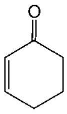
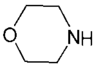
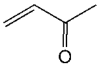
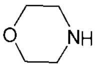
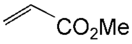
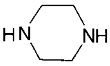
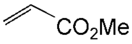
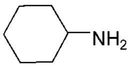
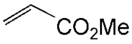
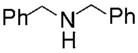
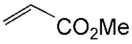
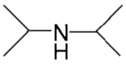
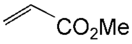
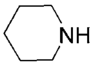
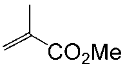
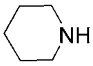
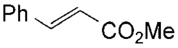
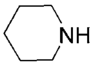
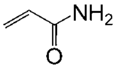
In conclusion, a soft, facile and clean aza-Michael reaction of amines with α,β-unsaturated carbonyl compounds and nitriles by $Cu(acac)_2$ immobilized in ionic liquids has been developed. The methodology works very well using a low catalyst loading with easy catalyst and solvent recycling. This method is capable of being scaled up, if desired.

Experimental Section

General Procedure for the Aza-Michael Reaction of Amines with α,β-Unsaturated Carbonyls or Nitriles

A mixture of $Cu(acac)_2$ (0.005 g, 2 mol %), amine (1 mmol) and α,β-unsaturated compound (1.2 mmol) in ionic liquid (1 mL) was stirred at room temperature for the appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the product was extracted with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated under vacuum and the resulting product was purified by column chromatography on silica gel with ethyl acetate and *n*-hexane (2:8) as eluent

Table 2. $Cu(acac)_2$-catalyzed aza-Michael reaction of amines with α,β-unsaturated carbonyl compounds and nitriles in $[bmim]BF_4$

Entry	Amine	α,β-Unsaturated Compound	Time [min]	Yield [%][a]
1			10	98, 98[b], 96[c], 97[d]
2			10	98
3			10	96
4			25	85
5			15	90
6			10	92
7			15	85[e]
8			25	80
9			15	90
10			10	86
11			20	88[e]
12			15	80[f]
13			120	60
14			90	70
15			30	85
16			60	62
17			30	80

[a] Yield of isolated product.
[b] With $Bmim[PF_6]$.
[c] Reaction on 20 mmol scale.
[d] Yield after fifth cycle.
[e] 8–15% of the bis-adducts were formed.
[f] With 2 mmol of α,β-unsaturated compound.

to afford the pure β-amino adduct. The ionic liquid containing Cu(acac)$_2$ was dried under vacuum for the next run. The products were characterized by comparison of their NMR, IR and mass spectra with those of authentic samples.

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