Aza-Michael Reactions in Ionic Liquids. A Facile Synthesis of β-Amino Compounds

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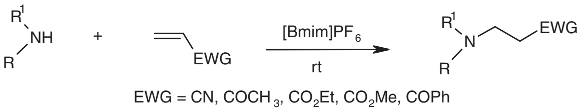
Electron-deficient olefins undergo smoothly aza-Michael reactions with a wide range of amines in ionic liquids in the absence of any acid catalyst to produce the corresponding β-amino compounds in excellent yields with high 1,4-selectivity. The recovered ionic liquids can be reused in subsequent reactions without loss of activity. Owing to the high polarity of ionic liquids, the enones show enhanced reactivity thereby reducing reaction times and improving the yields significantly.

β-Aminoketones are versatile synthetic intermediates for the synthesis of various complex natural products, antibiotics, β-amino alcohols and chiral auxiliaries.[1,2] They are present as a structural components in a number of biologically active compounds.[3] These compounds also find wide applications in fine chemicals and pharmaceuticals.[4] The most common method for the preparation of β-aminoketones is the Mannich reaction.[5] This classical reaction often suffers from the drawbacks of long reaction times and harsh reaction conditions, which limit its use in the synthesis of complex molecules. Alternative approach for the synthesis of β-aminoketones involves the conjugate addition of amines to α,β-unsaturated ketones.[6] A variety of reagents such as $SnCl_4$, $TiCl_4$, $InCl_3$, $CeCl_3{\cdot}7H_2O$, $Yb(OTf)_3$, and $Cu(OTf)_2$ have been reported as promoters for this conversion.[7,8] Other reagents including heterogeneous solid acids have also been utilized to promote the reaction.[9] Furthermore, acid or base induced conjugate addition frequently suffers from many side reactions such as polymerization of starting olefins. Since β-aminoketones have become increasingly useful and important in drugs and pharmaceuticals, the development of simple, more convenient and environmentally friendly approaches are desirable.

In recent times, ionic liquids have gained recognition as possible environmentally benign alternatives to more volatile organic solvents. Ionic liquids possess many interesting properties such as wide liquid range, negligible vapor pressure, high thermal stability and good solvating ability for a wide range of substrates and catalysts.[10] Their non-voltile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction mixture. Furthermore, ionic liquids are found to be efficient reaction media for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[11] The hallmark of such ionic liquids is our ability to alter their properties as desired by manipulating their structure with respect to the choice of organic cation or anion, and side chain attached to organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering for the needs of any particular process. Their unprecedented ability to solvate a broad spectrum of substrates of organic and inorganic nature has widened the horizon of their applicability. However, there are no reports of the use of ionic liquids as green solvents for the conjugate addition of amines to α,β-unsaturated ketones.

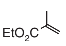
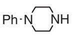
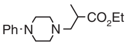
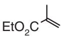
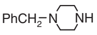
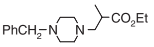
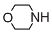
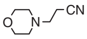
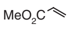
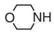
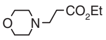
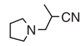
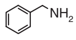
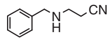
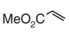
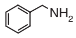
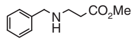
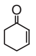
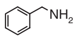
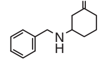
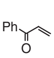
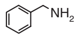
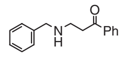
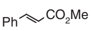
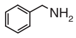
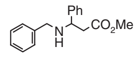
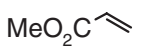
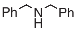
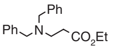
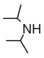
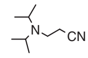
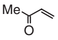
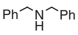
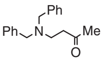
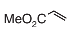
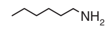
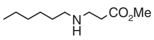
With an ever-increasing quest for exploration of newer reactions in ionic liquids, we herein report for the first time the use of ionic liquids as novel and recyclable reaction media for the 1,4-addition of amines to α,β-ethylenic compounds to afford the corresponding β-amino derivatives in high yields under mild and neutral conditions (Scheme 1).



Scheme 1.

For instance, the conjugate addition of benzylamine to methyl acrylate in 1-butyl-3-methylimidazolium hexafluorophosphate $[Bmim]PF_6$ afforded the corresponding methyl 3-benzylaminopropionate in 92% yield. The reaction proceeds smoothly at room temperature without the need of acid or base catalyst. Encouraged by the results obtained with benzylamine, we turned our attention to aliphatic amines and various α,β-ethylenic compounds. Interestingly, various α,β-unsaturated compounds such as acrylates, acylonitrile, alkyl vinyl ketones and α,β-unsaturated esters underwent 1,4-addition with a variety of aliphatic amines under the reaction conditions to furnish the corresponding β-amino compounds. These β-amino derivatives can be easily converted into the corresponding β-amino acids that are very useful intermediates in the synthesis of various biologically active compounds. Cyclic α,β-unsaturated ketone such as cyclohexenone reacted readily with benzylamine at room temperature to give the corresponding 1,4-adduct in 85% yield (Entry H). Benzylamine also added quite effectively to methyl cinnamate to give the corresponding β-amino ester in 80% yield after 12 h. Sterically hindered amines also gave the corresponding 1,4-adducts in excellent yields (Entries K, L, and M). In case of primary amine, a trace amount of bis-adduct was observed by GC analysis (Entries F, G, I, and N). In general, secondary amines gave higher yields than primary amines. Compared to conventional methods, the reactions are faster in ionic liquids and the products are obtained in excellent yields with improved selectivity. For instance, treatment of methyl acrylate with benzylamine in $[bmim]PF_6$ ionic liquid afforded the corresponding Michael adduct **3G** in 92% yield after 8.0 h whereas the same reaction in methanol after 24 h gave the mono-adduct in 75% yield along with the bis-adduct (15%). The same reaction in water gave the 1,4-adduct in 70% yield as a mixture of mono- and bis-adducts in a ratio of 7:3. In this reaction, the efficiency of ionic liquid was strongly influenced by the nature of the anion. The reactivity of various amines and α,β-unsaturated carbonyl

Table 1. Conjugate addition of amines to enones in ionic liquids

Entry	Enone **1**	Amine **2**	Product[a] **3**	[bmim]PF_6		[bmim]BF_4	
				Time/h	Yield/%[c]	Time/h	Yield/%[c]
A				8.0	89	9.0	85
B				8.5	87	9.5	83
C				2.0	96	2.5	95
D				2.5	93	3.0	91
E				10.0	78	12.0	72
F				7.5	87[c]	8.5	83[c]
G				8.0	92[c]	9.5	89[c]
H				10.0	85	12.0	78
I				12.0	83[c]	10.0	80[c]
J				15.0	80	16.5	75
K				8.0	88	9.0	85
L				9.5	85	12.0	80
M				5.5	90	6.0	87
N				12.0	92[c]	14.0	90[c]

[a] All the products were characterized by ^1H NMR, IR, and mass spectra. [b] Yield refers to the isolated pure products after column chromatography. [c] 5–9%of bis-adducts were observed by GC analysis.

compounds was studied in both hydrophobic [bimim]PF_6 and hydrophilic [bmim]BF_4 ionic liquids and the results are presented in the Table 1. Among these ionic liquids, [bmim]PF6 was found to be superior in terms of conversion. In most cases, the products could be easily isolated by simple extraction with diethyl ether. The recovered ionic liquid was reused in several times without loss of activity, even after fourth cycle the product **3C** was obtained with the similar yield and purity of those obtained in the first cycle. Ionic liquids used in this study have been prepared in our laboratory from the readily available and inexpensive *N*-methyl imidazole, 1-chlorobutane and sodium hexafluorophosphate or sodium tetrafluroborate[12] and their purity was determined by comparing of their ^1H NMR spectra with commercial samples. The purity of [bmim]PF_6 ionic liquid is $\geq$97.0% (NMR). The use of ionic liquids as reaction media for this transformation avoids the use of moisture sensitive reagents or heavy metal Lewis acids or solid acids as promoters thereby minimizing the production of toxic waste during work-up. The scope and generality of this process is illustrated with respect to various α,β-ethylenic compounds and amines and the results are presented in the Table 1.[13]

In summary, we have demonstrated the successful use of ionic liquids as green solvents for the 1,4-addition of amines to electron-deficient olefins to produce β-amino compounds, which are key intermediates in the syntheis of β-amino acids and β-lactam antibiotics. This method avoids the use of acid catalysts and environmentally unfavorable volatile organic solvents by playing the dual role of solvent and the promoter. The enones show significant increase in reactivity in ionic liquids thereby reducing the reaction times and improving the yields considerably. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green strategy for synthesis of β-amino compounds.

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13 Experimental procedure: The mixture of amine (1 mmol) and α,β-ethylenic compound (1.5 mmol) in 1-butyl-3-methylimidazolium hexafluorophosphate (3 mL) was stirred at room temperature for the appropriate time (Table 1). 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 in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate: *n*-hexane (2:8) to afford pure β-amino adduct. The rest of the ionic liquid was further washed with ether and recycled in subsequent reactions. The products were characterized by comparison of their NMR, IR, and mass spectra with authentic samples. The spectral data of all the products were identical with those of authentic samples.[7,9]