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A green, ionic liquid and quaternary ammonium salt-catalyzed aza-Michael reaction of α,β-ethylenic compounds with amines in water

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The first environmentally benign, highly efficient conjugate addition of aliphatic amines to α,β-unsaturated compounds catalysed by simple quaternary ammonium salts and ionic liquids in the green solvent, water, is described.

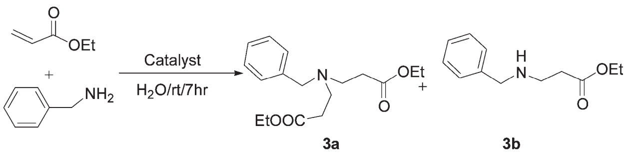
The hydroamination of olefins is a long-standing goal for transition metal catalysis,[1] and the conjugate addition of amines to carbon–carbon double bonds is an unsolved, synthetically important problem.[2,3] The products of aza-Michael additions, β-amino carbonyl compounds and derivatives, can be used in peptide analogues or as precursors to optically active amino acids, amino alcohols, diamines, and lactams, many of which serve as powerful antibiotics or other drugs.[4] As such, the development of efficient synthetic methods leading to β-amino carbonyl compounds and derivatives has attracted much attention in organic synthesis.[5] Among the methods for generating β-amino carbonyl compounds, the conjugate addition of nitrogen nucleophiles to α,β-unsaturated compounds is one of the most simple and effective methods for preparing β-amino carbonyl compounds.[6] However, most Lewis acid catalysts are likely to be poisoned by alkyl- and arylamine regents.[7] In the past few years, a number of alternative procedures have been developed, and in particular, various transition metal catalysts have been investigated, such as palladium,[7] $InCl_3$,[8] $CeCl_3{\cdot}7H_2O$–NaI,[9] $Bi(NO)_3$[10] and $Bi(OTf)_3$.[11] Although recent advances have made this route more attractive, the development of cheaper, simpler, and more efficient metal catalysts is highly desirable.

In our search for an economical, environmentally friendly route to β-amino carbonyl compounds, we have recently discovered iron salt catalysts for the addition of carbamates to enones and the aza-Michael addition of amines or azides to α,β-unsaturated compounds.[12] Herein, we report a new protocol that employs catalytic amounts of cheap, readily available and nontoxic quaternary ammonium salts and ionic liquids as efficient catalysts in the aza-Michael reaction under mild reaction conditions. Advantages of the protocol include high-yielding reactions that can be conducted at ambient temperature in the environmentally benign solvent, water.

The recent interest in aqueous medium metal-mediated carbon–carbon and carbon–heteroatom formations led to the conditions for such reactions.[13] The previous findings prompted us to investigate quaternary ammonium salts and ionic liquid catalysis in aqueous media in aza-Michael reactions, because reactions in such media have several advantages,[14] such as, it is not necessary to dry solvents, and substrates or hydrated substrates can be directly used without further drying. Furthermore, the development of organic reactions in water will contribute to the progress of green and biomimetic catalysis chemistry. Surprisingly however, there are few reports on the conjugate addition of amines to α,β-unsaturated carbonyl compounds in water.

Quaternary ammonium salts and ionic liquids have been shown to be extraordinarily effective and useful catalysts for alkylation,[15] aldol,[16] epoxidation,[17] and Michael reactions.[18] Room temperature ionic liquids such as $bmimBF_4$ are finding growing application as alternative reaction media and effective catalysts for separation and organic transformations. The desirable advantages of ionic liquids such as the lack of vapour pressure, wide liquid phase temperature range and thermal stability have made them exceptional reaction media and environmentally benign solvents. Accordingly, they are emerging as novel replacements for volatile organic synthesis and transformations.[19] Similarly, a systematic study of the Michael addition of thiols to α,β-unsaturated ketones in the presence of quaternary ammonium salts, *Cinchona* alkaloids and ionic liquids as a catalyst has been reported.[20,21] Although there have been reported ammonium salt- (1 M TBAF in THF)[22] and symmetric pentacyclic guanidine ion-[23] promoted aza-Michael reactions, no reports are available on a quaternary ammonium salt or ionic liquid-catalysed approach for the aza-Michael reaction in water.

We tried to explore the catalytic activities of quaternary ammonium salts in the aza-Michael reaction, so the initial studies were carried out using benzylamine and ethyl acrylate as a model system (Scheme 1). To our satisfaction, rapid conversion was observed when the reaction was carried out at room temperature in water, the total product (a mixture of mono and di-substituted products, **3b**/**3a** = 1.6/1 to 2.0/1) was obtained in high yield catalyzed by TBAB (tetrabutylammonium bromide), TBAI, THAB (tetrahexylammonium bromide), TEAB (tetraethylammonium bromide), TEAC (tetraethylammonium chloride), benzyltrimethylammonium chloride, (≥95% yield). We also found that the simple hydrophilic ionic liquid, $bmimBF_4$, was effective giving almost quantitative yields for the aza-Michael reaction. A control



Scheme 1

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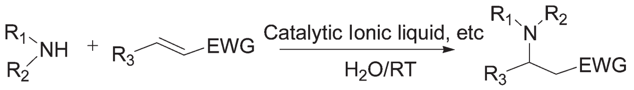
experiment was conducted in the absence of catalyst and it was observed that addition of benzylamine to ethyl acrylate resulted in the formation of the desired product only in low yields (20%). Furthermore, traditionally, the aza-Michael reaction can only be performed with special activation, such as high temperatures,[24] high pressures,[25] or use of appropriate catalysts *etc.*[26]

We then carried out the aza-Michael reaction of aromatic amines under the same conditions in water, and so aniline was subjected to this reaction with these quaternary ammonium salts as catalyst and ethyl acrylate as the Michael acceptor. This clearly shows that the quaternary ammonium salt is suitable only to activate aliphatic amines and failed in the case of aromatic amines for the aza-Michael addition reaction. This selectivity could be useful in synthetic applications.

Finally, we have utilized a variety of aliphatic amines successfully with different α,β-unsaturated compounds catalyzed by the simple hydrophilic ionic liquid, bmimBF_4 (Scheme 2).[27] Interestingly, all the aliphatic amines gave almost quantitative yields with α,β-ethylenic compounds (Table 1). The feasibility of recovery and reuse of the catalyst in the water was also examined through a series of sequential Michael reactions of benzylamine with ethyl acrylate as model substrate. In a typical reaction, the recovered bmimBF_4 catalyst was reused five times without loss of activity, and the product was obtained with similar yields.

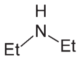
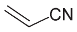
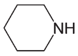
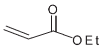
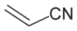
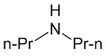
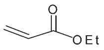
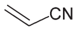
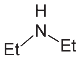
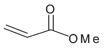
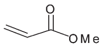
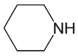
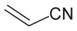
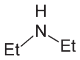
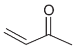
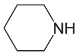
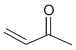
In conclusion, we have developed a new methodology for the conjugate addition of aliphatic amines to α,β-unsaturated compounds in the green solvent, water. The successful application of quaternary ammonium salts and ionic liquids bodes well for the development of asymmetric aza-Michael reactions and industrialization. Current efforts are focused on these approaches.



EWG = CN, COOEt, $COOCH_3$, $COCH_3$

Scheme 2

Table 1 Ionic liquid (bmimBF_4) catalyzed aza-Michael reaction of aliphatic amines with α,β-unsaturated compounds in water

Entry[a]	Amine	Unsaturated compound	Product[b]	Yield (%)[c]
1			M	97
2			M	95
3	Ph—CH_2NH_2		M/D	94/2
4			M	96
5	*n*-Bu—NH_2		M/D	78/17
6			M	97
7	Ph—CH_2NH_2		M/D	60/36
8			M	98
9			M	94
10			M	95

[a] All the reactions were performed in water and 10 mol% bmimBF_4 as catalyst at room temperature for 7 h. [b] M refers to mono-substituted product; D refers to di-substituted product. [c] Isolated yield.

Acknowledgements

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27 General procedure for the aza-Michael addition reactions. A mixture of amine (1.2 mmol), α,β-unsaturated compound (1 mmol) and quaternary ammonium salt or bmimBF_4 (10 mol%) in water was kept at room temperature under vigorous stirring for 7 h. After completion of the reaction, the reaction mixture was extracted with diethyl ether and purified by using column chromatography on silical gel to obtain the pure product. All the known compounds were fully characterized by GC-MS (Agilent 6890N GC/5973N MS, HP-5MS) and the usual spectral methods.