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Significant rate acceleration of the aza-Michael reaction in water

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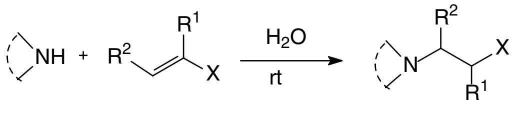
Abstract—The addition of amines to conjugated alkenes has been carried out in water at room temperature very efficiently without any catalyst. Significant rate acceleration of this reaction is observed in water compared to organic solvents.

Organic reactions in water have received increased attention primarily because of their environmental acceptability, abundance and low cost.[1] However, water also exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[2] Thus, the development of efficient procedures for useful chemical transformations in water without any catalyst is highly appreciated.

The aza-Michael addition, that is, addition of an amine to an electron deficient alkene, is of much synthetic importance since it provides an easy route to β-amino carbonyl derivatives[3] which are versatile intermediates for the synthesis of a variety of biologically important natural products, antibiotics, β-amino alcohols and other nitrogen-containing molecules.[4] Thus, a number of procedures have been developed for aza-Michael addition leading to β-amino carbonyl compounds. This reaction is usually carried out in the presence of an acid or a base. A variety of Lewis acids such as transition metal and lanthanide halides,[5] triflates[6] or silica gel[7] have been employed. Heterogeneous solid salts,[8] $Cu(acac)_2$/ionic liquid,[9] quaternary ammonium salt/ionic liquid/H_2O,[10] boric acid in H_2O,[11a] β-cyclodextrin in H_2O[11b] have also been used for this transformation. In addition, solvent-free and catalyst-free procedures at elevated temperature have been demonstrated.[12] However, despite satisfactory results, many of these methods used heavy metal salts and hazardous organic solvents, which is not desirable from a green chemistry point of view. We report here a very simple and greener procedure for the aza-Michael addition in water without any catalyst or organic solvent (Scheme 1).

The experimental procedure is very simple.[13] Several primary and secondary amines underwent smooth additions with α,β-unsaturated carboxylic esters, ketones, nitriles and amides in water at room temperature. The results are summarized in Table 1. Aromatic amines and tertiary amines did not undergo any reaction using this procedure. Addition to α,β-unsaturated aldehydes was also unsuccessful. Primary amines produced only monoaddition products and no bis-addition product was isolated in any reaction unlike several existing methods,[5a,11a] which led to mixtures of mono- and bis-addition products.

In general, the reactions were very clean and high yielding. All the reactions in water were very fast (20–50 min) compared to the reactions in organic solvents using catalysts which were reported to take longer periods (2–8 h).[5–11] The products were characterized from their spectroscopic (IR, ^1H and ^{13}C NMR) data. No catalyst or co-organic solvent was required. It was observed that the reactions in common organic solvents such as THF or methylene chloride under identical experimental conditions were very slow and proceeded only partially even after 10–15 h.



R^1, R^2 = H/alkyl; X = CO_2R, COR, $CONH_2$, CN

Scheme 1.

Keywords: Aza-Michael reaction; β-Amino carbonyl compound; Amine; Conjugated alkene; Water.

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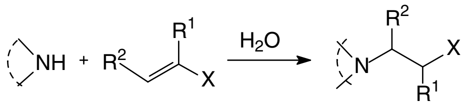
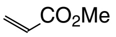
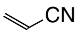
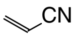
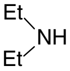
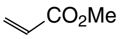
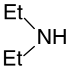
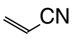
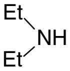
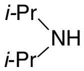
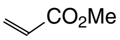
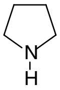
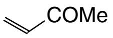
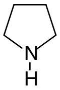
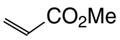
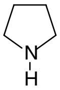
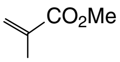
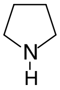
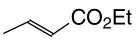
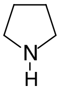
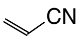
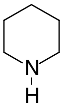
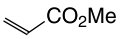
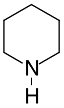
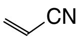
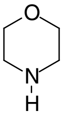
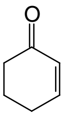
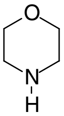
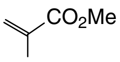
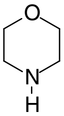
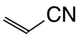
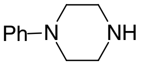
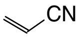
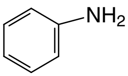
Table 1. Aza-Michael reaction in water

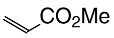
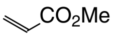
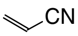
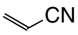
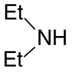
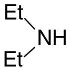
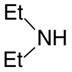


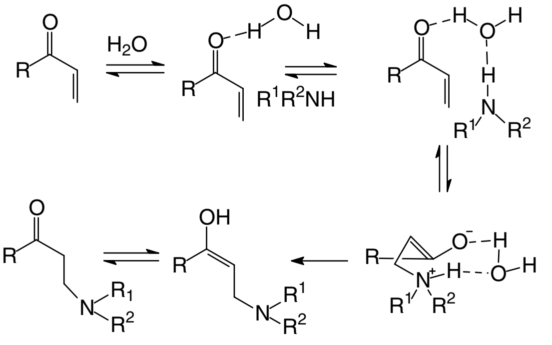
Entry	Amine	Michael acceptor	Time (min)	Yield[a] (%)	Ref.
1	n-BuNH$_2$		30	90	11a
2	n-BuNH$_2$		30	92	11a
3	PhCH$_2$NH$_2$		30	85	11a
4	PhCH$_2$NH$_2$		50	85	11a
5	c-HexNH$_2$		35	85	14
6			30	86	11a
7			30	88	8b
8			50	85	11a
9			35	85	6a
10			20	90	5e
11			20	95	8b
12			30	85	8b
13			35	86	12
14			25	90	8b
15			30	92	11a
16			25	90	11a
17			30	86	12
18			30	86	11a
19			30	90	11b
20			35	85	15
21			24 h	00	—

[a] Yields refer to those of pure isolated products characterized by spectroscopic data (IR,^{1}H, ^{13}C NMR).

A comparison of a few reactions in organic solvents with those in water is reported in Table 2. The amount of water used in the reaction did not have any significant influence on the overall rate of the reaction and yields of products. Without water, the neat reactions at room temperature were very inconsistent. The reactions of pyrrolidines (Table 1, entries 10–14) were extremely vigorous whereas additions of other acyclic primary and secondary amines were sluggish, particularly conjugated acid amides (Table 1, entries 4 and 8). It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the α,β-unsaturated carbonyl compound increasing the electrophilic character at the β-carbon, which is attacked by the nucleophilic amine. On the other hand, hydrogen bond formation involving the oxygen atom of water and the H-atom of the amine increases the nucleophilic character of the N atom of amine. Thus, water activates the amine as well as the conjugated alkene and thereby greatly facilitates the addition (Scheme 2).

Table 2. Comparison of several reactions in organic solvents with those in water

Entry	Amine	Michael acceptor	Solvent	Time (h)	Yield (%)
1	n-BuNH$_2$		THF	10	40
2	n-BuNH$_2$		H_2O	0.5	90
3	n-BuNH$_2$		CH_2Cl_2	10	70
4	n-BuNH$_2$		H_2O	0.5	92
5			THF	15	30
6			CH_2Cl_2	15	60
7			H_2O	0.8	85
8	PhCH$_2$NH$_2$		THF	15	30
9	PhCH$_2$NH$_2$		CH_2Cl_2	15	50
10	PhCH$_2$NH$_2$		H_2O	0.8	85



Scheme 2. *Mechanism*: dual action of water during the aza-michael reaction.

In conclusion, the present procedure provides an efficient methodology for the synthesis of β-amino carbonyl compounds via aza-Michael reaction. The notable advantages offered by this method are simple operation, mild (room temperature) and environment friendly reaction conditions, much faster (20–50 min) reactions, high yields of products and cost effectiveness. Most significantly, this demonstrates the potential of water as an efficient promoter and provides much promise for the use of water in other chemical transformations.

Acknowledgements

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13. Representative experimental procedure for the aza-Michael reaction (Table 1, entry 11): methyl acrylate (130 mg, 1.5 mmol) was added to pyrrolidine (71 g, 1 mmol) in water (1 mL) and the heterogeneous mixture was stirred (on standing, the progress of the reaction was very slow and it was only 50% complete even after 20 h) at room temperature for 20 min until completion as indicated by TLC. The reaction was found to be slightly exothermic; however no temperature control was necessary. The reaction mixture was extracted with ethyl acetate (2 × 10 mL) and the combined extract was dried (Na_2SO_4) and evaporated to leave a crude product which was purified by column chromatography over silica gel to provide a colourless oil (150 mg, 95%), which was identified as 3-pyrrolidin-1-yl-propionic acid methyl ester by comparison of its spectroscopic data (IR, ^{1}H and ^{13}C NMR) with reported values.[8b]
    This procedure was followed for all the reactions listed in Table 1. All the products are known compounds and were easily identified by comparison of their spectroscopic data with those reported. This procedure was also effective for gram-scale reactions.
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