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Boric acid: a novel and safe catalyst for aza-Michael reactions in water

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Abstract—Boric acid efficiently catalyzes the conjugate addition of aliphatic amines to α,β-unsaturated compounds to produce β-amino compounds, with great alacrity and excellent yields, in water under mild conditions. Aromatic amines do not participate effectively in the reaction.

Owing to their wide range of biological activities[1] and pharmacological properties,[2] β-amino ketones and derivatives are much sought after. Such compounds not only constitute components of biologically active natural products, they also serve as essential intermediates in the synthesis of β-amino acids and β-lactam antibiotics.[3] Consequently, the development of novel synthetic methods for their synthesis has attracted sustained interest in organic synthesis. The most common method for the preparation of β-amino ketones is the Mannich reaction.[4] Classical Mannich type reactions are certainly very powerful but need quite severe reaction conditions and are rather sluggish. Conjugate addition reactions are, to the contrary, atom economic and quite easy to carry out. However, these reactions require either basic conditions[5] or acidic catalysts,[6] which can be detrimental to the desired synthesis. Moreover, most Lewis acid catalysts are likely to be poisoned by alkyl and arylamine reagents.[7] In order to overcome some of these limitations, a number of alternative procedures have been reported over the past few years using a variety of catalysts such as palladium,[7] $InCl_3$,[8] supported $CeCl_3{\cdot}7H_2O$–NaI,[9] $Yb(OTf)_2$,[10] $Bi(NO_3)_2$,[11] $Bi(OTf)_2$,[12] $Cu(OTf)_2$,[13,14a] $LiClO_4$,[15] clay,[16] silica gel,[17] $FeCl_3$[18] and KF/alumina.[19] Heterogeneous solid acids have also been employed for this reaction. Recently, ionic liquids, either alone[20] or in combination with quaternary ammonium salts,[14b] have been shown to catalyze efficiently conjugate addition to α,β-unsaturated compounds albeit with long reaction times.

In continuation of our efforts towards a simplified version of catalytic aza-Michael condensation reactions and encouraged by the information gathered from the seminal contributions of Spencer and co-workers,[21] we are quite convinced that it is the Brønsted acid, which is important in bringing about aza-Michael type condensations irrespective of whether the reaction was catalytic or not. Considering all these and in view of our interest in developing reactions that use a catalytic amount of either a non-toxic or minimally toxic, readily available and ecologically favourable agent, we opted for boric acid as the catalyst of choice and water as the solvent.

The selection of boric acid as catalyst was because of one of its most fundamental properties, namely it produces a Brønsted acid from its reaction with water: $B(OH)_3 + H_2O \rightarrow H^+ + B(OH)_4^-$. Thus, boric acid in water is expected to be ideal for Michael type additions. The reaction in water is an important advantage of this protocol. Michael additions in water are relatively scarce but not unprecedented.[8,14] The use of water as a reaction solvent has received considerable attention[22] because reactions in this medium have several advantages including the fact that the solvent and substrates can be used directly without drying. Also, it is believed that

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Keywords: Aza-Michael; Boric acid; Amines; α,β-Unsaturated compounds; Water.

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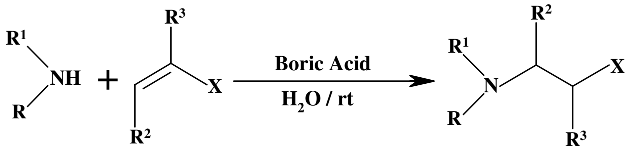


Scheme 1.

reactions in water contribute to green chemistry and pseudo natural catalysis chemistry.

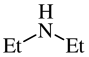
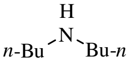
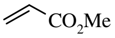
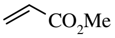
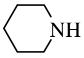
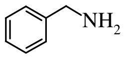
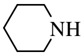
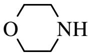
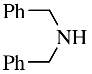
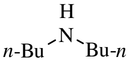
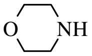
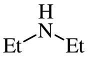
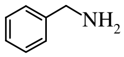
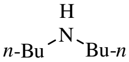
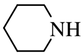
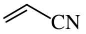
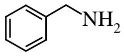
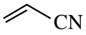
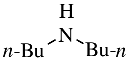
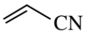
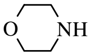
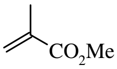
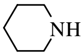
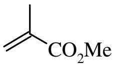
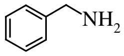
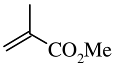
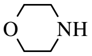
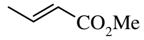
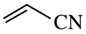
We have recently disclosed a Cu catalyst immobilized in an ionic liquid[23] for the facile addition of amines to α, β-unsaturated compounds. However, we have been looking for a simpler methodology for aza-Michael reactions. To this end, we have now succeeded in the use of boric acid as an innocuous and highly efficient catalyst for the Michael addition of amines to α,β-unsaturated compounds in water to afford the corresponding β-amino derivatives (Scheme 1). To our knowledge this is perhaps the most simple protocol for this type of reaction, which is expected to interest a wide range of organic chemists.

A variety of α,β-unsaturated compounds such as methyl acrylate, acrylonitrile, methyl vinyl ketone, acrylamide and methyl methacrylate underwent 1,4-addition with a wide range of aliphatic amines in the presence of 10 mol % of boric acid at room temperature to give the corresponding β-amino compounds in high yields. The results are summarized in Table 1. In general, secondary amines gave higher yields than primary amines. It is pertinent to mention that benzylamines gave only mono adducts (entries e, l, o, s) whereas with primary amines bis-adducts (entries u and v) were mostly formed. A sterically hindered amine also gave the corresponding 1,4-adduct in good yield (entry h).

In order to investigate the fate of attempted aza-Michael condensations involving aromatic amines such as aniline, *p*-methoxyaniline or *p*-nitroaniline with methyl acrylate as Michael acceptor, the $B(OH)_3$–water protocol was studied. Not surprisingly, only *p*-methoxyaniline reacted to afford a maximum of 15% of the addition product (reaction time 12 h). This enables us to state that the $B(OH)_3$–water protocol is more appropriate for aliphatic amines. In order to lend support to our assertions, a separate reaction was conducted between methyl acrylate and an equimolar mixture of *p*-methoxyaniline and diethylamine. The result is depicted in Scheme 2 and augments our assertion.

Finally, upon completion of the reaction, catalyst recyclability was examined through a series of reactions with piperidine and methyl acrylate using an aqueous phase containing boric acid (Table 2). The reaction continued to give good yields, however, only with relatively longer reaction times. This can be explained by leaching of the catalyst. It is also important to note that the reaction can be performed on a relatively larger scale (5 g) giving good yields (Table 1, entry d) showing its potential for industrial applications.

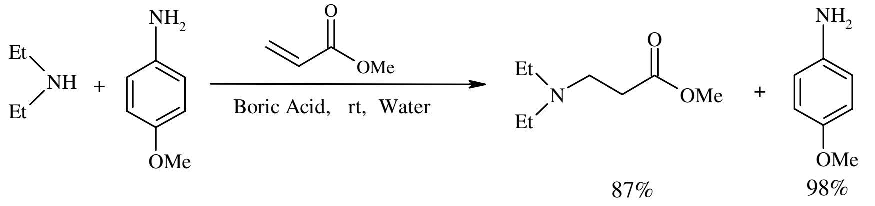
Table 1. Boric acid catalyzed conjugate addition of amines to α,β-unsaturated compounds in water at room temperature

Entry	Amine	α,β-Enone	Time (h)	Yield (%)[a]
a			3.5	90
b			4	88
c			1.5	85
d			1.5	90, 93[b]
e			2.5	90
f			2.5	80
g			3	85
h			5.5	70
i			5	80
j			4	87
k			6	78
l			4	85
m			5	85
n			1.5	95
o			2.5	92
p			2	90
q			2	88
r			2	90
s			3.5	90
t			5	80
u	n-BuNH$_2$		1	(85[c])
v	n-BuNH$_2$		1	30 + 35[c] (89[c])

[a] Isolated yields.

[b] Yield on a 5 g scale.

[c] Bis product (with 2 equiv of α,β-unsaturated compound).



Scheme 2.

Table 2. Recycling of the catalyst for the reaction of piperidine and methyl acrylate in water

Cycle	Yield (%)	Time (h)
1	92	1.5
2	90	2.5
3	90	5

To extend the scope of the $B(OH)_3$–water protocol, α- and β-substituted Michael acceptors were tested under the present conditions. It was found that with Me groups at either the α- or β-positions, the procedure gave good yields (Table 1, entries q–t), whereas with a Ph group at the β-position it failed.

In conclusion, we have developed a very easy way to operate, safe and cost-effective method for the 1,4-addition of aliphatic amines to α,β-unsaturated olefins using boric acid as the catalyst in water.

General experimental procedure: Boric acid (0.3 mmol, 0.018 g) was dissolved in water (3 mL) (pH = 5.7) followed by the addition of amine (3 mmol) and α,β-unsaturated compound (3.3 mmol) and the whole was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts (dried over Na_2SO_4) were concentrated in vacuo and the resulting product was purified by column chromatography on silica gel with ethyl acetate and *n*-hexane (ratio varied with product) (for amides, ethyl acetate and methanol (9:1)) as eluent to afford the pure β-amino adduct. The aqueous layer containing boric acid was reused for the next run.

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