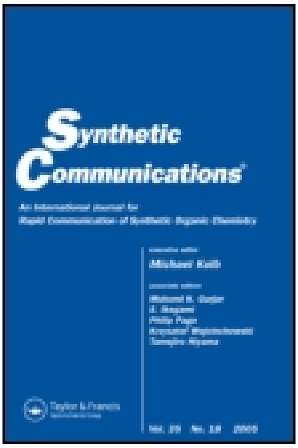

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Microwave-Induced Aza-Michael Reaction in Water: A Remarkably Simple Procedure

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MICROWAVE-INDUCED AZA-MICHAEL REACTION IN WATER: A REMARKABLY SIMPLE PROCEDURE

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Microwave-induced fast addition of several amines to conjugated carbonyl compounds has been carried out in water very efficiently in the absence of any catalyst.

Keywords: Amine; aza-Michael; enone; green synthesis; microwave irradiation

Michael reaction of nucleophiles to unsaturated carbonyl compounds requires basic[1] or acidic conditions.[2] Methods classified as Michael reactions require stoichiometric amounts or excess of acids and bases in organic solvents, and side reactions can occur if the reactive partners are sensitive to nucleophiles, such as amino compounds.[3] The most important feature of these reagents is their ability to limit the catalysts used to catalytic amounts.[4] Despite their tremendous advantage, however, the literature reveals that the success of the reaction depends on the choice of the catalyst and organic solvent. For example, indium salts are extremely effective for Michael reactions with indoles[5] and pyrroles,[6] but they are not excellent promoters in catalyzing a similar reaction with carbamates.[7] In contrast, platinum salts are very effective for this purpose.[7] These reactions were performed in organic solvents. An alternative attractive method using either an effective catalyst or no catalyst in aqueous medium would be highly desirable, timely, and challenging. The use of bismuth-derived reagents in several organic transformations has been demonstrated by our group.[8] The present communication describes the development of a remarkably simple, fast, and environmentally benign microwave-induced aza-Michael reaction of amines with unsaturated carbonyl compounds in water in the absence of any catalysts.

Organic reactions in water have received significant attention because of their environmental acceptability and selectivity. The rate acceleration in water has also been observed in many cases. Development of an efficient and simple procedure in water without any catalyst is difficult but important.

Many procedures[9] have been developed for aza-Michael reaction. Transition metals, lanthanide halides, triflates, silica gel, hetereogeneous solid salts,

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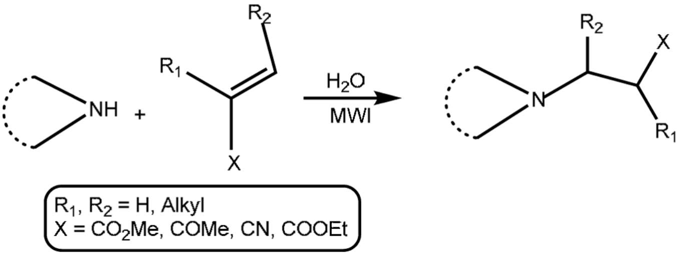
Cu(acac)$_2$/ionic liquid, quarternary ammonium salt/ionic liquid/H_2O, boric acid in H_2O, and β-cyclodextrin in H_2O all have been used for the aza-Michael reaction. Despite much progress, many of these methods used heavy-metal salts and hazardous organic solvents.

Our microwave-induced reaction (Scheme 1) in water has been tested with several amines, unsaturated ketones, unsaturated nitriles, and unsaturated ester, the results of which have been very encouraging (Table 1). The reactions are efficient and completed within 1 to 3 min. The products are isolated in excellent yields. All the reactions in water were very rapid compared to reactions in organic solvents under identical conditions (microwaves). No catalysts were necessary to complete the reaction.

Primary, secondary (cyclic, heterocyclic, and acyclic), benzylic, and aromatic amines produce excellent yields. This method suggests that it is not necessary to use a large excess of corrosive acid, catalytic amounts of Lewis acids, or solid acidic surfaces in Michael reactions of amines with unsaturated ketones, esters, and nitriles. Primary amines produced monoaddition products (entries 10–14) selectively, and no *bis*-addition product could be detected. The presence of water accelerates the reaction, probably through hydrogen bond formation with the carbonyl group, and this may increase the electrophilic character at the β-carbon of the unsaturated compounds. As a result, nucleophilic attack by the amine may increase significantly. On the other hand, hydrogen bond formation between the oxygen atom of water and the H atom of the amine may also increase the nucleophilic power of the N atom of the amine. Water has a very high dielectric constant and dipole moment, and therefore the role of water in the presence of microwave is unique. Water activates the amine as well as the enone system through hydrogen bond formation and thereby greatly facilitates the addition through a brief microwave exposure.

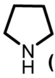
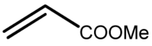
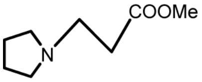
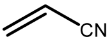
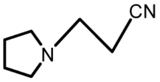
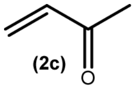
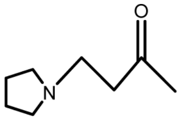
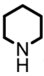
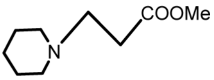
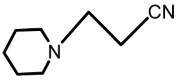
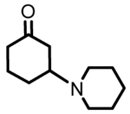
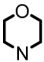
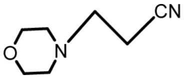
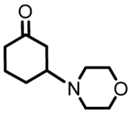
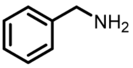
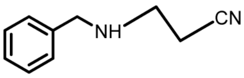
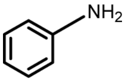
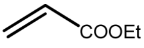
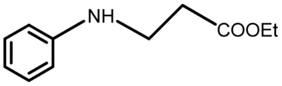
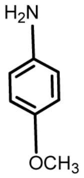
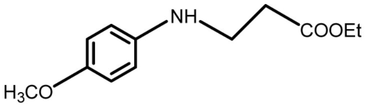
Several years ago, our laboratory demonstrated the aza-Michael reaction in the presence of bismuth nitrate in organic solvent.[9a] We proposed that the role of bismuth nitrate in this type of reaction results in a coordinating power with the carbonyl group. Later, we also demonstrated that bismuth nitrate–catalyzed Michael reactions have proceeded remarkably well in aqueous media.[10]

In conclusion, this method is completely devoid of the use of any metallic, enzymatic, or corrosive catalysts. The present procedure has notable advantages that include simple operational procedure, environmentally benign reaction conditions, faster (1–3 min) reactions, and good yields of products.



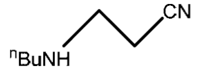
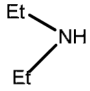
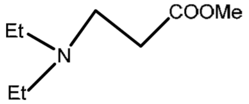
Scheme 1. Microwave-induced aza-Michael reaction in water.

Table 1. Microwave-assisted aza-Michael reaction in water

Entry	Amine	Enone	Product	Time (min)	Yield (%)[a]	Ref.
1	 **(1a)**	 **(2a)**		1	97	9c
2	**(1a)**	 **(2b)**		2	93	9c
3	**(1a)**	 **(2c)**		1	93	9d
4	 **(1b)**	**(2a)**		1	97	9b
5	**(1b)**	**(2b)**		1	98	9b
6	**(1b)**	 **(2d)**		3	88	9a
7	 **(1c)**	**(2a)**		1	90	9a
8	**(1c)**	**(2b)**		1	99	9a
9	**(1c)**	**(2d)**		3	88	9d
10		**(2b)**		3	82	9c
11		 **(2e)**		2	92	9c
12		**(2e)**		1	95	9c

(*Continued*)

Table 1. Continued

Entry	Amine	Enone	Product	Time (min)	Yield (%)[a]	Ref.
13	$^{n}BuNH_2$ **(1e)**	**(2a)**		1	92	9b
14	**(1e)**	**(2b)**		1	96	9b
15		**(2a)**		2	90	9b

Note. "Ref." indicates the corresponding literature syntheses.
[a]Isolated yield.

EXPERIMENTAL

A representative experimental procedure for the aza-Michael reaction (Table 1, entry 13) is as follows: methyl acrylate (1 mmol) was added to n-butyl amine (1 mmol) in water (1 mL), and the heterogeneous mixture was irradiated in a domestic microwave oven. Thin-layer chromatography (TLC) was checked after every 30-s interval. During the microwave exposure, a beaker (250 mL) containing cold water (100 mL) was kept next to the reaction vessel (as heat sink) to absorb excess heat. The mixture was then extracted with dichloromethane (2 × 5 mL), washed with brine solution (10 mL), and dried over Na_2SO_4. The extracts were then concentrated, and the crude product was purified using flash chromatography (silica gel, 30% EtOAc–70% hexane) to afford pure compound (92%). 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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