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PHOSPHORIC ACID CATALYZED AZA-MICHAEL REACTION IN WATER: AN ECOFRIENDLY PROCEDURE

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Abstract: Phosphoric acid catalyzed aza-Michael reaction in water has been carried out in an efficient manner at room temperature. The reaction is general for primary, secondary (cyclic, heterocyclic and acyclic), benzylic as well as aromatic amines. No *bis*-addition was observed for primary amines.

Keywords: Phosphoric acid, amine, water, catalysis, aza-Michael, ecofriendly.

Introduction: Aza-Michael reaction is the one of the most exploited reaction in organic chemistry to synthesize β-amino esters[1a]. The reaction of nucleophiles to unsaturated carbonyl compounds requires basic or acidic conditions. Methods classified as Michael reactions require stoichiometric amounts or excess acids and bases in organic solvents, and side reactions can occur if the reactive partners are sensitive (amino compounds) to nucleophiles. The most important improvement of these reagents is the ability to limit the catalysts used to catalytic amounts. Despite their tremendous improvement, however, the literature reveals that the success depends on the choice of the catalyst and organic solvent. Many procedures have been developed for aza-Michael reaction. Transition metal and lanthanide chloride[2a], alkaline Al_2O_3[2b], cinchona alkaloids[2c], ionic liquids e. g. tetraethylammonium acetate (TEAA)[2d], $Cu(acac)_2$/ionic liquid[2e,f], β-cyclodextrin[2g] in H_2O, polystyrenesulfonic acid in water[2h] DBU-derived ionic liquid etc. have been used for aza-Michael reaction. Despite much progress, many of these methods used heavy metal salts and hazardous organic solvents. As a part of our ongoing research in this field[3a-c] we describe herein the development of a remarkably simple, fast and environmentally benign aza-Michael reaction of amines with unsaturated carbonyl compounds at room temperature using phosphoric acid in water (Scheme 1).

Scheme 1

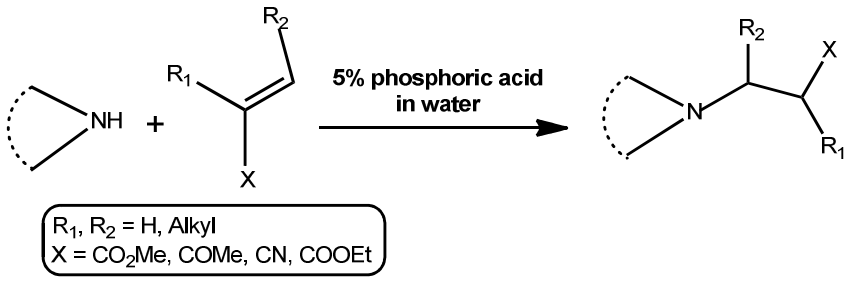
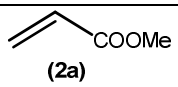
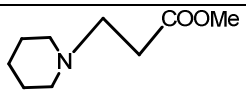
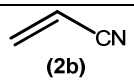
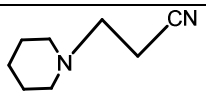
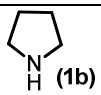
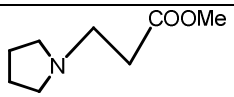
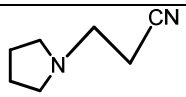
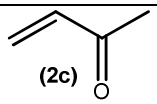
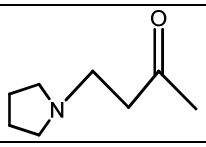
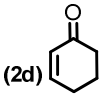
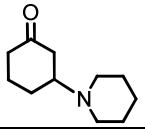
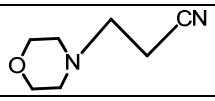
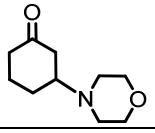
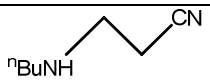
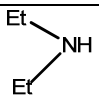
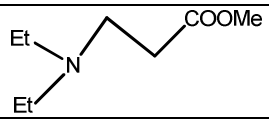
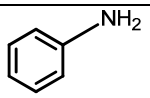
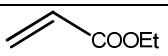
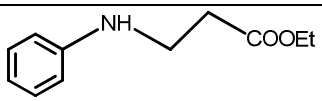
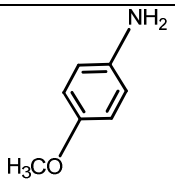
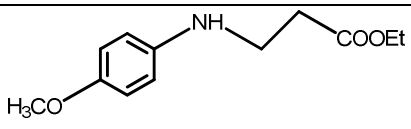
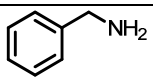
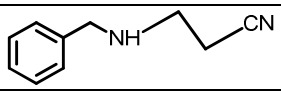


Table 1.

Entry	Amine	Enone	Product	Time (min)	Yield (%)[a]
1	 (1a)	 (2a)		45	90
2	(1a)	 (2b)		50	85
3	 (1b)	(2a)		45	92
4	(1b)	(2b)		60	86
5	(1b)	 (2c)		45	98
6	(1a)	 (2d)		90	84
7	 (1c)	(2a)		55	96
8	(1c)	(2b)		60	83
9	(1c)	(2d)		90	80
10	$^{n}BuNH_2$ (1e)	(2a)		45	90
11	(1e)	(2b)		50	91
12		(2a)		65	80
13		 (2e)		70	85
14		(2e)		65	85
15		(2b)		70	82

Results and Discussion: All the reactions were conducted in 5% phosphoric acid in water. Organic reactions in water have received significant attention because of their environmental acceptability and selectivity. Development of an efficient and simple procedure in water is challenging and timely. Our phosphoric acid catalyzed reaction (**Scheme 1**) in water has been tested with several amines and unsaturated ketones, unsaturated nitrile an unsaturated ester, the results which have been very encouraging (**Table 1**).

The reactions are efficient and completed within 45 minutes to 1.5 hours at room temperature. The products are isolated in high yields. Primary, secondary (cyclic, heterocyclic and acyclic), benzylic as well as aromatic amines produce excellent yield. This method suggests that it is not necessary to use large excess of corrosive acid, catalytic amounts of Lewis acids or solid acidic surfaces in Michael reaction of amines with unsaturated ketones, esters and nitriles. Primary amines produced monoaddition products (Entries 10, 11, 13, 14 and 15) selectively and no *bis* addition product could be detected. The reaction between piperidine with methyl acrylate (Entry 1) gave 90% yield. 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[4], 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. Moreover, organic reaction in water without using harmful organic solvents is also one of the current focuses because water is abundant, nontoxic and environment-friendly compared with organic solvents.

Experimental:

Melting points were determined in a Fisher Scientific electrochemical Mel-Temp manual melting point apparatus (Model 1001) equipped with a 300 °C thermometer. FT-IR spectra were registered on a Bruker IFS 55 Equinox FTIR spectrophotometer as KBr discs. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.4 MHz) spectra were obtained at room temperature with JEOL Eclipse-300 equipment using TMS as internal standard and $CDCl_3$ as solvent. Analytical grade chemicals (Sigma-Aldrich incorporation) were used throughout the project. Deionized water was used for the preparation of all aqueous solutions.

Representative experimental procedure for the aza-Michael reaction (**Table 1, entry 10**): methyl acrylate (1 mmol) was added to n-butyl amine (1 mmol) in 5% phosphoric acid solution in water (1 mL) and the mixture was stirred at room temperature. The reaction was monitored by TLC after each 5 minutes interval. After completion of the reaction, it was extracted with diethyl ether (2 x 5 mL), washed with brine solution (10 mL) and dried over $Na_2(SO_4)$. The extract was then concentrated and the crude product was purified using flash chromatography (silica gel, 30% EtOAc/70% hexane) to afford pure compound (90%). 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.

Conclusion:

In conclusion, the above method is completely devoid of the use of any metallic, enzymatic or corrosive catalysts. The present procedure has notable advantages that include simple operation procedure, environmentally benign reaction conditions, faster reactions and high yields of products.

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