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Squaric acid as an impressive organocatalyst for Michael addition in water

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ABSTRACT

A simple, green, and environmentally benign protocol for squaric acid (5 mg) catalyst conjugate addition of aromatic amines and thiols to unsaturated carbonyl compounds in water in good to excellent yields is developed. The advantages of low sensitivity toward moisture and oxygen, high tolerance of different functional groups, green reaction media and efficient recyclability make this organocatalyst suitable for both laboratory and industrial scale synthesis of β-substituted carbonyls under very mild conditions.

1. Introduction

In recent years, it has been established that small organic molecules, in addition to metal complexes and biocatalysts, can be highly selective and efficient catalysts. As a consequence, organocatalysis is gaining importance in asymmetric synthesis, complementing bio- and metal-catalysis [1,2].

On the other hand, the development of water as a green medium for organic synthesis has become an important research area. Other than the economical and environmental benefits of using water, it may exhibit unique reactivity and selectivity in comparison with conventional organic solvents. Therefore, development of simple reactivity and selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous media [3–6].

Nitrogen and sulfur-containing motifs are ubiquitous in natural products [7,8] biologically active molecules [9], and important synthetic intermediates for various pharmaceuticals and natural products [10–12].

Given the widespread availability of sulfur and nitrogen containing nucleophiles and α,β-unsaturated alkenes, there is substantial interest in developing efficient Michael addition from these simple starting materials. Thus, several efforts have been made to develop newer and simpler methodologies for thia-and aza-Michael addition that lead to the development of various base and acid catalysts and novel reaction media such as water and ionic liquids [13–53].

2. Results and dissociation

As a part of our research, aimed at developing green chemistry by using water as reaction medium or by performing organic transformations under solvent-free conditions [54–58], herein, we describe the use of simple small organic catalysts capable of promoting Michael addition of aromatic, aliphatic thiols and aromatic amines in water.

As a model reaction, benzylideneacetone was reacted with thiophenol with different loading of starting materials. It was found that by simple mixing of benzylideneacetone (1 mmol), and thiophenol (1 mmol), in the presence of squaric acid (5 mg) in water (2 mL) the desired products was obtained in 97% yield (Scheme 1).

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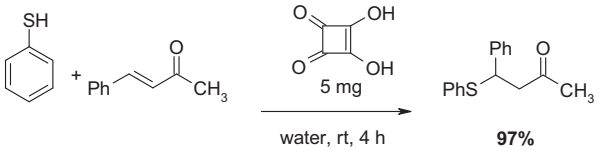
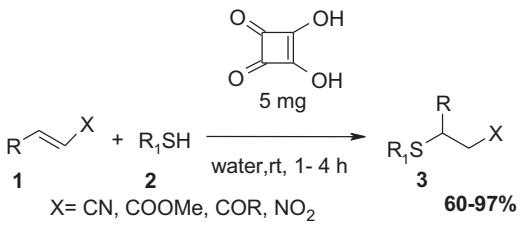


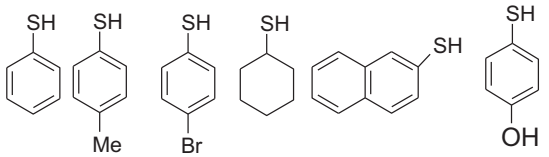
Scheme 1. The optimized reaction conditions for Michael addition in water.

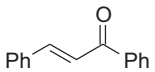
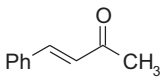
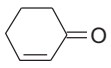
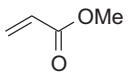
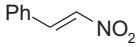
With the optimized reaction conditions in hand, the scope of the reaction was explored with different substances. Fortunately, these results proved to be quite general and a wide range of structurally different thiols underwent Michael addition with several Michael acceptors such as α,β-unsaturated ketones, esters and nitriles affording the corresponding products in quantitative yield. cyclohexenone, methyl vinyl ketone, chalcone, methyl acrylate, acrylonitrile, β-nitrostyrene and benzylideneacetone underwent 1,4-addition with a wide range of thiols, such as aliphatic, substituted aromatic thiols bearing an electron-withdrawing and electron-donating groups in the presence of very small amount of squaric acid in water at room temperature to give the corresponding products in high yields. The results are summarized in Table 1.

To further explore the scope of this simple protocol, a number of electron-deficient olefins and aromatic amines

Table 1
Reaction of thiols with Michael acceptors in water.





Entry	Thiol	Michael acceptor	Yield [%]	Time [min]
1	2a		90	240
2	2b		92	240
3	2c		85	240
4	2d		60	240
5	2e		78	240
6	2f		90	240
7	2a		97	240
8	2b		90	240
9	2c		90	240
10	2e		65	240
11	2f		82	240
12	2a		97	60
13	2b		95	80
14	2d		90	100
15	2f		92	80
16	2a		92	120
17	2b		84	120
18	2c		80	120
19	2a		92	150
20	2b		97	150
21	2c		80	150
22	2a		95	150
23	2b		95	150
24	2c		92	150
25	2a		90	80
26	2b		85	80
27	2c		82	80