

# Catalyst-Free Conjugated Addition of Thiols to $\alpha,\beta$ -Unsaturated Carbonyl Compounds in Water

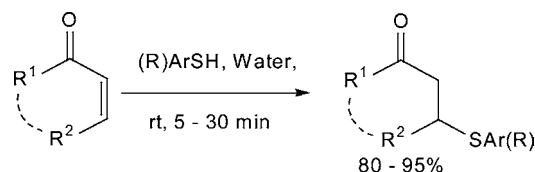
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## ABSTRACT



Catalyst-free conjugate addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds in water is reported.  $\beta$ -Sulfido carbonyl compounds were formed at room temperature, in short times and with excellent chemoselectivity. Competitive dithiane/dithiolane formation, transesterification, and ester cleavage were not observed. Water played a dual role in simultaneously activating the  $\alpha,\beta$ -unsaturated carbonyl compound and the thiol. This new methodology constitutes an easy, highly efficient, and green synthesis of  $\beta$ -sulfido carbonyl compounds.

The  $\beta$ -sulfido carbonyls are important organic compounds as they are starting materials for the generation of  $\beta$ -acylvinyl cation<sup>1</sup> and homoenolate anion<sup>2</sup> equivalents. One of the most practical and widely used routes for the synthesis of  $\beta$ -sulfido carbonyl compounds is the conjugate addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds. Conversion of  $\alpha,\beta$ -unsaturated carbonyl compounds to the corresponding  $\beta$ -sulfido carbonyl derivatives provides an elegant strategy for chemoselective protection of the olefinic double bond of conjugated enones<sup>3</sup> due to the ease of generation of the double bond by removal of the sulfur moiety by copper(I)-induced<sup>4</sup> and oxidative<sup>1</sup> eliminations. Thus, thia-Michael addition is an important transformation and, apart from its versatile applications in synthetic organic chemistry, it plays a crucial role in biosynthesis<sup>5</sup> and synthesis of bioactive compounds.<sup>6</sup> Thus, constant efforts have been made to develop newer methodologies for thia-Michael addition that lead to the development of various catalysts.<sup>7</sup> However, there

are various limitations with the reported methodologies such as long reaction times, use of halogenated solvents, difficulty in recovery of high boiling solvents, high temperatures, requirement of special efforts for preparation of catalysts, use of costly catalysts, moderate yields, use of toxic

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chemicals, etc. Although water has been employed as solvent for the conjugate addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds,<sup>7k,8</sup> these methodologies employed an additional reagent/catalyst and there is no report of the thia-Michael addition in water without the use of any catalyst. The catalyst-free preparation of  $\beta$ -sulfido carbonyl compounds in water is desirable as the tight legislation on the maintenance of greenness in synthetic pathways and processes demands us to prevent waste, avoid the use of hazardous (e.g., halogenated and high-boiling solvents) auxiliary substances (e.g., additional reagents), and minimize energy requirements.<sup>9</sup> Thus, the use of water instead of organic solvents has gained importance as an essential component of the development of sustainable chemistry.<sup>10,11</sup> Herein, we wish to report the conjugate addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds in water at room temperature without the use of any metal catalyst, leading to an easy and highly efficient synthesis of  $\beta$ -sulfido carbonyl compounds in concurrence with the triple bottom-line philosophy of green chemistry.<sup>12</sup>

In a model reaction, cyclohexenone **1** (2.5 mmol) was treated with thiophenol **2** (1.1 equiv) in water (5 mL) in the absence of any catalyst at room temperature. The crude product, isolated after workup, on being subjected to purification by column chromatography afforded  $\beta$ -phenylthiocyclohexanone **3** in 90% yield. The amount of water used to carry out the reaction did not have any significant influence on the overall rate of the reaction and the product yield. Thus, when **1** (2.5 mmol) was treated with **2** (1.1 equiv) in 10 and 20 mL of water, **3** was formed in 95 and 90% yields (GCMS), respectively, after 5 min. To test the feasibility of a large-scale reaction, **1** (10 mmol) was treated with **2** (1.1 equiv) in water (50 mL) at room temperature, and 94% conversion (GCMS) to **3** was observed after 5 min. The reaction mixture became turbid, and the excess (unreacted) thiol settled down as liquid droplets. The pure product was obtained in 87% yield after purification by column chromatography. Encouraged by this result, we planned to establish the generality of this reaction. Various cyclic and acyclic enones (e.g., cyclohexenone, cyclopentenone, and methyl vinyl ketone) and enoates (e.g., methyl acrylate) were treated with aryl thiols (e.g., thiophenol, 4-methylthiophenol, and 4-nitrothiophenol), aryl alkanethiols (e.g.,  $\alpha$ -toluene thiol and 2-furylmethane thiol), alkanethiols (e.g., ethane thiol), and

alkane dithiols (e.g., 1,2-ethane dithiol and 1,3-propane dithiol) in water at room temperature (Table 1). Excellent results were obtained in each occasion. The reactions were completed after 5–30 min affording 80–90% yields. In the case of reactions using dithiols (entries 7 and 8), the dithia-Michael adducts were obtained. The progress of the reactions was monitored by TLC and IR after intervals of 5, 10, 15, and 30 min. However, it was possible to monitor the reaction visually. A clear solution was obtained after addition of the thiol to the  $\alpha,\beta$ -unsaturated carbonyl compound in water, and the reaction mixture became turbid after the complete consumption of the starting  $\alpha,\beta$ -unsaturated carbonyl compound (TLC, IR). The reactions were highly chemoselective as no competitive dithiane/dithiolane formation was observed in the case of enones.<sup>13</sup> The exclusive formation of the methyl  $\beta$ -sulfidopropionates from methyl acrylate (entries 17–20) without any competitive transesterification and ester cleavage<sup>14</sup> further demonstrated the chemoselectivity.

The plausible role of water in promoting the reaction is rationalized by the mechanism depicted in Scheme 1. Hydrogen bond formation between water and the carbonyl oxygen atom of the  $\alpha,\beta$ -unsaturated carbonyl compound increased the electrophilic character at the  $\beta$ -carbon of the  $\alpha,\beta$ -unsaturated carbonyl compound. On the other hand, hydrogen bond formation involving the oxygen atom of water and the sulfhydryl hydrogen of the thiol increased the nucleophilicity of the sulfur atom of the thiol. Thus, simultaneous activation of the  $\alpha,\beta$ -unsaturated carbonyl compound and the thiol takes place through hydrogen bond formation with water via the transition state **I**. Intramolecular nucleophilic attack at the  $\beta$ -carbon atom of the  $\alpha,\beta$ -unsaturated carbonyl compound by the sulfur atom of the thiol (via the transition state **Ia**) followed by intramolecular proton transfer led to the conjugate adduct. The validity of this proposal demands that the efficiency of this dual activation should be dependent on the relative hydrogen bond formation capability of various thiols. In fact, the rate of reaction of various thiols with a common  $\alpha,\beta$ -unsaturated carbonyl compound was found to be influenced by the hydrogen bond formation ability of the thiols. In general, the rate of reaction of aromatic thiols with a common substrate was found to be faster than that of aryl alkanethiol, alkanethiol, and alkane dithiols (compare entries 1–3 with entries 4–8, entries 9 and 10 with entries 11 and 12, and entries 13 and 14 with entries 15 and 16). This observation supported the involvement of hydrogen bond formation between the thiols and water. As the sulfhydryl hydrogen atom of aliphatic thiols is less acidic compared to that of aromatic thiols, the hydrogen bond formation of the sulfhydryl hydrogen atom with water was less effective in the case of the aliphatic thiols. The faster rate of reaction of thiophenol compared to that of 4-methylthiophenol (compare entry 1 with 2 and entry 13 with 14) further supported the role of water in accelerating the conjugate addition by hydrogen

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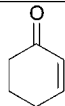
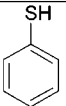

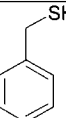
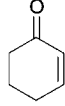
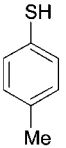


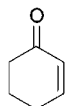
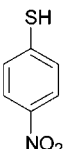


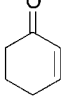
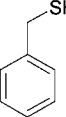

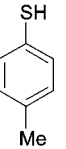
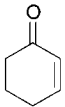
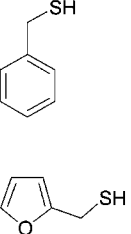

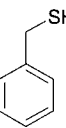
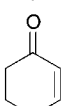



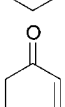

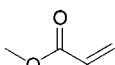
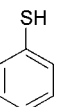
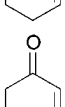

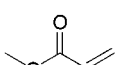
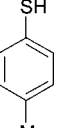
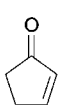
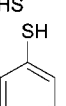
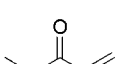
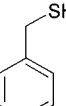
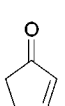
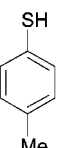
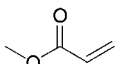

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**Table 1.** Conjugate Addition of Different Thiols to Various  $\alpha,\beta$ -Unsaturated Carbonyl Compounds in Water<sup>a</sup>

| entry | enone   | thiol   | time (min) | yield (%) <sup>b,c</sup> | entry | enone  | thiol   | time (min) | yield (%) <sup>b,c</sup> |
|-------|---|---|------------|--------------------------|-------|--|---|------------|--------------------------|
| 1     |    |    | 5          | 90                       | 11    |    |    | 10         | 90                       |
| 2     |    |    | 10         | 90                       | 12    |    |    | 15         | 90                       |
| 3     |    |    | 5          | 90                       | 13    |    |    | 5          | 95                       |
| 4     |    |    | 10         | 90                       | 14    |    |    | 10         | 95                       |
| 5     |    |    | 10         | 90                       | 15    |    |    | 15         | 95                       |
| 6     |    |    | 10         | 95                       | 16    |    |    | 15         | 90                       |
| 7     |   |  | 15         | 90 <sup>d,e</sup>        | 17    |   |   | 15         | 95                       |
| 8     |  |  | 30         | 80 <sup>d,e</sup>        | 18    |  |  | 15         | 95                       |
| 9     |  |  | 5          | 90                       | 19    |  |  | 15         | 90                       |
| 10    |  |  | 5          | 90                       | 20    |  |  | 15         | 80                       |

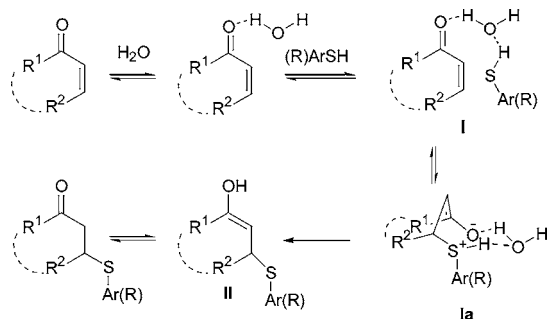
<sup>a</sup> The  $\alpha,\beta$ -unsaturated carbonyl compound (2.5 mmol) was treated with the thiol (1.1 equiv except for entries 7 and 8) in H<sub>2</sub>O (5 mL) at room temperature (30–35 °C). <sup>b</sup> Yield of the corresponding isolated and purified  $\beta$ -sulfido carbonyl compound. <sup>c</sup> The product was characterized by IR, NMR, and MS. <sup>d</sup> 0.55 equiv of the dithiol was used. <sup>e</sup> Yield of the corresponding dithia-Michael adduct.

bond formation with the thiol, as otherwise the reaction time of 4-methylthiophenol would have been shorter compared to that of thiophenol because of the better nucleophilicity of 4-methylthiophenol. Similarly the involvement of hydrogen bond formation with water made the reaction of 4-nitrothiophenol faster than that of 4-methylthiophenol (compare entries 2 and 3), although the former thiol is less nucleophilic/reactive. The rate of conjugate addition to an  $\alpha,\beta$ -unsaturated ester was slower compared to that of  $\alpha,\beta$ -unsaturated ketones (compare the results of entries 1, 9, 13, and 17). This was

due to the fact that the carbonyl oxygen atom of the  $\alpha,\beta$ -unsaturated ester was involved in hydrogen bond formation with water to an extent lower compared to the carbonyl oxygen atom of  $\alpha,\beta$ -unsaturated ketones. This made the  $\beta$ -carbon atom of  $\alpha,\beta$ -unsaturated ketones more electrophilic compared to that of the  $\alpha,\beta$ -unsaturated ester.

The importance of water in promoting the reaction was further demonstrated by the fact that the treatment of **1** (2.5 mmol) with thiophenol **2** (1.1 equiv) under neat conditions at room temperature resulted in 30, 40, and 50% (GCMS)

**Scheme 1.** Dual Activation Role of Water During Catalyst-Free Thia-Michael Addition Reactions



conversion to **3** after 5, 10, and 60 min, respectively. No conjugate addition took place after 30 min (TLC) during the reaction of methyl acrylate (2.5 mmol) with **2** (1.1 equiv) under similar conditions, and only 10% conversion to the thia-Michael adduct was observed after 60 min (GCMS).

Similarly, the reaction of **1** (2.5 mmol) with  $\alpha$ -toluene thiol (1.1 equiv) as a representative of aliphatic thiol under neat conditions and at room temperature did not afford any significant amount of formation of the conjugate addition product after 30 min (TLC).

We have described herein an efficient methodology for water-mediated conjugate addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds providing an easy synthesis of  $\beta$ -sulfido carbonyl compounds. The metal-free and non-hazardous experimental conditions, room-temperature operation, ease of reaction, short reaction times, and high yields fulfilled the triple bottom-line philosophy of green chemistry<sup>12</sup> and made this method environmentally benign.

**Supporting Information Available:** General experimental details, scanned spectra, and spectral data of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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