

# Formation of Zinc Thiolates by Reductive Cleavage of Disulfides with the Zn/AlCl<sub>3</sub> System in Aqueous Media, and their Use for Michael Addition

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A simple, convenient, and efficient one-pot protocol for the reductive cleavage of disulfides and Michael addition to  $\alpha,\beta$ -unsaturated carbonyl compounds mediated by the Zn/AlCl<sub>3</sub> system in aqueous media is reported.

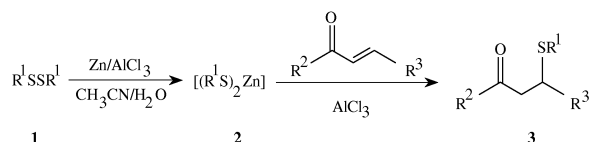
**Key words:** Zinc Thiolates, Disulfides, Michael Addition,  $\alpha,\beta$ -Unsaturated Carbonyl Compounds

## Introduction

The 1,4-conjugate addition of nucleophiles to electron deficient alkenes is a widely used process and has many applications in organic synthesis [1]. Among various nucleophilic additions, the conjugated addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds to form carbon-sulfur bonds constitutes a key reaction in organic synthesis as well as in the synthesis of biologically active compounds such as the calcium antagonist diltiazem [2, 3]. This reaction is usually based either on the activation of thiols by a base [4] or activation of the acceptor olefins with Lewis acids [5]. However, to avoid side reactions occasionally encountered in presence of a strong acid or a base, several inorganic salts such as alumina, zeolite, bismuth nitrate among others have been introduced [6]. Recently, ionic liquids such as tetrabutylammonium bromide [7], the [bmim]PF<sub>6</sub>/H<sub>2</sub>O solvent system [8], and [pmim]Br [9] have been introduced as efficient catalysts for Michael addition of thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds.

## Results and Discussion

In continuing our quest to exploit the synthetic potentials of zinc thiolates [10], easily generated from disulfides in the Zn/AlCl<sub>3</sub> system, we present herein the conjugate addition of thiolate anions to  $\alpha,\beta$ -unsaturated carbonyl compounds in CH<sub>3</sub>CN-H<sub>2</sub>O mixed solvent at 65 °C to afford Michael adducts in good to very good yields under neutral conditions



Scheme 1.

(Scheme 1). Such reactions in aqueous media offer numerous advantages over common reactions in organic solvents [10, 11].

A series of symmetrical alkyl and aryl disulfides were treated with various  $\alpha,\beta$ -unsaturated aldehydes and ketones in the Zn/AlCl<sub>3</sub> system with a molar ratio of disulfide: AlCl<sub>3</sub>: carbonyl compound = 0.5: 1: 2. The presence of aluminum chloride is essential in both steps (S-S bond cleavage and conjugate addition). In the absence of this Lewis acid, the reaction slows down considerably. The disappearance of zinc during the preliminary treatment of disulfides with Zn/AlCl<sub>3</sub> is attributed to the formation of zinc thiolate intermediates [10] which further undergo 1,4-addition of the thiolate to  $\alpha,\beta$ -unsaturated aldehydes and ketones to produce the corresponding Michael adducts. Representative results are summarized in Table 1. These reactions are in general very fast. The crude products were purified by preparative thin layer chromatography. As evident from the results in Table 1, the yields are comparable for various disulfides and  $\alpha,\beta$ -unsaturated ketones (cyclic and acyclic) and aldehydes. The highest yield is obtained for 3-(phenylthio)butanal (82%, entry 10, Table 1), and the lowest for 3-(butylthio)butanal (69%, entry 12, Table 1).

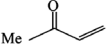
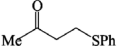
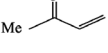
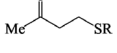
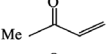
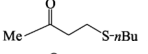












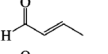
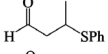
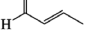
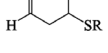
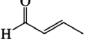
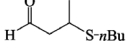
Entry	R	$\alpha,\beta$ -Unsaturated carbonyl compound	Product	Time (h)	Yield (%) <sup>a,b</sup>
1	Ph			1.3	81 <sup>7</sup>
2	PhCH <sub>2</sub>		 R = CH <sub>2</sub> Ph	1.25	79 <sup>5d</sup>
3	<i>n</i> -Bu		 R = <i>n</i> -Bu	1.5	72 <sup>7</sup>
4	Ph			1.75	75 <sup>7</sup>
5	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>		 R = <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	1	70 <sup>12</sup>
6	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>		 R = <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	1	71 <sup>12</sup>
7	Ph			1.5	74 <sup>5d</sup>
8	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>		 R = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	1	77 <sup>5d</sup>
9	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>		 R = <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	2	70 <sup>13</sup>
10	Ph			0.5	82 <sup>7</sup>
11	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>		 R = <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	0.5	77 <sup>13</sup>
12	<i>n</i> -Bu		 R = <i>n</i> -Bu	1.4	69 <sup>7</sup>

Table 1. Reductive cleavage of disulfides R<sub>2</sub>S<sub>2</sub> and conjugated addition to Michael acceptors in the Zn/AlCl<sub>3</sub> system.

<sup>a</sup> Yields refer to those of pure isolated products characterized by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy; <sup>b</sup> references for known compounds.

## Conclusion

In conclusion, we describe a simple, convenient, and efficient one-pot protocol for the reductive cleavage of disulfides and 1,4-conjugate addition to  $\alpha,\beta$ -unsaturated carbonyl compounds using the Zn/AlCl<sub>3</sub> system in aqueous media. The present method offers some advantages over procedures earlier reported, in that it avoids the use of free thiols and the use of dry solvents, as well as operational simplicity, mild reac-

tion conditions, lack of toxicity, good yields of products, and low costs.

## Experimental Section

All products were characterized by comparison of their spectroscopic data with those of known samples. IR spectra were obtained using a Shimadzu 470 instrument. <sup>1</sup>H NMR spectra were determined by a Bruker AQS Avance 300 MHz spectrometer.

### General experimental procedure

A mixture of disulfide (0.5 mmol), zinc powder (3.5 mmol), finely ground anhydrous aluminum chloride (1 mmol), acetonitrile (10 ml), and water (2.5 ml) was stirred at 65 °C for 1.5 h until the zinc powder had almost disappeared. The  $\alpha,\beta$ -unsaturated carbonyl compound (2 mmol) was then added at once to the solution and stirring was continued at that temperature for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the solution was filtered, acetonitrile was evaporated, di-

ethyl ether (30 ml) was added, the mixture washed with water ( $2 \times 20$  ml), and the organic layer dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure, and the crude mixture was purified by preparative TLC (silica gel; eluent, *n*-hexane/ethyl acetate, 4:1) to obtain the pure product.

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