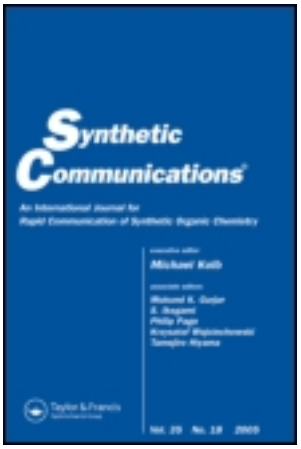

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# Catalyst-Free Conjugate Addition of Thioacids to Activated Olefins Accelerated in Water

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# CATALYST-FREE CONJUGATE ADDITION OF THIOACIDS TO ACTIVATED OLEFINS ACCELERATED IN WATER

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***Michael addition of thioacetic and thiobenzoic acids to activated olefins was investigated in the presence of water under catalyst-free conditions. This process, in addition to being green, has an excellent yield. With simple filtration, high-quality products were obtained on a large scale. Competitive dithiane formation and ester cleavage were not observed. Also, excellent yield was obtained using this simple process for the final step of spironolactone synthesis.***

***Keywords***: Activated olefins; Michael addition; thioacid; water

## INTRODUCTION

Aqueous media is attractive for many organic reactions. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple to handle, cheaper to operate, and especially important in industry.[1] Also catalyst-free synthesis is desirable as the tight legislations on maintaining green chemistry in synthetic pathways and processes demand us to prevent waste, avoid the use of hazardous auxiliary substances, and minimize energy requirements.[2]

Michael addition is one of the most important reactions in organic synthesis. Thiols are known as good nucleophiles for the reactions.[3,4] Generally, harsh reaction conditions are required for the conversion of the newly formed thioether group to more synthetically versatile SH group.[5] To avoid this problem, the use of a thioacid (RCOSH) as a nucleophile for the Michael addition is more attractive because the resulting thioester can be readily transformed into an SH group under mild reaction conditions.[5]

Conjugate addition of thioacids to enones has attracted considerable interest as it leads to the synthesis of biologically active compounds such as diltiazem,[6] thiobutacin,[7] captopril,[8] and spironolactone.[9] Usually, conjugate addition of thioacids to activated olefins has been done in the presence of a base or using thioacid salts in organic solvents.[10] However, there are various limitations with the reported works such as long reaction times, use of dry organic solvents, difficulty

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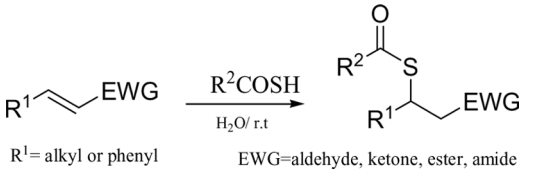
in recovery of solvents especially on an industrial scale, high temperatures, use of costly catalysts, moderate yields, and use of excess amount of thioacids. So, development of a simple, green, and cost-effective procedure would extend the scope of this reaction.

## RESULTS AND DISCUSSION

There are a few reports in the literature on reactions catalyzed by water without using any catalyst, such as the Michael addition of thiols to unsaturated compounds,[11] ring opening of epoxides by amines,[12] synthesis of dithiocarbamate,[13] and N-*tert*-butyloxy-carbonylation of amines.[14] Recently, we have disclosed a different approach, with excellent yields, for the Michael addition of naphthols, amines, and thiols to nitrostyrenes and dimethyl acetylenedicarboxylate (DMAD) in water without use of catalysts.[15] According to our knowledge, there are no reports on the Michael addition of thioacids to enones in water and in catalyst-free conditions. Herein, we report the conjugate addition of thioacids to α,β-unsaturated carbonyl compounds in water at room temperature without the use of any metal catalyst and Lewis bases, leading to an easy, cost-effective, and highly efficient synthesis of thioester derivatives in concurrence with the three-part philosophy of green chemistry (Scheme 1).

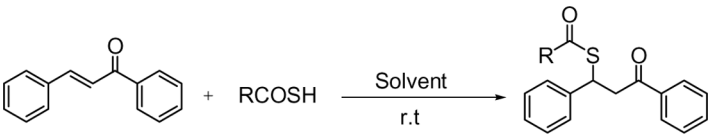
To show the importance of water in promoting this process, we screened the reaction of thioacetic acid and thiobenzoic acid with chalcone in different solvents such as methanol, ethanol, $CHCl_3$, tetrahydrofuran (THF), dimethylformanide (DMF), acetone and diethyl ether. As shown in Table 1, the great yield was obtained in water, while moderate to good yields were obtained in organic solvents. Also moderate yield was obtained in solvent-free conditions (Table 1, entry 6). This shows that water can facilitate the process because of dual activation of enones and thioacids by hydrogen bonding or more dissociation of thioacids. The same reaction was also carried out with different equivalents of thioacids with chalcone. Only about 1.1 equivalents of thioacid are sufficient for complete conversion of chalcone to thioester.

After optimization of the reaction conditions, the efficiency of the process was investigated with the reaction of thioacetic and thiobenzoic acids with different α,β-unsaturated carbonyl compounds. The results are summarized in Table 2. As shown in Table 2, the chalcone derivatives with electron-donating and electron-withdrawing substitutions give a good yield. Excellent yields were also obtained with cyclic α,β-unsaturated carbonyl compounds (Table 2, entry 24). Reaction of thioacids with acrylamide derivatives affords the products with complete conversion (Table 2, entry 26). However, cinnamaldehyde gives good yield of Michael adducts without affecting the aldehyde group. The reaction is also applicable for heterocyclic




**Scheme 1.** Conjugate addition of thioacids to activated olefins.

**Table 1.** Solvent effect on conjugate addition of thioacetic acid and thiobenzoic acid to chalcone




| Entry | Solvent | Yield (%, R=$CH_3$)[a,b] | Yield (%, R=Ph)[a,b] |
|---|---|---|---|
| 1 | $H_2O$ | 100 | 88 |
| 2 | DMF | 62 | 70 |
| 3 | $CH_3OH$ | 60 | 55 |
| 4 | $C_2H_5OH$ | 66 | 52 |
| 5 | $CHCl_3$ | 79 | 70 |
| 6 | Solvent-free | — | 57 |
| 7 | Diethyl ether | 100 | 78 |
| 8 | Tetrahydrofuran | 83 | 78 |
| 9 | Acetone | 100 | 73 |

[a]Isolated yield.
[b]Reaction conditions: chalcone (5 mmol), thioacid (5.5 mmol), and water (10 mL).

systems (entries 20–23, Table 2). The enones containing aliphatic groups were also converted to their thioesters with excellent yields.

In all cases, except in the case of entry 23 (Table 2), no hydrolysis of thioester group to SH is observed in water. In this case, because of the presence of the pyridine group in the structure of chalcone and the basicity of the aqueous solution, a hydrolysis product was observed.

The final step in the synthesis of spironolactone **2** is the conjugate addition of thioacetic acid to canrenone **1**. To show the ability of this process for industrial application, the reaction was carried out in water medium at room temperature and resulted in excellent yields (Scheme 2).

We also attempted the reaction of thioacids and chalcones in a large-scale system. The reaction proceeded well without using any organic solvents for extraction of products; filtration or decanting gives the crude products with high purity (more than 98%).

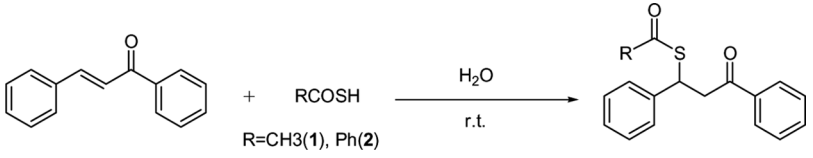
We have described herein an efficient methodology for water-mediated conjugate addition of thioacids to α,β-unsaturated carbonyl compounds, providing an easy synthesis of thioester compounds. The metal-free, catalyst-free, and nonhazardous experimental conditions, room-temperature operation, ease of reaction, short reaction times, and excellent yields of products are the advantages of this report, especially for industrial use.

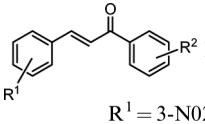
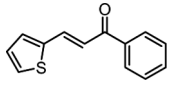
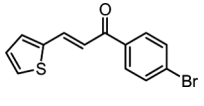
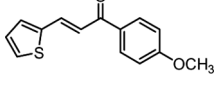
## EXPERIMENTAL

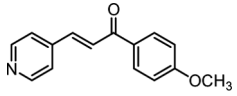
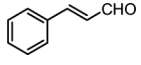
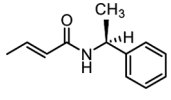
### Material

All reactions were carried out in an atmosphere of air. Chemicals and solvents were purchased from Merck and Fluka and used as received. The $^1H$ and $^{13}C$ NMR spectra were recorded on 300-MHz spectrometers.

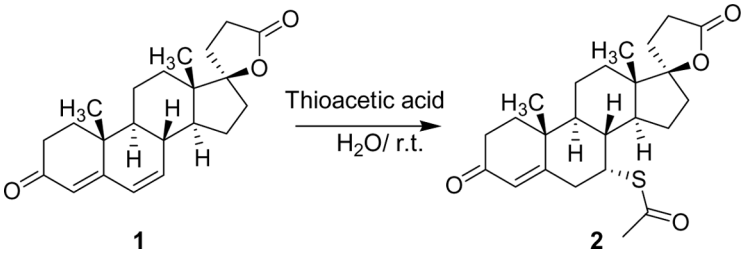
**Table 2.** Catalyst-free conjugate addition of thioacids to enones in water at room temperature




| Entry | Michael acceptor | Yield (%)[a,b] 1 | Yield (%)[a,b] 2 | Entry | Michael acceptor | Yield (%)[a,b] 1 | Yield (%)[a,b] 2 |
|---|---|---|---|---|---|---|---|
| 1 | $R^1$,$R^2$ = H | Quant. | 88 (41)[c] | | | | |
| 2 |  $R^1$ = 4-OMe, $R^2$ = H | Quant. | 86 | 20 |  | Quant. | 88 |
| 3 | $R^1$ = 3-N02, $R^2$ = H | Quant. | 89 | | | | |
| 4 | $R^1$ = 2-CI, $R^2$ = H | Quant. (75)[d] | 85 | 21 |  | 80 | — |
| 5 | $R^1$ = 4-CI, $R^2$ = H | Quant. | 85 | | | | |
| 6 | $R^1$ = 2,6-dichloro, $R^2$ = H | Quant. | 86 | | | | |
| 7 | $R^1$ = 4-N0$_2$, $R^2$ = H | 96 | 81 | 22 |  | Quant. | 87 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 | $R^1 = 4\text{-}CH_3$, $R^2 = H$ | Quant. | 91 | | | | |
| 9 | $R^1 = 2\text{-}N0_2$, $R^2 = H$ | Quant. | — | 23 |  | 60[d] | 80[e] |
| 10 | $R^1 = 4\text{-}Br$, $R^2 = H$ | Quant. | 86 | | | | |
| 11 | $R^1 = 2,4\text{-dichloro}$, $R2 = 4\text{-}OCH_3$ | Quant. | 78 | 24 |  | Quant. | 88 |
| 12 | $R^1 = 4\text{-}N0_2$, $R^2 = 4\text{-}OCH_3$ | 92 | 80 | | | | |
| 13 | $R^1 = 4\text{-}CH_3$, $R^2 = 4\text{-}OCH_3$ | Quant. | 80 | 25 |  | 70 | 55 |
| 14 | $R^1 = H$, $R^2 = 4\text{-}OCH_3$ | Quant. | 87 | | | | |
| 15 | $R^1 = 3\text{-}N0_2$, $R^2 = 4\text{-}OCH_3$ | Quant. | 80 | 26 |  | 95 | 87[f] |
| 16 | $R^1 = 2\text{-CI}$, $R^2 = 4\text{-}OCH_3$ | Quant. | 89 | | | | |
| 17 | $R^1 = 4\text{-}OCH_3$, $R^2 = 4\text{-}OCH_3$ | Quant. | 75 | | | | |
| 18 | $R^1 = 4\text{-Br}$, $R^2 = 4\text{-}OCH_3$ | Quant. | 80 | | | | |
| 19 | $R^1 = 3\text{-}N0_2$, $R^2 = 4\text{-Br}$ | Quant. | 85 | | | | |

[a]Isolated yield.
[b]Reaction conditions: activated olefin (5 mmol), thioacid (5.5 mmol), and water (10 mL).
[c]Reported yield by Li et al.[10b] is shown in parentheses.
[d]40% of thiol was obtained.
[e]20% of thiol was obtained.
[f]No diastereoselectivity was observed.




**Scheme 2.** Spironolactone synthesis in water.



### General Procedure for Conjugate Addition of Thioacids to α,β-Unsaturated Carbonyl Compounds

In a round-bottomed flask equipped with a magnetic stirrer, thioacid (5.5 mmol), α,β-unsaturated carbonyl compound (5 mmol), and water (10 mL) were charged. The reaction mixture was stirred vigorously at room temperature (2 h for thioacetic acid and 15 h for thiobenzoic acid). In most of the cases, filtration of solids in the reaction mixtures gave the crude products with excellent purity. Further purification was achieved by crystallization from ethanol or by column chromatography (silica gel; ethyl acetate/petroleum ether; 1:5). In the case of oily products, extraction by ethyl acetate, a wash of the organic layer with 10% aqueous $NaHCO_3$ solution, and evaporation of the solvent gave pure products. It is notable that on large scale no solvent was required for extraction; only filtration of the solids or decanting of oily products is sufficient.

### Selected Spectroscopic Data

**Table 2, Entry 5 (Thioacetic Acid).** $^1$H NMR (300 MHz, $CDCl_3$) δ 7.95 (2H, d, $^3J = 7.1$ Hz), 7.35–7.56 (5H, m), 7.17–7.22 (2H, m), 5.66 (1H, t, $^3J = 7.1$ Hz), 3.8 (2H, d, $^3J = 7.2$), 2.32 (3H, s) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$) δ 196.1, 194.1, 137.3, 136.2, 133.2, 129.9, 129.5, 128.6, 127.9, 126.8, 43.3, 40.9, 36.1 ppm.

**Table 2, Entry 8 (Thiobenzoic Acid).** $^1$H NMR (300 MHz, $CDCl_3$) δ 7.98–8.04 (4H, m), 7.42–7.58 (8H, m), 7.16 (2H, d, $^3J = 8.0$ Hz), 5.53 (1H, dd, $^3J = 8.5$ and 5.9 Hz), 3.77–3.93 (2H, m), 2.35 (3H, s) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$) δ 196.3, 190.6, 137.1, 136.5, 136.3, 133.3, 133.1, 128.8, 128.5, 128.3, 127.9, 127.6, 127.2, 127.1, 45.6, 43.2, 20.5 ppm.

**Table 2, Entry 15 (Thioacetic Acid).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.26 (1H, s), 8.06 (1H, d, $^3J = 8.2$ Hz), 7.91 (2H, d, $^3J = 8.8$ Hz), 7.77 (1H, d, $^3J = 7.7$ Hz), 7.45 (1H, t, $^3J = 8.1$ Hz), 6.90 (2H, d, $^3J = 8.8$ Hz), 5.32 (1H, t, $^3J = 6.8$ Hz), 3.84 (3H, s), 3.66 (2H, d, $^3J = 7.1$ Hz), 2.31 (3H, s) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$) δ 194.1, 193.7, 163.7, 148.1, 143.3, 134.4, 130.4, 130.2, 129.2, 122.5, 122.2, 113.7, 55.4, 43.3, 42.5, 30.2 ppm.

**Table 2, Entry 24 (Thioacetic Acid).** $^1$H NMR (300 MHz, $CDCl_3$) δ 3.75 (1H, m), 2.60 (1H, dd, $^3J = 4.9$ and 1.2 Hz), 2.26 (3H, s), 2.27–2.37 (3H, m),

1.96–2.23 (2H, m), 1.73 (2H, m) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$) δ 208.1, 194.2, 47.5, 42.7, 34.8, 29.8, 28.5, 20.8 ppm.

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