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Rapid, efficient and selective conjugate addition of thiols to α, β-unsaturated carbonyl compounds using silica supported sodium hydrogen sulfate under solvent-free conditions†

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The conjugate addition of thiols to α, β-unsaturated carbonyl compounds was carried out rapidly (within 2–5 min) and selectively in the presence of silica supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) to form the corresponding Michael adducts in excellent yields (86–95%) at room temperature and under solvent-free conditions.

Keywords: thiol; α, β-unsaturated carbonyl compounds; $NaHSO_4 \cdot SiO_2$; Michael adduct; heterogeneous catalyst

1. Introduction

The conjugate addition of thiols to α, β-unsaturated carbonyl compounds is an important reaction in biosynthetic processes (*1*) and also in organic synthesis of bioactive compounds such as the calcium antagonist diltiazem (*2, 3*). This conjugate addition is usually carried out by activation of thiols with bases (*4–7*) or by activation of the olefins with Lewis acids (*8–15*). Recently, ionic liquids have also been used for this conversion (*16–18*). However, many of these methods are associated with different drawbacks such as the harsh reaction conditions (*16*), long reaction times (*12, 15*), unsatisfactory yields (*11, 13*), and uses of expensive reagents and toxic solvents (*10–12*, *15*).

In continuation of our work (*19*) on the development of useful synthetic methodologies, we observed that silica supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) is a highly efficient catalyst for 1, 4- addition of thiols to α, β-unsaturated carbonyl compounds to afford the corresponding thia-Michael addition products in excellent yields (Scheme 1).

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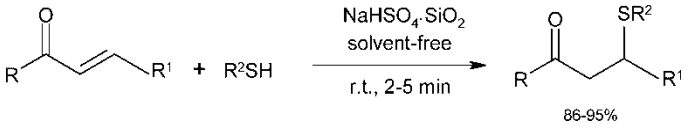


Scheme 1.

2. Experimental section

2.1. *General experimental procedure*

To a mixture of an α, β-unsaturated carbonyl compound (0.5 mmol) and a thiophenol (0.5 mmol), $NaHSO_4{\cdot}SiO_2$ (20 mg) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the mixture was diluted with CH_2Cl_2 (5 mL) and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (silica gel, 1% EtOAc in hexane) to obtain pure β-sulfidocarbonyl compound.

2.2. *Spectral (^{1}H NMR and MS) data of some representative products*

3d: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.38 – 7.12 (5H, m), 3.64 (3H, s), 3.13 (2H, t, $J = 7.0$ Hz), 2.59 (2H, t, $J = 7.0$ Hz); FABMS: m/z 197 $[M+H]^+$.

3g: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30 (2H, d, $J = 8.0$ Hz), 7.21 (2H, d, $J = 8.0$ Hz), 4.11 (2H, q, $J = 7.0$ Hz), 3.10 (2H, t, $J = 7.0$ Hz), 2.52 (2H, t, $J = 7.0$ Hz), 1.22 (3H, t, $J = 7.0$ Hz); FABMS: m/z 245, 247 $[M+H]^+$.

3i: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34 (2H, d, $J = 8.0$ Hz), 7.29 (2H, d, $J = 8.0$ Hz), 3.35 (1H, m), 2.62 (1H, dd, $J = 12.0$ Hz, 4.0 Hz), 2.37–2.25 (3H, m), 2.19–2.07 (2H, m); 1.78–1.62 (2H, m); FABMS: m/z 241, 243 $[M+H]^+$.

3l: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.88 (1H, d, $J = 8.0$ Hz), 7.60–7.12 (12H, m), 4.89 (1H, t, $J = 7.0$ Hz), 3.51 (2H, d, $J = 7.0$ Hz); FABMS: m/z 353, 355 $[M+H]^+$.

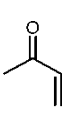
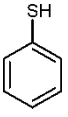
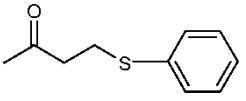
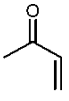
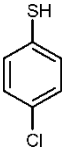
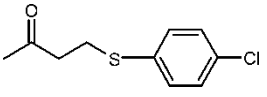
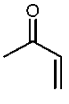
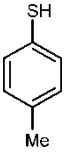
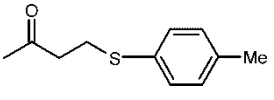
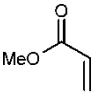
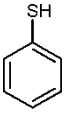
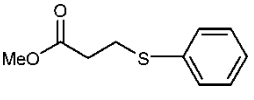
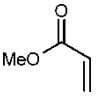
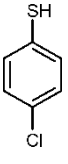
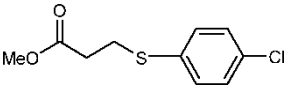
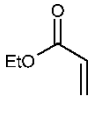
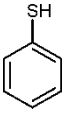
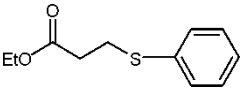
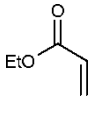
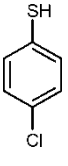
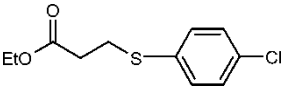
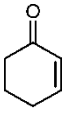
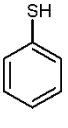
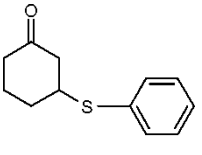
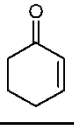
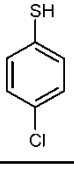
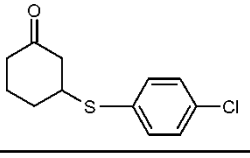
3q: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34 (1H, d, $J = 8.0$ Hz), 7.09 (1H, t, $J = 8.0$ Hz), 6.70–6.58 (2H, m), 4.34 (2H, brs), 4.10 (2H, q, $J = 7.0$ Hz), 2.92 (2H, t, $J = 7.0$ Hz), 2.51 (2H, t, $J = 7.0$ Hz), 1.23 (3H, t, $J = 7.0$ Hz),; FABMS: m/z 226 $[M+H]^+$.

3. Results and discussion

A series of β-sulfido carbonyl derivatives were prepared from various α, β-unsaturated carbonyl compounds and thiols following the procedure mentioned in the scheme. The conversion underwent at room temperature, and the products were formed within a short period of time (2–5 min). No additional solvent was required. Both open-chain and cyclic α, β-unsaturated carbonyl compounds afforded the desired products smoothly. The products were prepared from α, β-unsaturated ketones and also from α, β-unsaturated esters. The reaction showed excellent 1, 4-selectivity. No products of side reactions resulting from 1, 2-addition, polymerization, and bis-addition were observed. However, benzthiazole-2-thiol and the aliphatic thiols did not undergo the reaction. The structures of the products were established from their spectral (^{1}H NMR and MS) data.

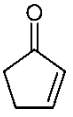
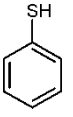
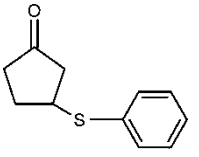
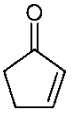
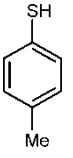
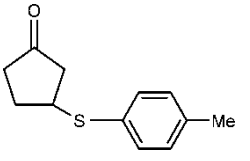
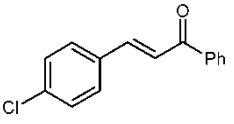
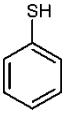
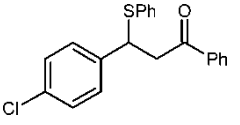
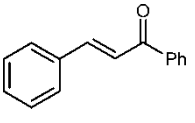
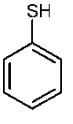
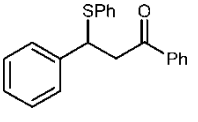
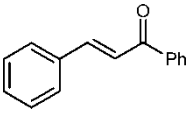
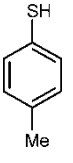
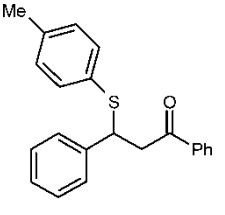
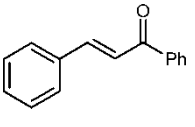
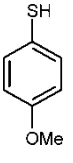
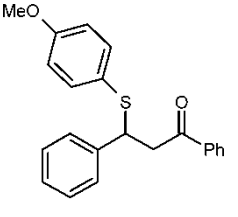
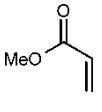
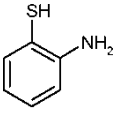
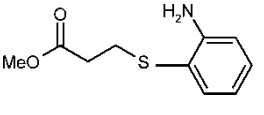
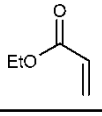
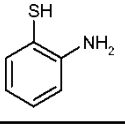
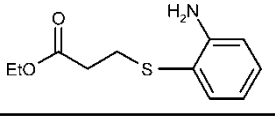
The present process is also associated with high chemoselectivity. When the reaction of an α, β-unsaturated carbonyl compound was carried out with an aminothiophenol, thia-Michael addition was favored over aza-Michael addition to furnish the corresponding β-sulfidocarbonyl derivative in excellent yield (Table 1, entries p and q).

Table 1. The conjugate addition of thiols to α, β-unsaturated carbonyl compounds.

Entry	α, β-Unsaturated carbonyl compound (**1**)	Thiol (**2**)	Product (**3**)	Time (min)	Isolated yield (%)
a				3	91
b				4	88
c				4	90
d				2	95
e				2	93
f				3	89
g				2	91
h				5	90
i				4	92

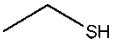
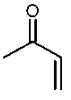
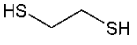
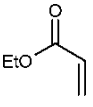
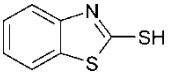
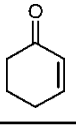
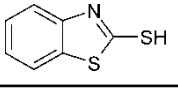
(*Continued*)

Table 1. Continued.

Entry	α, β-Unsaturated carbonyl compound (**1**)	Thiol (**2**)	Product (**3**)	Time (min)	Isolated yield (%)
j				5	90
k				5	89
l				5	89
m				4	88
n				3	91
o				3	92
p				4	86
q				5	90

(*Continued*)

Table 1. Continued.

Entry	α, β-Unsaturated carbonyl compound (**1**)	Thiol (**2**)	Product (**3**)	Time (min)	Isolated yield (%)
r			No reaction	60	–
s			No reaction	60	–
t			No reaction	60	–
u			No reaction	60	–

Note: The structures of the products were established from their spectral (^{1}H NMR and MS) data.

$NaHSO_4{\cdot}SiO_2$ (*20*) is an inexpensive catalyst works under heterogeneous conditions. It has weak acidic property, and increases the electrophilic character of the carbonyl group of the enone through protonation of its oxygen atom. Thus, the catalyst enhances the conjugate addition of thiols to enones.

In recent years, heterogeneous catalysts have gained much importance due to eco-economic benefits. The present catalyst can easily be prepared (*20*) from readily available $NaHSO_4$ and silica gel. It can easily be handled and removed from the reaction mixture by simple filtration. Its catalytic activity is higher than that of many other catalysts previously used. For example, in the presence of this catalyst, the reaction between phenyl thiol and cyclohexenone afforded the product **3h** in 5 min with an yield of 90% while in the presence of $Bi(OTf)_3$ (*12*),*n*-Bu_4NBr (*16*), and [pmin]Br (*18*), the same product was formed in 1.5, 0.5 and 0.5 h, respectively, with the yield of 72, 92 and 90%, respectively. In absence of the catalyst or in the presence of only $NaHSO_4$ or silica, a little conversion was observed.

4. Conclusion

In conclusion, we have developed a convenient and efficient method for the preparation of β-sulfido carbonyl compounds by $NaHSO_4{\cdot}SiO_2$-catalyzed conjugate addition of thiols to α, β-unsaturated carbonyl compounds at room temperature. The operational simplicity, mild heterogeneous reaction conditions, rapid conversion, application of an inexpensive catalyst, solvent-free reaction, and excellent yields and selectivity are the notable advantages of the present protocol.

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