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A Simple, Efficient, and Green Procedure for the 1,4-Addition of Thiols to Conjugated Alkenes and Alkynes Catalyzed by Sodium Acetate in Aqueous Medium

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A benign and inexpensive salt, sodium acetate, efficiently catalyzes 1,4-addition of thiols to a variety of conjugated alkenes such as α,β-unsaturated ketones, aldehydes, carboxylic esters, nitriles, nitro compounds, and chalcones in aqueous THF. The reactions are clean, fast, and high yielding.

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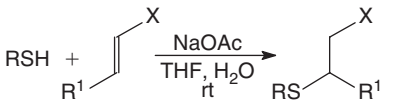
The 1,4-addition of thiols to conjugated alkenes has attracted considerable interest in recent times[1] as it leads to the synthesis of compounds with promising biological activities.[2] Traditionally, this conjugate addition is based either on the activation of thiol by a base[3] or activation of the acceptor olefins with Lewis acids.[4] However, to avoid side reactions occasionally encountered in the presence of a strong base or acid, several clays and inorganic salts such as montmorillonite K10,[4a] fluorapatite,[5] natural phosphate doped by potassium fluoride,[6] $Na_2CaP_2O_7$,[7] $Bi(OTf)_3$,[8] $Bi(NO_3)_3$,[9] and ionic liquids[10] have been introduced. However, these procedures are also associated with drawbacks such as use of hazardous solvents like benzene,[4a] chlorinated hydrocarbons,[9] acetonitrile,[8] the relatively high cost of reagents, and lower yields. Thus, a simple, cost-effective, green, and efficient procedure will be of much importance. We report here the novel application of a very cheap and benign reagent, sodium acetate, as an efficient catalyst for the 1,4-addition of thiols to conjugated alkenes (Scheme 1).

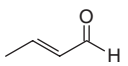
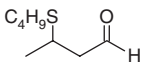
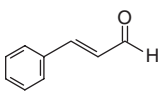
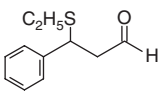
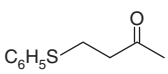
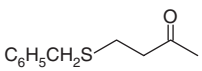
A very simple experimental procedure was developed for the conjugate addition of thiols to alkenes in aqueous THF (1:1) in the presence of sodium acetate (15 mol%) at room temperature. However, the reactions with conjugated alkynes needed to be carried out at 70°C. The products were isolated by usual workup



X = CHO, COMe, COPh, CO_2Me, CN, NO_2
R^1 = alkyl/aryl, R = alkyl/aryl

Scheme 1.

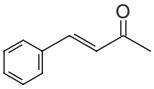
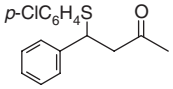
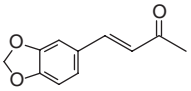
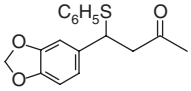
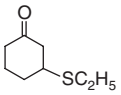
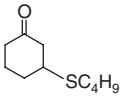
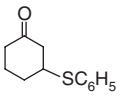
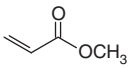
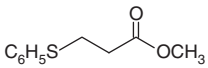
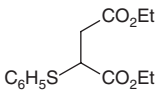
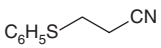
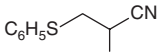
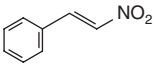
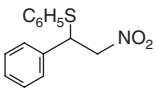
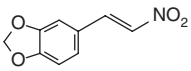
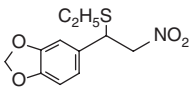
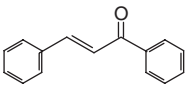
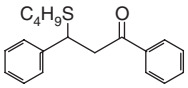
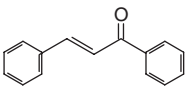
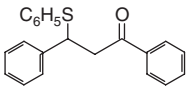
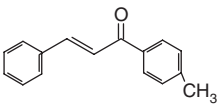
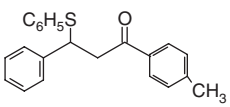
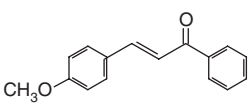
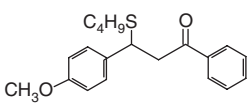
Table 1. 1,4-Addition of thiols to conjugated alkenes catalyzed by NaOAc

Entry	Conjugated alkene	Thiol	Time [h]	Product	Yield [%][A] ref.
1		*n*-C_4H_6SH	2.5		80 [10b]
2		C_2H_5SH	3.5		73
3		C_6H_5SH	2.0		85 [8]
4		$C_6H_5CH_2SH$	2.5		75 [1f]

(*Continued*)

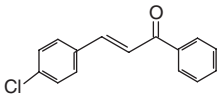
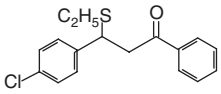
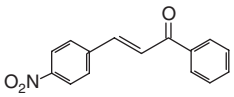
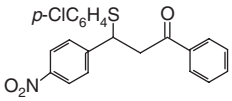
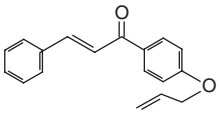
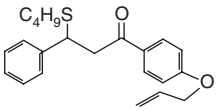
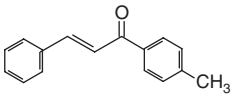
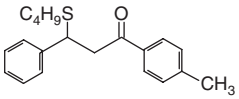
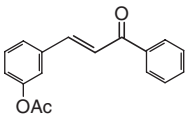
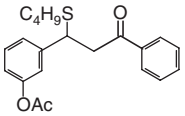
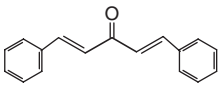
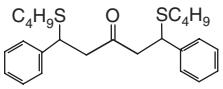
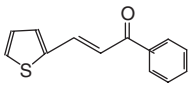
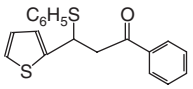
10.1071/CH06455 0004-9425/07/030223

Table 1. Continued

Entry	Conjugated alkene	Thiol	Time [h]	Product	Yield [%][A] ref.
5		*p*-ClC_6H_4SH	3.5		86
6		C_6H_5SH	3.5		85
7		C_2H_5SH	2.5		90 [10b]
8		*n*-C_4H_9SH	2.5		90 [9]
9		C_6H_5SH	2.0		90 [10c]
10		C_6H_5SH	2.5		75 [10b]
11		C_6H_5SH	3.0		82 [10b]
12		C_6H_5SH	2.5		72 [10b]
13		C_6H_5SH	3.0		70 [1f]
14		C_6H_5SH	45		80
15		C_2H_5SH	4.0		75
16		*n*-C_4H_9SH	3.5		80 [10c]
17		C_6H_5SH	3.0		90 [6]
18		C_6H_5SH	3.5		80 [10c]
19		*n*-C_4H_9SH	2.5		85 [10c]

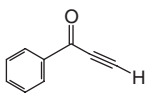
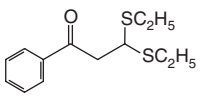
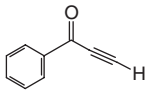
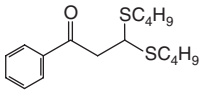
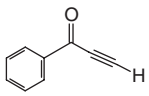
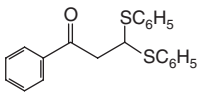
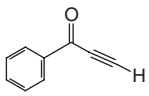
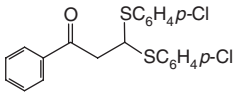
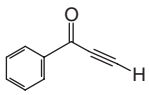
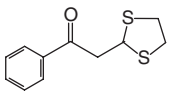
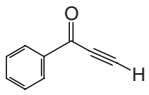
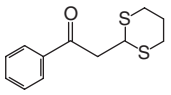
(*Continued*)

Table 1. Continued

Entry	Conjugated alkene	Thiol	Time [h]	Product	Yield [%][A] ref.
20		C_2H_5SH	3.0		75
21		*p*-ClC_6H_4SH	3.5		76 [10c]
22		*n*-C_4H_9SH	4.5		80
23		*n*-C_4H_9SH	4.0		80 [10c]
24		*n*-C_4H_9SH	4.0		80 [10c]
25		*n*-C_4H_9SH	3.5		70 [10c]
26		C_6H_5SH	3.0		78

[A]Yields refer to those of pure and isolated products characterized by IR, ^1H and ^{13}C NMR spectroscopic data.

Table 2. 1,4-Addition of thiols and dithiols to conjugated acetylinic ketones

Entry	Acetylenic ketone	Thiol	Time [h]	Product	Yield [%][A] ref.
1		C_2H_5SH	3.0		75 [13]
2		*n*-C_4H_9SH	3.0		70 [15]
3		C_6H_5SH	2.5		80 [14]
4		*p*-ClC_6H_4SH	2.5		75
5		$HS(CH_2)_2SH$	3.5		74 [14]
6		$HS(CH_2)_3SH$	3.5		72 [14]

[A]Yields refer to those of pure and isolated products characterized by IR, ^1H and ^{13}C NMR spectroscopic data.

Table 3. IR, and ^{1}H and ^{13}C NMR data and elemental analysis of products
Entries 2, 5, 6, 14, 15, 20, 22, 26 in Table 1 and entry 4 in Table 2

Entry	ν_{max} [cm^{-1}]	δ_H [ppm]	δ_C [ppm]	Analysis [%]
2	1452, 1478, 1724, 2727	1.17 (t, 3H, *J* 7.41), 2.30–2.39 (m, 2H), 2.95 (d, 2H, *J* 7.50), 4.37 (t, 1H, *J* 7.50), 7.25–7.38 (m, 5H), 9.6 (t, 1H, *J* 1.68)	14.6, 25.5, 43.2, 50.1, 127.9, 128.0 (2C), 129.1 (2C), 141.7, 199.9	Found: C 67.9, H 7.1 $C_{11}H_{14}OS$ requires C 68.0, H 7.3
5	1454, 1479, 1708	2.07 (s, 3H), 3.04 (d, 2H, *J* 7.2), 4.67 (t, 1H, *J* 7.2), 7.18–7.26 (m, 9H)	31.1, 48.6, 49.6, 127.9, 128.1 (2C), 128.9 (2C), 129.3 (2C), 132.9, 134.2, 134.7 (2C), 141.2, 205.6	Found: C 66.0, H 5.1 $C_{16}H_{15}ClOS$ requires C 66.1, H 5.1
6	1039, 1441, 1478, 1715	20.7 (s, 3H), 2.91–2.99 (m, 2H), 4.65 (t, 1H, *J* 7.52), 5.91 (s, 2H), 6.67–6.71 (m, 2H), 6.82–6.83 (m, 1H), 7.21–7.34 (m, 5H)	31.1, 48.3, 50.1, 101.4, 108.2, 108.3, 121.5, 127.9, 129.2 (2C), 133.0 (2C), 134.4, 135.2, 147.2, 148.1, 205.9	Found: C 67.8, H 5.3 $C_{17}H_{16}OS$ requires C 68.0, H 5.4
14	1434, 1479, 1546	4.68–4.88 (m, 3H), 7.18–7.21 (m, 2H), 7.27–7.40 (m, 8H)	49.6, 78.7, 129.3 (2C), 129.4 (2C), 129.6 (2C), 129.8 (2C), 134.3 (2C), 134.9, 135.3	Found: C 64.7, H 4.9 $C_{14}H_{13}NO_2S$ requires C 64.8, H 5.1
15	1039, 1444, 1479, 1504, 1556	1.22 (t, 3H, *J* 7.47), 2.46 (q, 2H, *J* 7.47), 4.50 (t, 1H, *J* 7.80), 4.66–4.71 (m, 2H), 5.96 (s, 2H), 6.75–6.79 (m, 2H), 6.85–6.87 (m, 1H)	14.7, 26.0, 46.6, 79.8, 101.7, 108.0, 108.8, 121.7, 131.4, 148.1, 148.6	Found: C 51.6, H 5.0 $C_{11}H_{13}NO_2S$ requires C 51.8, H 5.1
20	1448, 1477	1.18 (t, 3H, *J* 7.41), 2.29 (m, 2H), 3.50 (d, 2H, *J* 7.05), 4.57 (t, 1H, *J* 7.05), 7.26–7.28 (m, 2H), 7.35–7.57 (m, 5H), 7.89–7.92 (m, 2H)	14.7, 25.8, 43.6, 45.6, 128.4 (2C), 129.0 (2C), 129.1 (2C), 129.6 (2C), 133.7, 137.0, 141.2, 143.7, 197.0	Found: C 66.5, H 5.5 $C_{17}H_{17}ClOS$ requires C 67.0, H 5.6
22	1170, 1452, 1478, 1598, 1678	0.83 (t, 3H, *J* 7.29), 1.24–1.34 (m, 2H), 1.43–1.51 (m, 2H), 2.25–2.38 (m, 2H), 3.47 (d, 2H, *J* 7.05), 4.52–4.64 (m, 3H), 5.29–5.44 (m, 2H), 5.99–6.05 (m, 1H), 6.92 (d, 2H, *J* 8.79), 7.20–7.32 (m, 3H), 7.40–7.43 (m, 2H), 7.89 (d, 2H, *J* 8.79)	13.9, 22.3, 31.5, 31.6, 44.8, 45.4, 69.3, 114.8, 118.6, 127.5 (2C), 128.2 (2C), 128.8 (2C), 130.7 (2C), 132.8, 142.8, 144.4, 162.9, 195.8	Found: C 74.5, H 7.3 $C_{22}H_{26}O_2S$ requires C 74.5, H 7.4
26	1445, 1475, 1589, 1679	3.57–3.78 (m, 2H), 5.29 (dd, 1H, ^{1}J 7.53, ^{2}J 6.39), 6.84–6.88 (m, 2H), 7.27–7.30 (m, 3H), 7.39–7.59 (m, 6H), 7.92–7.95 (m, 2H)	44.1, 46.1, 124.9, 125.9, 126.9, 128.7, 128.8 (2C), 129.1 (2C), 129.3 (2C), 133.4 (2C), 133.8, 134.2, 136.9, 145.8, 196.9	Found: C 70.3, H 4.9 $C_{19}H_{16}OS_2$ requires C 70.3, H 5.0
4	1448, 1479, 1579, 1681	3.46 (d, 2H, *J* 6.81), 5.07 (t, 1H, *J* 6.81), 7.26 (d, 2H, *J* 8.49), 7.34–7.60 (m, 9H), 7.85 (d, 2H, *J* 8.49)	43.9, 53.3, 128.0 (2C), 128.5, 128.6, 129.1 (4C), 129.8 (2C), 131.6, 133.7, 134.4 (4C), 136.2, 136.9, 195.6	Found: C 72.2, H 4.6 $C_{21}H_{16}Cl_2OS_2$ requires C 72.4, H 4.6

followed by purification by column chromatography over silica gel.

Both aliphatic and aromatic thiols such as ethane thiol, butane thiol, and thiophenol react with a wide variety of conjugated alkenes by this procedure to provide the corresponding thio-adducts in high yields. The results are summarized in Table 1. As evident from the results, open-chain α,β-unsaturated aldehydes, ketones, carboxylic esters, nitriles, and nitro alkanes participated in the reaction with thiophenol, butane thiol, and ethane thiol without any difficulty. The addition of thiols to cyclohexenone also produced high yields. The conjugate addition of thiols to chalcones which is not always satisfactory with conventional reagents[10b] was also efficiently catalyzed by sodium acetate under the present reaction conditions. A variety of substituents on the aromatic ring such as OMe, NO_2, ethylenedioxy, and a thiophene moiety are compatible with this procedure. The reactions were complete within 2.5–4.5 h. The yields of isolated products are also very good (70–90%). The products were characterized by their spectroscopic data and elemental analysis.

The α,β-unsaturated terminal acetylenic ketones underwent bis-additions with two equivalents of thiol or with one equivalent of dithiol to provide the corresponding β-keto thioacetals, dithianes, and dithiolanes. The results are reported in Table 2. The dithianes are very useful intermediates[11] and β-keto 1,3-dithianes, in particular, have been used as key synthons in the total synthesis of several natural products.[12] The procedures for synthesis of β-keto dithianes are very limited and the first one by Michael addition was reported using Al_2O_3 in 1992.[13]

In general, the reactions are very clean and reasonably fast. The workup is very simple and short column chromatography is enough to provide the pure product. Commercial sodium acetate

and THF can be used without any pretreatment. Several sensitive functional groups are found to be safe under the reaction conditions.

Although there are several methods for Michael addition in the literature the present procedure for the conjugate addition of thiols to electron-deficient alkenes in aqueous medium demonstrates the potential of sodium acetate, a benign, readily available, and cheap material as an efficient catalyst. To the best of our knowledge sodium acetate has not been reported to be used in other C–C bond forming reactions. Certainly, this methodology offers an alternative reaction procedure with regard to yield of products, simplicity in operation, generality of the reaction, cost efficiency, and green aspects upon avoiding toxic catalysts. We believe that this methodology will provide a practical alternative to the existing procedures and will have useful synthetic applications.

Experimental

General

IR spectra were taken as neat for liquids and as KBr pellet for solids. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in $CDCl_3$ solutions. Elemental analyses were done by a Perkin–Elmer auto-analyzer. Column chromatography was performed on silica gel (60–120 mesh, SRL). Thiols and conjugated alkenes are mostly commercial materials and were distilled before use. Sodium acetate and THF were used as supplied.

General Procedure for 1,4-Addition

A mixture of thiol (1 mmol) and conjugated alkene (1 mmol) in THF/H_2O (1/1) was stirred in the presence of sodium acetate (15 mol%) at room temperature for a period of time as required to complete the reaction (monitored by TLC). After the reaction was complete THF was evaporated from the reaction mixture under reduced pressure. The mixture was then extracted with diethyl ether ($3 \times 15\,cm^3$). The combined ether extracts were washed with brine, dried over Na_2SO_4, and evaporated to leave the crude product which was purified by column chromatography (hexane/ether) to furnish the pure adduct. This procedure was followed for all the reactions listed in Tables 1 and 2 (for addition with acetylenic ketones the reaction was carried out at 70°C). The known products were identified by comparison of their spectroscopic data (IR, and ^{1}H and ^{13}C NMR) with those of reported ones (reference given in Tables 1 and 2). The unknown compounds were characterized by their spectra (IR, and ^{1}H and ^{13}C NMR) and elemental analyses. These data are reported in Table 3.

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