A Novel Method for the Synthesis of Thioacetates Using Benzyltriethylammonium Tetrathiomolybdate and Acetic Anhydride

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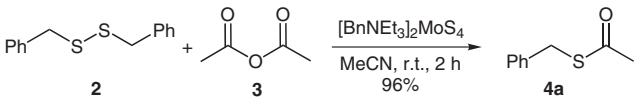
Abstract: Herein we report a simple and efficient methodology for the synthesis of thioacetates using benzyltriethylammonium tetrathiomolybdate and acetic anhydride as the key reagents, starting from alkyl halides in a multistep, tandem reaction process. Its application in the synthesis of orthogonally protected cysteine and anomeric β-thioglycosides has also been demonstrated.

Key words: benzyltriethylammonium tetrathiomolybdate, acetic anhydride, thioacetates

The synthesis of protected thiols and their deprotection to free thiols are increasingly important prerequisites in the development of chemical self-assembly methods, and many of the applications are dependent on this chemistry. These include the fabrication of nano and molecular electronic structures,[1–3] soft lithography,[4] contact printing,[5] fabrication of nanoparticulate composites,[6–8] surface immobilization of biomolecular[9] and synthetic dyes,[10] corrosion-resistance treatments,[11] biomolecular surface passivation,[12] and electrode modification.[13] The shelf life of thiols prior to use is an important factor in the design and synthesis of many molecules that are required for these applications. The thiol group undergoes slow oxidation to a disulfide or a sulfoxide under ambient conditions. As such, derivatization with a protecting group provides long-term stability.[14] Thiols are generally protected and used in the form of thioacetates because of the mild deprotection conditions.[15] Thioacetates are generally prepared from the corresponding thiols by acylation[16] or by reaction of alkyl halides with sodium or potassium salt of thioacetic acid.[17] The time required for displacement of halide by potassium thioacetate varies vastly, ranging from 3 to 96 hours.[17c] A reactive substrate like 4-iodobenzyl bromide required overnight stirring at room temperature to yield the corresponding thioester.[17d] The cleavage of disulfide bond has also been utilized for the synthesis of thioacetates.[18]

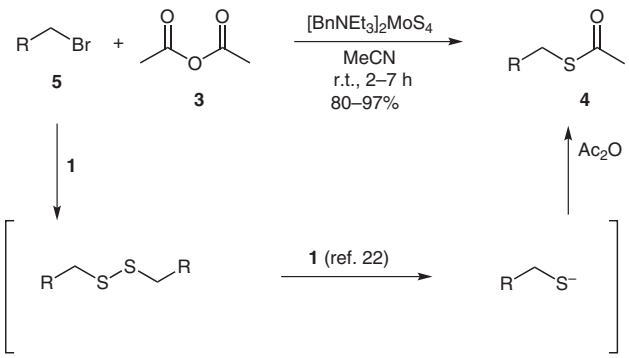
Earlier, we demonstrated that benzyltriethylammonium tetrathiomolybdate {$[BnEt_3N]_2MoS_4$, **1**} is a useful reagent that effects a tandem sulfur-transfer reduction–Michael addition in one pot.[19] In continuation of our investigation on the utility of **1** in organic synthesis,[20] we report herein a simple and efficient methodology for the preparation of thioacetate derivatives starting from diverse alkyl halides.

We began our investigation by treating dibenzyldisulfide **2** (1.0 equiv) with $[BnEt_3N]_2MoS_4$ (**1**, 1.2 equiv) and acetic anhydride (**3**, 4.0 equiv) in acetonitrile (28 °C, 2 h) which resulted in the formation of the corresponding thioacetate **4a** in 96% yield (Scheme 1). Encouraged by the result we decided to start with alkyl halides **5**, which are precursors to the alkyl disulfides in the reaction of tetrathiomolybdate **1**.[21]



Scheme 1 Synthesis of benzylthioacetate from dibenzyldisulfide using **1**

If this is successful, it would be a tandem sulfur-transfer reduction–acylation reaction in one pot (Scheme 2). Accordingly, benzyl bromide **5a** was treated with **1**[22] (2.2 equiv) and Ac_2O (4.0 equiv) (MeCN, 28 °C, 2.5 h), which gave the thioacetate **4a** as the only product in 94% yield. These studies were then extended to a wide variety of alkyl halides and in all the cases, the multistep reaction proceeded smoothly to give the corresponding thioacetate derivatives in excellent yields (Table 1). The reaction of benzyl halides (X = Cl, Br) **5a**,**b** were found to be equally fast to offer the corresponding thioacetate **4a** in excellent yield. Substituents present on the aryl ring did not have dramatic effect on the rate of the reaction. For instance, 4-methoxy benzyl bromide and 4-acetyl benzyl bromide



Scheme 2 Tandem sulfur-transfer reduction–acylation with **1**

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5c,**d** were converted into the corresponding thioacetates **4c**,**d** in 97% and 96% yield, respectively. The functionalized alkyl halides **5e**–**h** showed remarkable selectivity under the reaction conditions to give the corresponding thioacetates **4e**–**h**, respectively, in excellent yield at room temperature. Under similar reaction conditions the reaction of simple alkyl halides proceeded smoothly to offer the corresponding thioacetates and their reactivity was found to be dependent on the nature of halogen atom.

Table 1 Synthesis of Thioacetates from Alkyl Halides Using Tetrathiomolybdate **1**[23]

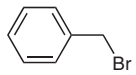
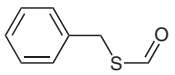
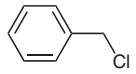
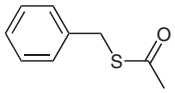
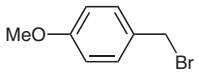
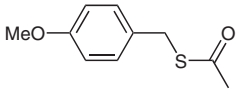
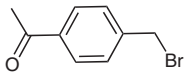
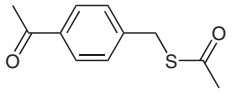
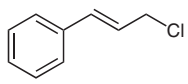
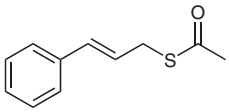
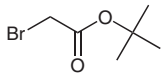
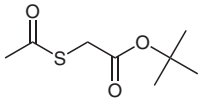
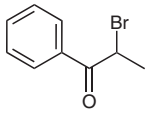
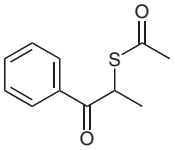
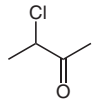
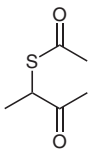
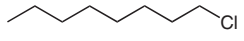
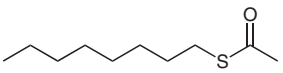
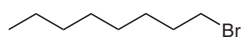
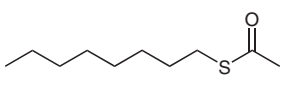
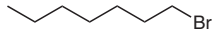
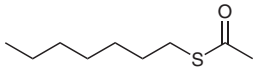
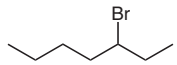
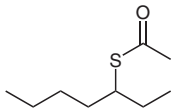
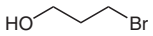
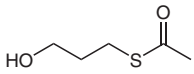
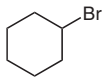
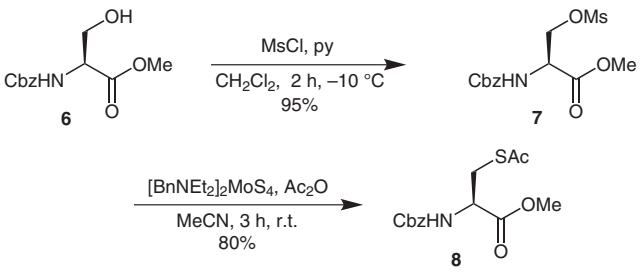
Entry[a]	Alkyl halide	Time (h)	Product	Yield (%)
1	 **5a**	2.5	 **4a**	94
2	 **5b**	2.5	 **4a**	92
3	 **5c**	2.5	 **4c**	97
4	 **5d**	2.5	 **4d**	96
5	 **5e**	2.5	 **4e**	95
6	 **5f**	2	 **4f**	95
7	 **5g**	2	 **4g**	92
8	 **5h**	2	 **4h**	93
9	 **5i**	4	 **4i**	84
10	 **5j**	2.5	 **4j**	84
11	 **5k**	2.5	 **4k**	85

Table 1 Synthesis of Thioacetates from Alkyl Halides Using Tetrathiomolybdate **1**[23] (continued)

Entry[a]	Alkyl halide	Time (h)	Product	Yield (%)
12	 **5l**	7	 **4l**	80
13	 **5m**	2.5	 **4m**	87
14	 **5n**	24	N.R.	–
15	 **5o**	24	N.R.	–

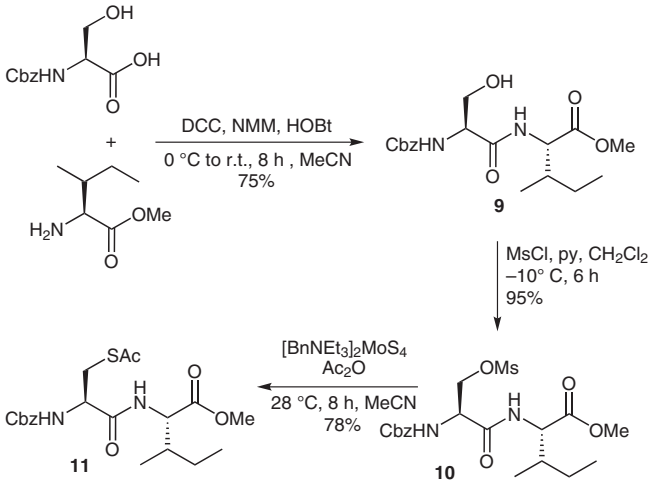
[a] Reaction conditions: alkyl halides (1 equiv), $[BnNEt_3]_2MoS_4$ (2.2 equiv), Ac_2O (4 equiv), 2–7 h.

n-Octyl chloride **5i** took longer time (4.0 h) to give the corresponding thioacetate compared to *n*-octyl bromide **5j** (2.5 h). Secondary alkyl halides were found to be less reactive than the corresponding primary alkyl halides. For instance 3-bromoheptane **5l** required 7 hours, whereas *n*-bromoheptane **5k** took only 2.5 hours to give the corresponding thioacetates **4l** and **4k**, respectively. The alkyl halide **5m**, containing a free hydroxyl group, was converted into the corresponding thioacetate **4m**, in 87% yield without affecting the hydroxyl group. Cyclohexyl bromide **5n** did not give even a trace of the corresponding thioacetate even after 24 hours. Tertiary alkyl halides were found to be inert under the reaction conditions, as shown in the reaction of *tert*-butyl bromide **5o**, which did not react with **1** even after 24 hours of stirring at room temperature. After the successful synthesis of various thioacetates from alkyl halides we applied this methodology for the synthesis of orthogonally protected cysteine derivative **8** (Scheme 3).



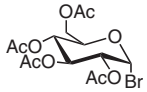
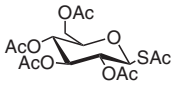
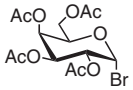
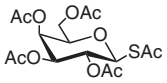
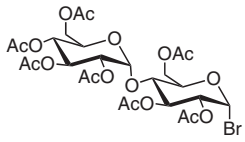
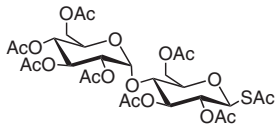
Scheme 3 Synthesis of orthogonally protected cysteine derivative **8**

The reaction of protected serine **7** with tetrathiomolybdate **1** and acetic anhydride (MeCN, 3 h, 28 °C) furnished the orthogonally protected cysteine **8** in high yield in optically pure form. This would be of use in solution-phase peptide synthesis. The utility of this reaction has been demonstrated in the synthesis of dipeptide **11** containing protected cysteine. The dipeptide **9** containing free hydroxyl group was converted into the corresponding mesylate[24] **10** which on treatment with **1** and acetic anhydride gave the cysteine-containing dipeptide **11** in 78% yield (Scheme 4).[25] The above methodology was further extended to the synthesis of anomeric thioacetates of carbohydrate derivatives which are very useful intermediates in the glycosylation reactions.[26] The most common methods available for their synthesis involve the displacement of anomeric halide with tetrabutylammonium salt of thioacetic acid,[27] potassium thioacetates,[28] or Lewis acid catalyzed reaction of peracetates with thiourea and thioacetic acid.[29] In the present methodology the α-anomeric bromides **12a–c** were treated with tetrathiomolybdate **1** (2.2 equiv) and acetic anhydride (4.0 equiv, MeCN, 2 h, 28 °C) to furnish the corresponding β-thioglycosides **13a–c**, respectively, in high yields (Table 2).



Scheme 4 Synthesis of dipeptide **11** containing protected cysteine

Table 2 Synthesis of Anomeric Thioacetates Starting from Anomeric Bromides Using Tetrathiomolybdate **1** and Acetic Anhydride[23]

Entry[a]	Alkyl halide	Time (h)	Product	Yield (%)
16	 **12a**	2	 **13a**	79
17	 **12b**	2	 **13b**	78
18	 **12c**	2	 **13c**	84

[a] Reaction conditions: anomeric bromide (1 equiv), $[BnNEt_3]_2MoS_4$ (2.2 equiv), Ac_2O (4 equiv), 2 h.

We have developed a simple and efficient methodology for the synthesis of thioacetates using benzyltriethylammonium tetrathiomolybdate (**1**) and acetic anhydride as the key reagents, starting from alkyl halides in a multistep, tandem reaction process. Its application for the synthesis of orthogonally protected cysteine derivative and anomeric β-thioglycosides has also been demonstrated.

Acknowledgment

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(23) **General Procedure for the Synthesis of Thioacetates – Synthesis of 4a**
To the solution of alkyl halide **5a** (0.169 g, 1 mmol,) in MeCN (5 mL), tetrathiomolybdate **1** (0.37 g, 2.2 equiv) was added and the reaction mixture was stirred for 1 h. To this solution, Ac_2O (0.408 g, 4.0 equiv) was added and the reaction mixture was stirred further for 1.5 h. The solvent was removed under vacuum, the solid residue was extracted with CH_2Cl_2–Et_2O (3:7) 5 × 10 mL, filtered through Celite and concentrated. The crude product was purified by silica gel (100–200 mesh) column chromatography; EtOAc–hexane (19:1); gummy liquid, yield 94%. IR (neat): 3030 (w), 2924 (m), 1692 (s), 1353 (w), 1133 (m), 627 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (s, 5 H), 4.09 (s, 2 H), 2.31 (s, 3 H). ^{13}C (75 MHz, $CDCl_3$): δ = 194.8, 137.4, 128.6, 128.4, 127.1, 33.2, 30.1. HRMS: *m/z* calcd for $C_9H_{10}OS$: 189.030 [M + Na]; found: 189.0358.

Compound **4d**: oily liquid, yield 96%. IR: 2988 (w), 1676 (s), 1416 (m), 1176 (s), 625 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 4.13 (s, 2 H), 2.57 (s, 3 H), 2.35 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 194.5.

Compound **4l**: oily liquid, yield 80%. IR (neat): 2903 (m), 2863 (w), 1732 (s), 1462 (m), 1110 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (m, 1 H), 2.37 (s, 3 H), 1.70–1.30 (m, 8 H), 1.00 (t, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.4, 54.4, 33.0, 26.7, 22.5, 13.8, 11.0. HRMS: *m/z* calcd for $C_9H_{18}OS$: 197.0976 [M + Na]; found: 197.0970.

Compound **8**: white solid, mp 77 °C, yield 80%; $[\alpha]_D^{28}$ –48 (*c* 1, $CHCl_3$). IR (neat): 3351 (br), 2951 (w), 1698 (s), 1517 (m), 1212 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 5.55 (d, *J* = 7.2 Hz, 1 H), 5.11 (s, 2 H), 4.50–4.60 (m, 1 H), 3.75 (s, 3 H), 3.42 (dd, *J* = 14.0, 4.8 Hz, 1 H), 3.40 (dd, *J* = 14.0, 4.8 Hz, 1 H), 2.32 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 170.5, 155.6, 136.0, 128.4, 128.1, 128.0, 67.0, 53.4, 52.7, 31.1, 30.3. HRMS: *m/z* calcd for $C_{14}H_{17}O_5S$: 334.0725 [M + Na]; found 334.0710.

Compound **11**: gummy solid, yield 78%; $[\alpha]_D^{28}$ +8.7 (*c* 1, $CHCl_3$). IR (neat): 3318 (br), 2965 (m), 2930 (m), 1736 (s), 1695 (s), 1682 (s), 1635 (m), 1262 (m), 1213 (m), 1139 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 5 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 5.67 (d, *J* = 8.0 Hz, 1 H), 5.12 (s, 2 H), 4.52 (dd, *J* = 8.6, 4.8 Hz 1 H), 4.40 (m, 1 H), 3.35 (dd, *J* = 16.0, 4.0 Hz, 1 H), 3.12 (dd, *J* = 16.0, 8.0 Hz, 1 H), 2.30 (s, 3 H), 1.90–1.86 (m, 1 H), 1.44–1.36 (m, 1 H), 1.18–1.12 (m, 1 H), 0.90–0.86 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6, 171.8,169.6, 156.3, 136.0, 128.4, 128.1, 128.0, 67.7, 56.6, 55.0, 52.1, 37.6, 31.4, 30.4, 25.0, 15.3, 11.2. HRMS: *m/z* calcd for $C_{20}H_{28}N_2O_8S$: 447.1506 [M + Na]; found: 447.1563.

(24) To a solution of dipeptide **9** (1.0 mmol, 0.366 g) and pyridine (5 mmol, 0.395 g) in CH_2Cl_2 (10 mL) at –10 °C MsCl (1.2 mmol, 0.136 g) was added and the reaction mixture was stirred for 6 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 15 mL). The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (100–200 mesh), white solid, mp 119 °C, yield 95%; $[\alpha]_D^{28}$ +15.7 (*c* 1, $CHCl_3$). IR (neat): 3334 (br), 2964 (m), 1731 (s), 1674 (s), 1529 (m), 1361 (m), 1170 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (s, 5 H), 6.95 (d, *J* = 7.5 Hz, 1 H), 5.68 (d, *J* = 7.2 Hz, 1 H), 5.14 (s, 2 H), 4.61–4.53 (m, 3 H), 4.35 (dd, *J* = 9.0, 7.2 Hz, 1 H), 3.80 (s, 3 H), 3.00 (s, 3 H), 1.93–1.84 (m, 1 H), 1.45–1.33 (m, 1 H), 1.25–1.00 (m, 1 H), 0.92–0.86 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 167.7, 155.9, 135.6, 128.54, 128.3, 128.1, 68.3, 67.5, 56.7, 53.6, 52.2, 37.6, 37.2, 24.9, 15.3, 11.4. HRMS: *m/z* calcd for $C_{19}H_{28}N_2O_8S$: 467.1467 [M + Na]; found: 467.1451.

(25) Compound **11** was obtained in optically pure form and there was no racemization or formation of diastereomer.

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