

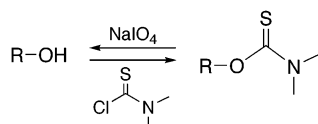
Dimethylthiocarbamate (DMTC): An
Alcohol Protecting GroupD. K. Barma,[†] A. Bandyopadhyay,[†] Jorge H. Capdevila,[‡] and J. R. Falck^{*,†}

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ABSTRACT



Dimethylthiocarbamates (DMTCs), prepared from the corresponding alcohols using commercial dimethylthiocarbamoyl chloride, are spectrally simple, achiral, and nonpolar. DMTCs are moderately to highly stable to a wide range of reagents and conditions including metal hydrides, hydroboration, ylides, NaOH, HCl, organolithiums, Grignards, DDQ, PCC, Swern, *n*-Bu₄NF, CrCl₂, heat, and Lewis acids. They are readily removed by NaIO₄ or H₂O₂ in the presence of other common alcohol protecting groups.

The introduction and removal of protecting groups (PGs) are among the most common transformations during the synthesis of polyfunctional molecules.¹ There is, consequently, continuing demand for more varied, robust, economical, and/or chemically differentiable PGs.² As part of our ongoing program in this area,³ we had occasion to evaluate thionocarbamates⁴ as potential PGs.⁵ Herein, we

propose *N,N*-dimethylthiocarbamate (DMTC) as a versatile alcohol PG and highlight some of its more germane qualifications.

Primary alcohols are smoothly derivatized in excellent yields using stoichiometric *N,N*-dimethylthiocarbamoyl chloride⁶ and NaH in THF at room temperature.⁷

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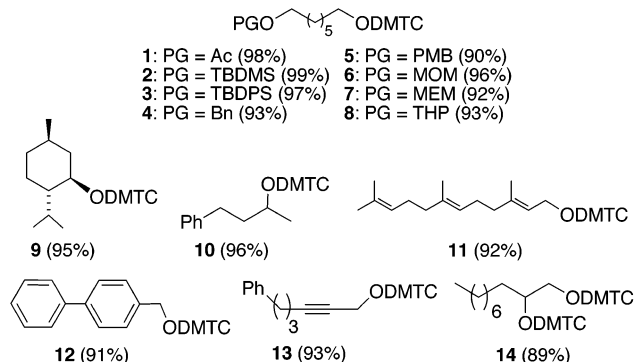
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(4) Review of thiocarbamate syntheses: Walter, W.; Bode, K. D. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 281–293.

(5) The ability of thionocarbamates to stabilize organocopper reagents has been exploited for the cross-coupling of α,β -dialkoxy- and α -alkoxy- β -aminostannanes: Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759–4762.

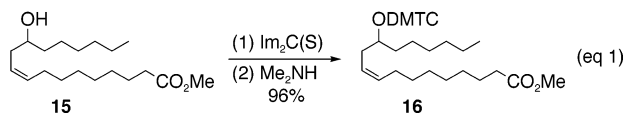


These conditions are compatible with a variety of functionality, e.g., acetate **1**, silyl ethers **2** and **3**, benzyloxy **4**,

(6) Commercial *N,N*-dimethylthiocarbamoyl chloride can vary in quality. Impure samples were refined by molecular (Kugelrohr) distillation, bp 65 °C at 0.2 mmHg, to give a white solid (mp 41 °C) that could be stored indefinitely at room temperature under an argon atmosphere.

p-methoxybenzyloxy **5**, MOM ether **6**, MEM ether **7**, and tetrahydropyranyloxy **8**. Likewise, cyclic secondary **9**, acyclic secondary **10**, allylic **11**, benzylic **12**, and propargyl **13** alcohols, as well as *vic*-diols **14**, are efficiently converted to DMTCs.⁸

For alkali-intolerant compounds, the alcohol is thiocarbamoylated via sequential treatment with 1,1'-thiocarbonyldiimidazole followed by a THF solution of dimethylamine, e.g., **15** → **16** (eq 1).⁷



The DMTC group is endowed with many features that make it an attractive protective group, *inter alia*, low polarity, no chiral centers, distinctive spectral signature,⁸ thermal stability,⁹ and low reactivity. As demonstrated in the accompanying reactions (Scheme 1), DMTCs are compatible under typical conditions with PCC (route a), Swern oxidation (route b), chromium reagents¹⁰ (routes c and l), Grignards (route d), alkyllithiums (route k), ylides (routes e and i), metal hydrides (routes f–h), and hydroboration (route j).

Results from the selective deprotection of several representative alcohol PGs in the presence of a DMTC moiety

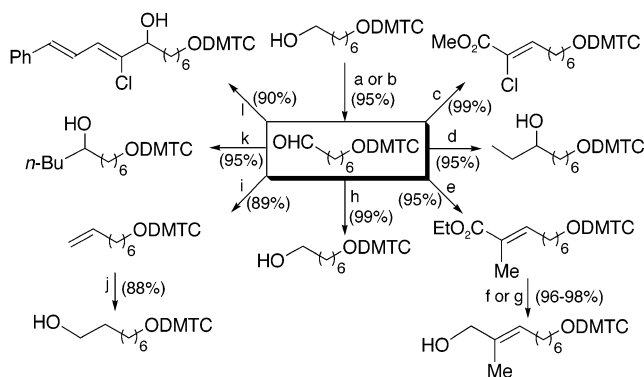
(7) **Dimethylthiocarbamoylation. Method A.** A solution of alcohol (5.0 mmol) in dry THF (5 mL) was added to a stirring, 0 °C suspension of NaH (5.1 mmol) in dry THF (20 mL) under an argon atmosphere. After 30 min, NaI (0.1 mmol) and *N,N*-dimethylthiocarbamoyl chloride (6.0 mmol, 1.2 equiv) were added successively, and the resulting mixture was stirred at room temperature for 10 h. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with water and brine and dried over Na₂SO₄. Removal of all volatiles in vacuo and chromatographic purification of the residue on SiO₂ furnished the DMTC protected alcohol. **Method B.** 1,1'-Thiocarbonyldiimidazole (1.1 mmol) was added to a stirring solution of alcohol (1 mmol) in dry CH₂Cl₂ (5 mL) containing DMAP (0.1 mmol) under an argon atmosphere. After 2–10 h, the reaction mixture was filtered through a small pad of silica gel, and the filter cake was washed with EtOAc (5 mL). The combined filtrate was concentrated under reduced pressure, and the residue was dissolved in a 2 M THF solution of dimethylamine (4 mL). After 2–4 h, all volatiles were removed in vacuo, and the residue was chromatographed over silica gel affording thiocarbamoylated alcohol.

(8) Spectral data for **6**: ¹H NMR (CDCl₃, 300 MHz) δ 1.32–1.44 (m, 6H), 1.54–1.63 (m, 2H), 1.67–1.77 (m, 2H), 3.08 (s, 3H), 3.35 (s, 6H), 3.51 (t, 2H, *J* = 6.3 Hz), 4.42 (t, 2H, *J* = 6.3 Hz), 4.61 (s, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 26.06, 26.26, 28.84, 29.20, 29.79, 37.78, 42.71, 55.18, 67.84, 71.74, 96.49, 188.46; IR (neat) 2933, 1520, 1393, 1293, 1193, 1146, 1110, 1043 cm⁻¹. Spectral data for **9**: ¹H NMR (CDCl₃, 300 MHz) δ 0.81 (d, 3H, *J* = 7.5 Hz), 0.86–0.93 (m, 7H), 1.01–1.17 (m, 1H), 1.43–1.59 (m, 2H), 1.63–1.73 (m, 2H), 1.81–1.94 (m, 1H), 2.17–2.26 (m, 1H), 3.07 (s, 3H), 3.35 (s, 3H), 5.24 (dt, 1H, *J* = 4.5, 10.8 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 17.10, 20.99, 22.25, 23.75, 26.65, 31.41, 34.52, 37.72, 41.06, 42.70, 47.66, 81.64, 187.86; IR (neat) 2953, 1520, 1390, 1293, 1196 cm⁻¹. Spectral data for **12**: ¹H NMR (CDCl₃, 400 MHz) δ 3.15 (s, 3H), 3.41 (s, 3H), 5.55 (s, 2H), 7.33–7.47 (m, 5H), 7.56–7.61 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 38.20, 43.16, 72.93, 127.31, 127.37, 127.53, 127.71, 128.80, 129.03, 129.09, 129.65, 135.46, 140.92, 141.36, 188.25. Spectral data for **14**: ¹H NMR (CDCl₃, 300 MHz) δ 0.84 (t, 3H, *J* = 7.2 Hz), 1.19–1.41 (m, 12H), 1.58–1.77 (m, 2H), 3.08 (s, 6H), 3.32 (s, 3H), 3.33 (s, 3H), 4.50–4.61 (m, 2H), 5.70–5.86 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 14.21, 22.74, 25.23, 29.28, 29.46, 29.60, 31.08, 31.92, 37.87, 38.06, 42.87, 72.19, 78.88, 187.82, 187.95.

(9) The Neuman–Kwart rearrangement (O → S migration) normally becomes significant only at temperatures of ≥220 °C, e.g.: Relles, H. M.; Pizzoloto, G. *J. Org. Chem.* **1968**, 33, 2249–2253.

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Scheme 1. DMTC Reagent Compatibility^a



^a Reagents and conditions: (a) PCC, CH₂Cl₂, 23 °C, 3 h. (b) DMSO, (COCl)₂, CH₂Cl₂, −78 °C, 1 h; Et₃N, −78 to 0 °C, 1 h. (c) Cl₃CCO₂Me, CrCl₂, THF, 23 °C, 0.5 h. (d) EtMgBr, Et₂O, 0 °C, 0.5 h. (e) EtO₂CC(PPh₃)CH₃, CH₂Cl₂, 23 °C, 12 h. (f) DIBAL-H, CH₂Cl₂, −78 °C, 0.5 h. (g) LiAlH₄, Et₂O, 0 °C, 0.5 h. (h) NaBH₄, MeOH, 0 °C, 0.5 h. (i) *n*-BuLi, Ph₃P⁺CH₃Br[−], Et₂O, −78 °C, 0.5 h; aldehyde, −78 to −20 °C, 1 h. (j) H₃B·Me₂S, THF, 0 °C, 3 h; H₂O₂, NaOH, 23 °C, 1 h. (k) *n*-BuLi, THF, −78 °C, 0.5 h. (l) PhCH=CHCH₂CCl₃, CrCl₂, THF, 23 °C, 12 h.

are summarized in Table 1. Parental alcohols are readily regenerated from *tert*-butyldimethylsilyl (entry 1) and *tert*-butyldiphenylsilyl (entry 2) ethers using fluoride, *p*-methoxybenzyl ether (entry 3) via DDQ, MOM (entry 4) and THP ethers (entry 5) by mild acid, MEM ether (entry 6) with the Lewis acid TiCl₄, and acetate (entry 7) upon exposure to base. As anticipated, catalytic hydrogenation of a benzyl ether in the presence of a DMTC failed; cleavage via in situ generated trimethylsilyl iodide, on the other hand, was successful, albeit in modest yield (entry 8).

Table 1. Cleavage of Alcohol Protective Groups in the Presence of DMTC

PGO—CH ₂ —CH ₂ —DMTC → HO—CH ₂ —CH ₂ —DMTC					
entry	PG	reagent	solvent/temp (°C)	time (h)	yield (%)
1	TBDMS	<i>n</i> -Bu ₄ NF	THF/23	2	92
2	TBDMS	<i>n</i> -Bu ₄ NF	THF/23	4	98
3	PMB	DDQ	CH ₂ Cl ₂ /23	1	96
4	MOM	HCl (1 M)	MeOH/50	10	95
5	THP	PTSA (5 mol %)	MeOH/23	3	94
6	MEM	TiCl ₄	CH ₂ Cl ₂ /0	0.5	92
7	Ac	K ₂ CO ₃	MeOH/0	1	98
8	Bn	Me ₃ SiCl/Nal	CH ₂ Cl ₂ /23	10	75

Importantly, the orthogonal removal of the DMTC group (Table 2) is readily effected with NaIO₄ in MeOH/H₂O at 45 °C for 2 h followed by brief exposure to dilute base to hydrolyze variable but usually minor amounts of formate

Table 2. NaIO₄ Cleavage of *N,N*-Dimethylthiocarbamates (DMTCs)^a

$\text{PGO}-(\text{CH}_2)_5\text{ODMTC} \longrightarrow \text{PGO}-(\text{CH}_2)_5\text{OH}$		
entry	PG	yield (%)
1	TBDMS	95
2	TBDPS	92
3	PMB	95
4	MOM	93
5	THP	93
6	MEM	92
7	Ac	94
8	Bn	94

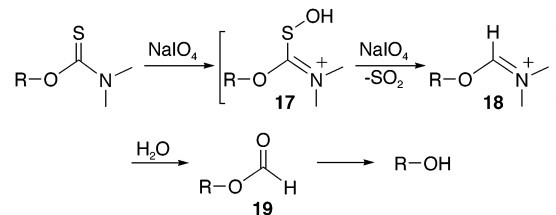
^a See ref 11 for general procedure.

ester **19** (Scheme 2).¹¹ Although the details of the overall transformation are obscure, it is known¹² that thionocarbamates undergo S-oxidation. We speculate that the resultant sulfenic acid **17** is further oxidized by excess NaIO₄ with

(11) **DMTC Cleavage. Method A.** NaIO₄ (4.0 mmol) was added to a stirring, room-temperature solution of DMTC (1.0 mmol) in MeOH/H₂O (10 mL, 20:1). The resulting solution was heated to 45 °C for 2 h and cooled to room temperature, and Na₂CO₃ (6.0 mmol) was added. Following another 2 h, the reaction mixture was extracted with ether (3 × 6 mL), and the combined ethereal extracts were washed with water and brine and dried over Na₂SO₄. Concentration under reduced pressure and chromatographic purification of the residue over silica gel afforded pure alcohol. **Method B.** The DMTC-protected alcohol (1.0 mmol) was stirred at 50 °C with 30% H₂O₂ (1 mL) in THF or CH₃CN (2 mL). After 4 h, an aqueous solution of NaOH (2 M, 1 mL) was added, and the stirring was continued at the same temperature overnight. The reaction mixture was cooled to room temperature and extracted with Et₂O (3 × 5 mL), and the combined ethereal extracts were washed with water (until the aqueous layer was negative to starch/iodine paper) and brine and dried over Na₂SO₄. Concentration under reduced pressure and purification of the residue over silica gel afforded pure alcohol (85–90%).

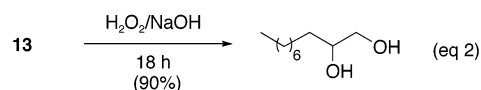
(12) Walter, W.; Wohlers, K. *Ann. Chem.* **1971**, 752, 115–135.

Scheme 2. Proposed Deprotection Mechanism



subsequent extrusion of SO₂, affording immonium **18**. Simple hydrolysis leads to formate **19** and finally to the parent alcohol.

Alternatively, DMTCs are severed, albeit slowly, in excellent yield by basic hydrogen peroxide at room temperature. This protocol has proven useful for *vic*-diols (eq 2) and other systems not compatible with periodate.



In summary, DMTC is a robust, spectrally simple, symmetrical, and nonpolar alcohol protective group. It is readily introduced using inexpensive reagents and is orthogonally differentiated from most other alcohol PGs.

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Supporting Information Available: Physical and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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