ORGANIC LETTERS

2003
Vol. 5, No. 25
4755−4757

Dimethylthiocarbamate (DMTC): An Alcohol Protecting Group

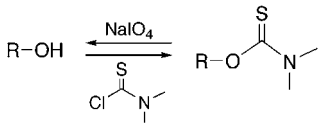
D. K. Barma,[†] A. Bandyopadhyay,[†] Jorge H. Capdevila,[‡] and J. R. Falck*,[†]

Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9038, and Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

j.falck@utsouthwestern.edu

Received August 1, 2003

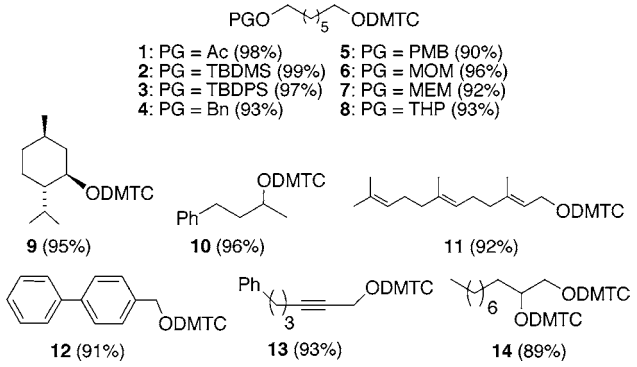
ABSTRACT



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*-Bu_4NF, $CrCl_2$, heat, and Lewis acids. They are readily removed by $NaIO_4$ or H_2O_2 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 thionocarbamates[4] 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 chloride[6] and NaH in THF at room temperature.[7]



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

[†] UT Southwestern.

[‡] Vanderbilt University School of Medicine.

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.

(2) Recent examples: (a) Almog, J.; Zehavy, Y.; Cohen, S. *Tetrahedron Lett.* **2003**, *44*, 3285−3288. (b) Kessler, M.; Glatthar, R.; Giese, B.; Bochet, C. G. *Org. Lett.* **2003**, *5*, 1179−1181. (c) Ellervik, U. *Tetrahedron Lett.* **2003**, *44*, 2279−2281. (d) Miura, T.; Inazu, T. *Tetrahedron Lett.* **2003**, *44*, 1819−1821. (e) Dinkel, C.; Wichmann, O.; Schultz, C. *Tetrahedron Lett.* **2003**, *44*, 1153−1155. (f) Csavas, M.; Borbas, A.; Janossy, L.; Liptak, A. *Tetrahedron Lett.* **2003**, *44*, 631−635.

(3) For other studies of protecting groups from our laboratories, see: (a) Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963−966. (b) Falck, J. R.; Barma, D. K.; Baati, R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1281−1283. (c) Baati, R.; Valleix, A.; Mioskowski, C.; Barma, D. K.; Falck, J. R. *Org. Lett.* **2000**, *2*, 485−487. (d) Cho, H.-S.; Yu, J.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 8354−8355. (e) Bolitt, V.; Mioskowski, C.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1988**, *29*, 4583−4586.

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

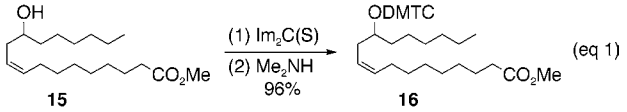
(5) The ability of thionocarbamates to stabilize organocopper reagents has been exploited for the cross-coupling of α,β-dialkoxy- and α-alkoxy-β-aminostannanes: Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759−4762.

(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.

10.1021/ol0354573 CCC: $25.00
Published on Web 11/19/2003

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]

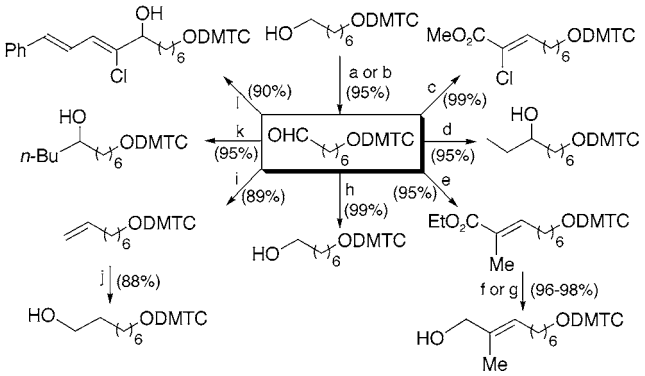
For alkali-intolerant compounds, the alcohol is thiocarbamoylated via sequential treatment with 1,1′-thiocarbonyldiimidazole followed by a THF solution of dimethylamine, e.g., **15** → **16** (eq 1).[7]



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 reagents[10] (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 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 $TiCl_4$, 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).

Scheme 1. DMTC Reagent Compatibility[a]



[a] Reagents and conditions: (a) PCC, CH_2Cl_2, 23 °C, 3 h. (b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1 h; Et_3N, −78 to 0 °C, 1 h. (c) Cl_3CCO_2Me, $CrCl_2$, THF, 23 °C, 0.5 h. (d) EtMgBr, Et_2O, 0 °C, 0.5 h. (e) $EtO_2CC(PPh_3)CH_3$, CH_2Cl_2, 23 °C, 12 h. (f) DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h. (g) $LiAlH_4$, Et_2O, 0 °C, 0.5 h. (h) $NaBH_4$, MeOH, 0 °C, 0.5 h. (i) *n*-BuLi, $Ph_3P^+CH_3Br^-$, Et_2O, −78 °C, 0.5 h; aldehyde, −78 to −20 °C, 1 h. (j) $H_3B{\cdot}Me_2S$, THF, 0 °C, 3 h; H_2O_2, NaOH, 23 °C, 1 h. (k) *n*-BuLi, THF, −78 °C, 0.5 h. (l) $PhCH{=}CHCH_2CCl_3$, $CrCl_2$, THF, 23 °C, 12 h.

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

entry	PG	reagent	solvent/temp (°C)	time (h)	yield (%)
1	TBDMS	*n*-Bu_4NF	THF/23	2	92
2	TBDMS	*n*-Bu_4NF	THF/23	4	98
3	PMB	DDQ	CH_2Cl_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_2Cl_2/0	0.5	92
7	Ac	K_2CO_3	MeOH/0	1	98
8	Bn	Me_3SiCl/NaI	CH_2Cl_2/23	10	75

Importantly, the orthogonal removal of the DMTC group (Table 2) is readily effected with $NaIO_4$ in MeOH/H_2O at 45 °C for 2 h followed by brief exposure to dilute base to hydrolyze variable but usually minor amounts of formate

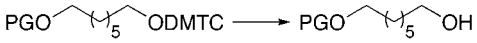
(7) **Dimethylthiocarbamoylation. Method A.** A solution of alcohol (5.0 mmol) in dry THF (5 mL) was added to a stirring, 0 °C suspension of NaH (5.1 mmol) in dry THF (20 mL) under an argon atmosphere. After 30 min, NaI (0.1 mmol) and *N*,*N*-dimethylthiocarbamoyl chloride (6.0 mmol, 1.2 equiv) were added successively, and the resulting mixture was stirred at room temperature for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with water and brine and dried over Na_2SO_4. Removal of all volatiles in vacuo and chromatographic purification of the residue on SiO_2 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 CH_2Cl_2 (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**: ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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**: ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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**: ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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**: ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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.; Pizzolato, G. *J. Org. Chem.* **1968**, *33*, 2249−2253.

(10) (a) Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218−3219. (b) Barma, D. K.; Baati, R.; Valleix, A.; Mioskowski, C.; Falck, J. R. *Org. Lett.* **2001**, *3*, 4237−4238.

Table 2. $NaIO_4$ Cleavage of *N*,*N*-Dimethylthiocarbamates (DMTCs)[a]

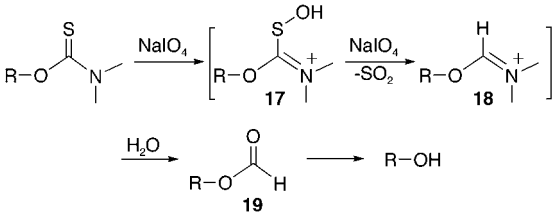


entry	PG	yield (%)
1	TBDMS	95
2	TBDPS	92
3	PMB	95
4	MOM	93
5	THP	93
6	MEM	92
7	Ac	94
8	Bn	94

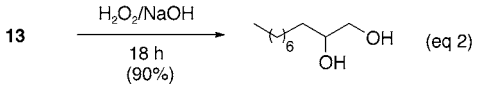
[a] See ref 11 for general procedure.

ester **19** (Scheme 2).[11] Although the details of the overall transformation are obscure, it is known[12] that thionocarbamates undergo S-oxidation. We speculate that the resultant sulfenic acid **17** is further oxidized by excess $NaIO_4$ with subsequent extrusion of SO_2, affording immonium **18**. Simple hydrolysis leads to formate **19** and finally to the parent alcohol.

Scheme 2. Proposed Deprotection Mechanism



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.

Acknowledgment. Financial support provided by the Robert A. Welch Foundation and NIH (GM31278, DK38226, GM37922).

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.

OL0354573

(11) **DMTC Cleavage. Method A.** $NaIO_4$ (4.0 mmol) was added to a stirring, room-temperature solution of DMTC (1.0 mmol) in MeOH/H_2O (10 mL, 20:1). The resulting solution was heated to 45 °C for 2 h and cooled to room temperature, and Na_2CO_3 (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 Na_2SO_4. 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% H_2O_2 (1 mL) in THF or CH_3CN (2 mL). After 4 h, an aqueous solution of NaOH (2 M, 1 mL) was added, and the stirring was continued at the same temperatrure overnight. The reaction mixture was cooled to room temperature and extracted with Et_2O (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 Na_2SO_4. 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.