







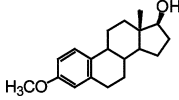
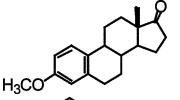
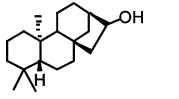
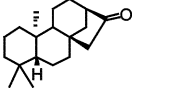


Table 4 Swern oxidations using **7**

alcohol		1) 7 (2–3 eq), (COCl) ₂ (1.5–2.5 eq) 2) NEt ₃ (3–6 eq), CH ₂ Cl ₂ , –60°C to rt		aldehyde or ketone	
Entry	Substrate	Product	Yield (%)	Recd 3a yield (%)	
1 ^a			94	84	
2 ^a			94	87	
3 ^a			92	81	
4 ^b			91	76	
5 ^a			96	90	
6 ^a			95	83	

^a **7**, (COCl)₂, Et₃N (2, 1.5, and 3 equiv., respectively). ^b **7**, (COCl)₂, Et₃N (3, 2.5, and 6 equiv., respectively).

was necessary to avoid formation of the corresponding chloride. In the case of 1,6-hexanediol (entry 4 in Table 4), 3 equivalents of the sulfoxide **7** and 2.5 equivalents of oxalyl chloride were used for an optimum yield of 91%. In all cases, we employed the acid–base extraction principle to separate the products and to recover the sulfide **3a** so that it could be oxidized back to the sulfoxide **7**.

Next, we examined the utility of the modified odorless thiol **2a** in thiolate anion induced dealkylation reactions. Several phenyl ethers and methyl esters were subjected to dealkylation in the presence of the sodium salt of **2a** (5 equiv.) under the reaction conditions described in Table 5. Although the yields of the products varied, compared to the inherently toxic and malodorous ethanethiol, our reagent **2a** could nonetheless be quite useful because it is odorless and can be reused.

Conclusion

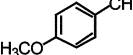
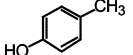
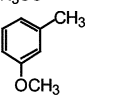
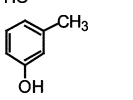
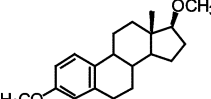
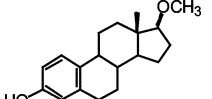
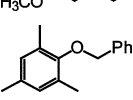
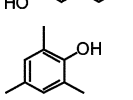
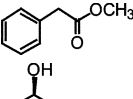
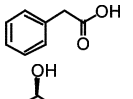
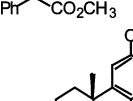
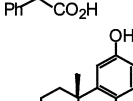
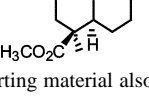
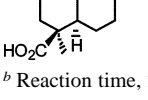
We have demonstrated the use of these modified, sulfur reagents **3a** (MMS) and **7** (MMSO) as odorless alternatives to DMS and DMSO in the Corey–Kim and the Swern oxidations, respectively. The morpholine based thiol **2a** could also act as an odorless alternative to the foul smelling ethanethiol commonly used in industrial settings. The products of these reactions can be easily purified using only acid–base extraction, thereby eliminating unpleasant odors, saving time and protecting the environment. In view of current environmental and economic factors, the utility of these simple reagents could be enormously beneficial.

Experimental

General

All reagents were purchased from commercial sources and used as received. All reactions were performed under a dry N₂ atmosphere unless otherwise indicated. Reaction solvents such as toluene, CH₂Cl₂, acetone, acetonitrile, ethyl acetate and DMF were dried prior to use. Analytical TLC was done on precoated (0.25 mm) silica gel plates. Column chromatography was conducted with 230–400 mesh silica gel. Infrared (IR) spectra were measured on a FTIR spectrometer. The ²H NMR (62 MHz) spectrum was recorded in chloroform using CDCl₃ (7.26 ppm) as the internal standard. All oxidation and dealkylation substrates were commercially available

Table 5 Dealkylation reactions using **2a**

phenyl ether or ester		2a (5 eq), NaH (6 eq) DMF, 120°C, 3 h		phenolic alcohol or acid	
Entry	Reactants	Product	Yield (%)		
1 ^a			77		
2 ^a			81		
3 ^a			72		
4 ^a			83		
5			92		
6 ^b			92		
7 ^b			97		

^a Some starting material also recovered. ^b Reaction time, 2 h.

or prepared by known procedures and used as such and the products were identical to commercial samples.

Typical procedure for the preparation of methyl 6-morpholinohexyl sulfide (**3a**)

To a solution of thiol **2a** (8.34 g, 41.04 mmol) in ethanol (15 mL) was added 50% aqueous NaOH (30 mL). The solution was cooled to 5 °C and MeI (3.83 mL, 61.56 mmol) was added dropwise with stirring. The reaction mixture was stirred at ambient temperature for 3 h. Excess ethanol was distilled off under reduced pressure, the solution diluted with water (100 mL) and extracted with diethyl ether (5 × 75 mL), washed with brine and dried (Na₂SO₄) and concentrated. The crude colorless oil was distilled at 145 °C/1.5 mmHg to give pure sulfide **3a** (7.4 g, 83%): bp 145 °C (1.5 mmHg); IR (CHCl₃): 3030, 2930, 2860, 2815, 2485, 1600, 1460, 1310 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 3.71 (t, *J* = 4.6 Hz, 4H), 2.48 (t, *J* = 6.8 Hz, 2H), 2.42 (br s, 4H), 2.30 (dd, *J* = 7.1, 2.0 Hz, 2H), 2.08 (s, 3H), 1.52–1.28 (m, 8H); ¹³C NMR (CDCl₃, 100 MHz): δ 66.9, 59.1, 53.8, 34.2, 29.1, 28.7, 27.1, 26.5, 15.6; MS (EI) *m/z* 217 (M⁺, 3.4), 202 (20), 170 (100), 156 (9.4), 100 (98.1), 87 (19.2); HRMS calcd for C₁₁H₂₃NOS: 217.1503, found 217.1500.

Methyl 6-morpholinobutyl sulfide (**3b**)

Methyl 6-morpholinobutyl sulfide (**3b**) was prepared similarly from **2b** (6.90 g, 39.36 mmol) and MeI (3.67 mL, 59.04 mmol) in 82% yield (6.10 g) as colorless oil: IR (CHCl₃): 3005, 2920, 2860, 2815, 2480, 1600, 1460, 1360 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 3.70 (t, *J* = 4.7 Hz, 4H), 2.50 (t, *J* = 7.1 Hz, 2H), 2.42 (br dd, *J* = 4.4, 4.0 Hz, 4H), 2.34 (t, *J* = 7.7 Hz, 2H), 2.08 (s, 3H), 1.69–1.52 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz): δ 66.5, 58.1, 53.4, 33.7, 26.5, 25.2, 15.1; MS (EI) *m/z* 189 (M⁺, 12.8), 142 (16.8), 100 (100), 156 (9.4), 100 (98.1), 83 (22.5); HRMS calcd for C₉H₁₉NOS: 189.1184, found 189.1187.

General procedure for the Corey–Kim oxidation using 3a

To a solution of *N*-chlorosuccinimide (63.76 mg, 0.48 mmol) in anhydrous dichloromethane (2 mL) under N₂ at –40 °C was added 3a (104 mg, 0.48 mmol) in dichloromethane (2 mL) dropwise. The reaction mixture was stirred at –40 °C for 30 min before the addition of the alcohol (0.32 mmol) in dichloromethane (2 mL). After the reaction had been stirred for 2 h at –40 °C, freshly distilled Et₃N (0.14 mL, 0.95 mmol) was added and the reaction mixture was stirred at the same temperature for a further period of 2.5 h. It was then allowed to warm to rt for 8 h with continued stirring before being poured into aq. 1 N HCl (60 mL) and extracted with ethyl acetate (3 × 30 mL). The organic component was washed again with aq. 1 N HCl (50 mL), brine and dried over Na₂SO₄. The solvent was evaporated *in vacuo* to afford the pure aldehyde or ketone.

General procedure for the recovery of 3a

The aq. 1 N HCl solution collected after work-up of Corey–Kim/Swern oxidation was made alkaline (pH > 9) using aq. 5 M NaOH and extracted with diethyl ether (3 × 30 mL), dried (Na₂SO₄) and concentrated followed by Kuegelruhr distillation (145 °C, 1.5 mmHg) to afford the pure 3a.

Procedure for the synthesis of methyl 6-morpholinohexyl sulfoxide (7) using *m*-CPBA

Method A. To a stirred solution of the sulfide 3a (518 mg, 2.39 mmol) in chloroform (10 mL) at –60 °C was added *m*-CPBA (642 mg from 77% *m*-CPBA, 2.86 mmol) in portions. The reaction mixture was stirred for 30 min followed by stirring at 0 °C (10 min). It was then quenched and washed with aq. sat. NaHCO₃, extracted with CHCl₃ and dried (Na₂SO₄). Purification of the crude sulfoxide by a short silica gel column using chloroform and methanol (10 : 1) as eluents afforded the title compound (482 mg, 86%) as a colorless oil.

Method B. To a stirred solution of the sulfide 3a (1.46 g, 6.74 mmol) in chloroform (20 mL) at ambient temperature was added acetyl chloride (0.5 mL, 6.75 mmol). The reaction mixture was cooled to –60 °C and *m*-CPBA (1.81 g from 77% *m*-CPBA, 8.09 mmol) was added in portions. The reaction mixture was stirred for 30 min followed by warming to 0 °C (10 min). It was then quenched and washed with aq. NaHCO₃, extracted with CHCl₃ and dried (Na₂SO₄). The crude sulfoxide was purified by a short silica gel column using chloroform and methanol (10 : 1) as eluents to afford 7 (1.50 g, 95.5%): IR (CHCl₃): 3030, 2940, 2815, 2475, 1600, 1460, 1425, 1305 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 3.72 (t, *J* = 4.6 Hz, 4H), 2.74–2.62 (m, 2H), 2.57 (s, 3H), 2.44 (br s, 4H), 2.33 (dd, *J* = 7.3, 0.6 Hz, 2H), 1.78 (quint, *J* = 7.7 Hz, 2H), 1.56–1.34 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 66.9, 58.9, 54.6, 53.7, 38.5, 28.7, 27.1, 26.3, 22.5; MS (FAB) *m/z* 234 (M⁺+1, 100), 216 (15), 170 (25), 147 (20), 100 (45); HRMS calcd for C₁₁H₂₃NO₂S (M⁺+H): 234.1540, found 234.1525.

General procedure for the Swern oxidation using 7

To a well-stirred solution of anhydrous CH₂Cl₂ (5 mL) under dry N₂ atmosphere at –60 °C was added oxalyl chloride (20.5 μL, 0.24 mmol). A solution of 7 (73.25 mg, 0.31 mmol) in CH₂Cl₂ (2 mL) was then added dropwise and the reaction mixture was stirred for an additional 20 min. The alcohol (0.16 mmol) dissolved in CH₂Cl₂ (2 mL) was added to this solution followed, after an additional 30 min to 1 h, by freshly distilled Et₃N (66 μL, 0.48 mmol). The reaction mixture was stirred for 2 h at –60 °C and allowed to warm to rt

where it was stirred for a further period of 1 h. The reaction mixture was then quenched with H₂O (5 mL), washed with aq. 1 N HCl (2 × 20 mL), extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (50 mL) followed by brine (50 mL) and dried (Na₂SO₄). After evaporation of the solvent under vacuum, the pure ketone or aldehyde was obtained.

General procedure for the dealkylation using 2a

To a stirred suspension of NaH (from 118 mg of 60% NaH dispersion in mineral oil, 2.46 mmol) in anhydrous DMF (2 mL) at ambient temperature was added 2a (416 mg, 2.05 mmol) in DMF (2 mL) and the mixture was stirred for 5 min. A solution of the phenolic ether or the methyl ester (0.41 mmol) in DMF (2 mL) was added and the reaction mixture was stirred at 120 °C for 3 h. Excess solvent was distilled off under low pressure. The residue was poured into aq. 1 N HCl and extracted with diethyl ether (2 × 50 mL). The ether layer was washed successively with aq. 1 N HCl and brine, and dried (Na₂SO₄). After evaporation of the solvent, the crude compound was purified either by a short silica gel column using hexane and ethyl acetate (5 : 1) as eluents or by recrystallization to afford the dealkylated products.

Acknowledgements

We are grateful for Grant-in-Aid (No. 15659005 to K. N. and No. 13470474 to M. N.) from the Ministry of Education, Science, Sports and Culture of Japan, in partial financial support of this research. P. K. P. acknowledges the JSPS for a postdoctoral fellowship.

Notes and references

- (a) G. Solladie, *Synthesis of Sulfides, Sulfoxides and Sulfones*, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, UK, 1991, vol. 6, pp. 133–170; (b) D. J. Procter, *J. Chem. Soc., Perkin Trans. 1*, 2001, 335; (c) K.-M. Roy, Thiols and Organic Sulfides, in *Ullmann's Encyclopedia of Industrial Chemistry*, 6th edn., Wiley-VCH, Weinheim, 2003, vol. 36, pp. 625–652.
- K. Nishide, S. Ohsugi, H. Shiraki, H. Tamakita and M. Node, *Org. Lett.*, 2001, 3, 3121.
- M. Node, K. Kumar, K. Nishide, S. Ohsugi and T. Miyamoto, *Tetrahedron Lett.*, 2001, 42, 9207.
- K. Nishide, T. Miyamoto, K. Kumar, S. Ohsugi and M. Node, *Tetrahedron Lett.*, 2002, 43, 8569.
- K. S. Ritter, *Chem. Eng. News*, 2003, 81, 30.
- (a) Y. Mitsumoto and M. Nitta, *Bull. Chem. Soc. Jpn.*, 2003, 76, 1029; (b) J. Muzart, *Tetrahedron*, 2003, 59, 5789; (c) S. S. Kim and D. W. Kim, *Synlett*, 2003, 1391.
- (a) S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639; (b) I. E. Markó, P. R. Giles, M. Tsukazaki, I. Chellé-Regnaut, C. J. Urch and S. M. Brown, *J. Am. Chem. Soc.*, 1997, 119, 12661; (c) I. E. Markó, P. R. Giles, M. Tsukazaki, I. Chellé-Regnaut, A. Gautier, S. M. Brown and C. J. Urch, *J. Org. Chem.*, 1999, 64, 2433; (d) D. R. Jensen, J. S. Pugsley and M. S. Sigman, *J. Am. Chem. Soc.*, 2001, 123, 7475; (e) E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, 2001, 123, 7725; (f) R. A. Sheldon, I. W. C. E. Arends, G.-J. Brink and A. Dijkman, *Acc. Chem. Res.*, 2002, 39, 774; (g) D. R. Jensen, M. J. Schultz, J. A. Mueller and M. S. Sigman, *Angew. Chem., Int. Ed.*, 2003, 42, 3810; (h) T. L. Stuchinskaya and I. V. Kozhevnikov, *Catal. Commun.*, 2003, 4, 417; (i) T. Ruether, A. M. Bond and W. R. Jackson, *Green Chem.*, 2003, 5, 364.
- (a) A. E. J. de Nooy, A. C. Besemer and H. van Bekkum, *Synthesis*, 1996, 1153; (b) D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, 48, 4155; (c) M. Frigerio, M. Santagostino, S. Spatore and G. Palmisano, *J. Org. Chem.*, 1995, 60, 7272; (d) K. C. Nicolaou, Y.-L. Zhong and P. S. Baran, *J. Am. Chem. Soc.*, 2001, 123, 3183; (e) A. Ozanne, L. Pouységou,

- D. Depernet, B. François and S. Quideau, *Org. Lett.*, 2003, **5**, 2903; (f) Z. Liu, Z.-C. Chen and Q.-G. Zheng, *Org. Lett.*, 2003, **5**, 3321.
- 9 E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, 1972, **94**, 7586.
- 10 (a) A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480. Reviews see (b) A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165; (c) T. T. Tidwell, *Org. React.*, 1990, **39**, 297; (d) T. T. Tidwell, *Synthesis*, 1990, 857.
- 11 (a) Y. Liu and J. C. Vederas, *J. Org. Chem.*, 1996, **61**, 7856; (b) J. M. Harris, Y. Liu, S. Chai, M. D. Andrews and J. C. Vederas, *J. Org. Chem.*, 1998, **63**, 2407.
- 12 (a) C. D. Cole, J. R. Stock and J. A. Kappel, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1791; (b) M. K. W. Choi and P. H. Toy, *Tetrahedron*, 2003, **59**, 7171.
- 13 (a) D. Crich and S. Neelamkavil, *J. Am. Chem. Soc.*, 2001, **123**, 7449; (b) D. Crich and S. Neelamkavil, *Tetrahedron*, 2002, **58**, 3865.
- 14 (a) K. Nishide, S. Ohsugi, M. Fudesaka, S. Kodama and M. Node, *Tetrahedron Lett.*, 2002, **43**, 5177; (b) S. Ohsugi, K. Nishide, K. Oono, K. Okuyama, M. Fudesaka, S. Kodama and M. Node, *Tetrahedron*, 2003, **59**, 8393.
- 15 (a) R. L. Frank and P. V. Smith, *J. Am. Chem. Soc.*, 1946, **68**, 2103; (b) V. Franzen, *Chem. Ber.*, 1957, **90**, 623.
- 16 (a) G. W. Anderson and C. B. Pollard, *J. Am. Chem. Soc.*, 1939, **61**, 3440; (b) V. K. Tammara, M. M. Narurkar, A. M. Crider and M. A. Khan, *J. Pharm. Sci.*, 1994, **83**, 644.
- 17 The sulfide **3a** was dried under Dean–Stark conditions for several hours before using in the Corey–Kim oxidation.