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PROTECTION OF PRIMARY HYDROXYL GROUPS AS METHYLTHIOMETHYL ETHERS

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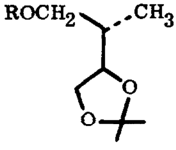
The selective protection of hydroxyl groups is a crucial element in synthesis of polyfunctional molecules.[1] This letter describes the formation, removal, and stability characteristics of the methylthiomethyl (MTM) protecting group which we expect to become an important new technique.[2]

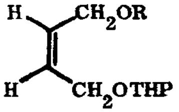
The conversion of a primary alcohol to an MTM ether can be carried out by reaction of the sodium alkoxide (from sodium hydride) in dimethoxyethane (DME) with iodomethyl methyl sulfide, formed *in situ* from commercially available chloromethyl methyl sulfide and sodium iodide in DME. The reaction of an alkoxide with chloromethyl methyl sulfide is very slow and eventually yields a complex mixture of products, which may explain why MTM ethers have not previously been exploited.[3] Using the above method, MTM ethers 1b-3b were prepared from the corresponding alcohols 1a-3a (yields of 1b-3b all >86%).[4]

$C_6H_5CH_2OR$

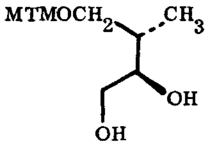
1a, R = H
1b, R = MTM



2a, R = H
2b, R = MTM



3a, R = H
3b, R = MTM



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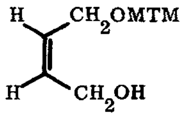

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The conversion of the MTM ethers to the corresponding alcohols 1a-3a could be effected cleanly by either of two procedures: (1) reaction with mercuric chloride in acetonitrile--water (ratio 4:1) at 25° or (2) reaction with silver nitrate in THF--water buffered with 2, 6-lutidine at 25°. Yields of 88-95% were observed without deviation from these standard conditions, the mildness of which is attested to by the retention of the tetrahydropyranyl group in the conversion of 3b to 3a (88% yield by Ag^+ method) and by a previously reported example[2] in which selective MTM cleavage was effected in the presence of dithioacetal and silyl ether units.

The MTM ether function is stable to basic and nucleophilic reagents, *e.g.*, NaH, RLi, or NaOR. In addition, it is fairly resistant to acid-catalyzed cleavage. For example, the acetonide protecting group could be selectively removed from 2b to form 4 (4:1 acetic acid--water, 45°, 1 hr) in 94% yield, and the tetrahydropyranyl group could be cleaved in 3b to afford 5 (3:2:1 THF--acetic acid--water, 40°, 8 hr) in 85% yield. The MTM group is achiral and allows the avoidance of diastereomeric mixtures in applications to substrates possessing chiral centers.

Representative procedures for the formation and cleavage of MTM ethers follow.[5, 6]

Formation of 1b: To a magnetically stirred suspension of sodium hydride (0.432 g, 18.0 mmol) in 10 ml of dimethoxyethane was added benzyl alcohol (0.978 g, 9.04 mmol) at 0° under argon. To this reaction mixture was added sodium iodide (1.349 g, 9.0 mmol) and then chloromethyl methyl sulfide (0.869 g, 9.0 mmol). After 1 hr at 0° the reaction mixture was warmed to room temperature over a 4-hr period, poured into 20 ml of water, and extracted with ether. The combined organic extracts were washed with brine, then dried (K_2CO_3) and concentrated. The crude product was filtered through a short column of silica gel (pentane--ether, 4:1) to afford 1.455 g (95%) of spectroscopically pure methylthiomethyl ether 1b.

Cleavage of 1b to 1a ($HgCl_2$ method): To a stirred solution of acetonitrile--water (4:1, v/v containing methylthiomethyl ether 1b (158 mg, 0.94 mmol) was added mercuric chloride (407 mg, 1.50 mmol) at room temperature. After 4 hr the reaction mixture was filtered through Celite (ether elution) and washed with ammonium acetate solution. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, dried (K_2CO_3), and concentrated under reduced pressure. Chromatography on silica gel (3 : 1 pentane--ether) afforded benzyl alcohol (94 mg, 94%) identical spectroscopically with an authentic sample.

Cleavage of 3b to 3a ($AgNO_3$ method): Silver nitrate (288 mg, 1.70 mmol) was added to 0.8 ml of THF--water (4:1, v/v) containing methylthiomethyl ether 3b (78 mg, 0.34 mmol) and 2,6-lutidine (107 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 45 min, diluted with ether, and filtered through Celite. The organic layer was washed with copper sulfate solution and water, then dried (K_2CO_3) and concentrated. Chromatography on silica gel (2:1 ether--pentane) afforded 51 mg (88%) of 3a which was identical spectroscopically with an authentic sample.

References

1. See (a) E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972); (b) M. F. Semmelhack and G. E. Heinsohn, *ibid.*, **94**, 5139 (1972); (c) E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **38**, 3224 (1973); and references cited therein.
2. For a recent application see E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 1975 (in press).
3. Secondary alcohols afford only modest yields (*ca.* 40%) of MTM ethers with iodomethyl methyl sulfide. This limitation is currently the subject of further research which will be reported later.
4. The structures assigned to the compounds reported herein were confirmed by infrared, proton magnetic resonance (pmr) and mass spectrometric data. The pmr peaks due to $-SCH_3$ and $-OCH_2S-$ protons in MTM derivatives appear characteristically at 2.1-2.2 δ and 4.5-4.6 δ, respectively. The methylthiomethyl ethers are thermally stable and sufficiently resistant to fragmentation during mass spectrometric measurements that molecular ions may be observed.
5. The formation and cleavage of MTM ethers have been carried out on larger scale than detailed here with no loss of efficiency.
6. This research was assisted financially by the National Institutes of Health.