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METHYLTHIOMETHYL ETHERS : GENERAL SYNTHESIS AND MILD CLEAVAGE. PROTECTION OF HYDROXYL GROUPS

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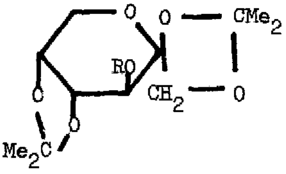
Methylthiomethyl ethers are well-known by-products of the oxidation of alcohols by acetic anhydride-dimethyl sulphoxide (DMSO)[1] but have received little systematic study. Reaction of a carbohydrate derivative containing a secondary hydroxyl group with sodium iodide and methyl chloromethyl sulphide gave only a moderate yield of methylthiomethyl ether,[2] but Corey and Bock developed the method into an efficient synthesis for methylthiomethyl ethers of primary alcohols and recommended the methylthiomethyl group for the temporary protection of hydroxyl groups.[3] Yamada *et al.* showed that compounds containing only tertiary hydroxyl groups give methylthiomethyl ethers with acetic anhydride and DMSO.[4] We now describe a general synthesis for methylthiomethyl ethers and a method for their cleavage to the parent alcohols.

Following a suggestion by Albright and Goldman in their study of the oxidation of alcohols,[1c] we have found that deliberate introduction of acetic acid into the mixture of acetic anhydride and DMSO gives good yields of methylthiomethyl ethers, with little or no ketone. The reaction has been applied to primary alcohols such as butan-1-ol, to secondary alcohols, including cyclohexanol and derivatives and suitably protected monosaccharides (*e.g.* 1a), and to *tert*-butanol. In the cyclohexanols, equatorial hydroxyl groups seem to react faster than axial hydroxyl groups.

Corey and Bock[3] removed the methylthiomethyl protecting group with mercuric chloride or silver nitrate, but we find that this can be done more conveniently with methyl iodide in moist acetone, with addition of solid sodium hydrogen carbonate for compounds which are acid-sensitive. A similar method has been used to liberate carboxylic acids from methylthiomethyl esters.[5]

Methods described here are superior to published procedures[2-4] when (i) methylthiomethyl ethers of secondary alcohols are required or (ii) a compound is sensitive to



1a, R = H
1b, R = CH_2SCH_3

strong bases such as sodium hydride. We confirm that these ethers are stable to bases and in weakly acidic media such as those used for removal of acetonide protecting groups. Raney nickel reduces methylthiomethyl ethers to the corresponding methyl ethers in high yield,[6] therefore this study provides a novel method for preparing methyl ethers under mildly acidic or neutral conditions. Thus, hydroxyl groups with neighbouring acyloxy groups could be methylated without occurrence of acyl migration, which is often impossible under the usual basic conditions of methylation.[7]

Procedures are illustrated by formation of the methylthiomethyl ether (1b) from 1,2:4,5-di-*O*-isopropylidene-β-*D*-fructopyranose (1a) and its cleavage to starting material.

Formation. - A reaction mixture prepared from 1a (8 g) in DMSO (100 ml) with acetic acid (20 ml) and acetic anhydride (66 ml) was stored at room temperature for two days, then poured into a cold solution of sodium carbonate (100 g) in water (1 l). The alkaline solution was extracted with chloroform (3 x 200 ml), the combined extracts were washed with water (5 x 200 ml) and evaporated, finally under high vacuum, to yield the product as a syrup (8.1 g, 82%), pure by thin-layer chromatography. Passage through a silica-gel column afforded methylthiomethyl ether 1b (7.5 g), m.p. 82-83° (lit.[8] m.p. 82-82.5°).

Similarly prepared were the methylthiomethyl ethers[9] of 1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose,[10] *cis*- and *trans*-4-tert-butylcyclohexanol,[11] butan-1-ol, *tert*-butanol and 1-methylcyclohexan-1-ol.

Cleavage. - Methylthiomethyl ether 1b (1 g) was dissolved in acetone (10 ml) and methyl iodide (1.5 ml) and sodium hydrogen carbonate (1.2 g) were added. The suspension was stirred at room temperature for 6 days (or several hours at reflux temperature). Water (5 ml) was added, organic solvents were evaporated and the aqueous concentrate was extracted with chloroform (2 x 5 ml). The combined extracts were dried (MgSO$_4$) and evaporated, yielding solid (0.8 g, 98%) which was recrystallised from ether-pentane to give pure 1a (0.7 g), m.p. 118-119° (lit.[12] m.p. 119°).

References

1. (a) W. W. Epstein and F. W. Sweat, Chem. Rev., *67*, 247 (1967); (b) R. F. Butterworth and S. Hanessian, *Synthesis*, 70 (1971); (c) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, *87*, 4214 (1965); *89*, 2416 (1967).
2. S. David, J. Eustache, and A. J. Lubineau, *J. Chem. Soc. Perkin I*, 2274 (1974).
3. E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 2643, 3269 (1975).
4. K. Yamada, K. Kato, H. Nagase, and Y. Hirata, *Tetrahedron Lett.*, 65 (1976).
5. T. L. Ho and C. M. Wong, *J. Chem. Soc. Chem. Commun.*, 224 (1973).
6. See for example G. J. F. Chittenden, *Carbohydr. Res.*, *15*, 101 (1970); see also ref. 10.
7. S. J. Angyal and G. J. H. Melrose, *J. Chem. Soc.*, 6501 (1965).
8. K. James, A. R. Tatchell, and P. K. Ray, *J. Chem. Soc.* (*C*), 2681 (1967).
9. Analytical data and spectra of all new compounds were consistent with assigned structures.
10. J. S. Jewell and W. A. Szarek, *Tetrahedron Lett.*, 43 (1969).
11. The *cis* compound required 4 days instead of 2 days for complete reaction.
12. R. S. Tipson, R. F. Brady, and B. F. West, *Carbohydr. Res.*, *16*, 383 (1971).