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METHODS FOR THE INTERCONVERSION OF PROTECTIVE GROUPS. TRANSFORMATION OF MEM ETHERS INTO ISOPROPYLTHIOMETHYL ETHERS OR CYANOMETHYL ETHERS

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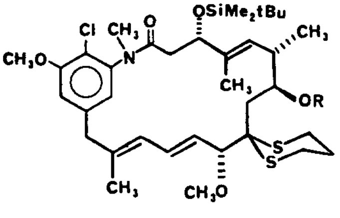
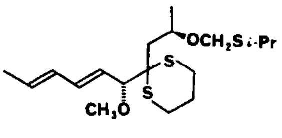
Abstract: This letter describes methods for the synthesis of isopropylthiomethyl and cyanomethyl ethers from the corresponding MEM ethers and also a process for the cleavage of MEM or MOM ethers of 1,2- and 1,3-diols which avoids cyclization to formals.

Some time ago in connection with research on the total synthesis of maytansine[1] a study was made of new and milder methods for removal of the methoxyethoxymethyl (MEM) hydroxyl protective group[2] and also for transforming the MEM and MOM (methoxymethyl) groups into other protective groups. In the maytansine synthesis the MEM-protected intermediate shown below (**1**) was transformed into the corresponding isopropylthiomethyl ether (**2**) by sequential treatment with boron trifluoride etherate (-78°, 5 min.) and tetrabutylammonium isopropylthioate.[1] Cleavage of the isopropylthiomethyl group was subsequently effected under non-acidic conditions to give the alcohol **3**.[1] During this study we also investigated the reaction of various MEM ethers



1 R = MEM
2 R = CH_2S*i*-Pr
3 R = H



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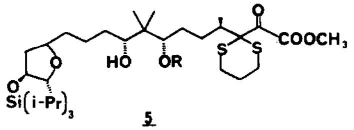
with the reagent series boron tribromide, *i*-PrSBBr$_2$, (*i*-PrS)$_2$BBr and (*i*-PrS)$_3$B[3] for which reactivity decreases in the forgoing order. The mildest reagent, (*i*-PrS)$_3$B, did not effect efficient conversion of MEM ethers to *i*-propylthiomethyl ethers, even at 23°. Instead, a complex gradually was formed which upon quenching with aqueous bicarbonate afforded deprotected alcohol. For example, a mixture of the MEM ether of *trans*-4-*t*-butylcyclohexanol and 1.2 equiv. of (*i*-PrS)$_3$B after stirring at 23° for 12 hr. in CH$_2$Cl$_2$ and quenching with aqueous bicarbonate gave 92% of *trans*-4-*t*-butylcyclohexanol along with only 3% of the desired alkylthiomethyl ether. Recently two groups have reported on the use of various Lewis acidic boron reagents for the deprotection of MEM ethers.[4,5]

Bis-*i*-propylthioboron bromide proved to be the most interesting reagent with respect to the MEM ether to *i*-propylthiomethyl ether conversion. The reagent was prepared in 90% yield by the addition of 1 equivalent of boron tribromide to a suspension of bis-(*i*-propyl)lead in dry pentane at 23°, addition of methylene chloride and subsequent distillation (b.p. $75\text{-}80^{\circ}$ at 2 mm.; ^{1}H nmr in CDCl$_3$: δ 3.64(h, 2H, J=6.8 Hz), 1.385(d, 12H, J=6.8 Hz)). Reaction of the MEM ether of cholesterol in methylene chloride at -95° with 3-5 equiv. of (*i*-PrS)$_2$BBr for 5 min followed by addition of 4-dimethylaminopyridine (2 equiv./equiv. of boron reagent) and further reaction at -95° for 15 min. and -50° for 10 min. afforded after quenching with aqueous potassium carbonate solution and column chromatographic purification on silica 89% yield of the *i*-propylthiomethyl ether of cholesterol in addition to 9% of cholesterol. By the same procedure *trans*-4-*t*-butylcyclohexanol MEM ether was converted to the isopropylthiomethyl ether in 85% isolated yield and the thioether *4* was synthesized from the corresponding MEM ether in 90% yield. In each case the only detectible byproduct is the corresponding alcohol.

4-Dimethylaminopyridine plays an essential role in the MEM to *i*-propylthiomethyl ether conversion, since its omission results in the formation of the cleavage product, i.e. alcohol, rather than thiomethyl ether. It is our view that the function of 4-dimethylaminopyridine is to displace *i*-propylthiolate from boron thereby providing a reactive S-nucleophile to attack the boron coordinated MEM ether.

We found that (*i*-PrS)$_2$BBr is also a useful reagent for the cleavage of mono MOM (or MEM) ethers of 1,2- or 1,3-diols. For such structures conventional acid-catalyzed processes (using protic or Lewis acids) produce cyclic diol formals as the major product. In contrast reaction of glycol mono MOM ethers with 1.2 equiv. of (*i*-PrS)$_2$BBr at -78° in CH$_2$Cl$_2$ followed by quenching with methanol and stirring at 23° for 1 hr. affords after concentration and chromatography on silica gel good yields of 1,2- or 1,3-diols. Thus the following diols were obtained by cleavage of mono MOM ethers in the isolated yields indicated in parentheses: *cis*-cyclopentan-1,2-diol (73); *cis*-cyclohexan-1,2-diol (96); *cis*-cyclodecan-1,2-diol (82); 2,2-dimethylpropan-1,3-diol

(91); 4-methyl-pentan-2,4-diol (70%, from 2° MOM ether); 5 (R=H)[6] from 5 (R=MOM)(94%).



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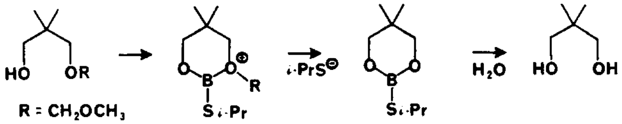
Our mechanistic rationale for the cleavage of diol mono MOM ethers by $(\textit{i}\text{-PrS})_2BBr$ is depicted below.



A conversion of MEM ethers to cyanomethyl ethers in one step has also been developed as part of this study. Cyanomethyl ethers are of interest to us as equivalents of $RO\text{-}\overset{O}{\overset{\|}{C}}{}^{\ominus}$ for intramolecular C-C bond formation through nucleophilic or sigmatropic reactions. Reaction of various MEM ethers in toluene at 0.5 *M* concentration with 5 equiv. of diethylaluminum cyanide[7] under argon at 100° for 3 hrs. effects direct conversion to the corresponding cyanomethyl ethers.[8]

$$ROCH_2OCH_2CH_2OCH_3 + Et_2AlCN \longrightarrow ROCH_2CN$$

The cyanomethyl ethers show characteristic cyano peaks in the infrared at 2260 cm^{-1} and in the ^{13}C nmr spectrum at 116 ppm downfield from $CHCl_3$, as well as pmr peaks due to $OC\underline{H}_2CN$ in the range 4.2-4.35 δ. For MEM ethers of alcohols which are not very acid sensitive, e.g. cholesterol or menthol, yields of *ca.* 80% are generally attainable. Lower yields are observed for MEM ethers of alcohols (e.g. allylic or benzylic type) for which heterolysis ($ROMEM \rightarrow R^{\oplus}$) is more favorable. The MEM ethers of geraniol and cyclohexylvinylcarbinol were transformed into the corresponding cyanomethylethers in yields of 67 and 70%, respectively. Previously described routes to cyanomethyl ethers are longer and less efficient.[9] The reaction of MOM ethers with diethylaluminum cyanide is considerably slower than that for the corresponding MEM ethers and, consequently, not as useful.[10]

References and Notes

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2. E. J. Corey, J.-L. Gras and P.Ulrich, *Tetrahedron Letters*, 809 (1976).
3. A. Pelter, T. E. Levitt, K. Smith and A. Jones, *J. Chem. Soc.* Perkin I, 1672 (1977).
4. (a) D. R. Williams and S. Sakdarat, *Tetrahedron Letters*, **24**, 3965 (1983);

   (b) Y. Guindon, H. E. Morton and C. Yoakim, *ibid*, **24**, 3969 (1983).
5. We had noted in previous work that MEM ethers of simple alcohols (e.g. 4-*t*-butylcyclohexanol) are cleaved to the free alcohols in *ca*. 95% yield by treatment with 1 equiv. of boron tribromide in CH_2Cl_2 at -78° for 10 min. with a subsequent quench by aqueous bicarbonate.
6. E. J. Corey, B.-C. Pan, D. H. Hua and D. R. Deardorff, *J. Am. Chem. Soc.*, **104**, 6816 (1982).
7. Available from Alfa Products, Danvers, Ma.
8. The following general procedure was employed for the conversion of MEM to cyanomethyl ethers. The MEM ether (1.0 mmol) was azeotropically dried with toluene (30 ml) and then placed in a flame dried flask with 2.6 ml. of toluene under argon. A solution of diethylaluminum cyanide (2.4 M in toluene, 2.2 ml, 5.2 mmol, 5 equiv.) was added, the mixture was then heated to 100° C. for three hours, and quenched by the careful addition of a saturated sodium potassium tartrate solution (20 ml). Stirring was continued for 30 min, when the reaction was diluted with ether (150 ml) and transferred to a separatory funnel. Additional tartrate (20 ml) was added. The quenched reaction was allowed to stand until the aluminum emulsion clarified. The ether layer was then washed with water (20 ml) and dried over magnesium sulfate. Filtration, evaporation, and flash silica gel column chromatography (20% ether in petroleum ether) gave the pure cyano ethers. *Important note*: the workup steps were carried out in an efficient hood to avoid contact with any evolved hydrogen cyanide gas.
9. For an excellent summary see J. Schwindeman and P. D. Magnus, *Tetrahedron Letters*, **22**, 4925 (1981). This paper describes a two-step conversion of MTM ethers via sulfoxides to cyanomethyl ethers using trimethylsilyl cyanide-zinc iodide.
10. This research was assisted financially by a grant from the National Institutes of Health.

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