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OPPORTUNITIES FOR SELECTIVE REMOVAL OF METHOXYETHOXYMETHYL (MEM) ETHERS

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Summary: An investigation of the selective cleavage of β-methoxyethoxymethyl (MEM) ethers using 2-chloro-1,3,2-dithioborolan at -78°C is reported.

Since the introduction of the β-methoxyethoxymethyl (MEM) group as suitable protection for primary, secondary, and tertiary alcohols,[1] a number of analgous substituted methyl ethers have been devised. These include the *tert*-butoxymethyl ethers,[2] 2,2,2-trichloroethoxymethyl (TEM) ethers,[3] and more recently the β-(trimethylsilyl)ethoxymethyl (SEM) ethers.[4,5] These protecting units are stable to a wide variety of conditions including many organometallic reagents, reducing conditions, oxidizing agents and mild acids, and introduce no stereochemical ambiguities. In fact, difficulties, encountered in the cleavage of MEM ethers, have undoubtedly contributed to the development of additional protecting groups such as those described above. The widespread use of MEM ethers continues especially for multistep syntheses of functionally complex organic molecules (MEM-Cl is commercially available).

A number of reagents have been reported for cleavage of MEM ethers. Corey had utilized two sets of conditions; (a) anhydrous $ZnBr_2$ in Et_2O at room temperature, and (b) $TiCl_4$ in CH_2Cl_2 at 0°C. Subsequently MEM ethers have been cleaved by fluoroboric acid in CH_2Cl_2(0°C, 3h),[6] and in a two step process by treatment with n-BuLi (hexane at room temperature) followed by $Hg(OAc)_2$ in aqueous THF.[7]

We have explored opportunities for selective cleavage of MEM ethers in the presence of benzyl, silyl and tetrahydropyranyl ethers as well as acetals, ketals, acetates and benzoates, by use of the modified Lewis acid, 2-chloro-1,3,2-dithioborolan (1).[8] Our results are shown in Table I.[9] The reagent is a clear, colorless, distillable liquid prepared from addition of 1,2-ethanedithiol to boron trichloride at -78°C.

General Procedure: The MEM ether (1.0 mmol) was dissolved in methylene chloride, and the solution was cooled to -78°C under argon. Addition of freshly distilled 2-chloro-1,3,2-dithioborolan (1.2 to 2.0 mmol, see Table) via syringe with continuous stirring at -78°C resulted in MEM ether cleavage within one hour. Reactions were quenched at -78°C with saturated aqueous ammonium chloride followed by aqueous sodium hypochlorite (to oxidize sulfur by-products and remove stench). Upon warming to room temperature, the organic layer was separated, dried ($MgSO_4$), and concentrated. Products were isolated by preparative thin-layer or flash column chromatography (silica gel).

Thus far, our studies have found esters and benzyl, allyl and methyl ethers to be stable to these reaction conditions. Fujita and coworkers have previously reported the dealkylation of methyl and benzyl esters, as well as the cleavage of methyl ethers, using a mix of aluminum trichloride and ethanethiol.[10] Our procedure is also suitable for the deprotection to allylic alcohols and cyclopropylcarbinols (Entries 4 and 6). Common silyl ether protecting units such as *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl ethers are neither cleaved by the reagent, nor have we evidence of intermolecular silyl ether transfer (Entries 4,5 and 10). On the other hand, methoxymethyl ethers, acetonides and benzylidene acetals are cleaved at rates which are generally comparable to MEM ethers, whereas methylene acetals (Entries 2 and 3) survive very well.

Although generalizations are not possible, tetrahydropyranyl ethers remain intact in certain cases with the use of the reagent (Entries 7 and 12). A number of experiments suggest that secondary THP ethers are cleaved more slowly than most primary MEM ethers at -78°C.[11] In addition, it seems feasible to anticipate selective cleavage of primary MEM ethers in the presence of more hindered secondary and tertiary MEM ethers as observed in Entry 9 (chromatography also afforded 12% of the diol and 12% of starting material), and Entry 12.

TABLE I

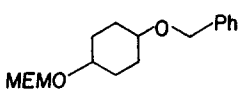
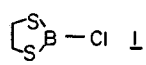
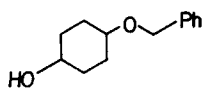
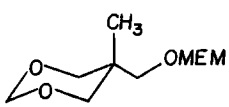
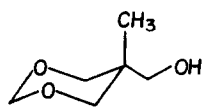
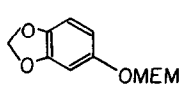
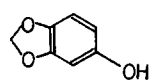
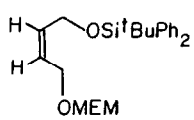
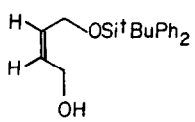
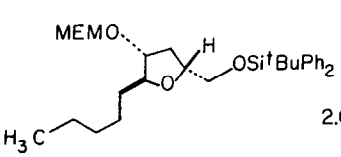
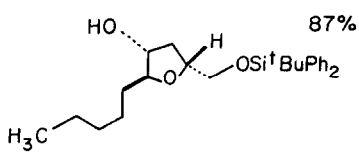
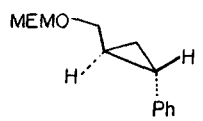
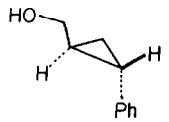
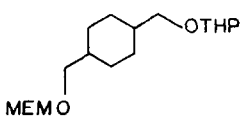
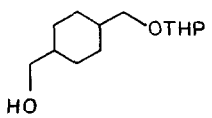
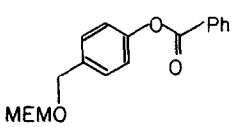
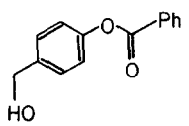
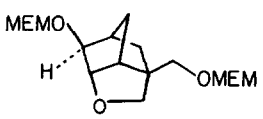
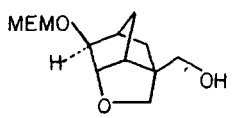
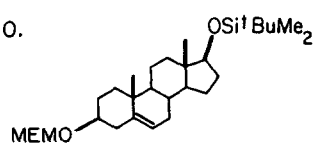
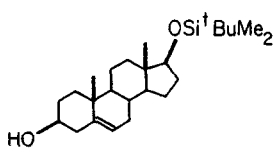
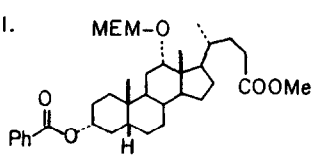
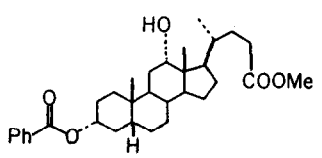
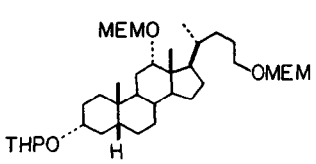
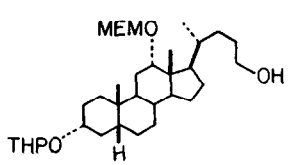
	Substrate	Conditions[a]	Product	Yield
1.		 2.0 equivs		91%
2.		1.2 equivs		86%
3.		1.2 equivs		94%
4.		2.0 equivs		90%
5.		2.0 equivs		87%

TABLE I (continued)

6.		1.2 equivs 1		91%
7.		1.2 equivs 1		89%
8.		2.0 equivs 1[(b)]		86%
9.		1.2 equivs 1[(c)]		72%
10.		2.0 equivs 1		91%
11.		2.0 equivs 1		93%
12.		2.0 equivs 1[(d)]		78%

(a) Reactions were conducted at -78°C for 45 min under argon.
(b) Stirring at -78°C for 1.5 h, then warming to 0°C and quench.
(c) A stock solution of 1 (.14 M in CH_2Cl_2) was added dropwise over 30 min with continued stirring at -78°C for 1 hour.
(d) A stock solution of 1 (.14 M in CH_2Cl_2) was added dropwise over 30 min with continued stirring at -110°C (in methylene chloride-pentane; 1:1 by volume).

Unfortunately, in circumstances for selective dealkylation of 1,2 and 1,3 diol derivatives, we find that even allyl and benzyl ethers are often removed along with the neighboring MEM ether as a result of proximate intramolecular coordination of the Lewis acid.[12] Although the exact mode of cleavage is not clear, the use of chlorodiphenylthioborane often afforded some production of ether exchange, yielding the corresponding phenylthiomethyl ethers along with the parent alcohols. Triphenylthioborane, itself, was totally ineffective.

Further improvements in selectivity may be achieved using similar reagents, thus encouraging the utility of MEM ethers as blocking units in the synthesis of complex natural products.

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9. All yields are reported for purified samples, characterized by infrared, nuclear magnetic resonance and mass spectral data. The 'H-NMR and ^{13}C-spectra were recorded on 220 MHz and 360 MHz instruments in $CDCl_3$ (0.1% Me_4Si) solutions.
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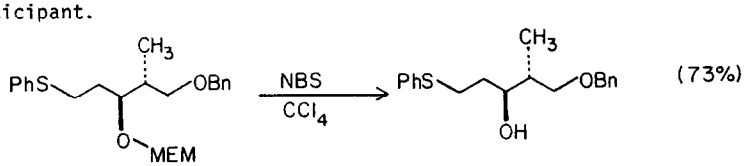
11. The use of freshly distilled reagent is imperative in these cases, as adventitious moisture obtained in storage generates hydrogen chloride.
12. In these more difficult situations, the oxidative removal of MEM ethers may be feasible. A striking example is illustrated below, although the neighboring phenylsulfide may be an important participant.



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