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A NEW GENERAL METHOD FOR PROTECTION OF THE HYDROXYL FUNCTION

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Recent studies in this laboratory have resulted in several useful new methods for protection/deprotection of hydroxyl groups including those involving t-butyldimethylsilyl (TBDMS) (removed by F^- or HOAc-H_2O)[1], tribenzylsilyl[2], allyl (removed by Rh(I) followed by H_2O-Hg^{++})[3], and methylthiomethyl[4] (MTM) (removed by Ag^+) groups.[5] These methods are complementary to one another and also to more established techniques based on acetate, benzoate, β,β,β-trichloroethyl ether, benzyl ether, tetrahydropyranyl ether (THP) and other groups. We describe herein techniques for application to synthesis of a new protecting group, the β-methoxyethoxymethyl (MEM) group, which in our opinion will prove to be of value in a wide variety of synthetic processes.

$$CH_3OCH_2CH_2OCH_2- = MEM$$

Two methods have been developed for the introduction of the MEM group. These are suitable for primary, secondary, or tertiary alcohols. One entails the use of aprotic-basic conditions and the other involves aprotic-neutral conditions. Removal of the MEM group can be accomplished under aprotic conditions under the influence of a mild Lewis acid, specifically either zinc bromide or titanium tetrachloride.

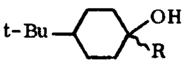
MEM ethers are stable under a wide variety of conditions including those attending the use of strong bases, reducing agents, organometallic reagents, many oxidizing agents and mild acids. Selective cleavage of MEM ethers is possible in the presence of acetates, benzoates, benzyl, allyl, THP, TBDMS, trichloroethyl or MTM ethers. Conversely any of these protecting units may be cleaved selectively in the presence of a MEM ether. Since the MEM group is devoid of chirality, its use introduces no stereochemical complications, an important factor with complex molecules.

One reagent for formation of MEM ethers is MEM chloride (1), which is easily made on either small or large scale. Thus 152 g of methoxyethanol and 66 g of s-trioxane are treated with dry HCl in a steady stream with stirring until the reaction mixture becomes clear, at which time it is diluted with pentane (900 ml) and dried (3 hr at 5° over 100 g of $MgSO_4$). Evaporation of pentane leaves MEM chloride in 90% yield (pure by pmr and infrared analysis).

Reaction of MEM chloride in ether with 1.3 equiv of triethylamine at 25° for 16 hr affords the colorless, crystalline ammonium salt 2 ($MEMNEt_3^+\ Cl^-$)[6] which is obtained pure in ca. 80% yield simply by filtration and drying *in vacuo*. The salt 2, m.p. 58-61°, is stable when kept in a sealed container, but must be protected from atmospheric moisture. It is an excellent reagent for the conversion of alcohols to MEM ethers in base-sensitive substrates.

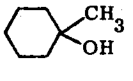
$$CH_3OCH_2CH_2OH \xrightarrow[HCl]{(CH_2O)_3} \underset{1}{CH_3OCH_2CH_2OCH_2Cl} \xrightarrow{Et_3N} \underset{2}{CH_3OCH_2CH_2OCH_2\overset{+}{N}Et_3Cl^-}$$

The formation of MEM ethers using MEM chloride has been effected by reaction of the chloride (usually 1.2 equiv) with either the sodio (from NaH) or lithio (from N-butyllithium) derivative of the alcohol to be protected in tetrahydrofuran (THF) or dimethoxyethane (DME) as solvent at 0° (under an inert atmosphere). The etherification reaction under these conditions is fast[7] and typically reaction times of 10-20 min suffice for unhindered primary and secondary alcohols and 30-60 min for tertiary or hindered alcohols (4, 5, 6, 7, 9, 10). The yield of MEM ether obtained with each of the substrates listed below (3-11) was greater than 95%.[8] The course of these reactions is easily followed by thin layer chromatographic (tlc) analysis.



(cis and trans)

3, R = H
4, R = CH_3



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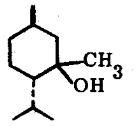

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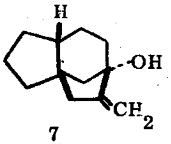

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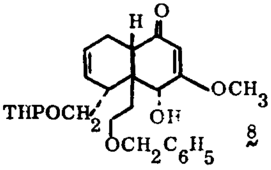

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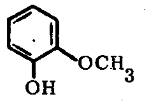

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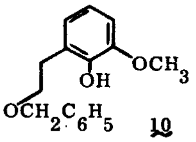

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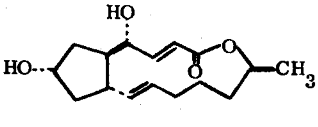


11

The conversion of alcohols to MEM ethers using the triethylammonium reagent 2 can be accomplished (under neutral conditions) simply by heating in dry acetonitrile solution at reflux. The reaction, which is conveniently monitored by tlc, is complete within 30 min for secondary alcohols such as 3 and 3 and yields are generally high (>90%). The by-product, triethylammonium chloride, is easily removed by either aqueous or non-aqueous workup.

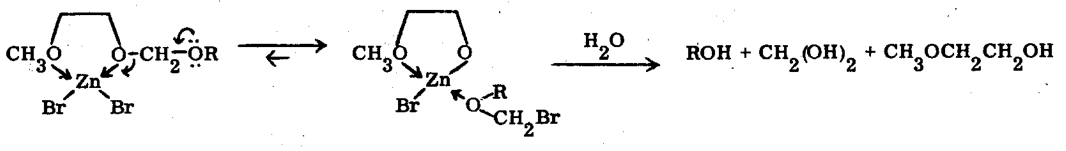
Finally MEM ethers may also be obtained in high yield from the reaction of MEM chloride and an alcohol in the presence of diisopropylethylamine. Thus, reaction of 4 with 1.5 equiv of MEM chloride and 1.5 equiv of the tertiary amine in methylene chloride (10 ml/g of 1) at 25° for 3 hr afforded quantitatively the MEM ether.

The cleavage of MEM ethers to form the corresponding alcohols is best effected in most cases by reaction of the ether in methylene chloride (ca. 2 ml/mmole of ether) with 5 equiv of finely powdered, anhydrous zinc bromide with efficient stirring at 25°. Isolation of deprotected alcohol is carried out by washing the reaction mixture successively with sat. sodium bicarbonate solution and brine, extraction of the aqueous washings with ether, combination of the organic extracts, and concentration after drying ($MgSO_4$). The cleavage reactions are also readily monitored by tlc analysis. The following data were obtained for the various substrates listed above (time of cleavage, yield): 3 (8 hr, 92%); 4 (8 hr, 90%); 5 (8 hr, 90%); 6 (5 hr, 90%); 7 (10 hr, 93%);

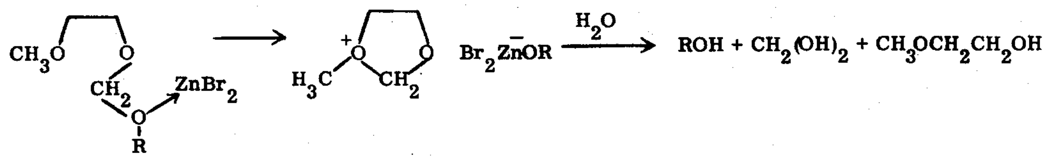
9 (5 hr, >90%); **10** (2 hr, >90%). In the case of the bis MEM derivative of **11** (the bis MEM ether of brefeldin A) the zinc bromide-promoted cleavage was not clean,[9] however, cleavage of the ether to brefeldin A occurred smoothly (*ca.* 95% yield) using excess titanium tetrachloride (*ca.* 10 equiv) at 0° for 20 min. Of course, less complex MEM ethers are also cleaved rapidly by titanium tetrachloride; for example, 4-*t*-butylcyclohexanol (**3**) was obtained (90%) from the MEM ether by exposure to 3 equiv of titanium tetrachloride in 2:1 methylene chloride-pentane at 0° for 30 min followed by quenching with conc. ammonium hydroxide and extractive workup.

Other Lewis acids studied, but found to be less effective for MEM ether cleavage than zinc bromide or titanium tetrachloride include ZnI_2, $ZnCl_2$, $SnBr_4$, $SnCl_4$, $ZrCl_4$, $MgCl_2$ and $MgBr_2$.

The rationale which led to the study of the MEM group for hydroxyl protection was based on the alternative hypotheses, 1) that bidentate coordination of the MEM group to a Lewis acid should markedly facilitate the cleavage of MEM ethers as indicated (for $ZnBr_2$) in equation **A**, or 2) that ready cleavage might occur by equation **B**.



A



Although the exact mode of cleavage is not yet clear, it is hoped that clarification of the mechanism will be obtained by future studies. It should be noted here that the cleavage of *methoxymethyl* ethers under aprotic conditions in the presence of $ZnBr_2$ or $TiCl_4$ is markedly slower than the reaction for the corresponding MEM ethers. The cyclic oxonium ion intermediate shown in equation **B** may be involved in the formation of MEM ethers from alcohols, the rates of which are also considerably faster than for methoxymethyl ether formation.

THP, TBDMS and other silyl groups are readily and selectively cleaved in the presence of MEM ethers; effective conditions for such selective deprotection include the use of 0.05 equiv of anhydrous *p*-toluenesulfoni acid in methanol at 23-25° for 3 hr (MEM ethers are unaffected even after 15 hr under these conditions), or 3:1 acetic acid-water at 35° for 4 hr. Obviously there is no difficulty (see ref. 5) in the removal of acetyl, benzoyl, benzyl, allyl, TBDMS, MTM, β,β,β-trichloroethyl or β-chloroethyl groups from hydroxylic oxygen in the presence of the MEM ether unit. The MEM group is recommended as a candidate for inclusion in the list of "standard" protecting groups for the hydroxyl function.[10]

References and Notes

1. E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972). See also E. J. Corey and R. K. Varma, *ibid.*, **93**, 7319 (1971) for isopropyldimethylsilyl.
2. E. J. Corey and H. E. Ensley, *J. Org. Chem.*, **38**, 3187 (1973).
3. E. J. Corey and J. W. Suggs, *ibid.*, **38**, 3224 (1973); see also *idem.*, *Tetrahedron Letters*, 3775 (1975).
4. E. J. Corey and M. G. Bock, *Tetrahedron Letters*, 3269 (1975).
5. For a review on functional group protection, see J. F. W. McOmie, "Protective Groups in Organic Chemistry," Plenum Press, London, 1973.
6. Dropwise addition of MEM chloride in ether to a well-stirred solution of triethylamine in a little ether containing seeds of **2** was found to facilitate smooth formation of crystalline product.
7. Formation of MEM ethers from MEM chloride typically proceeds several times faster than the corresponding reaction of methoxymethyl chloride with an alkoxide to give methoxymethyl ethers. In addition, the formation of MEM ethers of tertiary or hindered alcohols is cleaner and more efficient than formation of the corresponding methoxymethyl ethers.
8. Satisfactory spectral data have been obtained on all MEM ethers reported herein and in addition most have been converted back to the corresponding alcohols.
9. The data on the brefeldin A case were obtained by Mr. R. H. Wollenberg in these laboratories as part of a program on total synthesis, and will be reported later in more detail.
10. This research was assisted financially by a grant from the National Science Foundation.