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A Highly Efficient, Mild, and Selective Cleavage of β-Methoxyethoxymethyl (MEM) Ethers by Cerium(III) Chloride in Acetonitrile[†]

Gowravaram Sabitha,* R. Satheesh Babu, M. Rajkumar, R. Srividya, and J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500007, India

sabitha@iict.ap.nic.in

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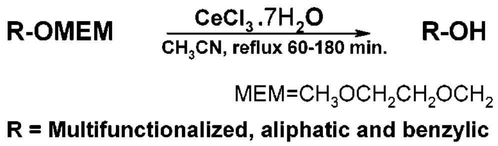
ABSTRACT



A highly selective cleavage of MEM ethers has been achieved in high yields using $CeCl_3{\cdot}7H_2O$ in refluxing acetonitrile under mild and neutral reaction conditions. The method is very rapid and compatible with other hydroxyl protecting groups such as Bn, TBDPS, Ac, Me, Tr, PMB, benzylidene, THP, MOM, BOM, and NHAc present in the substrate.

The selective protection and deprotection of hydroxyl groups has occupied a unique position on the stage of chemical synthesis[1] because of the fundamental importance of hydroxyl groups and their role in multistep synthesis of complex natural products. In recent years the β-methoxyethoxymethyl (MEM) group has been introduced as a suitable protection for alcohols in organic synthesis.[2] This protecting group provides a number of significant advantages such as ease of introduction and stability toward a wide variety of conditions including many organometallic reagents, reducing conditions, and oxidizing agents and introduces no stereochemical ambiguities. Even though MEM ethers are widely used in a multistep synthesis of functionally complex organic molecules, difficulties are encountered in its cleavage. As a consequence, several reagents have been introduced in order to facilitate the cleavage of MEM ethers. These include the use of anhydrous $ZnBr_2$,[3] $TiCl_4$,[3] fluoroboric acid,[4] and *n*-BuLi followed by treatment with mercuric acetate.[5] Alternatively, two boron reagents[6,7] and TMSCl/NaI[8] have been reported for MEM group removal. Many of these methods suffer from some drawbacks, which include use of toxic and/or hazardous materials,[5] strongly acidic conditions, unsatisfactory yields,[4] expensive reagents,[6,7] longer reaction times, lack of selectivity,[7] and necessity of anhydrous conditions.[3] In this context there is a need to develop a mild and efficient method for the selective cleavage of MEM ethers in the presence of acid-sensitive protecting groups. Recently, cerium(III) chloride has been used for several regio- and chemoselective transformations,[9] since this compound is a very cheap and water-tolerant reagent.[10] The activity of $CeCl_3$ was increased in combination with NaI.[11]

Herein, we report an exceedingly mild and efficient protocol (Scheme 1) for the cleavage of MEM ethers by using cerium(III) chloride heptahydrate in refluxing aceto-

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[†] IICT Communication 4709.

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Scheme 1

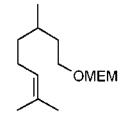
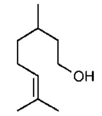
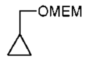
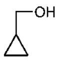
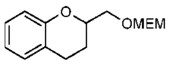
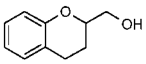
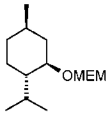
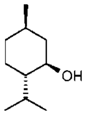
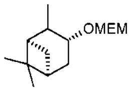
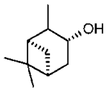
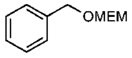
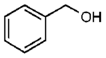
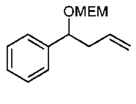
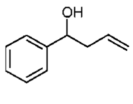
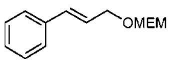
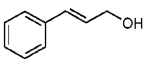
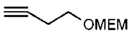
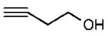
$$\text{R-OMEM} \xrightarrow[\text{CH}_3\text{CN, reflux 60-180 min.}]{\text{CeCl}_3\text{.7H}_2\text{O}} \text{R-OH}$$

$\text{MEM=CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2$

R = Multifunctionalized, aliphatic and benzylic

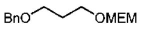
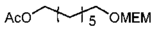
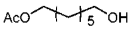
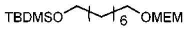
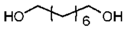
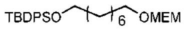
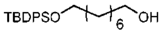
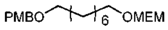
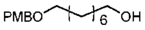
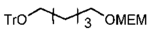
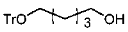
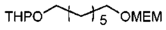
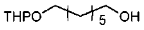
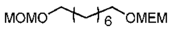
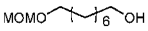
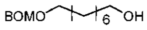
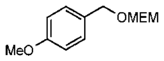
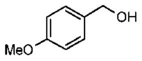
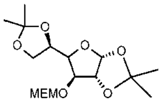
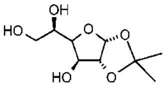
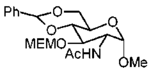
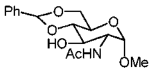
nitrile.[12] As a typical example, the MEM ether **1a** (Table 1) was deprotected smoothly to the parent alcohol **2a** in 1 h using 0.5 equiv of $CeCl_3{\cdot}7H_2O$ in refluxing acetonitrile. The rate of this reaction was slightly improved by adding 0.6 equiv of NaI, and the desired citronellol was obtained in 45 min. With respect to the other acid sensitive protecting groups, $CeCl_3{\cdot}7H_2O$ is better suited than the $CeCl_3{\cdot}7H_2O$/NaI system. We have also investigated the possibility of $CeCl_3{\cdot}7H_2O$ functioning catalytically or, at least, in less than stoichiometric amounts. But high yields of deprotected alcohols are found in $[CeCl_3{\cdot}7H_2O]/[substrate]$ ratios 0.5/1. Using this procedure the MEM ethers were selectively cleaved, giving the corresponding parent alcohols in high yields without affecting the other functional groups. In terms of selectivity and efficiency, this mild deprotecting protocol is superior to other conventional methods, where Lewis acids such as $AlCl_3$/ethanethiol[13] and TMSCl/NaI[8] are used. These two reagents sequentially remove the MEM ether and the methyl ether, whereas methyl ether survives under the present reaction conditions. The major drawback of the method using TMSCl/NaI is a significant formation of the corresponding iodides as byproducts from the MEM ethers derived from allylic and benzylic alcohols. But under the present reaction conditions, when MEM ethers of benzylic and allylic alcohols (Table 1, entries 1f and 1h; Table 2, entry 1j) were deprotected, only the desired alcohols were obtained in quantitative yields, with no trace of chlorinated compounds

Table 1. Cleavage of MEM Ethers Using $CeCl_3{\cdot}7H_2O$

Entry	MEM Ether **1**	Product [a] **2**	Reaction time min	Yield [b] %
a			60	96
b			60	95
c			60	97
d			90	94
e			90	91
f			180	98
g			180	95
h			90	94
i			90	90

[a] All products were identified by their IR, NMR, and mass spectra. [b] Yields of products isolated by column chromatography.

Table 2. Selective Cleavage of MEM Ethers Using $CeCl_3{\cdot}7H_2O$

Entry	MEM Ether **1**	Product [a] **2**	Reaction time min	Yield [b] %
a			60	97
b			60	95
c			60	92
d			60	96
e			60	94
f			60	92
g			60	95
h			60	94
i			60	92
j			180	94
k			90	94[c]
l			180	92

[a] All products were identified by their IR, NMR, and mass spectra. [b] Yields of products isolated by column chromatography. [c] Primary isopropylidene group was cleaved.

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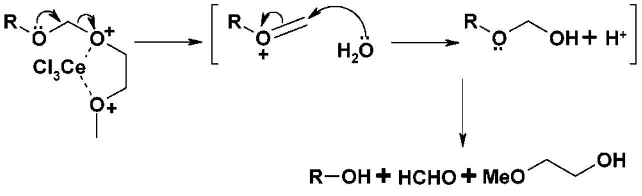
isolated. There was no substantial difference observed for the deprotection of MEM-protected primary and secondary alcohols. The major usefulness of this deprotection is in the selective cleavage of MEM ethers in the presence of highly acid sensitive tetrahydropyranyl (THP) ethers and other formaldehyde protecting groups such as methoxymethyl (MOM) and benzyloxymethyl (BOM) ethers. Tables 1 and 2 illustrates the scope of this deprotection method, and in all cases, the yields are excellent. It should be emphasized that a number of functional groups, which are capable of reacting with this reagent, survive intact due to the shorter reaction times required for this transformation. Thus, a number of other hydroxyl protecting groups such as Bn, PMB, Tr, Ac, Me, TBDPS, and NHAc also survived under the present reaction conditions. The limitation of the present method is that the *tert*-butyldimethylsilyl (TBDMS) ether group has not survived under the present reaction conditions (Table 2, entry 1c). Even though the primary isopropylidene group was cleaved, the secondary isopropylidene and benzylidene groups and the glycosidic bonds remained intact in the cleavage of MEM ethers in carbohydrate derivatives (Table 2, entries 1k and 1l). Further the compatibility of the reagent is illustrated by the selective deprotection of MEM group without affecting cyclopropyl, olefinic, and acetylenic systems. Optical integrity was intact when chiral MEM ethers were deprotected (Table 1, entries 2d and 2e; Table 2, entries 2k and 2l). There are many advantages to the use of cerium(III) chloride heptahydrate in acetonitrile when no strongly basic or acidic conditions are used and expensive reagents are not required, and no precautions need to be taken to exclude moisture or oxygen from the reaction system. Hence, the present protocol is efficient and mild and tolerates a wide range of functional groups. Such selectivity is a highly desirable feature in diversity-oriented synthesis.

For the mechanism of the deprotection of MEM ethers, Scheme 2 illustrates a proposed pathway for the reaction.

Scheme 2



We believe that the cleavage of the MEM ether proceeds by a mechanism similar to that described for the conversion of dioxolanes to carbonyl compounds.[11d] Cerium(III) chloride would coordinate with the oxygen of MEM ether to form a complex which gives an intermediate and methoxyethanol. The presence of water in the reaction medium facilitates easily the deprotection by attacking the intermediate, yielding the parent alcohol and formaldehyde.

In conclusion, we have described a novel and chemoselective method for the cleavage of MEM ethers using $CeCl_3{\cdot}7H_2O$ in refluxing acetonitrile under mild and neutral reaction conditions. The advantages of the present protocol are the shorter reaction times, the simplicity in operation, the low cost of the reagent, and the high yields of deprotected products. Further, its compatibility with sensitive functionalities and with regard to economic and ecological considerations of the $CeCl_3{\cdot}7H_2O$ allows us to believe that this procedure may represent a valuable alternative to the existing reagents reported in the literature.

Acknowledgment. R.S.B., M.R., and R.S. thank CSIR, New Delhi for the award of fellowships.

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(12) **General Procedure:** A mixture of MEM ether (1 mmol) and $CeCl_3{\cdot}7H_2O$ (0.5 mmol) in acetonitrile (5 mL) was stirred at reflux temperature for a specified time as required to complete the reaction (Table 1, 2). After completion as indicated by TLC, the reaction mixture was extracted with ethyl acetate, and the combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel (eluent: hexane/ethyl acetate) to provide the pure alcohol.

(13) Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, 46, 1991. (b) Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97.