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REMOVAL OF METHOXYETHOXYMETHYL ETHERS WITH TRIMETHYLSILYL CHLORIDE-SODIUM IODIDE

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Summary: Trimethylsilyl chloride-sodium iodide has been used for the mild removal of methoxyethoxymethyl ethers.

In recent years the 2-methoxyethoxymethyl (MEM) group has emerged as an important protecting group for alcohols in synthesis.[1,2] Although this group provides a number of significant advantages as a means of functional group protection, such as ease of introduction and stability toward many commonly encountered reaction conditions, it can occasionally present some difficulties in terms of removal. As a consequence, several methods have been developed in order to facilitate MEM ether cleavage. These procedures include the use of anhydrous $ZnBr_2$ or $TiCl_4$[1] for selective MEM group removal in the presence of a number of other protecting groups. Fluoboric acid[3] and n-butyllithium followed by treatment with mercuric acetate have also proven to be effective in some cases.[4] More recently, two boron reagents have been reported to offer mild and selective means for achieving MEM group removal.[5,6]

In this letter we wish to report that trimethylsilyl chloride-sodium iodide in acetonitrile can efficiently cleave MEM ethers to the corresponding parent alcohols in excellent yields. In a typical experiment, 1 eq of sodium iodide and 1 eq of trimethylsilyl chloride were added to a 0.1 M solution of the MEM ether in dry acetonitrile at -20° C.[7] After stirring at this temperature for 15-20 min, an additional equivalent of both NaI and TMSCl was added and the mixture stirred at -20° C until no starting material remained (TLC analysis).[8] The yellow-orange mixture was quenched with either methanol or water and the acetonitrile removed in vacuo. The residue was extracted with ethyl acetate and the organic layer washed with saturated sodium thiosulfate and brine. The crude alcohols were purified by column chromatography.

For many substrates the reaction can also be run at room temperature quite effectively. For example, Entry 1 (Table I) was treated at room temperature with 6 eq of TMSCl/NaI for 2-3 hr. The MEM ether and the methyl ether were removed sequentially under these conditions without affecting the lactone.

Table I illustrates the scope and limitations of this deprotection scheme. It is particularly noteworthy that a number of functional groups, which are capable of reacting with iodotrimethylsilane-type reagents, survive this process intact.[9] Using this procedure, MEM ethers can be selectively removed in the presence of certain lactones, methyl ethers, methyl esters and benzyl ethers. Select acetals are also stable to the reaction conditions as

TABLE I

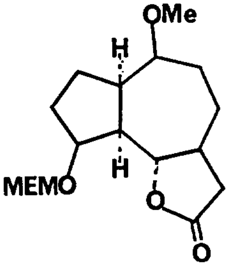
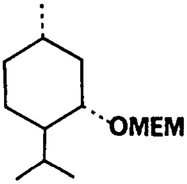
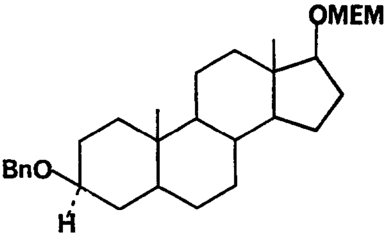
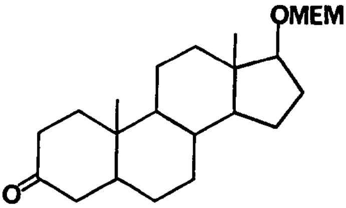
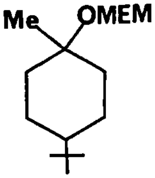
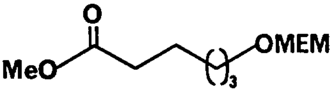
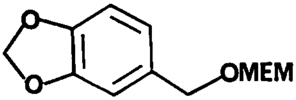
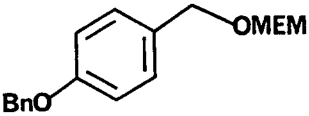
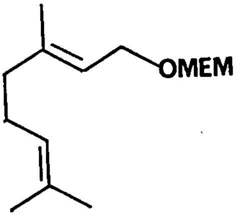
Entry	Substrate[a]	Method[b]	Time(min)	Yield of Alcohol[a,c]
1.		A	30	79%
2.		A	30	93%
3.		A	30	96%
4.		A	45	95%

TABLE I
(continued)

Entry	Substrate[a]	Method[b]	Time(min)	Yield of Alcohol[a,c]
5.		A B	20 5	81% 57%[d]
6.		A	30	95%
7.		A	150	71%[d]
8.		A B	90 30	47%[d] 11%[d]
9.		A	40	44%[d]

a) All new compounds gave satisfactory ^{1}H NMR, IR, and mass spectral data.

b) Method A: NaI/TMSCl in CH_3CN, -20° C; Method B: $TMSI/CH_2Cl_2$, -78° C.

c) Yields are for purified products.

d) A substantial amount of the corresponding iodide was isolated.

evidenced by Entry 7. However, it appears that in the substrates examined no selectivity in the cleavage rates of THP groups compared with MEM groups or 1,3-dioxolanes and MEM groups could be discerned. In addition, there was no substantial difference observed in competition between removing MEM groups on primary and secondary alcohols.

Significant formation of the corresponding iodides occurred only with substrates in which the MEM ether was derived from an allylic or benzylic alcohol (entries 7, 8, 9). A small amount of an iodide (~8%) was also isolated in the tertiary alcohol case, Entry 5. The poorest examples in terms of alcohol yield using the TMSCl/NaI conditions was Entry 9 in which a 44% yield of the alcohol was obtained accompanied by 50% of the corresponding iodide. It is interesting to note that in every case in which comparative studies were performed, TMSCl/NaI was superior to commercial iodotrimethylsilane for converting MEM ethers into alcohols (see Entries 5 and 8). For example, the MEM ether of benzyloxybenzyl alcohol (Entry 8) yielded 60% of the corresponding iodide and only 11% of the desired alcohol on treatment with iodotrimethylsilane at -78° C in methylene chloride while substantially less iodide (20%) was observed in this system using TMSCl/NaI.[10]

It is apparent from the examples illustrated here that TMSCl/NaI can be an effective, reasonably selective, and most importantly, convenient reagent for the removal of MEM ether protecting groups in a wide range of circumstances.

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7. All reagents and solvents were freshly purified although in some cases using materials without prior purification resulted in only slightly diminished yields.
8. It appears that two full equivalents of TMSCl/NaI are required for complete reaction. In many cases, both equivalents can be added at the beginning of the reaction without lowering the yield of alcohol, however, in sensitive substrates slightly lower yields may result due to iodide formation.
9. For an extensive review of iodotrimethylsilane chemistry, see: G. A. Olah, S. C. Narang Tetrahedron 38, 2225 (1982).
10. The iodide and alcohol isolated in this reaction retained the benzyloxy group.

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