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MILD CLEAVAGE OF METHOXYMETHYL (MOM) ETHERS WITH TRIMETHYLSILYL BROMIDE

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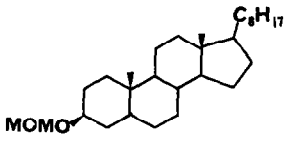
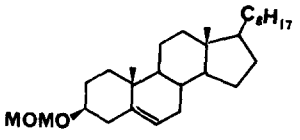
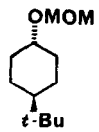
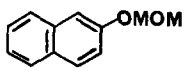
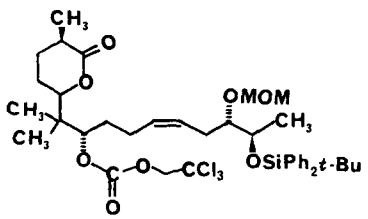
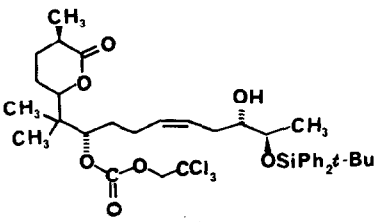
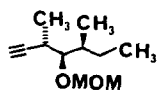
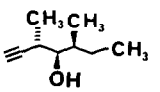
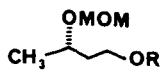
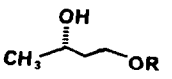
Summary. Trimethylsilyl bromide is an effective reagent for the deprotection of methoxymethyl ethers under mild conditions.

Since its introduction, the O-methoxymethyl (O-MOM) group has had widespread utility in synthetic organic practice[1]. Various procedures are reported for the regeneration of the hydroxyl group from MOM ethers, some of which are quite drastic and incompatible with the presence of other groups. Note for example the use of 6M aq. hydrochloric acid in THF (50°, 6-8h)[2]; conc. hydrochloric acid (cat.) in methanol at 60°[3] benzenethiol and $BF_3.Et_2O$,[4] trityl fluoroborate in CH_2Cl_2,[5]; aq. trifluoroacetic acid in THF[6]; anh. HCl (gas) in acetonitrile at 0°[7], etc. Recently, Guindon and coworkers[8] have found dimethyl boron bromide to be an efficient reagent for the cleavage of MEM, MOM and MTM ethers.

Expanding the repertoire of mild and often selective acetal and ether cleavage reagents is not without its merit particularly in view of the problem of functional group compatibility in organic synthesis. We required the selective removal of the O-MOM protecting group from an intermediate (entry 5, Table 1) obtained during synthetic studies related to boromycin[9], and we became intrigued by a reagent combination (trimethylsilyl chloride/n-Bu_4N Br, CH_2Cl_2, 0°) which was used by Woodward and coworkers[10] to deprotect a MOM ether in an advanced intermediate in their total synthesis of erythronolide A. Their conditions were too mild to effect complete cleavage of the MOM ether in our case, hence we decided to further explore the merits of organosilicon reagents in this type of cleavage.[11]

We wish to report that the commercially available trimethylsilyl bromide in dichloromethane cleaves MOM ethers at low temperature as shown in the examples in Table 1. A variety of functional groups (esters, methyl and benzyl ethers, t-butyldiphenylsilyl ethers[12], amides etc.) were found to be stable under the conditions of the cleavage even in the presence of excess reagent[13] and selective cleavage of the

TABLE 1 MOM ether	Time/temp.	Product/yield
 1	9h, 0	dihydrocholesterol 90 %
 2	12h, 0	cholesterol 91 %
 3	25min, -30	4-t-butylcyclohexanol 97 %
 4	7h, -30	-naphthol 80 %
 5	25min, -30	 88 %
 6	1.5h, -30	 97 %
 7,8;R = benzyl t-butyldiphenylsilyl	1.5h, -30	 95 %

MOM group could be effected. Interestingly, practically no bromide formation[14] was observed which indicates the propensity for MOM cleavage presumably via the intermediacy of oxonium ions rather than the O-TMSi ethers. It is well known that such oxonium species are formed in the presence of strong oxygenophilic reagents containing silicon[4,15,16]. Upon addition of triethylamine to the reaction mixtures, the corresponding O-trimethylsilyl ethers were quantitatively formed. This was also the case when the experiment was done in the presence of triethylamine and benzenethiol. No exchange of the MOM ether to the corresponding phenylthiomethyl ether was observed.[8] This may reflect on the presence of an O-silylated oxonium ion species which undergoes oxygen-assisted C-O bond cleavage to release the O-silyl ether. Isopropylidene acetals, O-tetrahydropyranyl, trityl and t-butyldimethylsilyl ethers were also cleaved during the deprotection of MOM ethers although in some cases these were cleaved preferentially. Thus trimethylsilyl bromide is a mild and effective reagent for the cleavage of MOM ethers, as well as acetals and trityl ethers, and it complements the well known trimethylsilyl iodide, which cleaves a variety of functional groups[1,11,15,17], including MOM, methyl, benzyl and related ethers, esters, etc., hence its lack of selectivity in some cases.

General formation of methoxymethyl ethers

The general procedure described by Stork and Takahashi[18] was used with some modification. A representative case is given. 4-tert-butylcyclohexanol (1g, 6.4 mmoles) was dissolved in dichloromethane (15ml), diisopropylethylamine (1.8 mL, 12.8 mmoles) was added, the solution was treated with chloromethylmethyl ether (0.73 ml, 9.6 mmoles) at room temperature then stirred for 12-18h. The reaction mixture was diluted with dichloromethane and washed successively with 10% aq. hydrochloric acid, saturated sodium bicarbonate and finally with brine. Drying over anhydrous magnesium sulfate and evaporation gave the methoxymethyl derivative as a chromatographically[19] homogeneous oil (1.2g, 94%). The MOM ethers of dihydrocholesterol, m.p. 64-65°; $[\alpha]_D$ + 18.5° ($CHCl_3$) and cholesterol, m.p. 81-82°; $[\alpha]_D$ - 37.1° ($CHCl_3$) were similarly prepared. The other entries in Table 1 were oils.

General procedure for the cleavage of the O-methoxymethyl ether group.

To a cooled solution (-30°) of β-dihydrocholesterol methoxymethyl ether (309 mg, 0.71 mmole) in 5ml of dichloromethane containing 4Å molecular sieves was added (375 μL, 2.8 mmoles, 4 equiv.) of trimethylsilyl bromide. The solution was stirred for 1h at

-30°C then 8-9h at 0°C. The reaction mixture was poured into a solution of saturated sodium bicarbonate, then extracted with ether, dried over anhydrous magnesium sulfate, evaporated and the residue was chromatographed[19] to give β-dihydrocholesterol (251 mg, 90%), m.p. 139-141° (acetone), identical in all respects with an authentic sample (m.p., NMR).

Acknowledgements

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