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DEPROTECTION OF 'SEM' ETHERS: A CONVENIENT, GENERAL PROCEDURE

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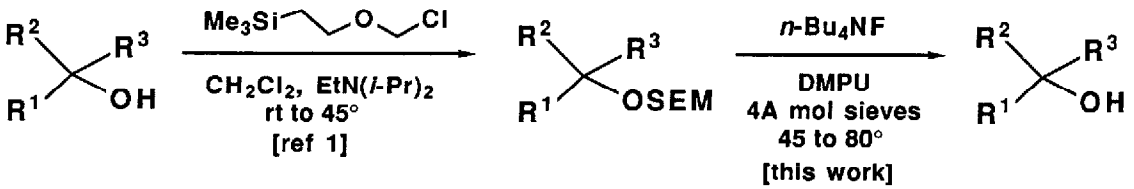
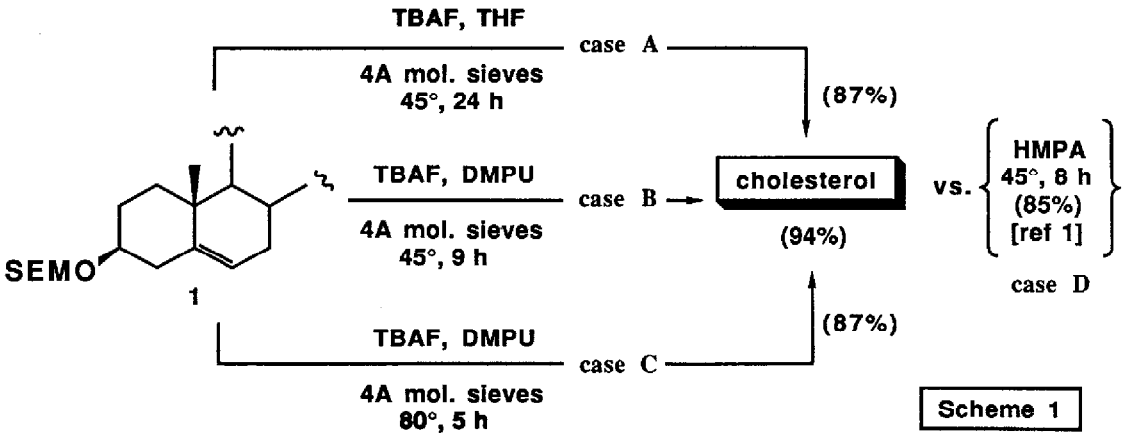
Summary: A new set of standard conditions for removal of SEM ethers is described.

Since introducing β-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) as a new hydroxyl protecting group about a decade ago,[1] it now seems reasonable for us to say that it has become a fairly routinely used reagent. The basic concept associated with the SEM moiety has also been extended to include this group's use for protection of both basic nitrogen[2] as well as the anomeric center in various pyranosides.[3] While formation of SEM ethers occurs quite smoothly, their removal has at times been problematic.[4,5] In light of these occurrences, we describe herein new conditions which seem to be general and efficient for SEM ether cleavage which are especially applicable to protected tertiary alcohols.

In essence, the procedure combines the virtues of (1) using a commercially available source of fluoride [n-Bu_4NF (TBAF) in THF]; (2) substituting N,N'-dimethylpropyleneurea (DMPU) for HMPA without noticeable decreases in rates of deprotections; (3) the presence of molecular sieves in the medium.[5]



Based on our original report,[1] TBAF in THF is usually acceptable in cases of secondary alcohol SEM unmasking. With, e.g., cholesterol SEM ether (1), use of TBAF in THF (case A, Scheme 1) requires 24h at 45° to consume educt. At this temperature but in DMPU (case B), the reaction is over in 9h. Increasing the temperature to 80° decreases the time still further (case C). By way of comparison, use of HMPA as solvent at 45°, as noted previously,[1] affords roughly comparable results (case D).



Scheme 1

Sterically more demanding tertiary alcohol SEM ethers were studied in some detail. Table I illustrates the variously functionalized substrates chosen, all of which were treated according to the "typical" procedure provided (vide infra). What is evident from these data is that both the time and temperature required for complete consumption of educt is quite substrate dependent. Ether 2, also investigated by Shirahama,[5] is highly prone to SEM removal at room temperature, while acyclic cases (entries 2-3) tend to unravel at 80° in a few hours. SEM ethers of especially hindered cases (entry 4) or cycloalkanols (entries 5-8), however, require longer reaction times.

The importance of 4Å molecular sieves (crushed, activated) in these reactions, as noted previously in HMPA,[5] was clear from treatment of 2 to afford mostly starting material after 15h, while an 84% yield of 3b was realized with the sieves present. Perhaps more intriguing is the observation that while use of molecular sieves did dramatically affect the rates of SEM removal in DMPU, they did not alter the nature of the reaction course, as seen with HMPA as solvent.[5] That is, essentially none of the solely desilylated material 3c is formed in DMPU.

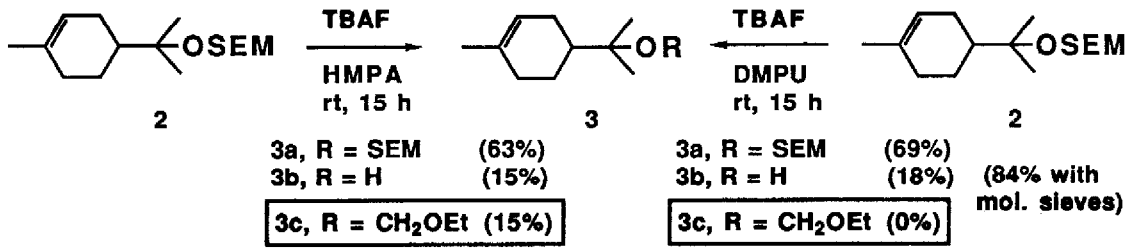
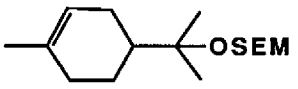
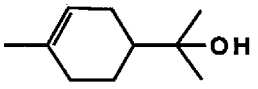
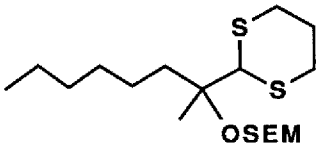
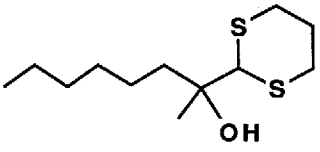
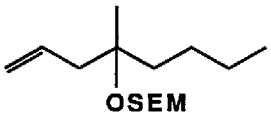
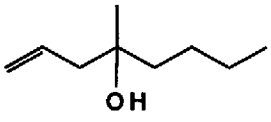
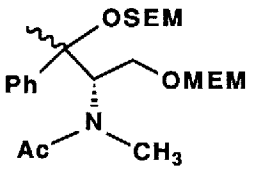
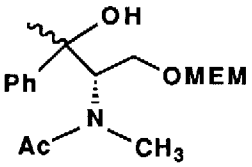
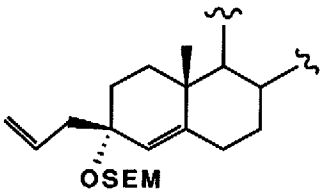
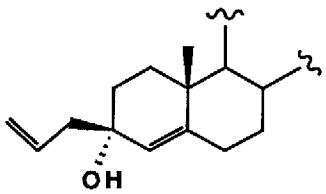
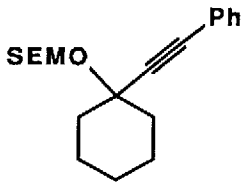
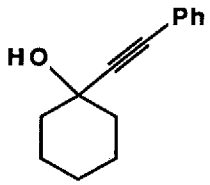
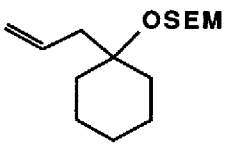
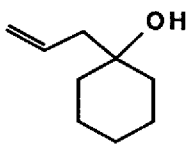


Table I. Deprotections of SEM ethers with *n*-Bu_4NF in DMPU containing mol. sieves (M.S.)

Entry	SEM ether	Time/Temp	Product	Yield(%)[a]
1		1 h, rt		84
2		5 h, 80°		95
3		3 h, 80°		91
4		7 d, 80°		86
5		20 h, 80°		89
6		20 h, 80°		83
7		16 h, 80°		80

[a]Isolated yields of chromatographically pure materials.

A typical procedure (Table I, entry 3) is as follows: A 1M solution of TBAF in THF (Aldrich, 1.90 mL, 5 equiv) was added to the SEM ether (105 mg, 0.38 mmol) and the solution concentrated *in vacuo*. The resulting oil was dissolved in dry DMPU (0.18 mL, distilled from BaO under vacuum at 146° at 44 mm) and crushed, activated molecular sieves (EM Science, Type 4A, 4-8 Mesh Beads, *ca*. 100 mg, flame dried under vacuum) were added. The reaction flask was then placed in an oil bath heated to 80° with stirring continued for 3h (TLC analyses done in 30% Et_2O/hexanes). The flask was then cooled, and the contents diluted with Et_2O and extracted (3x20 mL) from H_2O (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (SiO_2, 30% Et_2O/hexanes) afforded a clear oil (50 mg, 91%).

In summary, a simple, reproducible procedure for SEM ether cleavage which does not rely on carcinogenic HMPA as solvent[1,5] and which is applicable to a variety of substitution patterns and levels of substrate functionalization is provided.

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References and Notes

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4. See, for example, Pandey, R.K., Dougherty, T.J., Smith, K.M., Tetrahedron Lett., **1988**, 29, 4657.
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