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β-(TRIMETHYLSILYL)ETHOXYMETHYL CHLORIDE. A NEW REAGENT FOR THE PROTECTION OF THE HYDROXYL GROUP

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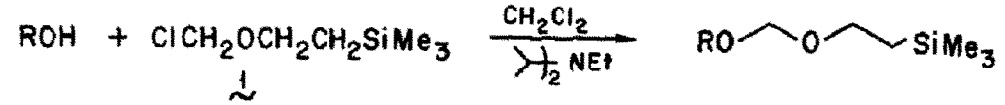
SUMMARY: *Reactions of β-(trimethylsilyl)ethoxymethyl chloride with alcohols afford the corresponding ethers in high yield. Deprotection using n-Bu$_4$NF in THF or HMPA cleanly regenerates the hydroxyl function.*

Protecting group chemistry continues to play a pivotal role in the execution of multistep organic syntheses. A great variety of reagents have been developed specifically designed to protect the hydroxyl function.[1] In particular, silyl ethers have found widespread use owing to the selective nature of their removal under the influence of fluoride ion.[2] Their lability under acidic conditions, however, often requires use of a less attractive derivative.[3] We now report on the preparation of β-(trimethylsilyl)ethoxymethyl chloride (or 'SEM-Cl', 1)[4] and the use of this new reagent for the formation of 'SEM' ethers. Such hydroxyl derivatives are stable over a wide range of conditions, yet can be readily cleaved in the presence of fluoride ion.

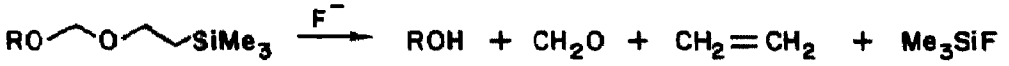


The preparation of SEM-Cl parallels a similar procedure reported by Corey and co-workers.[5] Thus, β-(trimethylsilyl)ethanol, readily available by any one of several known routes[6] is treated with paraformaldehyde[7] in the presence of dry HCl gas at 0° until a clear solution results. Dilution of the mixture with pentane followed by drying ($MgSO_4$), filtration, and removal of solvent *in vacuo* affords pure[8] SEM-Cl (87%) as a clear, colorless liquid[9] [bp 57-59° (8mm); $den^{25} = 1.05$; NMR ($CDCl_3$) δ: 5.38 (2H,s), 3.70 (2H, t, J = 8Hz), 0.88 (2H, t, J = 8Hz), 0.03 (9H,s)].

The formation of SEM ethers has been successful in all cases examined to date. Exposure of an alcohol, dissolved in CH_2Cl_2 (*ca.* 2M), under an inert atmosphere, containing

4-5 equiv of diisopropylethylamine, to SEM-Cl (ca. 3 equiv) at 25-40°, affords the SEM ether in high yield. Table I gives a listing of the hydroxy-containing substrates investigated.[10] The presence of additional functionality in the examples cited does not appear to interfere with the reaction process. Primary, secondary and tertiary alcohols were reactive, as was the phenol, eugenol. Acetals were unaffected, as were the enol ether and acetylene moieties. Carbohydrates seem amenable to protection with this group, and the bis-SEM ether of the protected methyl α-D-galactopyranoside (entry 10)[11] formed without incident.

Removal of the SEM group can be accomplished via reaction with n-Bu_4NF.[2a] We have found that reasonable rates (at concentrations ≥ 2M) are observed in dry THF (see Table I) at 45°. Standard extractive workup followed by rough SiO_2 filtration gives the desired alcohols. Substitution of HMPA for THF, in some cases (e.g. entry 2) seems to promote a more rapid unraveling, without loss of efficiency. This cascade effect, which



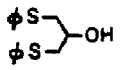
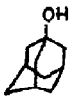
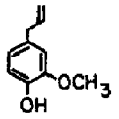
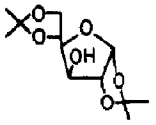
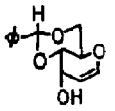
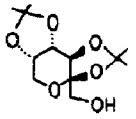
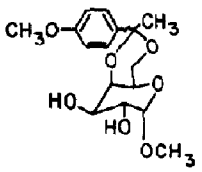
has been used successfully in somewhat related endeavors by others,[12] apparently, in this case, requires the presence of 'adventitious water', a phenomenon characteristic of the method of preparation of the fluoride source. Suprisingly, use of commercially available,[13] dry Et_4NF in different solvents (e.g. CH_3CN, THF, DMSO, DMF) with and without heat (up to 85°) led to none of the deprotected material.

SEM ethers remain intact under acidic conditions which would remove some of the more common protecting groups (e.g. THP, THF,[14] R_3Si-). Thus, exposure to acetic acid (3:1:1 HOAc/H_2O/THF) at 45° for 7 h leaves the starting material unchanged.

In conclusion, the SEM linkage offers several advantages as a hydroxyl protecting group which should make it valuable in planning synthetic strategy. These include: (1) its ready availability;[15] (2) its lack of introduction of a new chiral center; (3) its broad pH stability; (4) the SEM derivatives' low polarity facilitating purification; (5) the selective cleavage under mild, aprotic conditions with fluoride ion; (6) the efficient and mild protection and removal in the presence of other functionality.

Acknowledgements. Initial work on the development of SEM-Cl arose during work by B.H.L. on the total synthesis of (-)-N-Methylmaysenine in the laboratories of Professor E.J. Corey at Harvard University. Financial support from the Chemistry Department, UCSB, the Committee on Research of the University of California, and the Research Corporation is gratefully acknowledged. We thank Mr. M. Morey for the preparation of the bis-SEM ether, and Dr. H. Webb for recording the mass spectral data.

Table I. Reactions of Alcohols with β-(Trimethylsilyl)ethoxymethyl Chloride

entry	substrate	protection,[a] % yield,[b] time (h)	deprotection,[c] % yield,[b] time (h)
1		quant. (2)	90 (7.5)
2		91 (4)	93 (24) 96[d] (5)
3		87 (5)	
4		97 (1.5)	
5	Cholesterol	98 (2.5)	85[d] (8)
6		99[e] (24)	85 (10)
7		98 (5)	
8		99 (3) 99[e] (4.5)	86 (11)
9		98[e] (1)	92 (12)
10		86 (3)	

[a] SEM ethers were formed at 35–40° unless otherwise stated. [b] All yields refer to chromatographically pure material. [c] Reactions conducted in dry THF [d] Carried out in dry HMPA. [e] Reaction was run at room temperature

References & Notes

1. J.F.W. McOmie, in "Protective Groups in Organic Chemistry", Plenum Press, London, 1973.
2. (a) E.J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 6190(1972);
   (b) E.J. Corey and R.K. Varma, ibid., 93, 7319(1971).
3. For a recent review, see E.W. Colvin, Chem. Soc. Rev., 7, 15(1978).
4. For convenience, we use the expression 'SEM-Cl', from β-(trimethylSilyl)EthoxyMethyl chloride.
5. E.J. Corey, J.L. Gras and P. Ulrich, Tetrahedron Letters, 809(1976).
6. (a) from vinyltrimethylsilane, via hydroboration: J.A. Sonderquist and A. Hassner, J. Organomet. Chem., 156, C12(1978).
   (b) from vinyltrimethylsilane, via oxymercuration: J.A. Sonderquist and K.L. Thompson, J. Organomet. Chem., 159, 237(1978).
   (c) from ethyl bromoacetate, via a Reformatsky/LAH sequence: R.J. Fessenden and J.S. Fessenden, J. Org. Chem., 32, 3535(1967); H. Gerlach, Helv. Chim. Acta, 60, 3039(1977).
7. Use of paraformaldehyde is essential to the success of the reaction. Substitution of s-trioxane leads to impure SEM-Cl in ca. 15% yield.
8. NMR analysis revealed only the expected absorptions.
9. The reagent can best be stored in a refrigerator in a well-sealed container under an inert atmosphere.
10. All new compounds gave satisfactory ir, nmr, and mass spectral data (both low and high resolution).
11. Use of this mixed ketal derived from the dimethyl ketal of p-methoxyacetophenone will be reported shortly; M. Morey and B.H. Lipshutz, unpublished data.
12. For a similar effect involving the use of fluoride ion, see (a) L.A. Carpino and J. -H. Tsao, Chem. Comm., 358(1978); (b) P. Sieber, Helv. Chim. Acta, 60, 2711(1977); Other representative (carboxyl or hydroxyl) protecting groups wherein sequential elimination processes take place in an analogous fashion to that described herein include: (c) T. -L. Ho and T.W. Hall, Syn. Comm., 5, 367(1975); (d) T. -L. Ho, ibid., 8, 301(1978); (e) Idem., ibid., 8, 359(1978); (f) R.M. Jacobson and J.W. Clader, ibid., 9, 57(1979).
13. From Eastman Organic Chemicals, Rochester, New York.
14. The THF protecting group can be removed much more easily than the corresponding THP ether; for a review, see C.G. Kruse, F.L. Jonkers, V. Dert and A. van der Gen, Rec. Trav. Chim., 98 371(1979).
15. SEM-Cl will soon be available from the Aldrich Chemical Company, Milwaukee, Wisconsin.

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