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1-[2-(Trimethylsilyl)ethoxy]ethyl (SEE): A Novel Hybrid Hydroxy-protecting Group Between 1-(Ethoxy)ethyl (EE) and 2-(Trimethylsilyl)ethoxymethyl (SEM)

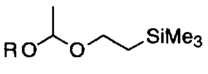
Junjun Wu, Brian K. Shull, and Masato Koreeda*†

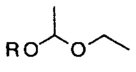
Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1055

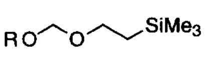
Abstract: The highly versatile 1-[(2-trimethylsilyl)ethoxy]ethyl (SEE) group, readily obtainable from an alcohol and 2-(trimethylsilyl)ethyl vinyl ether in the presence of a catalytic amount of PPTS, has been developed for the protection of hydroxyl groups. Its deprotection can be achieved under virtually neutral conditions with the use of a fluoride ion source, thus allowing for effective protection of hydroxyl groups of compounds that contain acid- and/or base-sensitive functional groups.

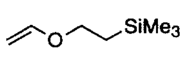
The increasing complexity of molecules organic chemists contemplate in their synthetic endeavors has created a continuous demand for the development of finely tuned protecting groups.[1] Among a diverse variety of reagents devised to protect hydroxyl groups, silyl ethers, e.g., *tert*-butyldimethylsilyl[2] and 2-(trimethylsilyl)ethoxymethyl (SEM)[3] ethers have distinct advantages as they can be removed under virtually neutral conditions through the use of a fluoride ion.[4] While these protecting groups are quite versatile, their formation often requires the use of a base such as lutidine and Hünig's base.[2,5] In one of our synthetic programs, there arose a need for the development of a hydroxy group-protecting reagent with which the protection can be achieved under non-basic conditions and the removal of the protecting group in turn effected under neutral conditions. In the following, we wish to report that the protection of diverse types of hydroxyl groups as their 1-[(2-trimethylsilyl)ethoxy]ethyl (SEE) derivatives (see **1**) can be realized under extremely mild, acidic conditions by the treatment with 2-(trimethylsilyl)ethyl vinyl ether and their deprotection through exposure to a fluoride ion source.

A new hydroxy-protecting group 1-[(2-trimethylsilyl)ethoxy]ethyl (SEE) was envisaged as a hybrid between 1-(ethoxy)ethyl (EE) and SEM groups (see **2** and **3**, respectively) where both the mildness of the


RO-SEE (**1**)


RO-EE (**2**)


RO-SEM (**3**)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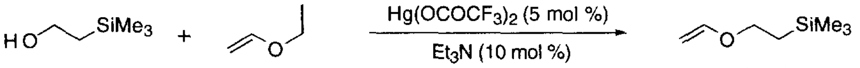
conditions to form the former derivative and the neutral conditions employed for the deprotection of the latter could be taken advantage of. The requisite reagent for the formation of the SEE derivatives of hydroxyl groups, 2-(trimethylsilyl)ethyl vinyl ether (**4**),[6] was readily prepared by the treatment of a solution of 2-(trimethylsilyl)ethanol in ethyl vinyl ether with a catalytic amount of mercuric trifluoroacetate and triethylamine at room temperature for 2.5 days (eq 1).



4 (96%)

(1)

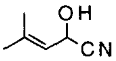
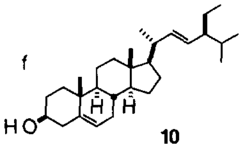
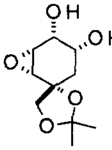
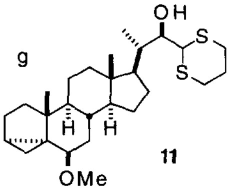
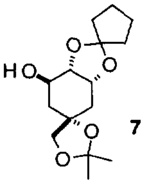
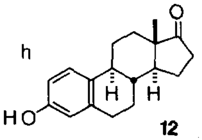
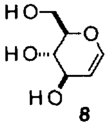
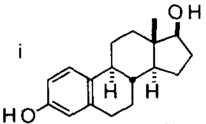
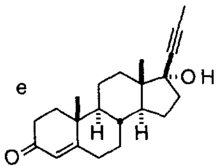
Unlike the formation of SEM ethers, SEE ether formation of the hydroxyl groups can be realized under extremely mild-acidic conditions. Thus, stirring of a solution or suspension of an alcohol/phenol, **4** (1.1 equiv per hydroxyl/phenol group), and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)[7] (e.g., 5 mg or less for the scale of a reaction involving 1 mmol of a compound regardless the number of hydroxyl groups to be derivatized in the molecule) in methylene chloride at room temperature under nitrogen provides, after purification by silica gel flash column chromatography, the fully SEE protected derivatives in high yields (see Table 1). It is quite noteworthy that SEE ether formation proceeds smoothly without complication even with highly acid-sensitive alcohols (see entries b, c, d, and g). Moreover, attempts at protection with SEM of substrate **5** resulted only in the decomposition of the starting material, whereas the SEE derivative was obtained in excellent yield (see entry a).

The removal of the SEE unit to regenerate the hydroxyl groups was also effected efficiently under virtually neutral conditions by exposing SEE-protected substrates to a fluoride ion source. Except for the tris-SEE ether of **8**, the treatment of SEE ethers with excess $(n\text{-Bu})_4NF$ in THF (at a 1 - 2 M fluoride concentration) at room temperature (entries e, f, and g) or 45 °C (entries b, c, h, and i) resulted in the complete removal of the SEE units. Interestingly, under these conditions, the tris-SEE protected glucal (see entry d) gave rise to only the bis-deprotected product (80% yield) whose structure is tentatively assigned as **8** 4-SEE ether. The full deprotection of this tris-SEE derivative was achieved by the use of CsF in DMF (115 °C for 24 h).

It needs to be noted here that the 1-(ethoxy)ethyl (EE) group[8] is also a widely used, versatile protecting group for hydroxyl groups. The protection as the EE group can be achieved under mild-acidic conditions, however, its removal usually requires acidic aqueous or alcoholic conditions under which effective EE deprotection of substrates containing acid-labile functional groups may not be realized. For example, while the formation of the tris-EE derivative of **8** did not present any significant problems, attempts at the deprotection of the EE group from it (catalytic *p*-TsOH or PPTS in 1/1 THF-H_2O, room temperature, 4 h) resulted in extensive decomposition.[9]

In summary, the highly versatile SEE group has been developed for the protection of hydroxyl groups. This hybrid hydroxyl-protecting group combines the distinct advantages of mildly acidic protection that the EE group possesses with that of neutral conditions of deprotection that the SEM group imparts. These salient

Table I. Protection of Various Alcohols and Phenols as their SEE Derivatives and their Deprotection.*

entry	substrate	% Yield for SEE ether formation and reaction time (h)	% Yield for SEE deprotection and reaction time (h)	entry	substrate	% Yield for SEE ether formation and reaction time (h)	% Yield for SEE deprotection and reaction time (h)
a	 **5**	92 (3)	-**	f	 **10**	96 (2)	90 (24)
b	 **6**	98 (2)	86 (24)	g	 **11**	79 (2)	81 (24)
c	 **7**	91 (1)	81 (24)	h	 **12**	94 (1.5)	82 (20)
d	 **8**	93 (4)	85 (24)	i	 **13**	79 (3)	81 (24)
e	 **9**	85 (2)	76 (24)				

* Yields represent those of isolated, spectroscopically and microanalytically pure products.

** No deprotection of the SEE derivative attempted.

features as well as the ease of preparation of the protecting reagent **4** are likely to help this new protecting group find its unique place as a highly versatile method for the protection of hydroxyl and/or phenolic groups.

2-(Trimethylsilyl)ethyl Vinyl Ether (4). To an oven-dried 500 mL round-bottomed flask containing a solution of 5.74 mL of 2-(trimethylsilyl)ethanol (40.0 mmol) in 200 mL of ethyl vinyl ether are added 0.56 mL of triethylamine (4.0 mmol) and 0.85 g of mercuric trifluoroacatate (2.0 mmol) while cooled with a water-bath. The reaction mixture is stirred at room temperature for 60 h, upon which time it is treated with 20 mL of 2M aqueous sodium hydroxide. The resulting two layers are separated and the aqueous layer is extracted with ether (2 x 25 mL). The combined organic layers are washed successively with saturated aqueous sodium bicarbonate (25 mL), saturated aqueous ammonium chloride (25 mL), and brine (25 mL), dried (Na_2SO_4), and concentrated. Kugelrohr distillation (oven temperature 80 - 85 °C; lit.[6] bp$_{29}$ 46 °C) of the crude oil obtained above affords 5.41 g of 2-(trimethylsilyl)ethyl vinyl ether (**4**) (96%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.534 (s, 9H), 1.02 (t, 2H, *J* = 8.1 Hz), 3.78 (t, 2H, *J* = 8.1 Hz). 3.97 (dd, 1H, *J* = 6.8, 1.8 Hz), 4.17 (dd, 1H, *J* = 14.4, 1.8 Hz), 6.45 (dd, 1H, J = 14.4, 6.8 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ -1.22 (q), 17.70 (t), 65.79 (t), 86.49 (t), 151.96 (d).

General Procedure for the SEE Protection of Hydroxyl and Phenol Groups: To a solution of an alcohol or phenol (1.0 mmol) in 5 mL of methylene chloride are added 2-(trimethylsilyl)ethyl vinyl ether (0.20 mL, 1.1 mmol per hydroxyl or phenol group to be derivatized) and a catalytic amount of pyridinium *p*-toluenesulfonate (5 mg). The reaction mixture is stirred at room temperature for 2 h, upon which time the reaction is quenched with 1 mL of 0.1M aqueous sodium hydroxide and the resulting mixture is extracted with ether (2x10 mL). The combined organic layers are washed first with saturated aqueous ammonium chloride (5 mL), then with brine (5 mL), and dried (Na_2SO_4). Purification of the crude product obtained upon rotary evaporation of the solvent by silica gel flash column chromatography provides spectroscopically and microanalytically pure SEE ether derivative.

General Procedure for the Removal of the SEE Protecting Groups: To a solution of an SEE ether (0.10 mmol) in 1 mL of THF is added tetra(*n*-butyl)ammonium fluoride monohydrate (0.26 g, 1.0 mmol). Note: In all cases presented in this report, the amount of the fluroride source is kept the same mol equivalent. The reaction mixture is stirred at room temperature or 45 °C (see the text) until the completion of the deprotection is indicated by the tlc analysis. The solution is then diluted with ether or chloroform (5 mL) and water (3 mL), the resulting two layers are separated and the aqueous layer is extracted with ether or chloroform (5 mL), respectively. The combined organic layers are washed first with saturated aqueous ammonium chloride (2x3 mL), and then with brine (3 mL), dried (Na_2SO_4), and the solvent is removed by rotary evaporation. Purification of the crude product by silica gel flash column chromatography gives the corresponding fully deprotected alcohol/phenol.

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† Fax and Tel #: 1-313-764-7371; E-mail address: koreeda@Chem.LSA.Umich.Edu

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9. Deprotection of the SEE derivatives of acid-stable substrates can also be effected with *p*-TsOH or PPTS (catalytic) in THF-H_2O at room temperature (4 h).

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