

# Chloromethoxysilanes as Protecting Reagents for Sterically Hindered Alcohols

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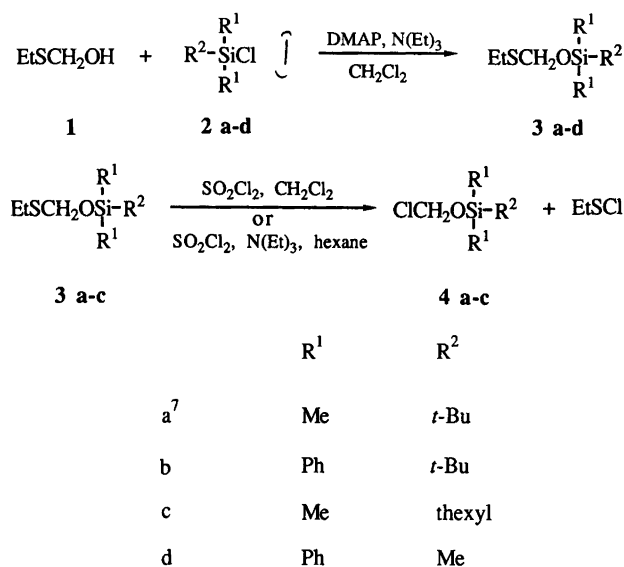
Organosilicon reagents have been widely used for the protection of hydroxy groups in organic synthesis.<sup>1</sup> The stability of the silyloxy function depends largely on the carbon substituents on silicon. The trimethylsilyl derivatives are sensitive to hydrolysis whereas the *tert*-butyldimethylsilyl (TBDMS) derivatives require stronger hydrolytic conditions for cleavage, and therefore have a wider application potential.<sup>2</sup> TBDMS chloride will convert most hydroxy groups into the corresponding TBDMS ethers except for sterically hindered hydroxy compounds for which the highly reactive but sensitive reagents TBDMS perchlorate or triflate<sup>†</sup> have to be used.<sup>3</sup> Recently thexyldimethylsilyl chloride (TDS-Cl)<sup>‡</sup> and TDS triflate have been introduced as alternatives to the corresponding TBDMS reagents with the argument that TDS-silyl ethers are more stable.<sup>4</sup> 2-(Trimethylsilyl)ethoxymethyl chloride (SEM-Cl) is another silyl reagent which has been found useful in the protection of sterically hindered alcohols.<sup>5</sup> The SEM ethers are cleaved by fluoride ion at ca. 60 °C. It has, however, been reported that fluoride cleavage of SEM ethers has failed.<sup>6</sup>

We have recently developed a related TBDMS reagent, (*tert*-butyldimethylsilyloxy)methyl chloride (**4a**) (Scheme 1), for the regiocontrol of alkylations in diazines.<sup>7</sup> The protecting group is stable to normal alkylation procedures and organometallic reagents, and is readily removed by fluoride-ion cleavage of the silicon–oxygen bond at ambient temperature. We thought that this and similar reagents might be useful in the protection of hindered alcohols, since the  $\alpha$ -chloromethyl ether function is very reactive and the rather bulky substituted silyl group will be at some distance from the reactive center in the protecting reaction. The advantage of the  $\alpha$ -chloromethyl ether function contained in the protecting reagents has been described.<sup>8</sup>

A number of silyl chlorides were treated under basic conditions with ethylthiomethanol (**1**) to give the hemithio-

acetals **3** (Scheme 1). This reaction is a demonstration of the hardness and oxygenophilicity of silyl chlorides, because softer electrophiles such as benzyl bromide react preferentially at the sulfur atom of **1** with extrusion of formaldehyde.

Reaction of the hemithioacetals **3** with sulfonyl chloride in dichloromethane (Method A) gave a good yield of the chloromethoxysilanes **4**, except for **3d** where cleavage of the phenyl–silicon bond was observed. This was no significant problem in the reaction of the *tert*-butyl analogue **3b**. The stability of the chloromethoxysilanes **4** was increased when one equivalent of triethylamine (Method B) was used in the cleavage reaction. The triethylamine probably ensures an acid-free product and hence acid-catalyzed degradation of the chloromethyl ether is avoided. Sulfonyl chloride in the presence of an amine base has been used in other chlorination reactions.<sup>9</sup>

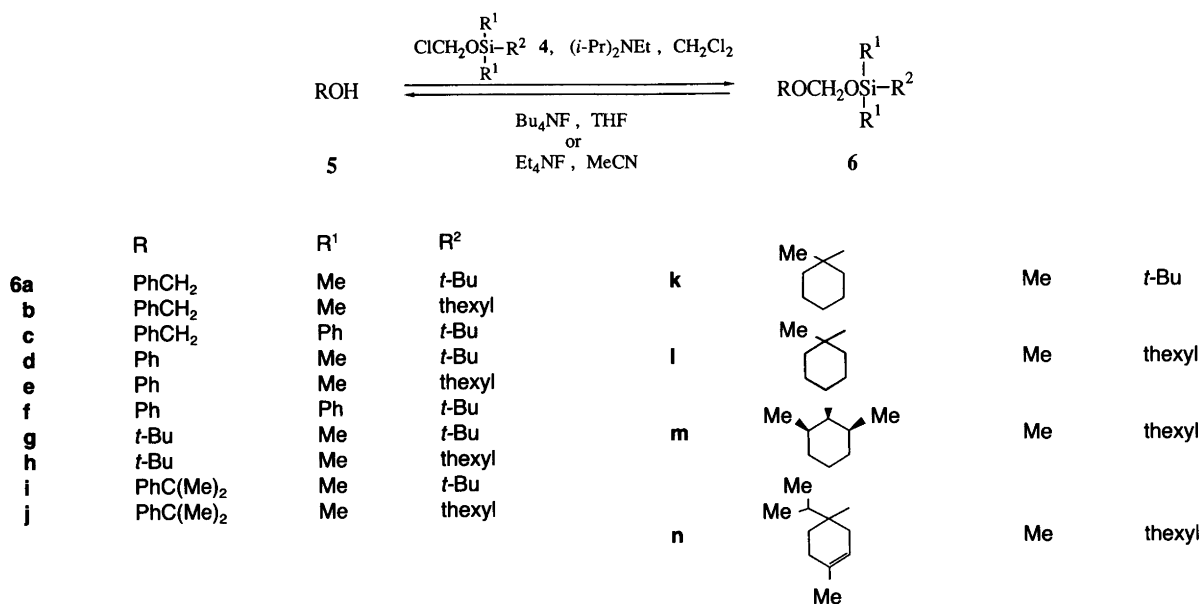


Scheme 1.

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†Triflate = trifluoromethanesulfonate.

‡Thexyl = 2,3-dimethyl-2-butyl.



Scheme 2.

For the alkylation of the alcohols **5** an excess of the chloromethyl ether reagent **4** (2–3.5 mol equiv.) and ethyldiisopropylamine (5 mol equiv.) were used (Scheme 2). Sodium hydride in 1,2-dimethoxyethane reduced the yield of the acetals **6**. The silyl acetals **6** from benzyl alcohol, phenol, *tert*-butyl alcohol, 2-phenyl-2-propanol and 1-methylcyclohexanol, were obtained in good yields using either **4a**,<sup>7</sup> or **4c** (Table 1, entries 1–5). The reaction of the chloromethoxysilane **4b** was much slower, and a satisfactory yield was obtained only for benzyl alcohol (entry 1). For phenol the yield was moderate (entry 2) and *tert*-butyl alcohol did not react at all even after a prolonged reaction time (entry 3). The steric effect of the phenyl substituents<sup>10</sup> is probably responsible for the reduced reactivity of **4b** compared with **4a**.

The reaction of *cis,cis*-2,6-dimethylcyclohexanol and terpinen-4-ol with **4a** gave a complex mixture, whereas **4c** gave the corresponding acetals **6m** and **6n** in good yields (Scheme 2 and Table 1, entry 6 and 7). A slightly larger excess of the alkylating agent **4c** and a longer reaction time had to be used.

Deprotection was accomplished using tetrabutylammonium fluoride in THF (Method A) at ambient temperature (Table 1). Tetraethylammonium fluoride in acetonitrile (Method B), which does not affect SEM ethers,<sup>5</sup> also cleaved **5** at ambient temperature. As expected, the acetals **6** were deprotected under acidic conditions (HOAc, H<sub>2</sub>O).

## Experimental

The <sup>1</sup>H NMR spectra were recorded at 300 MHz and the <sup>13</sup>C NMR spectra at 75 MHz. The solvent was deuteriochloroform. The mass spectra were recorded at 70 eV. Isobutane or ammonia was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.).

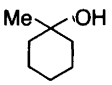
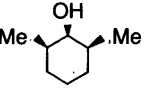
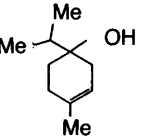
**General procedure for the synthesis of the O,S-acetals 3.** Chlorosilane **2** (55 mmol) was added to a solution of 4-(*N,N*-dimethylamino)pyridine (244 mg, 2 mmol), triethylamine (8.35 ml, 60 mmol) and ethylthiomethanol (**1**)<sup>7</sup> (4.60 g, 50 mmol) in dry dichloromethane (50 ml). The mixture was stirred at ambient temperature under N<sub>2</sub> for 4 h (**3b** and **3d**) or 6.5 h (**3c**), diluted with dichloromethane and washed successively with water (×2) and saturated aqueous ammonium chloride solution (×2). The dried (MgSO<sub>4</sub>) solution was evaporated, and the crude product was purified by flash chromatography.

(*tert*-Butyldiphenylsilyloxy)methyl ethyl sulfide (**3b**). Yield 74 % (SiO<sub>2</sub>; hexane/EtOAc 80:1). Anal. C<sub>19</sub>H<sub>26</sub>OSSi: C, H. <sup>1</sup>H NMR: δ 1.08 (*t*-Bu), 1.26 (t, *J* 7 Hz, Me), 2.68 (q, *J* 7 Hz, CH<sub>2</sub>), 4.82 (OCH<sub>2</sub>S), 7.4–7.7 (m, Ph). <sup>13</sup>C NMR: δ 14.9 (Me), 19.1 (C in *t*-Bu), 24.7 (CH<sub>2</sub>), 26.7 (Me in *t*-Bu), 66.6 (OCH<sub>2</sub>S), 127.6, 129.7 and 135.6 (CH in Ph), 133.0 (C in Ph). MS (CI-isobutane): 331 (2, *M*+1), 273 (38), 269 (100), 253 (26), 251 (21), 243 (29), 227 (14), 183 (7), 165 (9), 135 (8).

(Dimethylhexylsilyloxy)methyl ethyl sulfide (**3c**). Yield 78 % (SiO<sub>2</sub>; hexane/EtOAc 80:1). B.p. 71–74 °C/0.28 mmHg. Anal. C<sub>11</sub>H<sub>26</sub>OSSi: C, H. <sup>1</sup>H NMR: δ 0.14 (SiMe), 0.84 (Me in hexyl), 0.87 (d, *J* 7 Hz, Me in hexyl), 1.27 (t, *J* 7 Hz, Me), 1.60 (m, *J* 7 Hz, CH in hexyl), 2.64 (q, *J* 7 Hz, CH<sub>2</sub>), 4.77 (OCH<sub>2</sub>S). <sup>13</sup>C NMR: δ –3.3 (SiMe), 14.7 (Me), 18.4 and 20.1 (Me in hexyl), 24.4 (CH<sub>2</sub>), 24.9 (C in hexyl), 34.0 (CH in hexyl), 65.5 (OCH<sub>2</sub>S). MS (CI-NH<sub>3</sub>): 173 (6), 163 (4), 159 (11), 123 (70), 106 (36), 102 (5), 92 (100), 91 (23), 84 (12), 75 (45), 74 (53).

(Diphenylmethylsilyloxy)methyl ethyl sulfide (**3d**). Yield 41 % (SiO<sub>2</sub>; hexane/EtOAc 80:1). Anal. C<sub>16</sub>H<sub>20</sub>OSSi: C, H.

Table 1. Protection of alcohols with chloromethoxysilanes **4**.

Entry	Alcohol	<b>4a</b>		<b>4b</b>		<b>4c</b>	
		Protection % Yield (time/h) <sup>b</sup>	Deprotection <sup>a</sup>	Protection	Deprotection <sup>a</sup>	Protection	Deprotection <sup>a</sup>
1	PhCH <sub>2</sub> OH	73 (17)	69 (0.5)	73 (69)	80 (1.5)	91 (18)	79 (0.5)
2	PhOH	88 (16)	80 (1)	41 (69)	84 (1)	75 (18)	75 (0.5)
3	<i>t</i> -BuOH	92 (20)	72 (1.5)	0 (47)		97 (18)	74 (2)
4	PhC(Me) <sub>2</sub> OH	63 (19)	70 (3) 64 (5) <sup>c</sup>			70 (20)	66 (4) 75 (5) <sup>c</sup>
5		79 (22)	76 (2) 69 (7.5) <sup>c</sup>			78 (22)	75 (3) 72 (8) <sup>c</sup>
6		Complex mixture				63 (46) <sup>d</sup>	74 (2.5)
7		Complex mixture				80 (45) <sup>d</sup>	78 (2.5) 75 (10) <sup>c</sup>

<sup>a</sup>Bu<sub>4</sub>NF/THF/Room temp. <sup>b</sup>Yield of purified product. <sup>c</sup>Et<sub>3</sub>NF/MeCN/Room temp. <sup>d</sup>3.5 mol equiv. of **4c** were used.

<sup>1</sup>H NMR:  $\delta$  0.72 (SiMe), 1.22 (t, *J* 7 Hz, Me), 2.63 (q, *J* 7 Hz, CH<sub>2</sub>), 4.86 (OCH<sub>2</sub>S), 7.3–7.6 (m, Ph). <sup>13</sup>C NMR:  $\delta$  -2.7 (SiMe), 14.6 (Me), 24.5 (CH<sub>2</sub>), 66.1 (OCH<sub>2</sub>S), 127.8, 129.8 and 134.3 (CH in Ph), 135.2 (C in Ph). MS (CI-NH<sub>3</sub>): 306 (42, *M*+18), 288 (4, *M*), 273 (1), 232 (100), 228 (18), 216 (48), 199 (7), 154 (74), 92 (12).

**General procedure for the synthesis of chloromethoxysilanes 4. Method A.** Sulfuryl chloride (0.8 ml, 10 mmol) in dry dichloromethane (10 ml) was added dropwise at 0 °C to a solution of the *O,S*-acetal **3** (10 mmol) in dry dichloromethane (10 ml). The mixture was stirred under N<sub>2</sub> for 30 min at 0 °C and for 10 min at ambient temperature before the solvent and ethanesulfonyl chloride were evaporated off under reduced pressure; yield 97 % (**4b**), 98 % (**4c**).

**Method B.** Sulfuryl chloride (0.8 ml, 10 mmol) in hexane (10 ml) was added dropwise at 0 °C to a solution of *O,S*-acetal **3** (10 mmol) and triethylamine (1.4 ml, 10 mmol) in hexane (10 ml). The mixture was stirred under N<sub>2</sub> at 0 °C for 30 min and for 10 min at ambient temperature before the solid was filtered off and washed with hexane. The solution was evaporated; yield 97 % (**4a**), 97 % (**4b**) and 95 % (**4c**).

(*tert*-Butyldiphenylsilyloxy)methyl chloride (**4b**). Anal. C<sub>17</sub>H<sub>20</sub>OSSi: C, H. <sup>1</sup>H NMR:  $\delta$  1.09 (*t*-Bu), 5.54 (CH<sub>2</sub>), 7.3–7.7 (m, Ph). <sup>13</sup>C NMR:  $\delta$  18.9 (C in *t*-Bu), 26.5 (Me in *t*-Bu), 75.9 (CH<sub>2</sub>), 127.7, 130.1 and 135.6 (CH in Ph), 131.7 (C in Ph). MS (CI-isobutane): 305 (2, *M*+1), 275 (11), 269 (100), 247 (31), 227 (15), 217 (36), 199 (12), 185 (20), 91 (58), 78 (13).

(Dimethylhexylsilyloxy)methyl chloride (**4c**). Yield 70 % (Kugelrohr distillation). B.p. 50 °C/0.25 mmHg. Anal. C<sub>9</sub>H<sub>21</sub>ClOSi: C, H. <sup>1</sup>H NMR:  $\delta$  0.24 (SiMe), 0.86 (Me in thexyl), 0.88 (d, *J* 7 Hz, Me in thexyl), 1.63 (m, *J* 7 Hz, CH in thexyl), 5.60 (CH<sub>2</sub>). <sup>13</sup>C NMR:  $\delta$  -3.3 (SiMe), 18.3 and 19.8 (Me in thexyl), 24.7 (C in thexyl), 33.9 (CH in thexyl), 76.2 (CH<sub>2</sub>). MS (CI-NH<sub>3</sub>): 208 (1, *M*), 173 (14), 163 (9), 110 (4), 106 (100), 91 (10), 90 (27), 84 (5), 76 (5), 74 (4), 73 (4).

**General procedure for the protection of the alcohols 5.** (*tert*-Butyldimethylsilyloxy)methyl chloride (**4a**) (2.70 g, 15 mmol), (*tert*-butyldiphenylsilyloxy)methyl chloride (**4b**) (4.56 g, 15 mmol) or (dimethylhexylsilyloxy)methyl chloride (**4c**) (2.30 g, 11 mmol) in dry dichloromethane (10 ml) was added dropwise at 0 °C under N<sub>2</sub> to a mixture of the alcohol **5** (5 mmol) and ethyldiisopropylamine (4.28 ml, 25 mmol) in dry dichloromethane (10 ml). The mixture was stirred while reaching ambient temperature until TLC showed the reaction to be complete (Table 1). Dichloromethane was added and the mixture was washed with water (×2), saturated aqueous ammonium chloride solution (×2), dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc (**6a**, **6i**, **6m**, 40:1; **6b–6h**, **6j–6l**, **6n**, 50:1) as the eluant. All compounds were fully characterized spectrally and the elemental composition was established by combustion analysis.

**General procedure for the cleavage of the acetals 6 with tetraalkylammonium fluoride salts. Method A.** A 0.5 M solution of tetrabutylammonium fluoride in THF (2 mol

equiv.) was added to the compound **6**. The mixture was stirred at ambient temperature under N<sub>2</sub> for 0.5–4.0 h (Table 1), before water was added and the pH adjusted to ca. 4 with acetic acid. The solution was extracted with chloroform (×3), washed with saturated aqueous sodium chloride solution (×3), dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc as the eluant [5:1 or 4:1 (PhOH)].

*Method B.* A 0.25 M solution of tetraethylammonium fluoride in acetonitrile (2 mol equiv.) was added to the compounds **6i–6l**, and **6n**. The mixture was stirred at ambient temperature under N<sub>2</sub> for 5–10 h (Table 1). The reaction was worked up and the product was purified as above.

## References

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