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The Sisyl (tris(Trimethylsilyl)silyl) Group: A Fluoride Resistant, Photolabile Alcohol Protecting Group

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Summary: The use of the tris(trimethylsilyl)silyl (sisyl) group as a photolabile protecting group for primary and secondary alcohols was demonstrated. Sisyl ethers of a number of alcohols (yields 70-97%) were stable to many synthetic protocols, but could be deprotected using photolysis to give the starting alcohols (yields 62-95%).

INTRODUCTION

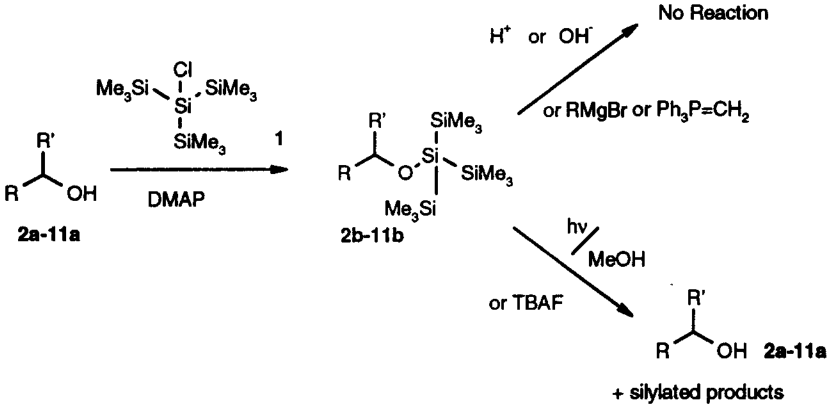
Silicon-based derivatives have become the protecting groups of choice for alcohols.[2,3] Among the many reasons for their universal adoption is the predictable way in which the steric bulk of the ligands on silicon affects the ease of preparation and deprotection of silyl ethers.[4] Thus, as the size of the groups increases from trimethylsilyl[5] to *t*-butyldimethylsilyl,[6,7] *t*-butyldiphenylsilyl[8] and triisopropylsilyl,[9] for instance, it is increasingly difficult to introduce the silyl group. As the bulk around silicon increases, the silyl ethers are also more resistant to cleavage by the reagents from which the alcohol must typically be protected. The most important beneficial feature of silyl ethers is their susceptibility to deprotection with fluoride, conditions under which the organic residue is generally not affected.

Polysilanes have many interesting and unusual properties. In spite of the absence of π-systems, these materials absorb in the UV region: the absorption wavelength and extinction coefficient increases with the length of Si-Si chain due to σ-conjugation.[10] Such compounds will undergo photolysis at 254 nm, fragmenting to form silylenes.[11] We are unaware of the exploitation of this property of polysilanes in the context of silicon protecting groups although other photochemical protecting groups, including silyl ethers,[12] are known.[13] Photolytic deprotection of silyl ethers offers an advantage over ionic methods in that selective deprotection can be employed.[14]

The development by Chatgilialoglu *et al.*[15] of tris(trimethylsilyl)silane and related polysilanes[16] as radical chain transfer agents has made functionalized sisyl compounds readily available.[17,18] As this reagent and silyl ethers derived from it show the requisite UV absorption at 204 and 254 nm, we have examined the utility of the (tris(trimethylsilyl)silyl) group as a UV-labile silyl protecting group. We report below the results of our investigations focusing both on the ease of preparation of sisyl ethers and their deprotection using UV light and selected fluoride sources.

RESULTS AND DISCUSSION

Tris(trimethylsilyl)silyl ethers were prepared from the corresponding chlorosilane in keeping with the method commonly used for the preparation of silyl ethers. Sisyl chloride **1** is simply formed from tris(trimethylsilyl)silane with stirring in the presence of carbon tetrachloride.[19] Conversion of the alcohol to the silyl ether was attempted using a number of bases such as triethylamine, imidazole and 4-dimethylaminopyridine (DMAP). DMAP (1.2 equiv.) was found to give the highest yield of protected alcohols. CH_2Cl_2 was chosen as solvent over DMF[7] both because of the excellent solubility of the alcohols examined and the efficient removal of solvent at the end of the reaction.



Scheme 1

A number of different alcohols were protected using 1. The reaction between primary or secondary alcohols and the sisyl compound in CH_2Cl_2 at room temperature in the presence of base gave yields of sisyl ethers ranging from 70-97% after purification (**2a-11a** → **2b-11b**, Scheme 1, Table 1).[20] The analogous reactions with a tertiary alcohol, triphenylmethanol, and a hindered secondary alcohol, diacetone-D-glucose, however, led to none of the desired products, presumably due to unfavorable steric interactions.

Table 1: Alcohols Protected with Tris(Trimethylsilyl)silyl Chloride and Their Deprotection Reactions

Compound (series b)	Alcohol (series a)	Protection[a] (% Yield **2-11b**)	Deprotection[a] (% Yield **2-11a**)
Geraniol	**2**	74	90
Decanol	**3**	85	68
2-Octanol	**4**	78	95
Cyclopentanol	**5**	70	88
Cholesterol	**6**	79	87[b]
2,2,2-Trifluoroethanol	**7**	97	62[c]
2-Chloroethanol	**8**	89	90
2,2,2-Trichloroethanol	**9**	83	89
2-Phenylethanol	**10**	85	82
Citronellol	**11**	81	91

[a] Yields reported are based on purified product. [b]Irradiation performed on a 0.01 M solution. [c]Lower isolated yields were due to the volatility of the starting alcohol.

The stability of the sisyl ethers to a number of different reagents was examined. The sisyl ethers were not stable towards nucleophiles such as *n*-BuLi or $LiAlH_4$. In both cases, a mixture of products including the unprotected alcohol was recovered. Presumably, the external $SiMe_3$ group is vulnerable to attack by strong nucleophiles.[21] The ethers were stable[22] to: organometallic reagents (3.0 M MeMgBr; $Ph_3P{=}CH_2$), oxidation (Jones reagent) and acidic conditions (*p*-TSA, 1 equivalent; acetone/0.2 M HCl, 1/1).[23] This stability to acids in organic solvents has not been illustrated for *t*-butyldimethylsilyl,[7] *t*-butyldiphenylsilyl[8] or triisopropylsilyl groups.[24]

The sisyl ethers were also stable towards selected fluoride reagents. Three such reagents were examined: KF + 18-crown-6, cesium fluoride and tetrabutylammonium fluoride. The silyl ether proved to be stable to the former two reagents in THF. These are conditions under which less bulky silyl ethers are susceptible to cleavage.[25] However, deprotection occurred in the presence of tetrabutylammonium fluoride as has previously been reported.[26]

The photodeprotection of each compound was attempted using a medium pressure mercury lamp. Since both the silyl ethers and the derived alcohols were soluble in CH_2Cl_2, it was used with methanol (a mixture of CH_2Cl_2 / MeOH 1:5) as the solvent of choice. The methanol (excess)[27] also serves as a trap for the silylene generated during photolysis. The irradiations were complete within 30 minutes using a Hanovia lamp and a Pyrex immersion well.[28] The deprotection proceeded rapidly to give high yields of the starting alcohol (purified yields, 62-95%, Table 1) and silicon-based products. The alcohols products were readily purified by flash chromatography. The exact nature of the silicon-based products has yet to be established. However, silylenes readily undergo dimerization and insertion into Si-Si or H-O bonds.[29] The expected by-products are non-polar materials: alkoxy(hydrido)polysilanes, hexamethyldisiloxane, and oligosiloxanes.

Finally, we have examined the reaction of *t*-BDMS protected cyclopentanol with MeOH/CH_2Cl_2 at low (8 equiv.) and high MeOH (1000 equiv.) concentrations using the same photolytic conditions as those described above for **5**. A small degree of desilylation of the *t*-BDMS ether occurred with 1000 equiv. of methanol, which we attribute to nucleophilic alcoholysis. Thus, we believe the desilylation of the sisyl groups to be exclusively a photo-reaction.

CONCLUSIONS

Sisyl ethers are readily prepared from primary and secondary alcohols: sisyl chloride **1** is derived in one step from commercial $(Me_3Si)_3SiH$. These groups are stable to many of the reaction conditions normally employed in organic synthesis as is the case for silyl ethers in general. They are also stable to CsF, conditions under which cleavage of silyl ethers is often observed. The sisyl ethers are, however, unstable to very mild photolysis conditions. This combination of reactivities should find application in organic synthesis.

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[20] *General Procedure - Protection of the Alcohol*: To a stirring solution of the alcohol **2a-11a** (1 mmol) and 4-dimethylaminopyridine (DMAP) (1.20 mmol) in CH_2Cl_2 was added a solution of tris(trimethylsilyl)silyl chloride **1** (1.20 mmol) in CH_2Cl_2 (1.2 M). The solution was stirred overnight at room temperature under N_2. Water was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. Separation by flash chromatography gave the products in 70-97% yields. e.g. **3,7-Dimethyl-1-[tris(trimethylsilyl)silyl)]-2,6-octadien-1-ol 2b**: Geraniol (161 mg, 1.00 mmol), DMAP (147 mg, 1.20 mmol), CH_2Cl_2 (1.0 mL), **1** (340 mg, 1.20 mmol) in CH_2Cl_2 (1.0 mL). After chromatography, 296 mg (74%) of a clear oil **2b** was obtained. ^{1}H NMR ($CDCl_3$): δ 5.22 (t, J=0.8 Hz, 1H), 5.07 (t, J=0.8 Hz, 1H), 4.03 (dd, J = 5.11 Hz, 2H), 2.01 (m, 4H), 1.65 (s, 3H), 1.56 (d, J=0.9 Hz, 6H), 0.17 (s, 27H); ^{13}C NMR ($CDCl_3$): δ 136.3, 131.5, 125.0, 124.1, 65.1, 39.5, 26.4, 25.7, 17.7, 16.5, 0.32; ^{29}Si NMR ($CDCl_3$): δ 2.75, -16.04; IR (neat, KBr): ν 2958, 2896, 1443, 1380, 1250, 1061, 840, 756 cm^{-1}; MS (EI, m/z): 263 ($Si(TMS)_3^+$, 48).

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[28] *General Procedure - Deprotection:* A 0.1 M solution of the protected alcohol **2b-11b** in methanol/methylene chloride was irradiated in a Pyrex immersion well at 10 °C for 30 min; monitoring by TLC showed that the reaction was complete. e.g.: The deprotection of **6b** was performed using a 0.01 M solution. The solvent was removed under reduced pressure and the alcohol purified by flash chromatography. For the yields, see Table 1. **2b**: 3,7-Dimethyl-1-[tris(trimethylsilyl)silyl]-2,6-octadien-1-ol (52 mg, 0.13 mmol), MeOH (5 mL, 0.12 mol), CH_2Cl_2 (1.3 mL); yield 18 mg (90%) of **2a**.

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