

THEXYLDIMETHYLSILYL CHLORIDE ¹, AN EASILY ACCESSIBLE
REAGENT FOR THE PROTECTION OF ALCOHOLS

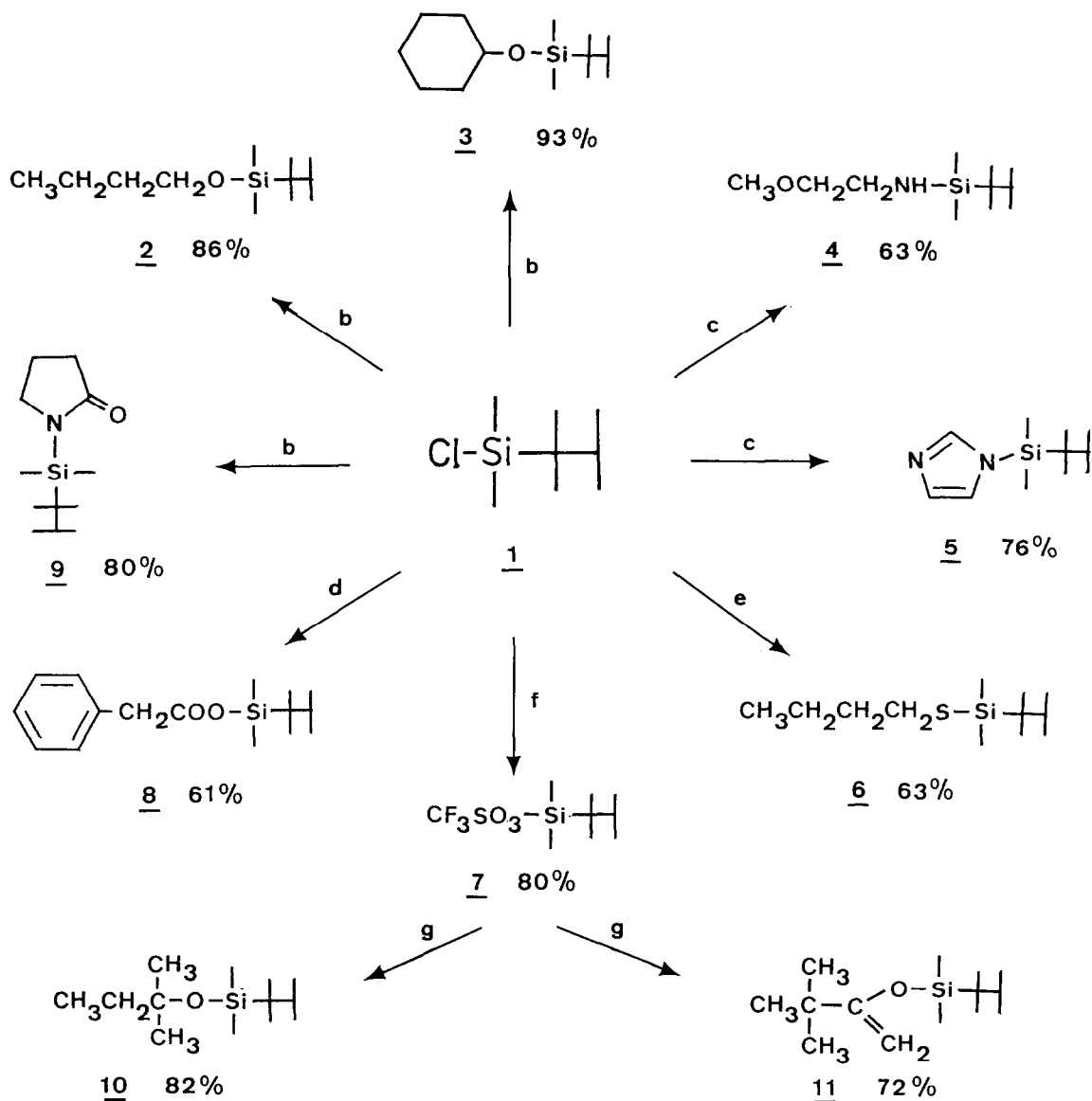
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Summary: The silylation of alcohols, amines, amides, mercaptans and acids with the readily available thexyldimethylsilyl chloride (TDS-Cl) is described. The stabilities of the silyl ethers are examined using different cleavage conditions and compared in part with the stabilities of the corresponding tert-butyldimethylsilyl derivatives.

Tert-butyldimethylsilyl chloride is a widespread reagent for the protection of alcohols ², mainly because of the stability of the corresponding silyl ethers towards various oxidative, reductive, mildly acidic or basic reaction conditions ^{2a} and the possibility of the selective cleavage of the Si-O bond by fluoride ions. The hazardous preparation of tert-butyldimethylsilyl chloride using tert-butyllithium ^{2a,3} causes a high price which limits its synthetic application on an industrial scale. In order to find a more easily available silicon reagent for protection that retains all the advantageous properties of the tert-butyldimethylsilyl group, a study of the hydrosilylation of tetrasubstituted olefins was undertaken ⁴. As a result it was found that the reaction of chlorodimethylsilane with 2,3-dimethyl-2-butene furnishes thexyldimethylsilyl chloride (1) (TDS-Cl) in high yield ⁴.

In this paper we would like to present applications of TDS-Cl 1 to mask functional groups (see Scheme 1). TDS-Cl not only silylates alcohols but also amines, amides, mercaptans and acids. Primary and secondary alcohols (including phenols) were routinely converted to the corresponding TDS-ethers (e.g. 2 or 3) in DMF with imidazole ^{2a} or Et₃N as a base in 80-95% isolated yields. A representative example is the silylation of cyclohexanol:

To thexyldimethylsilyl chloride (1,96 g, 11 mmol.) and imidazole (1,02 g, 15 mmol.) in 5 ml DMF was added cyclohexanol (1,1 g, 11 mmol.) at 25°C. The mixture was stirred for 16 hrs at ambient temperature and then diluted with hexane. The hexane phase was washed twice with water, dried with MgSO₄ and evaporated to furnish, after Kugelrohr distillation, 2,51 g (94% yield) of 3, bp. 100-105°C/0,03 torr.

Scheme 1: Silylation of various functional groups with TDS-Cl^a

- a) Yields of isolated products, purified by distillation or chromatography;
 b) Imidazole or Et₃N in DMF; c) Et₃N with or without solvent; d) Et₃N in DMF or Et₂O;
 e) BuSNa in hexane⁵⁾; f) see reference 6; g) 2,6-lutidine or Et₃N in CH₂Cl₂

Tertiary alcohols and ketones were silylated with the more reactive TDS-ester of trifluoromethanesulfonic acid 7 ⁶ in presence of 2,6-lutidine or Et₃N as base in CH₂Cl₂. Treatment of amines with TDS-Cl and Et₃N with or without solvent produced the corresponding silylated compounds (e.g. 4 or 5), whereby an aqueous workup had to be avoided due to the hydrolytic instability of silyl amines. N-silyl amide 9 on the other hand was stable enough to be isolated by standard aqueous workup and chromatography on silica gel. Surprisingly, there was no reaction observed when dodecyl mercaptan was treated with TDS-Cl and imidazole in DMF. However a suspension of sodium butylthiolate in hexane furnished 6 on reaction with TDS-Cl ⁵.

Table 1 shows various cleavage conditions that are commonly used in desilylation reactions ². The half-lives for the liberation of butanol and cyclohexanol from their silyl ethers were measured and compared with the half-lives of the corresponding tert-butyldimethylsilyl (TBDMS) ethers: The TDS-ethers are cleaved 2 to 3 times more slowly than the tert-butyldimethylsilyl ethers under otherwise identical conditions.

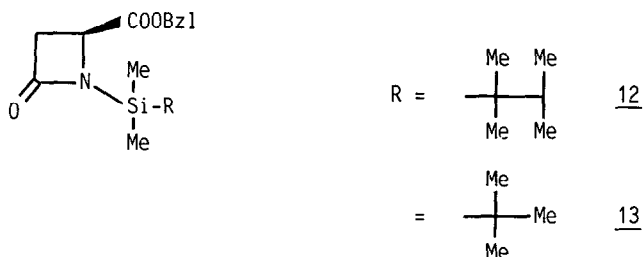
Table 1: Half-lives for the deprotection of silyl ether ^a

| | n-Butyl-0- | | Cyclohexyl-0- | |
|---|--|--|--|--|
| | $\begin{array}{c} \text{Me Me Me} \\ \\ -\text{Si}-\text{C}-\text{C}-\text{C} \\ \\ \text{Me Me Me} \end{array}$ | $\begin{array}{c} \text{Me Me} \\ \\ -\text{Si}-\text{C}-\text{Me} \\ \\ \text{Me Me} \end{array}$ | $\begin{array}{c} \text{Me Me Me} \\ \\ -\text{Si}-\text{C}-\text{C}-\text{C} \\ \\ \text{Me Me Me} \end{array}$ | $\begin{array}{c} \text{Me Me} \\ \\ -\text{Si}-\text{C}-\text{Me} \\ \\ \text{Me Me} \end{array}$ |
| AcOH / THF / H ₂ O 3:1:1, RT | (24 hrs) | | 48 hrs | |
| 1% conc. HCl / EtOH RT | 3 min (30 min) | 1.5 min | 20 min (2.3 hrs) | 6 min |
| 5 eq. HF / Urea ^b , Cyclohexane, RT | (25 min) | | (30 min) | (30 min) |
| 2-3 eq. Bu ₄ NF, THF, RT | 10 min (3 hrs) | 4 min | 3 hrs (18 hrs) | 70 min |

a) in parenthesis is the time after which complete cleavage is observed.

b) 57% HF in urea; produced by condensation of hydrogen fluoride onto urea ⁷.

The same difference of stability was observed in the deprotection of the two N-silyl



lactams 12 and 13. An NMR analysis in $\text{CD}_3\text{CN}/\text{CF}_3\text{COOH}/\text{D}_2\text{O}$ 3:1:1 at 35°C showed a half-life of 90 min. for the deprotection of 12 versus 40 min. for 13. As an additional feature it should be noted that the hydrolysis product of TDS derivatives, thexyldimethylsilanol, can be recycled to TDS-Cl by simply heating the silanol with thionyl chloride or phosphorous pentachloride⁸ furnishing TDS-Cl in 60-85% yield after distillation.

In summary, several advantages can be envisioned for the use of the thexyldimethyl group as a hydroxy-protecting moiety: (1) its ready availability and low cost; (2) its slightly greater stability compared with tert-butyldimethylsilyl ethers and (3) its improved ease of handling compared with tert-butyldimethylsilyl chloride (TDS-Cl is a liquid).

References and Notes

1. The thexyl group = 2,3-dimethyl-2-butyl, using the nomenclature of Brown, H.C., "Boranes in Organic Chemistry", Cornell University Press, 1972.
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6. TDS-Cl and trifluoromethanesulfonic acid are heated to 60° for 5 hrs and the resulting silyl ester is isolated by distillation, bp. $40-42^\circ\text{C}/0.15$ torr. In analogy to Emde, H.; Domsch, D.; Feger, H.; Frick, V.; Götz, A.; Hergott, H.H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G., *Synthesis* 1982, 1.
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