Registry No. 1, 5344-88-7; **2a**, 104-55-2; **2b**, 122-57-6; **2c**, 101-39-3; **2d**, 75032-63-2; **3a**, 63569-88-0; **3b**, 75032-64-3; **3c**, 75032-65-4; **3d**, 75045-87-3; **4a**, 63570-05-8; **4b**, 63570-09-2; **4c**, 63570-08-1; **4d**, 75032-66-5; **5a**, 75032-67-6; **5b**, 75032-68-7; **5c**, 75032-69-8; **6a**, 75032-70-1; **6b**, 75032-71-2.

The Triisopropylsilyl Group as a Hydroxyl-Protecting Function

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A number of hindered triorganosilyl groups have been employed for the purpose of masking hydroxyl functions.[1-3,6] Among the more well-known of these are the *tert*-butyldimethylsilyl (TBDMS)[1] and *tert*-butyldiphenylsilyl (TBDPS)[2] moieties. A central concern in these cases is the stability of silyl ethers thus obtained toward hydrolysis under acidic or basic conditions, as unmasking is ultimately desireable but must not occur in an untimely fashion. Relative hydrolytic stabilities are also of interest in those instances were two or more sites may be protected by different silyl groups.

Some time ago, we reported an improved method for the synthesis of triisopropylsilyl chloride (TIPS-Cl) by which this reagent could be readily obtained in high purity from inexpensive materials.[4] From data then available on the rates of alkoxysilane hydrolysis,[5] it appeared that the TIPS group would represent a useful hydroxyl-protecting moiety which would be less easily removed than the TBDMS function. Indeed, independent work detailing stabilities of TIPS and other silyl-protected nucleosides and nucleotides soon appeared, based on a less convenient preparation of TIPS-Cl.[6] However, wider use of TIPS-Cl as a blocking reagent has not occurred.

Table I contains data on the relative ease of removal of TBDMS, TIPS, and TBDPS groups from a primary (1-butanol) and a secondary (cyclohexanol) alcoholic site. All silyl ethers were readily prepared from the appropriate silyl chloride and alcohol in dimethylformamide with imidazole catalysis.[1,7] A comparison of hydrolysis rates under acidic conditions indicates progressively less facile cleavage for both classes of silyl ethers along the series TBDMS, TIPS, TBDPS. In both primary and secondary cases, the rate difference between the TBDMS ether and the TIPS derivative is such so as to make only the TIPS group acceptable if acidic conditions needed for the purpose of other transformations must be maintained for more than a minute or so. This rate difference is in fact large enough to allow the selective removal of the TBDMS group in the presence of the TIPS group at or just below ambient temperatures in a relatively short time. Acid hydrolysis rate differences observed between TIPS and TBDPS derivatives of the alcohols examined indicate significantly faster cleavage of the TIPS ethers, particularly for the primary silyl ethers.

Table I. Half-Life of Silyl Ethers R_3SiOR' Under Desilylation Conditions[a]

	R′				
	n-butyl		cyclohexyl		
R_3	H^+	OH^-	H^+	OH^-	F^-
TBDM	<1 min	1 h	<4 min	26 h	76 min
TIP	18 min	14 h	100 min	44 h	137 min
TBDP	244 min	<4 h	360 min	14 h	*b*

[a] Acid hydrolysis: 1% HCl/95% EtOH/22.5 °C. Base hydrolysis: 5% NaOH/95% EtOH/90 °C. Fluoride ion cleavage: 2 equiv of *n*-Bu_4NF/THF/22.5 °C. [b] Not determined.

Base-induced desilylation of all ethers examined was much slower than respective acid-catalyzed hydrolysis, and even at 90 °C, half-lives on the order of hours were observed. An interesting reversal in hydrolysis rates vs. the acid-catalyzed results is noted in that the TBDPS derivatives are cleaved faster than the TIPS ethers. These TBDPS rates are, in fact, close to the TBDMS rates, an observation which is presaged by Sommer's report that under basic conditions menthoxytriphenylsilane is cleaved at approximately the same rate as the corresponding trimethylsilyl ether.[5]

The method of choice for unmasking silyl ethers under weakly basic conditions has employed tetra-*n*-butylammonium fluoride in tetrahydrofuran.[1] This reagent was found to effect the removal of cyclohexyl TIPS ether within a convenient time frame (e.g., overnight) at ambient temperatures and thus provides a useful alternative to the acid-catalyzed cleavage conditions.

In sum, several advantages can be envisioned for the use of the TIPS group as a hydroxyl-protecting moiety: (1) low cost and ready availability of pure TIPS-Cl, (2) greater stability of TIPS over TBDMS ethers, (3) more facile acidic deprotection of TIPS over TBDPS derivatives, and (4) relatively high volatility of TIPS ethers for purposes of gas chromatographic and mass spectral analysis.

Experimental Section

General. Infrared (IR) data were obtained on neat films, using a Beckman Acculab 4 spectrophotometer. ^1H NMR data was obtained on CCl_4 solutions containing tetramethylsilane or benzene (taken as δ 7.24), using a Varian A60-A spectrometer. Gas chromatographic (GC) analyses were performed on a Varian 1720 gas chromatograph with a thermal-conductivity detector, using a 5 ft × 0.25 in. 3% SE-30 stainless steel column. TBDMS-Cl and TBDPS-Cl were commercially obtained; the latter was significantly contaminated with diphenyldichlorosilane. Triisopropylsilyl chloride was prepared from triisopropylsilane as reported.[4] Triisopropylsilane was obtained by a modification of the procedure of Nametkin et al.[8] The Grignard reagent prepared from 8.0 mol of isopropyl chloride and 8.3 mol of magnesium turnings in 4 L of THF was treated at 0 °C with 2.0 mol of trichlorosilane and allowed to stir for 3 days at 25 °C. Workup and distillation through a 10-in. Vigreux column gave triisopropylsilane (80% based on $HSiCl_3$), bp 53–63 °C (18 mm), which was 95% pure by GC analysis.

Alkyl Silyl Ether Preparation. All alkyl silyl ethers were prepared by stirring a mixture of alcohol, chlorosilane, imidazole (1:1.2:2.5 molar ratio), and dimethylformamide (2 mL/g of alcohol)

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for 12–20 h. After a dilute acid wash, vacuum distillation afforded the products. GC analysis (5-ft 3% SE-30, 70–100 °C) indicated a purity of 95% for *n*-butoxy-*tert*-butyldimethylsilane and ≥98% for the other silyl ethers purified by distillation. For TBDPS derivatives, the presence of dichlorodiphenylsilane in the sample of TBDPS-Cl led to mixtures, and the desired ethers were isolated by preparative GC (10-ft 20% SE-30, 200–220 °C).

Cyclohexoxy-*tert*-butyldimethylsilane: bp 78 °C (5 mm); IR and NMR data were consistent with literature values.[3]

***n*-Butoxy-*tert*-butyldimethylsilane**:[9] bp 38–42 °C (4 mm); IR 2960 (s), 2930 (s), 2860 (s), 1480 (m), 1470 (m), 1395 (w), 1370 (w), 1260 (s), 1130 (m), 1105 (s), 1045 (m), 1010 (w), 985 (m), 945 (w), 895 (m), 840 (s) cm^{-1}; ^1H NMR δ 3.44 (m, 2 H), 1.29 (m, 4 H), 0.85 (m, 3 H), 0.72 (s, 9 H), −0.15 (s, 6 H). Anal. Calcd for $C_{10}H_{24}OSi$: C, 63.76; H, 12.84. Found: C, 63.82; H, 12.89.

Cyclohexoxytriisopropylsilane: bp 88–95 °C (1 mm); IR 2940 (s), 2870 (s), 1470 (m), 1455 (m), 1390 (w), 1375 (m), 1260 (w), 1140 (m), 1110 (s), 1075 (m), 1060 (m), 1020 (m), 1000 (m), 920 (w), 885 (s), 860 (m), 815 (m), 780 (m) cm^{-1}; ^1H NMR δ 3.8 (m, 1 H), 1.2–2.0 (m, 10 H), 1.04 (s, 21 H). Anal. Calcd for $C_{15}H_{32}OSi$: C, 70.24; H, 12.58. Found: C, 70.04; H, 12.27.

***n*-Butoxytriisopropylsilane**: bp 90 °C (5 mm); IR 2960 (s), 2940 (s), 2900 (s), 2870 (s), 1470 (s), 1390 (m), 1370 (w), 1250 (w), 1130 (s), 1110 (s), 1070 (m), 1045 (m), 1015 (m), 1000 (m), 985 (m), 920 (w), 885 (s), 775 (m), 720 (m) cm^{-1}; ^1H NMR δ 3.53 (m, 2 H), 1.1–1.5 (m, 4 H), 0.90 (s, 21 H), 0.76 (m, 3 H). Anal. Calcd for $C_{13}H_{30}OSi$: C, 67.76; H, 13.12. Found: C, 67.80; H, 13.28.

Cyclohexoxy-*tert*-butyldiphenylsilane: IR 3070 (m), 3050 (m), 2930 (s), 2860 (s), 1960 (w), 1900 (w), 1830 (w), 1660 (w), 1590 (w), 1480 (m), 1465 (m), 1450 (m), 1430 (s), 1395 (m), 1380 (m), 1365 (m), 1260 (w), 1190 (w), 1115 (s), 1095 (s), 1055 (m), 1030 (m), 1020 (m), 1010 (m), 1000 (m), 940 (w), 890 (w), 860 (m), 825 (m), 785 (w), 740 (m), 705 (s) cm^{-1}; ^1H NMR δ 7.61 (m, 4 H), 7.29 (m, 6 H), 3.62 (m, 1 H) 1.1–1.9 (m, 10 H), 0.99 (s, 9 H). Anal. Calcd for $C_{22}H_{30}OSi$: C, 78.05; H, 8.93. Found: C, 78.15; H, 8.98.

***n*-Butoxy-*tert*-butyldiphenylsilane**: IR 3080 (m), 3060 (m), 2960 (s), 2940 (s), 2870 (s), 1960 (w), 1900 (w), 1830 (w), 1660 (w), 1595 (w), 1480 (m), 1465 (m), 1435 (s), 1395 (m), 1370 (m), 1310 (w), 1270 (w), 1240 (w), 1195 (w), 1115 (s), 1045 (m), 1010 (m), 1000 (m), 990 (m), 945 (w), 890 (m), 825 (m), 780 (m), 740 (m), 700 (s) cm^{-1}; ^1H NMR δ 7.52 (m, 4 H), 7.15 (m, 6 H), 3.52 (m, 2 H), 1.0–1.6 (m, 4 H), 0.91 (s, 9 H), 0.68 (m, 3 H). Anal. Calcd for $C_{20}H_{28}OSi$: C, 76.87; H, 9.03. Found: C, 76.66; H, 8.99.

Half-Life Determinations. Conditions reported by Barton and Tully were empolyed.[3] Acid cleavage was effected by using a stock solution of 1% HCl in aqueous ethanol prepared by mixing 2.9 g of concentrated (37%) hydrochloric acid and 97.1 g of 95% ethanol. A mixture of the silyl ether (50 μL) in 0.90 mL of the stock solution was thermostatted at 22.5 °C and aliquots were withdrawn periodically for GC determination of the remaining silyl ether. Base cleavage employed a stock solution of 5 g of NaOH in 95 g of 95% ethanol. A mixture of the silyl ether (50 μL) in 0.90 mL of the stock solution was stirred for 10 min at room temperature and 50-μL portions were transferred to melting-point tubes. These were sealed, thermostatted at 90 °C, and opened sequentially for GC determination of the amount of silyl ether remaining.

Tetra-*n*-butylammonium fluoride cleavages were carried out by thermostatting a mixture of 2.5 mmol of the silyl ether, 5.0 mmol of the fluoride reagent, 0.2–0.3 g of decane or undecane (internal standard) and sufficient THF to make 5.0 mL at 22.5 °C. Aliquots were periodically withdrawn, and the yield of cyclohexanol was determined by GC.

Registry No. Cyclohexoxy-*tert*-butyldimethylsilane, 67124-67-8; *n*-butoxy-*tert*-butyldimethylsilane, 37170-50-6; cyclohexoxytriisopropylsilane, 75031-66-2; *n*-butoxytriisopropylsilane, 75031-67-3; cyclohexoxy-*tert*-butyldiphenylsilane, 75031-68-4; *n*-butoxy-*tert*-butyldiphenylsilane, 75031-69-5; cyclohexanol, 108-93-0; butanol, 71-36-3; chloro(1,1-dimethylethyl)dimethylsilane, 18162-48-6; chlorotris(1-methylethyl)silane, 13154-24-0; chloro(1,1-dimethylethyl)diphenylsilane, 58479-61-1.

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Ortho Functionalization of *N*-(*tert*-Butoxycarbonyl)aniline[1]

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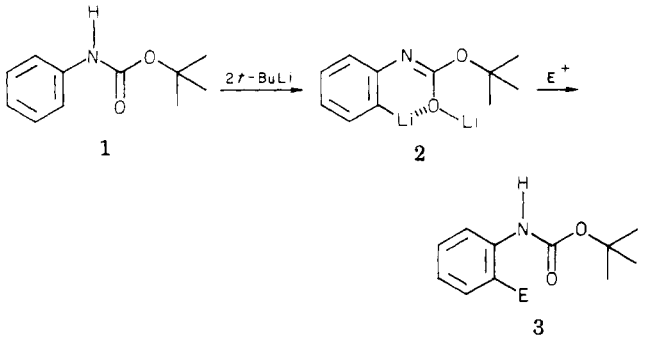
The direct ortho functionalization of aniline and derivatives thereof has been the subject of several recent publications.[2] Of particular note are those which describe the utilization of anilinodichloroboranes for the ortho acylation and ortho hydroxyalkylation of anilines and N-substituted anilines[3] and the specific ortho substitution of *N*-pivaloylanilines via the corresponding dilithio species.[4] The latter process is especially attractive because of the wide range of functional groups which can be incorporated but has the disadvantage that the pivaloyl group must be removed if the substituted aniline is required. Although it is reported[4,5] that this protecting group can be excised hydrolytically (HCl or Et_3OBF_4/H_2O), it was apparent to us that a more readily removable moiety would be advantageous. As a consequence, a study of the ortho lithiation of *N*-(*tert*-butoxycarbonyl)aniline (**1**) was undertaken.

When **1** was reacted with excess (2.5 equiv) *n*-butyllithium (with or without added tetramethylethylenediamine) or *sec*-butyllithium, in tetrahydrofuran-hexane solution, dilithiation did not occur, even after several hours at room temperature. Ortho metalation did, however, take place relatively rapidly with *tert*-butyllithium at low temperatures, as demonstrated by the isolation of *N*-(*tert*-butoxycarbonyl)-*o*-toluidine (**4**) from the mixture obtained when the reaction was quenched with 1 equiv of methyl iodide. Optimization of the reaction conditions for the formation of this product showed that the best yield thereof (59%; 92% based on recovered starting material) was obtained when metalation was effected with 2.4 equiv of *tert*-butyllithium at −20 °C for 2–2.5 h. No *N*-methyl-*N*-(*tert*-butoxycarbonyl)-*o*-toluidine (**5**) was formed, although this substance could be prepared in high



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