Photochemically-Removable Silyl Protecting Groups

Michael C. Pirrung* and Yong Rok Lee[1]

Department of Chemistry, P. M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27708-0346

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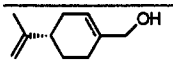
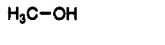
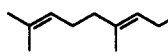
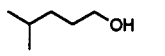
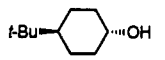
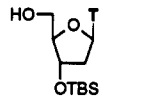
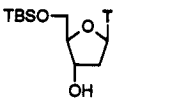
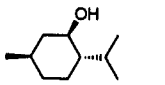
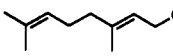
Summary: (Hydroxystyryl)dimethylsilyl (HSDMS) and (hydroxystyryl)diisopropylsilyl (HSDIS) reagents have been developed that readily protect primary and secondary alcohols and can be removed on irradiation with short wavelength light in polar solvent.

Photochemically-removable groups have many applications in bioorganic chemistry. Besides providing deprotection that can be accomplished under conditions that leave most other protecting groups untouched,[2] they can be used in the technique of caging,[3] wherein a biological molecule is rendered both inactive and membrane-permeable by the protecting group. Once located inside a cell or an enzyme active site,[4] the protecting group can be released on a time scale much faster than that of the biological or enzymatic process, permitting the study of the time evolution of the phenomena. Photoremovable groups are also key to the novel technique of light-directed synthesis, whereby the preparation of large arrays consisting of thousands of biopolymer sequences can be accomplished.[5] Many of the photoremovable groups currently in use are based on nitrobenzyl photochemistry that produces a byproduct nitrosocarbonyl compound. This substance can create problems with development of intensely-absorbing solutions during deprotection and reaction with functional groups such as amines. Nitrobenzyl ethers can also be difficult to form from alcohols, a functional group commonly requiring protection.[6] On the basis of our interest in photochemical DNA synthesis, a photoremovable replacement for the dimethoxytrityl group commonly used for the 5′-hydroxyl of nucleosides was required. We report here that styrylsilyl ethers are excellent reagents for the protection of primary and secondary alcohols and that their deprotection occurs under UV irradiation.

Our method for removing a silyl group photochemically draws on the previous results of Porter concerning the deprotection of serines at protease active sites that have been acylated with *o*-hydroxycinnamates.[7] Photochemical *trans–cis* isomerization brings the phenolic hydroxyl into proximity for lactonization, releasing the alcohol. A simple substitution of the cinnamate carbonyl by a silyl ether should permit the same chemistry to occur. The required silylating reagents **2** were easily prepared from *o*-hydroxyphenylacetylene[8] by acetylation, hydrosilation[9] (dimethyl- and diisopropylchlorosilane), and simultaneous deacylation and chloride substitution with lithium dimethylamide (70% overall) (eq 1). Simply stirring an alcohol in THF with **2** (R = Me) converts it to the protected derivative within 3 h (eq 2). Protection with **2** (R = *i*-Pr) requires overnight reaction at room temperature, and in some cases warming. As shown in Table I, protection of primary and secondary alcohols occurs in excellent yields. We have thus far been unable to protect tertiary alcohols with these reagents. These silyl ethers show a strong short wavelength

Table I. Alcohols Protected with Reagents 2 and Their Deprotection Reactions

compd		protection (% yield, procedure A or B)[a]	deprotection (% yield, procedure C)[a]
	**12**	80, A	83
	**13**	82, B	87
	**14**	92, A	91
	**15**	95, A	89
	**16**	86, A	84
	**17**	76, A[b]	92[c]
	**18**	72, A[b]	91[c]
	**19**	91, A	87
	**14**	70, B	75

[a] Procedure A: the alcohol (1.2 mmol) was dissolved in 5 mL of THF and added to a solution of 1.0 mmol of **2** (R = Me) in THF. After 3 h at rt, TLC showed the reaction was complete. Procedure B: the alcohol (1.2 mmol) was dissolved in 5 mL of THF and added to a solution of 1.0 mol of **2** (R = *i*-Pr) in THF. After 12 h at rt or 4 h at reflux, TLC showed the reaction was complete. Deprotection procedure C: the silyl ether (30 mg) was dissolved in acetonitrile at a concentration of 0.01 M and irradiated in a quartz cell in the Rayonet reactor (254 nm) at rt for 30 min, when monitoring by TLC showed that the reaction was complete. Silica gel chromatography provided the starting alcohol in the indicated yields. [b] Reflux, 4 h. [c] 40 min irradiation, >95% yield by NMR.

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(1) Postdoctoral fellow of the Korea Science and Engineering Foundation.

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(3) Adams, S. R.; Kao, J. P. Y.; Tsien, R. Y. *J. Am. Chem. Soc.* **1989**, *111*, 7957-7968.

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(5) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Liu, A. T.; Solas, D. *Science* **1991**, *251*, 767.

(6) For a recent example, see: Pirrung, M. C.; Nunn, D. S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1489.

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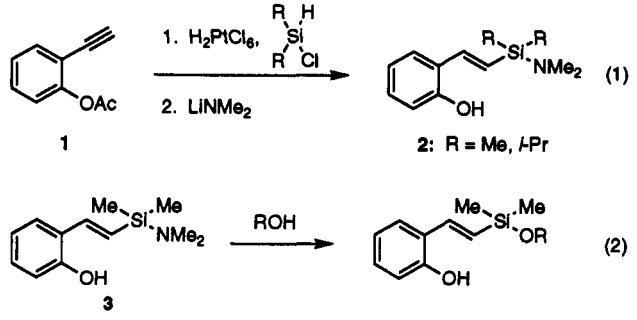
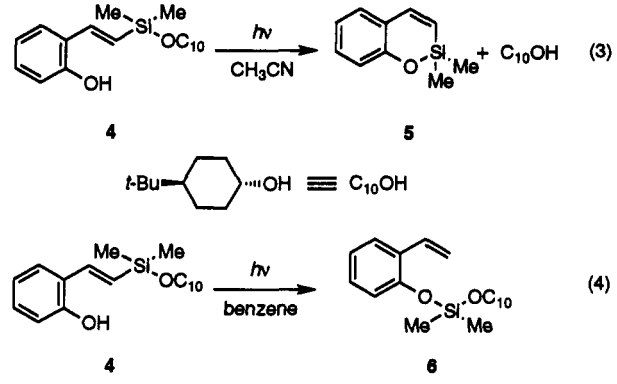


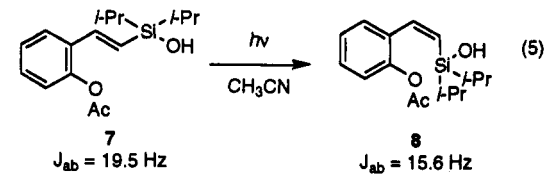
absorption band at 258 nm (log ϵ 4.28) and a weaker band at 309 nm (log ϵ 3.94).

The photochemistry of the (hydroxystyryl)silyl ethers shows an intriguing solvent dependence. Irradiation of 4 (Rayonet reactor, 254 nm, quartz reaction vessel) in acetonitrile produces 5[10] (84%) and the alcohol within 30 min (eq 3). Using benzene, 4 is converted to the interesting silylidene derivative 6[11] (91%) within 20 min (eq 4).

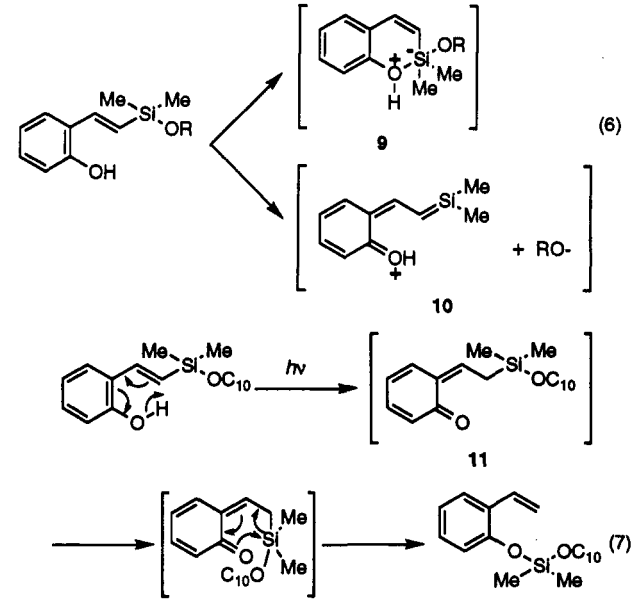


Support for the proposed mechanism of deprotection was gained by study of a substrate that cannot form a cyclic siloxane such as 5. When 7 (isolated by silica gel chromatography as a byproduct in a preparation of 2 (R = *i*-Pr)) is irradiated in acetonitrile, *cis* isomer 8[12] is produced as the minor component of a 60:40 mixture within 30 min (eq 5).

These reactions can be explained by two competing channels, one concerted and solvent independent, the other stepwise and highly solvent dependent. Deprotection may occur by an initial *trans–cis* isomerization to produce betaine 9, followed by elimination of alcohol, or by a



photosolvolysis to generate the highly conjugated quinone methide–silaalkene 10, followed by proton transfer and electrocyclic ring closure (eq 6). Rearrangement may occur



by an initial [1,5]-H shift to produce the quinone methide 11 followed by conformational change and a [1,5]-Si shift (eq 7), a postulate that is the subject of a mechanistic study reported elsewhere.[13] These observations made the choice of reaction conditions for the deprotection of (hydroxystyryl)silyl ethers straightforward: irradiations were conducted with 254-nm radiation in acetonitrile solvent.

Table I summarizes the rapid (within 30 min) deprotection reactions of a variety of silyl ethers prepared from primary and secondary alcohols and compounds 2. High yields of purified material are uniformly observed despite the pilot scale on which these reactions have been conducted. Noteworthy are the results with protected nucleosides 17 and 18, which serve as prototypes for DNA chains growing from their 5′ and 3′ ends, respectively.

It is important for many synthetic applications that these (hydroxystyryl)dimethylsilyl (HSDMS) and (hydroxystyryl)diisopropylsilyl (HSDIS) ether derivatives be stable to a variety of reaction conditions, particularly those used to remove other protecting groups. The instability of HSDMS ethers is comparable to simple trimethylsilyl ethers: TBAF (5 equiv, THF, 10 min), 1 N NaOH (5 equiv, THF, 30 min), and 1 N HCl (5 equiv, THF, 10 min) remove it readily, but aqueous workup conditions do not harm it. Conversely, HSDIS ethers have stability similar to TIPS ethers, since they survive tetrazole (the condensing catalyst for phosphoramidite-based DNA synthesis, 5 equiv, THF), EtMgBr (xs, 0 °C, THF), $NaBH_4$ (xs, rt, MeOH), and PDC (xs, rt, CH_2Cl_2). They are removed by TBAF (5 equiv, THF, 20 min) and 1 N HCl (5 equiv, THF, 20 min).

(10) Spectral data for 5: ^1H NMR ($CDCl_3$) δ 0.33 (s, 6H), 5.89 (d, J = 14.4, 1H), 6.87–7.13 (m, 4H), 7.23 (d, J = 14.4, 1H); IR (neat) 3061, 2995, 2974, 1599, 1552, 1480, 1449, 1273, 1263, 1101, 1030, 923, 795, 752 cm^{-1}; MS (m/z, CI) 177 (M^+ + 1); HRMS (CI) calcd for $C_{10}H_{13}OSi$ 177.0736, found 177.0726. The analogous diisopropylsiloxane derivative shows: ^1H NMR ($CDCl_3$) δ 1.02 (d, J = 4.2, 6H), 1.04 (d, J = 3.3, 6H), 1.06 (m, 2H), 5.84 (d, J = 14.4, 1H), 6.85–7.11 (m, 4H), 7.35 (d, J = 14.4, 1H); IR (neat) 2943, 2865, 1598, 1480, 1272, 1262, 1100, 920, 777, 751 cm^{-1}; MS (m/z, CI) 233 (M^+ + 1); HRMS (EI) calcd for $C_{14}H_{20}OSi$ 232.1283, found 232.1290.

(11) Spectral data for 6: ^1H NMR (600 MHz, $CDCl_3$) δ 0.24 (s, 6H), 0.81 (s, 9H), 0.93–1.93 (m, 9H), 3.72 (m, 1H), 5.21 (dd, J = 11.4, 1.2 Hz, 1H), 5.69 (dd, J = 17.4, 1.2 Hz, 1H), 6.92 (m, 2H), 6.99 (dd, J = 17.4, 11.4 Hz, 1H), 7.11 (ddd, J = 8.1, 7.5, 1.8 Hz, 1H), 7.46 (dd, J = 7.5, 1.8 Hz, 1H); IR (neat) 2946, 2867, 1598, 1552, 1484, 1452, 1255, 1088, 927, 801, 754 cm^{-1}; MS (m/z, CI) 333 (M^+ + 1); HRMS (EI) calcd for $C_{20}H_{32}O_2Si$ 332.2171, found, 332.2168.

(12) Spectral data for 8: ^1H NMR (600 MHz) δ 0.94 (m, 2H), 0.98 (d, J = 6.6 Hz, 12H), 1.77 (br s, 1H), 2.25 (s, 3H), 5.85 (d, J = 15.6 Hz, 1H), 6.98 (dd, J = 7.8, 1.2 Hz, 1H), 7.20 (dd, J = 7.8, 6.6 Hz, 1H), 7.28 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.35 (d, J = 15.6 Hz, 1H), 7.36 (d, J = 6.6 Hz, 1H); IR (neat) 3444, 2949, 2885, 1785, 1603, 1485, 1371, 1204, 1091, 846, 757 cm^{-1}; MS (m/z, CI) 293 (M^+ + 1), 275 (M^+ + 1 – H_2O); HRMS (EI) calcd for $C_{16}H_{24}O_3Si$ 292.1494, found 292.1494.

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In sum, photochemically-removable versions of the silyl protecting groups that have seen widespread use in organic synthesis have been developed. They are particularly intended for novel methods of combinatorial synthesis based on spatially localized, light-directed chemistry.

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Supplementary Material Available: ^{1}H NMR spectra of all new compounds (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.