JOC*Note*

p-Siletanylbenzylidene Acetal: Oxidizable Protecting Group for Diols

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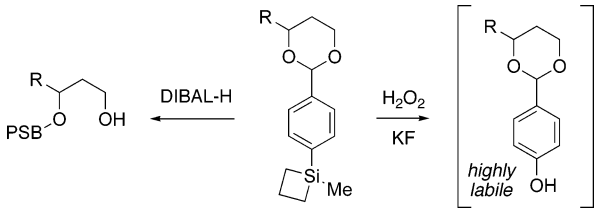
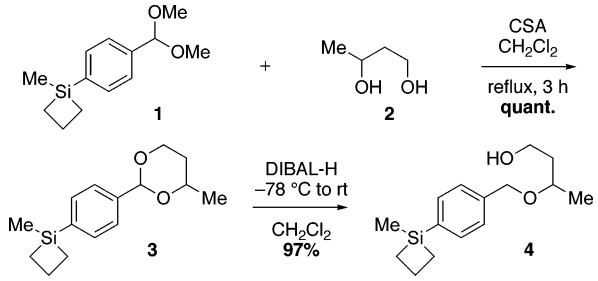


Hydrogen peroxide oxidation of benzylidene acetals (and derivative benzyl ethers) that incorporate a siletane ring at the para position creates a deprotection pathway without affecting other important chemical properties of the benzylidene acetal, such as regioselective reductive ring opening.

Our recent finding[1] that alkyl- and arylsiletanes are oxidized to the corresponding alcohols with alkaline peroxide under mild conditions prompted a follow-up study, in which the *p*-siletanylbenzyl (PSB) ether was designed and tested as a protecting group (PG) for alcohols and phenols.[2] Protecting group manipulations play a key role in organic synthesis.[3] We envision particular applications of the PSB group in carbohydrate synthesis.[4]

Arylmethyl ether PGs are routinely employed in glycosylations due to their tolerance of acidic reaction conditions and to exploit their increased reactivity relative to acyl-protected glycosyl donors.[5] Frequently the spectator hydroxyl groups require differential protection; for such cases there is a demand for diverse arylmethyl (modified benzyl) PGs[6] that support efficient glycosylations yet cleave under mild and mutually compatible conditions.

SCHEME 1. Synthesis and Reductive Opening of PSP Acetal 3



The *p*-siletanylbenzyl (PSB) ether fulfills the criteria necessary to meet this demand.[2] It is electronically similar to the benzyl ether and stable to the DDQ-promoted removal of the *p*-methoxybenzyl group, yet treatment with hydrogen peroxide or *tert*-butyl hydroperoxide (TBHP) under Tamao-type conditions[7] triggers its cleavage. However, siletanes succumb to ring-opening reactions in the presence of hard nucleophiles such as alkyllithiums and potassium or sodium alkoxides.[8] Silver oxide-promoted arylmethylation reactions do not affect the siletane functionality; this provides a convenient method for the formation of PSB ethers from primary alcohols, but secondary alcohols reacted sluggishly in our initial study. We therefore became interested in alternative methods for preparing PSB ethers from secondary alcohols.

Herein we describe the synthesis and utility of *p*-siletanylbenzylidene acetal **1**, which presents one option for introducing PSB ethers onto secondary alcohols in a manner consistent with many synthetic efforts. In a broader context, the *p*-siletanylphenyl (PSP)-substituted acetals provide an attractive complement to other alkylidene acetal PGs for the unique cleavage pathway enabled by peroxide oxidation of the arylsiletane moiety. Thus, in the course of developing PSP-substituted acetals as precursors to PSB ethers, we were also interested in (1) verifying that the chemistry of arylsiletane-derived acetals (e.g., **3**) is grossly analogous to other widely studied benzylidene acetals and (2) highlighting the primary difference in chemical reactivity, which is the ability to oxidize the arylsiletane moiety to the corresponding phenol with hydrogen peroxide. In this Note we report the results of our studies aimed at addressing these points, and we submit the *p*-siletanylbenzylidene acetal (**1**) as a novel reagent for the protection of diols.

The *para*-siletanylbenzylidene acetal undergoes reductive ring opening upon treatment with diisobutylaluminum hydride (DIBAL-H) to afford the more substituted PSB ether. We examined the protection of 1,3-butanediol and subsequent reductive ring opening of benzylidene acetal **3** (Scheme 1). Simple acetal formation occurred quantitatively with use of catalytic camphorsulfonic acid (CSA) in refluxing methylene chloride. Note the arylsiletane stability to acidic conditions. Subsequent treatment with DIBAL-H[9] afforded **4** in nearly quantitative yield; the overall yield for the two-step sequence

(1) Sunderhaus, J. D.; Lam, H.; Dudley, G. B. *Org. Lett.* **2003**, *5*, 4571−4573.

(2) Lam, H.; House, S. E.; Dudley, G. B. *Tetrahedron Lett.* **2005**, *46*, 3283−3285.

(3) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, Germany, 2003.

(4) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.

(5) The armed/disarmed tactic for glycoside coupling takes advantage of this reactivity difference. (a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584. (b) Paulsen; H.; Richter, A.; Sinnwell, V.; Stenzel, W. *Carbohydr. Res.* **1978**, *64*, 339−362.

(6) For recent arylmethyl PGs that were developed within the context of carbohydrate synthesis, see: (a) Jobron, L.; Hindsgaul, O. *J. Am. Chem. Soc.* **1999**, *121*, 5835−5836. (b) Plante, O.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148−7149.

(7) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96−105.

(8) Sheikh, R. K.; Tharanikkarasu, K.; Imae, I.; Kawakami, Y. *Macromolecules* **2001**, *34*, 4384−4389.

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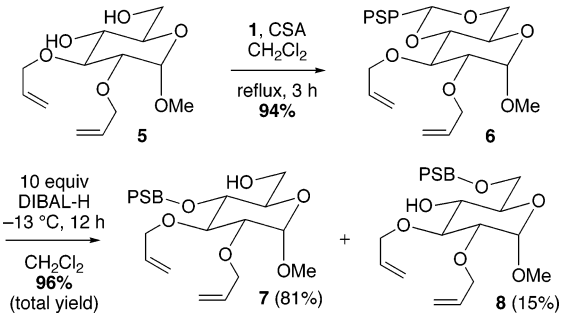
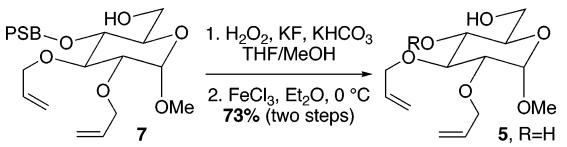
SCHEME 2. PSP Acetal and PSB Ether in a Carbohydrate System



SCHEME 3. Oxidative Activation/Deprotection of a PSB Ether



(**2** → **4**) was 97%. This goes toward addressing the difficulty we had in preparing PSB ethers from secondary alcohols;[2] it also illustrates behavior that parallels other benzylidene acetal PGs.

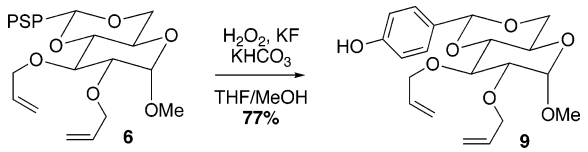
We next investigated *p*-siletanylphenyl (PSP)-substituted acetals within a carbohydrate framework. Glucose-derived diol **5**[10] was protected as shown in Scheme 2, and the PSP-substituted acetal (**6**) was subjected to reductive ring opening with DIBAL-H. As is the case with the parent benzylidene acetal,[11] regioselectivity for this process was high, though not perfect. By employing an excess of DIBAL-H and maintaining a cold reaction temperature,[12] PSB ether **7** was isolated in 81% yield. In this manner, the PSB ether was installed onto the free secondary hydroxyl of **5**.

In previous studies, we found that siletanes can be oxidized to alcohols in the presence of silyl (i.e., TBS) ether PGs and, conversely, that siletanes are stable to the acidic hydrolysis of TBS ethers.[1] Similarly, the oxidative cleavage of PSB and PMB ethers is mutually compatible: DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) selectively removes the PMB group, whereas alkaline hydrogen peroxide affects only the PSB ether.[2] Cleavage of the PSB ether protecting group from the carbohydrate substrate is depicted in Scheme 3.

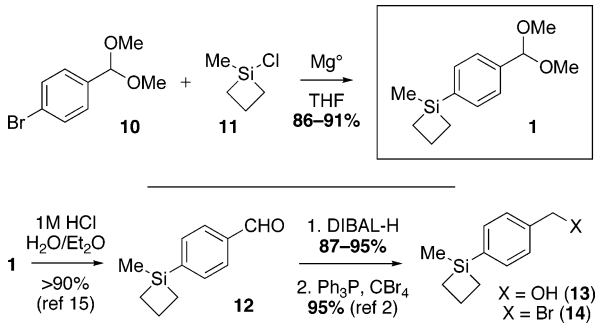
Oxidation of the arylsiletane moiety incorporated within PSB ether **7** afforded a metastable intermediate—the *p*-hydroxybenzyl (PHB) ether, R = PHB—that was easily decomposed to reveal the free alcohol (**5**, Scheme 3).[13] This finding is entirely consistent with our previously reported studies on the deprotection of PSB ethers.[2]

Alkylidene **6** is oxidized under identical conditions (Scheme 4). This stands in sharp contrast to other common alkylidene

SCHEME 4. Oxidative Activation of a PSP-Substituted Acetal



SCHEME 5. Synthesis of Arylsiletane-Based Protecting Group Reagents



acetals, which are generally stable to mildly oxidizing reaction conditions.[3] The resulting *p*-hydroxyphenyl (PHP)-substituted acetal (**9**) is thereby activated for cleavage (by analogy to the PHB ether).[13,14] The PSP-substituted acetal thus provides a useful complement to other common diol PGs.

PSP reagent **1** is conveniently prepared in one step from the commercially available reagents **10** and **11** (Scheme 5). Furthermore, hydrolysis[15] and reduction of **1** affords PSB-OH (**13**), which we disclosed previously for the protection of alcohols and phenols.[2] This alternative synthesis of **13** (and by extension, PSB-Br **14**) is significantly less expensive than our previously reported procedure.

Several notable findings resulted from this study:

1. *p*-Siletanylphenyl (PSP)-substituted acetals can be formed and reductively ring opened in analogy to other common benzylidene acetals, which introduces the PSB ether onto secondary alcohols in a manner consistent with many synthetic efforts.

2. PSP-substituted acetals are oxidized with mildly alkaline hydrogen peroxide, conditions that are highly unlikely to affect typical acetal PGs.

3. PSB reagents **13** and **14** are now available at a reduced cost by way of PSP acetal **1**.

We are continuing our efforts in this area; further synthetic applications of the arylsiletane oxidation will be reported in due course.

Experimental Section

4-(1-Methylsiletanyl)benzaldehyde Dimethyl Acetal (1). Magnesium turnings (146 mg, 6.00 mmol) and iodine (21 mg, 0.080 mmol) were placed in an oven-dried, two-neck, round-bottom flask with a stir bar under argon. THF (1.5 mL) was added, followed by 1,2-dibromoethane (50 μL, 0.32 mmol). The mixture was then cooled to 0 °C in an ice bath for 10 min. 1-Chloro-1-methylsilacyclobutane (0.34 mL, 2.8 mmol) was added dropwise. A solution

(9) Siletanes withstand DIBAL-H but decompose in the presence of lithium aluminum hydride.

(10) Prepared in two steps and 93% overall yield. See the Supporting Information.

(11) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033−2036.

(12) The reaction vessel was placed in the freezer overnight. See the Supporting Information.

(13) *p*-Hydroxybenzyl (PHB) ethers are moderately stable to isolation and purification, but they break down readily under a range of conditions including DDQ (CH_2Cl_2, 0 °C), $FeCl_3$ (Et_2O, 20 °C), NaOMe (MeOH, 60 °C), etc.; see ref 6a.

(14) For example, iron trichloride in ether is effective. See the Supporting Information.

(15) The conversion from **1** to **12** is essentially quantitative, but our starting material (**1**) was contaminated with a small amount of **12** from incidental hydrolysis that had occurred upon prolonged storage.

of 4-bromobenzaldehyde dimethyl acetal (350 μL, 2.1 mmol) in 5 mL of THF was then added dropwise over 45 min via a pressure-equalizing addition funnel at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight, quenched with 5 mL of water, and extracted with three 5-mL portions of diethyl ether. The combined organic layers were washed with 5 mL of brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (10% ethyl acetate in hexanes) provided 0.450 g (91%) of **1** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 5.40 (s, 1H), 3.34 (s, 6H), 2.19 (q, 2H), 1.35−1.12 (m, 4H), 0.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 139.0, 133.4, 126.2, 103.1, 52.7, 18.2, 14.3, −1.77. HRMS (EI^+) found 236.1235 (calcd for $C_{13}H_{20}O_2Si$ 236.1233).

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Supporting Information Available: Detailed experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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