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New and Efficient Procedure for the Preparation of Unsymmetrical Silaketals

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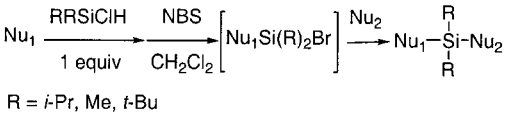
ABSTRACT



R = *i*-Pr, Me, *t*-Bu

A new and efficient procedure for the preparation of unsymmetrical silaketals via a three-step protocol without isolation of the intermediates is presented. The unsymmetrical silyl ethers and silanes can also be readily obtained via this sequence of reactions.

Silylated tethers have become very popular in organic synthesis over the past decade because they allow the transformation of intermolecular reactions into intramolecular ones. Furthermore, they are readily and selectively removed after the reaction, thus providing an easy delivery of the products.

Different aspects of the chemistry of these silicon linkers which are generally ethers have been compiled in several reviews.[1] They have been applied to many types of reactions: radical cyclizations,[1] [4+2] cycloadditions,[1] nucleophilic additions,[1] and more recently, Pauson−Khand reactions[2] and metathesis.[3]

From a practical point of view, the silicon linkage is created by simple silylation of a hydroxy group by a chlorosilane bearing the reactive unit. In addition, the availability of different dialkyldichlorosilanes has warranted the use of silaketals as disposable tethers.

Unfortunately, the synthesis of unsymmetrical silaketals is often complicated by the formation of the undesired symmetrical silaketals. Indeed, the usual protocol for dimethylsilaketal formation consists of the silylation of one alcohol with a large excess of Me_2SiCl_2, subsequent removal of the volatile dichlorosilane, and eventual addition of the second alcohol. However, this method suffers from major drawbacks: (i) the intermediate monochlorosilane has to be easily separated from the dichlorosilane and (ii) higher boiling dialkyldichlorosilanes make this procedure incompatible for the preparation of heavier silaketals. Different solutions have been proposed to circumvent these problems. *t*-$Bu_2Si(OTf)Cl$ was introduced for the preparation of di-*tert*-butylsilaketals, but the second silylation sometimes proved difficult due to the bulkiness of the *tert*-butyl group.[4] Stork used the chlorodimethylamino-dimethylsilane to selectively prepare alkenyl- and alkynylsilyl ethers,[5] but to our knowledge, this procedure has never been applied to unsymmetrical silaketals. The latter were efficiently prepared by the activation of 4-pentenyl silyl ethers with iodonium dicollidine perchlorate in the presence of an alcohol.[6] However, this two-step sequence has been employed only for glycosylations and requires the formation of the intermediate 4-pentenyl silyl ethers.

In this paper, we present a new and very efficient procedure for the preparation of unsymmetrical silaketals via a three-step protocol without isolation of the intermediates. This method is based upon the reaction of a first alcohol with a dialkylchlorosilane, transformation of the resulting alkoxysilane into the corresponding bromide by reaction with *N*-bromosuccinimide, and condensation of the bromide with a second alcohol. *N*-Bromosuccinimide has been used previously to prepare bromoalkylsilanes from trialkylsilanes in a sequence devoted to the preparation of 1-silyloxy-2,3-

(1) (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813−854. (c) Gauthier, D. R. J.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338. (d) Skrydstrup, T. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2001; Vol. 4, pp 439−530. (e) White, J. D.; Carter, R. G. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2001; Vol. 4, pp 371−412.

(2) Brummond, K. M.; Sill, P. C.; Rickards, B.; Geib, S. J. *Tetrahedron Lett.* **2002**, *43*, 3755−3738.

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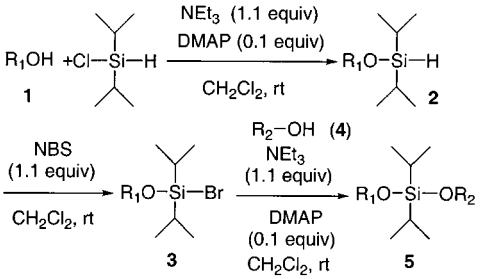
epoxyalkanes[7] but has been limited to these compounds and no silaketals have been prepared. The proposed sequence is carried out in only one solvent at room temperature and in addition, each step is performed with a stoichiometric amount of each reagent.

We have first chosen chlorodiisopropylsilane for the study (Scheme 1), because the corresponding silaketals **5** formed

Scheme 1. General Preparation of Silaketals



are known to be stable to aqueous workup and chromatography.[8]

The alcohol R_1OH was initially treated with 1 equiv of *i*-Pr_2SiClH in the presence of triethylamine and 4-(dimethylamino)pyridine in CH_2Cl_2 at room temperature. The reaction was monitored by TLC until completion. The corresponding alkoxydiisopropylsilane **2** was then transferred with filtration into another flask and the filtrate was treated with *N*-bromosuccinimide, added pure by small portions. The resulting solution was transferred into a solution of the second alcohol R_2OH **4** in the presence of triethylamine and 4-(dimethylamino)pyridine in CH_2Cl_2 to afford silaketals **5** in high overall yield. The results are summarized in Table 1.

Table 1. Preparation of the Diisopropylsilaketals **5**

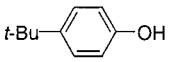
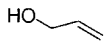
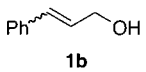
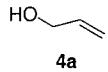
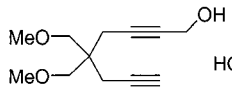
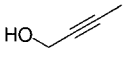
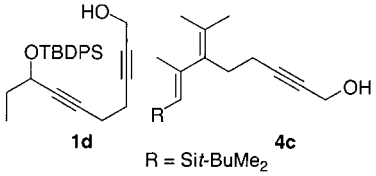
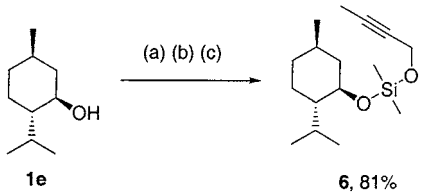
R_1OH (**1**)	R_2OH (**4**)	**5**, yield (%)
 **1a**	 **4a**	**5a**, 85
 **1b**	 **4a**	**5b**, 86
 **1c**	 **4b**	**5c**, 71
 **1d** R = Si*t*-BuMe$_2$	**4c**	**5d**, 52

Table 1 shows that the conditions of the reaction are compatible with aromatic, allylic, and propargylic alcohols. In the case of **5d**, the yield is moderate and whatever the reaction time, the reaction did not go to completion. Alcohols **1d** and **4c** were recovered.

Having these results in hands, we turned our attention to the preparation of dimethylsilaketals. As expected, the corresponding alkoxysilanes and silylbromides are quite unstable on TLC and, therefore, monitoring of the first two steps was difficult. In addition, when primary alcohols were used such as **4a** and **4b**, the reactions occurred but the resulting dimethylsilaketals were moderately stable and no representative yields could be obtained. However, in the case of menthol **1e** and 2-butyn-1-ol **4b**, silaketal **6** was isolated in 81% overall yield (Scheme 2).

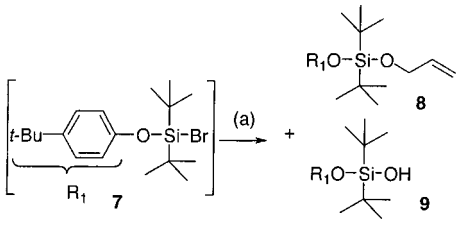
Scheme 2[a]



[a] Reagents and conditions: (a) $ClSiMe_2H$ (1 equiv), NEt_3 (1.1 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt. (b) NBS (1.1 equiv), CH_2Cl_2, rt. (c) 3-Butyn-1-ol, **4b**, NEt_3 (1.1 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt.

Upon use of di-*tert*-butylchlorosilane, the sequence had to be modified. Indeed, the alkoxydi-*tert*-butylsilylbromide **7**, derived from alcohol **1a**, did not react with **4a** under the previously described conditions. To overcome this lack of reactivity, we carried out the reaction in the presence of DMF in different conditions. The results are summarized in Table 2.

Table 2. Reaction Conditions for the Preparation of the Di-*tert*-butylsilaketals



conditions (a)	**8** (%)	**9** (%)
DMF, NEt_3 (1.1 equiv) DMAP (0.1 equiv)	50	50
DMF, DMAP (2.5 equiv)	60	40
DMF (1 equiv), CH_2Cl_2, K_2CO_3	0	100
DMF	0	100

Besides the desired silaketal **8**, we observed the formation of the corresponding silanol **9** in 50% to quantitative yield. In DMF and without DMAP or NEt_3, **9** is the sole product

of the reaction. We have noticed that bromosilane **7**, which is quite stable upon aqueous workup, led instantaneously to silanol **9** when first treated by DMF and then hydrolyzed. Thus, in DMF, the products **8** and **9** arose probably from intermediate **10** (Figure 1) which comes from the reaction

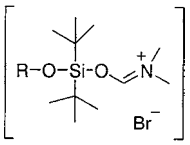


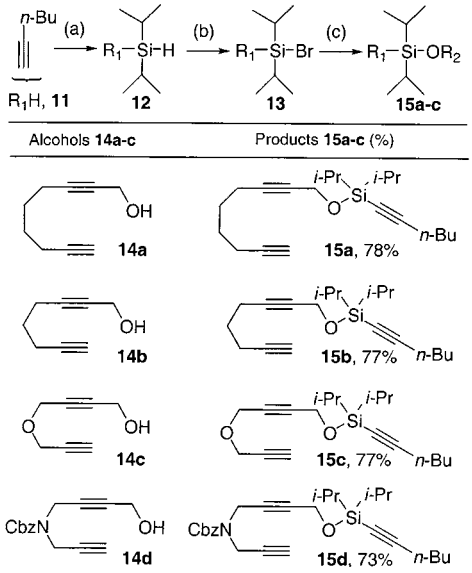
Figure 1. Possible intermediate **10**.

between the bromosilane and DMF. Such an intermediate already has been invoked.[9]

We then extended this procedure to the easy preparation of diisopropylsilyl ethers. In connection with our studies on [2+2+2] cyclizations,[10] we have chosen alcohols exhibiting triple bonds and heteroatomic tethers.

Condensation of 1-hexynyllithium **11** with chlorodiisopropylsilane in THF quantitatively furnished the corresponding silane **12**. After evaporation of THF, **12** was added into a solution of NBS in CH_2Cl_2 leading very quickly (15 min) to the silylbromide **13**. The solution of **13** was transferred to a solution of alcohols **14a**−**d** under the conditions described above to give the corresponding silyl ethers **15a**−**d** in very good yields (Table 3).

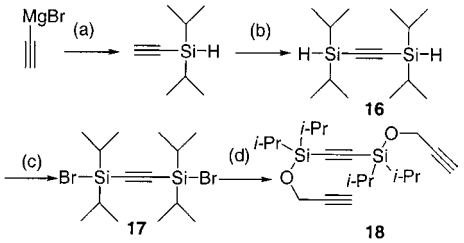
Table 3. Preparation[a] of Diisopropylsilyl Ethers **15**



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, $ClSi(i\text{-}Pr)_2H$ (1.2 equiv). (b) NBS (1.1 equiv), CH_2Cl_2, rt, 15 min. (c) **14a**−**d** (1 equiv), NEt_3, DMAP, rt, CH_2Cl_2.

By using this procedure, we also were able to prepare a disilyl ether **18** derived from 1,2-bis(diisopropylsilanyl)-

Scheme 3[a]

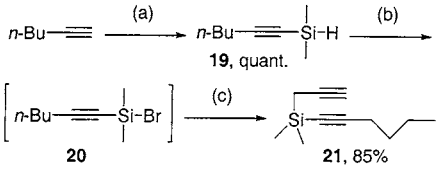


[a] Reagents and conditions: (a) HC≡CMgBr (1 equiv), THF, $ClSi(i\text{-}Pr)_2H$ (1 equiv), rt, 6 h. (b) EtMgBr (1 equiv), $ClSi(i\text{-}Pr)_2H$ (1 equiv), overnight. (c) NBS (2.2 equiv), CH_2Cl_2, rt, 15 min. (d) $HC{\equiv}CCH_2OH$ (2 equiv), NEt_3 (2.2 equiv), DMAP (0.2 equiv), CH_2Cl_2, rt.

ethyne **16** (Scheme 3), which was prepared in a two-step sequence: addition of ethynyl Grignard to a THF solution of $ClSi(i\text{-}Pr)_2H$/deprotonation of the resulting product with ethyl Grignard and condensation with $ClSi(i\text{-}Pr)_2H$. Compound **16** was then transformed into the disilyl ether **18** through the already described sequence in 60% overall yield.

Finally, we extended this procedure to the preparation of silanes. Few consecutive alkylations of dichlorosilanes are described in the literature.[11] As for the synthesis of unsymmetrical silaketals, the products of the reaction are usually contaminated with the undesired symmetrical compounds. On the contrary, in the sequence described in Scheme 4, no

Scheme 4[a]



[a] Reagents and conditions: (a) *n*-BuLi (1 equiv), THF, −78 °C. (b) NBS (1.1 equiv), CH_2Cl_2, 15 min, rt. (c) Transolvatation, $HC{\equiv}CCH_2MgBr$ (1.6 equiv), Et_2O, 0 °C.

symmetrical product was isolated. Indeed, the addition of 1-hexynyllithium to a solution of dimethylchlorosilane in

(3) (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757−4760. (b) Van de Weghe, P.; Aoun, D.; Boiteau, J. G.; Eustache, J. *Org. Lett.* **2002**, *4*, 4105−4108 and reference cited therein.
(4) (a) Gillard, J. W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnelle, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602−2608. (b) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145−1148.
(5) Stork, G.; Keitz, P. F. *Tetrahedron Lett.* **1989**, *30*, 6981−6984.
(6) Colombier, C.; Skrydstrup, T.; Beau, J. M. *Tetrahedron Lett.* **1994**, *35*, 8167−8170.
(7) Tanino, K.; Honda, Y.; Miyashita, M. *Tetrahedron Lett.* **2000**, *41*, 9281−9285.
(8) Hutchinson, J. H.; Daynard, T. S.; Gillard, J. W. *Tetrahedron Lett.* **1991**, *32*, 573−576.
(9) Simchen, G.; Kober, W. *Synthesis* **1976**, 259−261.
(10) Petit, M.; Chouraqui, G.; Phansavath, P.; Aubert, C.; Malacria, M. *Org. Lett.* **2002**, *4*, 1027−1029.
(11) Coelho, P. J.; Blanco, L. *Synlett* **2001**, 1455−1457.

THF furnished quantitatively the corresponding silane **19**. Subsequent transformation into the silylbromide **20**[12] and then condensation with propargyl Grignard led to the dimethylsilylated compound **21** in 85% overall yield.

In summary, a new and efficient procedure for the preparation of unsymmetrical silaketals in a three-step protocol without isolating the intermediates was developed. Yields are high particularly when diisopropylchlorosilane was employed. We have also shown that this procedure can be extended to silylated ethers and silanes with only a few modifications. Use of the silaketals as disposable tethers in [2+2+2] cyclizations is under investigation in our laboratory and will be reported in due course.

(12) Some chloroalkynyksilyanes have been prepared by using SO_2Cl_2, see: Buynak, J. D.; Strickland, J. B.; Lamb, G. W.; Khasnis, D.; Modi, S.; Williams, D.; Zhang, H. *J. Org. Chem.* **1991**, *56*, 7076−7083.

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Supporting Information Available: Experimental procedures and characterization data for **5a**−**d**, **6**, **15a**−**d**, **16**, **18**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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