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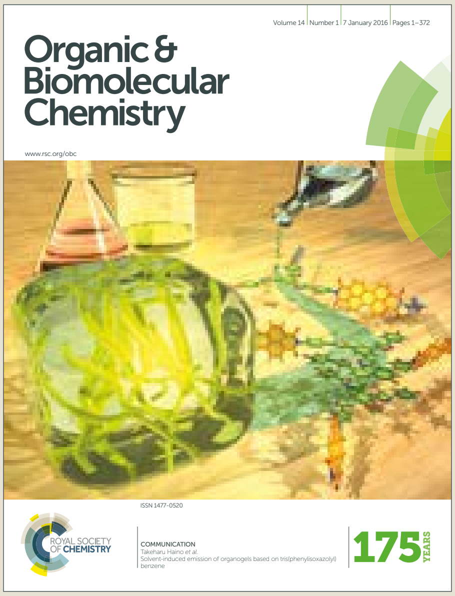

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Mild Synthesis of Silyl Ethers via Potassium Carbonate Catalyzed Reactions between Alcohols and Hydrosilanes

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Abstract

A method has been developed for the silanolysis of alcohols using the abundant and non-corrosive base K_2CO_3 as the catalyst. Reactions between a variety of alcohols and hydrosilanes generate silyl ethers under mild conditions. The use of hydrosilanes lead to the formation of H_2 as the only byproduct thus avoiding the formation of stoichiometric strong acids. The mild conditions lead to a wide scope of possible alcohol substrates and good functional group tolerance. Selective alcohol silanolysis is also observed in the presence of reactive C–H bonds, lending this method for extensive use in protection group chemistry.

Introduction

The protection of reactive functional groups, such as alcohols, amines, and thiols, is highly prevalent throughout organic syntheses. In particular, the silylation of alcohols to form silyl ethers is an important reaction in protecting group chemistry.[1] Hydroxy group protection via Si–O bonds has also extensively been used to alter the steric and electronic properties of substrates.[1] Silyl ethers have also played a large role in the development of organic semiconducting materials,[2] been used in the synthesis of medical compounds,[3] and utilized as directing groups for C–H activation reactions.[4, 5]

Sterically bulky silyl groups have exhibited a desired balance between protecting group abilities and ease of desilylation to reform the alcohol.[1] Much of the initial reports on the formation of silyl ethers with sterically bulky silyl groups focused on the treatment of alcohols with chlorosilanes, as shown in Scheme 1 A.[6] In addition to the moisture sensitivity of the chlorosilanes, this procedure requires an excess of base, such a pyridine or imidazole to neutralize the HCl byproduct.[7-9] The formation of HCl as a byproduct can also prevent the use of acid sensitive alcohol substrates and limits the practicality of scaling up the reaction to industrial levels. More recently, silanolysis of alcohols has focused on the use of hydrosilanes in the general form R_3SiH (Scheme 1 B). This procedure avoids the production of unwanted acid, as H_2 is the only byproduct generated. Hydrosilanes are also less sensitive to moisture compared to chlorosilanes. Dehydrogenative silylation of alcohols with hydrosilanes, however, does require a catalyst to promote the reaction.

Scheme 1. Comparison of silanolysis of alcohols using chlorosilanes versus hydrosilanes.

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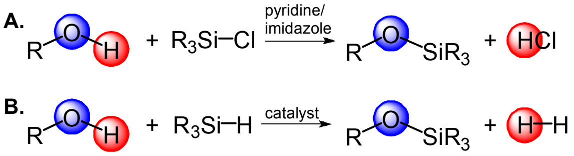

A variety of catalysts have been explored for the formation of O–Si bonds from alcohols and hydrosilanes.[10-21] Transition metal catalysts have been used to successfully construct O–Si bonds.[10-14] These catalysts, which range from rare earth metals such as ruthenium and iridium to earth abundant metals such as nickel and titanium, are not commercially available and have exhibited limited reactivity with tertiary alcohols and bulky hydrosilanes. Lewis acid catalysts, such as $B(C_6F_5)_3$, are commercially available and avoid use of transition metal catalysts.[15-17] These Lewis acid catalysts have also shown the ability to catalyze reactions involving secondary and tertiary alcohols and bulky hydrosilanes under mild conditions. Lewis acid catalysts, however, are commonly incompatible with Lewis basic functional groups such as pyridine. Alternatively, base-catalyzed dehydrosilylation of alcohols have also been explored.[18-20] Many of these base-catalyzed studies report harsh conditions such as high temperatures, strong bases, and excess of additives to promote reactivity and are more commonly employed for hydrosilylation reactions. A recent report, however, showed that the dehydrosilylation of alcohols with hydrosilanes can be achieved under more mild conditions with a catalytic amount of NaOH.[21] The strength of the base catalyst, however, could limit functional group tolerance.[21] There remains a need, therefore, for a mild, catalytic route for the dehydrosilylation of alcohols with a wide functional group tolerance.

The Oestreich group has shown that Cs_2CO_3 is an effective, mild catalyst for the dehydrogenative coupling of diols with hydrosilanes.[22] The authors showed that with 10 mol% base catalyst and excess hydrosilane, the protection of 1,3- and 1,4-diols could be achieved at room temperature in THF. Utilizing K_2CO_3 or Na_2CO_3 as the catalyst resulted in much lower reaction efficiency. In addition, alcohol substrates beyond diols were not reported.

Herein we report the K_2CO_3 catalyzed dehydrosilylation of a variety of alcohol substrates. The catalyst operates at conditions as mild as room temperature, and the relatively weak base catalyst is compatible with a wide range of functional groups. Alcohols that are sensitive to Lewis acid and strong Lewis base catalysts were successfully silylated. Substrates containing halogen, alkene, and alkyne functional groups all resulted in high yields of dehydrosilylated products without observation of unwanted side products from hydrosilylation. In addition, a variety of hydrosilanes were compatible with this catalytic approach.

Results and Discussion

Reactions were prepared by adding the chosen silane to a minimal amount of a DMF:THF solvent mixture (1:1, 1mL) containing the alcohol substrate and 20 mol% K_2CO_3 catalyst. A 1:1 DMF:THF ratio

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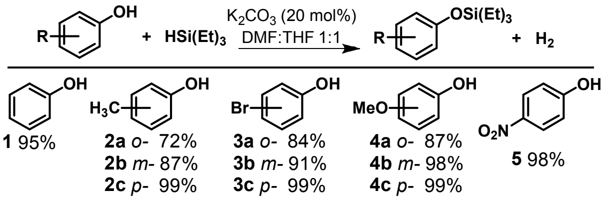
proved to be the optimized solvent over just DMF, just THF, or acetonitrile. Furthermore, a lesser concentration of K_2CO_3 resulted in diminished yields, while a greater concentration of the base catalyst did not improve yields beyond what is reported below. A small excess of silane was required to achieve optimized yields, as has been previously observed.[15, 21, 22] All solvents were purchased anhydrous and used without further purification. All glassware and the K_2CO_3 catalyst were dried in an oven to remove residue water. While water does not fully prevent product formation, the presence of water does result in formation of a siloxane.[15, 21] After the reaction, products were separated using flash chromatography and purity was determined by NMR spectroscopy.

Figure 1 shows that this method efficiently dehydrosilylates phenolic alcohols. Triethylsilane (TES) was chosen as a readily available and bulky silane that has not been extensively explored for silylation reactions. The moderately bulky nature of TES balances the ease of silylation with the ability to later remove the silane protecting group.[15] Triethylsilylation of unsubstituted phenol occurred with a 95% yield (entry **1**). Phenolic alcohols with substitutions of both electron donating and withdrawing groups at the para position (**2c** – **4c**, **5**) all resulted in excellent yields. Substrates with functional groups at the ortho- and meta- positions also were successfully silylated with yields between 62% and 98%.

Figure 1. K_2CO_3 catalyzed triethylsilylation of phenolic alcohols.



Reactions performed at 60 °C expect for substrates **2a**-**c** which were performed at 25 °C. 3 equiv of TES. 18 hrs.

With knowledge that K_2CO_3 is an efficient catalyst for the triethylsilylation of phenolic alcohols, we looked to show that this procedure was applicable for a range of different silanes. The steric and electronic character of silanes will have an effect on the reactivity. The ease of silylation and subsequent deprotection of alcohols is dependent on the identity of the silane.[1] Figure 2 illustrates that K_2CO_3 is a compatible catalyst for various silylation reactions. Yields for the protection of phenol with silanes that vary in steric bulk and electronic character were nearly quantitative with the exception of tri-isopropyl silane. For product 8 excess silane dimer was observed in the mass spectrum, which is what likely led to the lower (67%) yield.

Figure 2. K_2CO_3 catalyzed silylations of phenols.

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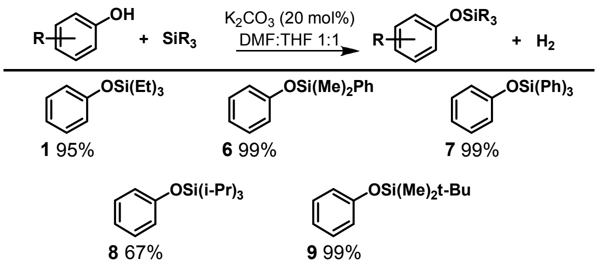


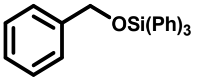
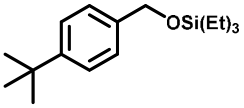
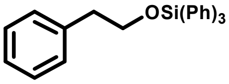
Reactions performed at 60 °C. 3 equiv of SiR_3. 18 hrs.

To further explore the scope of the K_2CO_3 catalyzed dehydrosilylation of alcohols, a range of alcohol substrates were examined. Both triethyl- and triphenylsilane (TPS) were used to achieve high yields of the desired silyl ethers. Unsubstituted and 4-substituted benzyl alcohols were successfully silylated (products **10** and **11**). Substrates containing unsaturated carbon atoms, such as cinnamyl alcohol (product **13**) were also successfully dehydrosilylated without observing any hydrosilation products. This catalytic procedure was also successful with both secondary (product **14**) and primary (product **15**) aliphatic alcohols. Lewis acid sensitive groups such as pyridine (product **16**) and furan (product **17**) also underwent efficient dehydrogenative silylation. The functional group tolerance of this catalytic approach was further shown with the nearly quantitative dehydrogenative silylation of phthalimide (product **18**),[23] which is a substrate that has previously been shown to be unsuitable for Lewis base catalyzed silylation.[24]

To demonstrate the ability of this approach to selectively generate silyl ethers in the presence of reactive C–H bonds, we performed the dehydrosilylation of 3-ethynylphenol. Facile hydrosilylation of alkynes has been reported,[25, 26] including a report on the base catalyzed hydrosilylation of alkynes.[27] In that recent report, an attempt to selectively silylate alcohols or alkynes led to only doubly silylated product. Our K_2CO_3-catalyzed silylation reaction, however, was selective for the dehydrosilylation of alcohol over the hydrosilylation of the alkyne moiety. The previously unreported (3-ethynylphenoxy)triethylsilane product (**19**) was obtained in 81% isolated yield, with a minor amount of the doubly silylated product being observed using mass spectrometry.

Table 1. K_2CO_3 Catalyzed Silylation of Alcohols.

$$R{-}OH + HSi(Et)_3 \xrightarrow[\text{DMF:THF 1:1}]{K_2CO_3\text{ (20 mol\%)}} R{-}OSi(Et)_3 + H_2$$

	Product	(°C)	% Yield
10		25	99
11		60	98
12		60	99

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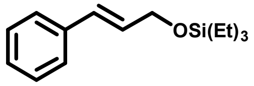
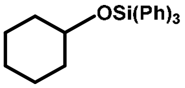
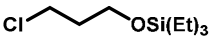
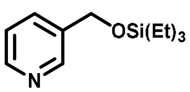
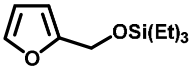
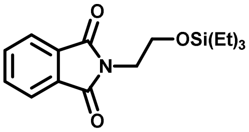
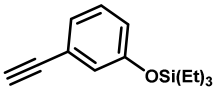
13		25	94
14		60	99
15		60	99
16		60	83
17		60	56
18		60	99
19		60	81

3 equiv of TES/TPS. 18 hrs.

A mechanistic pathway for the base catalyzed dehydrogenative silylation of alcohols has previously been prosposed.[22, 28] The mechanism proceeds via the base catalyst interacting with silicon atom to generate a more hydridic hydrosilane. This interaction promotes reactivity with alcohols to produce H_2 and form the Si–O bond. A similar mechanism has been assumed for NaOH catalyzed silylation of alcohols.[21] It is likely that the K_2CO_3 catalyzed silylation reactions in this report operate under a related mechanism, but a detailed mechanism will require future studies. This study has shown, however, that the relatively weak nature of the K_2CO_3 base compared to previous studies has led to exceptional functional group tolerance and operates through dehydrogenative silylation, and avoids acidic salt byproducts.

CONCLUSIONS

In summary, the K_2CO_3 catalyzed dehydrogenative silylation of a wide variety of alcohols has been achieved. The catalyst is readily commercially available, operates under mild conditions, and exhibits wide functional group tolerance. Substrates that had previously shown incompatibility with both Lewis acid and base catalyzed reactions were successfully silylated with high yields. The catalyst also exhibited selectivity for hydroxyl groups, allowing for protection chemistry during reactions involving C–H bonds. Overall, the ease of use and breadth of reactivity makes this an appealing approach for the formation of silyl ethers.

EXPERIMENTAL SECTION

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General Information

All starting materials were obtained from commercial sources and used without further purification. Yields refer to isolated compounds through column chromatography. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker Avance III-HD 300 MHz spectrometer in $CDCl_3$; chemical shifts are reported in parts per million (ppm) relative to chloroform-*d* (7.27 ppm) for ^{1}H NMR. For ^{13}C NMR, chloroform-*d* (77.0 ppm, center peak). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (mulitplet). ^{29}Si NMR spectra were obtained using a Bruker Avance III-HD 400 MHz spectrometer in $CDCl_3$.

General procedure for the dehydrogenative silylation of alcohols: products 1-19

Reaction vessels were dried under vacuum and the reactions carried out under an inert atmosphere using standard Schlenk line techniques. The silane (1.5 mmol) was added at room temperature to a solution of the alcohol (0.5 mmol) and K_2CO_3 (20 mol%, 12 mg) in DMF: THF (1:1, 1 mL). After stirring at 25 – 60 °C for 18 h, the reaction mixture was filtered through celite and the residue was analyzed with GC-MS. Further purification by column chromatography using ethyl acetate:hexane 90:10 solvent mixture gave the isolated silyl ether product. All products were characterized by the usual spectroscopic techniques or compared with data reported in the literature.

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REFERENCES

1. T. W. Greene and P. G. M. Wutz, *Protective Groups in Organic Synthesis*, Wiley, New York, 1991.
2. B. A. Kamino and T. P. Bender, *Chem. Soc. Rev.*, 2013, **42**, 5119-5130.
3. S. S. Rankin, J. J. Caldwell, N. B. Cronin, R. L. M. van Montfort and I. Collins, *Eur. J. Org. Chem.*, 2016, **2016**, 4496-4507.
4. N. Chernyak, A. S. Dudnik, C. Huang and V. Gevorgyan, *J. Am. Chem. Soc.*, 2010, **132**, 8270-8272.
5. C. Huang, B. Chattopadhyay and V. Gevorgyan, *J. Am. Chem. Soc.*, 2011, **133**, 12406-12409.
6. C. Eaborn, *J. Organomet. Chem.*, 1975, **100**, 43-57.
7. B. A. D'S and J. G. Verkade, *J. Am. Chem. Soc.*, 1996, **118**, 12832-12833.
8. S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, **21**, 99-102.
9. S. Kim and H. Chang, *Synth. Commun.*, 1984, **14**, 899-904.
10. Y. Wei, S.-X. Liu, H. Mueller-Bunz and M. Albrecht, *ACS Catal.*, 2016, **6**, 8192-8200.
11. R. L. Miller, S. V. Maifeld and D. Lee, *Org. Lett.*, 2004, **6**, 2773-2776.
12. D. Mukherjee, R. R. Thompson, A. Ellern and A. D. Sadow, *ACS Catal.*, 2011, **1**, 698-702.
13. X. L. Luo and R. H. Crabtree, *J. Am. Chem. Soc.*, 1989, **111**, 2527-2535.

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14. T. C. Bedard and J. Y. Corey, *J. Organomet. Chem.*, 1992, **428**, 315-333.
15. J. M. Blackwell, K. L. Foster, V. H. Beck and W. E. Piers, *J. Org. Chem.*, 1999, **64**, 4887-4892.
16. A. L. Liberman-Martin, R. G. Bergman and T. D. Tilley, *J. Am. Chem. Soc.*, 2015, **137**, 5328-5331.
17. P. T. K. Lee and L. Rosenberg, *J. Organomet. Chem.*, 2016, **809**, 86-93.
18. F. Le Bideau, T. Coradin, J. Henique and E. Samuel, *Chem. Commun.*, 2001, DOI: 10.1039/B103130A, 1408-1409.
19. M. J. Zacuto, S. J. O'Malle and J. L. Leighton, *J. Am. Chem. Soc.*, 2002, **124**, 7890-7891.
20. M. Ueno, M. Yonemoto, M. Hashimoto, A. E. H. Wheatley, H. Naka and Y. Kondo, *Chem. Commun.*, 2007, DOI: 10.1039/B700140A, 2264-2266.
21. A. A. Toutov, K. N. Betz, M. C. Haibach, A. M. Romine and R. H. Grubbs, *Org. Lett.*, 2016, **18**, 5776-5779.
22. A. Grajewska and M. Oestreich, *Synlett*, 2010, 2482-2484.
23. S. ADF2014.02, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands, 2006, http://www.scm.com.
24. S. Das, D. Addis, L. R. Knöpke, U. Bentrup, K. Junge, A. Brückner and M. Beller, *Angew. Chem. Int. Ed.*, 2011, **50**, 9180-9184.
25. K. Takaki, M. Kurioka, T. Kamata, K. Takehira, Y. Makioka and Y. Fujiwara, *J. Org. Chem.*, 1998, **63**, 9265-9269.
26. M. B. Ansell, D. E. Roberts, F. G. N. Cloke, O. Navarro and J. Spencer, *Angew. Chem. Int. Ed.*, 2015, **54**, 5578-5582.
27. A. A. Toutov, K. N. Betz, D. P. Schuman, W.-B. Liu, A. Fedorov, B. M. Stoltz and R. H. Grubbs, *J. Am. Chem. Soc.*, 2017, **139**, 1668-1674.
28. A. Weickgenannt and M. Oestreich, *Chem. Asian J.*, 2009, **4**, 406-410.

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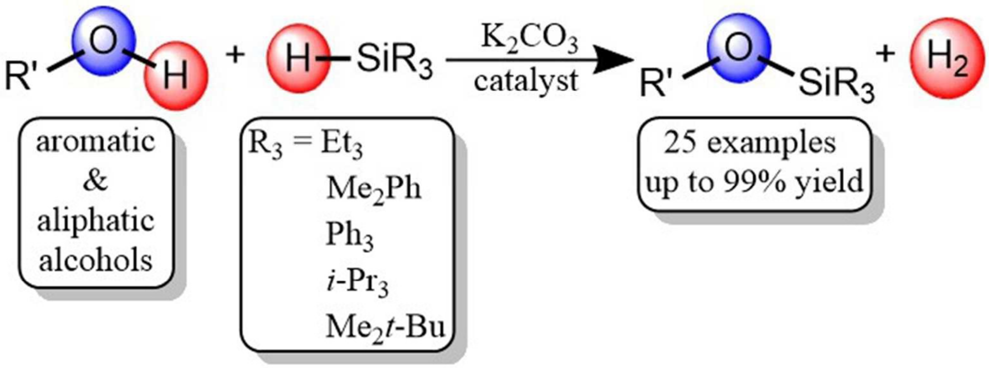
DOI: 10.1039/C8OB00464A



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