Communications to the Editor

Stereoselective Synthesis of Tetrahydropyrans via a Formal [4 + 2]-Cycloaddition of Allylsilanes

Steven R. Angle* and Nahla A. El-Said

Department of Chemistry
University of California-Riverside
Riverside, California 92521-0403

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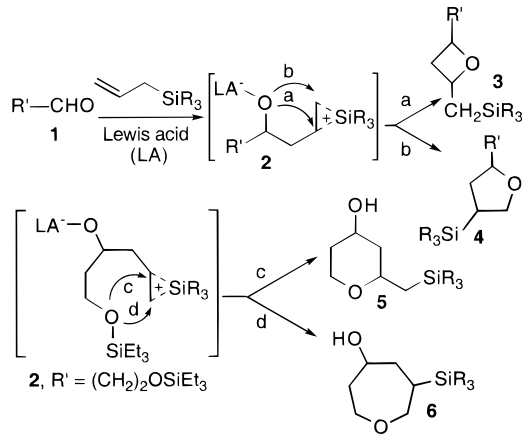
Allylsilanes are important reagents in organic synthesis.[1] For example, the introduction of allyl groups by Lewis acid-promoted conjugate addition of allylsilanes to α,β-unsaturated aldehydes and ketones (Hosomi−Sakurai reaction) has found wide application in organic synthesis.[2] In addition, the formal cycloaddition of allylsilanes has proven to be a general method for the construction of carbocyclic and heterocyclic ring systems.[3]

The formal cycloaddition of allylsilanes has been reported by a number of research groups and requires sterically demanding silyl groups to minimize the formation of allylation products.[3a,b,4] The reaction of aldehydes involves activation of the carbonyl by a Lewis acid followed by reaction with the allylsilane to afford a β-silylcation/siliranium ion intermediate[5] (**2**, Scheme 1). The oxygen in **2** can then attack the β-silylcation/siliranium ion[5] in one of two ways: (1) via pathway "a" to afford oxetane **3** or (2) via pathway "b" to afford tetrahydrofuran **4**. It is possible to control the pathway of the reaction to form either oxetane or tetrahydrofuran products by the careful choice of the Lewis acid.[6]

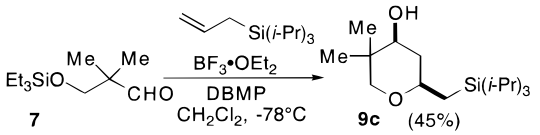
Previous work from our laboratory has shown a triethylsilyl ether to be an excellent oxygen nucleophile toward reactive electrophiles under Lewis acid conditions.[7] We hoped to develop a synthesis of tetrahydropyrans by exploiting the nucleophilicity of the triethylsilyl ether oxygen. This strategy relies on the triethylsilyl group hindering complexation of the ether oxygen with Lewis acids but still allowing it to function as a more potent nucleophile than the Lewis acid-complexed alkoxide ion. There are only a few isolated reports where an intermediate such as **2** (derived from addition of an allylsilane to an aldehyde carbonyl) retained the silicon and did not cyclize via pathway a or b.[8]

Scheme 1



We proposed to introduce a triethylsilyloxy group β to the aldehyde to provide an alternative to the normal reaction manifold, pathways a and b (Scheme 1). Such a substrate would afford β-silylcation/siliranium ion **2**, R′ = $(CH_2)_2OSiEt_3$, which might react via pathway "c" to afford the desired tetrahydropyran **5** or, less likely, via pathway "d" to provide oxepine **6**. Thus, reaction of a β-triethylsilyloxyaldehyde with an allylsilane might afford four different products: oxetane **3**, tetrahydrofuran **4**, tetrahydropyran **5**, or oxepine **6**.

To test this notion, the triethylsilyl-protected β-hydroxy aldehyde **7** was treated with allyltriisopropylsilane in the presence of $BF_3{\cdot}OEt_2$. The reaction afforded formal [4 + 2] cycloadduct **9c** as a single diastereomer in 45% isolated yield (eq 1).[9] No tetrahydrofuran, oxetane, or oxepine products were observed. In this case, and every one examined thus far, the hydroxyl and silylmethyl substituents were in a *cis*-orientation.[10] Preliminary studies established the optimal reaction conditions (1.5 equiv of allylsilane, 2 equiv of $BF_3{\cdot}OEt_2$, 1 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), −78 °C, 24 h reaction time, and 0.10 M in CH_2Cl_2). If DBMP is omitted the yield of the reaction decreases by at least 10%.



The versatility of this chemistry as a method for the construction of tetrahydropyran-containing natural products would be

(1) (a) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1−22. (b) Hosomi, A. *Acc. Chem. Res*. **1988**, *21*, 200−206. (c) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React*. **1989**, *37*, 57−575. (d) Masse, C. E.; Panek, J. S. *Chem. Rev*. **1995**, *95*, 1293−1316. (e) Langkopf, E.; Schinzer, D. *Chem. Rev*. **1995**, *95*, 1375−1408. (f) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev*. **1997**, *97*, 2063-2192. (g) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London; Boston, 1981.

(2) (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295−1298. (b) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673−1675.

(3) For leading references and recent reviews, see: (a) Knolker, H. J. *J. Prakt. Chem*. **1997**, *339*, 304−314. (b) Knolker, H. J.; Foitzik, N.; Gabler, C.; Graf, R. *Synthesis* **1999**, 145−151. (c) Knolker, H. J.; Foitzik, N.; Schmitt, O. *Tetrahedron Lett.* **1999**, *40*, 3557−3560. (d) Tietze, L. F.; Schunke, C. *Eur. J. Org. Chem.* **1998**, 2089−2099. (e) Meyers, A. I.; Brengel, G. P. *J. Org. Chem*. **1996**, *61*, 3230−3231. (f) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434−1435. (g) Dussault, P. H. Zope, U. *Tetrahedron Lett.* **1995**, *36*, 3655−3658. (h) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1994**, *35*, 6461−6464.

(4) (a) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem*. **1992**, *57*, 6094−6097. (b) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 8401−8404. (c) Akiyama, T.; Hoshi, E.; Fujiyoshi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2121−2122. (d) Akiyama, T.; Ishida, Y. *Synlett* **1998**, 1150−1152. (e) Knolker, H. J.; Jones, P. G.; Wanzl, G. *Synlett* **1998**, 613−616.

(5) Lambert and co-workers have shown that these intermediates are properly viewed as β-silylcations (Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X. Y.; So, J. H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183−190 and references cited therein). Intermediate **2**, Scheme 1, is depected as a siliranium ion rather than a β-silylcation to clearly show the relationships between products **3**, **4**, **5**, and **6**.

(6) (a) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett*. **1994**, 627−630. (b) Akiyama, T.; Kirino, M. *Chem. Lett.* **1995**, 723−724. (c) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517−5522.

(7) Angle, S. R.; Bernier, D. S.; El Said, N. A.; Jones, D. E.; Shaw, S. Z. *Tetrahedron Lett.* **1998**, *39*, 3919−3922.

(8) For examples, see: (a) Banuls, V.; Escudier, J. M. *Tetrahedron* **1999**, *55*, 5831−5838. (b) Kiyooka, S.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958−1960. (c) Akiyama, T.; Nakano, M.; Kanatani, J. Y.; Ozaki, S. *Chem. Lett.* **1997**, 385−386. (d) Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J. C.; Vanucci, C.; Lhommet, G. *J.. Chem. Soc., Perkin Trans. 1* **1997**, 2163−2165.

(9) THP **9c** is a single diastereomer by ^{1}H NMR analysis. The stereochemistry was assigned by an analysis of the H−H coupling constants and GOESY experiments (Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037−6038).

(10) See ref 3a, p 305 for an explanation of diastereoselectivity in allylsilane formal cycloadditions.

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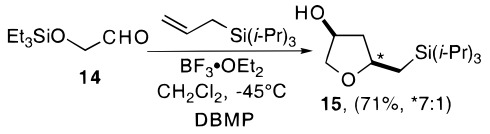
greatly increased if the silyl moiety could be oxidized to a hydroxyl via a Tamao[11] oxidation. This oxidation requires an activating group on silicon. Thus, we elected to study the reaction of tritylallyldimethylsilane[6c] and allyldimethylphenylsilane in which the silicon could be easily oxidized to a hydroxyl group. To complete the survey of allylsilanes, and examine the importance of a bulky silyl group in this reaction, allyltrimethylsilane was also studied. In an effort to investigate the scope and limitation of this methodology, several α-substituted triethylsilyl-protected *β*-hydroxy aldehydes were reacted with different allylsilanes (Table 1).[12]

Reaction of aldehyde **7** with allylsilanes **8a**−**d** afforded tetrahydropyrans **9a**−**d** in 22−56% yield as a single diastereomer (Table 1). We were surprised to find that increasing the bulk of the allylsilane resulted in a decreased yield of tetrahydropyran **9** (Table 1, entries 1−4); the least bulky allylsilane, allyltrimethylsilane **8a**, afforded the highest yield. It is also interesting to note that the reactions of trityldimethylallylsilane **8d** were much slower than those of the other allylsilanes, and complete consumption of the starting aldehyde required the reaction mixture to be warmed to 0 °C for 1 h prior to workup.

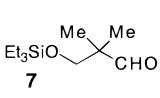
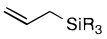
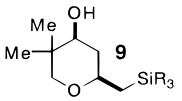
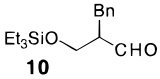
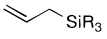
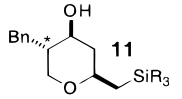
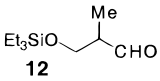
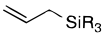
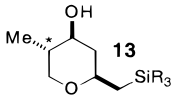
Aldehydes **10** and **12** possess an α-stereocenter which resulted in the formation of two diastereomeric tetrahydropyrans. The diastereomer ratio was dependent upon the substituents on silicon, with bulkier substituents affording higher diastereomer ratios. The lower yields for α-methyl aldehyde **12** appears to be due to decomposition of the aldehyde prior to reaction with the allylsilane.

The successful formation of tetrahydropyrans shows that closure of the triethylsilyl ether on the cation via a six-membered transition state is more favorable than attack of the Lewis acid-complexed alkoxide via a four- or five-membered transition state. Extension of this fact suggests that the formation of a five-membered ring from an aldehyde with an α-triethylsilyl ether should also be possible. To test this notion, a solution of aldehyde **14** and allyltriisopropylsilane was treated with $BF_3{\cdot}OEt_2$ under the standard reaction conditions to afford tetrahydrofuran **15** in 71% yield as a 7:1 mixture of diastereomers. The major diastereomer has been tentatively assigned as the *cis*-isomer based upon NOESY data.[12] This appears to be a general route to substituted tetrahydrofurans.



In summary we have developed a new route to tetrahydropyrans and tetrahydrofurans that exploits the nucleophilicity of a triethylsilyl ether toward a *β*-silylcation/siliranium ion intermediate. The generality of this process and application of the methodology to synthesis will be reported in due course.

Table 1. Synthesis of Tetrahydropyrans

	Aldehyde	AllylSilane	Tetrahydropyran (yield; diast. ratio)[a]
	 **7**	 **8**	 **9**
1	**7**	**8a**, $SiR_3 = SiMe_3$	**9a** (56%)
2	**7**	**8b**, $SiR_3 = SiPhMe_2$	**9b** (50%)
3	**7**	**8c**, $SiR_3 = Si(i\text{-}Pr)_3$	**9c** (45%)
4	**7**	**8d**, $SiR_3 = SiMe_2CPh_3$	**9d** (22%)[b]
	 **10**	 **8**	 **11**
5	**10**	**8a**, $SiR_3 = SiMe_3$	**11a** (46%; 1:1)
6	**10**	**8b**, $SiR_3 = SiPhMe_2$	**11b** (54%; 1.3:1)
7	**10**	**8c**, $SiR_3 = Si(i\text{-}Pr)_3$	**11c** (67%; 1.7:1)
8	**10**	**8d**, $SiR_3 = SiMe_2CPh_3$	**11d** (52%; 3.4:1)[b]
	 **12**	 **8**	 **13**
9	**12**	**8a**, $SiR_3 = SiMe_3$	**13a** (30%; 1:1)
10	**12**	**8b**, $SiR_3 = SiPhMe_2$	**13b** (34%; 1.7:1)
11	**12**	**8c**, $SiR_3 = Si(i\text{-}Pr)_3$	**13c** (40%; 1:1)
12	**12**	**8d**, $SiR_3 = SiMe_2CPh_3$	**13d** (30%; 3.2:1)[b]

[a] Diastereomer ratio at indicated (*) center determined by HPLC analysis. [b] The reaction mixture was stirred at −78 °C for 24 h, allowed to warm to 0 °C, and then stirred for an additional 1 h.

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Supporting Information Available: Copies of ^1H NMR, ^{13}C NMR, and a summary of ^1H NMR, ^{13}C NMR, IR, and HRMS data for compounds **9**, **11, 13**, and **15** (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

JA991861E

(11) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984,** *269*, C37−C39.

(12) All new compunds were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS. See Supporting Information for details and a General Experimental procedure.