Tetrahedron Letters, Vol.31, No.11, pp 1531-1534, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

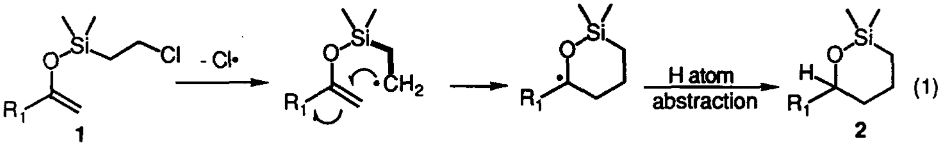
AN α-ALKYLATION/REDUCTION OF KETONES VIA RADICAL CYCLIZATIONS OF β-CHLOROETHYLSILYL ENOL ETHERS[1]

Robert D. Walkup,* Robert R. Kane, and Nihal U. Obeyesekere

Department of Chemistry & Biochemistry
Texas Tech University
Lubbock, TX 79409-1061

Abstract: β-Chloroethyldimethylsilyl enol ether derivatives of five ketones were allowed to react with tributylstannane in the presence of AIBN to yield the products of "reductive α-alkylation," 1-oxa-2-silacyclohexanes, plus ethyldimethylsilyl enol ether byproducts from direct reduction. The unstable oxasilacyclohexanes were treated with methyllithium to yield, upon workup, γ-(trimethylsilyl) alcohols.

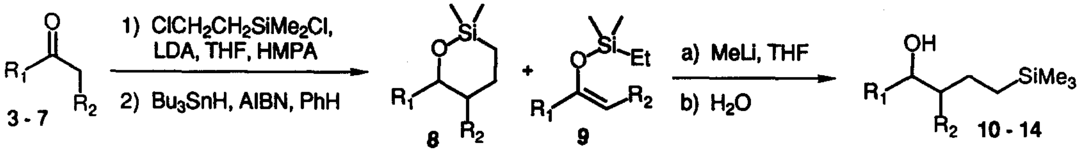
Pursuant to our goal of developing "silicon-functionalized" silyl enol ethers in which a silicon atom helps to direct a reaction between the enoxy substituent and another reactive substituent,[1] we report the free-radical cyclization of chloroethylsilyl enol ethers **1** in the presence of a hydrogen atom donor to produce 1-oxa-2-silacyclohexanes (**2**), as indicated in equation 1. Such a transformation represents a net α-alkylation and reduction of the carbonyl-containing precursors of **1**. This reaction is conceptually similar to free-radical cyclizations of (bromomethyl)dimethylsilyl ethers derived from allylic alcohols, as reported by numerous workers.[2] However, the **1** → **2** transformation is synthetically unique, both in the nature of the products obtained as well as the precursors (carbonyl compounds) utilized.

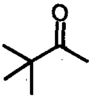
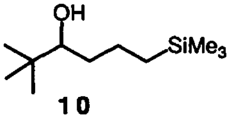
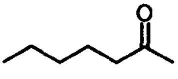
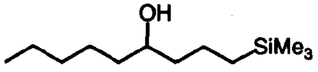
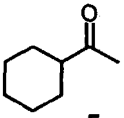
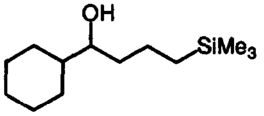
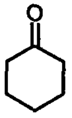
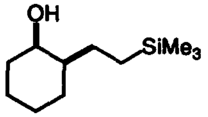
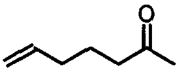
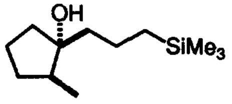


The general features of our initial observations are shown in the Scheme, and specific results are given in the Table. Chloroethyldimethylsilyl enol ether derivatives of the ketones **3**-**7** were synthesized in high yields from chloro(2-chloroethyl)dimethylsilane[3] using the procedure of Corey and Gross.[4] When each of these enol ethers was allowed to react with tributylstannane in the presence of AIBN,[5] the starting material was consumed and a mixture of the oxasilacyclohexane (**8**) and the uncyclized enol ether (**9**) was obtained, according to ^{1}H-NMR analysis of the crude product mixture.[6] Because of the volatility and instability of the oxasilacyclohexanes **8**,[7] and the added difficulty of separating them from the organotin byproducts,[8] the crude product mixtures were treated with excess methyllithium to yield, upon aqueous workup, the stable γ-(trimethylsilyl) alcohols **10**-**14**, which could be scrupulously purified and characterized.[9]

These results indicate that, by generating a free-radical center at a carbon β to the silicon atom of a silyl enol ether, one can achieve an "alkylation" of the carbon α to the carbonyl carbon of the

Scheme



Entry	Starting Ketone	8:9 Ratio[6]	Product	Yield (%)[a]
1	 **3**	90:10	 **10**	28
2	 **4**	50:50	 **11**	32
3	 **5**	60:40	 **12**	33
4	 **6**	55:45	 **13** (80:20 cis:trans)	20
5	 **7**	-b-	 **14** (86:14 (E):(Z))	30

[a]After purification by silica gel chromatography. [b]Not determined.

ketone precursor. In no cases were products from a 5-exo-trig cyclization detected. The synthetic potential of this transformation of carbonyl compounds is suggested by entries 4 and 5 of the Table. The conversion of ketone **6** into **13** represents the net conversion of cyclohexanone to a cis 2-alkylcyclohexanol with a good degree of diastereoselectivity. This stereoselectivity is attributed to a steric effect, where the tin hydride approaches the carbinol radical intermediate formed by the initial cyclization (see equation 1) from a direction trans to the newly-formed C-C bond.[10] The formation of the cyclopentanol **14** from 6-hepten-2-one (**7**) supports the intermediacy of the carbinol radical intermediate, and illustrates the potential for interposing an additional free-radical cyclization step between the "alkylation" and the "reduction" steps when a 4-penten-1-yl chain is attached to the carbonyl carbon of the ketone starting material. The diastereoselectivity of this transformation is notable and precedented.[11]

The cyclizations of 6-chloro-4-sila-1-hexenes, non-oxygenated analogues of **1**, were observed to proceed exclusively via the 6-endo-trig mode, but only to the extent of 2-5% of the product formed; the major products were the 4-sila-1-hexenes resulting from direct reduction.[12] Our reaction conditions closely resemble those used by these workers, so our results suggest that the replacement of a methylene group by an oxygen atom at the 3-position of 4-sila-1-hexenes increases the propensity of the system to undergo cyclization prior to hydrogen donation. However, our reaction still suffers from the production of significant amounts of byproduct from direct reduction. Furthermore, the yields from our reaction are consistently low (as measured by the overall yield of the γ-(trimethylsilyl) alcohols from the ketones), a fact that we attribute to a competing eliminative side reaction of the β-chloroethylsilyl enol ethers to chlorosilanes and ethene, a precedented thermal decomposition reaction of β-chloroethylsilanes,[13] under the reaction conditions. Attempts to improve these yields have so far failed. However, the results of this study indicate that *a synthetic strategy which uses a silicon atom as a "template" which brings together a carbon-centered free-radical and an enoxy group for a C-C bond-forming reaction is workable.*

When the crude reaction mixture from the cyclization of the chloroethylsilyl enol ether derivative of **3** was treated with the Tamao oxidation conditions,[14] a 20% yield of 5,5-dimethyl-1,4-hexanediol was obtained. This result indicates the promise of this methodology for performing "reductive α-hydroxyethylations" of ketones. This and other synthetic applications of silicon-functionalized silyl enol ethers are under investigation.[15]

REFERENCES

1) Silicon Functionalized Silyl Enol Ethers. 3. For part 2, see Walkup, R.D., Obeyesekere, N.U. *J. Org. Chem.* **1988**, *53,* 920.

2) See, e.g. a) Nishiyama, H., Kitajima, T., Matsumoto, M., Itoh, K. *J. Org. Chem.* **1984**, *49,* 2298; b) Stork, G., Kahn, M., *J. Am.Chem. Soc.* **1985**, *107,* 500; c) Stork, G., Sofia, M.J., *J. Am. Chem. Soc.* **1986**, *108,* 6826; d) Kurek-Tyrlik, A., Wicha, J. *Tetrahedron Lett.* **1988**, *29,* 4001; e) Tamao, K., Maeda, K., Yamaguchi, T., Ito, Y. *J. Am. Chem. Soc.* **1989**, *111,* 4984.

3) The addition of 1 molar equivalent of methyllithium to dichloro(2-chloroethyl)methylsilane (ether, 0° C.) yielded chloro(2-chloroethyl)dimethylsilane, b.p. 35-37° C. (10 mm Hg). [tends to decompose to dichlorodimethylsilane and ethene upon heating above 50° C.].

4) Corey, E.J., Gross, A.W. *Tetrahedron Lett.* **1984**, *25,* 495. Yields were improved by using HMPA as a cosolvent. We are grateful to Dr. Howard E. Morton of Abbott Laboratories for suggesting the use of this solvent.

5) A 0.025 M solution of the crude enol ether plus 0.2 molar equivalents of AIBN in dry deoxygenated benzene were brought to reflux under nitrogen, and a 0.1 M solution of one molar equivalent of tributylstannane, plus another 0.2 molar equivalents of AIBN, in dry benzene, was added over the course of 4-6 hr. The mixture was allowed to reflux for an additional 10 hr., then it was concentrated to about 20% of its original volume. This crude reaction mixture was submitted to ^{1}H-NMR analysis (ref. 6), then diluted with dry THF (~10 mmole per mmole of starting enol ether), then a 4-fold excess of methyllithium (1.4 M solution in ether) was added. The mixture was stirred under nitrogen for 3 hours at room temperature, then carefully mixed with water and worked up in the usual manner to yield the crude alcohols.

6) Observed, in each case: a) disappearance of the ABXY signal at 3.7 ppm [CH_2Cl for chloroethylsilyl group]; b) disappearance of the signals at 4.1 and 3.9 ppm [$=CH_2$ of starting silyl enol ether]; c) appearance of two new singlets at 0.10-0.17 ppm [methyl groups on silicon of the oxasilacyclohexane]; d) appearance of a new multiplet at ~0.55 ppm [CH_2 next to Si in the oxasilacyclohexane]; e) appearance of a new multiplet at ~3.50 ppm (not observed in the **7** → **14** system) [CH-O in the oxasilacyclohexane]; f) appearance of a new broad singlet at ~3.9 ppm (always ~0.1-0.2 ppm upfield from the $=CH_2$ signals of the starting silyl enol ether) [$=CH_2$ of the ethyldimethylsilyl enol ether byproduct]; g) appearance of a new singlet at 0.2 ppm [methyl groups on silicon in the ethyldimethylsilyl enol ether byproduct]. Relative integrations of the signals for the CH-O (cyclized) vs. the $=CH_2$ (uncyclized) hydrogens allowed the ratio of cyclized to uncyclized products to be estimated.

7) Previous approaches to 1-oxa-2-silacyclohexanes and discussions of their propensities to polymerize under protic conditions: a) Smith, C.L., Gooden, R. *J. Organometallic Chem.* **1974**, *81*, 33-40; b) Corriu, R.J.P., Moreau, J.J.E. *J. Organometallic Chem.* **1976**, *114*, 135-144; c) Barton, T.J., Revis, A. *J. Am. Chem. Soc.* **1984**, *106*, 3802-3805; d) Chen, Y.-L., Barton, T.J. *Organometallics* **1987**, *6*, 2590-2592; e) Pola, J., Jakoubkova, M., Chvalousky, V. *Coll. Czech. Chem. Commun.* **1976**, *41*, 374-385; f) Manuel, G., Mazerolles, P., Gril, J. *J. Organometallic Chem.* **1976**, *122*, 335-343; g) Hassner, A., Soderquist, J.A. *Tetrahedron Lett.* **1980**, *21*, 429-432; h) Pinnavaia, T.J., McClarin, J.A. *J. Am. Chem. Soc.* **1974**, *96*, 3012-3013.

8) In an attempt to minimize the amounts of tin byproducts produced, a "catalytic" recipe, after that of Stork, G. and Sher, P.M. *J. Am. Chem. Soc.* **1986**, *108*, 303, could be used. However, the results from this method were virtually identical to those obtained from the "stoichiometric" recipe, and the oxasilacyclohexanes still could not be isolated from the reaction mixture.

9) Each alcohol was purified by flash chromatography (90:10 hexanes:ethyl acetate eluent). In the cases of products **13** and **14**, diastereomer ratios were determined by HPLC analysis prior to purification. Each alcohol exhibited NMR and IR spectroscopic properties commensurate with the assigned structure, and upon analysis by high-resolution mass spectrometry gave molecular ion peaks and/or fragment ion peaks diagnostic for the assigned formula.

10) Giese, B., Gonzalez-Gomez, J.A., Lachhein, S., Metzger, J.O. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 479-480.

11) Recent accounts of the "reductive cyclizations" of 6-hepten-2-one systems, and similar free-radical cyclizations: a) Curran, D.P., Kim, D., Liu, H.T., Shen, W. *J. Am. Chem Soc.* **1988**, *110*, 5900; b) Molander, G.A., Kenny, C., *J. Am. Chem Soc.* **1989**, *111*, 8236.

12) a) Wilt, J.W. *Tetrahedron* **1985**, *41*, 3979-4000; b) Wilt, J.W., Lusztyk, J., Peeran, M., Ingold, K.U. *J. Am. Chem. Soc.* **1988**, *110*, 281-287. b) Saigo, K., Tateishi, K., Adachi, H., Saotome, Y. *J. Org. Chem.* **1988**, *53*, 1572-1574.

13) It should be noted that this elimination reaction proceeds via an ionic mechanism. Jarvie, A.W.P. *Organometallic Chem. Rev. A* **1970**, *6*, 153-207.

14) Tamao, K., Ishida, N., Tanaka, T., Kumada, M. *Organometallics* **1983**, *2*, 1694.

15) This research was made possible by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society (grant # 19870-AC1). The NMR spectrometer employed was purchased using funds provided by the National Science Foundation (#CHE-851404). RRK and NUO each thank the Graduate School of Texas Tech University for a Summer Research Award.

(Received in USA 20 December 1989)