ORGANIC
LETTERS

2005
Vol. 7, No. 22
4995−4998

Unusual Tandem Alkynylation and *trans*-Hydrosilylation To Form Oxasilacyclopentenes

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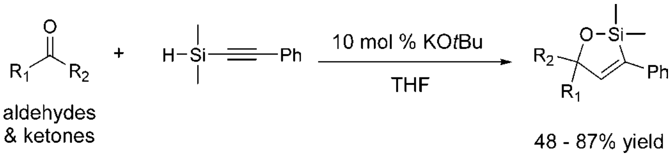
Received August 17, 2005

ABSTRACT



An unusual tandem reaction sequence to form oxasilacyclopentenes from carbonyls and alkynylsilanes in the presence of a catalytic amount of nucleophilic initiator has been discovered. The reaction proceeds readily at room temperature and is applicable to a wide variety of carbonyl substrates. While the reaction scope tolerates variable substitutions on the alkynylsilane, phenylacetylene-derived silane variants consistently achieved the best yield.

Organosilanes, such as silyl ethers and vinylsilanes, play an important and diverse role in organic chemistry.[1] The silyl ether functionality is widely employed as a protecting group[2] and also serves as a temporary tether to adapt intermolecular reactions to more favorable intramolecular processes.[3] Additionally, vinylsilanes can be employed for a variety of purposes[4] including palladium-catalyzed cross-coupling reactions.[5] For these reasons, we have been interested in developing a new and efficient methodology to synthesize these versatile building blocks based on catalytic activation of silane starting materials.[6]

An extensive variety of metal complexes have been reported to activate hydridosilanes during the dehydrogenative condensation with alcohols[6b,c,7] and the hydrosilylation of carbonyls[6c,8] and alkynes.[6a,9] Additionally, the Lewis base activation of silanes to form pentacoordinate hydrosilicates is a well-established method to activate the silicon−hydrogen bond toward the reduction of carbonyls with concomitant silylation of the resultant alkoxide yielding the corresponding

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[1] (a) Ojima, I.; Zhu, J. In *The Chemistry of Organosilicon Compounds*; Rappoport, S., Apeloig, Y., Eds.; Wiley: New York, 1998. (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375−1408. (c) Hiyama, T.; Kusumoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 763−792.

[2] (a) Green, W. T.; Wuts, P. G. M. In *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (b) Kocienski, P. J. In *Protective Groups*; Enders, D., Noyori, R., Trost, B. M., Eds.; Thieme: Stuttgart, Germany, 1994. (c) Muzart, J. *Synthesis* **1993**, 11−27.

[3] (a) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813−852. (c) Bols, M.; Skydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277.

[4] For oxidation of the carbon−silicon bond, see: (a) Jones, G. R. *Tetrahedron* **1996**, *52*, 7599−7662 and references therein. For halogenation, see: (b) Miller, R. B.; Reichenbach, T. *Tetrahedron Lett.* **1974**, *15*, 543−546.

[5] For reviews on the cross-coupling reactions of organosilicon compounds, see: (a) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, pp 163−216. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846. (c) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317−1350. (d) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845−853.

[6] (a) Maifeld, S. V.; Tran, M. N.; Lee, D. *Tetrahedron Lett.* **2005**, *46*, 105−108. (b) Miller, R. L.; Maifeld, S. V.; Lee, D. *Org. Lett.* **2004**, 6, 2773−2776. (c) Maifeld, S. V.; Miller, R. L.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 6363−6366.

[7] (a) Zhang, C.; Laine, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 6979−6988. (b) Blackwell, J. M.; Foster, K. L.; Beck, V. H.; Piers, W. E. *J. Org. Chem.* **1999**, *64*, 4887−4892 and references therein. (c) Ojima, I.; Kogure, T.; Nihonyangi, M.; Kono, H.; Inaba, S. *Chem. Lett.* **1973**, 501−504.

[8] (a) Chrisman, W.; Noson, K.; Lipschutz, B. H. *J. Organomet. Chem.* **2001**, *624*, 367−371. (b) Bushell, S. M.; Lawrence, N. J. *Tetrahedron Lett.* **2000**, *41*, 4507−4512. (c) Lee, S.; Kim, T. Y.; Park, M. K.; Han, B. H. *Bull. Korean Chem. Soc.* **1996**, *17*, 1082−1085. (d) Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1993**, *34*, 3095−3098. (e) Cornish, A. J.; Lappert, M. F.; Filatovs, G. L.; Nile, T. A. *J. Organomet. Chem.* **1979**, *172*, 153−163.

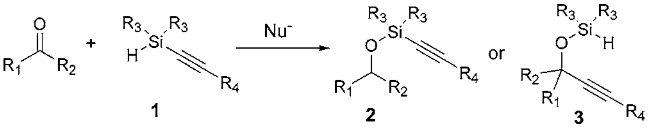
[9] See ref 1a, Vol. 2, pp 1687−1792.

10.1021/ol051996r CCC: $30.25

silyl ether.[10,11] Efforts in this area have mainly included electron deficient silanes such as trimethoxy- and triethoxysilane for the synthesis of silyl ethers, and the use of relatively simple alkyl- and arylsilanes is limited.

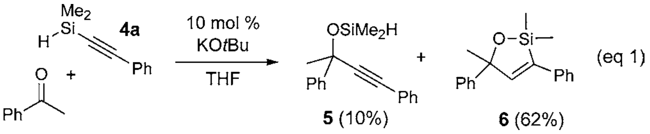
As an extension of our efforts to develop efficient routes to silyl ethers possessing alkynyl substituents in the products, we examined the reactivity of dialkyl- and diarylalkynylsilanes. We envisioned that the employment of an alkynyl hydridosilane of type **1** could result in either of the two silyl ethers, **2** or **3**, depending on the migratory aptitude of the more basic hydride versus the less basic acetylide (Scheme 1).

Scheme 1. Nucleophilic Activation of Hydrido Alkynylsilanes



Although previous reports have shown that the Lewis base activation of an alkynylsilane promotes the alkynylation of carbonyls and imines as well as alkyl halides,[12] the relative migratory aptitude between a hydride and an acetylide anion has not been examined. A simple basicity measure of these two migrating species indicates that the acetylide should migrate preferentially to give **3**; however, the second pathway involving hydride migration cannot be excluded because additional parameters, such as sterics and stereoelectronics, may affect the outcome. For example, transition metal catalysts normally activate the stronger (76 kcal/mol), yet less hindered Si−H bond over the weaker (72 kcal/mol), more hindered Si−C bond to provide **2** exclusively.[6b]

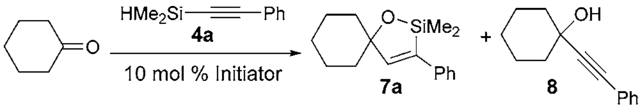
With these considerations in mind, we initiated our studies with commerically available dimethyl(phenylethynyl)silane **4a** and acetophenone in the presence of a catalytic amount of potassium *tert*-butoxide (eq 1). Although no products resulting from hydride migration to the carbonyl were observed, we isolated two products resulting from alkynyl transfer from the silane to the substrate. While the minor product corresponded to hydridosilyl ether **5**, the major product was identified as oxasilacyclopentene **6**, seemingly arising from alkynylation of the ketone followed by an intramolecular endo mode, *trans*-hydrosilylation of the triple bond by the intermediate hydridosilyl ether.[13]



In contrast to well-established examples of *cis*-hydrosilylation, *trans*-hydrosilylation is less documented,[14] and only a single example of a non-transition metal-mediated *trans*-hydrosilylation has been reported.[15] Herein, we report our investigation of an unusual tandem reaction sequence to generate oxasilacyclopentenes from carbonyls and alkynylsilanes through a formal intramolecular *trans*-hydrosilylation.

Employing cyclohexanone and silane **4a** as our representative carbonyl and silane compounds, we screened a variety of metal alkoxide and fluoride sources for efficacy of promoting both the alkynylation of the carbonyl as well as the subsequent hydrosilylation of the alkyne (Table 1).

Table 1. Screen of Nucleophilic Initiators[a]



entry	initiator	time	yield (%)[b]	
1	LiO^{i}Pr	1 h		
2	NaOMe	1 h		15
3	NaO^{t}Bu	1 h	28	27
4	KOMe	1 h	12	52
5	KOtBu	15 min	86	10
6	CsF	1 h	11	58
7	^{n}Bu$_4$N·SiPh$_3$F$_2$	1 h	21	14

[a] 1 equiv of cyclohexanone, 1.2 equiv of silane, THF, room temperature. [b] Isolated yield.

Among the nucleophiles tried, only potassium *tert*-butoxide gave complete conversion of the ketone resulting in the highest yield of oxasilacyclopentene **7a** (86%) and the smallest amount of tertiary propargylic alcohol **8** (10%), presumably derived from hydrolysis of the labile hydridosilyl ether during silica gel chromatography. Less coordinating cations promoted greater alkynylation of the carbonyl, and bulkier alkoxides increased oxasilacyclopentene formation.

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(10) For additional reviews, see: (a) Brook, M. A. In *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley-Interscience: New York, 1999. For reviews of pentacoordinate silicates, see: (b) Holmes, R. R. *Chem. Rev.* **1996**, *96*, 927−950. (c) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371−1448.

(11) (a) Nishikori, H.; Yoshihara, R.; Hosomi, A. *Synlett* **2003**, 561−563. (b) LaRonde, F. J.; Brook, M. A. *Tetrahedron Lett.* **1999**, *40*, 3507−3510. (c) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 2065−2068. (d) Schiffers, R.; Kagan, B. H. *Synthesis* **1997**, 1175−1178 and references therein. (e) Corriu, R. J. P.; Guerin, C.; Henner, B.; Wang, Q. *Organometallics* **1991**, *10*, 2297−2303 and references therein.

(12) (a) Lettan, R. B., II; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227−3230. (b) Kraus, G. A.; Bae, J. *Tetrahedron Lett.* **2003**, *44*, 5505−5506. (c) Baldewin, J. E.; Pritchard, G. J.; Rathmell, R. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2906−2908. (d) Busch-Petersen, J.; Bo, Y.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 2065−2068. (e) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901−6905. (f) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975−982.

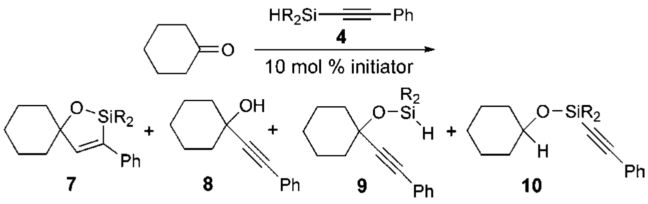
(13) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028−10038 and references therein.

(14) For intramolecular *trans*-hydrosilylation, see: (a) Denmark, S. E.; Pan, W. *Org. Lett.* **2002**, *4*, 4163−4166. For intermolecular *trans*-hydrosilylation, see: (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726−12727. (c) Na, Y.; Chang, S. *Org. Lett.* **2000**, *2*, 1887−1889. (d) Mori, A.; Takahisa, E.; Kajiro, H.; Hirabayashi, K.; Nishihara, Y.; Hiyama, T. *Chem. Lett.* **1998**, 443−444.

(15) (a) Sudo, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 8919−8923. For an additional example of a *trans*-hydrometalation with aluminum, see: (b) Eckrich, T. M.; Corey, E. J. *Tetrahedron Lett.* **1984**, *25*, 2415−2418.

The steric and stereoelectronic influences exerted by the groups at the silicon atom were also investigated (Table 2).

Table 2. Effect of Substituents at Silicon[a]



silane **4**	R	yield (%)[b]			
		7	**8**	**9**	**10**
a	Me	86[c]	10[c]		
b	Ph	67			10
c	^{i}Pr	trace	22	61	

[a] 1 equiv of cyclohexanone, 1.2 equiv of silane, THF, room temperature. [b] Isolated yield. [c] At 0 °C, the yields of **7** and **8** were 29% and 42%, respectively.

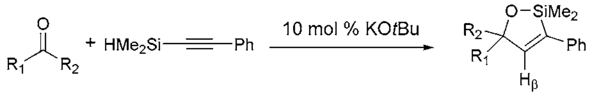
Replacing methyl groups (**4a**) with phenyl groups (**4b**) resulted in a good yield of the oxasilacyclopentene **7b** (67%) with a small amount of the alkynyl silyl ether **10b** (10%) resulting from hydride transfer to the carbonyl carbon. Although alkynylation proceeded readily in the presence of isopropyl substituents (**4c**), only a trace amount of oxasilacyclopentene **7c** was observed, and tertiary propargyl alcohol **8c** and hydridosilyl ether **9c** were isolated in 22% and 61% yield, respectively.

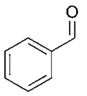
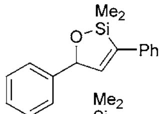
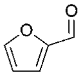
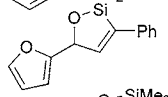
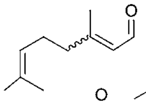
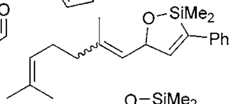
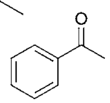
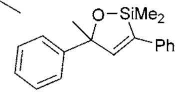
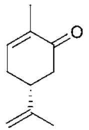
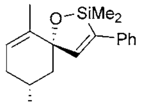
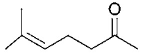
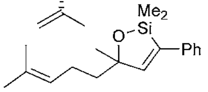
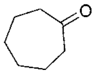
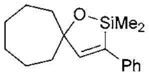
Using our optimized conditions employing **4a** and 10 mol % potasssium *tert*-butoxide, we examined the scope of the reaction toward a wide variety of ketones and aldehydes (Table 3). All reactions were extremely facile giving complete conversion within 20 min at room temperature. Aromatic as well as α,*β*-unsaturated aldehydes yielded oxasilacyclopentenes **11a**−**c** in moderate to high yields (entries 1−3). A variety of cyclic, acyclic, aromatic, and aliphatic ketones proved to be good substrates as well, providing the expected oxasilacyclopentenes **11d**−**f** in good yields (entries 4−8).

We next investigated the effect of the group occupying the alkyne terminus. Additional alknylsilanes bearing various groups including furyl, pyridyl, trimethylsilyl, alkyl, sulfonyl, and cyclohexenyl were prepared and tested.[16] Upon subjection to the reaction conditions, none of these alkynylsilanes were as efficient participants in the tandem alkynylation−hydrosilylation sequence as **4a**, which possesses a terminal phenyl substituent.

We also examined the electronic and steric effects exerted by the substituents on the aryl ring (Table 4). The presence of a strongly electron donating substituent in **12a** proved detrimental to the alkynylation of the carbonyl, presumably by retarding the silicon−carbon bond cleavage (entry 1). Although alkynylation proceeded well with **12b**, no formation of the corresponding oxasilacyclopentene **13b** was noted, likely due to steric hindrance around the triple bond presented by the *o*-methyl group on the arylsilane. In contrast, arylsilanes bearing *p*-methyl (**12c**), *p*-fluoro (**12d**), and *p*-trifluoromethyl substituents (**12e**) resulted in the formation of oxasilacyclopentenes **13c**−**e** in good to high yields (entries 3−5).

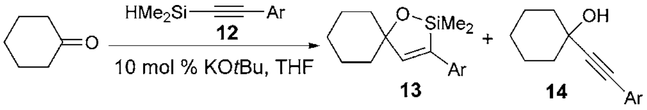
Table 3. Synthesis of Oxasilacyclopentenes[a]

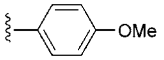
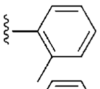
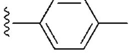
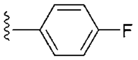
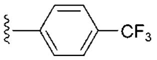


entry	substrate	product		yield[b]	δ (ppm) of H$_\beta$
1			**11a**	48	7.0
2			**11b**	72	7.01
3			**11c**	63	6.83 / 6.80 (1.3 : 1 *E/Z*)
4			**6**	62	7.15
5			**11d**	55	7.04 / 6.77 (5.5 : 1 dr)
6			**11e**	66	6.87
7			**11f**	87	7.06

[a] 1 equiv of carbonyl, 1.2 equiv of silane, THF, room temperature. [b] Isolated yield.

Table 4. Effect of Substituent on Phenylacetylene[a]



entry	silane	Ar	**13**	yield (%)[b] **14**
1	**12a**		0	35
2	**12b**		0	59
3	**12c**		72	10
4	**12d**		86	0
5	**12e**		55	31

[a] 1 equiv of cyclohexanone, 1.2 equiv of silane, THF, room temperature. [b] Isolated yield.

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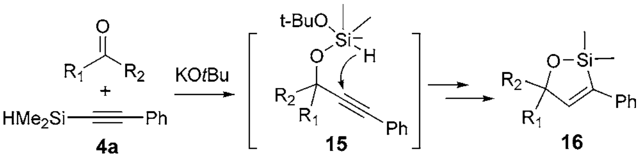
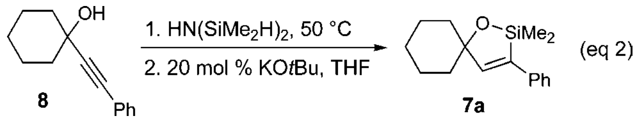
[16] See the Supporting Information for reaction details.

Although the mechanistic picture of oxasilacyclopentene formation is unclear, we propose a plausible scenario shown in Scheme 2. Following the formation of pentacoordinate silicate intermediate by the addition of *tert*-butoxide to silane **4a** and transfer of the alkyne to the carbonyl to form activated hydridosilyl ether **15**, subsequent hydride transfer from the silicon to the nearby alkyne would provide oxasilacyclopentene **16**.

Scheme 2. Mechanistic Proposal for the Tandem Alkynylation−Hydrosilylation Sequence

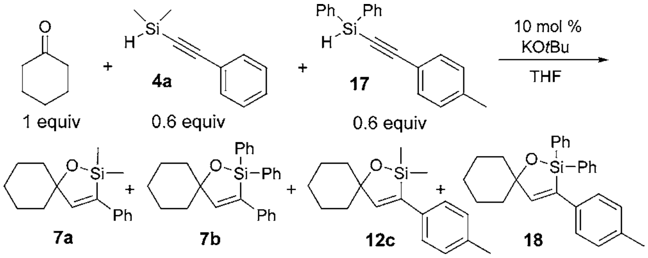


To validate the intermediacy of a hydridosilyl ether of type **3** (and also **5** and **15**) leading to oxasilacyclopentene formation, the corresponding silyl ether was synthesized from tertiary propargyl alcohol **8** and tetramethyldisilazane.[17] Treatment of the preformed hydridosilyl ether with 20 mol % of potassium *tert*-butoxide resulted in clean formation of the expected oxasilacyclopentene **7a** in 76% yield (eq 2).



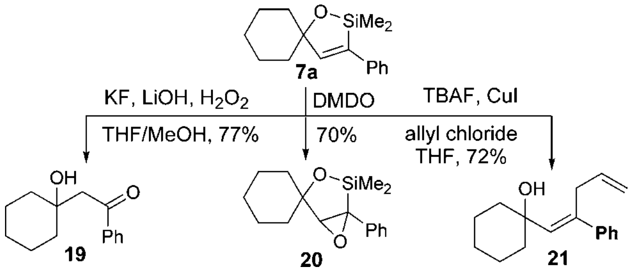
To ascertain whether the alkynyl transfer occurs via an organized transition state, a crossover experiment was carried out between cyclohexanone and two similar alkynylsilanes, **4a** and **17** (Scheme 3). The observation of all four possible oxasilacyclopentenes (**7a**, **7b**, **12c**, and **18**) by ^{1}H NMR and mass spectroscopy indicates that the reaction proceeds via a naked alkynyl anion rather than a tightly organized, chelated delivery of the alkynyl group from the pentacoordinate silicate.[18]

Scheme 3. Crossover Experiment



Oxasilacyclopentenes are versatile synthetic intermediates and undergo a variety of transfomations (Scheme 4).[19] Tamao oxidation of **7a** yielded the β-hydroxy ketone **19** efficiently (77%).[20] This transformation is notable as **19** formally results from an aldol reaction, which is known to encounter difficulties with ketone electrophiles.[21] Expoxidation of **7a** with dimethyldioxirane gave epoxide **20** in 70% yield based on recovered starting material. In particular, the trisubstituted vinylsilane moiety in **7a** is noteworthy since it is not easily accessed by conventional hydrosilylation of internal triple bonds due to issues of regioselectivity.[13b] By using the chemistry developed by Takeda and co-workers,[22] oxasilacyclopentene **7a** could also be transformed into 1,4-diene **21** in high yield.

Scheme 4. Synthetic Elaboration of Oxasilacylcopentene **7a**



In summary, the chemistry described above represents a novel tandem and mild base-promoted alkynylation of carbonyl substrates followed by in situ *trans*-hydrosilylation of the alkynyl moiety to generate oxasilacyclopentenes. This protocol avoids the use of highly basic metal alkynyl species while achieving two consecutive transformations by a substoichiometric amount of alkoxide initiator.

Acknowledgment. D.L. greatly acknowledges generous support of this research from the NIH (RO1 CA106673-01). We thank Professor Hans Reich for insights and helpful discussions. Support from the NSF and NIH for NMR and mass spectrometry instrumentation is also greatly appreciated.

Supporting Information Available: General procedures and characterization for the represented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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