ORGANIC
LETTERS

1999
Vol. 1, No. 7
1115−1118

Methyllithium-Promoted Wittig Rearrangements of α-Alkoxysilanes

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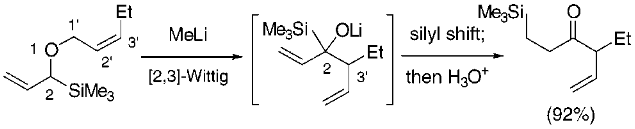
Received August 5, 1999

ABSTRACT



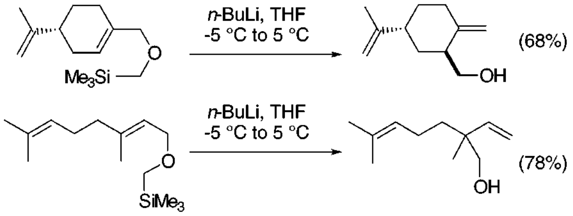
The Wittig rearrangements of α-alkoxysilanes, promoted by the action of methyllithium were studied. Depending on both the substrate and reaction conditions employed, [2,3]-, [1,2]-, or [1,4]-Wittig rearrangements can be realized. These rearrangements were shown to be initiated by either Si/Li exchange or deprotonation α to the silane. Furthermore the sigmatropic shifts can often be followed by other synthetically useful in situ chemical events.

The Wittig rearrangement is a very useful method for the conversion of ethers (usually allylic or benzylic) into alcohols with concomitant C−C bond formation.[1] These reactions proceed via metalation α to the ether oxygen, most generally accomplished by deprotonation with a strong base. In 1978, Still and Mitra introduced the idea of using α-alkoxystannanes which could be made to undergo selective tin−lithium exchange, thereby providing regiocontrol over α-alkoxy carbanion formation.[2] While this Wittig−Still protocol works well, it has the drawback of requiring the stoichiometric employment of relatively toxic[3] organostannanes.

As such, several groups have sought “tin free” alternatives to the regioselective generation of α-ethereal carbanions. Some successful approaches to this problem have been based on the reductive cleavage of *O*,*S*-acetals with lithium naphthalide,[4] while others involve SmI_2-mediated reduction of diallyl acetals[5] or vinyl halides capable of 1,5-hydrogen transfer.[6] Several years ago, Nakai[7] examined this issue through the study of fluoride ion-promoted [2,3]-Wittig rearrangements of *C*-silylated α-allyloxy esters. More recently, we reported that a variety of α-alkoxysilanes can be made to undergo efficient Wittig rearrangement by desilylation with CsF.[8]

Interestingly, the more straightforward alternative to the Wittig−Still rearrangement involving Si/Li exchange of α-alkoxytrimethylsilanes has received little attention, even though such exchange reactions are well precedented.[9] To the best of our knowledge, only two examples (Scheme 1), both by Muzler and List,[9a] stand alone as the only reported [2,3]-Wittig rearrangements triggered by Si/Li substitution. We found this fact surprising because in addition to serving

Scheme 1



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(1) (a) Nakai, T.; Tomooka, K. *Pure Appl. Chem.* **1997**, *69*, 595−600. (b) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 106−209. (c) Marshall, J. A. In *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon: London, 1991; Vol. 3, pp 975−1014. (d) Brückner, R. In *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon: London, 1991; Vol. 6, pp 873−908.

(2) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927−1928.

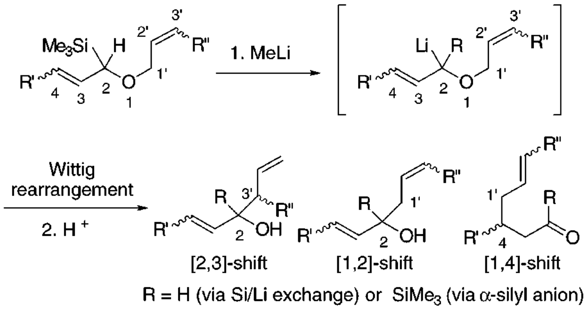
(3) (a) *Chemistry of Tin*; Smith, P. J., Ed.; Blackie Academic & Professional: New York, 1998. (b) Davies, A. G. In *Organotin Chemistry*; VCH: New York, 1997. (c) Pereyre, M.; Quintard, J.-P.; Rahm, A. In *Tin in Organic Synthesis*; Butterworth: Toronto, 1987.

(4) (a) Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 1471−1484. (b) Kruse, B.; Brückner, R. *Tetrahedron Lett.* **1990**, *31*, 4425−4428. (c) Kruse, B.; Brückner, R. *Chem. Ber.* **1989**, *122*, 2023−2025. (d) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981−2984.

10.1021/ol990912+ CCC: $18.00

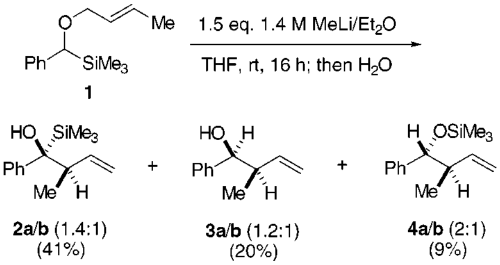
as a carbanion mask, the silyl moiety in α-alkoxysilanes can also be viewed as an anion-stabilizing group.[9b,c,10] As such, two Wittig rearrangement manifolds are available to α-alkoxysilanes: one involving Si/Li exchange and the other deprotonation (Scheme 2). Although the deprotonation path would afford a unique access to the synthetically malleable α-hydroxysilanes,[11] we are unaware of any examples where the direct deprotonation of α-alkoxysilanes has been used to initiate a [2,3]-Wittig rearrangement.[12,13]

Scheme 2



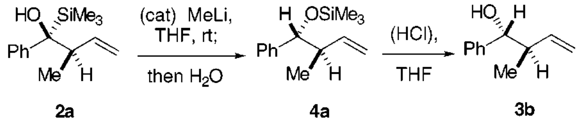
In light of these precedents, and in conjunction with our recent development of a Lewis acid-catalyzed method for the general synthesis of allyloxy and benzyloxy α-silyl ethers,[8] we thought it useful to evaluate these α-alkoxysilanes under "standard" Wittig rearrangement conditions.[1] Thus we began by subjecting a solution of α-alkoxysilane **1**[14] in THF to 1.5 equiv of a 1.4 M ethereal solution of MeLi (Scheme 3). We were immediately struck by the formation of *C*-silyl-containing reaction products (**2a**/**b**), providing clear evidence of **1** undergoing deprotonation followed by subsequent Wittig rearrangement. This is in contrast to exclusive silicon−lithium exchange reported for the two Wittig precursors studied by Muzler.[9a] The *C*-silyl alcohols were accompanied by a diasteromeric mixture of desilylated alcohols (**3a**/**b**) along with a small amount of the corresponding silyl ethers (**4a**/**b**).

Scheme 3



The formation of such a reaction mixture posed several challenges. First, although the level of stereocontrol displayed by the reaction was poor,[15] we wished to specifically identify the stereochemistry of **2a** and **2b**. Fortunately, both diastereomers proved readily separable by flash silica gel chromatography. Therefore, we could subject pure **2a** (the *major* isomer) to base-catalyzed Brook rearrangement (Scheme 4).[16] Since such rearrangements proceed with an inversion of configuration at carbon,[17] the reaction afforded a single silyl ether. Desilylation then afforded the known alcohol **3b**,[15,18] which was the *minor* alcohol produced by the reaction. Thus the Brook product could be assigned as **4a**, furthermore given the stereospecificity of the Brook, we could also confidently assign the relative stereochemistries of **2a** and **2b**.

Scheme 4



Additionally, the contrasting (albeit small) stereoselective preferences observed in the formation of the *C*-silyl alcohols (*syn* with respect to the oxygen and Me group preferred) vs the silyl ethers (*anti* with respect to the oxygen and Me group preferred) is evidence that **4a**/**b** are the result of **2a** and **2b** undergoing in situ Brook rearrangement. What was less clear was the mechanistic origin of the desilylated alcohols (**3a**/**b**). Obviously, Si/Li exchange-initiated [2,3]-rearrangement would account for their formation, but an alternative path

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(5) Hioki, K.; Kono, K.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* **1998**, *39*, 5229−5232.

(6) Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. *J. Org. Chem.* **1997**, *62*, 7542−7543.

(7) Takahashi, O.; Maeda, T.; Mikami, K.; Nakai, T. *Chem. Lett.* **1986**, 1355−1358.

(8) Preceding Letter this issue (Maleczka, R. E., Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1111−1113).

(9) (a) Mulzer, J.; List, B. *Tetrahedron Lett.* **1996**, *37*, 2403−2404. (b) Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553−559. (c) For a general review, see: Weber, W. P. In *Silicone Reagents for Organic Synthesis*; Springer-Verlag: New York, 1983.

(10) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 939−943.

(11) (a) Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392−2398. (b) Brook, A. G.; Pascoe, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 6224−6627. (c) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84. (d) Brook, A. G.; Bassendale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, pp 149−227.

(12) For examples of the directed deprotonation and rearrangement of vinylogous α-alkoxysilanes, see: (a) Mikami, K.; Kishi, N.; Nakai, T. *Chem. Lett.* **1989**, 1683−1686. (b) Greeves, N.; Lee, W.-M. *Tetrahedron Lett.* **1997**, *38*, 6445−6448.

(13) The [1,2]-Wittig rearrangement of [(aryloxy)methyl]silanes has been initiated by deprotonation and affords α-silylbenzyl alcohols. See: Eisch, J. J.; Galle, J. E.; Piotrowski, A.; Tsai, M.-R. *J. Org. Chem.* **1982**, *47*, 5051−5056.

(14) The starting α-alkoxysilanes were prepared by reaction of the corresponding α-silyl alcohols with allyl or benzyl trichloroimidates in the presence of catalytic quantities of TMSOTf. For details, see the preceding Letter this issue (see ref 8).

(15) [2,3]-Wittig rearrangement of the dessilyl analogue of **1** proceeds with similar (2:1) preference for the erythro product (Schöllkopf, U.; Fellenberger, K.; Rizk, M. *Liebigs Ann. Chem.* **1970**, *734*, 106−115).

(16) The same reaction sequence applied to **2b** provided analogous results.

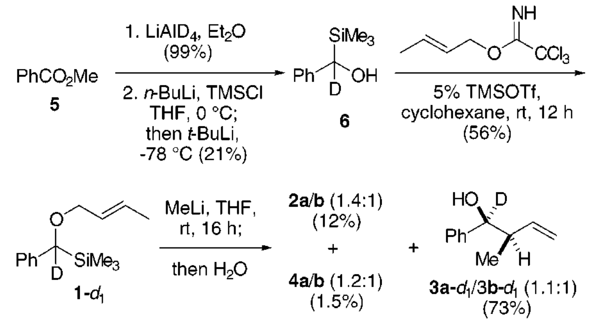
(17) (a) Reference 7b. (b) Biernbaum, M. S.; Mosher, H. S. *J. Am. Chem. Soc.* **1971**, *93*, 6221−6223.

(18) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513−3526.

involving in situ loss of the silyl group from either **2a**/**b** or **4a**/**b** was also envisaged.

While the stereochemical course of the reaction could again be used to argue against the in situ conversion of **4** to **3**, the very low levels of selectivity made it difficult to rule out this option with any significant degree of certainty. So to bring more clarity to this issue, we decided to prepare and react (Scheme 5) the deuterated analogue of **1** (**1**-d_1).

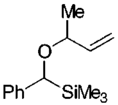
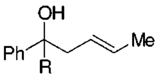
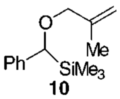
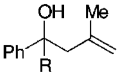
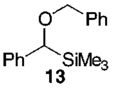
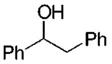
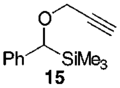
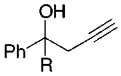
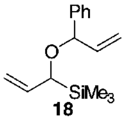
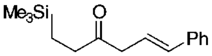
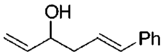
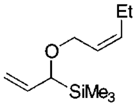
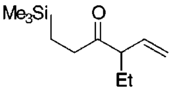
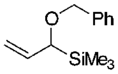
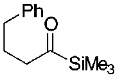
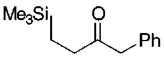
Scheme 5



The starting material was prepared by LAD reduction of methyl benzoate,[19] followed by a retro-Brook sequence[20] and then etherifcation.[14] Wittig rearrangement of **1**-d_1 gave the *C*-silyl, dessilyl, and *O*-silyl materials, although in this case the dessilyl alcohols (**2a**/**b**-d_1) were the major products, reflecting a relatively large deuterium isotope effect.[21] Significantly this material appeared to be fully deuterated as judged by ^{1}H NMR, providing strong evidence that it is produced solely via the Si/Li exchange pathway.

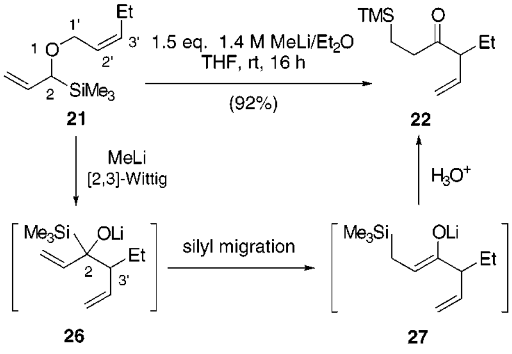
Having gained a reasonable understanding of the behavior of **1** toward Wittig−Still conditions, we next subjected several other α-alkoxylsilanes[14] to methyllithium (Table 1). With substrates set up for [2,3]-Wittig reaction (entries 1 and 2), the overall efficiency of the rearrangements were good. However, once again, the rearrangements proceeded via both the Si/Li exchange and α-silyl anion manifolds. With substrates set up to only undergo [1,2]-Wittig rearrangement (entries 3 and 4), the anticipated reaction did occur but as is often the observation with [1,2]-Wittigs,[23] the yields were low and again both Si/Li exchange and α-silyl anion formation appeared operative. Unfortunately, our attempts to drive these rearrangements down a single reaction path via standard methods were less than fruitful.[9,10]

Table 1. Reaction of α-Alkoxysilanes with MeLi[22]

entry	starting material	products (yield)
1	 **7**	 **8** R = H (75%) **9** R = SiMe$_3$ (21%) [3,2]-Wittig
2	 **10**	 **11** R = SiMe$_3$ (50%) **12** R = H (32%) [3,2]-Wittig
3	 **13**	 **14** (9%) [1,2]-Wittig
4	 **15**	 **16** R = H (33%) **17** R = SiMe$_3$ (15%) [1,2]-Wittig
5	 **18**	 **19** (60%) via [2,3]-Wittig  **20** (20%) [2,3]-Wittig
6	 **21**	 **22** (92%) via [2,3]-Wittig
7	 **23**	 **24** (60%) [1,4]-Wittig  **25** (21%) via [2,3]-Wittig

Intriguingly, when we moved from the α-alkoxylbenzylsilanes to α-alkoxylallylsilanes[14] (entries 5−7), the extent of Si/Li exchange was significantly curtailed. However, these substrates did display a propensity for silyl migration to afford *β*-silyl ketones. For example, α-alkoxylallylsilane **21** gave the *β*-silyl ketone **22** in a remarkable 92% yield. We propose that this product comes about via [2,3]-Wittig rearrangement of the α-silyl anion followed by a net 1,3-silyl migration[24] (Scheme 6). In a further departure from the α-alkoxylbenzylsilanes, allylsilane **23** rearranged in high yields albeit via a mixture of both [1,4]- and [1,2]-Wittigs (**24** and **25**). Given the synthetic utility reported for both

Scheme 6



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(19) Biellmann, J.-F.; d'Orchymont, H. *J. Org. Chem.* **1982**, *47*, 2882−2886.

(20) While the retro-Brook sequence only gave 21% of the desired α-hydroxysilane, 67% of the silyl ether was also recovered. Presumably this material could be recycled; however, no attempt to optimize the process was made.

(21) Lowry, T. H.; Richardson, K. S. In *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1987; Chapter 2.

(22) Except for entry 4 which required 2.5 equiv of base, all reactions were run in THF with 1.5 equiv of a 1.4 M solution of MeLi in Et$_2$O at room temperature over 16 h. See Supporting Information for more details.

(23) (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann. Chem.* **1997**, 1275−1281. (b) Maleczka, R. E., Jr.; Geng, F. *J. Am. Chem. Soc.* **1998**, *120*, 8551−8552 and references therein.

acylsilanes[9c,25] and β-silyl ketones,[9c,26] we are currently investigating these rearrangements in greater detail. Additionally, since both these compounds are formed via an enolate intermediate, we are also looking at combining these rearrangements with the capture of various electrophiles.

In summary, α-alkoxysilanes can be made to undergo efficient Wittig rearrangement by direct deprotonation with MeLi. Depending on the substrate, [2,3]-, [1,2]-, or [1,4]-Wittig rearrangements can be realized. These sigmatropic shifts can often be followed by other synthetically useful in situ chemical events, such as silyl migration to afford β-silyl ketones. Further studies aimed at expanding the scope and increasing our knowledge of these rearrangements are currently underway and will be reported in due course.

Acknowledgment. Generous support was provided by the National Institutes of Health (Institute of Heart, Blood, and Lung) through grant HL-58114 and the MSU Department of Chemistry (start-up funds for R.E.M. and a Harold Hart Graduate Fellowship for F.G.). We also thank Dr. P. G. Spoors (SmithKline Beecham) for valuable discussions.

Supporting Information Available: Spectroscopic data for all new compounds pictured as well as detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Although we have no direct evidence of any *O*-silyl products, the 1,3-silyl migration probably takes place via Brook rearrangement (ref 11) of **26** followed by rearrangement of the resulting homoenolate. For similar examples, see: (a) Kuwajima, I. *J. Organomet. Chem.* **1985**, *285*, 137−148. (b) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002−2021. (c) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063−3064. (d) For a related review, see: Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665−722.

(25) (a) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A. *J. Organomet. Chem.* **1998**, *567*, 181−189. (b) Maleczka, R. E., Jr.; Geng, F. *Tetrahedron Lett.* **1999**, *40*, 3113−3114 and references therein.

(26) (a) Fleming, I.; Mandal, A. K. *J. Chem. Soc., Chem. Commun.* **1999**, 923−924. (b) Furin, G. G.; Vyazankina. O. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron* **1988**, *44*, 2675−2749. (c) Hsiao, C. N.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2688−2699 and references therein.