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ALLYLSILANES IN ORGANIC SYNTHESIS: A FACILE INTRAMOLECULAR ALLYL TRANSFER, EVIDENCE FOR A NON-CONCERTED PROCESS

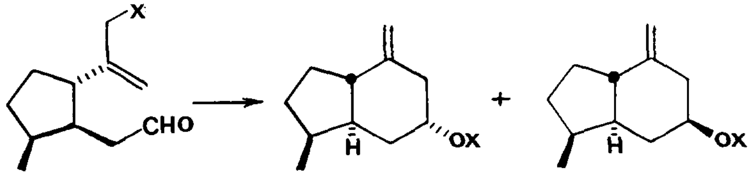
Tarun K. Sarkar and Niels H. Andersen
Department of Chemistry, University of Washington, Seattle, WA 98195

The enhanced π-bond nucleophilicity of allylsilanes has been demonstrated by Lewis acid catalyzed: additions to carbonyl compounds[1] (1,4-addition with α,β-unsaturated enones[1c,2]), acylation,[1c,3] and even alkylation.[4a] However, not a single intramolecular reaction of an allylsilane and a carbonyl compound has been reported.[5] Although a pericyclic mechanism, (1) with X = $SiMe_3$, has been invoked,[1a] no evidence bearing on this suggestion has appeared. We now supply intramolecular examples and evidence inconsistent with a concerted pericyclic mechanism.

The allyl transfer from an allylsilane to a carbonyl bears a close formal analogy to the ene reaction of olefinic aldehydes (which is also catalyzed by Lewis acids).[6] The latter, (1) with X = H, is clearly a concerted process under both the thermal and catalyzed conditions.[6c] Among the probes of this mechanism (X = H) which we have employed is the stereospecificity of the reaction of aldehyde 1: only the axial alcohol isomer (3) is obtained.[6c] The more stable equatorial isomer (5) cannot be formed in a pericyclic process. We have now prepared (<u>vide infra</u>) the silyl analog (2) and examined its cyclization with Lewis acids ($SnCl_4$ and $BF_3{\cdot}Et_2O$), with F^- ion, and on silica gel.

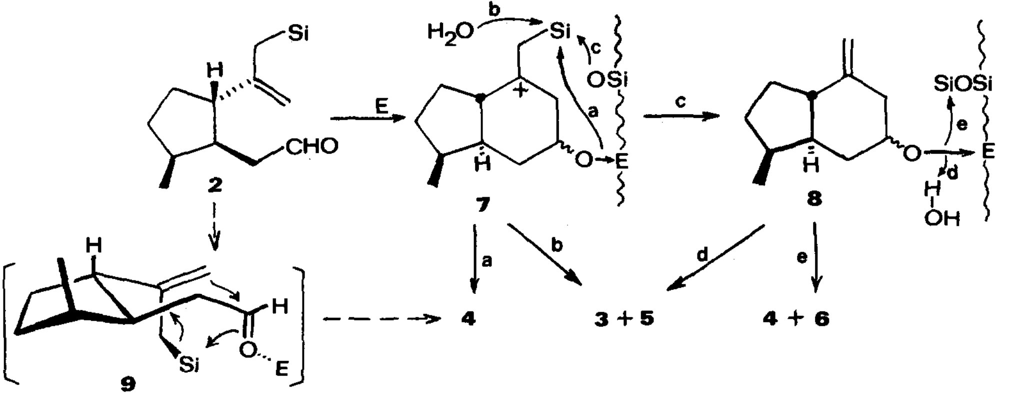
(1)

(2)



1 (X-H)
2 (X=$SiMe_3$)
3 (X=H)
4 (X=$SiMe_3$)
5 (X=H)
6 (X=$SiMe_3$)

The facilitating role of the $SiMe_3$ group was immediately evident on attempting a purification of aldehyde 2 by rapid chromatographic filtration (through SiO_2 previously deactivated with moist benzene) which afforded, instead, mixtures of axial and equatorial alcohols and silyl ethers (3-6).[7] Silyl aldehyde 2 also cyclized on thin layer chromatographic analysis and was unstable to our usual gc analysis conditions.[8a] The ratio of products varied from 2:1 (favoring the equatorial isomer) in a run affording only the silyl ethers to 56:44 (favoring the axial isomer) in runs affording largely the alcohols.[8b]



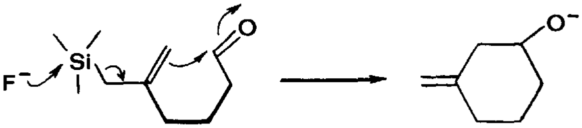
Scheme I

The production of the equatorial isomer eliminates the concerted pericyclic mechanism (9, Scheme I) as a major contribution to the mechanism. Rather, interaction at an electrophilic site affords cationic intermediate 7 which is subject to a variety of silicophilic attacks: a, internal; b, by water; and c, by a nucleophilic silica site.

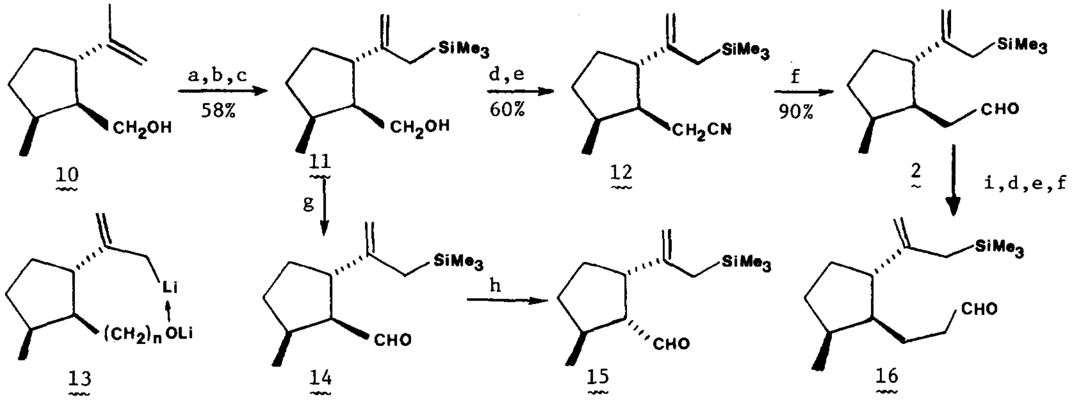
Turning to the cyclizations observed with soluble Lewis acids, unlike aldehyde 1, the silyl aldehyde (2) does not react completely with 0.1 equiv. of $SnCl_4$ at -35°. As in previous studies,[1-4] stoichiometric catalysis is required. Aldehyde 2 cyclizes in 78% isolated yield with $SnCl_4/CH_2Cl_2$ at -78° or -35° in less than 15 min. The initial products are silyl ethers 4 and 6 (51:49 at -35°, 59:41 at -78°) which undergo hydrolysis on quenching with saturated aqueous NH_4Cl.[9] We rationalize their production as the reaction of two molecules of 7 (Scheme I, attack b) with intermolecular C→O transfer of the silyl group. Again there is no evidence for the pericyclic process (9).

With $BF_3 \cdot Et_2O/CH_2Cl_2$ (-78° or 0°, 15 min), aldehyde 2 affords alcohols 3 and 5 (85:15 ratio) independent of the quench employed.[9] To determine whether the increased stereoselectivity reflects a change in mechanism, toward participation of 9 or to a fluoride promoted cyclization, eq. (3), we have examined the reaction of aldehyde 2 with Bu_4NF in anhydrous THF. After a two-hour exposure to 3 equivalents of the fluoride at 55°,[10] only alcohols 3 and 5 could be detected. The equatorial isomer (5) constitutes 82% of the volatile product. The "push" and "pull" mechanisms display diametrically opposed stereoselectivities.

(3)



The synthesis of silyl aldehydes 2, 14, 15, and 16 should dispel the notion that allylsilanes are too reactive to survive normal chemical operations (see Scheme II). The silyl alcohol (11) was prepared via the dilithio derivative (13, n=1) by treatment with trimethylchlorosilane and hydrolysis of the silyl ether in refluxing methanol. Homologation via cyanide displacement of the tosylate proceeds in 60% overall yield when the displacement reaction is carried out overnight at ambient temperature.[12] The nitrile reduction and hydrolysis of the imine proceed without incident. A potentially shorter synthesis via C-silylation of the homolog of 10 failed. Alkoxide coordination at the allyllithium, as shown in 13 appears essential for a facile C-silylation and does not occur when n=2 or 3. Reduction of aldehyde 2 followed by repetition of the previous homologation sequence affords aldehyde 16 (28% from 2, not optimized). Aldehyde 14 can be converted (→55%) to its less stable epimer (15) via kinetic protonation of the enolate.



Scheme II:[11] a, nBuLi, TMEDA, hexane 25°; b, Me_3SiCl; c, 9:1 $MeOH-H_2O$, reflux; d, TosCl, pyridine; e, NaCN, HMPT, 25°; f, iBu_2AlH, Et_2O, 0°C; then aq. NH_4Cl; g, $HCrO_3Cl\cdot pyr$, CH_2Cl_2; h, NaH, DME, then aq. KH_2PO_4; i, $LiAlH_4$, Et_2O.

With recent advances in methods for introducing the allylsilane function in complex molecules,[13] we expect the cyclization methods reported here to take on increasing importance. Evidence for their generality has already come from studies on aldehydes 14, 15, and 16. Unlike aldehyde 2, aldehydes 14→16 are stable to chromatography on silica; but each reacts rapidly with $SnCl_4$ even at -78°: aldehyde 14 affords intermolecular products while aldehydes 15 and 16 each give the bicyclic alcohols expected from intramolecular allylation of the carbonyl. Applications of this cyclization reaction to natural products synthesis are in progress.

Acknowledgement. Support for this research has been drawn from National Institutes of Health and Dreyfus Foundation grants and awards.

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5. This may reflect the hesitancy of practitioners of the synthesis of complex molecules to contemplate carrying a presumably labile allylsilane group through routine synthetic transformations needed to set the stage for the use of the allylsilane function. Based on the present studies (see also ref. 4) this chariness is largely unwarranted. A single intramolecular reaction of an allylsilane and an acetal has appeared: I. Fleming, A. Pearce, and R. L. Snowden, J. Chem. Soc., Chem. Commun., 182 (1976).
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7. The structure of alcohol **3** was established by NMR and gc comparison with authentic material and an undepressed mixed melting point.[6c] The equatorial disposition of the hydroxyl in **5** was established by NMR (CHOH, symmetric 7-line pattern, $J_{ax}=10$, $J_{eq}=5$) and an LIS experiment with $Eu(FOD)_3$. Both alcohols afford the identical single ketone which returns a 92:8 mixture (**5**:**3**) on $LiAlH_4$ reduction. Silylation of the pure alcohols afforded comparison samples of ethers **4** and **6**.

8a. The instability of aldehyde **2** to gc at 140° is not due to ready thermal cyclization: none of the expected products (**3**→**6**) are obtained on collecting the eluted materials. Upon heating at 140-180° C in xylene, aldehyde **2** polymerizes without producing detectable quantities of cyclic products.

8b. The variables (mesh size, storage history, and precise degree of deactivation of the silica) that need to be controlled in order to direct the cyclization to alcohols or ethers are not fully determined.

9. In order to detect the silyl ether intermediates in the $SnCl_4$-catalyzed process, the reaction must be quenched by addition of Et_3N prior to adding aq. NH_4Cl. Silyl ether hydrolysis occurs only when the ethers are present as the Lewis acid complexes on aqueous quenching. $BF_3 \cdot Et_2O/CH_2Cl_2$ hydrolyses silyl ethers **4** and **6** independent of the quench employed.
10. Experiments designed to determine whether the aldehyde serves as a participating neighboring group in this type of allylsilane cleavage are in progress. Ammonium and metal fluorides have been used to generate enolates and to initiate β-elimination of R_3Si-X: I. Kuwajima and E. Nakamura, J. Am. Chem. Soc., **97**, 3257 (1975); T. H. Chan, Accounts Chem. Res., **10**, 442 (1977).
11. The structures (and purity) of all numbered compounds in Scheme II are supported by the full complement of spectral data (NMR, IR, MS), including high resolution mass data (±5 mmass), and homogeneity by GC and HPLC or TLC.
12. Cyanide displacement at elevated temperatures leads to partial C-Si bond cleavage. A related, but more facile, cleavage is observed with NaI in acetone at reflux.
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