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A Si-Based Benzylic 1,4-Rearrangement/Cyclization Reaction

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Abstract

The trans-selective hydrosilylation of ynones (1) yields β -silylated enones (2) that undergo a benzylic 1,4-rearrangement/cyclization reaction in the presence of base, yielding 2,5-dihydro-1,2-oxasiloles (3).

Use of silicon compounds for the formation of C–C bonds has largely revolved around electrophilic substitutions involving allyl, vinyl, or aryl systems.¹ More recently, their use as nucleophilic partners in cross-coupling reactions has shown great promise.² In conjunction with our studies directed at a trans hydrosilylation,³ we investigated a geminal alkylation-hydroxylation of alkynyl carbonyl compounds as shown in Scheme 1.^{3b}

In conjunction with our studies of exploiting this process in complex natural product chemistry, we discovered a totally different and, to the best of our knowledge, unprecedented 1,4-shift in such substrates (2→3) in the presence of non-fluoride base to give 2,5-dihydro-1,2-oxasiloles (see abstract).⁴

The initial observation evolved from our efforts to examine a Peterson-style olefination as shown in Figure 1, path A. Surprisingly, none of the expected enoate was observed. The mass spectrum and elemental analysis indicated a molecular formula of $C_{17}H_{20}O_2Si$. The infrared spectrum showed no carbonyl peaks. Combined with the 1H and ^{13}C nmr spectra, the only structure that can be assigned is depicted as **3a** (see Table 1) which was further confirmed by subsequent transformations (vide infra).⁵ Since the olefinating agent was clearly not involved, the reaction was repeated just with LDA and an even more hindered amide base, lithium *t*-butyl-tritylamide (LiTTA). Adding the base at -78° and allowing the reaction to warm to 0° before quenching gave the same product **3a** which, in the case of LiTTA as base was isolated in 86% yield (98% based on recovered starting material). A non-amide base, trityllithium, also promoted the reaction. In this case, keeping the reaction at -78° and quenching at that temperature gave a 66% conversion after 5.5h.

To explore the generality of the process a series of ynones was hydrosilylated using the Ru catalyzed trans hydrosilylation protocol^{3b} using the appropriately functionalized benzyldimethylsilane as summarized in Table 1. It is interesting to note that in the 1,4-

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Supporting Information **Available** Experimental procedures and full spectroscopic data for all new compounds are available free of charge via the Internet at <http://pubs.acs.org>.

rearrangement/cyclization reaction electron deficient benzyl silanes work as well as benzylosilane itself. While LDA or trityllithium was generally used, LiTTA gave the cleanest reactions with the furyl substrates **2a** – **2d**. Given the basic nature of the reaction conditions, the effect of the presence of enolizable hydrogens in both R and R' were explored. Interestingly, aryl-aryl, aryl-alkyl, alkyl-aryl, and alkyl-alkyl (for R and R' respectively) all work with the alkyl-alkyl enones being the slowest. Regarding the migrating benzyl group, the more electron deficient ones migrate the fastest.

In order to provide further proof of the structures of the 2,5-dihydro-1,2-oxasiloles **3**, we performed degradation reactions on several silacycles. Applying protodesilylation conditions to the silyl ethers provided trans allylic alcohols (Table 2), thus proving both the correctness of our structural assignment and the unusual nature of the benzylic 1,4-shift. The transformation **3** → **4** represents a method for accessing stereodefined allylic alcohols from ynones that is complementary to known protocols with respect to reaction conditions and reagents.

Furthermore, we subjected silacycle **3f** to Tamao-Fleming oxidation conditions (Scheme 2), leading to the isolation of the aldol **5**. The independent synthesis of this aldol structure by the addition of a benzyl Grignard-reagent to 1,3-diphenyl-1,3-propanedione provided another proof for the structure of the silacycles **3**.

Earlier, we reported^{3b} a benzylic 1,2-rearrangement which had been applied to substrates that are similar to the enones **2** used for the benzylic 1,4-rearrangement/cyclization reaction presented here. In order to verify that the two rearrangement reactions are independent processes, we subjected a β -silylated enone used herein to the reported reaction conditions (Figure 2). The experiment showed that the nature of the rearrangement (1,2 vs. 1,4 shift) is determined by the reaction conditions, not by the structure of the substrate and thus proved that the two processes under comparison are complementary. Mechanistically, initiation of the transformation by deprotonation appears unlikely given that non-enolizable substrates react the fastest. The lack of deuterium incorporation in the benzylic position upon quenching the reaction with D₂O at partial conversion also rules out any deprotonation there.

The attractive interaction between carbonyl functions and silyl substituents in respective cis-olefins⁶ increases the electrophilicity of the Si nucleus. The coordination of a relatively small fluoride anion to Si^{3b} presumably puts the benzyl substituent in a pseudoaxial position thus facilitating a benzylic 1,2-shift. Since the use of sterically demanding bases as reagents excludes a coordination to Si, a single electron transfer mechanism seems most likely, leading to a benzylic 1,4-shift. Following the reduction of the substrate to a radical anion, the benzyl substituent migrates as an anion. This view is supported by the fact, that electron withdrawing substituents at the benzyl substituents increase the rate of the reaction.

In summary, we have discovered a benzylic 1,4-rearrangement/cyclization reaction. Our current efforts focus on deepening our mechanistic understanding of this transformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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5. The structural assignment for the 2,5-dihydro-1,2-oxasiloles products by NMR experiments was verified based on two-dimensional NMR measurements for **3b**.
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Scheme 1.
A Si-based benzylic 1,2-shift.

Figure 1.
Discovery of the benzylic 1,4-shift.

Scheme 2.

Further proof for structure. Use of the rearrangement as an alternative access to the aldol structural motif.

Figure 2.
Benzylic 1,4-shift vs. 1,2-shift: a mechanistic proposal.

Table 1

A novel 1,4-rearrangement/cyclization reaction^{a,b}

entry	R	R'	Ar	silacycle 3	base	yield
a		CH ₃	Ph		LiTTA ^c	86%
b		C ₂ H ₅	Ph		LiTTA ^c	71%
c			C ₆ F ₅		LiCPh ₃	95%
d			p-CF ₃ C ₆ H ₄		LiCPh ₃	87%
e	Ph	C ₂ H ₅	Ph		LDA	76% ^d
f		Ph	Ph		LiCPh ₃ ^e	86%
g			C ₆ F ₅		LDA	88%
h			p-CF ₃ C ₆ H ₄		LDA	90%
i	n-C ₅ H ₁₁	Ph	C ₆ F ₅		LDA	60%
j	n-C ₅ H ₁₁	CH ₃	C ₆ F ₅		LDA	56%
k			p-CF ₃ C ₆ H ₄		LiCPh ₃	43%

^a A solution of the enone was treated with 1.00–1.25 equiv of the base indicated at –78 °C. The solution was either stirred and quenched at –78 °C (entries 3,4,7,8,9,10,11) or quenched after warming to 0 °C (entry 1), to 4 °C (entry 6) or rt (entries 2,5).

^b Protocol of a typical rearrangement/cyclization reaction (2h → 3h): A solution of (Z)-3-(dimethyl(4-(trifluoromethyl)benzyl)silyl)-1,3-diphenylprop-2-en-1-one (2h; 160 mg, 377 μmol, 1.00 equiv) in 0.8 ml THF was treated with Lidisopropylamide (798 mM solution in THF/hexanes; 590 μl, 471 μmol, 1.25 equiv) at –78 °C. After stirring for 1h 40min, the reaction was quenched by addition of phosphate buffer (pH=7), extracted with diethyl ether, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by column chromatography yielded 2,2-dimethyl-3,5-diphenyl-5-(4-(trifluoromethyl)benzyl)-2,5-dihydro-1,2-oxasilole (3h; 144 mg, 338 μmol, 90%) as a colorless solid. ¹H NMR (CDCl₃, 400 MHz): δ = 0.00 (s, 3 H, SiCH₃), 0.40 (s, 3 H, SiCH₃), 3.29 (d, J = 13.2 Hz, 1 H, CH₂), 3.38 (d, J = 13.2 Hz, 1 H, CH₂), 7.23–7.36 (m, 9 H, 9 CH), 7.38–7.42 (m, 2 H, 2 CH), 7.49 (d, J = 7.6 Hz, 2 H, 2 CH), 7.53–7.56 (m, 2 H, 2 CH). ¹³C {¹H, ¹⁹F} NMR (CDCl₃, 100 MHz): δ = 0.65 (SiCH₃), 1.48 (SiCH₃), 49.7 (CH₂), 89.1 (C_{quat}), 124.6, 124.7, 125.1, 127.0, 127.1, 127.7, 128.7, 128.9, 129.0, 131.7, 137.3, 141.0, 141.4, 146.0, 147.1, ¹⁹F {¹H} NMR (CDCl₃, 376.3 MHz):

$\delta = -62.6$. IR (neat): ν (cm^{-1}) 3058, 3026, 2954, 1618, 1491, 1446, 1418, 1326, 1254, 1164, 1122, 1067, 1020, 955, 922, 881, 849, 824, 789, 756, 697, 635, 609, HRMS (EI): $(\text{MNa})^+$ calcd. for $\text{C}_{25}\text{H}_{23}\text{OF}_3\text{SiNa}$: 447.1368, found. 447.1360. $\text{C}_{25}\text{H}_{23}\text{F}_3\text{OSi}$ (424.53): calc. C 70.73, H 5.46; meas. C 70.52, H 5.62. mp = 90.0 °C.

^c LiTTA is lithium tert-butyl(trityl)amide.

^d This reaction was performed on a 1.52 g (4.92 mmol) scale.

^e 2.00 equiv of base were employed.

Table 2Trans allylic alcohols: *proof of structure*.

The reaction scheme shows a cyclic silyl enol ether (3) with an aryl group (Ar), a substituent R', and a substituent R on the double bond. It reacts with TBAF, CuI, and THF to form a trans allylic alcohol (4) with the same substituents.

entry	substituent R	substituent R'	aryl substituent Ar	yield
1	C ₆ H ₅	CH ₂ CH ₃	C ₆ H ₅	90%
2	3-furyl	CH ₃	C ₆ H ₅	81%
3	3-furyl	CH ₂ CH ₃	C ₆ F ₅	87%
4	3-furyl	CH ₂ CH ₃	4-(F ₃ C)C ₆ H ₄	88%