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Received April 1, 1977

Reactions of Lithium Alkoxide of 1,1-Bis(trimethylsilyl)alkan-1-ol with Benzophenone. A Novel Way to Silyl Enol Ether of Acylsilane

Sir:

Much attention has been focused on the preparation of acylsilane because of its interesting spectral behavior.[1] Among the various methods reported hitherto, the most effective one involves an acyl anion equivalent such as 2-lithio-1,3-dithiane[2] or 1-ethoxyvinyllithium.[3] We wish to report herein an effective method for the preparation of silyl enol ether[4] or its parent acylsilane.[5] We have recently reported that 1,1-bis(trimethylsilyl)alkan-1-ol can be prepared effectively from the corresponding trimethylsilyl carboxylate through reductive silylation,[6] and its lithium alkoxide has proved to be an efficient base for specific generation of ketone[7] or ester enolate.[8] In the course of further studies on the reaction with carbonyl compounds, it has been found that this type of alkoxide **1** is easily oxidized with benzophenone to afford the silyl enol ether of the corresponding acylsilane **2**, accompanied by the precipitation of lithium alkoxide of benzhydrol. The following procedure is illustrative. The lithium alkoxide of 1,1-bis(trimethylsilyl)-3-phenylpropan-1-ol was prepared by treating the alcohol (280 mg, 1.0 mmol) with an equimolar amount of butyllithium in *n*-hexane (2 mL). To the resulting solution was added an *n*-hexane (2 mL) solution of benzophenone (182 mg, 1.0 mmol) and it was stirred for 2 days at room temperature. During this period, the lithium alkoxide of benzhydrol was deposited. The reaction mixture was quenched with water and was extracted with ether. From the ether extracts, the trimethylsilyl enol ether of 3-phenylpropionyltrimethylsilane[9] (207 mg, 74%) and benzhydrol (140 mg, 76%) were isolated by TLC separation, along with the recovered alcohol (38 mg, 14%) and benzophenone (40 mg, 22%). If desired, 3-phenylpropionyltrimethylsilane was obtained in 70% yield by treating the reaction mixture with 6 N hydrochloric acid, followed by TLC purification.

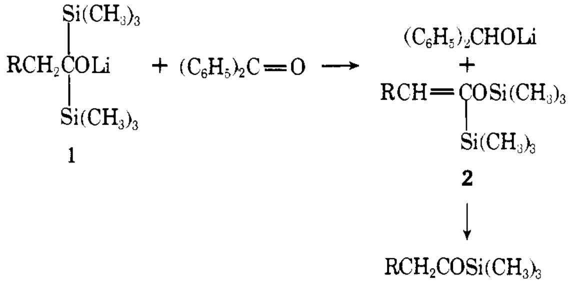
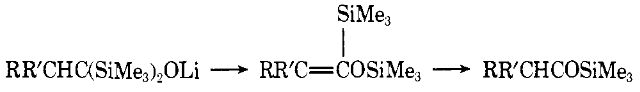

$$\underset{\mathbf{1}}{RCH_2C(Si(CH_3)_3)_2OLi} + (C_6H_5)_2C{=}O \longrightarrow (C_6H_5)_2CHOLi + \underset{\mathbf{2}}{RCH{=}C(Si(CH_3)_3)OSi(CH_3)_3} \longrightarrow \underset{\mathbf{3}}{RCH_2COSi(CH_3)_3}$$

Table I. Reactions of Lithium Alkoxide of 1,1-Bis(trimethylsilyl)-alkan-1-ol with Benzophenone[a,b]


$$RR'CHC(SiMe_3)_2OLi \longrightarrow RR'C{=}C(SiMe_3)OSiMe_3 \longrightarrow RR'CHCOSiMe_3$$

1 **2** **3**

R	R′	Yield of **2** (**3**[c])	Recovery of **1**
C_4H_9	H	64 (61)	24
C_6H_{13}	H	67 (63)	18
$C_6H_5CH_2$	H	74[d] (70)	14
$C_6H_5CH_2$	H	67[e]	25
$C_6H_5CH_2$	H	33[f] (31[f,g], 64[f,h])	0
$CH_2{=}CH(CH_2)_7$	H	69 (62)	15
$(CH_3)_2CH$	H	56 (52)	6
$(CH_3)_3CCH_2CH(CH_3)$	H	54 (51)	12
C_4H_9	C_2H_5	30[i]	9

[a] The reaction was performed in *n*-hexane under refluxing for 14 h, unless otherwise noted. In all of the reactions, benzhydrol was obtained in the yield almost comparable with that of **2**. [b] Satisfactory spectral and elemental analyses were obtained on all new compounds. [c] Acylsilane was obtained by quenching the reaction mixture with 6 N hydrochloric acid. [d] The reaction was carried out in *n*-hexane at room temperature for 2 days. [e] The reaction was carried out in benzene at room temperature for 1 day. [f] The reaction was carried out in THF at room temperature for 2 hr. [g] 3-Phenylpropanoic acid was also formed in 33%. [h] The reaction mixture was treated with anhydrous cupric chloride before quenching with hydrochloric acid. [i] The carboxylic acid was also formed in 24%.

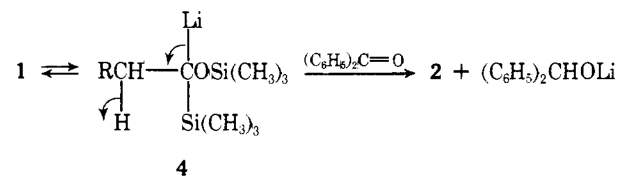
As shown in Table I, silyl enol ether or its parent acylsilane is generally obtained in good conversion yield (~80%) from the alcohol of type $RCH_2CH_2C(SiMe_3)_2OH$, while introduction of a substituent into the α or β position decreases the yield of conversion and an appreciable amount of the corresponding carboxylic acid is also formed.

Employment of the nonpolar solvent such as *n*-hexane or benzene appears to be crucial to complete this oxidation reaction. For example, when THF was used as the solvent in the reaction of the lithium alkoxide of 1,1-bis(trimethylsilyl)-3-phenylpropan-1-ol, the reaction mixture became a dark-green solution immediately, probably owing to the formation of benzophenone ketyl radical, from which, on quenching with hydrochloric acid, the corresponding acylsilane was isolated in only 31% yield, accompanied by the concomitant formation of 3-phenylpropanoic acid (33%). The yield of the acylsilane was contrarily raised to 64% yield with little formation of the carboxylic acid when an excess amount of anhydrous cupric chloride was added to the reaction mixture and it was stirred for 1 h at 0 °C.[10] These results have revealed that the precursor of the carboxylic acid can be converted effectively into the acylsilane through the reaction with cupric chloride.

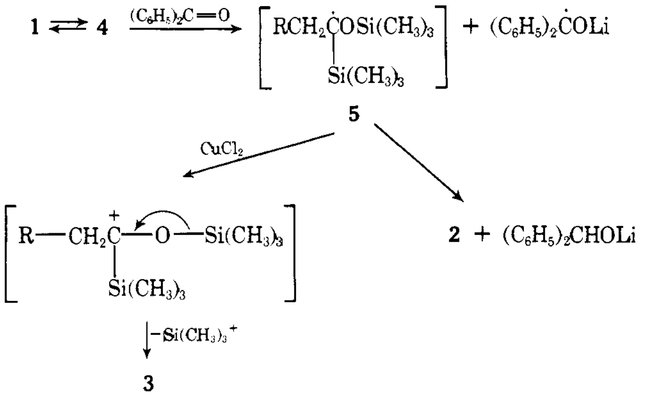
Similar reactions with other carbonyl compounds[11] such as benzaldehyde or benzalacetophenone were also attempted, but the former was almost inert toward this oxidation reaction,[12] and the reaction with the latter resulted in the formation of complex mixture.

On the mechanistic point of view, the following observations have strongly suggested intermediary existence of radical species:[13] (1) while benzaldehyde is unattacked by the alkoxide,[12] a stable radical such as galvinoxyl oxidizes the alkoxide to give **2**, which may exclude an alternative ionic mechanism (Scheme I) and (2) characteristic color of benzophenone ketyl radical is developed through the reaction. The reaction can be explained reasonably by assuming one-electron-transfer process.[14] Thus, one-electron transfer takes place initially between benzophenone and the carbanionic intermediate **4**, which is

Scheme I



Scheme II



considered to be in equilibrium with **1**,[15] to yield the radical **5** and benzophenone ketyl. From the radical **5** thus formed, the β hydrogen is removed by the ketyl radical to afford **2** (Scheme II). In the case that the final step is somewhat retarded, the radical **5** is considered to be oxidized with oxygen, on quenching, to form the carboxylic acid, or with cupric chloride[16] to afford acylsilane **3** through the formation of the corresponding carbonium ion, followed by removal of trimethylsilyl group.

References and Notes

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(4) Silyl enol ether of acylsilane was previously prepared from the corresponding acylimidazole in 30~35% yield.[3e] It has also been found in our laboratory that the silyl enol ether is an excellent precursor to α-haloacylsilane, which is easily converted into α,β-unsaturated acylsilane.

(5) See also I. Kuwajima, T. Abe, and N. Minami, *Chem. Lett.*, 993 (1976).

(6) I. Kuwajima, T. Sato, N. Minami, and T. Abe, *Tetrahedron Lett.*, 1591 (1976).

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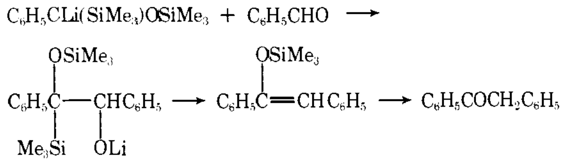
(8) I. Kuwajima, N. Minami, and T. Sato, *Tetrahedron Lett.*, 2253 (1976).

(9) The silyl enol ether obtained was composed of two geometrical isomers (5:1). Major (**2a**) and minor (**2b**) fractions have exhibited the following NMR spectra, respectively. **2a** (CCl_4): δ 0.20 (s, 9 H, $(CH_3)_3Si$), 0.26 (s, 9 H, $(CH_3)_3SiO-$), 3.50 (d, $J = 8$ Hz, 2 H, $C_6H_5CH_2CH=$), 5.67 (t, $J = 8$ Hz, 1 H, $C_6H_5CH_2CH=$), 7.30 (s, 5 H, aromatic protons). **2b** (CCl_4): δ 0.23 (s, 9 H), 0.31 (s, 9 H), 3.51 (d, $J = 7$ Hz, 2 H), 5.30 (t, $J = 7$ Hz, 1 H), 7.25 (s, 5 H). A mixture of **2a** and **2b** was obtained in ~1:5 ratio when 3-phenylpropionyltrimethylsilane was treated with lithium diisopropylamide, followed by silylation with trimethylchlorosilane.

(10) The reaction of this lithium alkoxide with cupric chloride was very slow and the corresponding acylsilane was isolated in 40% yield after stirring for 1 day at room temperature.

(11) *p*-Benzoquinone or ethyl azocarboxylate was also found to be less effective for this type of reaction.

(12) With lithium alkoxide of 1,1-bis(trimethylsilyl)benzyl alcohol, benzaldehyde reacts to give phenyl benzyl ketone (56%), which is probably formed through the following sequences. However, benzaldehyde remains unattacked with other alkoxides.



$$C_6H_5CLi(SiMe_3)OSiMe_3 + C_6H_5CHO \longrightarrow C_6H_5\overset{OSiMe_3}{\underset{Me_3Si}{C}}-\underset{OLi}{C}HC_6H_5 \longrightarrow C_6H_5\overset{OSiMe_3}{C}=CHC_6H_5 \longrightarrow C_6H_5COCH_2C_6H_5$$

(13) Existence of radical species other than benzophenone ketyl radical is definitely confirmed by measurement of ESR.

(14) For recent discussions about electron-transfer process involving carbonyl compounds, see H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770, 2778, 2785 (1976); H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976).

(15) About similar equilibrium between **1** and **4**, see, for example; A. G. Brook, *Acc. Chem. Res.*, **7**, 77 (1974).

(16) About oxidation of radical species with cupric salt, see J. K. Kochi, Ed., "Free Radicals," Wiley, New York, N.Y., 1973, Vol I, Chapter 11.

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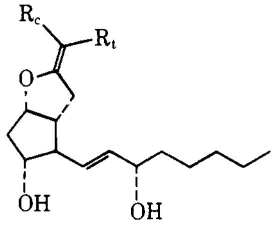
Received November 4, 1976

Synthesis and Stereochemistry of Prostacyclin and Synthesis of 6-Ketoprostaglandin $F_{1\alpha}$

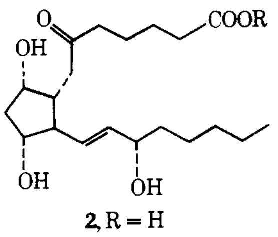
Sir:

The enzymatic transformation of the prostaglandin endoperoxides, PGH_2 and PGG_2, into a substance that inhibits platelet aggregation and causes relaxation of blood vessel walls was described recently by Vane and his colleagues.[1-4] Originally called prostaglandin X, this substance has been renamed prostacyclin.[5] The structure of prostacyclin, except for the stereochemistry of the C_5-C_6 double bond, has also been determined and accords with 9-deoxy-6,9α-epoxy-Δ^5-$PGF_{1\alpha}$ (**1**).[5] The enol-ether functionality of prostacyclin is rapidly hydrolyzed, even at pH 7.6, resulting in the formation of 6-ketoprostaglandin $F_{1\alpha}$ (**2**).[5] The isolation of 6-keto-$PGF_{1\alpha}$ from various biological tissues has been reported recently by several groups.[6-8] In this report, we outline the synthesis of both 6-keto-$PGF_{1\alpha}$ and prostacyclin and we assign stereochemistry to the C_5-C_6 double bond of prostacyclin.

When prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) methyl ester is treated (2 h, 5 °C) with iodine (2 equiv) in water in the presence of potassium iodide and sodium carbonate, or in methylene chloride in the presence of sodium carbonate, two less polar products are formed which we identified as iodo ether **3a** (90% yield aqueous; 45% yield, 90% if corrected for recovered starting material in CH_2Cl_2; high resolution mass spectrum of TMS derivative 638.2340, calcd for $C_{27}H_{51}Si_2O_5I$ 638.2322 and for $C_{21}H_{35}O_5I$, I 25.67, found 25.97)[9] and iodo ether **3b** (10% yield aqueous; 2% yield in CH_2Cl_2). Structure **3a** was assigned to the major new product on the following basis:



1, $R_c = -(CH_2)_3COOH$; $R_t = H$
8, $R_c = -(CH_2)_3COOCH_3$; $R_t = H$
9, $R_c = -(CH_2)_3COONa$; $R_t = H$
11, $R_c = H$; $R_t = -(CH_2)_3COOCH_3$
12, $R_c = H$; $R_t = -(CH_2)_3COONa$



2, R = H
7, $R = CH_3$