Stereoselective Synthesis of 2,3,5-Substituted Tetrahydrofurans by Silicon-Directed Cyclization of Allylsilanes Bearing a Hydroxy Moiety

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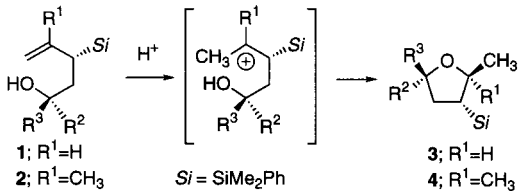
Received 23 June 1998

Abstract: Acid promoted cyclization of bishomoallylic alcohols bearing allylsilanes proceeded smoothly by way of β-silyl carbocation intermediate to furnish tetrahydrofurans highly stereoselectively.

It is well recognized that a silyl group stabilizes β-silyl carbocation by σ-π conjugation,[1] and numerous kinds of synthetic reactions, which take advantage of the effect, have been developed.[2] Although these reactions usually proceed by way of desilylation of the β-silyl cationic intermediate, nucleophilic attack onto the β-silyl carbocation has recently attracted attention as a novel method for the formation of carbon-carbon bond[3,4] as well as carbon-hetero atom bond.[5,6]

There is currently widespread interest in the stereoselective synthesis of substituted tetrahydrofurans since tetrahydrofuran units are frequently found in polyether antibiotics.[7] Cyclization of alkenyl alcohols promoted by acid or electrophiles furnished tetrahydrofurans.[8] Silicon-directed formation of tetrahydrofuran from vinylsilane mediated by acid,[9] and those from allylsilane promoted via epoxidation[10] have been reported recently. As part of our continued interest in the development of novel synthetic methods utilizing the β-silyl carbenium ion species,[4p,6,11] we wish to report herein highly stereoselective synthesis of tetrahydrofurans by internal attack of the hydroxyl moiety to the β-silyl carbenium ion generated from allylsilane by means of proton acid.

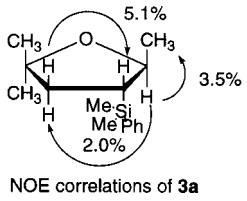


Scheme 1

Table 1. Effect of Acids

Entry	Lewis Acid	mol equiv	Reaction Conditions	Yield / %
1	*p*-TsOH	0.20	rt, 20 min	89
2	*p*-TsOH	0.10	rt, 2 h	86
3	*p*-TsOH	0.05	rt, 4.5 h	87
4	CSA	0.20	rt, 50 min	82
5	BF_3•OEt_2	0.20	0 °C, 2 h	79
6	$TiCl_4$	0.20	0 °C, 2 h	12

At the outset, an allylsilane bearing homoallylic alcohol (**1a**; R^1=H, R^2=R^3=CH_3)[12] was treated with several acids in CH_2Cl_2 and the results are shown in Table 1. *p*-TsOH was found to be the most effective for the present cyclization. Although 5 mol% of the acid sufficed for the smooth cyclization, the desired cyclization product (**3a**) was instantaneously obtained in an excellent yield as well as highly stereoselectively under the influence of 20 mol% of *p*-TsOH (Entry 1). Methyl group and silyl moiety turned out to be *trans* by multiple NOE experiments as shown in Figure 1. The corresponding *cis* isomer was not detected by 400 MHz ^{1}H NMR analysis.



NOE correlations of **3a**

Figure 1

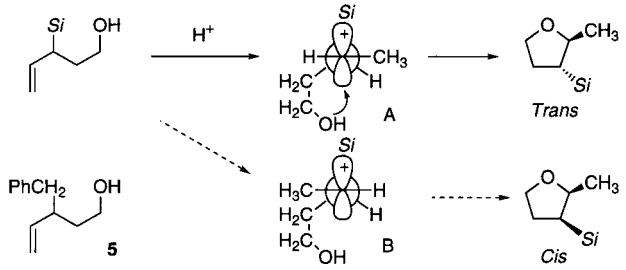
Table 2. *p*-TsOH Mediated Preparation of Tetrahydrofurans

Entry	Starting Material	R^1	R^2	R^3	Reaction Conditions	Product	Yield/%
1	**1a**	H	CH_3	CH_3	rt, 20 min	**3a**	89
2	**1b**	H	CH_3	H	rt, 1 h	**3b**	78
3	**1c**	H	H	CH_3	rt, 2 h	**3c**	50
4	**1d**	H	H	H	rt, 2.5 h	**3d**	77
5	**1e**	H	–$(CH_2)_5$–		rt, 40 min	**3e**	88
6	**2a**	CH_3	CH_3	CH_3	0 °C, 20 min	**4a**	88
7	**2b**	CH_3	H	H	0 °C, 20 min	**4b**	70
8	**2c**	CH_3	–$(CH_2)_5$–		0 °C, 20 min	**4c**	88

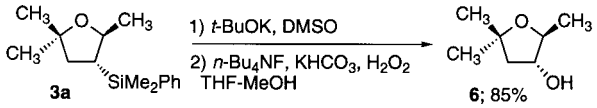
Formation of various tetrahydrofurans was studied by use of 20 mol% of *p*-TsOH in CH_2Cl_2 and the results are shown in Table 2.[13,14] Introduction of alkyl group on the carbon bearing hydroxy group facilitated the cyclization (Entry 1). This result indicates that the nucleophilicity of the hydroxy group was increased by the presence of the methyl group. Spirocycles were also obtained smoothly (Entries 5 and 8). Furthermore, methallylsilane **2** (R^1=CH_3) underwent cyclization much faster than **1** (R=H), which was accounted for by the higher stability of the β-silyl carbocation intermediate derived from **2** in comparison to that from **1**.

Stereochemical outcome of the present cyclization can be rationalized by considering the stability of the β-silyl carbocation intermediate (Scheme 2). Thus, 2,3-*trans* isomer was obtained via β-silyl carbocation (**A**) which is more favorable than **B**. To confirm that the present cyclization is directed by the silyl group, the cyclization reaction of **5** with *p*-TsOH was attempted under the same conditions. No cyclization product was obtained under the identical reaction conditions and the starting material was recovered quantitatively. It is noted that cyclization of present allylsilane is much faster than that of vinylsilane.[9]

Next, oxidative cleavage of the carbon-silicon bond was investigated (Scheme 3).[15] Treatment of **3a** with *t*-BuOK in DMSO[6b,16] at room temperature for 1 h followed by H_2O_2 in the presence of *n*-Bu_4NF[17] at room temperature for 15 min furnished the corresponding alcohol (**6**) in a high yield with retention of the stereochemistry.



Scheme 2



Scheme 3

In summary, hydroxy-substituted tetrahydrofurans were prepared highly stereoselectively by the silicon-directed cyclization of allylsilanes bearing a hydroxy group.

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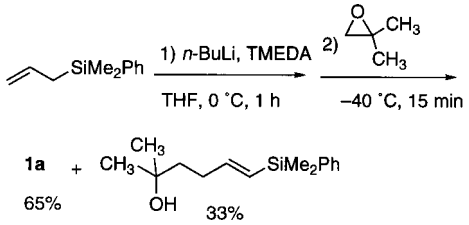
(12) Requisite allylsilanes were readily prepared by the reaction of α-silyl allyl anion and oxiranes (Scheme 4). A representative result is shown below for the preparation of **1a**, thereby γ-adduct was readily separated by silica gel column chromatography.



Scheme 4

(13) Data for selected compounds follow: **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.51-7.48 (m, 2H), 7.37-7.34 (m, 3H), 3.91 (dq, 1H, *J*= 10.6, 6.0 Hz), 1.82 (dd, 1H, *J*= 12.3, 7.8 Hz), 1.65 (dd, 1H, *J*= 12.8, 12.3 Hz), 1.39 (ddd, 1H, *J*= 12.8, 10.6, 7.8 Hz), 1.19 (s, 3H), 1.18 (s, 3H), 1.13 (d, 3H, *J*=6.0 Hz), 0.32 (s, 3H), 0.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.72 (C), 133.75 (CH), 129.12 (CH), 127.81 (CH), 79.45 (C), 77.18 (CH), 43.26 (CH_2), 34.90 (CH), 29.40 (CH_3), 28.81 (CH_3), 22.32 (CH_3), 4.20 (CH_3), 4.12 (CH_3).

3d: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.42 (m, 2H), 7.31-7.27 (m, 3H), 3.83-3.71 (m, 2H), 3.59 (ddd, 1H, *J*= 8.1, 8.0, 4.0 Hz), 1.96 (dddd, 1H, *J*= 12.0, 8.8, 6.8, 4.0 Hz), 1.71 (dddd, 1H, *J*= 12.0, 11.2, 8.1, 8.1 Hz), 1.07 (d, 3H, *J*= 6.0 Hz), 1.06-1.01 (m, 1H), 0.26 (s, 3H), 0.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.55 (C), 133.75 (CH), 129.15 (CH), 127.81 (CH), 77.73 (CH), 67.18 (CH_2), 33.91 (CH), 30.16 (CH_2), 21.69 (CH_3), 4.28 (CH_3), 4.16 (CH_3).

6: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.95 (ddd, 1H, *J*= 7.3, 6.0, 5.9 Hz), 3.85 (dq, 1H, *J*= 6.0, 6.0 Hz), 2.12 (dd, 1H, *J*= 12.8, 7.3 Hz), 1.76 (dd, 1H, *J*= 12.8, 5.9 Hz), 1.68 (brs, 1H), 1.35 (s, 3H), 1.27 (s, 3H), 1.26 (d, 3H, *J*= 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ =

80.10 (CH), 79.88 (C), 77.94 (CH), 47.08 (CH_2), 30.30 (CH_3), 28.88 (CH_3), 19.24 (CH_3).

(14) A typical experimental procedure for the preparation of **3a** is described (entry 1, Table 2). To predried *p*-TsOH•H_2O (11 mg, 0.052 mmol) was added a solution of **1a** (65 mg, 0.26 mmol) in CH_2Cl_2 (0.7 ml) at room temperature. After being stirred at the temperature for 20 min, the reaction was quenched by addition of water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the crude mixture by column chromatography (SiO_2, hexane: ethyl acetate = 12:1, v/v) gave **3a** (57.9 mg, 89%).

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