

Stereoselective Synthesis of 2,2,5-Trisubstituted Tetrahydrofurans via the Lewis Acid-Assisted Reaction of Cyclic Hemiketals with Nucleophiles

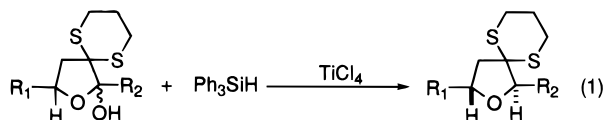
Yutaka Nishiyama,* Takeshi Katoh, Katsuya Deguchi, Yorikazu Morimoto, and Kazuyoshi Itoh

Department of Applied Chemistry, Faculty of Engineering and High Technology Research Center, Kansai University, Suita, Osaka 564, Japan

Received May 28, 1997

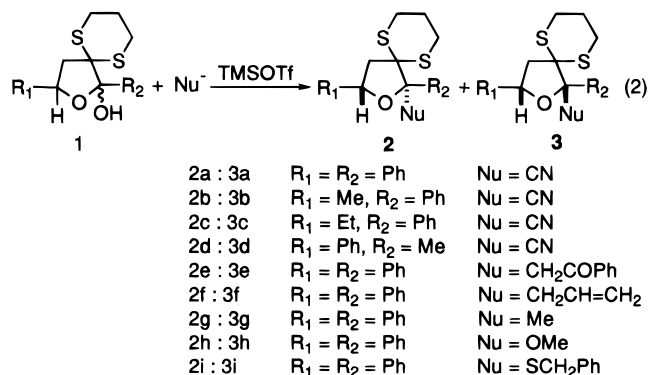
As the development of efficient and stereoselective construction methods of tetrahydrofurans are desirable in connection with the synthesis of polyether antibiotics and natural products containing oxacyclic units,¹ various tetrahydrofuran synthetic methods have been developed.² However, there are only a limited number of stereoselective synthetic methods for trisubstituted tetrahydrofurans (e.g., the intramolecular cyclization methods such as intramolecular cyclization of homoallylic alcohols in the presence of iodine,³ or a palladium catalyst,⁴ the acetic acid promoted intramolecular cyclization of epoxy alcohols,⁵ and the Lewis acid assisted reaction of various nucleophiles with γ -hydroxy ketones followed by cyclization⁶).

Recently, we reported a convenient and highly stereoselective synthetic method of 2,5-disubstituted tetrahydrofurans by the Lewis acid-assisted reduction of cyclic hemiketals (1), 2,5-disubstituted 3,3-(trimethylenedithio)furan-2-ol, with triphenylhydrosilane (eq 1).⁷ In the course of our study on the development of the high stereoselective synthesis of tetrahydrofuran derivatives,⁸



we found a new stereoselective synthetic method of 2,2,5-trisubstituted tetrahydrofurans (2 and 3) based on the reaction of dithioacetal functionalized cyclic hemiketals

(1) with various nucleophiles in the presence of a Lewis acid (eq 2).⁹

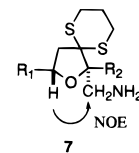


The reaction was carried out as follows: To a CH₂Cl₂ (2 mL) solution of cyclic hemiketal (1) (0.2 mmol) and 2 equiv of trimethylsilyl cyanide (4) was added 2 equiv of trimethylsilyl triflate (TMSOTf) as a Lewis acid at -78 °C. The color of the reaction solution immediately changed to a wine red color, the spot of 1 disappeared, and the spots of 2,2,5-trisubstituted tetrahydrofurans (2 and 3) appeared on TLC. After the neutralization with aqueous NaHCO₃ and extraction with diethyl ether, the product was isolated by column chromatography on silica gel.

Dihydro-2,5-diphenyl-3,3-(trimethylenedithio)furan-2-ol (1a) was chosen as a model substrate and allowed to react with trimethylsilyl cyanide (4) under various reaction conditions (Table 1). In contrast, the use of TiCl₄ shows a high yield and excellent stereoselectivity for the synthesis of 2,5-disubstituted tetrahydrofurans by the reduction of 1a with triphenylhydrosilane, the reaction of 1a with 4 was not induced at all by TiCl₄ (run 4). However, when TMSOTf instead of TiCl₄ was used as a Lewis acid, the reaction of 1a with 4 smoothly proceeded to give 2-cyano-2,5-diphenyl-3,3-(trimethylenedithio)furan in almost quantitative yield with high stereoselectivity (2a:3a = 38.5:1.0) (run 2).¹⁰ Lowering the amount of 4 from 2 equiv to 1 equiv led to the decrease of the yields of 2 and 3 (run 1). At a higher reaction temperature (0 °C), stereoselectivity is lower than that at -78 °C, and the ratio of 2 to 3 is approximately 7.8:1.0 (run 3). In the cases of BF₃·OEt₂ and Et₂AlCl, the cyanated products were obtained in 93% and 91% yields, respectively, but the stereoselection of 2 is lower than that of TMSOTf (runs 5 and 8). The use of aluminum trichloride (AlCl₃) and ethyl aluminum dichloride (EtAlCl₂)

(9) Suzuki, K. et al. have already reported that the stereoselective synthesis of disubstituted cyclic ethers, tetrahydrofurans and tetrahydropryrans, by the reaction of lactols with organometallic reagents in the presence of Lewis acid: see Tomooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6339.

(10) The configuration of each isomer was assigned by the NOE analysis of the ring protons of compounds 7, which were the reduction products of 2 and 3 with LiAlH₄. In the case of the minor products, when irradiated at the frequency of the C-5 proton signal, NOE was observed for the C-4 proton signal. On the other hand, irradiation of the C-5 proton of a major proton did not show an NOE difference.



(1) For example, see: (a) Westley, J. W. *Polyether Antibiotics: Naturally occurring acid ionophores*; Marcel Dekker: New York, 1982, Vols I and II. (b) Cave, A.; Cortes, D.; Figadere, B.; Hocquemiller, R.; Laprevote, O.; Laurens, A.; Leboeuf, M. *Phytochemical Potential of Tropical Plants: Recent Advances in Phytochemical 27*; Downum, K. R., Romen, J., Stafford, H. H. A., Eds.; Plenum Press: New York, 1993. (c) Boivin, M. H. D. *Tetrahedron* **1992**, *48*, 8545.

(2) For reviews, see Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 2209 and references cited therein.

(3) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

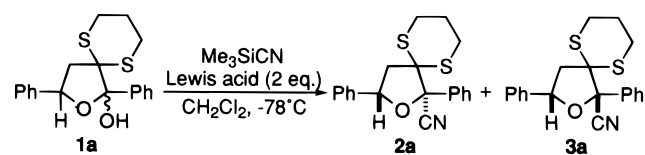
(4) Hosokawa, T.; Hirata, M.; Murahashi, S.-I.; Sonoda, A. *Tetrahedron Lett.* **1978**, *21*, 1821.

(5) Fukuyama, T.; Uranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *31*, 2741.

(6) Ressig, H. U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3139.

(7) Nishiyama, Y.; Tujino, T.; Yamano, T.; Hayashishita, M.; Itoh, K. *Chem. Lett.* **1997**, 165.

(8) (a) Chikashita, H.; Ishihara, M.; Takigawa, K.; Itoh, K. *Chem. Lett.* **1992**, 195. (b) Chikashita, H.; Fukushima, H.; Uemura, H.; Itoh, K. *Chem. Lett.* **1992**, 599. (c) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett.* **1993**, 477. (d) Chikashita, H.; Hirao, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1992**, *66*, 195. (e) Chikashita, H.; Nikaya, T.; Takigawa, K.; Itoh, K. *Natur. Prod. Lett.* **1992**, *2*, 183.

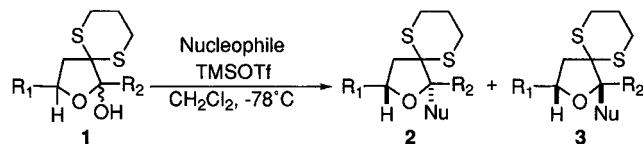
Table 1. Reaction of **1a** with Trimethylsilyl Cyanide in the Presence of Various Lewis Acids

Run	Lewis acid	Me ₃ SiCN (equiv)	time, min	yield, % ^a (2a/3a) ^b
1	TMSOTf	1	5	79 (39.3/1.0)
2	TMSOTf	2	1	99 (38.5/1.0)
3 ^c	TMSOTf	2	1	91 (7.8/1.0)
4	TiCl ₄	2	240	no reaction
5	Et ₂ AlCl	2	240	91 (6.5/1.0)
6	EtAlCl ₂	2	5	96 (37.2/1.0)
7	AlCl ₃	2	1	98 (35.5/1.0)
8	BF ₃ ·OEt ₂	2	15	93 (2.4/1.0)

^a Isolated yield based on **1a**. ^b Determined by ¹H NMR. ^c The reaction was carried out at 0 °C.

gave almost the same yield and stereoselectivity as that of TMSOTf (runs 6 and 7).

In order to determine the scope and limitation of the stereoselective synthesis of 2,2,5-trisubstituted tetrahydrofurans using the Lewis acid assisted reaction of cyclic hemiketals (**1**) with organometallic compounds, the reaction of hemiketals with various organometallic compounds was examined (Table 2).¹¹ It is interesting to note that the stereoselectivity of the products and the reactivity of the substrates depended on their substituents at both the C-1 and C-4 positions of the cyclic hemiketals. When 4-alkyl-substituted cyclic hemiketals, dihydro-5-ethyl- (**1b**) or dihydro-5-methyl-2-phenyl-3,3-(trimethylenedithio)furan-2-ol (**1c**), and 2-alkyl-substituted cyclic hemiketals, dihydro-2-methyl-5-phenyl-3,3-(trimethylenedithio)furan-2-ol (**1d**), instead of **1a** which possesses phenyl groups at both the C-1 and C-4 positions, were used as the substrate, cyanation of these compounds required a longer reaction time than that of **1a**, and the stereoselectivities of tetrahydrofurans are slightly lower than **1a** (runs 1–3). In the reaction of **1d**, TiCl₄ also shows the same activity as that of TMSOTf, in contrast with having no activity in the cases of **1a**, **1b**, and **1c**. The reaction of **1a** with enol silyl ethers and allyl silanes, which are often used as good carbon nucleophiles in organic synthesis, was next examined in the presence of TMSOTf. In the case of the enol silyl ether, 1-phenyl-1-(trimethylsilyloxy)-2-ethene, the corresponding 2,2,5-trisubstituted tetrahydrofuran was formed in 53% yield with high stereoselectivity (run 5). On the other hand, allyltrimethylsilane did not give a good result (run 6). However, when allyltributylstannane instead of allyltrimethylsilane was used as an allylated reagent, an allylated product was obtained in good yield (91% yield) with high stereoselectivity (**2f:3f** = 15.4:1.0) (run 7). In the case of the synthesis of a 2-methyl-2,5-diphenyl-substituted tetrahydrofuran by the reaction of **1a** with dimethylzinc, a satisfactory yield was not obtained due to the formation of several byproducts (run 8). When methanol was employed under the same reaction conditions, the corresponding cyclic ketal was formed in poor yield (run 9). However, the yield of the cyclic ketal was increased by the addition of MgSO₄ as a dehydrating

Table 2. Reaction of Cyclic Hemiketals with Various Nucleophiles in the Presence of TMSOTf^a

Run	Hemiketal	Nucleophiles	Time, min.	Products	Yield, % ^b (2 / 3) ^c
1	R ₁ =Me, R ₂ =Ph (1b)	Me ₃ SiCN (4)	180	2b / 3b	84 (15.3 / 1.0)
2	R ₁ =Et, R ₂ =Ph (1c)	4	180	2c / 3c	84 (16.3 / 1.0)
3	R ₁ =Ph, R ₂ =Me (1d)	4	1	2d / 3d	91 (17.9 / 1.0)
4 ^d	R ₁ =Ph, R ₂ =Me (1d)	4	360	2d / 3d	72 (13.8 / 1.0)
5	R ₁ =R ₂ =Ph (1a)		270	2e / 3e	53 (3.8 / 1.0)
6	1a	CH ₂ =CHCH ₂ SiMe ₃	30	2f / 3f	58 (2.6 / 1.0)
7	1a	CH ₂ =CHCH ₂ SnBu ₃	5	2f / 3f	91 (15.4 / 1.0)
8 ^e	1a	Me ₂ Zn	120	2g / 3g	44 (1.8 / 1.0)
9	1a	CH ₃ OH	420	2h / 3h	53 (1.9 / 1.0)
10 ^f	1a	CH ₃ OH	420	2h / 3h	84 (2.0 / 1.0)
11	1a	PhCH ₂ SH	180	2i / 3i	79 (1.0 / 1.0)

^a Reaction conditions: cyclic hemiketal (0.2 mmol), nucleophile (0.4 mmol), TMSOTf (0.4 mmol) in CH₂Cl₂ (2 ml) at -78 °C. ^b Isolated yield based on cyclic hemiketal. ^c Determined by ¹H NMR. ^d TiCl₄ was used as a Lewis acid. ^e Reaction was carried out at 25 °C. ^f In the coexistence of 0.5 equiv amount of MgSO₄.

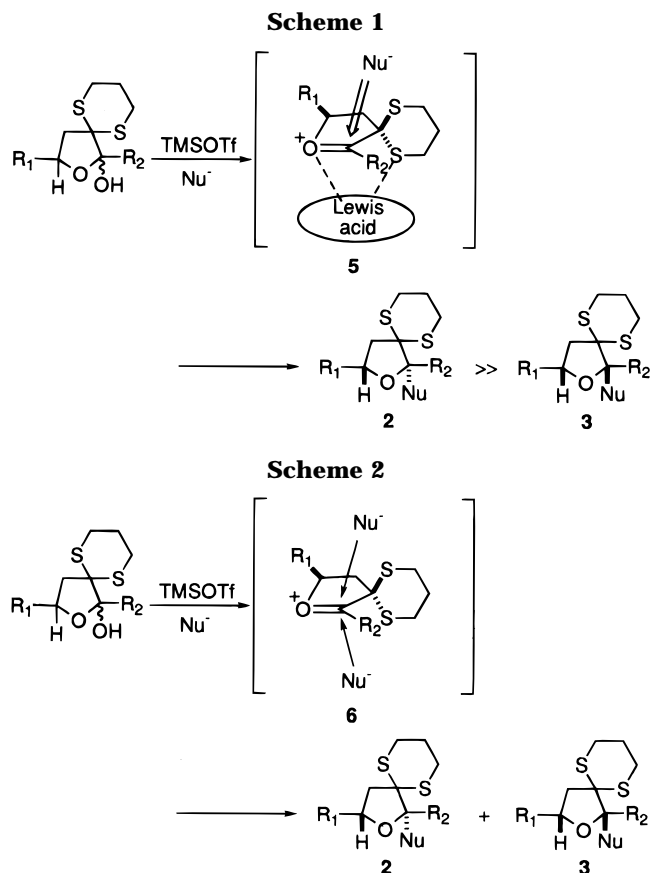
agent (**2h:3h** = 1.9:1.0) (run 10). The monothiofuran was also obtained by the reaction of **1a** with thiol in 79% yield (run 11).

Although we have so far not been able to obtain clear evidence for the high selectivity, we suggested that the nucleophiles attacked an oxonium ion intermediate (**5**) from the peripheral side owing to the steric hindrance of 3,3-trimethylenedithio group, in which the Lewis acid was coordinated on one of the sulfur atoms of the 3,3-trimethylenedithio group, to form **2** predominantly (Scheme 1).¹² However, in the case of alcohol or thiol the coordination of the Lewis acid on the sulfur atom was suppressed by these compounds, and the steric interaction of **6** appeared to be smaller than that of **5** (Scheme 2). Therefore, the decrease of steric effect led to the decrease of stereoselectivity.

In summary, we succeeded in the stereoselective synthesis of 2,2,5-trisubstituted tetrahydrofurans based

(12) Reissig, H. U. et al. has already reported the stereoselective synthesis of 2,2,5-trisubstituted tetrahydrofurans by the Lewis acid assisted reaction of γ -hydroxy ketones with various organosilicon reagents.⁶ In this paper, he suggested that the reaction proceeded by Lewis acid induced cyclization of γ -hydroxy ketones followed by addition of organosilicon reagents to the similar oxocarbenium cation intermediates. However, the stereoselectivity of products with H. U. Reissig's method was opposite to that observed by our method. From these results, we suggested that the 3,3-trimethylenedithio group played an important role on the stereoselectivity.

(11) The configuration of all products was assigned by the NOE analysis.



on the reaction of cyclic hemiketals with various nucleophiles in the presence of TMSOTf.

Experimental Section

Materials. ^1H and ^{13}C NMR spectra were measured with 400 and 100 MHz using tetramethylsilane as the internal standard. IR spectra were obtained on an FT-IR spectrophotometer. Styrene oxide, methanol, α -toluenethiol, ethyl benzoate, ethyl acetate, and HMPA were purified by the usual methods and freshly distilled before use. All Lewis acids, trimethylsilyl cyanide, allyltrimethylsilane, allyltributylstannane, dimethylzinc (in toluene solution), *n*-BuLi (in hexane solution), butylene oxide, and propylene oxide were high grade commercially available product and used without purification. 1,3-Dithiane was synthesized by a reported method.¹³

Synthesis of Dithianyl Alcohols. To a THF (30 mL) solution of 1,3-dithiane (3.17 g, 26 mmol) was added dropwise a 15% hexane solution of *n*-BuLi (24.5 mL, 39 mmol) at -40°C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h at -40°C and then for 2 h at 0°C . The solution was cooled to -40°C and epoxide (22 mmol) was added dropwise and stirred for 2 h at -40°C . The reaction mixture was quenched by the addition of aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (50 mL \times 3). The combined organic layers were dried over MgSO_4 , concentrated under reduced pressure, and then purified by column chromatography on silica gel to give the corresponding dithianyl alcohols.

(13) Corey, E. J.; Seebach, P. *Organic Syntheses*; Wiley: New York, 1988; Coll. Vol. 6, p 556.

Synthesis of Cyclic Hemiketals. To a THF (60 mL) solution of dithianyl alcohol (12.5 mmol) was added *n*-BuLi (15% hexane solution) (75 mmol, 48 mL) dropwise at -40°C under a nitrogen atmosphere. The reaction mixture was stirred at -40°C for 2 h and then at -15°C for 3 h. After the solution was cooled to -40°C , HMPA (75 mmol, 13.2 mL) was added. After the solution was stirred at -40°C for 2 h, ethyl benzoate (75 mmol, 12 mL) was added dropwise and stirred for 5 h at -40°C and then at -15°C for 15 h. The reaction mixture was quenched by the addition of aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (100 mL \times 3). The combined organic layers were dried over MgSO_4 , concentrated under reduced pressure, and then purified by column chromatography on silica gel to give the corresponding cyclic hemiketals.

Lewis Acid-Assisted Reaction of Cyclic Hemiketals with Organometallic Reagent. To a CH_2Cl_2 (2 mL) solution of cyclic hemiketal (0.2 mmol) and organometallic compound (0.4 mmol), was added TMSOTf (0.4 mmol) dropwise at -78°C and stirred for 1 min. After the reaction, the reaction mixture was quenched with aqueous NaHCO_3 (10 mL) and extracted with diethyl ether (10 mL \times 3). The combined organic layers were washed with brine solution (30 mL) and dried over MgSO_4 . The solution was concentrated with reduced pressure, and the resulting solution was purified by column chromatography on silica gel to afford the corresponding 2,2,5-trisubstituted tetrahydrofuran derivatives.

Mixture of **2a** and **3a** (**2a:3a** = 0.8:0.2): ^1H NMR (CDCl_3) δ 1.71–1.90 (c, 3H), 2.17–2.23 (m, 0.2H), 2.45–2.51 (m, 0.8H), 2.61–2.71 (c, 0.4H), 2.73–2.79 (m, 0.8H), 2.82 (dd, J = 11.0, 14.0 Hz, 0.8H), 2.92–3.03 (c, 1H), 3.07–3.13 (c, 1H), 5.48 (dd, J = 6.2, 9.5 Hz, 0.2H), 5.61 (dd, J = 5.5, 11.0 Hz, 0.8H), 7.31–7.49 (c, 6H), 7.53–7.58 (c, 2H), 7.87–7.97 (c, 1.6H), 7.99–8.00 (c, 0.4H); ^{13}C NMR (CDCl_3) δ 23.7, 26.6, 27.7, 50.5, 50.6, 50.7, 60.5, 81.5, 81.5, 81.6, 90.1, 119.5, 126.2, 127.0, 128.0, 128.3, 128.7, 129.9, 134.4, 139.5; IR (KBr) 2358, 1045, 763, 748, 698 cm^{-1} ; exact mass calcd for $\text{C}_{20}\text{H}_{19}\text{NOS}_2$ 353.5090, found 353.5066.

Reduction of 2a. To a THF (5 mL) solution of LiAlH_4 (0.9 mmol, 34 mg) was added **2a** (0.18 mmol, 63 mg) dropwise at 0°C and stirred at room temperature for 18 h. After the reaction, the reaction mixture was quenched with H_2O (10 mL) and extracted with diethyl ether (10 mL \times 3). The combined organic layers were washed with brine solution and dried over MgSO_4 . The solution was concentrated with reduced pressure, and the resulting solution was purified by column chromatography on silica gel (benzene:EtOAc = 1:1) to afford **7**.

7: ^1H NMR (CDCl_3) δ 1.36 (s, 2H), 1.80–1.91 (m, 1H), 2.01–2.07 (m, 1H), 2.57 (dt, J = 3.3, 14.0 Hz, 1H), 2.67 (dd, J = 11.0, 13.0 Hz, 1H), 2.80–2.85 (m, 1H), 2.95–3.08 (c, 2H), 3.24 (d, J = 14.0 Hz, 1H), 3.37–3.41 (c, 2H), 5.49 (dd, J = 5.1, 11.0 Hz, 1H), 7.31–7.47 (c, 8H), 7.70–7.72 (c, 2H); ^{13}C NMR (CDCl_3) δ 25.4, 28.7, 28.7, 49.8, 50.3, 62.7, 80.1, 92.1, 126.3, 127.0, 127.9, 128.1, 128.1, 128.9, 139.5, 141.4; IR (KBr) 1031, 756, 700 cm^{-1} .

Acknowledgment. We thank the donors of Grant-in-Aid (09750958) from the Ministry of Education, Science, and Culture of Japan and The Science Research Promotion Fund administered by the Japan Private School Promotion Foundation for this research.

Supporting Information Available: ^1H and ^{13}C NMR spectra and data for compounds **2a–i**, **3a–i**, and **7** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9709312