Stereoselective Synthesis of *trans*-2,5-Disubstituted Tetrahydrofurans *via* the Lewis Acid Mediated Reduction of Cyclic Hemiketals with Triphenylsilane

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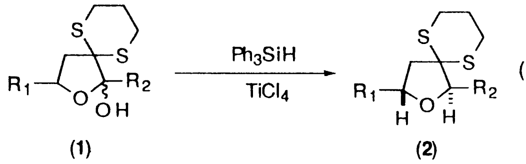
An efficient method for the synthesis of *trans*-2,5-disubstituted tetrahydrofuran derivatives has been developed. Dithioacetal-functionalized cyclic hemiketals are reduced by triphenylsilane (Ph_3SiH) in the presence of $TiCl_4$ to afford the corresponding *trans*-2,5-disubstituted tetrahydrofuran derivatives in good yield and high stereoselectivity. Asymmetrical synthesis of (2*S*,5*S*) disubstituted tetrahydrofuran was also achieved by using this reduction method.

There is an increasing interest in the stereocontrolled construction of 2,5-disubstituted tetrahydrofurans[1] in connection with the synthesis of polyethers antibiotics and natural products containing oxacyclic units.[2] In a previous papers on the synthesis of polytetrahydofuran compounds,[3] we have reported a novel and efficient construction of *trans*-2,5-disubstituted tetrahydrofurans *via* stereocontrolled hydride reduction of cyclic hemiketals (**1**) into 1,4-diols followed by their stereospecific one-step cyclodehydration.[3a]

In the course of our study on the synthesis of chiral polytetrahydofuran compounds, we found a high stereoselective synthetic method of *trans*-2,5-disubstituted tetrahydrofurans (**2**) *via* reduction of dithioacetal-functionalized cyclic hemiketals (**1**) with Ph_3SiH (**3**) in the presence of $TiCl_4$ (Eq. 1).[4,6]

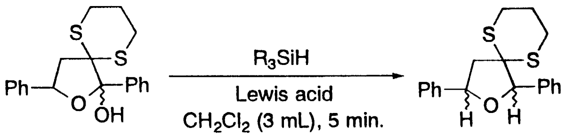


(Eq. 1)

(1) (2)

Dihydro-2,5-Diphenyl-3,3-trimethylenedithiofuran-2-ol (**1a**) was chosen as a model substrate and allowed to react with organosilanes in the presence of Lewis acid. Table 1 shows the results of the reduction of **1a** under various reaction conditions. When **1** was treated with one equivalent of **3** and $TiCl_4$ in CH_2Cl_2 solution at 0°C, *trans*-2,5-diphenyl-3,3-trimethylendithiotetrahydrofuran (**2a**) was formed in 76 % yield and moderate *trans* selectivity (*trans*:*cis* = 15:1) (Run 1). However, good yield of **2a** was satisfactorily achieved by the use of small excess amount of $TiCl_4$ (1.2 equiv.) (Run 2). Lowering the reaction temperature (-78 °C) led to increase in the stereoselectivity of **2a** (Run 3). Other Lewis acids such as $BF_3{\cdot}Et_2O$, Et_2AlCl, $EtAlCl_2$, $AlCl_3$, and TMSOTf gave a considerable yield of **2a**, but the stereoselectivity is a lower than that of $TiCl_4$ (Runs 3-8). In the case of organoaluminum compounds, Et_2AlCl, $EtAlCl_2$, and $AlCl_3$, increase of the number of the alkyl group on the aluminium compounds led to increase of the stereoselectivity (Run 5-7). In addition, it is noted that the kind of alkyl group on the organosilanes is also contributed to the stereoselectivity on **2a** (Runs 3 and 9-11). Thus, when less bulky organosilanes e. g. Ph_2MeSiH, $PhMe_2SiH$, and Et_3SiH, than **3**, were used as organosilanes, stereoselectivity of **2a** decreased (Runs 3 and 9-11).

Table 1. Selectivity on the Reduction of Hemiketal with R_3SiH in the Presence of Lewis acid[a]



(1a) (2a)

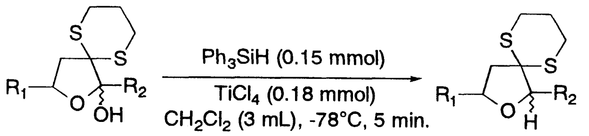
Run	R_3SiH	Lewis acid	Yield, %[b] (trans / cis)[c]
1[d]	Ph_3SiH	$TiCl_4$	76 (15 / 1)
2[e]	Ph_3SiH	$TiCl_4$	87 (16 / 1)
3	Ph_3SiH	$TiCl_4$	88 (82 / 1)
4	Ph_3SiH	$BF_3{\cdot}OEt_2$	86 (10 /1)
5[f]	Ph_3SiH	Et_2AlCl	82 (28 /1)
6	Ph_3SiH	$EtAlCl_2$	73 (18 / 1)
7	Ph_3SiH	$AlCl_3$	76 (11 /1)
8	Ph_3SiH	TMSOTf	88 (17 / 1)
9	Ph_2MeSiH	$TiCl_4$	70 (34 /1)
10	$PhMe_2SiH$	$TiCl_4$	79 (30 / 1)
11	Et_3SiH	$TiCl_4$	75 (7 / 1)

[a] Reaction conditions: **1a** (0.15 mmol), R_3SiH (0.15 mmol), Lewis acid (0.18 mmol), CH_2Cl_2 (3 mL), -78°C, 5 min.
[b] Isolated yield. [c] Determined by 400 Mz ^1H NMR.
[d] One equivalent of Lewis acid was used. [e] 0°C. [f] 35 min.

In order to know the scope and limitation of the stereoselective synthesis of *trans*-2,5-disubstituted tetrahydrofurans derivatives, the reduction of various cyclic hemiketals with Ph_3SiH in the presence of $TiCl_4$ was examined under the same reaction conditions as shown in run 3 in Table 1 (Table 2).[8] The transformation of 5-methyl-2-phenyl, 5-ethyl-2-phenyl, and 5-isopropyl-2-phenyl substituted hemiketals to the corresponding *trans* 2,5-disubstituted tetrahydrofuran derivatives proceeded very effectively (81-83%) and high stereoselectivity (trans:cis = 13:1 - 83:1) (Runs 1-3). 2-Alkyl substituted derivative, dihydro-2-methyl-5-diphenyl-3,3-trimethylene-dithiofuran-2-ol, was also reduced by **3** in the presence of $TiCl_4$ to afford trans-2-methyl-5-phenyl tetrahydrofuran derivatives in substantial yield and high stereoselectivity (Run 4)

Next, we examined the application of this method on the synthesis of the asymmetrical 2,5-disubstituted tetrahydrofuran. (2SR, 5S)-5-Methyl-2-phenyl-3,3-trimethylenedithiofuran-2-ol

Table 2. Reaction of Various Hemiketals with Ph$_3$SiH in the Presence of TiCl$_4$



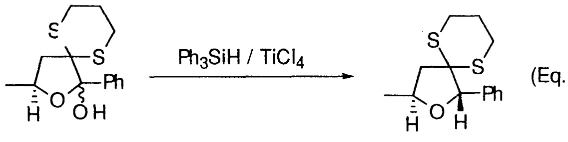
(0.15 mmol)

Run	R$_1$	R$_2$	Yield / %[a] (trans / cis)[b]
1	CH$_3$	Ph	83 (13 / 1)
2	C$_2$H$_5$	Ph	81 (16 / 1)
3	CH(CH$_3$)$_2$	Ph	82 (9 / 1)
4	Ph	CH$_3$	72 (63 / 1)
5	CH$_3$	CH$_3$	70 (10 / 1)
6	CH$_3$	C$_2$H$_5$	63 (7 / 1)

[a] Isolated yield.

[b] Determined by 400 Mz ^{1}H NMR.

(4) was treated with Ph$_3$SiH in the presence of TiCl$_4$ to afford (2*S*, 5*S*)-dihydro-5-methyl-2-phenyl-3,3-trimethylenedithiofuran in 84 % yield and high stereoselectivity [(2*S*,5*S*):(2*R*,5*S*) = 12.7:1.0] (Eq. 2).[9] We have already shown the stereoselective synthesis of (2R,5R)-**5** *via* one-step cyclodehydration of *anti*-diol, generated by stereoselective reduction of **4** with LiAlH$_4$.[3a] Both results show that synthesis of respective both enatiomers of *trans* disubstituted tetrahydrofurans from one chiral starting materials was successfully achieved by using these two methods.



(Eq. 2)

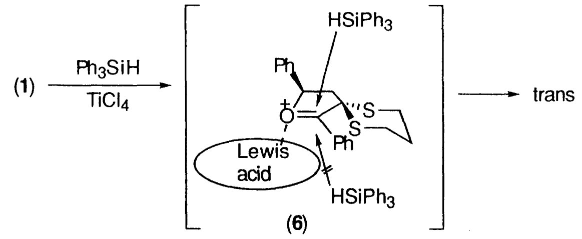
(2RS, 5S) (**4**)

(**5**) 84%

(2S, 5S) : (2R, 5S) 12.7 : 1.0

Although we can not explain the reason of the high stereoselectivity in detail yet, we suggest that the organosilane attacks an oxonium ion intermediate (**6**), which was generated *in situ* from **1** and Lewis acid, from the perisheral side owing to the steric hindrance of 3,3-trimethylenedithio group and/or Lewis acid coodinated on oxygen atom of oxonium ion intermediate leading to *trans* isomer (Scheme 1).[10]

Scheme 1



Since 3,3-trimethylenedithio group can easily converted into the methylene by Raney nickel, the present method is a simple one for the synthesis of trans-2,5-disubstituted tetrahydrofuran derivatives. Further investigation is now under way on the mechanism and the synthetic application of the process.

We thank the donors of The Science Research Promotion Fund administered from the Japan Private School Promotion Fundation for this research.

References and Notes

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

2 For examples, see: J. W. Westley, "Polyether Antibiotics: Naturally Occurring Acid Ionophores" Vol I and II, Marcel Dekker, New York (1982): A, Cave, D. Cortes, B. Figadere, R. Hocquemiller, O. Laprevote, A. Laurens, and M. Leboeuf, " Phytochemical Potential of Tropical Plants: Recent Advances in Phychemical 27," ed by K. R. Downum, J. Romeo, and H. H. A. Stafford, Plenum Press, New York (1993): M. H. D. Boivin, *Tetrahedron*, **48**, 8545 (1992).

3 a) H. Chikashita, H. Yasuda, Y. Kimura, and K. Itoh, *Chem Lett.*, **1992**, 195. b) H. Chikashita, T. Fukushima, H. Uemura, and K. Itoh, *Chem Lett.*, **1992**, 599. c) H. Chikashita, Y. Nakamura, H. Uemura, and K. Itoh, *Chem. Lett.*, **1993**, 477. d) H. Chikashita, K. Hirao, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **66**, 1738 (1993). e) H. Chikashita, T. Nikaya, and K. Itoh, *Natur. Prod. Lett.*, **2**, 183 (1992).

4 Some workers reported that ketals and acetals were reduced by organosilane in the presence of Lewis acid to afford the corresponding ethers in moderate to good yields.[5] However, to the best of our knowledge, there is no reports on the reduction of hemiketals and hemiacetals with organosilane.

5 For example, see: T. Tunoda, M. Suzuki, R. and R. Noyori, *Tetrahedron Lett.*, **1979**, 4679: D. Rolf and G. R. Gray, *J. Am. Chem. Soc.*, **104**, 3539 (1982): G. A. Olah, T. Yamato, P. S. Iyer, G. K. S. Prakash, *J. Org. Chem.*, **51**, 2826 (1986): A. Mori, K. Ishihara, and H. Yamamoto, *Tetrahedron Lett.*, **27**, 4679 (1986): J. A. Bennek and G. R. Gray, *J. Org. Chem.*, **52**, 892 (1987): T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake, and A. Oku, *J. Am. Chem. Soc.*, **109**, 527 (1987): S. Danishefsky, D. M. Armistead, F. E. Wincott, H. G. Selnick, and R. Hungate, *J. Am. Chem. Soc.*, **109**, 8117 (1987).

6 K. Tomooka, K. Matsuzawa, K. Suzuki, and G. Tsuchihashi have shown the stereoselective synthtic method of disubstituted cyclic ethers by the reaction of lactols with organometals in the presence of a Lewis acid: K. Tomooka, K. Matsuzawa, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 6339 (1987).

7 Configuration of each isomers was assigned by the NOE analysis for the ring protons. In the case of miner product (*cis* isomer), when irradiated at the frequency of C2 proton signal, NOE was observed of C5 proton signal. On the other hand, irradiation of C2 proton of major product (*trans* isomer) did not show an NOE fifference spectroscopy.

8 To a dichloromethane (3 mL) of cyclic hemiketal (0.15 mmol) was added TiCl$_4$ (0.18 mmol) under nitrogen atmosphere at -78°C, and the mixture was stirred at that temperature for 15 min. Triphenylsilane (0.15 mmol) was added to the resulting solution at -78°C, and the solution was stirred at that temperature for 5 min. The resulting mixture was quenched with aq. NaHCO$_3$, and extracted with diethyl ether. The combined extracts was dried over MgSO$_4$. Removal of the solvent under the reduced pressure afforded yellow liquid, which was purified by column chromatography on silica gel (n-hexane:AcOEt =10:1 v/v as eluant) to give the corresponding 2,5-disubstituted tetrahydrofuran derivatives.

9 The compounds was identified by comparision of its ^{1}H NMR with those of authentic samples.[3a]

10 On the stereoselective synthesis of disubstituted cyclic ethers by the reaction of lactols with organometals in the presence of Lewis acid, high trans selectivity was exaplained by considering the attack of the nucleophiles on the oxonium ion intermediate from the opposite face to the substituent, see: Ref 6.