

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

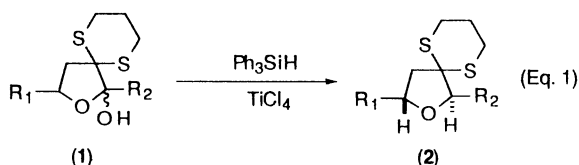
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An efficient method for the synthesis of *trans*-2,5-disubstituted tetrahydrofuran derivatives has been developed. Dithioacetal-functionalized cyclic hemiketals are reduced by triphenylsilane (Ph_3SiH) in the presence of TiCl_4 to afford the corresponding *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 tetrahydrofurans¹ in connection with the synthesis of polyethers antibiotics and natural products containing oxacyclic units.² In a previous papers on the synthesis of polytetrahydrofuran 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 cyclo-dehydration.^{3a}

In the course of our study on the synthesis of chiral polytetrahydrofuran 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}



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 **1a** was treated with one equivalent of **3** and TiCl_4 in CH_2Cl_2 solution at 0°C , *trans*-2,5-diphenyl-3,3-trimethylenedithiotetrahydrofuran (**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 $\text{BF}_3\cdot\text{Et}_2\text{O}$, 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 aluminum 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

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

Run	R_3SiH	Lewis acid	Yield, % ^b (<i>trans</i> / <i>cis</i>) ^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	$\text{BF}_3\cdot\text{OEt}_2$	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.

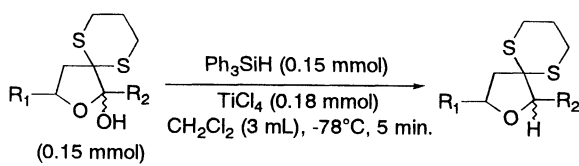
^b Isolated yield. ^c Determined by 400 Mz ^1H NMR.

^d One equivalent of Lewis acid was used. ^e 0°C . ^f 35 min.

organosilanes, stereoselectivity of **2a** decreased (Runs 3 and 9-11).

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).

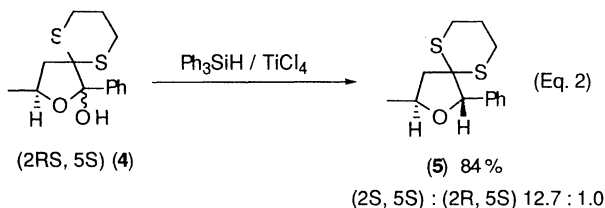
Next, we examined the application of this method on the synthesis of the asymmetrical 2,5-disubstituted tetrahydrofuran. (2*SR*, 5*S*)-5-Methyl-2-phenyl-3,3-trimethylenedithiofuran-2-ol

Table 2. Reaction of Various Hemiketals with Ph_3SiH in the Presence of TiCl_4


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 ¹H NMR.

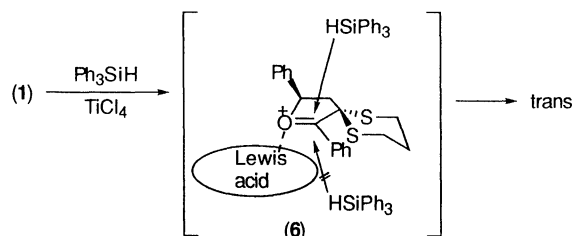
(4) was treated with Ph_3SiH in the presence of TiCl_4 to afford (2*S*, 5*S*)-dihydro-5-methyl-2-phenyl-3,3-trimethylenedithiofuran in 84 % yield and high stereoselectivity [(2*S*, 5*S*): (2*R*, 5*S*) = 12.7:1.0] (Eq. 2).⁹ We have already shown the stereoselective



synthesis of (2*R*, 5*R*)-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 enantiomers of *trans* disubstituted tetrahydrofurans from one chiral starting materials was successfully achieved by using these two methods.

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 periphery side owing to the steric hindrance of 3,3-trimethylenedithio group and/or Lewis acid

Scheme 1



coordinated on oxygen atom of oxonium ion intermediate leading to *trans* isomer (Scheme 1).¹⁰

Since 3,3-trimethylenedithio group can easily be 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.

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References and Notes

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- 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 Phytochemical 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).
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- 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 report on the reduction of hemiketals and hemiacetals with organosilane.
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- K. Tomooka, K. Matsuzawa, K. Suzuki, and G. Tsuchihashi have shown the stereoselective synthetic 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).
- Configuration of each isomer was assigned by the NOE analysis for the ring protons. In the case of minor 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 difference spectroscopy.
- 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 were 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.
- The compounds were identified by comparison of its ¹H NMR with those of authentic samples.^{3a}
- 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 explained by considering the attack of the nucleophiles on the oxonium ion intermediate from the opposite face to the substituent, see: Ref 6.