Highly Stereoselective Synthesis of *cis*-2-Substituted-3-vinyltetrahydrofurans from (Z)-Trimethyl(5-trimethylsiloxy-2-pentenyl)silane and Acetals

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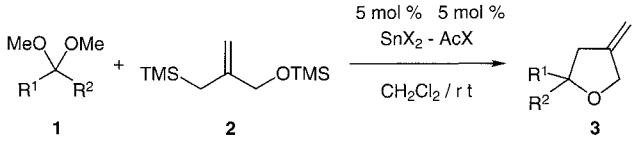
Abstract: A variety of *cis*-2-substituted-3-vinyltetrahydrofurans are easily and stereoselectively produced by the reaction of acetals with (Z)-trimethyl(5-trimethylsiloxy-2-pentenyl)silane under the influence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate under very mild conditions.

Tetrahydrofuran is one of the most common skeletal elements among a wide range of biological natural products. Markó *et al.* reported that the TMSOTf-catalyzed Intramolecular Silyl Modified Sakurai (ISMS) reaction[1] is a powerful tool for the construction of various cyclic ethers such as tetrahydropyrans, spiroethers, and spiroketals from aldehydes, ketones, and orthoesters. However, Markó *et al.* reported that none of the tetrahydrofuran was formed by the silyl-modified Sakurai reaction of trimethyl(2-trimethylsiloxy-methyl-2-propenyl)silane with aldehydes but the *exo*-methylenetetrahydropyran was obtained.[2]

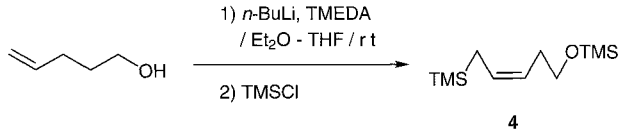
On the other hand, our previous investigation[3] documented the novel and convenient synthesis of 2-aryl-4-methylenetetrahydrofurans from aromatic acetals and trimethyl(2-trimethylsiloxymethyl-2-propenyl)silane (**2**). In this reaction, the acetals **1** and the silane **2** act as geminal dication equivalent and dianion equivalent of 4-atom unit respectively to give directly the tetrahydrofurans **3** by a simple one-pot procedure (Scheme 1). As a logical extension, we have envisioned to extend our new methodology to the synthesis of 2-substituted-3-vinyltetrahydrofurans by the use of one-carbon homologous silane, (Z)-trimethyl(5-trimethylsiloxy-2-pentenyl)silane (**4**), in place of **2**. The expectation has been successfully realized, and in this communication, we wish to report an expedient method for the highly stereoselective synthesis of 2-substituted-3-vinyltetrahydrofurans from various acetals under very mild conditions.



1 2 3

Scheme 1

The starting silane **4** was prepared from commercially available alcohol, 4-penten-1-ol,[4] by the procedure similar to that for the synthesis of **2** (Scheme 2). However, to the best of our knowledge, a condensation of this silane with carbonyl compounds or their equivalents has never been reported in the literature.



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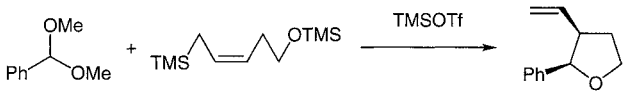
Scheme 2

First, we undertook to examine the reaction of benzaldehyde dimethyl acetal (**5**) with **4** in the presence of $SnCl_2$-AcCl (5 mol % each to the acetal) according to the procedure similar to that for the synthesis of 2-aryl-4-methylenetetrahydrofurans reported in the previous paper.[3] The corresponding cyclization products, mixture of isomers (*cis* : *trans* = 97 : 3) were obtained in 92% yield (Table 1, Entry 1).[5] After a screening the activator and solvent effect, we found that the reaction performed under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf)(5 mol %) at -20 °C in acetonitrile afforded 2-phenyl-3-vinyltetrahydrofuran quantitatively with excellent *cis*-selectivity (>99 : 1)(Entry 5).[6] Other solvents such as hexane provided lower levels of *cis*-selectivity.

Table 1. The Effect of Solvent and Reaction Temperature of the Reaction between Benzaldehyde Dimethyl Acetal and Allylsilane **4** [a]



5 4

Entry	Solvent	Temp	Time / min	Yield / % [b]	*cis* : *trans* [c]
1	CH_2Cl_2 [d]	0 °C	20	92	97 : 3
2	CH_2Cl_2	0 °C	120	90	96 : 4
3	CH_2Cl_2	-78 °C	120	55	>99 : 1
4	MeCN	0 °C	20	92	>99 : 1
5	MeCN	-20 °C	20	100	>99 : 1
6	THF	0 °C	20	95	>99 : 1
7	hexane	0 °C	20	90	90 : 10

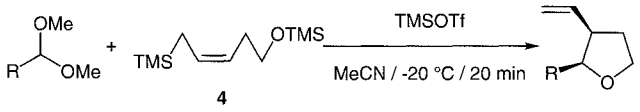
a) Molar ratio of acetal : allylsilane : TMSOTf = 1 : 1.2 : 0.05.
b) Isolated yields of purified products.
c) Determined by ^{1}H-NMR analysis.
d) $SnCl_2$ - AcCl were used as an activator instead of TMSOTf.

The reaction was conducted at -20 °C in acetonitrile with various dimethyl acetals including those of aromatic and aliphatic aldehydes. Representative results are summarized in Table 2. As can be seen, the reaction is successful for all of the acetals of both aromatic and aliphatic aldehydes. Various *cis*-2-substituted-3-vinyltetrahydrofurans are readily obtained with excellent stereoselectivities in excellent yields.

Next, we examined the reaction of ketone acetals with **4**, and the successful results are summarized in Table 3. A little lower selectivities were obtained with ketone acetals as compared to aldehyde acetals. Bulky alkyl groups such as isopropyl lowered the stereoselectivity (Entry 3). In the case of symmetrical ketone acetals, single cyclization products were obtained in good to excellent yields (Entries 5, 6, 7, and 8).

Treatment of mixed acetal **6** with a catalytic amount of TMSOTf (5 mol %) gave 2-phenyl-3-vinyltetrahydrofuran in 71% yield (*cis* : *trans* = >99 : 1)(Scheme 3).[7] However, treatment of allylated product of benzaldehyde dimethyl acetal **7** with TMSOTf gave no cyclization product (Scheme 4).[8] These results can be explained by assuming the intermediary of mixed acetal **6** after transacetalization in the present direct formation of tetrahydrofuran derivatives from acetals.[9]

Table 2. Synthesis of Various 2-Substituted-3-vinyltetrahydrofurans from Aldehyde Dimethyl Acetals and Allylsilane **4** [a]



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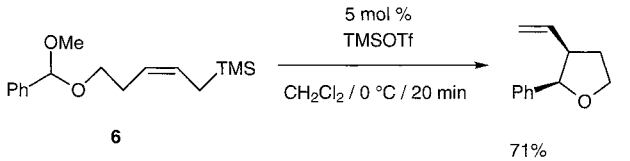
Entry	R	Yield / % [b]	*cis* : *trans* [c]
1	Ph	100	>99 : 1
2	*o*-$MeOC_6H_4$ [d]	93	98 : 2
3	*m*-$MeOC_6H_4$	99	100 : 0
4	*p*-$MeOC_6H_4$ [d]	96	100 : 0
5	*p*-MeC_6H_4	92	100 : 0
6	*p*-$NO_2C_6H_4$	94	100 : 0
7	α-Naphthyl	92	95 : 5
8	2-Furyl [d]	72	100 : 0
9	(*E*)-PhCH=CH [d]	91	98 : 2
10	$Ph(CH_2)_2$	90	100 : 0 [e]
11	*cyclo*-C_6H_{11}	93	100 : 0 [e]
12	*n*-Bu	82	100 : 0 [e]

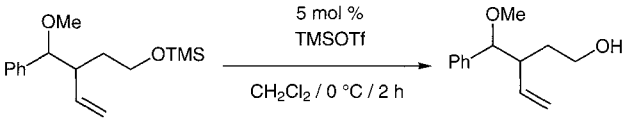
a) Molar ratio of acetal : allylsilane : TMSOTf = 1 : 1.2 : 0.05.
b) Isolated yields of purified products.
c) Determined by ^{1}H-NMR analysis.
d) Carried out at -78°C in EtCN instead of MeCN.
e) Tentative stereochemical assignment.



6

71%
cis : *trans*
= >99 : 1

Scheme 3



7

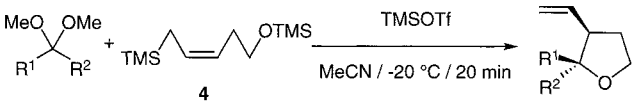
100%

Scheme 4

In brief, the salient features of the present one-step synthesis of 2-substituted-3-vinyltetrahydrofurans from (*Z*)-trimethyl(5-trimethylsiloxy-2-pentenyl)silane and acetals include 1) the ease of operation, 2) mild reaction conditions, and 3) excellent stereoselectivity. Further studies to broaden the scope and synthetic application of this reaction are under way in our laboratory.

Acknowledgement. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

Table 3. Synthesis of Various 2,2-Disubstituted-3-vinyltetrahydrofurans from Ketone Dimethyl Acetals and Allylsilane **4** [a]



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Entry	R^1	R^2	Yield / % [b]	Stereoselectivity [c]
1	Ph	Me	86	92 : 8
2	Ph	*n*-Pr	92	90 : 10
3	Ph	*i*-Pr	88	57 : 43
4	$Ph(CH_2)_2$	Me	99	75 : 25
5	Ph	Ph	91	-
6	*n*-Pr	*n*-Pr	79	-
7	$PhCH_2$	$PhCH_2$	92	-
8	$-(CH_2)_5-$		76	-

a) Molar ratio of acetal : allylsilane : TMSOTf = 1 : 1.2 : 0.05.
b) Isolated yields of purified products.
c) Determined by ^{1}H-NMR analysis.

References and Notes

(1) Mekhalfia, A.; Markó, I. E.; Adams, H. *Tetrahedron Lett.* **1991**, *32*, 4783. Markó, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. Markó, I. E.; Bayston, D. J.; Mekhalfia, A.; Adams, H. *Bull. Soc. Chim. Belg.* **1993**, *102*, 655.

(2) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595.

(3) Oriyama, T.; Ishiwata, A.; Sano, T.; Matsuda, T.; Takahashi, M.; Koga, G. *Tetrahedron Lett.* **1995**, *36*, 5581.

(4) (*Z*)-Trimethyl(5-trimethylsiloxy-2-pentenyl)silane was obtained in 41-43% yield after distillation. Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (m, H-2, 1H), 5.27 (m, H-3, 1H), 3.58 (t, *J*=7.7 Hz, CH_2OTMS, 2H), 2.27 (m, H-4, 2H), 1.51 (d, *J*=8.8 Hz, CH_2TMS, 2H), 0.13 (s, $(CH_3)_3Si$, 9H), 0.02 (s, $(CH_3)_3Si$, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.60, 122.81, 62.41, 30.80, 18.66, -0.47, -1.82. IR (neat) cm^{-1} 2955, 1250, 1097, 841.

(5) The assignment of stereochemistry was determined by the conversion of 2-phenyl-3-vinyltetrahydrofuran into the known compound, *cis*-3-methyl-2-phenyltetrahydrofuran. Dana, G.; Touboul, E.; Convert, O.; Pascal, Y. L. *Tetrahedron*, **1988**, *44*, 429.

(6) Typical experiment proceeded as follows: To a solution of benzaldehyde dimethyl acetal (51.7 mg, 0.340 mmol) and (*Z*)-trimethyl(5-trimethylsiloxy-2-pentenyl)silane (94.9 mg, 0.412 mmol) in acetonitrile (3 ml) were added a solution of TMSOTf (3 μl, 0.017 mmol) in acetonitrile (1 ml) at -20 °C under an argon atmosphere. The reaction mixture was stirred for 20 min at this temperature, and then quenched with phosphate buffer (pH 7). The organic materials were extracted with dichloromethane and combined extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and *cis*-2-phenyl-3-vinyltetrahydrofuran (59.2 mg, 100%) was isolated by

thin layer chromatography on silica gel (AcOEt : hexane = 1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, H-Ar, 5H), 5.26 (ddd, *J*=17.2, 10.3, 8.8 Hz, =CH-, 1H), 5.03 (d, *J*=7.0 Hz, H-2, 1H), 4.96 (d, *J*=17.2 Hz, $=CH_2$(*cis*), 1H), 4.83 (d, *J*=10.3 Hz, $=CH_2$(*trans*), 1H), 4.26 (m, H-5a, 1H), 3.95 (m, H-5b, 1H), 3.11 (m, H-3, 1H), 2.16 (m. H-4a, 1H), 1.97 (m, H-4b, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 137.6, 127.8, 126.9, 126.5, 115.4, 83.3, 67.9, 48.4, 32.1. IR (neat) cm^{-1} 2873, 1639, 1493, 1063, 914, 724.

Chemical shift of vinylic methine proton of *trans*-isomer showed lower field (δ 5.82) which corresponded to δ 5.26 of *cis*-isomer.

(7) Compound **6** was obtained in 27% yield by the reaction of benzaldehyde dimethyl acetal with the silane **4** under the influence of a catalytic amount of $TiCl_2(O$*i*-$Pr)_2$.

(8) Compound **7** was prepared from benzaldehyde dimethyl acetal, 1) allylation with (*Z*)-trimethyl(5-acetoxy-2-pentenyl)silane in the presence of $SnCl_2$-AcCl, 2) deacetylation (K_2CO_3/MeOH), and 3) trimethylsilylation (TMSCl / imidazole).

(9) Mohr, P. *Tetrahedron Lett.* **1993**, *34*, 6251.