Pergamon

Tetrahedron Letters, Vol. 37, No. 4, pp. 487-490, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02187-6

Stereoselective Synthesis of 2,5-Disubstituted Tetrahydrofurans by Silicon-Directed Cyclization of Vinylsilanes Bearing a Hydroxy Group[1]

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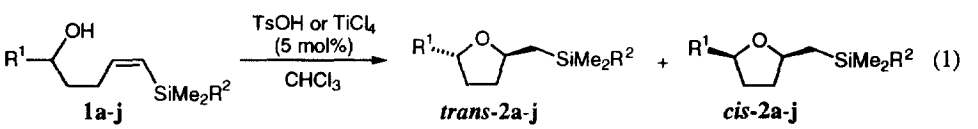
Abstract: In the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) or $TiCl_4$, (*Z*)-1-substituted-5-silyl-4-penten-1-ols can be easily transformed into 2,5-disubstituted tetrahydrofurans with high *trans*-selectivities.

Recently, much attention has been paid to the stereoselective synthesis of substituted oxygen-containing heterocycles since tetrahydrofuran and tetrahydropyran units are frequently found in polyether antibiotics and other biologically active natural products.[2] Cyclization of 4- or 5-alkenyl alcohols is one of the most straightforward routes to these heterocycle skeletons. It is well established that the reaction is promoted by an acid or an electrophile.[3] Acid-catalyzed cyclization requires vigorous conditions, and the yields are generally low. In contrast, electrophile-initiated reaction is a powerful method for the synthesis of highly functionalized heterocycles. This method, however, has some drawbacks in efficiency and selectivity. There is still a need for a new method for preparation of oxygen-containing heterocycles from alkenyl alcohols.

We have previously reported that vinylsilanes bearing a hydroxy group could be cyclized to 2-silylmethyl-substituted cyclic ethers by the aid of TsOH or $TiCl_4$.[4] In particular, this silicon-directed reaction is efficient for the construction of a tetrahydrofuran ring. Therefore, we next directed our efforts to the stereoselective synthesis of disubstituted tetrahydrofurans, and herein report the results on the acid-catalyzed cyclization of (*Z*)-1-substituted-5-silyl-4-penten-1-ols (**1**).[5] (eq. 1)



1a-j *trans*-**2a-j** *cis*-**2a-j** (1)

Treatment of (*Z*)-1-phenyl-5-trimethylsilyl-4-penten-1-ol (**1a**; R^1=Ph, R^2=Me) with a catalytic amount of TsOH at 60 °C gave tetrahydrofuran **2a** in 90% yield with a *trans*-selectivity as shown in entry 1 of Table 1. The prolonged reaction time caused the isomerization of ***trans*-2a** to ***cis*-2a**, which, however, it did not occur when the substrate was present in the reaction mixture. The cyclization at room temperature, which was much slower than that at 60 °C, slightly improved the stereoselectivity. On the other hand, $TiCl_4$-catalyzed cyclization of **1a** smoothly proceeded even at room temperature, giving an 86:14 mixture of ***trans*-2a** and ***cis*-2a** in 88% yield. *E*-isomer of **1a** was also cyclized to **2a** in a good yield, but with low reactivity and selectivity.

Table 2 delineated the scope of the cyclization of vinylsilanes **1**. In all entries, the reactions induced by $TiCl_4$ at room temperature exhibited higher *trans*-selectivity than those induced by TsOH at 60°C as described

above. The selectivity is also affected by substituents R^1 and R^2. The use of a hexyl group as R^1, which is less bulky than the phenyl and isopropyl groups, reduced the ratios of ***trans*-2** to ***cis*-2**, while the ratios are independent of the bulkiness of R^2. The change of the methyl group to a *tert*-butyl group in R^2 was not effective to improve the *trans*-selectivity although the cyclization of **1d** was markedly accelerated.[6] Vinylsilanes **1e-g** bearing a phenyl group as R^2 could be cyclized in higher selectivities. When R^2=H, the best results were obtained in stereoselectivity. Unfortunately, the yields decreased to some extent because of desilylation of the substrates **1h-j** and cleavage of the Si-H bond of the products **2h-j**.

Table 1. Acid-catalyzed Cyclization of (*Z*)- and (*E*)-1-Phenyl-5-trimethylsilyl-4-penten-1-ol (**1a**)

Entry	Substrate	Catalyst	Temp / °C	Time / h	Yield / %	*trans* / *cis* [b]
1	**1a**	TsOH	60	7	90	83 / 17
2	**1a**	TsOH	60	16	90	78 / 22
3	**1a**	TsOH	60	2	77	83 / 17
4	**1a**	TsOH	rt	114	84	85 / 15
5	**1a**	$TiCl_4$	rt	7	88	86 / 14
6	(*E*)-**1a**	TsOH	60	16	90	60 / 40
7	(*E*)-**1a**	$TiCl_4$	rt	25	82	66 / 34

[a]A mixture of substrate (1.0 mmol) and a catalyst (0.05 mmol) in $CHCl_3$ (5 ml) was employed. [b]The ratios were determined by ^1H NMR analysis.

Table 2. Cyclization of (*Z*)-1-Substituted-5-silyl-4-penten-1-ols (**1**)[a]

Entry	Substrate			TsOH / 60 °C			$TiCl_4$ / rt		
	R^1	R^2		Time / h	Yield / %	*trans* / *cis*[b]	Time / h	Yield / %	*trans* / *cis*[b]
1	Ph	Me	(**1a**)	7	90	83 / 17	7	88	86 / 14
2	C_6H_{13}	Me	(**1b**)	8	93	81 / 19	7	86	82 / 18
3	*i*-Pr	Me	(**1c**)	7	89	85 / 15	7	73	87 / 13
4	*i*-Pr	*t*-Bu	(**1d**)	2	93	83 / 17	0.3	98	88 / 12
5	Ph	Ph	(**1e**)	8	92	83 / 17	7	89	90 / 10
6	C_6H_{13}	Ph	(**1f**)	7	95	83 / 17	7	89	86 / 14
7	*i*-Pr	Ph	(**1g**)	6	95	89 / 11	6	92	92 / 8
8	Ph	H	(**1h**)	9	76	90 / 10	7	84	96 / 4
9	C_6H_{13}	H	(**1i**)	6	66	89 / 11	7	82	91 / 9
10	*i*-Pr	H	(**1j**)	11	66	91 / 9	7	68	93 / 7

[a,b]See Table 1.

In order to determine the stereochemistry of the products, we performed the derivatization of tetrahydrofurans **2h-j** with retention of the stereochemistry. (eq. 2 and Table 3) The hydrodimethylsilyl group of **2h-j** could be easily converted to the hydroxy group by the treatment of H_2O_2 and $KHCO_3$.[7] Tosylation of the resultant alcohols **3** followed by substitution with NaI gave iodides **4** in good yields with the same isomeric ratios as those of the starting materials. Bartlett *et al.* have shown that the use of 4-alkenyl alcohols **5** leads to **4** with moderate *trans*-selectivity, while iodocyclization of 4-alkenyl 2,6-dichlorobenzyl ethers **6** gives ***cis*-4** exclusively.[8] (eq. 3) The major isomers of iodides **4** prepared from tetrahydrofurans **2h-j** were consistent with

those from alcohols **5**. In addition, hydrodeiodination of the iodide derived from **2h** with Bu_3SnH gave *trans*-2-phenyl-5-methyltetrahydrofuran as a major product, whose ^1H NMR data have been reported.[9] Therefore, we concluded that the major isomers of tetrahydrofurans **2h-j** had *trans*-geometry. The stereochemical assignments of the other tetrahydrofurans **2a-g** rest on analogy with **2h-j** in ^1H NMR spectra.

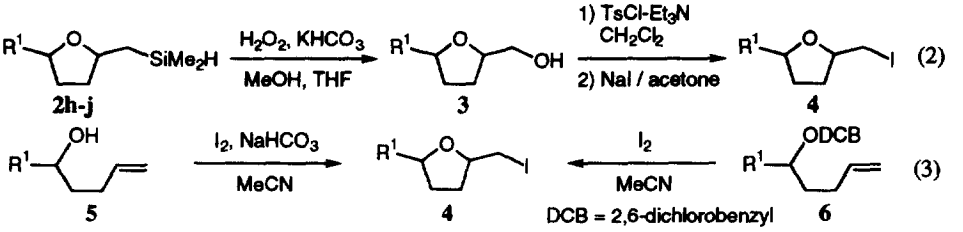


Table 3. Derivatization of **2h-j** and Iodocyclization of **5** and **6**

R^1	*trans* / *cis*[a] of **2h-j**	Yield / % (*trans* / *cis*)[a]			
		3	**4** from **3**	**4** from **5**	**4** from **6**
Ph	96 / 4	93 (96 / 4)	89 (96 / 4)	61 (74 / 26)	56 (5 / 95)
C_6H_{13}	86 / 14	85 (-)[b]	79 (87 / 13)	68 (69 / 31)	83 (<5 / 95)
i-Pr	93 / 7	83 (-)[b]	82 (93 / 7)	88 (80 / 20)[c]	95 (5 / 95)[c]

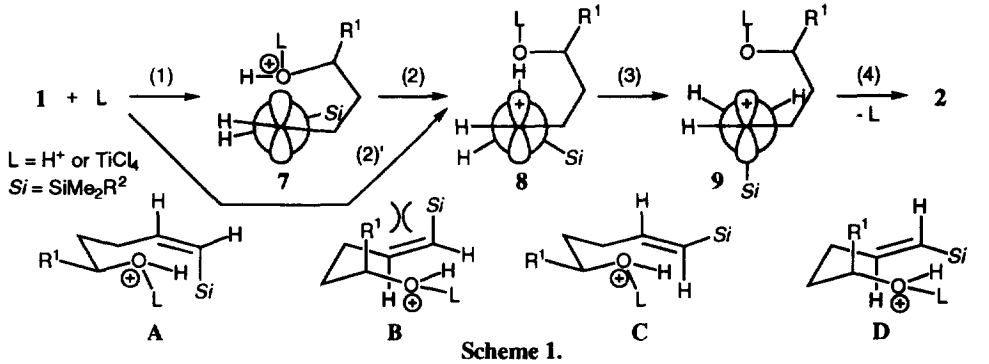
[a]The ratios were determined by ^1H NMR analysis. [b]The ratio could not be determined. [c]Literature values.[8]

As shown in Table 3, the present acid-catalyzed cyclization exhibited higher *trans*-selectivity than iodocyclization of **5**. The following mechanism for the cyclization of **1** is possibly suggested (Scheme 1)[4]: (1) the coordination of the hydroxy group to a proton or $TiCl_4$ forms oxonium ion **7**, (2) the proton on the oxygen of **7** shifts to the carbon adjacent to silicon, (3) the resultant β-silyl carbenium ion **8** rapidly turns into its rotamer **9** stabilized by σ-π conjugation,[11] (4) attack of the oxygen atom to the β-silyl carbenium ion center from the side opposite to the silyl group gives 2,5-disubstituted tetrahydrofuran **2** to regenerate a proton or $TiCl_4$. In the TsOH-catalyzed cyclization, intermolecular protonation of **1**, which affords **8** directly, may be a possible (step (2)').

In the cyclization of (*E*)- and (*Z*)-5-deuterio-5-phenyldimethylsilyl-4-penten-1-ol, we have found that addition of a hydroxy group to a carbon-carbon double bond proceeds in *syn* fashion predominantly.[4] This result supports the finding that proton transfer (step (2) or (2)') and nucleophilic attack of oxygen (step (4)) take place on the same side of π-face as shown in Scheme 1. Accordingly, the stereochemistry of products would mainly depend on the diastereoface-selection of the proton transfer. In other words, the observed high *trans*-selectivity can be attributed to the diastereoface-selective protonation. Considering the fact that the reaction site is away from the stereogenic center, it is difficult to explain the face-selective protonation on the basis of an intermolecular path in step (2)'. In contrast, an intramolecular path in step (2) can easily rationalize the protonation affording the products with *trans*-selectivity.

In step (2), two transition states arising from chair-like conformers **A** and **B** are possible.[12] **B** has a repulsive non-bonding interaction between R^1 and the silyl group, which makes **B** an energetically unfavorable conformer. Thus, proton transfer proceeds *via* conformer **A** exclusively. The subsequent nucleophilic attack of oxygen occurs on the same side that the proton attacks, giving *trans*-isomer selectively. In the cyclization of (*E*)-**1**, the corresponding conformers **C** and **D** leading to transition states of proton

transfer can be also employed. However, the energy difference between these conformers is smaller than that between **A** and **B**, because **D** does not have such a severe steric repulsion as **B** has. This is the reason that the cyclization of (*E*)-**1a** results in a low *trans*-selectivity.



Scheme 1.

In conclusion, the acid-catalyzed cyclization of vinylsilanes **1** is an efficient method for the synthesis of *trans*-2,5-disubstituted tetrahydrofurans. We are studying the further application of this silicon-directed reaction for the synthesis of polyfunctionalized tetrahydrofurans, and the results will be reported in due course.

Acknowledgments: Financial support for our work is provided by Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Japan. We thank Dow Corning Toray Silicone Co. Ltd., Chisso Co. Ltd., and Shin-Etsu Chemical Co. Ltd. for gifts of organosilicon compounds.

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12 Transition states arising from boat-like conformers are strictly inhibited by a 1,3-allylic strain between the hydroxyalkyl and silyl groups.

(*Received in Japan* 6 *October* 1995; *revised* 13 *November* 1995; *accepted* 17 *November* 1995)