CHEMISTRY LETTERS, pp. 627-630, 1994.

Stereoselective Construction of Tetrahydrofuran by Tin (IV) Chloride Promoted [3+2] Cycloaddition of Allylsilane to α-Keto Ester

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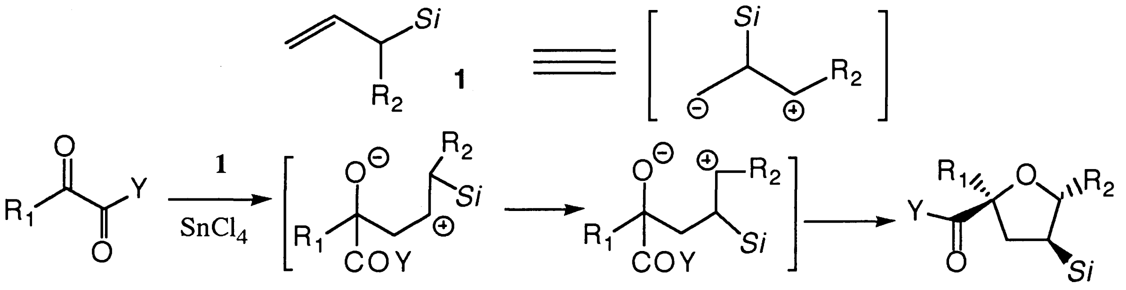
$SnCl_4$ promoted [3+2] cycloaddition reactions of allylsilane to α-keto esters afforded tri- and tetrasubstituted tetrahydrofurans with excellent stereoselectivity via 1,2-silyl migration in good yields.

Substituted tetrahydrofuran are present in so many biologically interesting natural products.[1] Preparation of substituted tetrahydrofuran in stereo-defined manner continues a challenge. Herein we describe a novel method for the stereoselective synthesis of 2,2-disubstituted tetrahydrofuran, which is constructed by $SnCl_4$ promoted [3+2] cycloaddition of allylsilane[2] and α-keto ester via 1,2-silyl migration. Thus, allylsilane (**1**) represents a very useful synthetic equivalent of 2-silyl-substituted 1,3-dipole.[3-5] Recently Panek have reported Lewis acid promoted addition of allylsilane to aldehyde leading to substituted tetrahydrofurans via 1,2-silyl migration.[6] The reaction of allylsilane with ketone, however, has not been documented except one example, in which a tetrahydrofuran was obtained as a minor product.[7]



At first, the reaction of an α-keto ester (**2**) with allyltrimethylsilane (**3a**) was examined. The order of the addition of the reagents appears to be crucial for the formation of the tetrahydrofurans. Addition of **2** to a solution of **3a** (1.2 equiv) and $SnCl_4$ (1.1 equiv) in CH_2Cl_2 at –78 °C for 30 min afforded a homoallyl alcohol **5** in 81% yield and none of the tetrahydrofuran was obtained. Either addition of $SnCl_4$ to a solution of **2** and **3a** or addition of **3a** to a mixture of **2** and $SnCl_4$ afforded **4a** albeit in a low yield (19%). After screening the reaction conditions in consideration of the fact that **4a** is labile under acidic conditions,[8] we have found that **4a** was best obtained by a dropwise addition of a dilute solution of $SnCl_4$ (1.1 equiv) in CH_2Cl_2 to a mixture of **3a** and **2** in CH_2Cl_2, affording **4a** in 50% yield (Table 1, Entry 1). It should be added that the present cycloaddition with several conventional Lewis acids such as $TiCl_4$, $AlCl_3$, $SnCl_2$, $Sn(OTf)_2$, $BF_3•OEt_2$, and

$ZnCl_2$ gave none of the desired [3+2] adduct **4a**. The effects of the substituents on silicon were next examined. The reaction with allyldimethylphenylsilane (**3b**) gave **4b** in 54% yield (Entry 2). Use of a sterically demanding allylsilane **3c** led to the preferential formation of **4c** in 85% yield (Entry 3).[9,10]

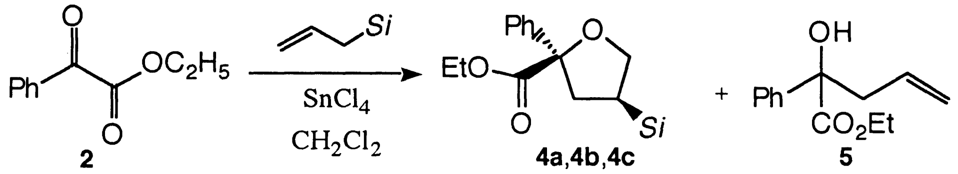


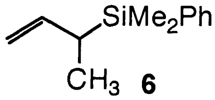
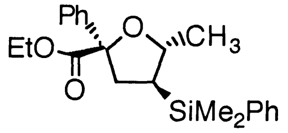
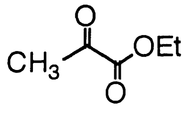
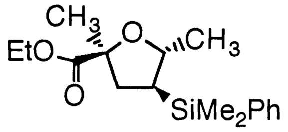
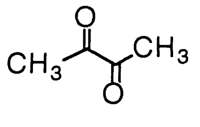
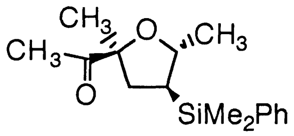
Table 1. Results of the addition of allylsilanes to **2**[a)]

Entry	*Si*	Reaction Conditions	Product	Yield /%	Yield of **5** /%
1	$SiMe_3$ (**3a**)	r.t., 5 min	**4a**	50	41
2	$SiPhMe_2$ (**3b**)	r.t., 5 min	**4b**	54	46
3	$SiMe_2Bu^t$ (**3c**)	−78 °C, 5 min	**4c**	85	6

a) The reactions were run in CH_2Cl_2 with $SnCl_4$ (1.1 equiv) and allylsilane (1.2 equiv).

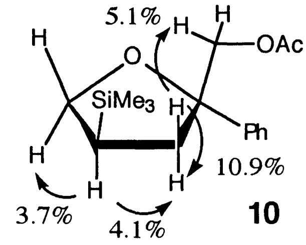
Next butenylsilane (**6**) was employed as an allylsilane and the results are shown in Table 2. It is noted that **6** showed higher propensity to form tetrahydrofurans. The cycloaddition reactions of **6** to **2** took place smoothly to afford a 2,2,4,5-substituted tetrahydrofuran **7** in an excellent yield (Entry 1). The cycloaddition to ethyl pyruvate as well as biacetyl proceeded smoothly to afford tetrahydrofurans **8** and **9** in good yields (Entries 2 and 3). Alkyl-substituent α to silicon appears to facilitate the tetrahydrofuran formation.

Table 2. $SnCl_4$ promoted cycloaddition of allylsilane (**6**) to α-keto ester and 1,2-diketone[a)]

Entry	Substrate	Allylsilane	Products	Yield/%
1	**2**		 **7**	82
2		**6**	 **8**	75
3		**6**	 **9**	55

a) α-Keto ester or 1,2-diketoene was treated with allylsilane (1.2 equiv) and $SnCl_4$ (1.1 equiv) in CH_2Cl_2 at room temperature for 5 min.

The present cycloaddition reactions exhibited excellent levels of diastereoselection, producing the tetrahydrofurans with de's reaching >96% as determined by ^1H and ^{13}C NMR.[10)] The relative stereochemisty of **4a** and **7** was unambiguously determined by multiple NOE study of an acetate **10** derived from **4a** and **11** derived from **7** respectively. The stereochemistry of other tetrahydrofurans were estimated by the analogy.



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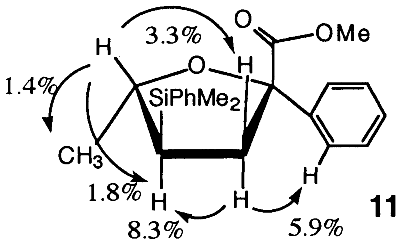

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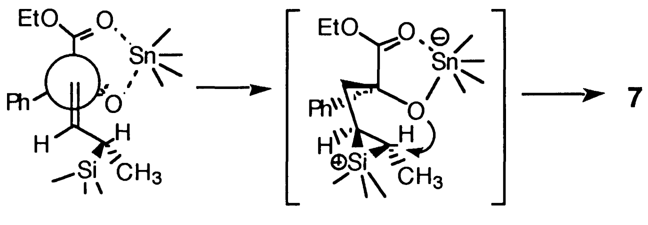
Present cycloaddition reaction takes place via 1,2-silyl migration in competition with elimination of the silyl group, which results in homoallyl alcohols. *t*-Butyldimethylsilyl group plays a role of both stabilizing the β-carbocation and retarding the elimination. Thus *t*-butyldimethyl-substituted allylsilane **3c** afforded the tetrahydrofuran in a high yield. α-Alkyl-substituted allylsilane **6** also showed higher propensity to form 5-membered ring (Table 2) presumably because 1,2-silyl shift is favorable due to the formation of a secondary carbocation.

The stereochemical outcome exerted in the $SnCl_4$-mediated cycloaddition of allylsilane to α-keto esters leading to the tetrahydrofuran can be rationalized by synclinical transition state and the stereochemistry of methyl substituent was explained by the antiperiplanar transition state.6)



Thus tri- and tetrasubstituted tetrahydrofurans were obtained with excellent diastereoselectivity. Furthermore, because a trimethylsilyl group can be cleaved under basic conditions,11) and dimethylphenylsilyl group are to be transformed into hydroxyl group with retention of the configuration by oxidation,6a,12) the present reaction provides a novel method for the preparation of 2,2-disubstituted tetrahydrofurans.

The authors are grateful to Dr. Katsuhiko Tomooka (Tokyo Institute of Technology) for the valuable suggestions about NOE experiments.

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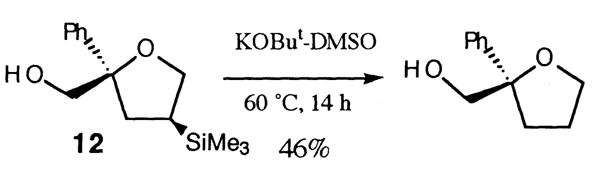
8) Treatment of **4a** with $SnCl_4$ (1.2 equiv) in CH_3CN at room temperature for 25 min afforded **5** in 74% yield.

9) A typical experimental procedure is as follows: To a solution of **2** (80.0 mg, 0.449 mmol) and **3c** (84.3 mg, 0.539 mmol) in CH_2Cl_2 (1.0 ml) was added dropwise a 0.2 mol/l solution of tin (IV) chloride in CH_2Cl_2 (2.3 ml, 0.46 mmol) at −78 °C. After being stirred at room temperature for 5 min, the reaction mixture was quenched by addition of triethylamine (0.1 ml) followed by H_2O (5 ml). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4, and concentrated to dryness. Purification of the crude mixture by preparative TLC (SiO_2, hexane : ethyl acetate = 7:1, v/v) afforded **4c** (128 mg, 85.2%) and **5** (6.4 mg, 6.4%).

10) The structure was established by ^1H NMR, ^{13}C NMR and DEPT spectra. Significant spectral data are shown; **4a**: ^1H NMR (270MHz, $CDCl_3$) δ= 7.64-7.19 (5H, aromatic), 4.26 (1H, t, J=8.2 Hz, H-5), 4.17 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 3.83 (1H, dd, J=8.2 and 11.9 Hz, H-5), 2.45 (1H, dd, J=8.5 and 12.5 Hz, H-3), 2.39 (1H, dd, J= 11.9 and 12.5 Hz, H-3), 1.43-1.23 (1H, m, H-4), 1.22 (3H, t, J= 7.0 Hz, $OCH_2C\underline{H}_3$), and 0.01 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (68 Hz, $CDCl_3$) δ= 173.20 (C=O), 141.80, 128.01, 127.45, 125.44, 87.55 (C-2), 71.79 (C-5), 61.41 ($O\underline{C}H_2CH_3$), 40.39 (C-3), 25.90 (C-4), 14.00 ($OCH_2\underline{C}H_3$), and −2.93 ($Si(CH_3)_3$); **4c**: ^1H NMR (270MHz, $CDCl_3$) δ= 7.61-7.47 (2H, m, aromatic) 7.20-7.40 (3H, m, aromatic), 4.28 (1H, t, J=8.2 Hz, H-5), 4.17 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 3.83 (1H, dd, J=8.2 and 11.9 Hz, H-5), 2.51-2.38 (2H, m, H-3), 1.53-1.34 (1H, m, H-4), 1.21 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 0.85 (9H, s, $SiC(CH_3)_3$), −0.02 (3H, s, $Si(CH_3)$, and −0.05 (3H, s, $Si(CH_3)$); ^{13}C NMR (68 Hz, $CDCl_3$) δ=173.26 (C=O), 144.75, 128.02, 127.45, 125.42, 87.18 (C-2), 72.04 (C-5), 61.39 ($O\underline{C}H_2CH_3$), 40.99 (C-3), 26.63 ($SiC(\underline{C}H_3)_3$), 23.06 (C-4), 16.62 ($Si\underline{C}(CH_3)_3$), 14.01 ($OCH_2\underline{C}H_3$), −7.19 ($SiCH_3$), and −7.93 ($SiCH_3$).



12 46%

11) Treatment of an alcohol (**12**), obtained by $LiAlH_4$ reduction of **4a**, with potassium t-butoxide in dimethylsulfoxide afforded desilylated product in 46% yield although the yield is not optimized.

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(Received December 20, 1993)