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A Stereocontrolled Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans from Aldolized γ-Diketones *via* Cyclization-reduction Process

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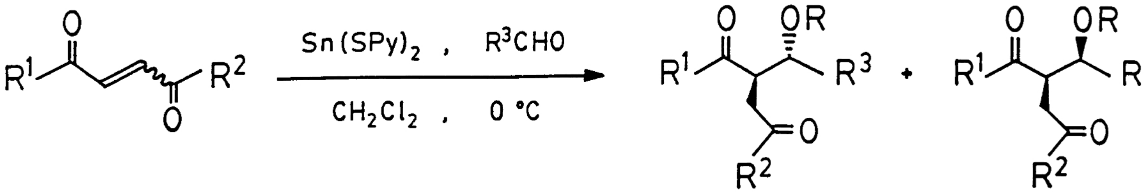
2,3,5-Trisubstituted tetrahydrofurans with *cis*-2,5 relationship are obtained in good yields by cyclization of the silyl ethers of aldolized γ-diketones followed by successive stereocontrolled reduction with triethylsilane in the presence of trityl perchlorate as a catalyst.

Over the last several years, the stereocontrolled construction of the substituted tetrahydrofurans is receiving considerable attention,$^{1)}$ because these tetrahydrofuran units are found in many natural products including important polyether antibiotics.$^{2)}$ However, there are few reports concerning synthesis of 2,3,5-trisubstituted tetrahydrofurans,$^{1b,3)}$ especially those with the thermodynamically less stable *cis*-2,5 relationship.$^{4)}$

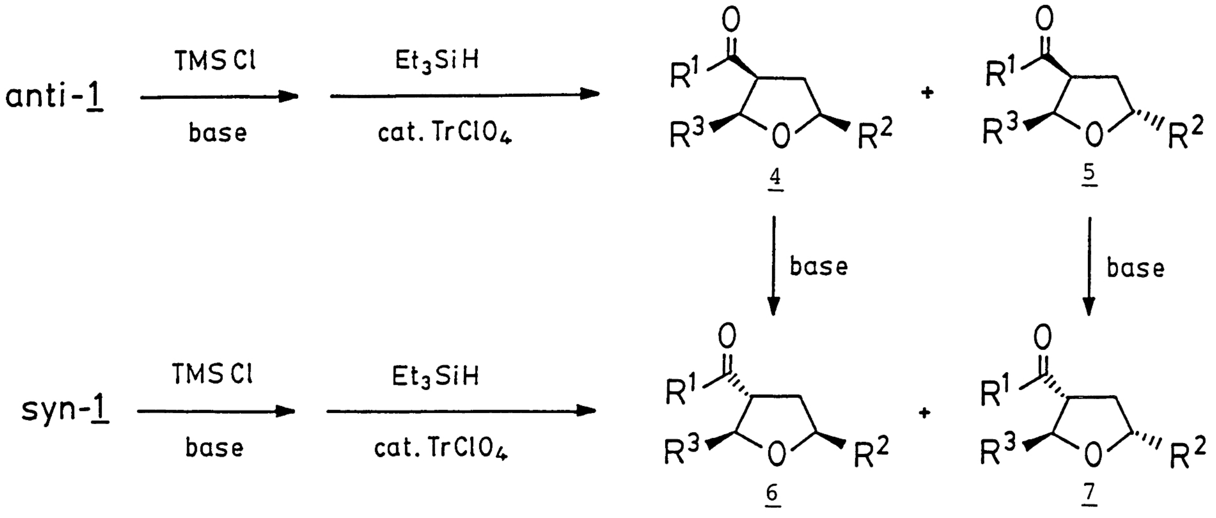
In the previous paper,$^{5)}$ we have reported a useful method for a regio- and stereoselective condensation of α,β-unsaturated γ-diketones with aldehydes by utilizing the reducing ability of bis(2-pyridinethiolato)tin(II) ($Sn(SPy)_2$).$^{6)}$ This reaction provides a general and convenient methodology for construction of aldolized γ-diketones <u>1</u>, which are considered to be valuable synthetic intermediates. So, next we turned our attention to the stereocontrolled synthesis of substituted tetrahydrofurans utilizing these aldolized γ-diketones.

Recently, it was found in our laboratory that a wide variety of ethers can be prepared from carbonyl compounds and alkoxytrimethylsilanes by the reduction with triethylsilane in the presence of a catalytic amount of trityl perchlorate.$^{7)}$ In this reaction, initially formed silyl acetals are reduced to give ethers. These results suggest that an intramolecular cyclization of silyl ethers of the above mentioned aldols <u>1</u> affords the cyclic acetals <u>3</u>, which are in turn reduced stereoselectively *via* the cyclic carbocation formed by the action of trityl perchlorate to give tetrahydrofurans. Now, we wish to report here a stereocontrolled synthesis of 2,3,5-trisubstituted tetrahydrofurans according to the following synthetic scheme.

In the first place, 2-(1-hydroxy-3-phenylpropyl)-1,4-diphenylbutane-1,4-dione ($R^1=R^2=Ph$, $R^3=-(CH_2)_2Ph$) (*anti*-<u>1a</u> : *syn*-<u>1a</u> = 81 : 19)$^{5)}$ was transformed into the corresponding silyl ether <u>2a</u>, and then reduced with triethylsilane in the presence of a catalytic amount of trityl perchlorate$^{8)}$ and the desired 2,3,5-trisubstituted



R=H *anti*-1 *syn*-1
R=TMS *anti*-2 *syn*-2



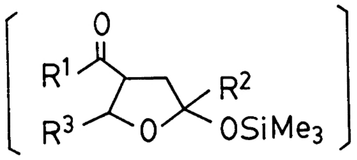


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Table 1. The Effect of Reducing Agents and Reaction Conditions[a]
($R^1=R^2=Ph$, $R^3=-(CH_2)_2Ph$)

Entry	Reducing agent	Solvent	Temp/°C	Time/h	Yield/%	4a : 5a
1	Et_3SiH	CH_2Cl_2	0	2	68	57 : 43
2	Et_3SiH	CH_3CN	0	1	79	89 : 11
3	$PhSiH_3$	CH_2Cl_2	25	1	74	84 : 16
4	$PhSiH_3$	CH_3CN	0	1	77	80 : 20

a) Reaction was carried out in the presence of 5 mol% trityl perchlorate.

tetrahydrofuran was obtained in good yield. Concerning the stereoselectivities at the 5 position in this reduction, *syn*-1a, a minor aldol product, afforded only 2,5-*cis* tetrahydrofuran 6a, however, unfortunately *anti*-1a, a major aldol product, afforded a mixture of 2,5-*cis* and 2,5-*trans* tetrahydrofurans (4a : 5a = 57 : 43).

Then, reaction conditions and reducing agents were examined in the same reaction. The results are summarized in Table 1, which reveal that the reduction with triethylsilane in acetonitrile gave the best diastereoselectivity (Entry 2).

Next, the reaction of several other aldols 1 was tried and 2,5-*cis* trisubstituted tetrahydrofurans were produced as major products (Table 2). In the case of 1c (*anti*-1c : *syn*-1c = 15 : 85),[5)] the reduction proceeded stereoselectively to afford only 2,5-*cis* trisubstituted tetrahydrofuran 4c and 6c (Entry 3).

Table 2. Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans[a)]

Entry	R^1	R^2	R^3	1	(*anti*:*syn*)[5)]	Yield/%[b)]	4 : 5 : 6 : 7[c)]
1	Ph	Ph	$-(CH_2)_2Ph$	1a	(81 : 19)	79	78 : 10 : 12 : 0
2	Ph	Ph	n-C_5H_{11}	1b	(90 : 10)	84	69 : 9 : 22 : 0
3	Ph	Ph	Ph	1c	(15 : 85)	89	9 : 0 : 91 : 0
4	Me	Me	$-(CH_2)_2Ph$	1d	(65 : 35)	58	65 : 23 : 12 : 0
5[d)]	Ph	Me	$-(CH_2)_2Ph$	1e	(89 : 11)	81	——[e)]
	Me	Ph			(74 : 26)		

a) Reaction was carried out in CH_3CN at 0 °C in the presence of 5 mol% trityl perchlorate.

b) Isolated yield from 1. All samples gave satisfactory ^1H NMR and IR spectra.

c) The ratios were determined by separating each isomer and ^1H NMR measurements.

d) Mixture of regioisomers.

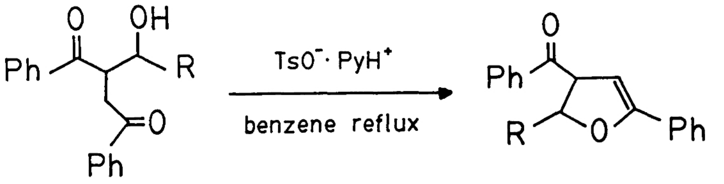
e) Not determined.

A typical reaction procedure is as follows: To a solution of 2-hydroxyphenylmethyl-1,4-diphenylbutane-1,4-dione (*anti*-1c : *syn*-1c = 15 : 85)[5)] (83 mg, 0.24 mmol) in CH_2Cl_2 (4 ml) was successively added hexamethyldisilazane (78 mg, 0.48 mmol), trimethylsilyl chloride (52 mg, 0.48 mmol) and pyridine (38 mg, 0.48 mmol) at room temperature, and the resulting mixture was stirred for 2 h. Usual work-up gave crude 2c as a colorless oil. Then, under an argon atmosphere to a solution of trityl perchlorate (4 mg, 0.01 mmol) in CH_3CN (1 ml) was added a solution of crude 2c in CH_3CN (1 ml) at 0 °C. After 5 min, a solution of triethylsilane (34 mg, 0.29 mmol) in CH_3CN (1 ml) was added to the mixture, and stirring was continued for 2 h at the same temperature. The phosphate buffer (pH 7) was added and the organic materials were extracted with Et_2O and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (Et_2O : hexane = 1 : 4). Thus 3-benzoyl-2,5-diphenyltetrahydrofuran 6c (64.5 mg, 81.5%) was obtained with its C-3 epimer 4c (6 mg, 7.5%). 6c: ^1H NMR ($CDCl_3$) δ 2.27-2.48 (1H, m), 2.53-2.84 (1H, m), 4.02 (1H, ddd, J=11 Hz, 7 Hz, 5 Hz), 5.16 (1H, dd, J=9 Hz, 7 Hz), 5.40 (1H, d, J=7 Hz), 7.19-7.87 (15H, m); IR 1680 cm^{-1}, Found: C, 84.31; H, 6.03%, Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14%, 4c: ^1H NMR ($CDCl_3$) δ 2.32-3.00

(2H, m), 4.58 (1H, q, J=9 Hz), 5.08 (1H, dd, J=11 Hz, 6 Hz), 5.45 (1H, d, J=9 Hz), 6.91-7.70 (15H, m); IR 1680 cm^{-1}.

In addition, 2,3-*trans* trisubstituted tetrahydrofurans 6 and 7 are effectively obtained from 2,3-*cis* isomers 4 and 5 by the treatment with a base such as ^{t}BuOK and NaOMe. This epimerization also played an important role in the determination of the stereochemistry at the 5 position of the tetrahydrofurans.9) The relative configuration of 4a was determined by X-ray analysis.

It is also found that the treatment of 1 with pyridinium *p*-toluenesulfonate in refluxing benzene affords 8, which is useful synthetic intermediate for preparation of 2,3,4,5-tetrasubstituted tetrahydrofurans.



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R = Ph : 71%
R = $-(CH_2)_2Ph$: 58%

It should be noted that 2,3,5-trisubstituted tetrahydrofurans, which have an acyl function at the 3 position and *cis*-2,5 relationship, are obtained easily from aldolized γ-diketones with high stereoselectivities. Further studies on the application of aldolized γ-diketones to the syntheses of 2,3,4,5-tetrasubstituted tetrahydrofurans and other compounds are currently in progress.

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9) This epimerization has substantiated the original assignment of the stereochemistry concerning *anti*-*syn* of the aldolized γ-diketones (1a-e).5)

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