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Electrophilic Sulphenylation of Silyl Ketene Acetals Derived from 3-Hydroxy-esters. Diastereoselective Synthesis of Protected Epoxyalcohols

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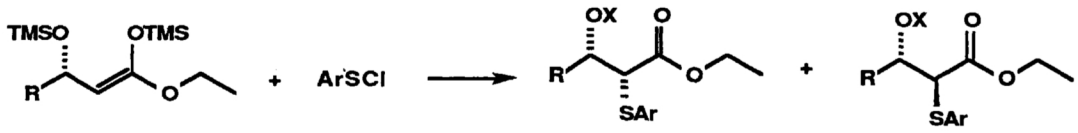
Anti-3-Hydroxy-2-phenylsulphenyl esters are stereoselectively synthesized by reaction between silyl ketene acetals and phenyl sulphenyl chloride. Subsequent elaboration leads to protected epoxyalcohols.

Silyl ketene acetals[1] are particularly useful intermediates in organic synthesis, since they can easily be generated and react with a variety of electrophiles under mild conditions. 3-Hydroxyesters, which are now available in optically pure form,[2] are attractive chiral starting materials, since they allow further functionalization at C-2 and chain elongation at C-1. Stereochemistry of functionalization at C-2 has been studied with some electrophiles mainly under basic conditions.[3] Recently, we examined both aminoalkylation under acidic conditions[4a] and amination[4b] under basic and acidic conditions.



1a-d

2 : Ar= 2-NO_2-C_6H_4

3 : Ar= Ph

SYN ANTI

4a : X= TMS, Ar= 2-NO_2-C_6H_4

5a-d : X= H, Ar= Ph

6a-d : X= TMS, Ar= Ph

(**a**) : R= Me (**b**) : R= n-Hex = n-C_6H_{13}

(**c**) : R= cy-Hex = cyclohexyl (**d**) : R= CF_3

Scheme 1.

Table 1.

Entry	R	ArSCl	mmol of ArSCl/ mmol of 1	Conditions	Yield/%	Diastereomeric ratio 4[a,b]	5[c]
1	Me	(2)	1.1	CH_2Cl_2, r.t.,3 h	50	35 : 65	
2	Me	(2)	1.1	CH_2Cl_2, 0 °C,22 h	16	28 : 72	
3	Me	(2)	2.0	PhMe, -65 °C,3.5 h	38	21 : 79	
4	Me	(3)	1.5	CH_2Cl_2, r.t.,1.5 h	66		26 : 74[d]
5	Me	(3)	1.5	CH_2Cl_2,-78 °C,20 h	68		20 : 80[d]
6	Me	(3)	1.5	PhMe, r.t., 1.5 h	73		8 : 92[d]
7	Me	(3)	1.5	PhMe, -78 °C,20 h	74		6 : 94[d]
8	n-Hex	(3)	1.5	PhMe, -50 °C,20 h	66		15 : 85[e]
9	cy-Hex	(3)	1.5	PhMe, -85 °C,20 h	62		18 : 82[e]
10	CF_3	(3)	1.5	PhMe, -85 °C,20 h	63		35 : 65[f]

a) Stereochemical attribution was not made. b) Determined by CGC. c) syn : anti ratio.
d) Determined by TLC spectrodensitometry (254 nm) and/or by weighing isolated isomers.
e) Determined by weighing isolated isomers. f) Determined by ^{1}H NMR spectroscopy.

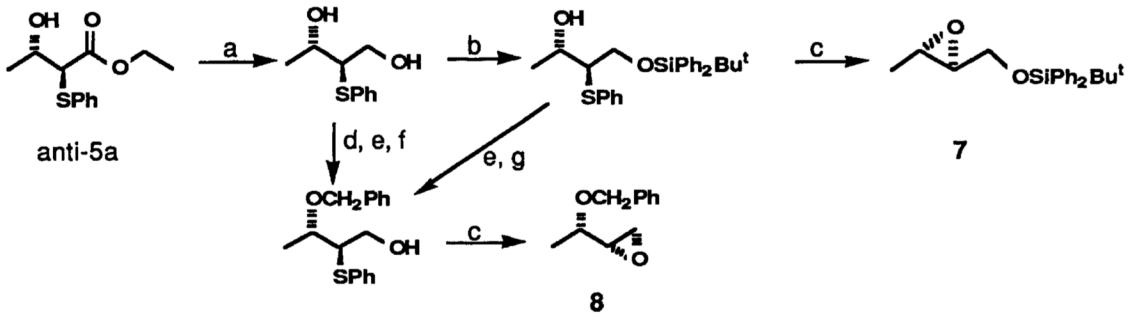
In order to extend our observations on the stereoselectivity of electrophilic additions to β-hydroxy esters, we decided to examine the course of sulphenylation of silyl ketene acetals[5] derived from 3-hydroxy esters, under neutral conditions. Arenesulphenyl chlorides were chosen as sulphur electrophiles (Scheme 1 and Table 1).[6] The reaction of 1-ethoxy-1,3-bis(trimethylsilyloxy)but-1-ene (**1a**) with 2-nitrosulphenyl chloride (**2**) was tried first under various conditions, but ethyl 3-trimethylsilyloxy-2-(2-nitrophenylthio)-butyrate (**4a**) was always obtained in rather disappointingly low chemical and stereochemical yield. On the contrary, phenylsulphenyl chloride (**3**) gave ethyl 3-hydroxy-2-(phenylthio)butyrate (**5a**) in good chemical and stereochemical yield.[7] Most likely **5a** derives from desilylation of **6a** under reaction work-up. The two stereoisomers could be easily separated by column chromatography and identified on the basis of coupling constants $^3J_{2,3}$ in their ^{1}H NMR spectra.[8] Quite surprisingly, the major isomer was the anti one, opposite to the stereoselectivity observed in reaction of **1a** with other electrophiles like benzylideneaniline[4a] (carbon electrophile) and benzenediazonium tetrafluoroborate[4b] (nitrogen electrophile). Solvent seems to influence to some extent the stereochemical outcome (entries 4,6 vs. 6,7). It must be stressed that in the present case, where no catalyst is required, the electrophile is a formally neutral species, while both diazonium salt and imine-trimethylsilyl triflate complex have cationic character; nevertheless, it has also been reported[5c] that phenylsulphenyl chloride and 1,3-dithienium tetrafluoroborate (cationic electrophile) attack in the

same stereochemical sense, when chiral O-silylated imide enolates (with the asymmetric centre located in the amine moiety) are used. Other electrophiles should be tried before any sound hypothesis could be drawn.

In a typical procedure, 6.15 mmol of **1a** were dissolved in dry PhMe (40 ml) at -78 °C and treated with phenylsulphenyl chloride (9.22 mmol) dissolved in 15 ml of dry PhMe. After 20 h, column chromatography of the crude reaction mixture afforded pure anti and syn **5a**.

In order to test the generality of this sulphenylation, the reaction was applied to various silyl ketene acetals (**1b,c**): chemical and stereochemical results are reported in entries 8-10 of Table 1. It must be stressed that, when **1c** and **1d** were used (entries 9 and 10), a mixture of 5 and 6 was obtained. Efforts to deprotect **6** to **5** in situ, adding a CH_2Cl_2 solution of n-$Bu_4NF.3H_2O$ (TBAF) after completion of the reaction at -85 °C, were fruitless. Thus, **6** obtained from column chromatography of the crude reaction mixture was subsequently treated either with HCl in THF-water (for **6c**) or with TBAF in CH_2Cl_2 (for **6d**) for 1 min at room temperature to give **5** in quantitative yield. Yields and diastereomeric ratios reported in Table 1 are determined on deprotected product **5**. Low stereoselectivity of entry 10 could be due to the high reactivity of **1d**.

In order to show an application of these α-sulphenyl-β-hydroxyesters, we converted racemic anti-**5a** into both protected trans-2,3-epoxybutan-1-ol (**7**) and syn-3,4-epoxybutan-2-ol (**8**) following Scheme 2.[9-10] It should be noted that, while epoxides like **7** can be synthesized enantioselectively through Sharpless epoxidation,[11] the preparation of **8** and its analogues by the epoxidation with kinetic resolution of racemic 3-hydroxy-1-alkenes is not feasible, since that method is known to afford anti-derivatives, which are diastereomeric to **8**.[12]



a) $LiAlH_4$, THF, 0 °C, 60%; **b**) t-Bu$(Ph)_2SiCl$, imidazole, CH_2Cl_2, r.t., 85%; **c**) Me_3OBF_4, CH_2Cl_2, then 0.5 M NaOH, r.t., 40%; **d**) Ph_3CCl, pyridine, r.t., 48 h, 71%; **e**) $PhCH_2Br$, NaH, DMF, r.t., 30 min, 95%; **f**) CF_3COOH, t-BuOH, r.t., 69%; **g**) n-$Bu_4NF.3H_2O$, CH_2Cl_2, r.t., 24 h, 51%.

Scheme 2.

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5) Reaction between enol silyl ethers or silyl ketene acetals and sulphenyl chlorides was already reported: a) S. Murai, Y. Kuroki, H. Hasegawa, and S. Tsutsuli, J. Chem. Soc., Chem. Commun., 1972, 946; b) B.M. Trost and D.P. Curran, J. Am. Chem. Soc., 102, 5699 (1980); c) R.P. Alexander and I. Paterson, ibid., 26, 5339 (1985); d) V.K. Aggarwal and S. Warren, Tetrahedron Lett., 27, 101 (1986).

6) Although racemates were used in this work, only one enantiomer is arbitrarily shown for the sake of clarity.

7) Diphenyldisulphide did not react with **1a** either in the presence or in the absence of a catalyst (Me_3Si-OTf or $TiCl_4$). Reaction with PhSCl or PhSSPh *via* the enolate gave only poor yields.

8) 6.3 Hz for *syn*-**5a** and 7.3 Hz for *anti*-**5a** (see T. Fujisawa, T. Itoh, and T. Sato, Tetrahedron Lett., 25, 5083 (1984)).

9) We were not able to transform directly *anti*-**5a** into *trans*-methyl 2,3-epoxy-butanoate, probably because of lability of **5a** and of its methylsulphonium derivative under basic conditions (see R.W. Hoffmann and B. Kemper, Tetrahedron, 40, 2219 (1984)).

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