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SYNTHESIS AND REACTIONS OF CYCLIC α-HYDROXY SULFIDES

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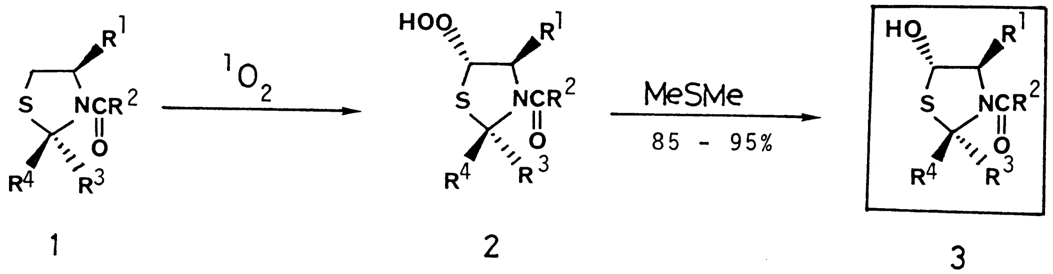
Stable, optically active α-hydroxy sulfides are prepared in high yields by reduction of corresponding α-hydroperoxy sulfides obtained by stereospecific photohydroperoxidation of optically active thiazolidine derivatives. A few reactions as well as spectroscopic data characterize the alcohol structure.

α-Hydroxy sulfides(i.e. hemimercaptal or hemimercaptol) are known to be too unstable to be definitely characterized,[1a] and are in an equilibrium with mercaptan and carbonyl compound.[1] The hydroxy sulfides have often been assumed as key intermediates in reactions of aldehyde and ketone with mercaptan or formation of mercaptal and mercaptol,[1d] hydrolysis of sulfur-stabilized carbocation,[2] oxidation of sulfide with monooxygenase,[3] and so on.[1] Although a stable α-hydroxy sulfide has been reported; that is a hemimercaptal of chloral,[1a,4] no detail studies have been done for α-hydroxy sulfide[5] so far as we know.

Recently, we have synthesized α-hydroperoxy sulfide 2 in photooxidation of thiazolidine derivatives 1, in which the hydroperoxide can be reduced to corresponding α-hydroxy sulfide 3.[8-10] Now, we describe the preparation and a few reactions characterizing stable α-hydroxy sulfides 3 derived from thiazolidine 1.

A mixture of a thiazolidine derivative 1[9] (1 - 5 mmol) and TPP(meso-tetraphenylporphyrin, 15 mg/ mmol of 1) in dry THF([C]=0.05 - 0.15 M) was irradiated with 500W halogen lamp at -30 °C - 0 °C under bubbling oxygen. After the irradiation, 1 - 2 cm^3 of dimethyl sulfide was added and the mixture was allowed to stand at room temperature. The resulting mixture was chromatographed to give pure alcohol 3 as colorless crystals in a yield ranging from 85 to 95%. Physical properties of the remarkably stable alcohols obtained from some selected thiazolidines are listed in Table 1.

Reaction time taken clearly depends on both amount and structure of substrate used. Namely, in the case of 1a or 1c, it took 1.0 - 1.5 h per mmol of substrate. On the other hand, in each case of 1e - 1h, owing to bulkiness at 2-position prolonged reaction time(2.0 - 2.5 h per mmol of substrate) was needed. However, 4-hydroxymethyl derivative(1b, 1d, 1f, or 1h) took shorter reaction time(two-third) than the corresponding 4-carbomethoxy derivative in any case. In all the reactions temperature change(e.g. -30 °C ⟶ 0 °C) little affected the reaction rate, in



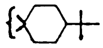
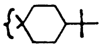
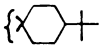
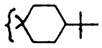
accordance with rate-determining step of formation of singlet oxygen.11) In the reaction of 2-monosubstituted thiazolidines(1i and 1j), the yield of the alcohol was low(40%(GLC) and 32%(isolated), respectively). The bulkiness of the substrate is important because the photohydroperoxidation is competitive with S-oxidation producing sulfoxide as an usual photooxidation product.10) Therefore, less bulky substance requires lower concentration(for example, in the case of 1j) to prevent sulfoxide formation since the hydroperoxidation is intramolecular.10)

The structures of the alcohols thus obtained were determined by spectroscopic and analytical data. Alcohol absorption around 3300 cm^{-1} in IR was agreeable as that of usual secondary alcohol. It was suggested that the alcohol formation was stereospecific to yield one isomer of two possible diastereomers. ^{1}H-NMR strongly indicated that the isomer is 4,5-trans form in any case, since little or no coupling constant between 4- and 5-positions was consistent with 90° dihedral angle between protons at 4- and 5-positions. ^{13}C-NMR spectra of 3c and 3d showed resonances of 5-methine carbons substituted by sulfur and oxygen at 77.6(d) and 77.9 (d) ppm, respectively, supporting the proposed structure. Since reduction of 2 to 3 should not influence the product stereochemistry, such stereochemistry is introduced in the step of the photohydroperoxidation.10)

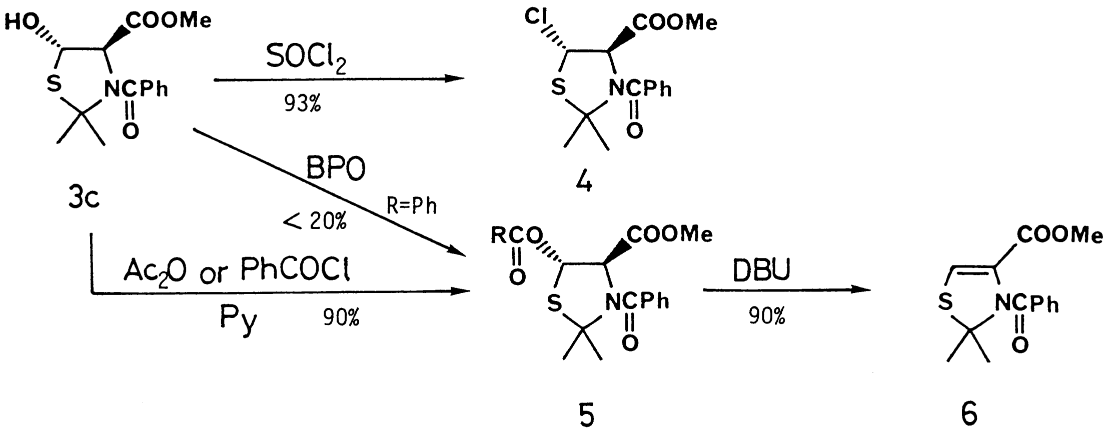
Chlorination6) with thionyl chloride proceeded via S_Ni reaction to afford stereospecifically 90% yield of trans-chloride 4 which was a stable crystal(mp 162 - 164 °C). Meanwhile, the alcohol 3c easily underwent acylation to produce exclusively trans diester 5 which was identical with that prepared independently by Sosnovsky reaction12) using benzoyl peroxide(BPO) in a low yield.13) Treatment of 5 with 1,8-diazabicyclo[5.4.0]undecene(DBU) gave elimination product 6 in a high yield. These reactions well characterize the alcohol structure.

This method of preparation is limited by substrate, being available only when five-membered ring sulfide is used,10) while six- and seven-membered ring sulfides give only S-oxidation products. Simple five-membered ring sulfide such as tetrahydrothiophene gave small amounts of ring-opening products probably via α-hydroxy sulfide, along with a large amount of sulfoxide.10) Therefore, some rigid ring structure may stabilize the α-hydroxy sulfide.

Table 1. Physical Properties of α-Hydroxy Sulfides

Product 3a)					Mp θm/°C	$[\alpha]_D^{24}$/°(c,solv)b)	IRν/cm^{-1}(KBr)		^{1}H-NMR/ppm(CDCl$_3$)		
	R^1	R^2	R^3	R^4			-OH	C=O	4-H	5-H	-OH
3a	CO_2Me	Me	Me	Me	161-163	+36.0(0.88,C)	3190	1740 1615	5.10(s)	5.88(s)	6.15(brs)c)
3b	CH_2OH	Me	Me	Me	140-142	+32.0(2.31,E)	3410 3290	1605	4.47(t)	5.59(s)	6.00(brs)c) 5.11(brs)
3cd)	CO_2Me	Ph	Me	Me	181-183	-75.3(1.36,C)	3360	1740 1630	4.96(s)	5.53(s)	3.85(brs)
3dd)	CH_2OH	Ph	Me	Me	158-161	+51.2(1.01,E)	3400 3150	1590	4.52(t)	5.44(s)	5.86(brs)c) 4.52(brs)
3ee)	CO_2Me	Me			140-142	+21.1(1.73,C)	3350	1745 1620	5.05(s)	5.74(s)	3.75(brs)
3fe)	CH_2OH	Me			248-250		3225	1610	4.34(t)	5.39(s)	4.87(brs)c)
3ge)	CO_2Me	Ph			174-176	-43.9(1.22,C)	3225	1735 1610	5.03(s)	5.53(s)	4.79(brs)
3he)	CH_2OH	Ph			220-222		3300	1600	4.50(dd)	5.39(s)	4.05(brs)c) 4.63(brs)
3i	CO_2Me	H	H	^tBu	148-149	+9.80(0.80,C)	3380	1735 1640	5.25(s)	6.07(s)	3.17(s)f)
3j	CO_2Me	Me	H,Me		129-130		3300	1740 1670	4.90(s)	5.90(s)	4.13(brs)g)

a) Satisfactory analytical data were obtained for most of the products. b) Optical purity of the products was assumed to be 100%. Solvent(C: chloroform; E: ethanol). c) CDCl$_3$-dimethylsulfoxide-d$_6$ mixed solvent was used. d) A part of the data appears in Ref.9. e) Although the hydroperoxide(2d - 2h) is a pure diastereomer derived from L-cysteine, orientation of t-butyl group is not thoroghly defined. f) ^{1}H-NMR data of major conformer of two conformers is shown. The two had the same melting point. g) All data are those of one of the two diastereomers.



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5) Only values of density for $RSCH_2OH$(R=Et, Pi, ^{i}An, Ph, and $PhCH_2$) were measured1b) other than $PhCH_2SCH_2OH$ whose boiling point was shown(84 - 86 °C/ 0.1 mmHg).6) 2,5-Dihydroxy-1,4-dithiane was reported to be gradually decomposing crystals and be in an equilibrium with two moles of mercaptoacetaldehyde in solution.7)
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