A Positive Halogen Mediated Ring-Opening Reaction of 2-(α-Phenylthiobenzyl)cycloalkanol Derivatives

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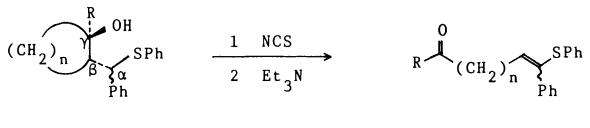
(Received July 4, 1985)

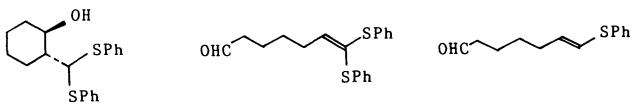
Synopsis. A new ring-opening reaction of the title cycloalkanols (**1** and **3**) takes place upon treatment with *N*-chloro-succinimide and triethylamine to give ω-oxo α,β-unsaturated sulfides (**2**) in fairly good yields.

Halosulfonium salts are useful synthetic intermediates and have been used in alcohol oxidation,[1] alkaloid synthesis,[2] and many other reactions. However, in spite of their fascinating properties, sulfide derivatives, having internal nucleophiles such as hydroxyl and amino groups, have rarely been employed as substrates for halosulfonium chemistry.[3] Therefore, we undertook to study a reaction of 2-(α-phenylthiobenzyl)cycloalkanol derivatives (**1** and **3**) with a positive halogen with the hope that the internal hydroxyl group would participate in the halosulfonium center and control the reaction course and stereochemistry of the reaction. In this note we wish to describe an interesting ring-opening reaction of the cycloalkanols (**1** and **3**) with *N*-chloro-succinimide.

trans-2-(α-Phenylthiobenzyl)cyclohexanol (**1c**), a 2:1 mixture of threo and erythro isomers, was allowed to react with *N*-chlorosuccinimide (NCS), followed by treatment with triethylamine to give 7-phenyl-7-phenylthio-6-heptenal (**2c**). The product was labile but isolated rapidly by MPLC in 75% yield as a mixture of (*E*)- and (*Z*)-isomers (2:1). The structure of **2c** was determined by spectral data and by a comparison with an authentic sample. The results are summarized in Table 1. Similarly, aldehydes (**2a** and **2e**) were obtained in 10 and 64% yields, respectively. The ring-opening reaction of the tertiary substrates (**1b**, **1d**, and **1f**) took place to afford ketones (**2b**, **2d**, and **2f**). In every case, the (*E*)-isomers were the major products from the *trans*-cycloalkanols (**1**) as shown in the Table 1. On the other hand, *cis*-2-(α-phenylthiobenzyl)cyclopentanol (**3a**) (threo:erythro, 1:1) and *cis*-1-methyl-2-(α-phenylthiobenzyl)cyclohexanol (**3d**) (threo:erythro, 1:3), were also converted to ω-oxo α,β-unsaturated sulfides (**2a** and **2d**) in 60 and 68% yields, respectively. Interestingly, the stereochemistry of the products was just reversed (*E*:*Z*=1:3 in both cases). Although the stereoselectivity of the present reaction is low, these results suggest that *trans*-cycloalkanols (**1**) are changed mainly to (*E*)-isomers and *cis* derivatives (**3**) mainly to (*Z*)-isomers.



1 **2**



4 **5** **6**

Semmelhack has reported a Grob-type ring-opening reaction of *trans*-2[bis(phenylthio)methyl]-cyclohexanol derivatives by a metal catalyst to give ω-oxo α,β-unsaturated sulfides.[4] This result prompted us to carry out a reaction of bis(phenylthio)-compound (**4**) with NCS and triethylamine. The reaction gave the ketene thioacetal (**5**), in contrast to

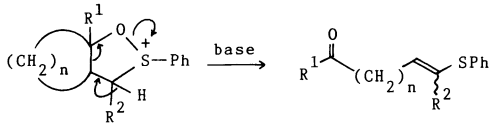
Table 1. Synthesis of ω-oxo α,β-Unsaturated Sulfides (**2**) from 2-(α-Phenylthiobenzyl)cycloalkanol Derivatives (**1**)

n	R	Substrate	Ratio of threo/erythro[a]	Product	Yield[b] %	Ratio of *E*/*Z*[c]
3	H	**1a**	3 : 2	**2a**	10	3 : 1
3	Me	**1b**	2 : 1	**2b**	36	2 : 1
4	H	**1c**	2 : 1	**2c**	76	7 : 3
4	Me	**1d**	1 : 1	**2d**	67	3 : 1
5	H	**1e**	1 : 1	**2e**	64	3 : 2
5	Me	**1f**	3 : 2	**2f**	63	3 : 2

a) Threo and erythro indicate a stereochemical relation between C_α and C_β of **1**. b) Isolated yield. c) Stereochemistry of **2** which was determined on the basis of δ value of vinyl proton (^{1}H NMR) as previously described.[10]

the metal-catalyzed reaction in which the α,β-unsaturated sulfide (**6**) was obtained. However, the yield was low (14%, isolated), presumably due to the decomposition of the product during workup.[5]

The ring-opening reaction mediated by NCS could be explained as follows. Cycloalkanols (**1**, **3**, and **4**) are converted to five-membered oxasulfonium salts (**7**) by a reaction with NCS,[6] which undergo a cycloelimination reaction induced by α-proton abstraction[7] to give ω-oxo α,β-unsaturated sulfides (**2**) or ketene thioacetal (**5**).



7

2 (R^2=Ph)
5 (R^2=SPh)

Experimental

General. *IR spectra were recorded with a Hitachi* 215 using liquid films. ^{1}H NMR spectra were obtained on a JEOL PMX-60 for a solution in $CDCl_3$ with Me_4Si as the internal standard. Mass spectra were taken with a Hitachi RMU-6D at 70 eV. Microanalyses were determined on a Yanagimoto CHN-Corder.

Material. *trans*-2-(α-Phenylthiobenzyl)cycloalkanols (**1a—f**) were prepared from the corresponding cycloalkene oxides and α-lithiobenzyl phenyl sulfide[8] (≈80%). *cis*-Cycloalkanols (**3a** and **3d**) were obtained by a base-catalyzed thiophenol addition to the corresponding 2-benzylidenecycloalkanones, followed by the reaction with $NaBH_4$ or MeMgI and separation from the trans isomer in 43 and 13% yields, respectively. *trans*-2-[Bis(phenylthio)methyl]cyclohexanol (**4**) was prepared by the reaction of cyclohexene oxide with bis(phenylthio)methyllithium in 80% yield.[8]

General Procedure for the Ring Opening Reaction of 1, 3, and 4. To a stirred solution of NCS (10 mmol) in dry dichloromethane (20 ml) was added an equimolar amount of the hydroxyl sulfide (**1**, **3**, or **4**) under N_2 with cooling (−40 °C). After 3 h, triethylamine (15 mmol) in dichloromethane (5 ml) was added dropwise and allowed to react at room temperature for 3 h. The reaction mixture was quenched with brine (10 ml), extracted with ether, and dried over anhydrous magnesium sulfate. The extract was concentrated in vacuo to give a crude product (**2** or **5**), which was purified by a MPLC (SiO_2, benzene–ethyl acetate 10:1 v/v as an eluent). Several data for the purified ring-opening products, ω-oxo, α,β-unsaturated sulfides (**2a—f**) and ketene thioacetal (**5**), are shown below.

2a: IR 1730 cm^{-1}; ^{1}H NMR δ=1.42—2.87 (m, 6H), 5.93 (t, *J*=7 Hz, 0.75 H), 6.33 (t, *J*=7 Hz, 0.25 H), 6.82—7.65 (m, 10H), 9.45—9.78 (m, 1H); MS, *m/z* 282 (M$^+$). Found: C, 76.38; H, 6.32%. Calcd for $C_{18}H_{18}OS$: C, 76.56; H, 6.42%.

2b: IR 1720 cm^{-1}; ^{1}H NMR δ=1.08—2.61 (m, 9H, at δ=2.01 acetyl methyl), 6.30 (t, *J*=7 Hz, 0.67 H), 6.78 (t, *J*=5 Hz, 0.33H), 6.42—7.72 (m, 10H); MS, *m/z* 296 (M$^+$). Found: C, 76.54; H, 6.77%. Calcd for $C_{19}H_{20}OS$: C, 76.99; H, 6.80%.

2c: IR 1730 cm^{-1}; ^{1}H NMR δ=1.17—1.90 (m, 4H), 2.83—3.40 (m, 4H), 6.02 (t, *J*=7 Hz, 0.7H), 6.35 (t, *J*=7 Hz, 0.3H), 6.77—7.42 (m, 10H), 9.53—9.77 (m, 1H); MS, *m/z* 296 (M$^+$). Found: C, 76.70; H, 6.80%. Calcd for $C_{19}H_{20}OS$: C, 76.99; H, 6.80%.

2d: IR 1715 cm^{-1}; ^{1}H NMR δ=1.27—2.80 (m, 11H, at δ=2.07 acetyl methyl), 6.03 (t, *J*=7 Hz, 0.75H), 6.35 (t, *J*=7 Hz, 0.25H), 7.00—7.42 (m, 10H); MS, *m/z* 310 (M$^+$). Found: C, 77.17; H, 7.11%. Calcd for $C_{20}H_{22}OS$: C, 77.38; H, 7.14%.

2e: IR 1730 cm^{-1}; ^{1}H NMR δ=1.12—1.92 (m, 6H), 1.92—2.78 (m, 4H), 6.05 (t, *J*=7.5 Hz, 0.6H), 6.35 (t, *J*=7.5 Hz, 0.4H), 6.92—7.40 (m, 10H), 9.55—9.75 (m, 1H); MS, *m/z* 310 (M$^+$). Found: C, 77.38; H, 7.13%. Calcd for $C_{20}H_{22}OS$: C, 77.38; H, 7.14%.

2f: IR 1715 cm^{-1}; ^{1}H NMR δ=0.86—2.73 (m, 13H, at δ=2.07 acetyl methyl), 6.06 (t, *J*=7 Hz, 0.6H), 6.36 (t, *J*=7 Hz, 0.4H), 6.73—7.66 (m, 10H); MS, *m/z* 324 (M$^+$). Found: C, 77.70; H, 7.42%. Calcd for $C_{21}H_{24}OS$: C, 77.73; H, 7.45%.

5: IR 1720 cm^{-1}; ^{1}H NMR δ=1.35—1.81 (m, 4H), 2.20—2.64 (m, 4H), 6.23 (t, *J*=7.4 Hz, 1H), 7.07—7.40 (m, 10H), 9.62 (t, *J*=1.5 Hz, 1H); MS, *m/z* 328 (M$^+$), Found: C, 69.29; H, 6.14%. Calcd for $C_{19}H_{20}OS_2$: C, 69.47; H, 6.14%.

Preparation of Authentic Samples 2c and 5. An authentic sample of **2c** was synthesized by the Peterson olefination of aldehydic acid ester ($EtO_2C(CH_2)_4CHO$) with α-phenylthio-α-(trimethylsilyl)toluene ($PhSCH(SiMe_3)Ph$)[9] and butyllithium (30%), followed by reduction ($LiAlH_4$) (80%) and PCC oxidation (80%): (Z)-**2c** (δ=6.35) predominated over *E*-isomer (δ=6.02) (9:1). Similar sequence using $(PhS)_2CHSiMe_3$[11] gave an authentic sample of **5** (δ=6.23) in 23% yield.

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