Reduction of β-Keto Sulfoxides Having an Alkyl Group and a Chlorine Atom on the α-Carbon: A Synthesis of (*E*)-α,β-Epoxy Sulfoxides[1)]

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Oxidation of the chlorohydrins derived from 1-chloroalkyl phenyl sulfoxides and aldehydes gave the β-keto sulfoxides having an alkyl group and a chlorine atom on the α-carbon. The β-keto sulfoxides were reduced with diisobutylaluminum hydride to afford the *syn*-chlorohydrins as sole products, which were converted to the (*E*)-α,β-epoxy sulfoxides.

Keywords α,β-epoxy sulfoxide; epoxide; β-keto sulfoxide; chlorohydrin; reduction

Recently, reduction of β-keto sulfoxides (for instance, see Chart 1[2b)]) has received considerable attention for diastereoselective- and/or enantioselective synthesis of β-hydroxy sulfoxides.[2)] This technique is quite useful for synthesis of various kinds of natural products in enantiomerically pure form.[2)] However, these reductions have been studied only with β-keto sulfoxides having no substituent on the α-carbon except for one report.[3)]

On the other hand, we have recently reported a novel method for stereospecific preparation of epoxides (**6** and **8**)[4)] utilizing the chlorohydrins (**3** and **4**) through α, β-epoxy sulfoxides (**5** and **7**); however, the addition of 1-chloroalkyl phenyl sulfoxides (**1a**) to the aldehydes (**2**), leading to the chlorohydrins (**3** and **4**), was found to be almost stereorandom (Chart 2). For example, treatment of **1b** with benzaldehyde (**2a**) gave the chlorohydrins **3a** (*syn*)[5)] and **4a** (*anti*)[5)] in 47% and 53% yields, respectively. In our synthesis of optically active (+)-disparlure (**6**: $R=CH_3(CH_2)_9$, $R^1=(CH_3)_2CH(CH_2)_4$),[4c)] the sex attractant of female gypsy moth, this approach called for the preparation of the *syn*-chlorohydrin; however the addition of 1-chloroundecyl *p*-tolyl sulfoxide to the aldehyde (**2c**) gave the *syn*-chlorohydrin and *anti*-chlorohydrin in 39% and 51% yields, respectively. To overcome this problem, we recently examined a reduction of β-keto sulfoxides having an alkyl group and a chlorine atom on the α-carbon (**9**).

Swern oxidation[6)] of **4a** and **4b** (synthesized from **1b** and **2a** or **2b**) gave the β-keto sulfoxides (**9a** and **9b**) in 86% and 92% yields, respectively. These β-keto sulfoxides (**9**) were reduced with diisobutylaluminum hydride (DIBAL-H) and

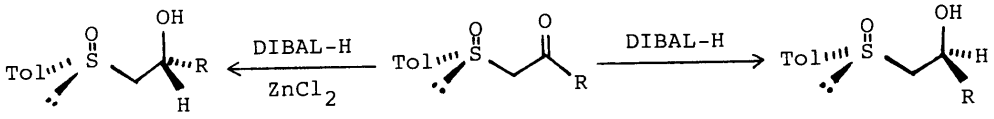
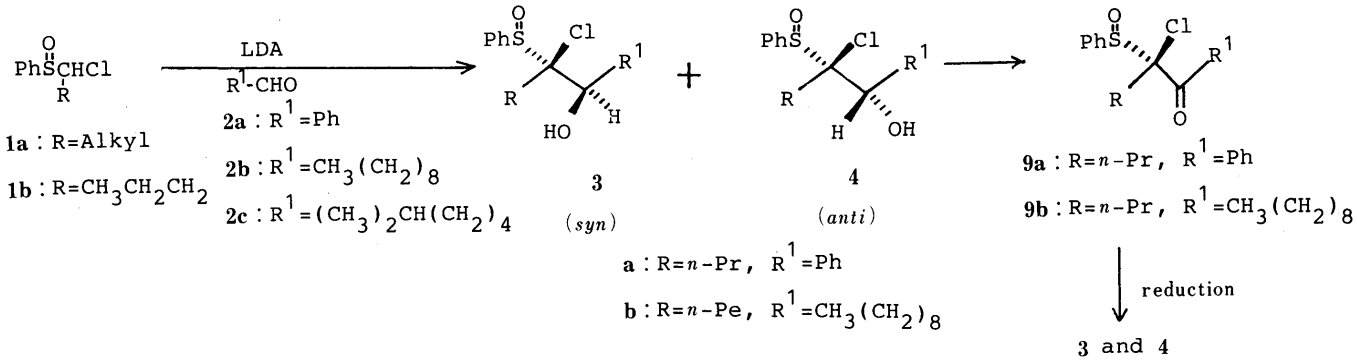
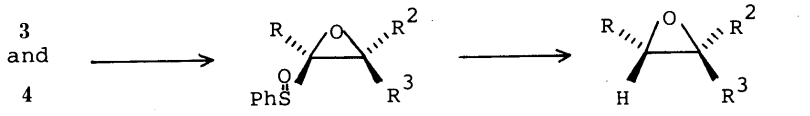


Chart 1





5 : $R^2=R^1$, $R^3=H$ (from 3) 6 : $R^2=R^1$, $R^3=H$

7 : $R^2=H$, $R^3=R^1$ (from 4) 8 : $R^2=H$, $R^3=R^1$

Chart 2

sodium borohydride ($NaBH_4$) at −60°C in tetrahydrofuran (THF), ether, or EtOH, and the results are summarized in Table I. As shown in Table I, **9a** and **9b** showed quite similar results with the reducing agents. With DIBAL-H, the ketones (**9**) gave only the *syn*-chlorohydrins (**3**). On the other hand, this reduction in the presence of $ZnCl_2$ gave a mixture of **3** and **4**; however, the *syn*-chlorohydrins (**3**) were still the main products. $NaBH_4$ reduction gave somewhat different results. With $NaBH_4$, **9** predominantly gave the *anti*-chlorohydrins (**4**).

These results can be explained as follows. Reduction of the β-keto sulfoxides (**9**) with DIBAL-H was thought to proceed with non-chelation control (Fig. 1A).[7] In this case,[8] the right side of the carbonyl group is blocked by the phenyl group and alkyl group (R), and the reduction proceeds from the side opposite to the phenyl and alkyl groups to give the *syn*-chlorohydrins (**3**) exclusively. In the case of the reduction with DIBAL-H in the presence of $ZnCl_2$, and with $NaBH_4$, the situation is not so clear. However, in the case with $NaBH_4$ (chelated conformation **B** was expected), it was anticipated that the chlorine atom and phenyl group would mainly block the left side of the ketone group to give predominantly the *anti*-chlorohydrins (**4**).

The *syn*-chlorohydrins (**3**) thus obtained gave (*E*)-α,β-epoxy sulfoxides (**5**: R = *n*-Pr) quantitatively upon treatment with potassium *tert*-butoxide.

In conclusion, although this reduction of (**9**) was not so clear-cut as the reduction of β-keto sulfoxides having no substituent on the α-carbon,[2] (*E*)-α,β-epoxy sulfoxides (**5**) were exclusively obtained from 1-chloroalkyl aryl sulfoxides and aldehydes *via* the β-keto sulfoxides (**9**). These results are also helpful for synthesis of (*Z*)-epoxides (**6**) as reported previously.[4]

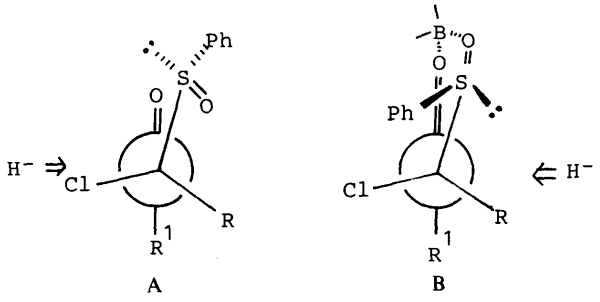


Fig. 1

TABLE I. Reaction of β-Keto Sulfoxides **9** with Reducing Agents

β-Keto sulfoxide[a]	Reducing agent (eq)	Solvent[b]	Time	Chlorohydrin Yield (%)[c] 3	4
9a	DIBAL-H (2)	THF	30 min	95	0
9a	DIBAL-H + $ZnCl_2$ (2) (1.2)	THF	25 min	65	26
9a	$NaBH_4$ (5)	EtOH	30 min	31	64
9b	DIBAL-H (2)	Et_2O	10 min	85	0
9b	DIBAL-H + $ZnCl_2$ (2) (1.2)	Et_2O	15 min	61	29
9b	$NaBH_4$	EtOH	2 h	20	65

a) See Chart 2. *b*) All reactions were conducted at −60 °C. *c*) Isolated yield.

Experimental

General Infrared (IR) spectra were measured directly on an NaCl plate or in KBr disks with a Hitachi 215 spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured in $CDCl_3$ solution with a JEOL FX-100 spectrometer using Me_4Si as an internal standard. Electron-impact mass spectra (MS) were obtained on a Hitachi M-80 double-focusing spectrometer at 70 eV by direct insertion. In experiments requiring dry solvents, THF and ether were distilled from benzophenone ketyl and CH_2Cl_2 was distilled from CaH_2.

General Procedure for the Preparation of Chlorohydrins (3 and 4) Synthesis of chlorohydrins **3a** and **4a** is described as an example. A solution of 1-chlorobutyl phenyl sulfoxide (**1b**; 1.07 g; 4.93 mmol) in 3 ml of dry THF was added dropwise to a solution of lithium diisopropylamide (LDA) (5.92 mmol) in 20 ml of dry THF at −60°C with stirring. The solution was stirred at −60°C for 20 min, then benzaldehyde (**2a**; 6 mmol) was added through a syringe. The reaction mixture was stirred for an additional 5 min then the reaction was quenched by adding saturated aqueous NH_4Cl. The whole was extracted with ether. The usual work-up gave a mixture of chlorohydrins, which was separated by silica gel column chromatography to afford the *anti*-chlorohydrin (**4a**) and *syn*-chlorohydrin (**3a**) in 53% (850 mg) and 47% (744 mg) yields, respectively. (*R**)-1-Chloro-1-[(*S**)-1-hydroxybenzyl]butyl phenyl sulfoxide **4a**: Colorless oil. IR (neat): 3350 (OH), 1080, 1035 (SO) cm^{-1}. ^{1}H-NMR δ: 0.73 (3H, t, *J* = 7 Hz), 1.0—2.1 (4H, m), 3.45 (1H, d, *J* = 4 Hz, OH), 5.29 (1H, d, *J* = 4 Hz), 7.1—7.9 (10H, m). MS *m/z* (%): 196 ([M − PhSOH]$^+$, 20), 161 (40), 126 ([M − $C_{11}H_{13}ClO$]$^+$, 100). (*R**)-1-Chloro-1-[(*R**)-1-hydroxybenzyl]butyl phenyl sulfoxide **3a**: Colorless prisms (AcOEt–hexane). mp 130—133°C. IR (KBr): 3350 (OH), 1090, 1045 (SO) cm^{-1}. ^{1}H-NMR δ: 1.02 (3H, t, *J* = 7 Hz), 1.4—2.1 (4H, m), 4.92 (1H, s), 7.25 (5H, s), 7.5—8.0 (5H, m). MS *m/z* (%): 199 (9), 179 (11), 161 (12), 126 ([M − $C_{11}H_{13}ClO$]$^+$, 100).

Chlorohydrins **3b** and **4b** were synthesized from **1b** and decanal (**2b**). (1*R**, 2*S**)-1-Chloro-2-hydroxy-1-pentylundecyl phenyl sulfoxide **4b**: 42% yield; colorless oil. IR (neat): 3390 (OH), 1080, 1035 (SO) cm^{-1}. ^{1}H-NMR δ: 0.6—2.2 (26 H, m), 3.55—3.82 (1H, m), 7.4—7.8 (5H, m). MS *m/z* (%): 320 (trace), 303 (trace), 247 ([M − PhSO]$^+$, 3), 126 ([M − $C_{14}H_{27}ClOS$]$^+$, 71), 119 (100). (1R*, 2R*)-1-Chloro-2-hydroxy-1-penylundecyl phenyl sulfoxide **3b**: 34% yield; colorless oil. IR (neat): 3375 (OH), 1085, 1040 (SO) cm^{-1}. ^{1}H-NMR δ: 0.86 (3H, t, *J* = 7 Hz), 0.9—2.3 (23H, m), 3.79 (1H, m), 7.3—7.9 (5H, m). MS *m/z* (%): 303 (trace), 247 ([M − PhSO]$^+$, 7), 126 ([M − $C_{14}H_{27}ClOS$]$^+$, 100).

Oxidation of *anti*-Chlorohydrins (4) A synthesis of 2-chloro-1-phenyl-2-phenylsulfinylpentan-1-one (**9a**) is described. Dimethyl sulfoxide (8.76 mmol) was added dropwise to a solution of oxalyl chloride (4.38 mmol) in dry CH_2Cl_2 (20 ml) at −60°C with stirring. The mixture was stirred at −60°C for 2 min, then a solution of the chlorohydrin (**4a**; 1.18 g; 3.65 mmol) in 5 ml of dry CH_2Cl_2 was added within 5 min. The stirring was continued for 15 min, then triethylamine (18.3 mmol) was added. The reaction mixture was allowed to warm to room temperature. Water (10 ml) was added to the reaction mixture and the whole was extracted with ether. Usual work-up gave an oily residue, which was purified by silica gel column chromatography to afford 1.01 g (86%) of the β-keto sulfoxide (**9a**) as a low-melting solid. IR (KBr): 1670 (CO), 1080, 1050 (SO) cm^{-1}. ^{1}H-NMR δ: 0.91 (3H, t, *J* = 7 Hz), 1.0—1.9 (2H, m), 1.9—2.7 (2H, m), 7.2—8.0 (10H, m). MS *m/z* (%): 194 ([M − PhSOH]$^+$, 10), 159 (6), 125 (12), 105 ([M − $C_{10}H_{12}ClOS$]$^+$, 100).

4-Chloro-4-phenylsulfinyltetradecan-5-one (9b) Colorless oil; 93% yield. IR (neat): 1705 (CO), 1090, 1060 (SO) cm^{-1}. ^{1}H-NMR δ: 0.7—2.8 (26H, m), 7.2—7.8 (5H, m). MS *m/z* (%): 234 (4), 215 ([M − $C_{10}H_{19}O$]$^+$, 16), 132 (100).

Reduction of 9a with DIBAL-H and $NaBH_4$ With DIBAL-H: A solution of DIBAL-H in hexane (0.52 mmol) was added dropwise through a syringe to a solution of **9a** (85 mg; 0.26 mmol) in 3 ml of dry THF at −60°C under N_2 with stirring. The reaction mixture was stirred for 30 min, then the reaction was quenched with MeOH. The solvent was evaporated off and the resuidue was extracted with ether. The extract was washed with 5% NaOH. Usual work-up gave a residue, which was purified by silica gel column chromatography to give **3a** as a sole product in 95% (82 mg) yield.

With DIBAL-H in the Presence of $ZnCl_2$: Anhydrous $ZnCl_2$ (0.34 mmol; 1.2 eq) was added to a solution of **9a** (88 mg; 0.28 mmol) in dry THF (6 ml). The mixture was stirred at room temperature for 1 h, then cooled to

−60°C. DIBAL-H (0.56 mmol) was added, and the reaction mixture was stirred at −60°C for 25 min. Work-up as described above gave the chlorohydrins **3a** and **4a** in 65% (57 mg) and 26% (23 mg) yields, respectively.

With $NaBH_4$: A solution of **9a** (87 mg; 0.27 mmol) in 1 ml of dry EtOH was added to a solution of $NaBH_4$ (1.35 mmol) in 2 ml of dry EtOH at −60°C. The reaction mixture was stirred at −60°C for 30 min, then the solvent was evaporated off. Water and ether were added to the residue and the whole was extracted with ether–benzene. The organic layer was washed with saturated aqueous NH_4Cl. Usual work-up and chromatography on silica gel gave **3a** and **4a** in 31% (27 mg) and 64% (56 mg) yields, respectively.

Reduction of 9b Reduction of **9b** was conducted with DIBAL-H, DIBAL-H with $ZnCl_2$, or $NaBH_4$ in ether or EtOH in the same way as described above. The results are summarized in Table I.

A Synthesis of (*E*)-α,β-Epoxy Sulfoxides (5) from 3 A synthesis of **5** (R = *n*-Pr, R^2 = Rh) is described. A solution of **3a** (497 mg; 1.54 mmol) in a mixture of benzene (4 ml) and *tert*-BuOH (10 ml) was treated with *tert*-BuOK (1.85 mmol) and the reaction mixture was stirred at room temperature for 10 min. The reaction was quenched with NH_4Cl then the solvent was evaporated off. The residue was extracted with ether and after the usual work-up, the (*E*)-α,β-epoxy sulfoxide (**5**: R = *n*-Pr, R^2 = Ph) was obtained in quantitative yield (442 mg) as colorless crystals. mp 83—85°C (AcOEt–hexane). IR (KBr): 1085, 1060 (SO) cm^{-1}. ^{1}H-NMR δ: 0.73 (3H, t, *J* = 6 Hz), 0.9—1.8 (4H, m), 4.78 (1H, s), 7.1—7.9 (10H, m). MS *m/z* (%): 286 (M^+, 0.8), 161 ([M − PhSO]$^+$, 39), 91 (100). Found: C, 71.32; H, 6.42; S, 11.35%; *m/z* 286.1037. Calcd for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.34; S, 11.20%; M, 286.1027.

(*E*)-α,β-Epoxy Sulfoxide (5: R = *n*-Pr, $R^2 = CH_3(CH_2)_8$) Colorless oil, 91% yield. IR (neat): 1080, 1045 (SO) cm^{-1}. ^{1}H-NMR δ: 0.5—2.0 (26 H, m), 3.62 (1H, t, *J* = 6 Hz), 7.3—7.8 (5H, m). MS *m/z* (%): 336 (M^+, 0.6), 211 ([M − PhSO]$^+$, 7), 71 (100). High-resolution MS: *m/z* 336.2127. Calcd for $C_{20}H_{32}O_2S$: M, 336.2121.

References and Notes

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8) In these reactions the β-keto sulfoxides (**9**) were racemic compounds. The relative stereochemistry of sulfoxide and the substituents on the α-carbon has been determined to be as shown in Fig. 1: see reference 4*c*.