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Stereochemistry of Alkylation of Cyclic β-Ketosulfoxides. II.[1] Alkylations of 2-Methylbenzo[*b*]thiophen-3(2*H*)-one 1-Oxide

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Alkylation of the carbanion derived from 2-methylbenzo[*b*]thiophen-3(2*H*)-one 1-oxide (**3**) with alkyl halide was found to occur *cis* to the S–O bond with high stereoselectivity. A pyramidal structure is proposed for the intermediary carbanion based on the results of carbon-13 nuclear magnetic resonance spectroscopy.

Keywords——alkylation; carbanion; 2-methylbenzo[*b*]thiophen-3(2*H*)-one 1-oxide; β-ketosulfoxide; cyclic sulfoxide stereochemistry

In the preceding paper[1] on the stereochemistry of alkylation of β-ketosulfoxides, it was shown that the alkylation of the carbanions derived from 3-methylisothiochroman-4-one 2-oxide (**1**) and 2-methylthian-3-one 1-oxide (**2**) with alkyl halide occurs *trans* to the S–O bond with high stereoselectivity. In the present paper we examined the alkylation of the anion derived from 2-methylbenzo[*b*]thiophen-3(2*H*)-one 1-oxide (**3**), and found that the alkylation occurred in a quite different manner to that of **1** and **2**, giving the *cis* (to the S–O bond)-alkylated product highly stereoselectively.

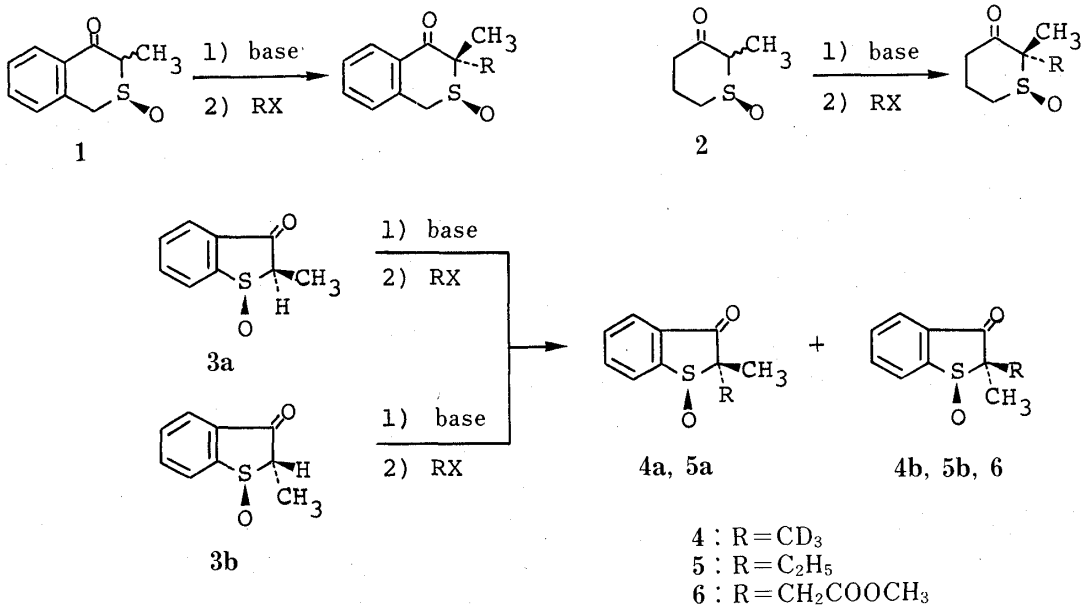


Chart 1

cis-[2] **3a** and *trans*-3-methylbenzo[*b*]thiophen-3(2*H*)-one 1-oxide (**3b**) were prepared by oxidation of 2-methylbenzo[*b*]thiophen-3(2*H*)-one[3] with *m*-chloroperbenzoic acid. The structures **3a** and **3b** were confirmed by the following evidence. In the proton nuclear magnetic

resonance (^{1}H-NMR) spectra, the signal due to the methyl protons of **3a** moved further than that of **3b** (see Fig. 1) on addition of increasing amounts of a shift reagent, Eu(fod)$_3$.[4]

Metallation of **3a** with *n*-butyllithium (*n*-BuLi) in tetrahydrofuran (THF) followed by alkylation with trideuteriomethyl iodide (CD_3I) gave a 18 : 82 mixture of two stereoisomers, **4a**

Table I. Alkylations of **3a, b** with Alkyl Halides

Substrate	Base	RX	Product	Selectivity (*trans* : *cis*)	Yield (%)
3a	*n*-BuLi	CD_3I	**4a**+**4b**	18 : 82	69
3b	*n*-BuLi	CD_3I	**4a**+**4b**	17 : 83	65
3a	NaH	CD_3I	**4a**+**4b**	15 : 85	70
3b	NaH	CD_3I	**4a**+**4b**	14 : 86	82
3a	*tert*-BuOK	CD_3I	**4a**+**4b**	10 : 90	87
3b	*tert*-BuOK	CD_3I	**4a**+**4b**	10 : 90	84
3a+**3b**	*n*-BuLi	C_2H_5I	**5a**+**5b**	14 : 86	67
3a+**3b**	NaH	C_2H_5I	**5a**+**5b**	10 : 90	70
3a+**3b**	NaH	$BrCH_2COOCH_3$	**6**	0 : 100	86

Table II. ^{1}H- and ^{13}C-NMR Spectral Data for **3**—**8**

Compound	^{1}H-NMR[a]			^{13}C-NMR[b]		
	C-2 *cis*	C-2 *trans*	Others	C-2	Substituent on C-2	
					cis	*trans*
3a	CH_3 1.59 (d)[c] (*Δ*1.11)	H 3.88 (q)[c] (*Δ*0.61)	7.65—8.15 (4H, m)	60.8	CH_3 8.2	—
3b	H 3.77 (q)[d] (*Δ*1.04)	CH_3 1.78 (d)[d] (*Δ*0.32)	7.65—8.20 (4H, m)	72.0	—	CH_3 10.6
4a	CH_3 1.48 (s) (*Δ*1.01)	—	7.6—8.1 (4H, m)	68.5	CH_3 18.2	
4b	—	CH_3 1.61 (s) (*Δ*0.33)	7.6—8.1 (4H, m)	68.5	—	CH_3 20.4
5a	CH_3 1.46 (s) (*Δ*1.11)	CH_2[e]	0.96 (3H, t)[c] 7.5—8.2 (4H, m)	75.4	CH_3 16.4	CH_2 27.7
5b	CH_2[e]	CH_3 1.58 (s) (*Δ*0.40)	0.98 (3H, t)[c] 7.5—8.2 (4H, m)	72.5	CH_2 25.0	CH_3 17.5
6	CH_2 3.08 (d)[f] (*Δ*0.77) 3.14 (d)[f] (*Δ*0.88)	CH_3 1.56 (s) (*Δ*0.36)	3.67 (3H, s) 7.7—8.2 (4H, m)	67.4	CH_2 35.6	CH_3 19.4
7	H 3.64 (d)[g]	H 4.31 (d)[g]	7.7—8.3 (4H, m)	62.0 (t)[h]	—	—
8	[i]	[i]	[i]	49.8 (d)[j]	—	—

a) Chemical shifts in ppm relative to tetramethylsilane; solvent, $CDCl_3$; values in parentheses are LIS values obtained by adding 0.15 molar eq of Eu(fod)$_3$ to the sulfoxide solution.
b) Chemical shift in ppm relative to tetramethylsilane; solvent, $CDCl_3$ for **3**—**6** and THF-d_8 for **7**—**8**; diagnostic data only.
c) J=7.5 Hz. *d*) J=8 Hz. *e*) Not clear. *f*) J=17.5 Hz. *g*) J=18 Hz.
h) J=143 Hz. *i*) Not measured. *j*) J=138 Hz.

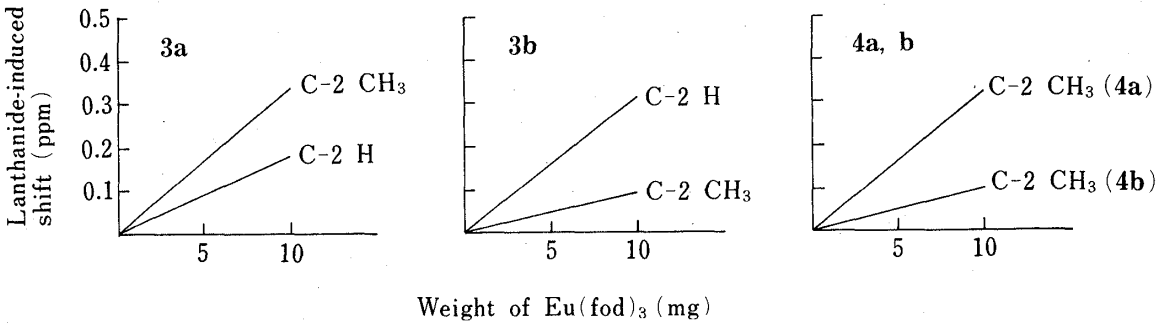
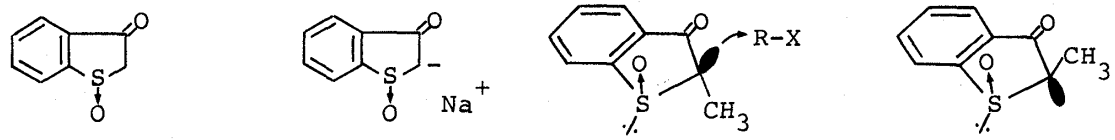


Fig. 1. Plot of $\Delta\delta$ against Weight of $Eu(fod)_3$ for **3a, b** and **4a, b** (0.2 mmol in 0.4 ml of $CDCl_3$)

and **4b**. A similar trideuteriomethylation of **3b** gave a mixture (17:83) of **4a** and **4b**. The results of other experiments using different bases and different alkylating agents are summarized in Table I. The structures **4a, b, 5a, b**, and **6** were established by the same method as described above for **3a, b** (see Table II and Fig. 1), and the product ratios were determined from the areas of the signals due to the methyl protons in the ^{1}H-NMR spectra. As can be seen from Table I, the alkylations occurred in all cases *cis* to the S–O bond with high stereoselectivity.

In order to clarify the structure of the intermediary carbanion in the alkylation of **3**, we examined the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of benzo[*b*]thiophen-3(2*H*)-one 1-oxide (**7**)[5] and its sodium salt (**8**). As a result, the salt (**8**) was shown to have a pyramidal structure, based on the following evidence. i) The signal due to the C-2 carbon of **7** appeared at δ 62.0 ppm and the corresponding signal of **8** was shifted up-field to δ 49.8 ppm. Since the signals due to carbon α to a carbonyl group are known to appear at δ 35—65 ppm and to be shifted down-field to δ 90—120 ppm in the enolate form,[6] this result indicates that the negative charge of the salt (**8**) is localized at its C-2 position.[7] ii) The coupling constant of C_2–H is $J=143$ Hz in **7** and is $J=138$ Hz in **8**, indicating that the C-2 carbon of **8** has sp^3 character. If the salt **8** had an enolate (sp^2) structure, the coupling constant of C_2–H would be larger (about 10—20 Hz) than that of **7**.[8] Consequently, the alkylation of **3** is strongly suggested to proceed *via* a pyramidal carbanion **9**.



7 8 9a 9b

Chart 2

The following mechanism is therefore proposed for the stereoselective *cis* alkylation of **3a, b**. Taking into account the repulsive interaction between the anion lobe and sulfinyl lone pair, the structure of the carbanion **9a** would be more favorable than that of the alternative **9b**. If the alkyl halide attacks the carbanion **9a** from the same face as the anion lobe, the reaction would give the observed product **4b**, **5b**, or **6**.

Experimental[9]

***cis*- (3a) and *trans*-2-Methylbenzo[*b*]thiophen-3(2*H*)-one 1-Oxide (3b)**——*m*-Chloroperbenzoic acid (*m*CPBA)

(1.36 g, 6.7 mmol, 85%) was added to a stirred solution of 2-methylbenzo[*b*]thiophen-3(2*H*)-one (1.1 g, 6.7 mmol) in $CHCl_3$ (100 ml) in small portions at 0—5 °C, and stirring was continued for 1.5 h at room temperature. The reaction mixture was washed with 5% $NaHCO_3$ and brine, then dried ($MgSO_4$). After removal of the solvent the residue was chromatographed on silica gel with AcOEt as an eluent to give a mixture (5 : 3) of **3a** and **3b** as an oil (844 mg, 70%). The precipitates triturated with benzene and *n*-hexane (1 : 1) were recrystallized from the same solvent to give **3b** in a pure form, mp 91—93 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1035 (SO). MS *m/e*: 180 (M^+). *Anal.* Calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47. Found: C, 59.72; H, 4.30. The mother liquor of the initial crystallization was evaporated and the residue was further crystallized from benzene and *n*-hexane (1 : 2) to give **3b**. The final mother liquor was concentrated to give pure **3a** as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO), 1040 (SO). MS *m/e*: 180 (M^+). Compound **3a** or **3b** epimerized easily in a protic solvent or in the presence of acid or base to give an equilibrium mixture of **3a** and **3b** (5 : 3), but no epimerization was observed in an aprotic solvent such as benzene, $CHCl_3$, or THF even under refluxing conditions.

***trans*-2-Trideuteriomethyl-*cis*-2-methyl- (4a) and *cis*-2-Trideuteriomethyl-*trans*-2-methyl-benzo[*b*]thiophen-3(2*H*)-one 1-Oxide (4b)**——Potassium *tert*-butoxide (490 mg, 4.4 mmol) was added in one portion to a stirred solution of **3a** or **3b** (775 mg, 4.3 mmol) in anhydrous THF (60 ml) at room temperature, and stirring was continued for 15 min. CD_3I (500 μl, 8 mmol) was added to the solution, and the mixture was stirred for 8—10 h at 40 °C. The reaction was quenched by addition of NH_4Cl (2 g), which was then removed by filtration. The solvent was evaporated off and the residue was chromatographed on silica gel using AcOEt as an eluent to give a mixture of **4a** and **4b** (712—733 mg, 84—87%), mp 49.5—50.5 °C (from benzene and *n*-hexane, 1 : 3). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO), 1040 (SO). MS *m/e*: 197 (M^+). *Anal.* Calcd for $C_{10}H_7D_3O_2S$: C, 60.89; H, 6.64. Found: C, 60.70; H, 6.53.

When *n*-BuLi was used as a base in this reaction, *n*-BuLi (1.05 eq, 15% in *n*-hexane) was added to a solution of **3a, b** in THF at 0—5 °C. When sodium hydride (NaH) was used as a base, a solution of **3** in THF was added to the flask containing NaH (1.1 eq, 50% dispersion in mineral oil; previously washed with 1 ml of petroleum ether) with stirring, and stirring was continued for 20—30 min at room temperature until evolution of hydrogen ceased.

***trans*-2-Ethyl-*cis*-2-methyl- (5a) and *cis*-2-Ethyl-*trans*-2-methyl-benzo[*b*]thiophen-3(2*H*)-one 1-Oxide (5b)**——A mixture of **3a** and **3b** was metallated with *n*-BuLi or NaH by the same method as described above and then ethyl iodide (1.2 eq) was added to the mixture. The reaction mixture was stirred for 8—10 h at 40 °C and worked up to give a mixture of **5a** and **5b** in 67—70% yield as a viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1035 (SO). MS *m/e*: 208 (M^+). High MS Calcd for $C_{11}H_{12}O_2S$: 208.049. Found: 208.052. Oxidation of the mixture of **5a** and **5b** with *m*CPBA (2 eq) gave the same sulfone, mp 63—65 °C (from *n*-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (CO), 1310 (SO_2), 1150 (SO_2). *Anal.* Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 58.76; H, 5.42.

***cis*-2-Methoxycarbonylmethyl-*trans*-2-methylbenzo[*b*]thiophen-3(2*H*)-one 1-Oxide (6)**——Compound **6** was obtained from a mixture of **3a, b** and methyl bromoacetate (1.2 eq) in 86% yield by the same procedure as described above for the preparation of **5a** and **5b**. mp 163—164 °C (from benzene and *n*-hexane, 1 : 2). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (CO), 1705 (CO), 1030 (SO). MS *m/e*: 252 (M^+). *Anal.* Calcd for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.79. Found: C, 57.10; H, 4.70.

Measurement of the ^{13}C-NMR Spectrum of the Salt (8)——Sodium methoxide (1 mmol) in absolute methanol was added to a stirred solution of **7**[5] (166 mg, 1 mmol) in anhydrous THF (3 ml) (*via* a syringe) at room temperature, and stirring was continued for 5—10 min at the same temperature. The solvent was removed under reduced pressure and the residual white powder of **8** was dissolved in THF-d_8. The mixture was stirred for 10—15 min at room temperature and the supernatant was placed in an NMR sample tube. The spectral data are given in Table II.

References and Notes

1) Part I: Y. Tamura, J. Uenishi, and H. Ishibashi, *Chem. Pharm. Bull.*, **32**, 891 (1984).
2) The terms *cis* and *trans* used here refer to the relationship to the S–O bond.
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9) All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotometer. The ^{1}H-NMR spectra were measured on a Hitachi R-22 (90 MHz) spectrometer with tetramethylsilane as an internal standard, and the ^{13}C-NMR spectra were obtained by Fourier transformation carried out on a Hitachi R-900 spectrometer at 22.6 Hz. The low and high resolution mass spectra (MS) were obtained with a JMS-D-300 instrument with a direct inlet system operating at 70 eV.