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One-Flask Synthesis of Sulfides from Alcohols and Alkyl Halides Using Benzoxazoline-2-thione

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The synthesis of sulfides from alcohols and benzoxazoline-2-thione (I) was studied to establish its generality and the mechanism of the reaction. A one-flask synthesis of sulfides from alcohols was developed. According to this procedure, various sulfides were prepared without the use of ill-smelling thiols. Moreover, partial sulfenylation of diols to give sulfenyl alcohols was achieved.

Keywords——one-flask synthesis; benzoxazoline-2-thione; partial sulfenylation; sulfide; sulfenyl alcohol

In the previous paper,[1] we described a new method for conversion of alcohols to sulfides using 2-(alkylthio)benzoxazoles (II). The present work was undertaken as an extension of that study.

In order to evaluate this method, the scope and limitations of the reaction were explored. The reaction involves three steps, that is, *S*-alkylation of benzoxazoline-2-thione (I) to give II, attack of an alcoholate ion at the C-2 position of II to give 2-alkoxybenzoxazole (III), and attack of an alkanethiolate ion on the alkyl group of III to give sulfides and 2-benzoxazolinoate (IV) (Chart 1).

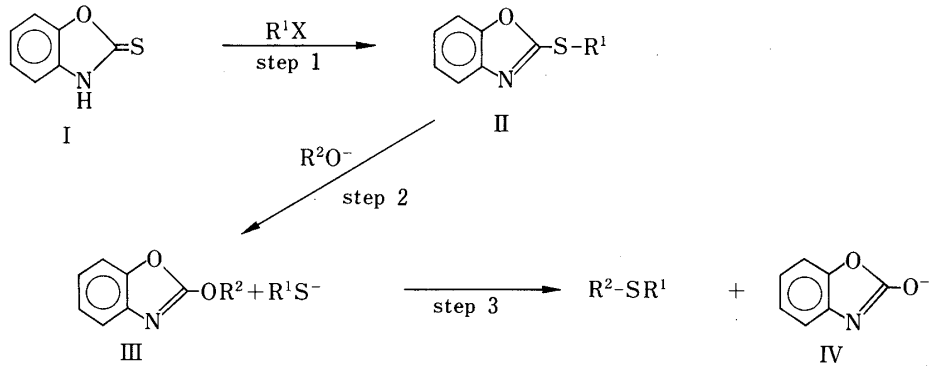
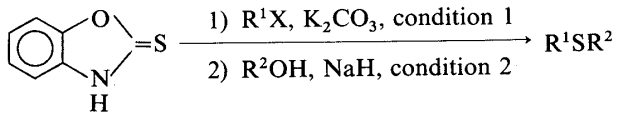


Chart 1

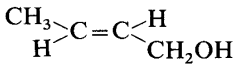
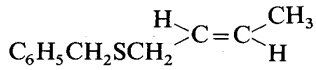
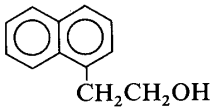
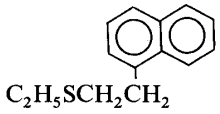
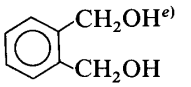
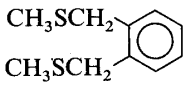
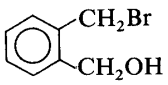
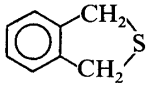
The above mechanism supported by the following facts: stirring of a mixture of I and ethyl bromide in the presence of potassium carbonate at room temperature gave 2-(ethylthio)benzoxazole (IIa) in 75% yield; stirring of a mixture of IIa, sodium hydride, and phenethyl alcohol in the presence of methyl iodide, added to trap ethanethiolate ions generated in the course of this reaction, gave 2-(phenethyloxy)benzoxazole (IIIa) in 40% yield; treatment of IIIa with ethanethiol in the presence of sodium hydride gave IV and ethyl phenethyl sulfide in 70% and 87% yields, respectively.

A study on the limitations of this reaction was undertaken by testing the scope of each

TABLE I. One-Flask Synthesis of Sulfides

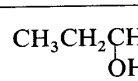
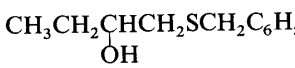
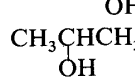
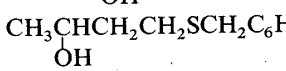
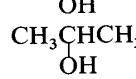
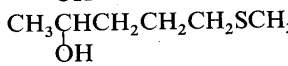
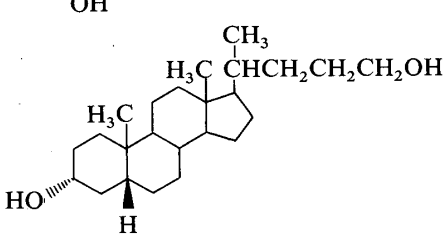
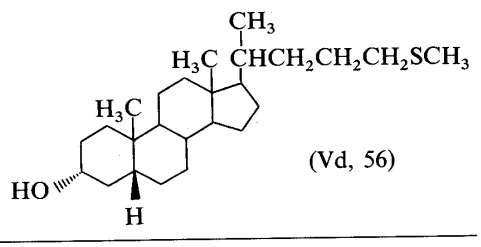


I

Condition 1[a]		Condition 2[b]		Sulfide (R^1SR^2)	
R^1X[c]	Reaction time (h)	R^2OH[c]	Reaction time (h)	Structure	Yield (%)[d]
C_2H_5Br	1.5	$C_6H_5CH_2OH$	2.0	$C_2H_5SCH_2C_6H_5$	77
C_2H_5Br	1.5	$C_6H_5CH_2CH_2OH$	4.0	$C_2H_5SCH_2CH_2C_6H_5$	55
$C_6H_5CH_2Cl$	2.0		2.0		71
C_2H_5Br	1.5		2.0		57
CH_3I	1.0		3.0		58
	1.0	—	1.0		59

a) At room temperature in DMF. b) At 100 °C. c) An equimolar amount of I was used. d) Isolated yields based on I. e) A half molar amount of I was used.

TABLE II. Selective Sulfenylation[a] of Diols

Diol[b]	Alkyl halide[b]	Reaction time (h)[c]	Product[d] (compd. No., yield %)
	$C_6H_5CH_2Cl$	2.0	 (Va, 53)
	$C_6H_5CH_2Cl$	2.0	 (Vb, 49)
	$C_6H_5CH_2Cl$	2.0	 (Vc, 25)
	CH_3I	4.0	 (Vd, 56)

a) Run in the same manner as described in Table I. b) An equimolar amount of I was used. c) At 100 °C. d) Isolated yields based on I.

reaction associated with the three steps. In the first step, *S*-alkylation of I with primary and secondary alkyl halides gave II in moderate yield, while *S*-alkylation of I with a tertiary (*i.e.* *tert*-butyl bromide) or cyclic alkyl halide (*i.e.* cyclohexyl bromide) was unsuccessful. As regards the second step, it has already been reported[2] that the substitution of the alkylthio group of II by an alkoxyl group becomes increasingly difficult in the order of primary,

secondary, and tertiary alkoxyl groups. In the third step, when the alkyl group of III is sterically bulky, the thiolate ion can not attack the alkyl group. For example, heating of a mixture of 2-(cyclohexyloxy)benzoxazole and sodium benzenemethanethiolate in dimethylformamide (DMF) at 100 °C for 16 h did not give benzyl cyclohexyl sulfide.

On the basis of a consideration of the reaction mechanism, shortening of the process was attempted and a variety of sulfides were prepared from alkyl halides and alcohols in one flask. A mixture of I, alkyl halide, and potassium carbonate in DMF was stirred at room temperature and then alcohols and sodium hydride were added, followed by heating at 100 °C to give sulfides in 55—77% yield (Table I).

By means of this one-flask synthetic method, 1,2-bis[(methylthio)methyl]benzene was obtained in 58% yield from 1,2-benzenedimethanol, and 1,3-dihydrobenzo[*c*]thiophene from 2-(bromomethyl)benzyl alcohol in 59% yield. This method was clearly improved and is more convenient than the method reported previously.[1,3]

The results of the study on the scope of the second step reaction suggested the possibility of partial sulfenylation of diols having a primary and a secondary hydroxyl group to give sulfides having a hydroxyl group. Sulfenylation of 1,2-, 1,3-, and 1,4-diols with benzyl chloride produced benzylthio-alcohols (Va—c) in moderate yields (Table II). Further, 24-(methylthio)-5β-cholan-3α-ol (Vd) was prepared from 5β-cholane-3α,24-diol[4] and methyl iodide in 56% yield. This selective sulfenylation of dihydroxy compounds should be useful for the molecular modification of alcohols.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (NMR) were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer, and infrared absorption spectra (IR) on a JASCO A-102 spectrometer. Optical rotations were measured on a JASCO DIP-4 spectrometer. All reactions were run under Ar gas.

One-Flask Synthesis of Sulfides from Alcohols and Alkyl Halides. Typical Procedure; Ehyl 2-(1-Naphthyl)ethyl Sulfide——Ethyl bromide (0.23 ml, 3.1 mmol) was added dropwise to a mixture of benzoxazoline-2-thione (I, 0.45 g, 3.0 mmol) and anhydrous K_2CO_3 (0.42 g, 3.0 mmol) in dry DMF (5 ml) under cooling. The mixture was stirred at room temperature for 1.5 h, then NaH (50% dispersion in oil, 0.15 g, 3.1 mmol) and 2-(1-naphthyl)ethyl alcohol (0.52 g, 3.0 mmol) were added. After evolution of H_2 gas had completely ceased, the mixture was heated at 100 °C for an additional 2 h and then diluted with AcOEt. The organic layer was washed sequentially with 10% NaOH and saturated NaCl solutions and dried over anhydrous $MgSO_4$, and the solvent was removed. Purification of the oily residue by column chromatography (silica gel, hexane) yielded 0.37 g (57%) of the sulfide. *Anal.* Calcd for $C_{14}H_{16}S$: C, 77.73; H, 7.45. Found: C, 77.44; H, 7.32, ^{1}H-NMR (in $CDCl_3$) δ: 1.15 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 2.43 (2H, q, J=7 Hz, $\underline{CH_2}CH_3$), 2.56—2.91 (2H, m, $S\underline{CH_2}CH_2$), 3.07—3.42 (2H, m, $SCH_2\underline{CH_2}$).

The other sulfides shown in Table I were prepared similarly.

Benzyl Ethyl Sulfide: 77%, bp 90—95 °C (8 mmHg).[5]

Ethyl Phenethyl Sulfide: 55%, bp 93—95 °C (5 mmHg).[6]

Benzyl (*E*)-2-Butenyl Sulfide: 71%, bp 100—105 °C (4 mmHg). *Anal.* Calcd for $C_{11}H_{14}S$: C, 74.10; H, 7.91. Found: C, 73.91; H, 7.95. ^{1}H-NMR (in $CDCl_3$) δ: 1.68 (3H, d, J=4 Hz, $=CH\underline{CH_3}$), 2.99 (2H, d, J=4 Hz, $\underline{CH_2}CH=$), 3.63 (2H, s, $\underline{CH_2}C_6H_5$), 5.35—5.66 (2H, m, $\underline{CH=CH}$).

1,2-Bis[(methylthio)methyl]benzene——Methyl iodide (0.19 ml, 3.1 mmol) was added dropwise to a mixture of I (0.45 g, 3.0 mmol) and anhydrous K_2CO_3 (0.42 g, 3.0 mmol) in dry DMF (5 ml) under cooling. After the mixture had been stirred at room temperature for 1 h, NaH (50% dispersion in oil, 0.15 g, 3.1 mmol) was added portionwise under cooling, and then 1,2- bis(hydroxymethyl)benzene (0.21 g, 1.5 mmol) was added under cooling. The whole was heated at 100 °C for 3 h, poured into cold 10% NaOH solution, and extracted with AcOEt. The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$, then the solvent was removed. The resulting oily residue was purified by column chromatography (silica gel, hexane) to give 0.17 g (58%) of the sulfide, bp 95—100 °C (2 mmHg). *Anal.* Calcd for $C_{10}H_{14}S_2$: C, 60.56; H, 7.11. Found: C, 60.34; H, 7.02. ^{1}H-NMR (in $CDCl_3$) δ: 2.05 (6H, s, $CH_3\times2$), 3.91 (4H, s, $CH_2\times2$).

1,3-Dihydrobenzo[*c*]thiophene——A mixture of I (0.30 g, 2.0 mmol), 2-(bromomethyl)benzyl alcohol[1] (0.40 g, 2.0 mmol), and anhydrous K_2CO_3 (0.28 g, 2.0 mmol) was stirred at room temperature for 1 h. Sodium hydride (50%

dispersion in oil, 0.10 g, 2.1 mmol) was added to the mixture under cooling. After heating at 100 °C for 1 h, the mixture was poured into cold 10% NaOH solution and extracted with AcOEt. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. The resulting oily residue was purified by column chromatography (silica gel, hexane) followed by distillation to give 0.16 g (53%) of the sulfide, bp 100—105 °C (7 mmHg).[7]

Reaction of Benzoxazoline-2-thione (I) and Ethyl Iodide——Ethyl bromide (1.50 ml, 20.1 mmol) was added dropwise to a mixture of I (3.02 g, 20.0 mmol) and anhydrous K_2CO_3 (2.76 g, 20.0 mmol) in dry DMF (10 ml) under cooling. After being stirred at room temperature for 1.5 h, the mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. Distillation of the residue afforded 2.68 g (75%) of 2-(ethylthio)benzoxazole (IIa), bp 120—125 °C (8 mmHg).[8]

Reaction of 2-(Ethylthio)benzoxazole (IIa) with Phenethyl Alcohol in the Presence of Sodium Hydride——Under cooling, NaH (50% dispersion in oil, 0.12 g, 2.50 mmol) was added portionwise to phenethyl alcohol (0.24 ml, 2.0 mmol) in dry DMF (5 ml). After evolution of H_2 gas had ceased, IIa (0.30 ml, 2.0 mmol) and MeI (0.15 ml, 2.4 mmol) were sequentially added dropwise to the mixture. After being stirred at room temperature for 2 h, the mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. The resulting oily residue was purified by column chromatography on silica gel (AcOEt: hexane = 1 : 15) to give 0.19 g (40%) of 2-(phenethyloxy)benzoxazole (IIIa), bp 183—185 °C (7 mmHg).[9]

Reaction of 2-(Phenethyloxy)benzoxazole (IIIa) and Ethanethiol with Sodium Hydride——Ethanethiol (0.15 ml, 2.0 mmol) was added dropwise to a suspension of NaH (50% dispersion in oil, 0.11 g, 2.3 mmol) in DMF with cooling. After addition of IIIa (0.48 g, 2.0 mmol), the mixture was stirred at room temperature for 2 h and poured into a mixture of 10% NaOH solution and AcOEt. The resulting mixture was shaken. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. Distillation of the residue afforded 0.29 g (87%) of ethyl phenethyl sulfide, bp 90—95 °C (2 mmHg).[5] The aqueous layer was acidified with 10% HCl solution and extracted with AcOEt. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, then the solvent was removed. Recrystallization of the residue from hexane gave 0.19 g (70%) of benzoxazolin-2-one, mp 137—139 °C.[10]

Partial Sulfenylation of Diols. Typical Procedure; 1-(Benzylthio)-2-butanol (Va)——Benzyl chloride (0.23 ml, 2.0 mmol) was added to a mixture of I (0.30 g, 2.0 mmol) and anhydrous K_2CO_3 (0.28 g, 2.0 mmol) in dry DMF (6 ml). The mixture was stirred at room temperature for 2 h, then NaH (50% dispersion in oil, 0.15 g, 3.1 mmol) and 1,2-butanediol (0.18 g, 2.0 mmol) were added. The mixture was heated at 100 °C for 2 h, poured into ice-water, and extracted with AcOEt. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, then the solvent was removed. The resulting oily residue was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 15) to give 0.21 g (53%) of the sulfide, bp 110—111 °C (4 mmHg). *Anal.* Calcd for $C_{11}H_{16}OS$: C, 67.30; H, 8.21: Found: C, 67.02; H, 8.17. IR $\nu_{max}^{liq.}$ cm^{-1}: 3450 (OH). ^{1}H-NMR (in $CDCl_3$) δ: 0.92 (3H, pseudo t, J=7 Hz, CH_3), 1.22—1.78 (2H, m, $\underline{CH_2}CH_3$), 2.35—2.62 (2H, m, $\underline{CH_2}SCH_2C_6H_5$), 2.79 (1H, br, OH), 3.33—3.82 (1H, m, $\underline{CH}$–OH), 3.72 (2H, s, $\underline{CH_2}C_6H_5$).

The other sulfenyl alcohols shown in Table II were similarly prepared.

4-(Benzylthio)-2-butanol (Vb): 49%, bp 130—135 °C (2 mmHg). *Anal.* Calcd for $C_{11}H_{16}OS$: C, 67.30; H, 8.21. Found: C, 67.10; H, 8.29. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400 (OH). ^{1}H-NMR (in $CDCl_3$) δ: 1.15 (3H, d, J=6 Hz, $CH\underline{CH_3}$), 1.46—1.92 (2H, $\underline{CH_2}CH$–OH), 2.51 (2H, t, J=7 Hz, $\underline{CH_2}SCH_2C_6H_5$), 2.83 (1H, br, OH), 3.75—4.08 (1H, m, $\underline{CH}$–OH), 3.72 (2H, s, $\underline{CH_2}C_6H_5$).

5-(Benzylthio)-2-pentanol (Vc): 25%, bp 130—135 °C (4 mmHg). *Anal.* Calcd for $C_{12}H_{18}OS$: C, 68.53; H, 8.63. Found: C, 68.24; H, 8.52. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400 (OH).

24-(Methylthio)-5β-cholan-3α-ol (Vd)——Methyl iodide (0.13 ml, 2.0 mmol) was added dropwise to a mixture of I (0.30 g, 2.0 mmol) and anhydrous K_2CO_3 (0.28 g, 2.0 mmol) in dry DMF (5 ml). After the mixture had been stirred at room temperature for 2 h, NaH (50% dispersion in oil, 0.15 g, 3.1 mmol) was added portionwise and the 5β-cholan-3α,24-diol[4] (0.36 g, 1.0 mmol) in dry DMF (5 ml) was added dropwise. After evolution of H_2 gas had ceased completely, the mixture was heated at 100 °C for 4 h and then diluted with AcOEt. The organic layer was washed sequentially with 10% NaOH and saturated NaCl solutions and dried over anhydrous $MgSO_4$, and the solvent was removed. The resulting residue was purified by column chromatography on silica gel (AcOEt : hexane = 1 : 7) to give 0.22 g (56%) of the sulfide, mp 88—90 °C. $[\alpha]_D^{20}$ +34.7° (c=2.0, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{44}OS$: C, 76.47; H, 11.29. Found: C, 76.18; H, 11.57. IR ν_{max}^{Nujol} cm^{-1}: 3220 (OH). ^{1}H-NMR (in $CDCl_3$) δ: 2.07 (3H, s, SCH_3), 2.47 (2H, t, J=7 Hz, CH_2S), 3.31—4.04 (1H, m, $W1/2$=20 Hz, CH–OH). MS m/z: 392 (M^+), 377 ($M^+ - CH_3$), 374 ($M^+ - H_2O$), 359 ($M^+ - CH_3 - H_2O$).

References and Notes

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