A New Synthesis of β-Keto Sulfoxides from Chloromethyl Aryl Sulfoxide and Aldehydes

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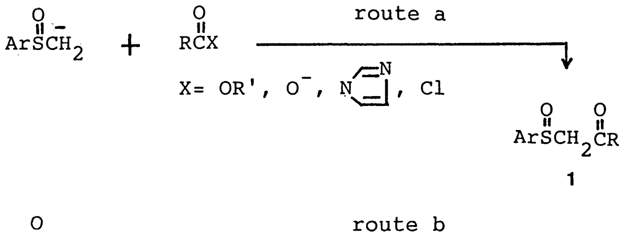
Synopsis. Addition of the carbanion of chloromethyl aryl sulfoxide to aldehyde gave the adduct, which was treated with three-equivalents of lithium diisopropylamide (LDA) to afford β-keto sulfoxide in high overall yield.

Sulfoxides have recently come to be used widely in synthetic organic chemistry,[1] and, in particular, optically active sulfoxides have been shown to be a most useful chiral auxiliary in the synthesis of optically active compounds. Solladie et al. have reported on stereoselective reduction[2] or alkylation[3] of the carbonyl group in optically active β-keto sulfoxides giving optically active alcohols and the use of reactions in the synthesis of natural products.[4]

β-Keto sulfoxides are usually prepared from the carbanion of methyl aryl sulfoxide with carboxylic acid derivatives such as carboxylic esters,[2d,5] lithium carboxylates,[6] imidazolides,[2c,4b] and acid chlorides[7] (Scheme 1; route a); however, in some cases the yields are not satisfactory. Recently, we have reported some new synthetic methods using 1-chloroalkyl aryl sulfoxides.[8] In continuation of our study concerning the use of 1-chloroalkyl aryl sulfoxides in organic synthesis, we present here a new synthesis of β-keto sulfoxides from chloromethyl aryl sulfoxide and **aldehydes** (Scheme 1; route b).

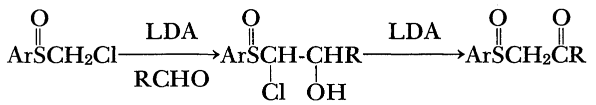


Scheme 1.

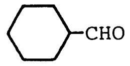
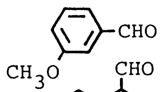
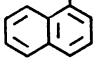
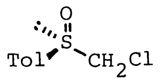
Results and Discussion

A representative example of this procedure using chloromethylphenyl sulfoxide **2**[9] and decanal as the aldehyde is reported (Scheme 2). Addition of the carbanion of **2**, using LDA as a base, in THF at −60 °C to decanal gave the chloro alcohol **3** in quantitative yield as a mixture of two diastereomers. The adduct **3** was again treated with three-equivalents of LDA in THF at −60 to −45 °C for 1 h. The reaction mixture slowly changed in color from light yellow to bright orange-red; quenching the reaction with saturated aqueous NH_4Cl gave the β-keto sulfoxide **4** in 95% yield as colorless crystals. Representative exam-

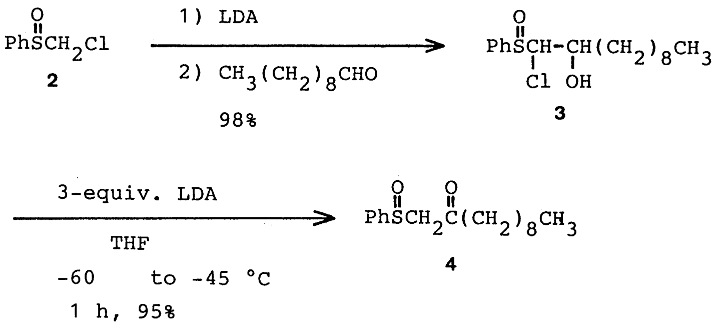
Table 1. Synthesis of β-Keto Sulfoxides from Chloromethyl Aryl Sulfoxide and Aldehydes



$$\mathrm{Ar\overset{O}{\overset{\|}{S}}CH_2Cl \xrightarrow[RCHO]{LDA} Ar\overset{O}{\overset{\|}{S}}\underset{Cl}{\underset{|}{C}}H\text{-}\underset{OH}{\underset{|}{C}}HR \xrightarrow{LDA} ArSCH_2\overset{O}{\overset{\|}{C}}R}$$

$\mathrm{Ar\overset{O}{\overset{\|}{S}}CH_2Cl}$	RCHO	Chloro Alcohol Yield (%)[a]	β-Keto Sulfoxide Yield (%)[b]
$\mathrm{Ph\overset{O}{\overset{\|}{S}}CH_2Cl}$	$CH_3(CH_2)_8CHO$	98	95
	CH_3CH_2CHO	85	71 (64)[g]
	$PhCH_2CH_2CHO$	87	91
		87	98
	$(CH_3)_3CCHO$	96	93[c]
	PhCHO	92	78[d] (67)[g]
		98	93[e]
		95	—[f]
	$CH_3(CH_2)_4CHO$	95	92

a) Isolated yield. b) Isolated yield. Unless otherwise noted the reactions were carried out at −60 to −45 °C for 1 h. c) Conditions: at −60 to 0 °C for 1 h, then at 0 °C for 30 min. d) Conditions: at −60 to 0 °C for 1.5 h. e) Conditions: at −65 to −20 °C for 2 h. f) A complex mixture. g) The yield obtained from the one-pot reaction (see text).



Scheme 2.

ples of this method are shown in Table 1.

This reaction can be carried out as a one-pot reaction; after the addition of aldehyde to the carbanion of **2**, two-equivalents of LDA was added to the reaction mixture to give the desired product in reasonable yield (see Table 1). While this reaction can be carried out as a one-pot reaction, the two-step procedure described above was found to give much cleaner reaction mixture.

The formation of β-keto sulfoxide is considered to take place via dehydrochlorination of the alcoholate of the chloro alcohol with LDA.

Experimental

All melting points are uncorrected. The IR spectra were measured directly on a NaCl plate or in KBr disks with a Hitachi 215 spectrometer. ^{1}H NMR spectra were measured in a $CDCl_3$ 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. Silica gel BW-127 ZH (Fuji-Devison) containing a 2% fluorescence reagent (254) and a quartz column were used for column chromatography; products showing ultraviolet (UV) absorption were detected by UV irradiation. THF was dried with sodium diphenylketyl; diisopropylamine was dried over CaH_2 and distilled.

General Procedure for the Preparation of β-Keto Sulfoxides from Chloromethyl Aryl Sulfoxide and Aldehydes. A typical procedure is described for the synthesis of 1-phenylsulfinyl-2-undecanone (**4**) from chloromethyl phenyl sulfoxide and decanal. To a solution of LDA (6 mmol) in 10 ml of THF at −65 °C was added with stirring a solution of chloromethyl phenyl sulfoxide (873 mg; 5 mmol) in 2 ml of THF. The reaction mixture was stirred at −65 °C for 15 min, then decanal (6 mmol) was added to the mixture. The mixture was stirred for 5 min, then the reaction was quenched with saturated aqueous NH_4Cl. The whole was extracted with chloroform. The usual workup followed by silica-gel column chromatography gave the chloro alcohol **3** (1.62 g; 98%) as colorless crystals (diastereomeric mixture). IR (KBr): 3400 (OH), 1045 (SO) cm^{-1}; ^{1}H NMR δ=0.85 (3H, t, J=7 Hz), 1.0—2.0 (16H, m), 4.0—4.7 (2H, m), 7.4—7.8 (5H, m).

A solution of **3** (166 mg; 0.5 mmol) in 1 ml of THF was added dropwise to a solution of LDA (1.5 mmol) in 3 ml of THF at −60 °C with stirring. The reaction mixture was stirred at −60 to −45 °C for 1 h, then the reaction was quenched with saturated aqueous NH_4Cl. The whole was extracted with benzene-ether. The usual workup followed by silica-gel column chromatography (hexane : AcOEt=4 : 1) gave 139 mg (95%) of **4** as colorless crystals. Mp 81—83 °C; IR (KBr): 1715 (CO), 1040 (SO) cm^{-1}; ^{1}H NMR δ=0.87 (3H, t, J=7 Hz), 1.0—1.9 (14H, m), 2.46 (2H, m), 3.76, 3.86 (each 1H, d, J=13 Hz), 7.4—7.7 (5H, m); MS m/z (%) 294 (M$^+$, 2), 277 ([M−OH]$^+$, 45), 182 (22), 169 (40), 125 (100); Found: C, 69.62; H,9.17; S, 11.02%. Calcd for $C_{17}H_{26}O_2S$: C, 69.34; H, 8.90; S, 10.89%.

1-Phenylsulfinyl-2-butanone. Colorless crystals; mp 61—62.5 °C (AcOEt-hexane); IR (KBr): 1720 (CO), 1040 (SO) cm^{-1}; ^{1}H NMR δ=1.01 (3H, t, J=7 Hz), 2.50 (2H, t, J=7 Hz), 3.77, 3.85 (each 1H, d, J=13 Hz), 7.4—7.7 (5H, m); MS m/z (%) 196 (M$^+$, 30), 125 ([M−C_4H_7O]$^+$, 100), 97 (17); Found: C, 61.23; H, 6.23; S, 16.34%. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; S, 16.33%.

4-Phenyl-1-(phenylsulfinyl)-2-butanone. Colorless oil; IR (neat): 1720 (CO), 1095, 1050 (SO) cm^{-1}; ^{1}H NMR δ=2.81 (4H, m), 3.72, 3.82 (each 1H, d, J=13 Hz), 7.0—7.3 (5H, m), 7.3—7.7 (5H, m); MS m/z (%) 272 (M$^+$, 3), 255 ([M−OH]$^+$, 7), 147 ([M−PhSO]$^+$, 97), 91 (100); Found: m/z 272.0861. Calcd for $C_{16}H_{16}O_2S$: M, 272.0870.

1-Cyclohexyl-2-(phenylsulfinyl)ethanone. Colorless crystals; mp 78—80 °C (AcOEt-hexane); IR (KBr): 1685 (CO), 1030 (SO) cm^{-1}; ^{1}H NMR δ=1.0—2.0 (10H, m), 2.30 (1H, m), 3.80, 3.97 (each 1H, d, J=13 Hz), 7.4—7.7 (5H, m); MS m/z (%) 250 (M$^+$, 2), 233 ([M−OH]$^+$, 63), 125 ([M−PhSO]$^+$, 100); Found: C, 67.17; H, 7.29; S, 12.62%. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25; S, 12.81%.

3,3-Dimethyl-1-(phenylsulfinyl)-2-butanone. Colorless crystals; mp 67—69 °C (AcOEt-hexane); IR (KBr): 1710 (CO), 1050 (SO) cm^{-1}; ^{1}H NMR δ=1.06 (9H, s), 3.84, 4.15 (each 1H, d, J=15 Hz), 7.4—7.8 (5H, m); Found: C, 64.33; H, 7.31; S, 14.36%. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29%.

1-Phenyl-2-(phenylsulfinyl)ethanone. Colorless crystals; mp 69—72 °C (AcOEt-hexane); IR (KBr): 1675, 1665 (CO), 1040, 1030 (SO) cm^{-1}; ^{1}H NMR δ=4.29, 4.54 (each 1H, d, J=15 Hz), 7.3—7.9 (10H, m); MS m/z (%) 244 (M$^+$, 54), 196 ([M−SO]$^+$, 18), 125 ([M−C_8H_7O]$^+$, 100); Found: C, 68.67; H, 4.85; S, 13.12%. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12%.

1-(3-Methoxyphenyl)-2-(phenylsulfinyl)ethanone. Colorless oil; IR (neat): 1680 (CO), 1090, 1050 (SO) cm^{-1}; ^{1}H NMR δ=3.79 (3H, s), 4.28, 4.51 (each 1H, d, J=14 Hz), 7.0—7.7 (9H, m); MS m/z (%) 274 (M$^+$, 52), 226 ([M−SO]$^+$, 34), 135 ([M−C_7H_7OS]$^+$, 100); Found: m/z 274.0663. Calcd for $C_{15}H_{14}O_3S$: M, 274.0662.

(−)-1-(*p*-Tolylsulfinyl)-2-heptanone. Colorless crystals; mp 73—75 °C (AcOEt-hexane) (lit,[2d] mp 74—75 °C); $[\alpha]^{25}_{D}$ −183.3° (c 0.84, $CHCl_3$) (lit,[2d] $[\alpha]_D$ +190°); IR (KBr): 1710 (CO), 1095, 1045 (SO) cm^{-1}; ^{1}H NMR δ=0.86 (3H, t, J=7 Hz), 1.0—1.7 (6H, m), 2.3—2.6 (2H, m), 2.41 (3H, s), 3.73, 3.65 (each 1H, d, J=13 Hz), 7.2—7.5 (4H, m).

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