Synthesis and Stereomutation of Optically Active α-Cyanosulphoxides

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Reaction of (−)-menthyl (S)-toluene-p-sulphinate with nitriles and lithium NN-di-isopropylamide (LDA) in 1 : 1 : 1 and 1 : 2 : 1 ratios affords optically active α-cyano- and α-cyano-β-imino-sulphoxides, respectively. α-Cyano-benzyl sulphoxide racemizes through a homolytic process in a temperature range (35—50 °C) well below that required for benzyl aryl sulphoxides.

α-FUNCTIONALIZED sulphoxides are useful substrates for asymmetric synthesis of a series of optically active derivatives [1-3] either via reaction of the corresponding carbanions with electrophiles or via nucleophilic attack at

toluene-p-sulphinate (4) to the α-cyanocarbanion (2 mol equiv.), prepared from the nitrile and lithium NN-di-isopropylamide (LDA) (Scheme 1).

In the case of prochiral nitriles the diastereoisomeric
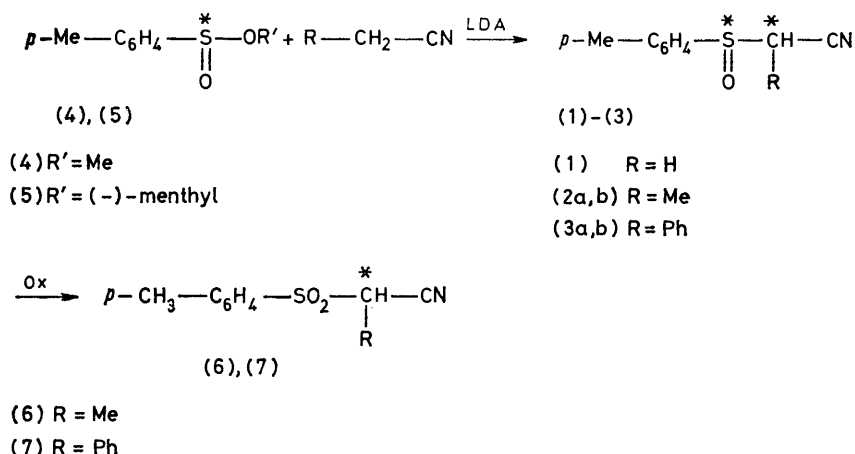
SCHEME 1

the substituent α to the sulphinyl group. In this line is the synthesis of α-cyano-sulphoxides, so far virtually unknown.[4,5] They have been previously prepared as a racemic mixture by oxidation of the corresponding

PhCH₂—SO—C(Ph)₂—SO—CH₂Ph

(10)

(11) cis – Me
(12) trans – Me
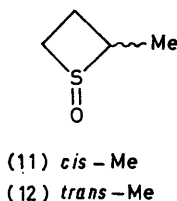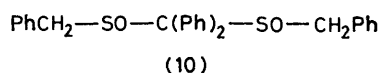
sulphides.[4] On the other hand, for the only example of optically active α-cyanosulphoxide,[5] namely α-cyano-methyl p-tolyl sulphoxide (1), no synthetic procedure is given.

In this paper we report that α-metallated nitriles react with sulphinate esters to afford the title compounds in excellent yields (see Tables). The reactions were carried out in anhydrous tetrahydrofuran by adding methyl

sulphoxides (2a, b) and (3a, b) are formed in unequal amounts (see Table 1). Starting from optically pure (−)-menthyl (S)-toluene-p-sulphinate (5), optically active α-cyano-sulphoxide are obtained. As expected on the basis of steric factors, the reaction is slower with respect to the methyl analogue (4); yields and optical rotations are reported in Table 1.

The reaction proceeds with a very high stereospecificity; indeed the optical purity of compounds (1)—(3), determined with the aid of the chiral shift reagent Eu(tfc)₃, was found to be ≥95%. The ¹H n.m.r. spectra of racemic (1)—(3) in the presence of Eu(tfc)₃ showed two different sets of peaks corresponding to the enantiomers. The (+)-(R) absolute configuration at sulphur of compounds (1)—(3) can be assigned on the basis of the reasonable assumption that reaction of (5) with metal-
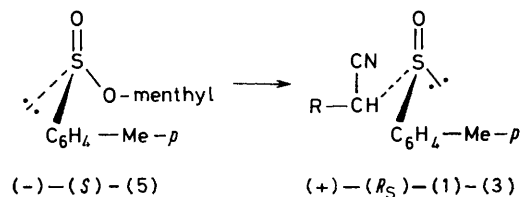
SCHEME 2

lated nitriles proceeds with inversion of chirality (Scheme 2), as already established in various nucleophilic substitutions in sulphinate esters.[6]

In the conversion (5) ⟶ (2), (3), transmission of chirality from sulphur to carbon is at work, as indicated by the formation of optically active α-cyanosulphones (6), (7) obtained *via* oxidation of the diastereoisomeric mixture of the parent sulphoxide (see Table 1).*

TABLE 1

α-Cyanosulphoxides (1)—(3) and α-cyanosulphones (6), (7)

Sulphoxide	Yield (%)	$[\alpha]_D^{25}$ ^{a} (°)	Diastereo-isomeric ratio ^{b}	Sulphone	$[\alpha]_D^{25}$ ^{a} (°)
(1)	81 ^{c}				
(2a), (2b)	84 ^{c}		9 : 11		
(3a), (3b)	69 ^{c}		9 : 11		
(1)	68 ^{d}	+141			
(2a), (2b)	67 ^{d}	+97 ^{e}	9 : 11	(6)	+1.7
(3a), (3b)	71 ^{d}	+112 ^{e}	9 : 11	(7)	+1.5

^{a} In CHCl$_3$. ^{b} By ^{1}H n.m.r. ^{c} From methyl toluene-*p*-sulphinate. ^{d} From (−)-menthyl toluene-*p*-sulphinate. ^{e} As a mixture of diastereoisomers.

Thermal Stability.—α-Cyanosulphoxides (1) and (2a, b) are optically stable; indeed no change in their optical rotations was observed after heating at reflux for 60 min in ethyl acetate. On the contrary the benzyl derivative (3) is ' thermolabile ' and easily undergoes racemization and epimerization. Indeed crystallization from ethyl acetate of a racemic mixture of (3a) and (3b) (diastereoisomeric ratio 3 : 7) afforded diastereoisomerically pure (3a) (30%), the diastereoisomeric ratio (3a) : (3b) in the mother liquors being 1 : 3. Thus the overall diastereoisomeric ratio changes from 3 : 7 to 53 : 47. Starting from optically active (3a), (3b), the process leads to complete racemization. Furthermore the epimerization is accompanied by some decomposition (*ca.* 15%), which becomes predominant on prolonged heating in ethyl acetate, affording as major products 2,3-diphenyl-succinonitrile (8) and S-*p*-tolyl toluene-*p*-thiosulphonate (9) (see Experimental section). The observation that for the α-cyanosulphoxide (3a, b) both epimerization and racemization occur under very mild conditions is striking. Only allenic sulphoxides,[7] benzophenone bis(benzylthio-acetal S-oxide) (10),[8] and *cis*- (11) and *trans*- (12) -2-methylthietan 1-oxide [9] have been shown to epimerize at room temperature. Rates of racemization for compound (3) were measured in acetone at four temperatures and the results are collected in Table 2.

Mislow and his co-workers have studied [10] the mechanisms of thermal stereomutation of sulphoxides, namely pyramidal inversion, homolytic scission, and [2,2]-sigmatropic rearrangement involving formation of an achiral sulphenate ester.

The activation parameters reported in Table 2,

* The enantiomeric purity of sulphones (6), (7) can be inferred from the diastereoisomeric ratio of the starting sulphoxides (2), (3).

TABLE 2

Rate constants and activation parameters for the racemization of (3)

$T/^\circ$C	$10^5 k/\text{s}^{-1}$	Activation parameters	
35	3.1	$\Delta H^{\ddagger}$	28.1 kcal mol^{-1}
40	6.4	$\Delta S^{\ddagger}$	12.2 cal mol^{-1} K^{-1}
45	13.5	$\Delta G^{\ddagger}$	24.2 kcal mol^{-1}
50	27.6	log (A/s^{-1})	15.9

especially the large positive value of the entropy of activation and the high value of the A factor, together with the formation of decomposition products (*ca.* 10%), clearly indicate that stereomutation occurs by dissociation–recombination involving radicals, each act of homolysis involving racemization at both chiral centres (Scheme 3). The radical mechanism has been previously shown [10] to occur in the case of benzyl *p*-tolyl sulphoxide in a temperature range (130—150 °C) well above that required for racemization of the sulphoxide (3).
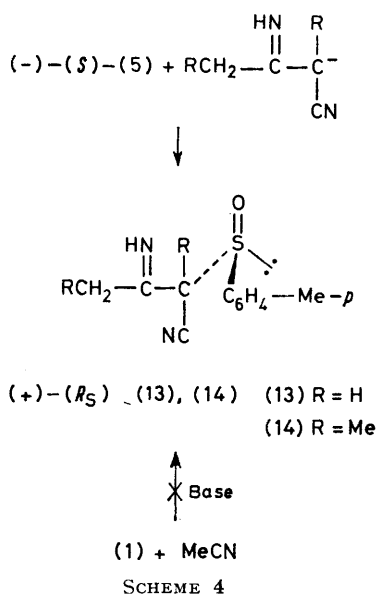

SCHEME 3
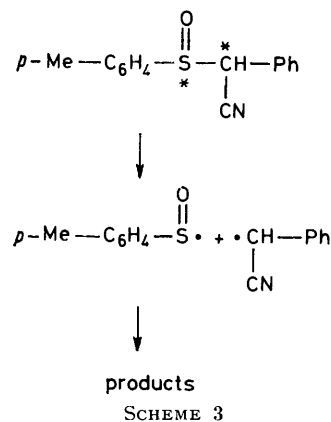
Synthesis of α-Cyano-β-iminosulphoxides.—In the reaction of sulphinate esters (4), (5) with LDA the nitrile : base ratio is critical, and can divert the reaction to the formation either of α-cyanosulphoxides or of α-cyano-β-imino-derivatives. Indeed with a 2 : 1 ratio, compounds (13) and (14) are obtained starting from acetonitrile and propionitrile, respectively.

α-Cyano-β-iminosulphoxides derive from self-condensation of the nitrile followed by nucleophilic attack at the sulphur atom of the sulphinate ester. The alternative pathway, *i.e.* attack on the nitrile by α-metallated-α-cyanosulphoxides is ruled out since (1) does not react with acetonitrile in the presence of bases such as LDA, NaH, MeONa, or Bu^{t}OK.

Starting from diastereoisomerically pure (−)-(S)-(5), optically active derivatives (13), $[\alpha]_D^{25}$ +34.0° (c, 1 in tetrahydrofuran), and (14), $[\alpha]_D^{25}$ +25.0° (c 1 in tetrahydrofuran), are obtained in 47% and 60% yield, respectively. The (+)-(R) absolute configuration at sulphur can be assigned to (13) and (14) on the assumption that nucleophilic substitution proceeds with inversion of chirality (see above). The reaction is highly stereoselective, indeed the α-cyano-β-iminosulphoxide (14) is diastereoisomerically pure by ^{1}H and ^{13}C n.m.r. spectro-

scopy, whereas (13) is a mixture of two diastereoisomers in a 23 : 77 ratio.

Compound (13) must be in equilibrium with the tautomeric enamine, present in amounts not detectable by n.m.r., since a sample of (13) in $CDCl_3$–D_2O shows slow H–D exchange of the proton α to the sulphinyl group.

HN   R
 ‖ |
(-)-(S)-(5) + RCH₂—C—C⁻
              |
              CN

↓

              O
              ‖
    HN   R   S
     ‖ | ╱ ╲
RCH₂—C—C—C₆H₄—Me-p
         |
         NC

(+)-(R_S) ⌐(13), (14)   (13) R = H
                          (14) R = Me

↑ Base

(1) + MeCN

SCHEME 4

EXPERIMENTAL

Light petroleum refers to the fraction of b.p. 40—60 °C. Ether was dried over sodium and tetrahydrofuran was distilled from lithium aluminium hydride. Di-isopropylamine was distilled from potassium hydroxide, n-butyl-lithium was used as ca. 2M-solutions in hexane. Extractions were performed using dichloromethane and extracts were dried over sodium sulphate. I.r. spectra were recorded on a Perkin-Elmer 377 spectrometer. ¹H N.m.r. spectra were recorded on a Varian HA 100 instrument for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Acetonitrile, propionitrile, phenylacetonitrile, and ethyl acetate were distilled over molecular sieves. (−)-Menthyl (−)-toluene-p-sulphinate [11] had m.p. 105—106 °C, $[\alpha]_D^{25}$ −202° (c, 2 in Me_2CO) {lit.,[11] $[\alpha]_D^{25}$ −202° (c 2 in Me_2CO)}. Methyl toluene-p-sulphinate had b.p. 135 °C at 14 mmHg, n_D^{20} 1.540 7 [lit.,[12] b.p. 135 °C at 14 mmHg, n_D^{20} 1.543 6].

α-Cyanosulphoxides (1)—(3).—n-Butyl-lithium (2 mmol) in n-hexane was added dropwise at −78 °C to a stirred

solution of di-isopropylamine (2 mmol) in tetrahydrofuran (10 ml). The mixture was kept at −10 °C for 30 min, cooled to −78 °C, and the appropriate nitrile (2 mmol) in tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to reach room temperature. The toluene-p-sulphinate ester (1 mmol) in tetrahydrofuran (5·ml) was added at −78 °C. The mixture was stirred for 2 h at −70 °C and then for 1—2 h at room temperature in the case of (4), for 12—18 h in the case of (5). After quenching with saturated aqueous ammonium chloride, the organic layer was separated off and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried and concentrated and the residue was chromatographed on silica with ether–light petroleum as eluant. Yields, specific rotations, and diastereoisomeric ratio are reported in Table 1, physical and analytical data in Table 3.

Oxidation of α-Cyanosulphoxides (2), (3) to α-Cyanosulphones (6), (7).—The α-cyanosulphoxides were oxidized with a stoicheiometric quantity of m-chloroperbenzoic acid at 20 °C for 18 h in dichloromethane and purified by column chromatography on silica (light petroleum–ether as eluant). Yields were in the range 90—95%; optical rotations are reported in Table 1, physical properties and analytical data in Table 3.

Synthesis of α-Cyano-β-Iminosulphoxides (13)—(14).—n-Butyl-lithium (2 mmol) in n-hexane was added dropwise at −78 °C to a stirred solution of di-isopropylamine (2 mmol) in tetrahydrofuran (10 ml). The mixture was kept for 30 min below −10 °C, cooled to −78 °C, and acetonitrile or propionitrile (4 mmol) in tetrahydrofuran was added. The mixture was allowed to reach room temperature, cooled again to −78 °C, and the toluene-p-sulphinate ester (4) or (5) (1 mmol) in tetrahydrofuran (5 ml) was added. The mixture was kept at −78 °C for 2 h and then at room temperature overnight. After quenching with saturated aqueous ammonium chloride, the organic layer was separated off and the aqueous layer extracted with dichloromethane. The organic phases were dried and evaporated, and the residue was chromatographed on silica with ether–light petroleum as eluant. Starting from diastereoisomerically pure (−)-(S)-(5) the α-cyano-β-iminosulphoxide (14) was seen to be diastereoisomerically pure by ¹H and ¹³C n.m.r.; (13), however, was a mixture of two diastereoisomers in a 23 : 77 ratio. Physical and analytical data are reported in Table 3.

Thermal Stability of (3).—The racemic α-cyano-sulphoxide (3a, b) (diastereoisomeric ratio 3 : 7) (0.23 g) was dissolved in ethyl acetate (10 ml) and refluxed for 60 min. After cooling, diastereoisomerically pure (3a) (0.06 g) was obtained. The mother-liquors were evaporated and the residue was chromatographed on silica with ether–light petroleum as eluant to afford a mixture of diastereoisomers

TABLE 3

Physical and analytical data for compounds (1)—(3), (6), (7), (13), and (14)

| Compound | Found (%) | | | Formula | Required (%) | | | m.p. (°C) | [n_D^{20}] |
	C	H	N		C	H	N	Racemic	Optically active
(1)	60.3	5.0	7.8	C_9H_9NOS	60.3	5.05	7.8	65—67	64—65
(2) a	62.1	5.8	7.25	$C_{10}H_{11}NOS$	62.15	5.75	7.25	[1.5687]	[1.5687]
(3) a	70.5	5.1	5.4	$C_{15}H_{13}NOS$	70.6	5.1	5.5	130—132	131—132
(6)	57.25	5.25	6.7	$C_{10}H_{11}NO_2S$	57.4	5.3	6.7	43—44	43—44
(7)	66.35	4.75	5.1	$C_{15}H_{13}NO_2S$	66.4	4.8	5.15	140	140
(13) a	60.1	5.6	12.8	$C_{11}H_{12}N_2OS$	60.0	5.5	12.7	100—103	100—103
(14)	62.8	6.4	11.2	$C_{13}H_{16}N_2OS$	62.9	6.5	11.3	83—84	82—84

a As a mixture of diastereoisomers.

(3a), (3b) (0.140 g) in a 1 : 3 ratio, and minor amounts of 2,3-diphenylsuccinonitrile, m.p. 220 °C [lit.,[13] 239—240 °C for the *meso-* and m.p. 164 °C for the (±)-form], and 2-*p*-tolyl toluene-*p*-thiosulphonate, m.p. 74 °C (lit.,[14] 74 °C).

Kinetics of Racemization of (3).—A solution of (3) (0.2 mmol) in acetone (10 ml) was contained in a temperature-controlled polarimeter cell, and rotations were continuously recorded as a function of time over a period of 2—4 half lives. End-point values were determined after at least 10 half-lives. First-order rate constants and activation parameters, calculated as described in ref. 15, are reported in Table 3.

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