Reaction of Lithioenamines with Sulphinate Esters. Stereospecific and Stereoselective Synthesis of β-Enamino and β-Imino Sulphoxides

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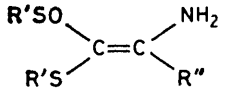
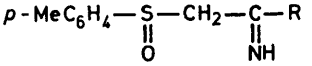
Reaction of lithioenamines with (−)-menthyl (*S*)-toluene-*p*-sulphinate affords optically active β-enamino and/or β-imino sulphoxides, depending on the structure of the starting imine. The optical stability of both these classes of compounds is investigated.

HIGHLY successful asymmetric carbon–carbon bond formation has been achieved by exploiting chiral enamines as intermediates.[1] To the best of our knowledge the only source of chirality in this class of compounds is an asymmetrically substituted carbon atom. On the basis of the widely recognized [2] ability of chiral



(1)



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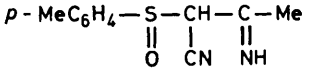


(3)

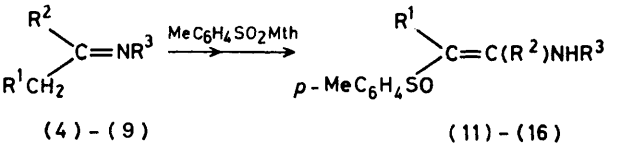
sulphur moieties to promote efficient enantioselective transformations, a synthesis of optically active β-enamino sulphoxide is of interest.

Only a few examples, even in the racemic form, of enamino or imino sulphoxides are known so far. Namely, Tsuchihashi and his co-workers reported the synthesis of compounds of type (1) by the reaction of metallated methyl methylthiomethyl sulphoxide with nitriles.[3,†] A structural analogue of compound (1) was obtained by oxidation of the corresponding enamino sulphide.[4] On the other hand, reaction of optically active α-lithiomethyl sulphoxides with nitriles lead to the imino-derivatives (2).[5] β-Imino sulphoxides, such as compound (3), were also obtained by the reaction of nitriles (2 mol equiv.) with lithium di-isopropylamide (LDA) (1 mol equiv.) and a sulphinic ester.[6] At least in the latter case the enamine tautomer, although definitely present, was not detectable by spectroscopic means.[6]

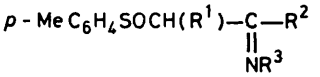
A completely different approach was exploited by Stirling and his co-workers [7] and Truce and Markley [8] in the synthesis of racemic β-enamino sulphoxides by the addition of primary and secondary amines to acetylenic and allenic sulphoxides (*vide infra*). A direct approach to optically active β-enamino sulphoxides can be envisaged in the reaction of readily available lithioenamines [9] with diastereomerically pure sulphinate esters.

In order to check this hypothesis we synthesized the imines (4)—(9) by standard methods (see Experimental section). Treatment of compounds (4)—(9) with LDA (2 mol equiv.) in tetrahydrofuran (THF) and subsequent reaction with (−)-(menthyl) (*S*)-toluene-*p*-sulphinate (10) (1 mol equiv.) afforded the corresponding enamines (11)—(16) and/or imines (17)—(19) (Scheme 1) in fair to good yields (see Table 1), which were isolated directly from the reaction mixture in a satisfactorily pure state (see Experimental section). The nature of the reaction product(s) depends mainly on the structural features of the starting imines.

Indeed, from the aldimines (4)—(6) only the enamine derivatives (11)—(13) were obtained, while from the aldimines (7) and (8) mixtures of the enamines (14) and (15) and of the corresponding imines (17) and (18) were obtained in 4 : 1 and 3 : 1 ratios, respectively. On the



(4)-(9) (11)-(16)

and / or 

(17)-(19)

	R^1	R^2	R^3
(4), (11)	Me	H	c-C_6H_{11}
(5), (12)	Me	H	Bu^t
(6), (13)	Me	H	Pr^i
(7), 1(4), (17)	H	H	c-C_6H_{11}
(8), (15), (18)	H	H	Bu^t
(9), (16), (19)	H	Ph	Ph

SCHEME 1 Mth = menthyl

contrary, the ketimine (9) gave the imine (19) as the sole product. In every case the structure can be easily assigned to the products on the basis of spectroscopic evidence (i.r. and ^1H and ^{13}C n.m.r.).

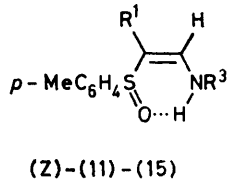
The isolation of stable secondary enamines, such as compounds (11)—(15), although not unexpected, is uncommon, since secondary enamines are generally the

† Compounds (1) were obtained as a 9 : 1 mixtures of the *Z*- and *E*-isomers (ref. 3).

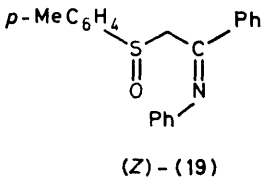
unstable counterparts of their tautomeric imines.[10,11] In a few instances, however, the enamine form is present and even predominant,[7,8,10,12-14] the most effective stabilizing factors being: (i) interaction of the carbon–carbon double bond with an aromatic system and/or electron-withdrawing substituents; (ii) intramolecular hydrogen bonding. Both of these factors can be invoked to account for our observation, provided that some structural requirements are satisfied.

The fact that compounds (11)—(13) exist only as enamines, while compounds (14) and (15) are obtained together with minor amounts of the imines (17) and (18), may be a consequence of the greater stability of trisubstituted carbon–carbon double bonds with respect to disubstituted carbon–carbon bonds. It must be noted that compounds (20), (21), and (23) were obtained also only in the enamino-form, *vide infra*.

The β-enamino sulphoxides (11)—(15) synthesized by our procedure are obtained stereoselectively in the *Z*-configuration at the carbon–carbon double bond. This configuration, though more sterically demanding than the corresponding *E*-configuration, enjoys the stabilizing



(*Z*)-(11)-(15)



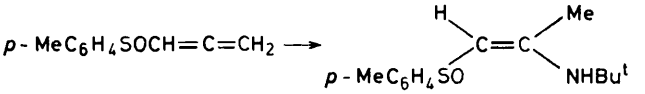
(*Z*)-(19)

The role of intramolecular hydrogen bonding in affecting the position of the $E \rightleftharpoons Z$ equilibrium in sulphonyl and sulphinyl enamines has been elucidated in the classical work of Stirling and his co-workers.[7] In particular, while the β-enamino sulphoxide (21) was shown [7] to exist in the *E*-configuration only, compound (20) is present in chloroform solution as a 4 : 1 mixture of the *Z*- and *E*-isomers.

Along these lines we treated racemic propa-1,2-dienyl *p*-tolyl sulphoxide (22) with t-butylamine to give the *Z*-enamine (23) as the sole product in 80% isolated yield (see Experimental section). Note that compound (23) cannot be obtained by the direct procedure described in this paper because of the well known instability of acetone imines. Unfortunately, the low racemization

$PhCH_2SOCH{=}C(Me)NR^1R^2$

(20) $R^1 = H$ $R^2 = PhCH_2$
(21) $R^1 = R^2 = PhCH_2$



(22) (23)

barrier at the sulphur atom in allenic sulphoxides [15] precludes the use of this approach to obtain enantiomerically pure β-enamino sulphoxides.

As mentioned before, compound (19) was obtained only in the imino-form. This tallies with the behaviour of similar systems which contain electron-withdrawing groups such as C=O and P=O in the β-position in *N*-aryl substituted derivatives.[10]

Also, in the case of compound (19) the reaction turned out to be stereoselective, since only the isomer with the *Z*-configuration at the carbon–nitrogen double bond was obtained, as clearly indicated by ^1H and ^{13}C n.m.r. spectroscopy.

The reaction of lithioenamines with the diastereomerically pure sulphinate ester (10) proceeds with a high stereospecificity; indeed, the enantiomeric excess of compounds (12) and (19), determined with the aid of the chiral shift reagent $Eu(hfc)_3$,* was found to be $\geqslant 95\%$. The ^1H n.m.r. spectra of the racemic compounds (12) and (19) (obtained by a similar procedure from racemic methyl toluene-*p*-sulphinate) in the presence of $Eu(hfc)_3$ showed two different sets of peaks which correspond to the enantiomers. The enantiomeric excess of compounds (11), (13)—(15), and (17)—(18) was accordingly assumed to be $\geqslant 95\%$.

The absolute configuration at the sulphur atom of compounds (11)—(15) and (17)—(19) can be assigned on the basis of the reasonable assumption that reaction of compound (10) with lithioenamines proceeds with inver-

* hfc = 3-(heptafluoropropylhydroxymethylene)-(+)-camphorato.

TABLE 1

Synthesis of optically active β-enamino and β-imino sulphoxides from the imines (4)—(9)

Imine	Sulphoxide	$[\alpha]_D^{25}$ [a] (°)	$[\alpha]_{436}^{25}$ [a] (°)	Absolute configuration	M.p. [b,c] (°C)	Yield (%)
(4)	(11)	−213.2	−521.3	*S*	184—185.5	71
(5)	(12)	−225.9	−556.0	*S*	175—176	78
(6)	(13)	−212.7	−523.0	*S*	153—154	60
(7)	(14), (17) [d]	−38.3	−102.9	*R* [e]	137—137.5	57
(8)	(15), (18) [f]	−113.7	−279.4	*R* [e]	123—124	78
(9)	(19)	−7.9	−60.3	*R*	124—128	27

[a] *c* 1 in chloroform. [b] From ethyl acetate. [c] With decomposition. [d] Enamine : imine ratio *ca.* 4 : 1. [e] Absolute configuration of both enamino and imino sulphoxide. [f] Enamine : imine ratio *ca.* 3 : 1.

sion of chirality, as already established in a number of nucleophilic substitution reactions of sulphinate esters.[16]

The reaction of lithioenamines with sulphinate esters, here described, represents a synthetically simple and efficient entry to β-enamino and β-imino sulphoxides, which are obtained stereoselectively and stereospecifically.

Optical Stability.—The optically active β-enamino sulphoxides (11)—(15), although definitely optically stable in the solid state, rapidly undergo variation in their optical rotations in solution at room temperature. However, after a certain period of time, the optical rotation becomes stable again, as shown in Table 2.

TABLE 2

Isomerization of optically active β-enamino and β-imino sulphoxides

	Starting values		Final values		
Compound	E : I ratio [a]	$[\alpha]_D^{25}$ [b] (°C)	E : I ratio [a]	$[\alpha]_D^{25}$ [b] (°)	Time (min)
(11)	*c,d*	−213.2	*e*	−180.6	270
(12)	*c,f*	−225.9	*g*	−204.8	390
(13)	*c,h*	−212.7	*i*	−184.0	180
(14), (17)	4 : 1	−38.3	2 : 1	−10.3	300
(15), (18)	3 : 1	−113.7	2 : 1	−54.1	240
(19)	*j*	−60.3 [k]	*l*	+16.5 [k]	*m*

[a] E = enamine, I = imine. [b] *c* 1 in chloroform. [c] *Z*-Enamine only. [d] M.p. 184—185.5 °C. [e] M.p. 158—159 °C. [f] M.p. 175—176 °C. [g] M.p. 153—154 °C. [h] M.p. 153—154 °C. [i] M.p. 146—147.5 °C. [j] *Z*-Imine only. [k] $[\alpha]_{436}^{25}$. [l] *E*-Imine only. [m] 15 Days.

Three different situations were encountered. The slow, but quite dramatic, change of optical rotation found with the β-imino sulphoxide (19) is explained in terms of a complete *Z*- ⟶ *E*-isomerization at the carbon–nitrogen double bond. Indeed, a comparison of the ^{13}C n.m.r. spectra recorded at the beginning and at the end of the stereomutation showed that the CH_2 group signal moved upfield from δ_C 66.0 to 58.0 p.p.m.[17] ^1H N.m.r. spectra of the starting and the final product are similar, and the enamine tautomer (16) was not observed during the process.* Thus, compound (19), obtained in the kinetically favoured *Z*-configuration, slowly isomerizes to give the thermodynamically more stable *E*-diastereoisomer.

In the case of the mixtures (14), (17) and (15), (18), ^1H n.m.r. spectroscopy allows us to explain the observed variations as a consequence of a *Z*-enamine ⇌ imine tautomerism † to give equilibrium mixtures of the two species in a *ca.* 2 : 1 ratio, in both cases.

Furthermore, the enamine tautomer present in the equilibrium mixture retains the original *Z*-configuration, thus excluding the possibility that *Z*- ⟶ *E*-enamine isomerization may have appreciably affected the variation in the optical rotation.

* Nevertheless, compound (16) must be present, since a sample of compound (19) in $CDCl_3/D_2O$ solution showed slow H–D exchange of the protons α to the sulphinyl group.

† As far as the configuration at the carbon–nitrogen double bond in the imines (17)—(18), generated by isomerization, is concerned, no clear-cut evidence is available so far.

More puzzling is the behaviour of the β-enamino sulphoxides (11)—(13) since we could not observe any evident change in the ^1H and ^{13}C n.m.r. spectra of these compounds, in spite of both optical rotation and melting point differences in the recovered products.

Partial racemization at the sulphur atom, another possible process, does not take place since the product (12), after 'isomerization,' was still found to be ⩾95% enantiomerically pure, as determined with the aid of $Eu(hfc)_3$ (see above). It is likely that the process involved in these last cases is the same as that observed for the enamines (14) and (15), namely a partial isomerization to the corresponding imines, albeit at an extent undetectable by ^1H and ^{13}C n.m.r. spectroscopy.

EXPERIMENTAL

General.—Tetrahydrofuran (THF) was distilled from lithium aluminium hydride; diethyl ether was dried over sodium. Di-isopropylamine was distilled from and stored over potassium hydroxide pellets. n-Butyl-lithium was used as a *ca.* 1.5M solution in hexane. Extractions were performed using dichloromethane and extracts were dried over sodium sulphate. The amines and the carbonyl compounds used in the syntheses of the imines were commercial products and were distilled before use. I.r. spectra were recorded on a Perkin-Elmer 377 spectrometer. ^1H and ^{13}C N.m.r. spectra were recorded on a Varian XL 100 or a Varian EM 390 instrument, with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. (−)-Menthyl (*S*)-toluene-*p*-sulphinate had m.p. 105—106 °C, $[\alpha]_D^{25}$ −202° (*c* 2 in acetone) {lit.[18] $[\alpha]_D^{25}$ −202° (*c* 2 in acetone)}. Methyl toluene-*p*-sulphinate had b.p. 135 °C at 14 mmHg, n_D^{20} 1.5407 (lit.,[19] b.p. 135 °C at 14 mmHg, n_D^{20} 1.5436).

Synthesis of the Imines (4)—(9).—The imines were prepared following literature methods. Propionaldehyde cyclohexylimine (4) had b.p. 63—64 °C at 15 mmHg, n_D^{16} 1.4450 (lit.,[20] b.p. 62—63 °C at 12 mmHg). Propionaldehyde t-butylimine (5) had b.p. 48—50 °C at 115 mmHg (lit.,[21] b.p. 103 °C). Propionaldehyde isopropylimine (6) had b.p. 85 °C (lit.,[22] b.p. 86—87 °C at 778 mmHg). Acetaldehyde cyclohexylimine (7) had b.p. 44—45 °C at 14 mmHg, n_D^{22} 1.4600 (lit.,[23] b.p. 54 °C at 18 mmHg, n_D^{15} 1.4647). Acetaldehyde t-butylimine (8) had b.p. 80—81 °C (lit.,[21] b.p. 81 °C). Acetophenone anil (9) had m.p. 39—40 °C (lit.,[24] m.p. 40—41 °C).

Synthesis of β-Enamino and β-Imino Sulphoxides.—n-Butyl-lithium (6 mmol) in hexane was added as drops at −40 °C to a stirred solution of di-isopropylamine (6 mmol) in THF (20 ml). The mixture was kept at −10 °C for 30 min, cooled to −40 °C, and the imine (3 mmol) in THF (10 ml) was added as drops during *ca.* 45 min. The mixture was kept at −10 °C for 45—60 min, cooled to −78 °C, and the sulphinic ester (10) (3 mmol) in THF (10 ml) was added as drops. After being stirred for 2 h at −78 °C the reaction mixture was quenched with few drops of methanol; the mixture was brought to room temperature and the solvents evaporated off under reduced pressure at room temperature. The residue was dissolved in dichloromethane, the organic phase was washed with water, separated off, and dried. The solvent was removed under reduced pressure at room temperature and the residue washed with cold pentane–

diethyl ether (1 : 1) to give a solid material, already satisfactorily pure. Analytical samples were obtained by crystallization from ethyl acetate. Analytical data are reported in Table 3. In a similar way, the racemic compound (12), m.p. 156—157 °C, and the racemic compound (19), m.p. 135—139 °C, were synthesized in comparable yields starting from methyl toluene-*p*-sulphinate as the ester. They had n.m.r. spectra analogous to those of the optically active compounds.

Synthesis of the β-Enamino Sulphoxide (23).—Freshly

TABLE 3

Analytical data for β-enamino and β-imino sulphoxides

	Found (%)				Requires (%)		
Compound	C	H	N	Formula	C	H	N
(11)	69.15	8.3	5.1	$C_{16}H_{23}NOS$	69.27	8.36	5.05
(12)	66.65	8.4	5.6	$C_{14}H_{21}NOS$	66.88	8.42	5.57
(13)	66.0	8.1	5.85	$C_{13}H_{19}NOS$	65.68	8.07	5.90
(14), (17)	68.35	7.9	5.3	$C_{15}H_{21}NOS$	68.40	8.03	5 32
(15), (18)	65.6	8.1	5.9	$C_{13}H_{19}NOS$	65.78	807	5.90
(19)	75.6	5.8	4.1	$C_{20}H_{19}NOS$	75.64	5.74	4.20

distilled t-butylamine (2.2 mmol) was added to a stirred solution of 1-tolyl-*p*-sulphinylpropa-1,2-diene (2 mmol) [25] in anhydrous diethyl ether (15 ml) at room temperature. After being stirred overnight at room temperature a solid was formed which was removed by filtration to give pure 2-*t-butylamino propenyl* p-*tolyl sulphoxide* (23) in 80% yield, m.p. 108—110 °C, from ethyl acetate (Found: C, 66.75; H, 8.6; N, 5.35. $C_{14}H_{21}NOS$ requires C, 66.88; H, 8.42; N, 5.57%). ^1H N.m.r. spectrum of the residue, obtained by evaporation of the mother liquor of the reaction mixture, showed the residue to be a mixture of the starting material (22) and the product (23).

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