Synthesis of Optically Active Sulphilimines *via* Chiral Discrimination

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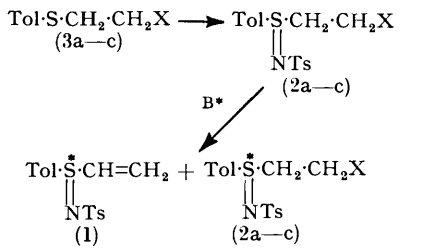
Both vinyl and β-halogenoethyl sulphilimines can be obtained in optically active form *via* kinetic resolution in the elimination reaction of the latter promoted by chiral bases, with enantiomeric excesses of up to 73%; the influence of the resolving agent and of the leaving group on the chiral discrimination has also been examined.

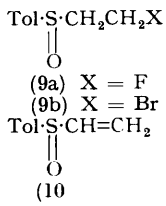
HIGH values of enantiomeric discrimination have been achieved in nucleophilic [1,2] and electrophilic [1,3] additions to α,β-unsaturated sulphoxides. They can be obtained in optically pure state by reaction of sulphinate esters with vinylic Grignard reagents [1,4] or by a Horner-Wittig reaction of carbonyl derivatives with α-phosphoryl sulphoxides.[5,6] α,β-Unsaturated sulphilimines (1) could also be of relevant interest in asymmetric synthesis. We here report that they can be obtained in optically active form *via* kinetic resolution by reaction of β-halogeno-sulphilimines (2) with a deficiency of optically active tertiary amines.

Compounds (2), easily accessible from the corresponding β-halogeno-sulphides (3) and chloramine T, were treated at room temperature with a deficiency of the alkaloids (1)—(8). Both the vinylsulphilimine (1) and the unchanged β-halogeno-sulphimine (2) were recovered in optically active form (see Table).



(2a), (3a) X = F
(2b), (3b) X = Cl
(2c), (3c) X = Br

(4) (−)-quinine
(5) (+)-quinidine
(6) (+)-cinchonine
(7) (−)-*N*-methylephedrine
(8) (−)-strychnine



(9a) X = F
(9b) X = Br
(10)

Tol = *p*-tolyl
Ts = tosyl

Since in preliminary experiments higher optical yields were achieved with acetonitrile as solvent, this was employed in all the successive runs. Most of the reactions were carried out using 0.5 molar equivalents of the chiral base. Under these conditions, provided that the reaction was complete, the enantiomeric enrichment (e.e.) of the unsaturated derivative (1) had to be equal, within experimental error, to that of the recovered starting material. Of the bases tested, (+)-quinidine (5) proved to be the best, the chiral discrimination being 50% in the reaction with (2b) (see Table). The optical purity of the recovered (2b) was increased by increasing the amount of base; with 0.7 molar equivalents of (+)-(5) it reached a value of 73%.

Enantiomeric enrichments were determined by ^{1}H n.m.r. spectroscopy in the presence of a chiral shift reagent [Eu(t.f.c.)$_3$ or Eu(h.f.c.)$_3$] in the case of the vinyl-sulphilimine (1) and of the bromo-derivative (2c), and by conversion of (2b) into (1) *via* dehydrohalogenation with triethylamine in the case of the chloro-derivative (2b). A satisfactory agreement was found between the enantiomeric enrichments of the recovered compound (2) and of the vinyl sulphilimine (1) formed. It should be mentioned that particular care had to be devoted to the separation of (1) and (2) by column chromatography, since relevant enantiomeric resolution can occur during the elution.

The absolute configurations of the vinylic sulphilimine (1) and of the unchanged halogeno-sulphilimine (2) were found to depend on the chirality of the amine used: for example (+)-(1) and (−)-(1) were obtained with (+)-quinidine and its 'quasi enantiomer' (−)-quinine, respectively. Thus unsaturated and β-halogenoethylsulphilimines can be prepared in both enantiomeric forms by appropriate choice of the chiral base. Furthermore the unchanged

Kinetic resolution of sulphilimines (2) in acetonitrile at room temperature

Halogeno-sulphilimine	Base	Base Substrate ratio	Reaction time (days)	Recovered (2) $[\alpha]_D^{25}$ [a]	Recovered (2) e.e.	Vinyl-sulphilimine (1) $[\alpha]_D^{25}$ [a]	Vinyl-sulphilimine (1) e.e.
(2b)	(4)	0.5	4	+55°	32	−74°	31
(2b)	(5)	0.5	4	−82°	48	+116°	50
(2b)	(5)	0.7	4	−125°	73	+68.5°	29
(2b)	(6) [b]	0.5	9	−43.5°	25	+84°	36
(2b)	(7)	0.5	9	+5°	3	−8°	3
(2b)	(8)	0.5	9	−18°	10	+22°	9
(2a)	(5)	0.5	6	+11°		−18°	8
(2c)	(5)	0.5	4	−81°	25	+56°	24

[a] In acetone. [b] Slow reaction, 30% conversion.

(2) can be converted into (1) by reaction with an achiral base such as triethylamine, affording an α,β-unsaturated sulphilimine which is of opposite configuration with respect to that obtained *via* kinetic resolution.

In the chiral discrimination the leaving group also played a very important role. Indeed in the series fluoro- (2a), chloro- (2b), bromo-sulphilimine (2c), kinetic resolution with (+)-quinidine was higher with (2b) than with (2c); the fluoro-derivative (2a) not only gave the worst chiral discrimination, but the sign of optical rotation of the sulphilimine (1) was opposite to that obtained by starting from the chloro- and bromo-derivatives (2b) and (2c). In ancillary experiments carried out with triethylamine in acetonitrile it was shown that the reactivity order of 2-halogeno-sulphilimines is (2c) > (2b) > (2a).

A comparison with the kinetic resolution of β-halogeno-sulphoxides (9a, b) with optically active amines [7] indicates that (i) sulphimines (2) give higher chiral discrimination than sulphoxides (9); (ii) kinetic resolution gives better results with bromo- and chloro- than with fluoro-derivatives in the case of sulphilimines, while the opposite situation occurs when starting from β-halogeno-sulphoxides; (iii) the prevailing isomers of unsaturated compounds (1) and (9) obtained from the fluoro- and bromo-derivatives are in both cases of opposite configuration. A tentative explanation of the peculiar behaviour of substrates (2a) and (9a) is that the β-elimination shifts towards a syn-peri-planar mechanism.

EXPERIMENTAL

General.—^{1}H N.m.r. spectra were recorded with a Varian EM 390 instrument; i.r. spectra were recorded on a Perkin-Elmer 377 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter with acetone as solvent. Quinine, $[\alpha]_{546}^{20}$ −154° (*c* 1.5 in $CHCl_3$); quinidine, $[\alpha]_{546}^{20}$ +286° (*c* 0.8 in EtOH); cinchonine $[\alpha]_{546}^{23}$ +228° (*c* 0.5 in EtOH); *N*-methylephedrine, $[\alpha]_{546}^{25}$ −24° (*c* 1 in EtOH); strychnine, $[\alpha]_{546}^{18}$ −139° (*c* 1 in $CHCl_3$) were commercial products.

The *S*-2-chloroethyl-*N*-tosyl-*S*-*p*-tolylsulphilimine [4] (2b) and *S*-2-bromoethyl-*N*-tosyl-*S*-*p*-tosylsulphilimine [8] (2c) were prepared as previously reported [4,8] from the corresponding sulphides (3b, 3c).

The p-*tolyl* 2-*fluoroethyl sulphide* (3a) was prepared from 1-bromo-2-fluoroethane and toluene-*p*-thiol.[9] It had b.p. 70 °C at 6 mmHg and n_D^{18} 1.553 (Found: C, 63.6; H, 6.5. $C_9H_{11}FS$ requires C, 63.6; H, 6.5%). The *S*-2-fluoroethyl-*N*-tosyl-*S*-*p*-tolylsulphilimine (2a) was obtained from the halogeno-sulphide (3a) and chloramine T by the method described [4,8] for the chloro- and bromo-sulphilimines (2b, 2c). It had m.p. 94—95 °C (from methanol) (Found: C, 56.3; H, 5.4; N, 4.1. $C_{16}H_{18}FNO_2S_2$ requires C, 56.6; H, 5.3; N, 4.1%).

Kinetic Resolution of the Halogeno-sulphilimines (2*a*—*c*) *by Optically Active Bases* (4)—(8). *General procedure.*—The optically active base (0.5 mol equiv.) was treated, at room temperature, with the halogeno-sulphilimine (1 mol equiv.) in acetonitrile.

The mixture was stirred (see Table) and then the solvent was removed under reduced pressure. The residue was diluted with methylene chloride, washed with 10% aqueous sulphuric acid and then with water; the organic layer was separated, dried (Na_2SO_4), and evaporated to dryness. The crude mixture was separated by column chromatography (SiO_2, diethyl ether as eluant). Optical rotations of the *N*-tosyl-*S*-*p*-tolyl-*S*-vinyl-sulphilimine (1) and of the recovered halogeno-sulphilimines (2a—c), and the enantiomeric excesses of (1), are reported in the Table.

Dehydrohalogenation of Halogeno-sulphilimine (2*a*—*c*) *by Triethylamine.*—Triethylamine (1 mmol) was added to a stirred solution of halogeno-sulphilimine (2a—c) (1 mmol) in acetonitrile (8 ml). The mixture was stirred at room temperature for a suitable time [48 h for (2a) (conversion 75%); 4 h for (2b) (conversion 100%); 80 min for (2c) (conversion 100%)] and the precipitate of triethylammonium salt was filtered off. Evaporation of the solvent gave the vinyl-sulphilimine (1). Starting from the optically active chloro-sulphilimine (2b), $[\alpha]_D^{20}$ −82° (*c* 1 in Me_2CO), the vinyl-sulphilimine (1) obtained had $[\alpha]_D^{20}$ −113° (*c* 1 in acetone).

Determination of the Enantiomeric Purity of the Vinyl-sulphilimine (1) *and of recovered Sulphilimine* (2*c*) *by* ^{1}H *N.m.r.*—^{1}H N.m.r. spectra of the racemic vinyl-sulphilimine (1) showed two different AA′ BB′ systems for the aromatic protons of tosyl and tolyl groups, centred at δ 7.5 and 7.3, which both revealed doubling of the two lower field signals in the presence of the chiral shift reagents $Eu(hfc)_3$ or $Eu(tfc)_3$. For the racemic bromo-sulphilimine (2c) the methyl groups at δ 2.35 and 2.40 showed a doubling in the presence of $Eu(hfc)_3$. The ratio of $Eu(tfc)_3$ and/or $Eu(hfc)_3$ to compounds (1) and (2c) was 1 : 1. The enantiomeric purities of the optically active derivatives were determined under the aforementioned conditions.

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