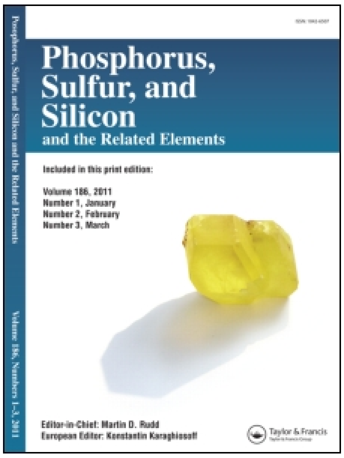

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A NEW TYPE OF ASYMMETRIC SYNTHESIS OF SULPHINIC ACID DERIVATIVES USING CHIRAL CARBODIIMIDES[1]

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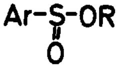
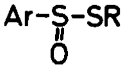
Treatment of arylsulphinic acid with alcohols, thiols or secondary amines in the presence of equimolar amount of optically active carbodiimides afforded the corresponding optically active sulphinic acid esters, S-alkyl thiosulphinates and sulphinamides. The e.e. values vary between 0, 1 and 10%.

INTRODUCTION

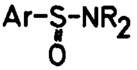
Optically active arylsulphinic acid derivatives such as sulphinates **1**, thiosulphinates **2** and sulphinamides **3** have been known to be attractive precursors for the synthesis of a variety of chiral sulphinyl compounds and useful as models for stereochemical investigations of the mechanism of nucleophilic substitution at the sulphinyl sulphur atom.


$Ar{-}\underset{\|}{\overset{}{S}}{-}OR$ (S=O)

1

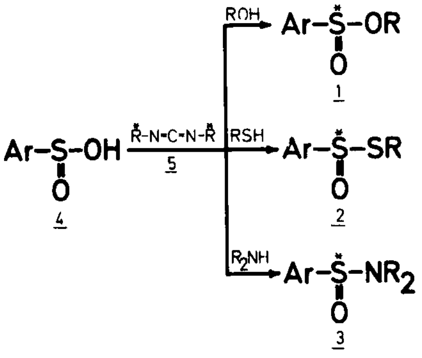

$Ar{-}S(=O){-}SR$

2


$Ar{-}S(=O){-}NR_2$

3

The majority of optically active sulphinates **1** and thiosulphinates **2** of high optical purity have been prepared by the reaction of optically active sulphinamides **3** with the corresponding alcohols[3] or thiols[4] in the presence of organic acids. Chiral sulphinamides **3** of high optical purity have been prepared via the reaction of diastereoisomeric sulphinates with lithiumamides[5] or N,N-dialkylaminomagnesium halides.[6] Optically active sulphinyl derivatives **1**, **2** or **3** of low to moderate optical purities were formed by an asymmetric oxidation of the corresponding sulphenyl derivatives.[7,8] It was also found that the chiral sulphinic acid derivatives **1**, **2** or **3** of relatively high optical purity were formed when racemic sulphinyl chlorides were allowed to react at low temperature with achiral alcohols,[9] thiols[10] or secondary amines[11] in the presence of an optically active tertiary amine as an asymmetric reagent. Optically active sulphinates **1** have also been prepared by the kinetic resolution of racemates in the reaction with chiral Grignard reagents[12] or with an achiral Grignard reagent and optically active aminoalcohols.[13] Very recently an asymmetric synthesis of chiral alkyl *t*-butylsulphinates of high optical purity, which involves the reaction of symmetrical sulphites with *t*-butylmagnesium chloride in the presence of optically active aminoalcohols, was reported from our laboratory.[14]



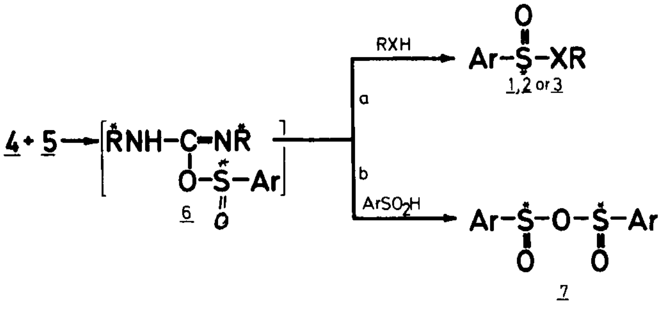
*means center of optical activity

SCHEME 1

Here we would like to present a new asymmetric synthesis of chiral sulphinic acid derivatives **1**, **2** or **3** which consists in the condensation of aryl sulphinic acids **4** with achiral alcohols, thiols or secondary amines in the presence of optically active carbodiimides **5** as chiral condensing agents (Scheme 1).

RESULTS AND DISCUSSION

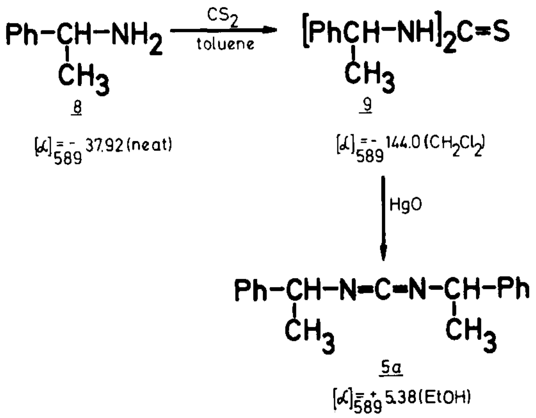
Kobayashi and coworkers[15] reported in 1971 that arylsulphinic acids **4** can be easily converted into the corresponding sulphinates **1** by treatment with an equimolar amount of dicyclohexylocarbodiimide and an excess of an appropriate alcohol. Later on, this procedure has been used by Furukawa *et al.*[16] for the preparation of thiosulphinates **2** and sulphinamides **3**. The mechanistic aspects of the reaction of sulphinic acids with alcohols, thiols or amines in the presence of carbodiimide are not yet completely clear. However, it is quite probable that in the first step of the reaction an unstable O-sulphinylisourea should be formed. Due to the prochirality of the supphur atom in **4** its interaction with the chiral carbodiimide **5** should lead to the formation of isourea **6**, as a diastereoisomeric mixture, in which diastereoisomers ratio may be different from 1:1. In such a case this intermediate can react either with an RXH nucleophile to give directly the corresponding optically active sulphinic acid derivatives **1**, **2**, **3** (path a in Scheme 2) or with another molecule of sulphinic acid **4** to form unstable, but



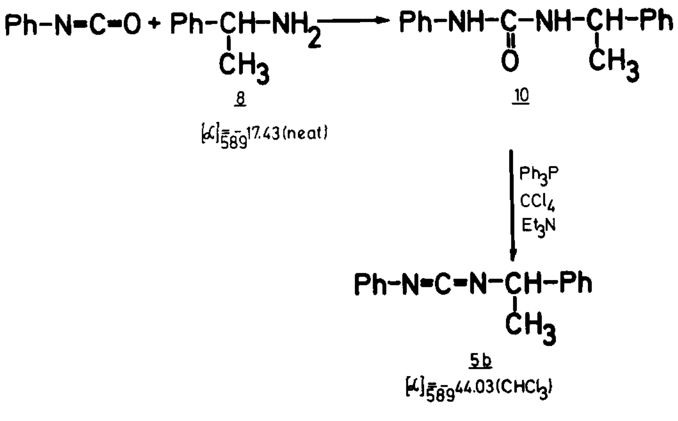
SCHEME 2

chiral sulphinic acid anhydride 7 (path b in Scheme 2). The latter on reacting with an RXH molecule should produce the corresponding optically active sulphinyl derivatives **1**, **2** or **3**.

Chiral carbodiimides **5a** and **5b** used as condensation agents were prepared starting from optically active α-phynylethylamine **8** via thiourea **9** and urea **10**, respectively, as outlined in schemes **3** and **4**. Thiourea **9** prepared, according to A. W. Hofmann,[17] by heating of amine **8** with carbon disulfide in toluene solution was converted into chiral carbodiimide **5b** by desulphurization with yellow mercuric oxide.[18] N-Phenyl-N'-α-phenylethyl urea **10** prepared in situ by mixing amine **8** with phenyl isocyanate in ethanol solution was converted into the corresponding optically active carbodiimide **5b** by the reaction with an equimolar amount of triphenylphosphine, carbon tetrachloride and triethylamine according to the general procedure of Appel.[19]



SCHEME 3



SCHEME 4

The condensation reactions were carried out according to the reported procedure[15,16] i.e. arylsulphinic acids **4** and an equimolar amount of anhydrous alcohol (amine or thiol) were dissolved in dichloromethane and an equimolar

TABLE I

Optically active arylsulphinic acid derivatives ArS(O)XR (**1**, **2** or **3**) prepared by the reaction of arylsulphinic acids **4** with alcohols thiols or amines in the presence of optically active carbodiimide **5**

Compounds	**5**	Ar	XR	Yield%[a]	$[\alpha]^{b}_{589}$	E.e.[%][c]	Abs. conf.
1a	a	Ph	Ome	64	−9.5	5.0	S
1b	a	Ph	OEt	44	−19.4	10.0[d]	S
1c	a	Ph	OPr^{i}	35	−17.8	7.5[d]	S
1d	a	Ph	Obu^{t}	25	+6.2	2.8[d]	R
1e	a	p-Tol	OMe	44	−2.4	1.1	S
1f	b	p-Tol	OEt	50	+2.1[f]	1.5[e]	R
1g	b	p-Tol	OPr^{i}	40	+1.9[f]	1.1[c]	R
2a	a	Ph	SBu^{t}	28	−5.7	2.3	S
2b	a	p-Tol	SBu^{t}	86	−0.5	0.15	S
3a	a	Ph	NEt_2	66	+6.5	3.0[d]	S
3b	a	Ph	NPr^{f}_{2}	31	−4.5	—	R
3c	a	Ph	$N(CH_2)_4$	36	−8.4	4.2[d]	R
3d	a	p-Tol	NPr^{i}_{2}	40	−6.0	2.8	R

[a] Yield of the products after purification by column chromatography.

[b] Optical rotations were measured in ethanol solution.

[c] Optical purity calculations were based on the following data:
$[\alpha]_{589} = -188.0$ for S-**1a**, $[\alpha]_{589} = -219.8$ for S-**1e** from reference 8,
$[\alpha]_{589} = -242.2$ for S-**2a**, $[\alpha]_{589} = -278.8$ for S-**2b** from reference 9,
$[\alpha]_{589} = -214.0$ for R-**3d** from reference 6.

[d] Ee values and absolute configuration of **1b**–**d**, **3a** and **3c** were determined chemically via their conversion into the known methyl phenyl sulphoxide[20] assuming that the reaction with methylmagnesium iodide or methyllithimn proceeds with full inversi on of configuration at sulphur.

[e] Ee values and absolute configuration of **1f** and **1g** were determined chemically via their conversion into the known methyl p-tolyl sulphoxide[21] assuming that the reaction with methylmagnesium iodide proceeds with full inversion of configuration at sulphur.

[f] Neat.

amount of an optically active carbodiimide **5** was slowly added. The reaction mixture was stirred for several hours. After removal of the optically active urea formed, chiral sulphinyl derivatives **1**, **2** or **3** were isolated by column chromatography on silica gel. The optical rotations, optical purities and absolute configurations of **1**, **2** and **3** obtained by this procedure are given in Table I.

An inspection of the table reveals that the condensation reactions of sulphinic acids **4** with alcohols, thiols and amines in the presence of chiral carbodiimides **5a** and **5b** afforded optically active sulphinyl derivatives **1**, **2** or **3** in all cases, however their optical purities are relatively low (in the range 0.1–10%). It should be stressed that the procedure presented above allows for the first time to convert directly prochiral sulphinic acids into optically active sulphinyl derivatives. Another advantage of the procedure described here is the use of easily available optically active carbodiimides as asymmetric reagents. The data listed in the Table 1 show further the complexity of the stereochemical course of the reaction studied. Thus, O-alkyl p-toluenesulphinates **1f** and **1g** obtained after the reaction with carbodiimide **5b** have R-configuration whereas the chirality at sulphur in the case of O-methyl-p-toluene-sulphinate **1e** prepared using carbodiimide **5a** is S. O-Alkyl phenylsulphinates **1a**, **1b** and **1c** obtained after the reaction with carbodiimide **5a** have S configuration whereas the absolute configuration of the O-T-butyl ester **1d** is R. Moreover, the chirality at sulphur in S-t-butyl thiosulphinate **2a** prepared using the same carbodiimide **5a** is again S. The optically active sulphinamide **3a** obtained after reaction with carbodiimide **5a** has S configuration at the sulphinyl sulphur atom, which is opposite to the chirality of sulphinamides **3b, c** and **d**. These observations clearly show that there is no simple way to correlate the chirality at the sulphur atom of the products and the carbon atom in the chiral condensing agent. Different absolute configurations of the sulphinyl derivatives **1**, **2** or **3** formed in the reaction of sulphinic acids **4** with the same chiral carbodiimide **5** clearly indicate that the detailed mechanism of this reaction needs further studies, which are currently carried out.

EXPERIMENTAL PART

^{1}H-NMR spectra were taken on a Perkin–Elmer R-20 spectrometer in deuterochloroform solution with TMS as internal standard. The optical activity measurements were performed on a Perkin Elmer 241 MC photopolarimeter. Solvents and commercial reagents were distilled and dried by conventional methods before use. Racemic α-phenylethylamine **8** was resolved into enantiomers according to Theilacker and Winkler.[22] Free sulphinic acids **4** were liberated from their sodium salts by acidification with diluted hydrochloric acid[23] and kept in ether solution up to the time of the use.

N,N'-di-α-phenylethylthiourea **9**. Optically active α-phenylethylamine **8** $[\alpha]_{589} = -37.92$ (heat) (49.6 g – 0.4 mol) and carbon disulfide (219 ml) were heated in toluene solution (300 ml) under reflux for 25 h. Evaporation of toluene afforded the crude optically active thiourea **9** as white crystals which were washed with hexane, 53 g (90%) m.p. 213–214°C, $[\alpha]_{589} = -144°$ (1.51 CH_2Cl_2), ^{1}H-NMR $\delta = 1.37$ (d, 6H, $\underline{CH_3}$-CH, $J = 7$ Hz), 4.96 (quintet, 2H CH_3-$\underline{CH}$-NH, $J =$ 7 Hz), 6.20 (bs, 2H, Ch_3Ch-$\underline{NH}$), 6.75–7.25(m, 10H, Ar). Anal. Calculated for $C_{17}H_{20}N_2S$: C, 71.73; H, 7.09; N, 9.90; S, 11.27. Found C, 71.45; H, 7.32; N, 10.01; S, 11.47.

N,N'-di-α-phenylethylcarbodiimide **5a**. The thiourea **9** prepared above (13.6 g – 0.053 mol) was dissolved in carbon disulfide (250 ml) and shaken with yellow mercuric oxide (31.45 g, 0.055 mol) and magnesium sulphate (6.4 g) for 8 h at room temperature. Next, mercuric sulphide formed was filtered off and washed with ether (3 × 50 ml). The filtrate was evaporated and the residue was distilled to give carbodiimide 5a, 9g (66%), b.p. 147/1 mmHg, $[\alpha]_{589} = +5.38°$ (c 7.08 EtOH); ^{1}H-NMR $\delta = 1.37$ (d, 6H, $\underline{CH_3}$-CH, $J = 7$ Hz) 4.40(q, 2H, $CH_3\underline{CH}$, $J = 7$ Hz); 7.17 (s, 1OH, Ar)
Anal. Calculated for $C_{17}H_{18}N_2$: C, 79.90; H, 7.88; N, 12.33.
Found: C, 80.31; H, 7.77; N, 12.43.

N-α-Phenylethyl-N-phenylcarbodiimide **5b**. Optically active α-phenylethylamine **8**, $[\alpha]_{589} = -17.43°$ (neat), (13.5 g, 0.11 mol) and phenyl isocyanate (14.8 g, 0.11 mol) were mixed in ethanol solution (50 ml) and kept at room temperature for 4 h. After evaporation of ethanol, the crude urea **10** formed was dissolved in methylene chloride (70 ml) containing carbon tetrachloride (17 g,

0.11 mol) and triethylamine (11.5 g, 0.11 mol). To this solution equimolar amount of triphenylphosphine was added at room temperature. The reaction solution was stirred and refluxed for 5 h. After evaporation of methylene chloride, the solid residue was extracted with petroleum ether (4 × 60 ml). The extract was evaporated and the residue was distilled to give optically active carbodiimide **5b**, 17.2 g (68%), b.p. 119–1200°C/2.5 mmHg, $[\alpha]_{589} = -44.03°$ (6.03 $CHCl_3$).
Anal. Calculated for $C_{15}H_{14}N$: C, 80.97; H, 6.36; N, 12.67.
Found: C, 80.65; H, 6.49; N, 12.69.

Reaction of Arylsulphinic Acids (4) with Alcohols, Amines or Thiols in the Presence of Chiral Carbodiimide 5—General Procedure

Aryl sulphinic acid **4** (0.01 mol) and an equimolar amount of an anhydrous alcohol (amine or thiol) were dissolved in dichloromethane (30 ml) and placed in a 50 ml round-bottom flask containing a magnetic stirring bar. To this solution optically active carbodiimide **5** (0.01 mol) dissolved in 10 ml of dichloromethane was slowly added at room temperature. Stirring was continued for several hours. White precipitates of optically active urea formed was filtered off, the solvent was removed by evaporation and the residue was dissolved in hexane-ether (1:1). White precipitate possibly formed was removed by filtration. The organic extracts were washed with a sodium carbonate solution and water and dried over magnesium sulphate. After evaporation pure sulphinic acid derivatives **1–3** were obtained by column chromatography on silica gel using hexane-ethyl ether as a eluent.

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