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Synthesis of new axial chiral diisothiocyanates

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Abstract: The first example of the preparation of enantiomerically pure atropisomeric mustard oils is described. Both enantiomers were obtained by simple acylation of the corresponding diamines with thiophosgene. © 1997 Elsevier Science Ltd

The demand for large-scale enantioselective processes by chemical and pharmaceutical industries has been a major driving force for fundamental work in asymmetric synthesis mainly in asymmetric catalysis by chiral metal complexes. Especially promising among chiral ligands endowed with C_2-symmetry is the axially chiral 2,2′-substituted 1,1′-binaphthyl system[1,2]. Derivatives such as BINOL **1**[3,4], BINAP **2**[5] and BINAM **3**[6] have been shown to be important chiral auxiliaries with numerous applications in asymmetric synthesis. Due to the axial chirality the chelating compounds **1–3** have a number of advantageous features: the X-group provides an important steric influence, provides polarizability and enhances Lewis acidity of the metal complexes; its conformational flexibility allows accommodation of a diversity of transition metals by rotation about the C_1–$C_{1'}$ axis and C_2 or $C_{2'}$ bonds without significant increase in torsional strain. The seven-membered heterocyclic systems resulting upon metal complexation contain only planar sp^2-hybridized carbons and transmits the chirality of the binaphthyl skeleton to the other metal coordination sites.

In contrast to **1** and **2**, the corresponding 1,1′-binaphthalene-2,2′-diamine BINAM **3** has not received similiar extensive attention. Only few examples for its application in asymmetric synthesis are known to date[7–9].

In order to provide a variety of axial chiral macrocyclic systems for study in asymmetric catalysis and supramolecular chemistry we shall first develop a new route to such systems via cycloacylation of **3** with C_1- and C_2-building blocks. Whereas oxalyl chloride reacts with (S)-**3** to yield a new enantiomerically pure macrocycle[10] the C_1-building block thiophosgene leads finally to a new chiral diisothiocyanate **4**.

Thus, by treatment of both enantiomeric forms of **3** with two equivalents thiophosgene in the presence of triethylamine enantiomerically pure (R)- or (S)-2,2′-diisothiocyanato-1,1′-binaphthalene **4** can be obtained in satisfactory yield (Scheme 1). The functional isothiocyanato group was indicated by ^{13}C-NMR (δ (C=S): 138.36 ppm) and by IR-spectroscopy (strong absorption at 2032 cm^{-1}). The primary step is thought to be formation of a cyclic thiourea **5**, which could be isolated as a white, high melting crystalline compound. In the presence of an excess of thiophosgene this primary product dissolved to a clear solution with formation of **4**. Analogous behaviour has been described for the reaction of ortho-phenylene diamines[11], but only traces of the appropriate diisothiocyanate were isolated. The use of one of the most attractive and mild methods for preparing isothiocyanates, the transacylation with thiocarbonyl-bisimidazole only yields **5**. All attempts to minimize the formation of **5** in favour of **4** by changing the solvent or the temperature were in vain.

The CD spectra of (R)-**4** and (S)-**4** were measured and they constitute enantiomorphic curve diagrams as shown in Figure 1, indicating that the compounds are enantiomers. The enantiomeric purity of (R)- and (S)-**4** has been furthermore determined by chiral HPLC (columns: β-cyclodextrin, Daicel-OD/ODR/AD/AS, whelk 01; mobile phase: acetonitrile/methanol, methanol/water, 2-propanol/water,

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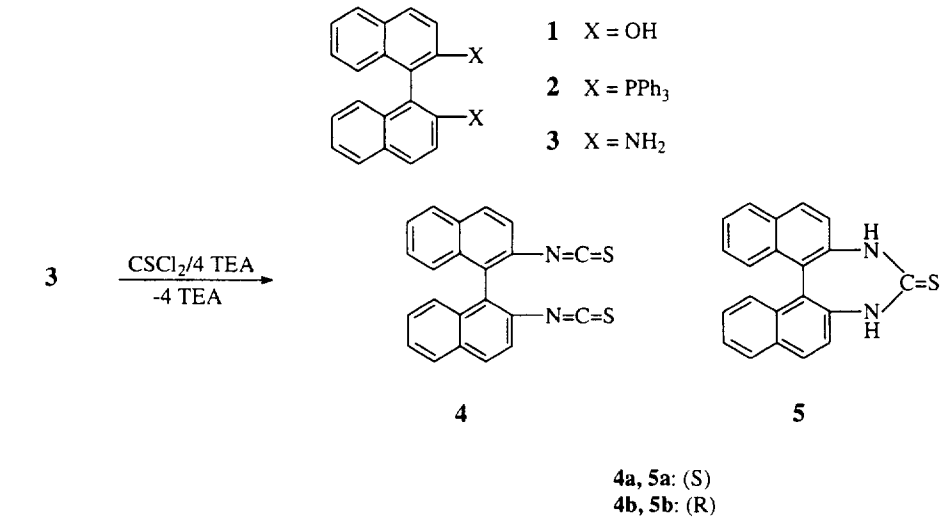

Scheme 1.

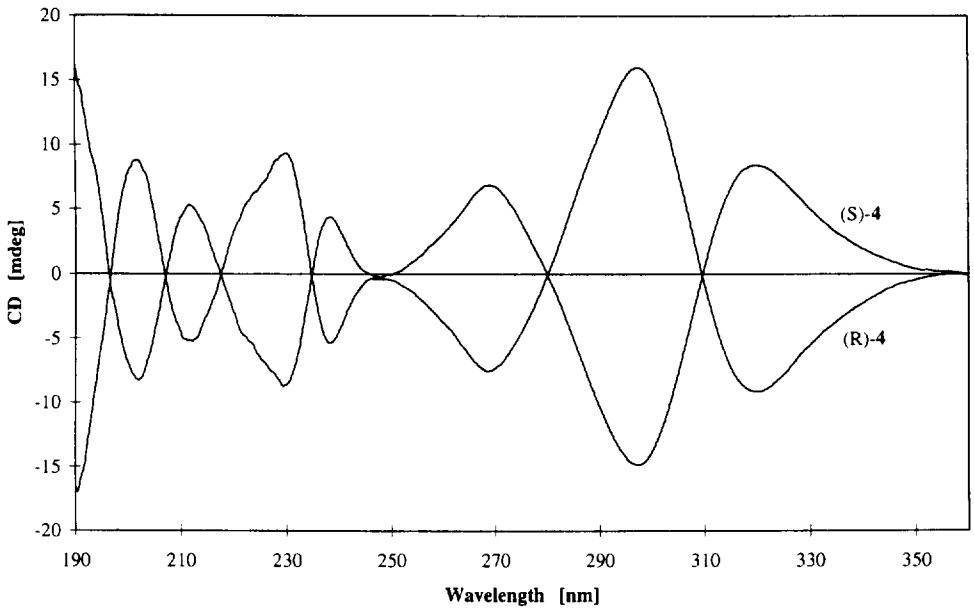

Figure 1. CD-spectra of (R)-**4** and (S)-**4**.

in various ratios at 1 ml/min, temperature 25°C and 7°C respectively, comparision with a racemic sample; in the case of both enantiomers no splitting was observed). In addition, the reaction of **4** with selected enantiomerically pure amines ((S)-sec.-butylamine) in nmr tubes gave no evidence for any racemization. We are continuing our study on the properties of **4** including the reactions with different kinds of nucleophilic compounds as amines, hydrazines and amino acids and will report the results separately soon.

Experimental

General: Melting points were measured using a Cambridge Instruments hot stage Galen III and are uncorrected. Optical rotations were recorded on a Schmidt and Haensch polarimeter polartronic

as solution sample in a 2 dm cell. ^{1}H-NMR and ^{13}C-NMR were determined on a Bruker DRX 400 spectrometer. Chemical shifts are expressed in ppm relative to ^{1}H signals of the solvent. Mass spectra were performed on a FISONS TRIO 2000. Infrared spectra were recorded on a BIO-RAD IR-spectrometer FTS-25. CD spectra were recorded on a Jasco 720 Spektropolarimeter and HPLC on a Merck La CHrome. For thin-layer chromatography (TLC) analysis precoated silica gel plates (E. Merck) were used. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Enantiomerically pure (R)- and (S)-2,2′-Diamino-1,1′-binaphthalene were purchased from FLUKA.

(R)- Respectively (S)-2,2′-diisothiocyanato-1,1′-binaphthalene **4**

A 100 ml round bottom two neck flask charged with a solution of 1.42 g (5.00 mmol) (R)- or (S)-2,2′-diamino-1,1′-binaphthalene and 2.50 g (20 mmol) triethylamine in 40 ml dry THF was fitted with a magnetic stirring bar, a 25 ml pressure-equalized addition funnel with a rubber septum and an oil bubbler with a stopcock. Under argon, a solution of 2.50 g (10.50 mmol) thiophosgene in 20 ml dry THF was added dropwise with stirring at room temperature. During 5 hours of stirring the solution turned from orange to slightly yellow. After completion of the reaction (control by TLC), the triethylamine hydrochloride was filtered off and was washed with 30 ml THF. Evaporation of the solvent under reduced pressure gave a crude product which was purified by recrystallisation (n-hexane/ethyl acetate) affording the enantiomers.

(R)-**4** Yield, 76% yellowish quaders, Mp, 145–146°C, $[\alpha]_D^{23}=-171.5$ (1.00, acetone), CD (acetonitrile, 0.03125 mg ml^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$): 320 (−0.09); 297 (0.15); 268 (−0.07); 238 (−0.05); 230 (0.09); 212 (−0.05); 202 (0.08). (S)-**4** Yield, 67% yellowish needles, Mp, 145–146°C, $[\alpha]_D^{23}=+170.5$ (1.00, acetone), CD (aceto-nitrile, 0.03125 mg ml^{-1}) λ_{max} (nm) ($\Delta\epsilon_{max}$): 320 (0.08); 297 (−0.14); 269 (0.07); 238 (0.04); 229 (−0.08); 212 (0.05); 202 (−0.08). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, ^3J=8.6 Hz, 2H); 7.94 (d, ^3J=8.2 Hz, 2H); 7.51 (m, 2H); 7.47 (d, ^3J=8.8 Hz, 2H); 7.35 (m, 2H); 7.14 (dd, ^3J=8.5 Hz, ^4J=0.8 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 138.36; 132.86; 132.06; 130.60; 130.34; 129.67; 128.52; 127.85; 126.87; 125.53; 123.34 ppm. MS (CI with H_2O) m/e: 369 (100%, M^+); 309 (14%); 276 (41%); 252 (18%); 146 (17%); 132 (20%); 125 (25%). IR (Nujol) cm^{-1}: 2032 (N=C=S); 1459; 1376; 812; 723 cm^{-1}. Anal. Calcd. For $C_{22}H_{12}N_2S_2$: C 71.74%, H 3.26%, N 7.61%, S 17.39%; Found: C 71.93%, H 3.22%, N 7.71%, S 17.37%.

3,5-Diaza-cyclohepta[2,1-a;3,4-a′]dinaphthalen-3H,5H-4-thione **5**

The residue of filtration, obtained by work-up described above containing triethylamine hydrochloride and small amounts of **5** was washed with cold water and with methanol. After drying in vacuo, pure **5** can be obtained as a white, microcrystalline compound.

Yield, 22%. Mp, 242–244°C. ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.00 (d, ^3J=8.7 Hz, 2H); 7.98 (s, 2H, NH); 7.95 (d, ^3J=8.1 Hz, 2H); 7.54 (m, 2H); 7.42 (m, 2H); 7.21 (m, 2H); 7.04 (dd, ^3J=8.6 Hz, ^4J=0.8 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, acetone-d_6) δ: 197.94 (C=S); 141.93 (ipso-C); 132.23; 131.58; 129.56; 128.24; 126.55; 126.26; 125.24; 124.06; 121.55 ppm. MS (CI with H_2O) m/e: 326 (100%, M^+); 267 (36%); 133 (63%). Anal. Calcd. For $C_{21}H_{14}N_2S$: C 77.30%, H 4.29%, N 8.59%, S 9.82%; Found: C 77.05%, H 4.35%, N 8.54%, S 9.94%.

Acknowledgements

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