Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 1, pp. 111-114, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(94)00365-3

Separation of Racemic Binaphthol Into Enantiomers. Synthesis of Neomenthylthioacetic Acid Chloride - A New Chiral Resolving Agent

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Abstract: *Treatment of racemic binaphthol (1) with neomenthylthioacetic acid chloride (2) gave monoesters 7 and 8. Their separation by column chromatography followed by reduction afforded enantiomerically pure binaphthols.*

INTRODUCTION

The enantiomers of binaphthol (1,1'-binaphthalene-2,2'-diol **1**) are important C_2-symmetrical compounds. Optically pure binaphthols have been extensively used as a chiral auxiliary reagents for a variety of asymmetric reactions[1-8].

Several methods for the separation of enantiomers of **1** have been reported, e.g.: enzymatic resolution of racemic **1** *via* its acetate esters[9]; oxidative coupling of 2-naphthol using chiral amines - Cu(II) complexes[10]; resolution by crystallization of salts of racemic phosphoric ester of **1** with chiral amines such as cynchonine[11,12], strychnine[13], (R)-2-aminobutanol[14] or by formation of inclusion complexes with chiral hosts[15]. However, these methods require preparation of the requisite chiral host compounds, or employ expensive chiral amines.

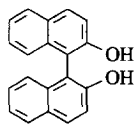
In this work we wish to report, that a readily available and inexpensive chiral acyl chloride (neomenthylthioacetic acid chloride, **2**) can be used as a resolving agent for simple, two step separation of enantiomers of **1**.

RESULTS

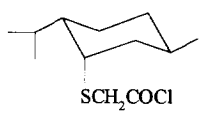
Preparation of acyl chloride 2

The substrate in the synthesis of **2** was neomenthanethiol (**4**). This compound was obtained by Beretta et al.[16] from (-)-menthyl p-toluenesulfonate and potassium ethylxantogenate, but in 14% yield only. Using a slightly modified procedure of Beretta, van Leusen et. al.[17] obtained **4** in 45% yield. However, no proof of its diastereomeric and optical purity was provided. Similarly, in the paper of Mukaiyama[18], who obtained **4** from (-)-menthol *via* the corresponding N,N-dimethyldithiocarbamate, no physicochemical data and yield of the product were given. Kellog[19] and Mikołajczyk[20] used the thioacetate anion as nucleophile in reaction with (-)-menthyl mesylate[19] or tosylate[20]. Under these conditions a clean S_N2 substitution occurred. Reduction of the neomenthyl thioacetate with lithium aluminum hydride (LAH) gave pure neomenthanethiol (**4**).

We used as a precursor of thiol **4**, thiocyanate **3**. Reduction of **3** with LAH gave thiol **4** in 87% yield. Alternatively, we used the method of Mikołajczyk[20].



1



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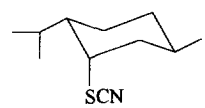

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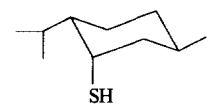

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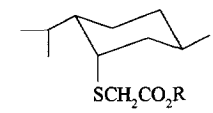
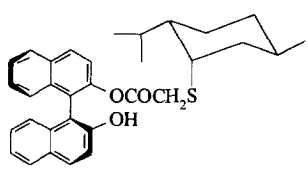


5. R = Me
6. R = H

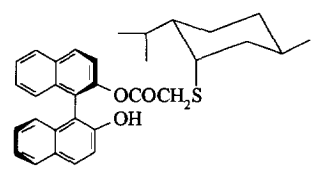
Alkylation of **4** with methyl bromoacetate in the presence of sodium hydride gave ester **5** (85%). Its hydrolysis with lithium hydroxide in THF / water solution gave free acid **6** (quantitatively), which reacted with thionyl chloride to give acid chloride **2** (84% isolated yield), or with oxalyl chloride to afford crude **2**, sufficiently pure for the next reaction step (see **Experimental**).

Separation of enantiomers of binaphthol

Treatment of the racemic binaphthol (**1**) with chiral acyl chloride **2** in the presence of triethylamine in dichloromethane solution gave diastereoisomeric monoesters **7** and **8** in 48% total yield. The formation of monoesters of binaphthol with sterically hindered acid was not surprising since from (-)-menthoxyacetyl chloride and **1** also a monoester was obtained[22]. Compounds **7** and **8** can be readily separated by column chromatography. Deacetylation of **7** or **8** with butylamine in benzene solution was very effective. After aprox. 10 min. no substrate was observed (TLC). However, separation of binaphthol and neomenthanethioacetic acid butylamide from each other was impossible. Therefore, reduction of esters **7** and **8** was indispensable.



7



8

Treatment of the esters **7** and **8** with LAH at -20°C followed by column chromatography gave pure enantiomers of binaphthol with high yield (85% each).

EXPERIMENTAL

General methods. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ under argon prior to use. Other solvents were purified and dried according to literature methods. TLC was performed on Silica Gel HF-254 and column chromatography on Silica Gel 230 - 400 mesh (Merck). ^1H NMR spectra were recorded with a Bruker AM-500 (500 MHz) and Varian AC-200 (200 MHz) spectrometers in deuterobenzene (C_6D_6) and deuterochloroform ($CDCl_3$) with Me_4Si as internal standard. High resolution mass spectra (HR-MS) were measured with AMD-604 mass spectrometer. IR spectra were recorded on a Perkin -Elmer 1640 FT-IR spectrophotometer. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter.

***(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl thiocyanate* (3)**

A solution of (-)-menthyl p-toluenesulfonate[20] (31.0 g, 0.1 M) and potassium thiocyanate (48.6 g, 0.5 M, dried at 110°C for 12 h under vacuum) in DMF (250 mL) was heated at 110 - 120°C for 3 h. After cooling, the mixture was diluted with water (600 mL) and extracted with ether (5 × 100 mL). Combined organic extracts were washed with water (100 mL), dried over magnesium sulphate, and the solvents were

evaporated. The residue was distilled at 77 - 83°C / 0.5 mmHg to afford 10.9 g (55%) of **3**, $[\alpha]_D^{20}$ +116.6 (*c* 1.4, chloroform); lit.[21]: $[\alpha]_D^{25}$ +91.8 (*c* 1.08, ethanol); HR-MS/EI: $C_{11}H_{19}NS$ $(M)^+$. Calc.: 197.1238. Found: 197.1232.

***(1S,2S,5R)-2-Isopropyl-5-methylcyclohexylthiol* (4)**

To a cooled (-20°C) suspension of $LiAlH_4$ (4.02 g, 106 mM) in ether (150 mL) a solution of **3** (9.63 g, 48.8 mM) in ether (150 mL) was added dropwise. The temperature was maintained below -10°C. The mixture was allowed to attain room temp. and stirring was continued for 2 h. After cooling (ice bath) water (4.5 mL) was slowly added, and the mixture was stirred for 1 h. The suspension was filtered through a silica gel column (**Warning** - free HCN are present), and the product was eluted with hexane - chloroform, 9 : 1. The solvents were evaporated to give 7.30 g (87%) of **4**, $[\alpha]_D^{20}$ +53.2 (*c* 1.36, chloroform); lit.[20]: $[\alpha]_D^{20}$ +53.9 (*c* 1.85, chloroform).

***(1S,2S,5R)-2-Isopropyl-5-methylcyclohexylthioacetic acid methyl ester* (5)**

To a cooled (-20°C) suspension of NaH (50% in oil, 1.32 g, 27.5 mM) in THF (10 mL) a solution of **4** (4.31 g, 25.0 mM) in THF (10 mL) was slowly added. The stirring was continued for 30 min. and a solution of methyl bromoacetate (4.6 g, 30.0 mM) in THF (10 mL) was slowly added. The mixture was stirred 1 h at -20°C, and water (1 mL) in THF (5 mL) was added. After attaining room temperature the solvents were evaporated. The remaining syrup was purified by chromatography on a silica gel column with hexane -acetone, 4 : 1 to yield **5** (5.19g, 85%), $[\alpha]_D^{20}$ +103.2 (*c* 3.7, chloroform); IR (film): 1745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.73 (s, 3H, $COOCH_3$), 3.30 (m, 1H, SCH), 3.23 and 3.18 (ABq, 2H, *J* 14.4 Hz, SCH_2), 0.87 - 1.96 (m, other protons). HR-MS/EI: $C_{13}H_{24}O_2S$ $(M)^+$. Calc.: 244.1497. Found: 244.1505.

***(1S,2S,5R)-2-Isopropyl-5-methylcyclohexylthioacetic acid* (6)**

To a solution of **5** (4.79 g, 19.6 mM) in THF (20 mL) a 1M aqueous of LiOH (22 mL) was added, and stirring was continued for 2 h. THF was evaporated and 1 M HCl (50 mL) was added. Product was extracted with ether (5 × 50 mL). Combined organic extracts were washed with brine, dried over $MgSO_4$, and the solvents were evaporated. The residue was purified by chromatography on a silica gel column (eluent: hexane -acetone, 2 : 1) to give **6** (4.50 g, quantitatively) as a colorless gum, $[\alpha]_D^{20}$ +100.2 (*c* 1.2, ethyl ether); IR (KBr): 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.33 (m, 1H, SCH), 3.25 and 3.20 (ABq, 2H, *J* 14.7 Hz, SCH_2), 0.85 - 2.00 (m, other protons). HR-MS/EI: $C_{12}H_{22}O_2S$ $(M)^+$. Calc.: 230.1341. Found: 230.1353.

***(1S,2S,5R)-2-Isopropyl-5-methylcyclohexylthioacetic acid chloride* (2)**

Method A: The mixture of **6** (5.29 g, 23.0 mM) and $SOCl_2$ (10 mL) was stirred at r.t. for 2 h, and refluxed for 3 h. After removing of excess of $SOCl_2$, product was distilled under vacuum with a short Vigreux column to give 4.80 g (84%) of **2** (b.p. 126 - 128°C at 4 mmHg); $[\alpha]_D^{20}$ +120 (*c* 1.7, benzene); ^1H NMR (C_6D_6): δ 3.06 (m, 1H, SCH), 3.03 and 2.92 (ABq, 2H, *J* 15.3 Hz, SCH_2), 0.60 - 2.00 (m, other protons). HR-MS/EI: $C_{12}H_{21}ClOS$ $(M)^+$. Calc.: 248.1002. Found: 248.1002.

Method B: To a solution of **6** (2.38 g, 10.3 mM) in benzene (20 mL) oxalyl chloride (3.17 g, 25 mM) in benzene (5 mL) was slowly added. The mixture was stirred for 3 h at room temperature and refluxed for 3 h. The solvents were evaporated to give acid chloride **2** (2.6 g, quantitatively). This product was sufficiently pure for the next step.

Preparation of monoesters 7 and 8

To a solution of **2** (2.52 g, 10.0 mM) in dichloromethane (50 mL), triethylamine (50 mM) and racemic binaphthol (1.43 g, 5.0 mM) were added. The stirring was continued for 24 h. Methanol (5 mL) and, after 1 h, water (50 mL) were added. The products were extracted with dichloromethane (3 × 50 mL). Combined organic extracts were washed with 1 M HCl (50 mL), water (50 mL), dried over anh. sodium sulphate and concentrated to dryness. Column chromatography (hexane - ethyl acetate, 10 : 1) of the residue gave first **7** (0.60 g, 24%), next **8** (0.60 g, 24%) followed by unreacted racemic **1** (0.64 g, 45%).

7: $[\alpha]_D^{20}$ -39.5 (*c* 1.23, chloroform); ^1H NMR ($CDCl_3$): δ 7.0 - 8.1 (m, 12H, Ar-CH), 5.19 (s, 1H, OH), 3.04 (m, 1H, SCH), 2.97 (s, 2H, SCH_2), 0.75 - 1.70 (m, other protons). ^{13}C NMR ($CDCl_3$): δ 20.71, 21.11, 22.04 (CH_3); 25.67, 31.78, 35.29, 39.05 (CH_2); 26.03, 29.89, 46.30, 48.59 (CH); 120.30, 123.10, 127.66, 129.04, 132.30, 133.42, 148.00, 151.77 (Ar-C); 118.31, 121.36, 123.57, 124.51, 125.73, 126.38, 126.76, 127.51, 128.00, 128.30, 130.42, 130.91 (Ar-CH), 170.06 (C=O). HR-MS/EI: $C_{32}H_{34}O_3S$ $(M)^+$. Calc.: 498.2228. Found: 498.2227.

8: $[\alpha]_D^{20}$ +77.2° (*c* 1.84, chloroform); ^1H NMR ($CDCl_3$): δ 7.0 - 8.1 (m, 12H, Ar-CH), 5.14 (s, 1H, OH), 2.98

(s, 2H, SCH_2), 2.94 (m, 1H, SCH), 0.75 - 1.70 (m, other protons). ^{13}C NMR ($CDCl_3$): δ 20.70, 21.03, 22.06 (CH_3); 25.61, 32.33, 35.24, 39.46 (CH_2); 26.13, 29.80, 46.85, 48.66 (CH); 122.96, 129.03, 132.27, 133.44, 148.00, 151.66 (Ar-C); 118.16, 121.41, 123.53, 124.57, 125.73, 126.36, 126.73, 127.49, 127.98, 128.29, 130.41, 130.86 (Ar-CH), 170.11 (C=O). HR-MS/EI: $C_{32}H_{34}O_3S$ $(M)^+$. Calc.: 498.2228. Found: 498.2227.

Reduction of esters 7 and 8

To a cooled (-20°C) suspension of $LiAlH_4$ (115 mg, 3.0 mM) in THF (2 mL), a solution of **7** (500 mg, 1.0 mM) in THF (5 mL) was slowly added. After 30 min., water (0.2 mL) and 10% HCl (1 mL) were added and the mixture was allowed to attain room temperature. Silica gel (3 g) was added and the solvents were evaporated. Column chromatography (hexane - ethyl acetate, 4 : 1) of the residue gave S-(-)-binaphthol (245 mg, 85%); $[\alpha]_D^{20}$ -33.7 (*c* 1.1, THF); lit.[23]: $[\alpha]_D^{20}$ -33.2 (*c* 1.1, THF); m.p.: 206 - 207°C; lit.[24]: m.p.: 209 - 211°C.

Reduction of **8** (as above) gave R-(+)-binaphthol (245 mg, 85%); $[\alpha]_D^{20}$ +33.5 (*c* 1.0, THF); lit.[12]: $[\alpha]_D^{25}$ +33.6 (*c* 1.11, THF); m.p.: 206 - 207°C; lit.[12]: 207 - 209°C.

ACKNOWLEDGMENTS

This work was financed from the Grant No. P303 013 05 obtained from the State Committee for Scientific Research (KBN).

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(*Received in UK* 22 *November* 1994)