Mechanical Resolution of 1-Phenylethyl 2-Pyridyl Sulfide and Determination of Its Absolute Configuration

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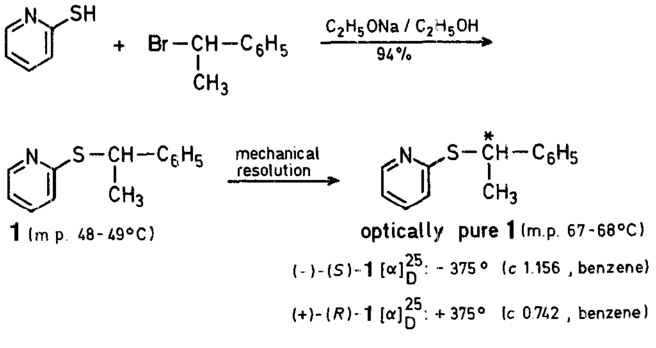
Optically active compounds are usually prepared by chemical or biological methods[1]. However, the simplest way to obtain optically active compounds is to separate a racemate into enantiomers by recrystallization or chromatography. In the field of organosulfur chemistry there is an increasing demand to prepare optically active compounds[2]. Recently it was reported that anthracenyl-sulfoxides can be separated into enantiomers by liquid chromatography[3]. It has been found that upon crystallization methanesulfinic acid forms single crystals containing a single enantiomer having the *R*- or *S*-configuration, as identified by X-ray crystallographic analysis[4]. We have found that 2-methoxyphenyl-phenyl-*N*-tosylsulfilimine can be readily separated into its pure enantiomers by simple mechanical resolution[5]. In order to find further applications of this method to organosulfur compounds, we attempted the resolution of other racemic organosulfur compounds by mechanical separation and found that 1-phenylethyl 2-pyridyl sulfide (**1**) can also be separated into its enantiomers by hand.

Racemic 1-phenylethyl 2-pyridyl sulfide (**1**) was prepared from 2-mercaptopyridine and 1-bromo-1-phenylethane in the presence of alkali[6] and was separated into its enantiomers by simple mechanical resolution. The optically pure sulfide **1** thus separated from the racemate could be used as a seed crystal for the inoculation method so that the optically active sulfide **1** could then be obtained on a large scale. The enantiomeric excess of the sulfide **1** separated by mechanical resolution was determined by ^{1}H-N.M.R. spectrometry in $CDCl_3$ using $Eu(tfc)_3$, tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium, as shift reagent and observing the ratio of the methyl signals. It was found that by the present method both enantiomers can be obtained in optically pure form (o.p. = 100%).



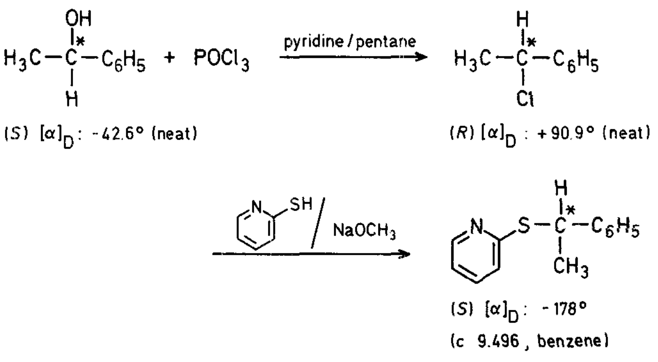
1 (m.p. 48–49°C)

optically pure **1** (m.p. 67–68°C)

(−)-(*S*)-**1** $[\alpha]_D^{25}$: −375° (c 1.156, benzene)

(+)-(*R*)-**1** $[\alpha]_D^{25}$: +375° (c 0.742, benzene)

In order to determine the absolute configuration of the enantiomeric sulfides (+)-**1** and (−)-**1**, the authentic optically active 1-phenylethyl 2-pyridyl sulfide was prepared starting from (−)-1-phenylethanol having the (*S*)-configuration by converting it into (+)-(*R*)-1-chloro-1-phenylethane which upon reaction with sodium pyridine-2-thiolate afforded the enantiomer (−)-**1** having an optical rotation of −178°.

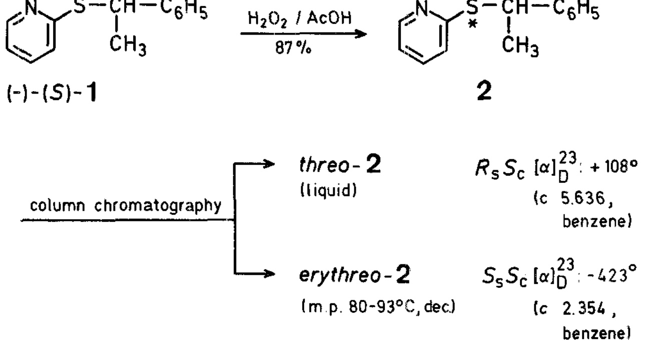


(*S*) $[\alpha]_D$: −42.6° (neat)

(*R*) $[\alpha]_D$: +90.9° (neat)

(*S*) $[\alpha]_D$: −178° (c 9.496, benzene)

The (*S*)-configuration of the sulfide (−)-**1** obtained by mechanical resolution was further proven by oxidation to the corresponding sulfoxide (**2**) which could be separated into its diastereoisomers (*threo*-**2** and *erythro*-**2**) by column chromatography on alumina (200 mesh) using petroleum ether (b.p. 30–60°C)/ethyl acetate/ether (16/3/2) as eluent[6].



threo-**2** (liquid) R_SS_C $[\alpha]_D^{23}$: +108° (c 5.636, benzene)

erythreo-**2** (m.p. 80–93°C, dec.) S_SS_C $[\alpha]_D^{23}$: −423° (c 2.354, benzene)

The absolute configurations of both S and C atoms in *erythro*-**2** were determined by X-ray crystallographic analysis and the absolute configuration of *erythro*-**2** was determined as S_SS_C as shown in the figure.

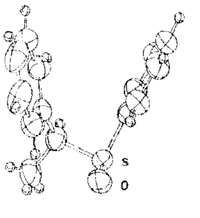


Figure. Absolute Configuration of *erythro*-**2** (S_SS_C) as determined by X-Ray Analysis

Thus, the absolute configuration of (−)-**1** has been determined to be the (*S*)-configuration[7].

Resolution of 1-Phenylethyl 2-Pyridyl Sulfide (1)[6]; Typical Procedure: The racemic sulfide **1** is recrystallized slowly from hexane. The optical rotation of each crystal thus obtained is measured (polarimeter). The crystals having the same optical rotation are collected and recrystallized from hexane once or twice until the maximum rotation has been reached. As the maximum rotation of (+)-**1**, $[\alpha]_D^{25}$: +375° (*c* 0.742, benzene) is obtained; m.p. 67–68 °C. By this mechanical resolution, both the (−)- and (+)-enantiomers of **1** are obtained. Once the optically pure (+)-**1** or (−)-**1** has been isolated it can be used as a seed crystal to separate the racemic compound **1** into the optically pure forms by an inoculation procedure. For example, the solution of **1** (7 g) in hexane (~ 15 ml) in a 50 ml flask loosely capped with aluminum foil is warmed at 50–55 °C for 1 h using an oil bath (careful temperature control!) and then the temperature is lowered to 38 °C. After 1 h, the small crystals of optically pure (+)-**1** are added to this saturated solution and the solution is allowed to stand overnight at 38 °C. Almost optically pure (+)-**1** is obtained: 168 mg; $[\alpha]_D^{23}$: +373° (*c* 3.518, benzene). Then, the mother liquor is warmed again at 50–55 °C for 1 h, the temperature lowered to 38 °C as before, and small crystals of optically pure (−)-**1** are added. Almost optically pure (−)-**1** is obtained: 168 mg; $[\alpha]_D^{23}$: −375° (*c* 3.36, benzene). A new portion of racemic **1** is added to the solution and the procedure repeated.

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[7] Detailed data will be reported soon by F. Iwasaki.