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An improved synthesis of (*S*)-(+)- and (*R*)-(−)-[2.2]paracyclophane-4-carboxylic acid

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Abstract

Treatment of 4-bromo[2.2]paracyclophane with n-butyllithium followed by CO_2 produced [2.2]paracyclophane-4-carboxylic acid, **1**. Both enantiomeric forms [63% of (+)-(*S*)-**1** and 48% of (−)-(*R*)-**1**] were obtained by resolution via the corresponding diastereomeric α-(*p*-nitrophenylethylammonium salts.

Historically [2.2]paracyclophane-4-carboxylic acid **1** proved to be the first representative of optically active derivatives in the [2.2]paracyclophane series.[1] To date **1** has provided a basis for the synthesis of numerous mono-[2] and several disubstituted[3] planar chiral paracyclophanes.

On the other hand a host of chiral auxiliaries for asymmetric synthesis could be elaborated starting with **1**. However only few applications of **1** in stereochemical practice have been reported, amongst which a determination of the configuration of paracyclophane derived helicenes[4] and an attempted resolution of racemic ephedrine into enantiomers[5] have been described. Such a neglect of **1** could be explained at least in part by some disadvantages of the procedures employed for its synthesis and resolution.

Two different techniques for the resolution of acid **1** into enantiomers have been outlined previously. The salt prepared from acid **1** and brucine gave (*R*)-**1** in 54% yield after five successive crystallizations. Attempts to obtain the other enantiomer of **1** *via* various alkaloid salts failed but it was isolated by the fractional crystallization of partially resolved **1** in low yield (less than 8%).[1] An alternative method involved the crystallization of the diastereomeric salts of **1** with (*S*)-α-phenylethylamine.[2,6,7] In this way, the (*S*)-enantiomer of **1** was reportedly obtained as a result of repeated crystallizations of a less soluble (*S*,*S*)-diastereomeric salt. The isolated yield of (*S*)-**1** was not reported, however the yield of the initial (*S*,*S*)-salt was 40–47%. There were no attempts made at isolating the other enantiomer. In our hands the resolution of **1** using α-phenylethylamine gave unsatisfactory results. The (*S*,*S*)-diastereomer did not crystallize selectively and satisfactory diastereomeric purity was achieved only after the third

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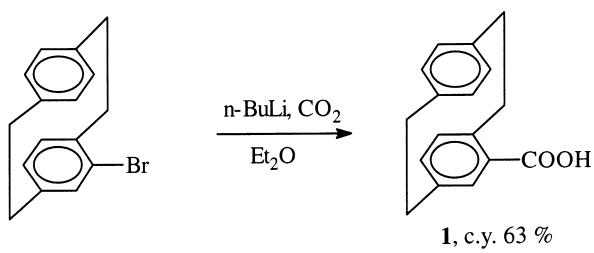
crystallization. As a result the chemical yield of enantiomerically pure (*S*)-**1** was much less than claimed earlier.[7]

According to the literature data racemic **1** could be obtained by the acylation of the parent [2.2]paracyclophane followed by oxidation of the resultant 4-acetyl[2.2]paracyclophane in a 64% overall yield.[1] Another known approach which involved bromination of [2.2]paracyclophane and its conversion to the activated [2.2]paracyclophane Grignard reagent, followed by carboxylation gave crude **1** (m.p. 210–221°C) in 97.5% yield.[7] However this method suffers badly from the necessity to use potassium metal and requires special high vacuum equipment, low-temperature conditions and a long reaction time (about 20 h).

In this article we report a modified resolution of **1** together with a convenient procedure for its synthesis.

In the present work the synthesis of racemic **1** was carried out as indicated in Scheme 1 by the lithiation of 4-bromo[2.2]paracyclophane[8] with n-butyllithium in Et_2O at room temperature. The one-pot carboxylation of the resultant lithium intermediate with CO_2[9] furnished analytically pure **1** in 63% yield (Scheme 1).

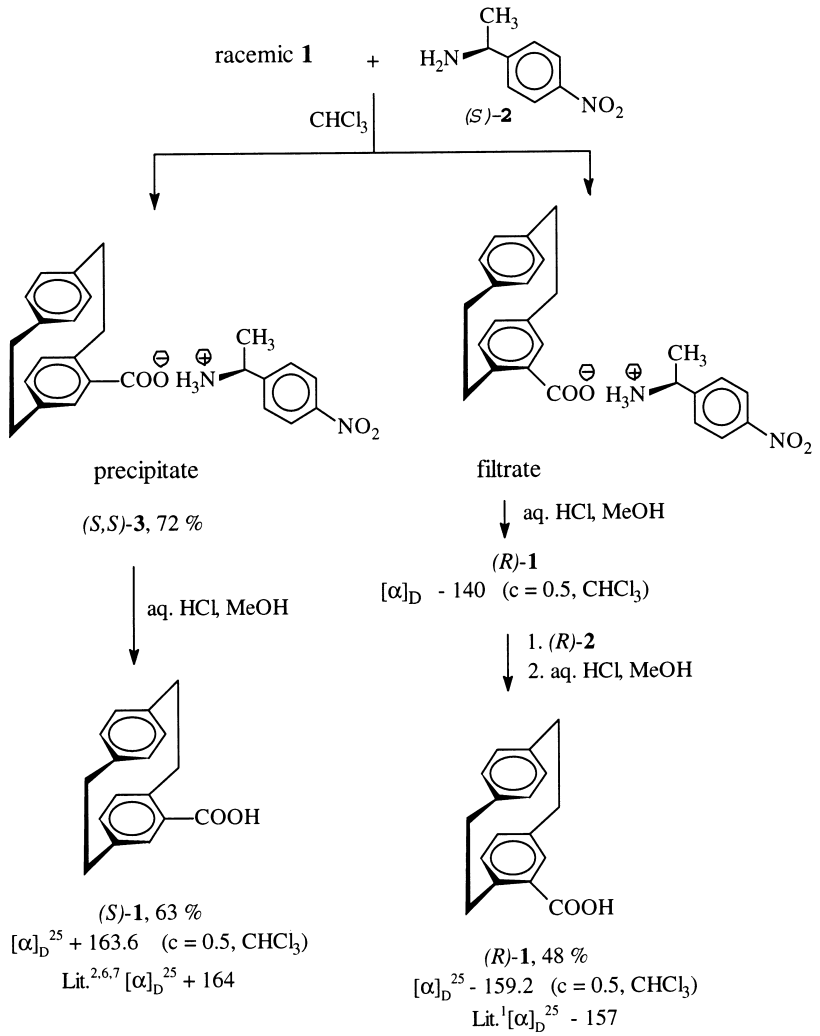


1, c.y. 63 %

Scheme 1.

We applied α-(*p*-nitrophenyl)ethylamine **2**[10] as an agent to resolve **1**. The addition of (*S*)-**2** to a solution of racemic **1** in $CHCl_3$ at room temperature afforded a mixture of two diastereomeric salts from which a single diastereomer, (*S*,*S*)-**3** precipitated at −5°C with a chemical yield of 72%. Enantiomerically pure (+)-(*S*)-[2.2]paracyclophane-4-carboxylic acid ((*S*)-**1**) was recovered in 63% yield upon hydrolysis of the salt with aqueous HCl in MeOH. Then the (*R*,*S*)-diastereomer, which remained in the mother liquor, was decomposed in the same way and (*R*)-**1** was isolated with 84% e.e. The enantiomeric purity of (*R*)-**1** could be upgraded to e.e.≥97% by reaction with (*R*)-**2** and precipitation of (*R*,*R*)-**3** from ethanol. After hydrolysis of (*R*,*R*)-**3** the chemical yield of (*R*)-**1** was 48%. The whole procedure is represented in Scheme 2. It should be mentioned that the specific rotation of the salts may vary somewhat from one sample to another ($[\alpha]_D$ values are between +38.3 and +46.2 for (*S*,*S*)-**3** and −51.5 for (*R*,*R*)-**3**), nevertheless the acid released always had reproducible specific rotation values.[11]

The method described above greatly simplifies the synthesis of **1** in both enantiomeric forms and consequently makes the derivative more available for synthetic applications, including stereochemical ones.



Scheme 2.

1. Experimental section

1.1. General

Optical rotations were measured with a Perkin–Elmer-241 polarimeter in a thermostated cell at 25°C. TLC analysis was performed on silica-gel precoated plates Silufol UV-254 (Chemapol). Et_2O was distilled from benzophenone ketyl under argon immediately before use.

4-Bromo[2.2]paracyclophane[8] and (−)-(*S*)- and (+)-(*R*)-α-(*p*-nitrophenyl)-ethylamines [(*S*)- and (*R*)-**2**][12] were prepared by literature methods.

*1.2. [2.2]Paracyclophane-4-carboxylic acid **1***

n-Butyllithium (11.2 ml of a 2.8 M solution in hexane, 33.6 mmol) was added to a stirred solution of 4-bromo[2.2]paracyclophane (6.24 g, 21.76 mmol) in Et_2O (400 ml) under argon and the reaction mixture

was stirred at room temperature for 2 h, then an excess of dry ice was added. The reaction mixture was allowed to warm to room temperature, the solvent was evaporated to dryness and the solid residue was dissolved in H_2O (500 mL). Insoluble [2.2]paracyclophane was filtered off and the aqueous phase was thoroughly washed with ether (3×75 mL) and CH_2Cl_2 (3×75 mL) to remove traces of the latter. 50 mL of 2 N HCl solution was added to an aqueous phase, the precipitate formed was collected by filtration, washed with H_2O (3×100 mL) and dried at reduced pressure to yield 3.44 g (63%) of racemic **1**. M.p. 223–224°C (lit.[1] m.p. 223.5–224.5°C).

*1.3. Resolution of **1***

A mixture of racemic **1** (1.0 g, 4.0 mmol) and (−)-(*S*)-α-(*p*-nitrophenyl)ethylamine (0.6 mL, 4.3 mmol) in $CHCl_3$ (35 mL) was stirred at room temperature for 1 h, then at 50°C for 2 h until the white solid precipitated from the solution. To complete the precipitation the reaction mixture was kept overnight at −5°C. The filtration and drying of the precipitate formed gave (*S*,*S*)-**3** as colorless crystals (0.6 g, 72%). $[\alpha]_D$=+38.3 (c 0.24 acetone). The salt was dissolved in MeOH and hydrolyzed with 2 N HCl. The precipitated solid was washed twice with H_2O (2×50 mL) to yield 0.315 g (63%) of (*S*)-(+)-[2.2]paracyclophane-4-carboxylic acid: $[\alpha]_D$=+163.6 (c 0.5 $CHCl_3$), (lit.[2] $[\alpha]_D$=+164); m.p. 212–214°C (lit.[1] m.p. 211–213°C).

The $CHCl_3$ filtrates, containing partially enriched (*S*,*R*)-**3**, after evaporation and hydrolysis gave a partially resolved (*R*)-**1** (0.56 g) with $[\alpha]_D^{25}$=−140 (c 0.5, $CHCl_3$). This compound was mixed with (+)-(*R*)-α-(*p*-nitrophenyl)ethylamine (0.32 mL, 2.25 mmol) in $CHCl_3$ (20 mL). Single crystallization of the resultant diastereomeric mixture from EtOH afforded 0.42 g (50%) of diastereomeric salt (*R*,*R*)-**3**, $[\alpha]_D$=−51.5 (c 0.25 acetone). Hydrolysis of (*R*,*R*)-**3** gave 0.24 g (48%) of (*R*)-**1** with $[\alpha]_D^{25}$=−159.2 (c 0.5 $CHCl_3$), (lit.[1] $[\alpha]_D$=− 157). M.p. 213.5–215.5°C (lit.[1] m.p. 211.5–213°C).

Acknowledgements

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