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A New Procedure for the Synthesis of Optically Active *t*-Butylphenylphosphinothioic Acid

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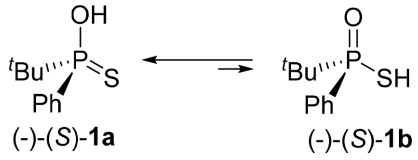
ABSTRACT: *A new procedure for the synthesis of optically active t-butylophenylphosphinothioic acid as an enantiomerically pure dextrorotatory enantiomer having the absolute configuration (R), by a reaction of the racemate of secondary t-butylphenylphosphine oxide with elemental sulfur in the presence of a molar equivalent of the levorotatory enantiomer of enantiomerically pure (S)-α-phenylethylamine, is reported. It is obvious that with the use of the dextrorotatory enantiomer of α-phenylethylamine, the levorotatory enantiomer of this thioacid will be isolated.* © 2014 Wiley Periodicals, Inc. Heteroatom Chem. 25:674–677, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21206

INTRODUCTION

In recent years, determining the enantiomeric excesses of chiral compounds has become a very important research topic [1]. This result is mainly based on the recent advances in the stereoselective (especially in enantioselective) synthesis [2] that induce the need for rapid and accurate determination of this parameter. Among the techniques used for this purpose, the NMR measurements have found so far the widest application [1]. The most advantageous and simple experiments are based on the use of chiral solvating agents (CSAs).

They form with an enantiomeric pair diastereoisomeric solvation complexes, which are in dynamic equilibrium and should show in principle nonequivalent spectra. At present, more than 50 compounds have been used to determine the enantiomeric excess values for a variety of organic derivatives with a stereogenic carbon or heteroatom such as sulfur or phosphorus. Most of them are applied for the determination in a particular group of organic compounds and only a few have wider application scope. Among CSAs reported in the literature, (–)-(*S*)- and (+)-(*R*)-*t*-butylphenylphosphinothioic acid **1** (which exists in only one tautomeric structure and one conformation in CCl_4 solution [3] [Eq. (1)]) turned out to have the widest application for NMR analysis of many classes of chiral organic compounds. They are listed in the recent minireview prepared in our group [4].



(-)-(*S*)-**1a** ⇌ (-)-(*S*)-**1b** (1)

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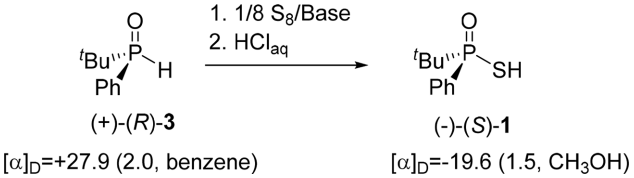
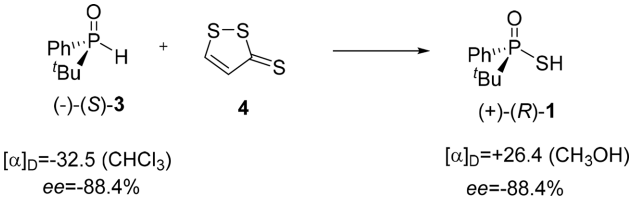
Dedicated to the 77th birthday of Professor Okazaki.



SCHEME 1



SCHEME 2

RESULTS AND DISCUSSION

The resolution of racemic *t*-butylphenylphosphinothioic acid **1** via the diasteromeric quinine salt was mentioned (without giving any details) as early as in 1971 [5]. A few years later, it was reported [6–9] that this thioacid readily forms crystalline salts with enantiomers of α-phenylethylamine **2**, both of which have been used to effect a resolution of the thioacid. Optically active thioacid **1** was also prepared directly by the addition of elemental sulfur to optically active *t*-butylphenylphosphine oxide **3** [10–12] for which the (*R*) absolute configuration was assigned by chemical correlation (Scheme 1) [10–12] and using vibrational circular dichroism [13].

Moreover, the levorotatory phosphine oxide (–)-(*S*)-**3** and thione **4** gave also the dextrorotatory enantiomer of *t*-butylphenylphosphinothioic acid (+)-(*R*)-**1** with full retention of configuration at the stereogenic phosphorus atom (Scheme 2) [14].

Here, we would like to report details of a recently patented, new protocol for the synthesis of an optically active *t*-butylophenylphosphinothioic acid **1** in the form of the enantiomerically pure dextrorotatory enantiomer having the absolute configuration (*R*), by the reaction of the racemate of a secondary *t*-butylphenylphosphine oxide **3** with elemental sulfur in the presence of enantiomerically pure (*S*)-α-phenylethylamine **2** [15]. A new procedure shown in Scheme 3 consists in that a molar equivalent of elemental sulfur is added to a solution of racemic oxide **3** and molar equivalent of the levorotatory enantiomer of enantiomerically pure (*S*)-α-phenylethylamine **2** in a mixture of ether and chloroform, after which the formed and precipitated from solution, harder soluble salt of the optically active dextrorotatory thioacid **1** of configuration (*R*) with (*S*)-α-phenylethylamine **2** is filtered and crystallized, and converted to the optically active dextrorotatory enantiomer of thioacid **1** of the absolute configuration (*R*) by an aqueous basic-acidic work-up. The optically active levorotatory thioacid **1** of configuration (*S*) was isolated by a similar work-up of the mother liquor, which contains a better soluble salt of the optically active levorotatory thioacid **1** of configuration (*S*) with (*S*)-α-phenylethylamine **2**. Obviously with the use of the dextrorotatory enantiomer of α-phenylethylamine **2**, the levorotatory enantiomer of this thioacid **1** will be isolated from the harder soluble salt.

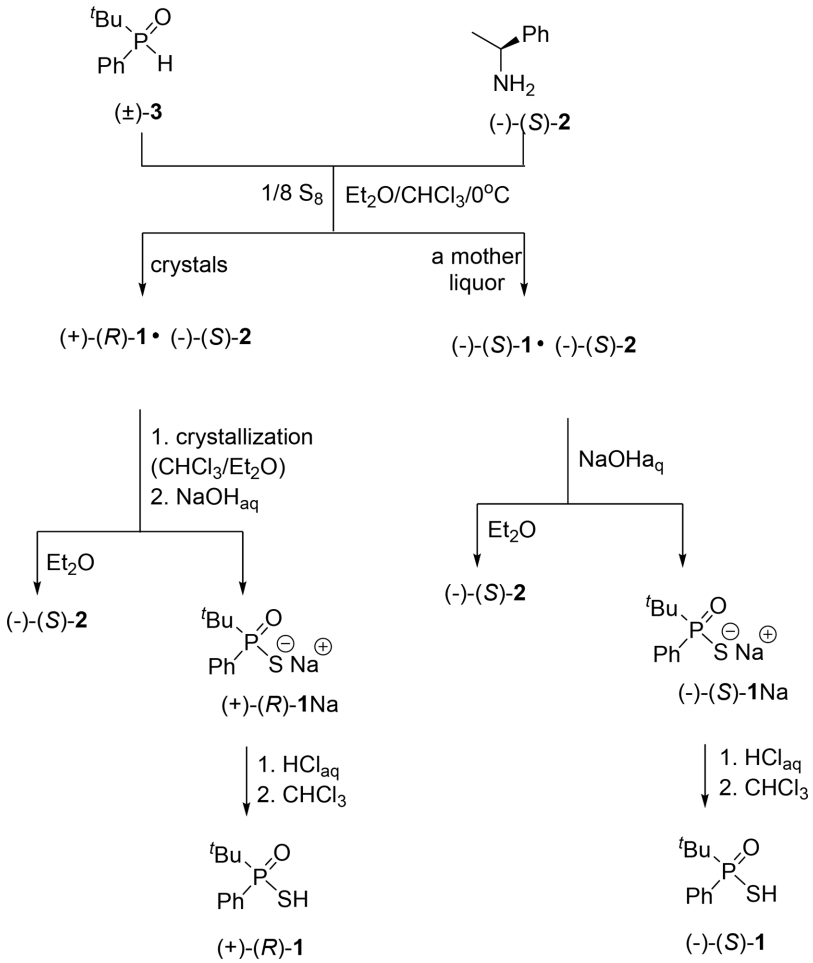
EXPERIMENTAL

General

All the reagents and solvents were commercially available and were used without further purification. Thin-layer chromatography was carried out on glass plates coated with silica gel (Merck (Darmstadt, Germany), Kiesegel 60F254, precoated 0.25 mm). The NMR spectra were obtained on a Bruker spectrometer Avance AV 200 (Bruker, Karlsruhe, Germany) (200.16 MHz (1H), 50.30 MHz (^{13}C NMR) in $CDCl_3$). Mass spectral data were collected on a MAT95–Finnigan spectrometer (Finnigan MAT, Bremen, Germany). Optical rotation was determined on a 241 MC–Perkin Elmer polarimeter (Perkin Elmer, Vienna, Austria) at room temperature. Melting point was determined on a Betius apparatus (PHMK VEB Analytik, Dresden, Germany) and is uncorrected. Diethyl ether was dried and distilled over metal sodium with the addition of benzophenone in dry argon. The reactions were carried out under dry argon. Racemic *t*-butylphenylphosphine oxide **3** was obtained by the modified Hoffmann and Schellenbeck method [16].

Optically Active t-Butylphenylphosphinothioic Acid

To a magnetically stirred solution of racemic *t*-butylphenylphosphine oxide **3** (5.52 g, 30 mmol) and the enantiomerically pure (–)-(*S*)-α-phenylethylamine **2** (3.63 g, 30 mmol) in a mixture of diethyl ether (40 mL) and chloroform (30 mL), elemental sulfur (0.96 g, 30 mmol) was added in two portions at 0°C. After the addition of a second portion of the sulfur, the reaction mixture was kept at a temperature below 15°C for 1 h. After this time, the formed crystalline salt was filtered (3.389 g, 34.5%). It is characterized by the following spectroscopic and analytical data:



SCHEME 3

$[\alpha]_{589}$ = + 28.2 (c = 1.46,$CHCl_3$), mp = 182–192°C; ^{1}H NMR ($CDCl_3$) δ = 0.96 and δ = 1.06 (d, J = 16.26 Hz, 9H) (the composition of δ = 0.96/δ = 1.06 = 3/21), δ = 1.47 (d, J = 6.85 Hz, 3H), δ = 4.19 (q, J = 6.85 Hz, 1H), δ = 6.63 (very broad singlet, 3H), δ = 7.22 – 7.39 (m 8H), δ = 7.69 – 7.79 (m, 2H); ^{31}P NMR ($CDCl_3$) δ = 80.65 (s) and δ = 80.98 (s) the composition of δ = 80.65/δ = 80.98 = 52.67/5.17. The isolated salt was crystallized by dissolving in refluxing $CHCl_3$ (20 mL) and adding diethyl ether (25 mL). The resulting crystals (2.7 g, 27.4%) were characterized by the following spectroscopic and analytical data:

$[\alpha]_{589}$ = +32.8 (c = 1.49, $CHCl_3$), mp = 189–192°C; ^{1}H NMR ($CDCl_3$) δ = 1.00 (d, J = 16.25 Hz, 9H), δ = 1.47 (d, J = 6.85 Hz, 3H), δ = 4.21 (q, J = 6.85 Hz, 1H), δ = 7.21 – 7.38 (m, 11H), δ = 7.67–7.77 (m, 2H); ^{31}P NMR ($CDCl_3$) δ = 80.39 (s) and δ = 80.88 (s) the composition of δ = 80.39 / δ = 80.88 = 8.34/0.31. These crystals were dissolved in water (30 mL) and solid sodium hydroxide (4 g) was added to this solution. The resulting slurry was extracted with ethyl ether (3 × 15 mL). The aqueous layer was acidified with aqueous 3.5 molar HCl until strongly acidic, and the precipitate was transferred to the organic layer by shaking the water layer with chloroform (3 × 15 mL). The chloroform extract was dried over anhydrous magnesium sulfate. The concentration of the organic solution initially at a pressure of 15 mm Hg and then at 1 mm Hg at room temperature provided a chemically pure (+)-(*R*)-**1** (1.86 g, 29.0%). It is characterized by the following spectroscopic and analytical data:

$[\alpha]_{589}$ = 28.7 (c = 1.24, MeOH); mp = 97–99°C [lit. for the racemate mp = 124–125°C; for (+)-(*R*) enantiomer mp = 103–106°C (softens at 96°C [6a]. ^{1}H NMR ($CDCl_3$) δ = 1.14 (d, J = 17.61 Hz, 9H), δ = 7.27 – 7.46 (m, 4H), δ = 7.67 – 7.77 (m, 2H), ^{31}P NMR ($CDCl_3$); δ = 98.39 (s), MS (CI/isobutane): *m/z* 215.1 [M + 1]. The remaining solution after filtration of the crystalline salt (3.389 g, 34.5%) was concentrated to give an oily residue, which was slowly crystallized (7.125g, 65.5%). It is characterized by the following spectroscopic and analytical data: [α] 589 = – 21.0

(c = 1.4, $CHCl_3$), mp = 90–101°C; ^{1}H NMR ($CDCl_3$) δ = 0 .96 and δ = 1.06 (d, J = 16.26 Hz, 9H) (the composition of δ = 0.96 / δ = 1.06 = 68.87/26.79), δ = 1.47 (d, J = 6.85 Hz, 3H), δ = 4.19 (q, J = 6.85 Hz, 1H), δ = 6.63 (broad singlet, 3H), δ = 7.22 – 7.39 (m, 8H), δ = 7.69 – 7.79 (m, 2H). ^{31}P NMR ($CDCl_3$) δ = 80.84 (s) and δ = 80.93 (s) the composition of δ = 0.80.84/δ = 80.93 = 21.88/39.48. The levorotatory enantiomer (–)-(*S*)-**1** (3.21 g, 50.0%) was isolated from the diastereomeric salt by following the procedure described above for the diastereomeric salt comprising (+)-(*R*)-enantiomer of the thioacid **1**. It is characterized by spectroscopic data analogous to those described for the dextrorotatory isomer (+)-(*R*)-**1** and the specific rotation $[\alpha]_{589} = -14.7$ (c = 1.4, MeOH) and mp = 97–106°C.

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