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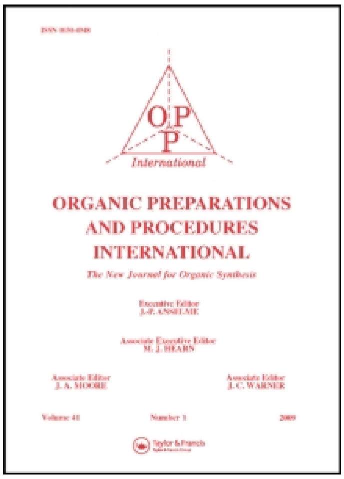

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IMPROVED PROCEDURE FOR THE LARGE SCALE SYNTHESIS OF 1,2,3,4,4a,9b-HEXAHYDRODIBENZOTHIOPHENE

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IMPROVED PROCEDURE FOR THE LARGE SCALE SYNTHESIS OF 1,2,3,4,4a,9b-HEXAHYDRODIBENZOTHIOPHENE

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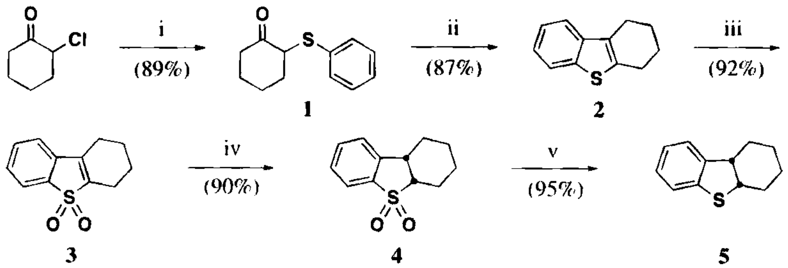
1,2,3,4,4a,9b-Hexahydrodibenzothiophene (**5**) is an important intermediate[1] in the hydrodesulfurization of dibenzothiophene. Hydrodesulfurization is the catalytic process by which sulfur is removed from petroleum feed stock by treatment with hydrogen. Dibenzothiophene is a source of residual sulfur in gasoline and is used as a standard for evaluating catalysts employed in hydrodesulfurization.[1] The new standards recently promulgated by the EPA will require processors to lower the sulfur content of gasoline from 300 ppm to 30 ppm by the year 2004 at a time when the sulfur content in crude oil is increasing. Knowledge of the precise thermochemical properties of **5** is required to implement improvements in catalyst design and other petroleum processing technology. Despite the utility and importance of this compound, it remains poorly characterized in the literature.[2] A large (75 g), high purity (>99.9 %) sample of **5** was needed for thermodynamic studies.[3] A preparation[4] producing milligram quantities of compound **5** has been reported, giving only 80 mg of compound **5** as an oil in an overall yield of 22%.[5] The step responsible for the low yield was the oxidation of compound **2** to sulfone **3** with hydrogen peroxide. We now report an improved synthesis of *cis*-1,2,3,4,4a,9b-hexahydrodibenzothiophene utilizing sodium perborate in the oxidation step. The present procedures yield a solid product, mp 41-42°, in an overall yield of 61% (*Scheme*).



i)PhSH, K_2CO_3, RT, 3 days ii) PPA, 100°, 5 h iii) $NaBO_3 \cdot 4H_2O$, HOAC, 50-60°
iv) H_2, Pd/C, HOAC, 60 psi v) $LiAlH_4$, ether, Δ, 2 h.

Scheme 1

The synthesis of **2** proceeded in a fashion similar to published reports.[4] In an effort to achieve high purity intermediates, the preparation of **1** was carried out at room temperature instead of in acetone at reflux. Compound **1** was added to polyphosphoric acid (PPA) and the temperature maintained at 100°. Effective mixing and stirring was essential to afford complete cyclodehydration. In initial attempts of the large scale synthesis of **2**, the use of a standard round bottom flask did not allow efficient mixing and a small amount of **1** was left unreacted. Several efforts to purify **2** through vacuum distillation *via* a vacuum jacketed Vigreux column resulted in co-distillation of **1** and **2**. Use of a Morton flask with mechanical stirring allowed the complete conversion of **1** to **2**.

The remaining steps of the synthesis involve a series of oxidation and reduction reactions. In the previously published procedure, compound **2** was oxidized to sulfone **3** with hydrogen peroxide in 43% yield (crude). Our attempts to reproduce this result gave a 56% yield (crude) and a 32% yield of purified product. This compares to a 95% yield for the conversion of benzothiophene to benzothiophene sulfone.[6] Attempts to improve the hydrogen peroxide method were unsuccessful. Benzothiophene had also been converted to the corresponding sulfone with sodium perborate in good yield and purity (95%), although the methodology was not extended to the oxidation of alkyl substituted benzothiophenes.[7] Treatment of **2** with sodium perborate resulted in a 92% yield of **3**. Large scale hydrogenation of compound **3** was carried out using a 5 liter pressure reactor and a "Super Magnet" stirrer with a raised ring stirbar[8] which afforded compound **4** in a 90% yield. The combination of "Super Magnet" and pressure reactors allowed the convenient scale-up of reactions without the need for two different sized hydrogenation shakers. In the final step, sulfone **4** was reduced to compound **5** with lithium aluminum hydride. Compound **5** was fractionally distilled under reduced pressure to yield an oil which solidified upon cooling in a 95% yield.

In the previous preparations, compound **5** was reported to be an oil at room temperature and there was no indication of the stereochemistry of the fused rings. The title compound can be *cis* or *trans*, depending upon the stereochemistry of the thiophene-cyclohexane ring juncture. The catalytic hydrogenation of **3** to **4** would be expected to lead to the *cis*-isomer. However, the sulfone group makes compound **4** susceptible to epimerization and could lead to the *trans*-isomer during the hydrogenation step or the step involving the reduction of **4** to **5**. The H_{4a}-C_{4a}-C_{9b}-H_{9b} dihedral angles obtained from Hartree-Fock calculations with the STO-3G basis set, are approximately 40° and 169° for the *cis* and *trans*-isomers, respectively.[9] The calculated coupling constants between these hydrogen atoms are expected to be about 6 Hz for the *cis*-isomers and 11 Hz for the *trans*-isomer.[10] As only two signals are observed for the ring juncture hydrogens (H_{4a} and H_{9b}) and as GC analysis shows a single peak, the sample is believed to consist only of one isomer. The coupling constant of the ring juncture hydrogens, J_{4a-9b}, was determined to be 5.7 Hz,[11] a value much more reasonable for the *cis*-isomer than for the *trans*-isomer. In addition to the NMR data, molecular calculations predict the *cis*-isomer to be more stable. Based on these data, the synthesized compound is assigned to be the *cis*-isomer.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp apparatus and are uncorrected. All reagents were reagent grade and were used as received; the ether used in reactions was anhydrous grade from freshly opened containers. NMR spectra were determined on 200 MHz and 400 MHz Varian instruments; all chemical shifts (δ) are relative to TMS. Gas chromatographic data was obtained from a HP 5890A instrument with FID, 30 M x 0.32 mm column coated with 0.25 micron of DB-1 (J & W Scientific). The elemental analysis were carried out by Atlantic Microlab, Inc., Norcross, Georgia.

1,2,3,4-Tetrahydrodibenzothiophene (2).- A mixture of 2-chlorocyclohexanone (300 g, 2.26 mol), thiophenol (220 ml, 2.14 mol) and potassium carbonate (307 g, 2.22 mol) in acetone (2.0 L) was stirred for 3 days (magnetic stirrer). Ether (2.0 L) was then added and the resulting solution was washed with water, dried ($MgSO_4$) and evaporated to afford 395 g (89%) of **1** as an oil which slowly solidified upon standing to form yellow needles, mp. 46-48°, *lit.*[4a] mp. 53-54°. A solution of **1** (395 g, 1.91 mol) in polyphosphoric acid (2 Kg) was stirred for 3 h. at 80-100°. The resulting red solution was cooled to room temperature, poured onto ice, then extracted with ether. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The crude product was distilled *in vacuo* to afford 312 g (87%) of **2** as a pale yellow oil, bp. 114-115° (0.04 mmHg), *lit.*[4a] bp. 110-120° (0.04 mmHg). ^1H NMR (200 MHz, $CDCl_3$): δ 7.74 (d, 7.6 Hz, 1H), 7.54 (d, 7.3 Hz, 1H), 7.35-7.15 (m, 2H), 2.95 -2. 75 (m, 2H), 2.75-2.65 (m, 2H), 2.00-1.80 (m, 4H).

1,2,3,4-Tetrahydrodibenzothiophene Sulfone (3).- Sodium perborate tetrahydrate (368 g, 2.40 mol) was added in portions to a stirring solution of **2** (150 g, 0.80 mol) in acetic acid (2.5 L) at 45-50° for 1 h. The reaction mixture was cooled and the volatile materials were evaporated *in vacuo*. The non-volatile material was triturated by stirring overnight with water (4 L) and filtered. The collected product was dissolved in ethyl acetate and filtered. The aqueous solution was extracted with ethyl acetate. The combined organic solutions were dried ($MgSO_4$) and evaporated. The crude product was recrystallized from 95% ethanol to afford 163 g (92%) of **3** as shiny white crystals, mp. 195-197°, *lit.*[4b] mp. 188-189°. ^1H NMR (200 MHz, $CDCl_3$): δ 7.71 (d, 7.3 Hz, 1H), 7.60 -7. 35 (m, 2H), 7.29 (d, 8.4 Hz, 1H), 2.53 (s, 4H), 1.87 (s, 4H).

***cis*-1,2,3,4,4a,9b-Hexahydrodibenzothiophene Sulfone (4)**.- To a 5-L glass pressure reactor was added a 3 inch stirring magnet, a solution of **3** (300 g, 1.36 mol) in acetic acid (4L), and 10% Pd/C (50 g, 0.047 mol). The resulting slurry was stirred using a "Super Magnet" and pressurized to 56 psig with hydrogen. The reactor was periodically recharged to between 52 and 56 psig over the next 6.5 h. before being left overnight at a pressure of 52 psig. After16 h, the pressure had dropped to 40 psig which corresponded to the calculated total consumption of hydrogen.[8] The reaction mixture was filtered through diatomaceous earth and evaporated, producing a thick oil which slowly solidified. The solid was dissolved in ethyl acetate (6 L), washed with water, brine, dried ($MgSO_4$) and evaporated. Recrystallization (heptane/ethyl acetate) afforded 272 g (90%) of **4** as yellow crystals, mp. 86-87°, *lit.*[4b] mp. 82-84°. ^1H NMR (200 MHz, $CDCl_3$): δ 7.74 (d, 7.7 Hz, 1H), 7.57 (d, 7.3 Hz, 1H), 7.50-7.30 (m, 2H), 3.63 (q, 6.0 Hz, 1H), 3.50 (q, 6.5 Hz, 1H), 2.20-1.65 (m, 6H), 1.65-1.35 (m, 2H).

***cis*-1,2,3,4,4a,9b-Hexahydrodibenzothiophene** (**5**).- Compound **4** (107 g, 0.48 mol) was added over a 20 min. period to a suspension of lithium aluminum hydride (110 g, 2.91 mol) in ether (3 L) in a Morton flask. After the addition was complete, the reaction mixture was heated at reflux for 1.5 h, then stirred overnight at room temperature, after which time a TLC analysis showed that the reaction was complete. The excess $LiAlH_4$ was quenched by slow addition of 20% aqueous HCl (2.5 L), and extracted with ethyl acetate (4 L). The solution was washed with water, brine, dried ($MgSO_4$) and evaporated. The crude product was distilled *in vacuo* to afford 87 g (95%) of **5** as a white solid, bp. 110-111° (0.05 mmHg), *lit.*[4b] bp. 143-145° (5 mmHg), mp. 41-42°. GC analysis indicated that this material had a purity of greater than 99.9%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (dd, J = 2.0, 6.3 Hz, 1H), 7.18-6.95 (m, 3H), 3.83 (q, J = 6.2 Hz, 1H), 3.30 (q, J = 5.7 Hz, 1H), 2.15-1.95 (m, 2H), 1.95-1.50 (m, 4H), 1.50-1.30 (m, 2H).

Anal. Calcd for $C_{12}H_{14}S$: C,75.73; H, 7.41; S, 16.86. Found: C, 75.60; H, 7.39; S, 16.83

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8. Ace Glass # 6436-265 and 13660-50. The need to repressurize the reaction flask could be eliminated with the use of a reservoir tank.

9. Spartan SGI 5.0.3 by Wavefunction, Inc. The actual values are 39.56 and 40.72 for the two *cis*-isomer conformers where the sulfur is axial and equatorial respectively and 168.62 for the *trans*-isomer.

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11. Both ring juncture hydrogens appear as a quartet (even at 400 MHz) indicating equal coupling from the three adjacent hydrogens. The measured coupling constants to each hydrogen was 5.7 and 6.1 Hz. The smaller of the numbers was determined to be the proper coupling, J_{4a-9b}. The *cis*-isomer has two low energy conformations; one in which the sulfur is axial to the cyclohexane ring and one in which the sulfur is equatorial. A rapid interconversion of the two conformations would account for the observed quartets for the juncture hydrogens.

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