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Benzo[*b*]thiophene Derivatives II. 4- and 6-Substituted Benzo[*b*]thiophenes (1)

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Conflicting melting points have been reported for benzo[*b*]thiophene-6-carboxylic acid. Hansch and Schmidhalter gave a melting point of 215-216° (3). A melting point of 162° was reported by Badger *et al.*, who also reported that they were unsuccessful in an attempt to prepare benzo[*b*]thiophene-4-carboxylic acid (4). In each case, assignment of structure of the products was based on deduction from the starting materials. More recently, Matsuki and Kanda (5) gave 211.5-212.5° as the melting point of the 6-isomer.

The synthesis of benzo[*b*]thiophene-6-carboxylic acid by a different route and determination of the structure of the acid were therefore undertaken. The method used afforded both benzo[*b*]thiophene-4-carboxylic acid and benzo[*b*]thiophene-6-carboxylic acid, as well as several new monosubstituted benzo[*b*]thiophenes.

Our results and those of Matsuki and Kanda indicate that the original description of benzo[*b*]thiophene-6-carboxylic acid by Hansch and Schmidhalter is correct.

EXPERIMENTAL

Melting points were taken on a hot stage and are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

3-Bromophenyl 2,2-Diethoxyethyl Sulfide.

The procedure used to prepare the starting sulfide was that used by Tilak (6) to prepare the corresponding chloro compound.

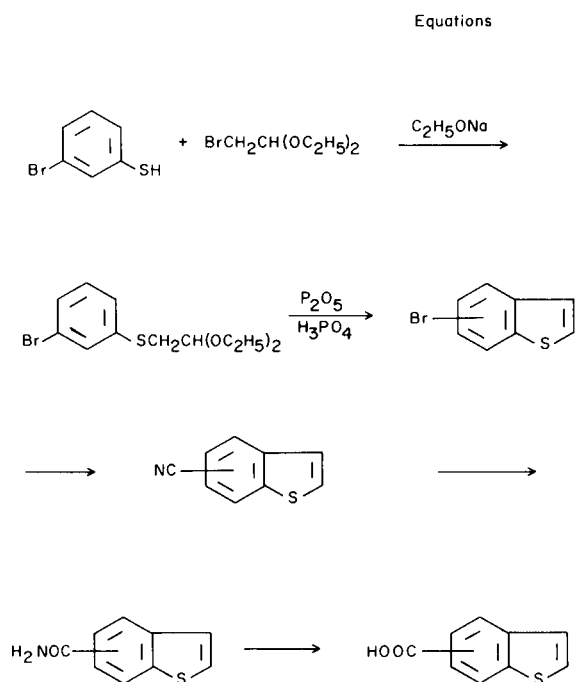
A 100 g. (0.53 mole) quantity of 3-bromothiophenol was added to sodium ethoxide prepared from 12.3 g. (0.54 g.-atom) of sodium and 267 ml. of absolute ethanol. To the stirred solution of sodium 3-bromothiophenoxide was added 8.1 g. (0.054 g.-atom) of sodium iodide, followed by 104.7 g. (0.53 mole) of bromoacetaldehyde diethyl acetal, added dropwise. The mixture was stirred and refluxed for eight hours. The ethanol was removed under reduced pressure and 300 ml. of water was added to the residue. The oily product was separated. The aqueous layer was extracted with three 100-ml. portions of diethyl ether. The combined product and extracts were dried with anhydrous magnesium sulfate. The solvent was removed by distillation. Fractionation of the residue gave 127.5 g. (78%) of product boiling at 97-105° (0.045 mm.).

4- and 6-Bromobenzo[*b*]thiophene.

A one-liter, three-necked round bottom flask was fitted with a stopper, take-off adapter and receiver, and a dropping funnel with capillary tip extending to the bottom of the flask. The system pressure was maintained at 4 mm. Polyphosphoric acid (81.0 g., 0.57 mole of phosphorus pentoxide in 48.5 ml. of 85% phosphoric acid) was heated to 160-165°. Intermittently, 20 g. (0.66 mole) of 3-bromophenyl 2,2-diethoxyethyl sulfide was added in two or three drop quantities. The sulfide reacted vigorously and the product distilled immediately. When all the sulfide had been added the temperature was raised to 200° to distil any remaining product. The crude product was redistilled at 0.045 mm. to yield 10.5 g. (75%) of mixed 4- and 6-bromobenzo[*b*]thiophene.

The mixture of isomers was separated by vapor phase chromatography using a Barber Colman model 5340 thermal conductivity unit. The 10' long, 3/8" O.D. column was packed with 20% carbowax on chromosorb W, 80-100 mesh. The inlet pressure of helium was 30 p.s.i. and the flow rate was 90 ml. min.⁻¹. The column temperature was maintained at 205°, the injector at 250°, and the detector at 250°.

A total of 7 g. of the mixture of isomers was fractionated, in 20 μ l. portions, yielding 1.5 g. of 4-bromobenzo[*b*]thiophene and 1.5 g. of 6-bromobenzo[*b*]thiophene, m.p. 55-56°; literature m.p. 56° (3). The halides were further purified by conversion to their picrates, recrystallization of the picrates, decomposition of the picrates, and crystallization or sublimation of the halides. The



melting point of 4-bromobenzo[*b*]thiophene picrate was 135-136°; 6-bromobenzo[*b*]thiophene picrate melted at 69-72°.

4-Bromobenzo[*b*]thiophene recovered in this manner was sublimed at 40° (10 μ) and melted at 31-32°; it had previously been reported as an oil (7).

4-Cyanobenzo[*b*]thiophene.

A mixture of 1.5 g. (0.00705 mole) of 4-bromobenzo[*b*]thiophene, 0.77 g. (0.00806 mole) of anhydrous cuprous cyanide, and 0.89 ml. (0.0112 mole) of pyridine which had been dried with barium oxide was heated in a sand bath at 210-220° for 24 hours. The hot solution was poured into 30 ml. of concentrated ammonium hydroxide. Diethyl ether (30 ml.) and water (30 ml.) were added and the mixture was filtered. The organic layer was separated from the filtrate and washed with four 30-ml. portions of dilute ammonium hydroxide, two 30-ml. portions of 4 *N* hydrochloric acid, and two 30-ml. portions of water. The solvent was removed by distillation. Sublimation of the residue at 0.03 mm. yielded 0.69 g. (61%) of crystals melting at 47-48°.

Anal. Calcd. for C₉H₅NS: C, 67.90; H, 3.17. Found: C, 67.91; H, 3.19.

6-Cyanobenzo[*b*]thiophene.

Treatment of 1.5 g. (0.00705 mole) of 6-bromobenzo[*b*]thiophene in the manner described above gave 0.67 g. (60%) of 6-cyanobenzo[*b*]thiophene, m.p. 37-38°, (literature m.p. 41.5-42° (2)).

Benzo[*b*]thiophene-4-carboxamide.

A mixture of 0.46 g. (0.0029 mole) of 4-cyanobenzo[*b*]thiophene, 30 ml. of 3% hydrogen peroxide, and 1 g. of sodium hydroxide was stirred vigorously at room temperature for 18 hours. The crude amide (0.35 g., 69%) was recovered by filtration and after recrystallization from 95% ethanol melted at 232-233°.

Anal. Calcd. for C₉H₇NOS: C, 61.00; H, 3.98. Found: C, 61.14; H, 3.91.

Benzo[*b*]thiophene-6-carboxamide.

6-Cyanobenzo[*b*]thiophene (0.46 g., 0.0029 mole), treated at 40° as described above, yielded 0.25 g. (49%) of amide which melted at 160-161° after recrystallization from 95% ethanol.

Anal. Calcd. for C₉H₇NOS: C, 61.00; H, 3.98. Found: C, 61.04; H, 4.25.

Benzo[*b*]thiophene-4-carboxylic Acid.

A 0.2 g. (0.0011 mole) quantity of benzo[*b*]thiophene-4-carboxamide was added to a solution of 2.25 g. of potassium hydroxide in 15 ml. of 95% ethanol. The mixture was refluxed until evolution of ammonia ceased (about eight hours), then 25 ml. of water was added. The alcohol was removed by distillation. The residue was cooled and filtered. The filtrate was acidified with 4 *N* hydrochloric acid. The product was recovered by filtration, washed with cold water, and recrystallized from aqueous ethanol. The yield was 0.1 g. (50%) of needles melting at 190-191°.

Anal. Calcd. for C₉H₆O₂S: C, 60.65; H, 3.39. Found: C, 60.89; H, 3.73.

Desulfurization of benzo[*b*]thiophene-4-carboxylic acid with Raney nickel (8) gave 2-ethylbenzoic acid, m.p. 61-62°, (literature m.p. 68°).

Benzo[*b*]thiophene-6-carboxylic Acid.

Treatment of 0.2 g. (0.0011 mole) of benzo[*b*]thiophene-6-carboxamide in the manner described above yielded 0.07 g. (35%) of benzo[*b*]thiophene-6-carboxylic acid, m.p. 216-217°.

Desulfurization of benzo[*b*]thiophene-6-carboxylic acid with Raney nickel (8) gave 4-ethylbenzoic acid, m.p. 109-110°, (literature m.p. 113°).

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Received October 25, 1967

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