

The Synthesis of Benzo[*b*]thiophene-3-carboxaldehydes and -3-Carboxylic Acids by Light Catalyzed NBS Bromination of 3-Methylbenzo[*b*]thiophenes

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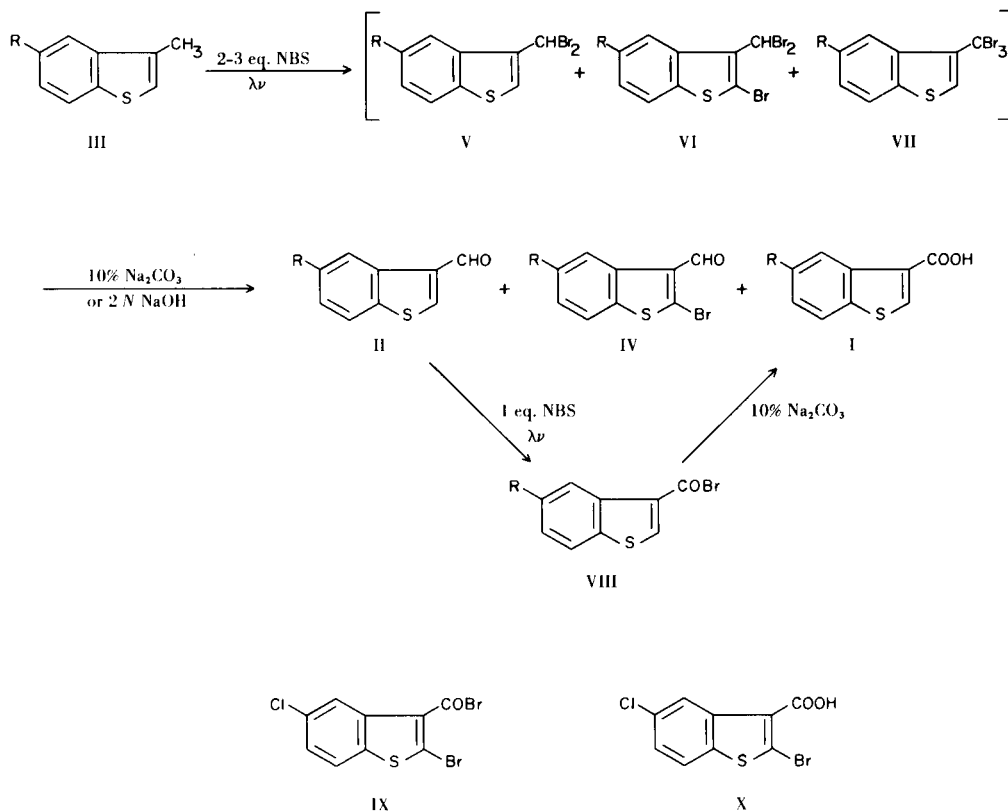
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Benzo[*b*]thiophene-3-carboxylic acid (I, R = H) and 5-halo substituted congeners were required as intermediates for the preparation of compounds of potential pharmacological interest.

Of the several methods for preparation of I and the corresponding 3-carboxaldehydes, II, which have been previously described (1-6), the method in most common usage is the Sommelet procedure (7). Campaigne and Neiss (8) have employed this method for the preparation of II (R = H) in 48% yield from 3-bromomethylbenzo[*b*]thiophene, and of I in 36% overall yield from 3-methylbenzo[*b*]thiophene (III, R = H). Other workers (1,4,9) have prepared II in comparable yield.

The direct conversion of methyl substituted aromatic compounds to aldehydes by reaction with *N*-bromosuccinimide followed by alkaline hydrolysis of the brominated intermediates is a known literature procedure. J. J. Brown and R. K. Brown (10) have reported the light catalyzed bromination with *N*-bromosuccinimide of *N,N*-diacetyl *o*- or *p*-toluidine for the preparation of *o*- or *p*-acetaminobenzaldehyde in 66% to 70% yield. Yamaguchi (11) has described the oxidation of piperonal with *N*-bromosuccinimide and benzoyl peroxide in chloroform, to piperonic acid in 29% yield. This paper describes a convenient synthesis of I and II based on some modifications of the above literature procedures.



When 5-chloro-3-methylbenzo[*b*]thiophene (III, R = Cl) and two equivalents of *N*-bromosuccinimide in carbon tetrachloride were irradiated with a 500 W GE Photospot lamp, a mixture of brominated intermediates was obtained. This mixture was hydrolyzed in 10% sodium carbonate solution. The aldehydic products which were extracted into benzene, were obtained in 88% crude yield. Gas chromatography of the crude aldehyde fraction produced a major peak (94%) corresponding to 5-chlorobenzo[*b*]thiophene-3-carboxaldehyde (II, R = Cl). A minor peak (2.5%) was found to be 2-bromo-5-chlorobenzo[*b*]thiophene-3-carboxaldehyde (IV, R = Cl). This structure was assigned on the basis of microanalysis and the nmr spectrum which lacked a strong singlet at δ 8.29. This peak is present in II and is attributed to the C₂ proton. Aldehydes II and IV presumably arise from dibromomethyl intermediates V and VI. A low yield (6%) of the 3-carboxylic acid, (I, R = Cl) was obtained upon acidification of the alkaline fraction. The presence of a tribromomethyl intermediate (VII, R = Cl) would account for this product.

Treatment of the unpurified aldehyde with one molar equivalent of *N*-bromosuccinimide, followed by hydrolysis of the acid bromide intermediate (VIII), yielded 5-chlorobenzo[*b*]thiophene-3-carboxylic acid (I, R = Cl) in 64% yield. The total yield of I based on both reactions in the synthetic sequence was 62%. Microanalysis of this product after one recrystallization from methanol revealed 0.23% of bromine, suggesting that bromo intermediate IX was present in the reaction mixture. This intermediate upon hydrolysis, would be converted to a trace amount of 2-bromo-5-chlorobenzo[*b*]thiophene-3-carboxylic acid (X).

By the same above procedures, 5-fluorobenzo[*b*]thiophene-3-carboxaldehyde (II, R = F) was obtained from III (R = F) in 76% crude yield. The yield of the 3-carboxylic acid (I, R = F) in the first step was 16%. The 3-carboxaldehyde was converted to I in 68% yield.

The occurrence of nuclear bromination in the 2-position of the thiophene ring increased markedly when III was brominated with more than two equivalents of *N*-bromosuccinimide. The reaction of III (R = Cl) with three molar equivalents of *N*-bromosuccinimide, followed by hydrolysis in 10% sodium carbonate solution and acidification gave I (R = Cl) in 28% yield. Gas chromatography of the benzene soluble component indicated incomplete hydrolysis of this fraction. This crude mixture of bromo intermediates was then heated in 2 *N* sodium hydroxide and acidified to yield additional I (11%). Examination of the benzene soluble components by gas chromatography revealed a 9:1 ratio of IV:II. The total crude yield of 5-chlorobenzo[*b*]thiophene-3-carboxylic acid in this reaction was 39%.

EXPERIMENTAL

Ir spectra were determined with a Perkin-Elmer Model 137 Infracord Spectrophotometer and nmr spectra were taken with a Varian HA-100D instrument using TMS as an internal reference. Gas chromatography was performed by the hydrogen flame technique with an F and M Scientific Corporation Model 400 Gas Chromatograph using a 6 foot 2.5% DC-200 Silicone Column at 190° with a hydrogen-nitrogen-air flow rate of 20-30 ml./min. Carboxylic acid samples were silylated with *N*-trimethylsilylimidazole (Tri-Sil Z Marketed by the Pierce Chemical Co.). Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected.

Phenylthiopranones.

These intermediates were prepared by the procedure of Banfield *et al.* (12).

p-Fluorophenylthiopranone was prepared in 85% yield, b.p. 100-105° (0.7 mm.), n_D^{24} 1.5461.

Anal. Calcd. for C₉H₉FOS: C, 58.7; H, 4.92; F, 10.3; S, 17.4. Found: C, 58.8; H, 4.83; F, 10.5; S, 17.8.

3-Methylbenzo[*b*]thiophenes (III).

These compounds were prepared according to the procedure of Campaigne and Neiss (13) by the cyclization of the corresponding phenylthiopranones (12).

5-Fluoro-3-methylbenzo[*b*]thiophene (III, R = F) was obtained in 46% yield, b.p. 75-80° (0.1-0.15 mm.), n_D^{25} 1.5931.

Anal. Calcd. for C₉H₇FS: C, 65.0; H, 4.25; F, 11.4; S, 19.3. Found: C, 65.2; H, 4.22; F, 10.9; S, 19.4.

5-Chlorobenzo[*b*]thiophene-3-carboxaldehyde (II, R = Cl) and 5-Chlorobenzo[*b*]thiophene-3-carboxylic Acid (I, R = Cl).

A. The Reaction of III with 2 Molar Equivalents of *N*-Bromosuccinimide.

A mixture of 23.8 g. (0.13 mole) of III (R = Cl) and 48 g. (0.27 mole) of *N*-bromosuccinimide in 550 ml. of carbon tetrachloride was irradiated with a 500 W (G.E. Photospot) lamp while heating at reflux temperature for 2 hours. The reaction mixture was cooled and filtered, and the solvent was distilled off on the steam bath. The residue was made alkaline with 265 ml. of 10% sodium carbonate solution and was heated with stirring on the steam bath for 1.75 hours. The mixture was cooled and extracted with 450 ml. of benzene. The benzene extracts were washed with water, dried over sodium sulfate and concentrated to yield 22.7 g. (88.5%) of tan crystals, m.p. 95-98°. A portion of the 5-chlorobenzo[*b*]thiophene-3-carboxaldehyde (II, R = Cl) was recrystallized from ethyl acetate, m.p. 104-106°, ir (potassium bromide) 5.95 μ (C=O), nmr (deuteriochloroform) δ 8.29 (1H, s, C₂-H); 8.58 (1H, d, C₄-H) J_{4,6} 2 Hz; 7.34 (1H, dd, C₆-H) J_{4,6} 2 Hz; J_{6,7} 9 Hz; 7.70 (1H, d, C₇-H) J_{6,7} 8 Hz; 10.02 (1H, s, CHO).

Anal. Calcd. for C₉H₅ClOS: C, 55.0; H, 2.56; Cl, 18.0; S, 16.3. Found: C, 54.8; H, 2.51; Cl, 18.3; S, 16.2.

Acidification of the aqueous sodium carbonate portion with 6 *N* hydrochloric acid, precipitated the 3-carboxylic acid by-product, which was filtered, washed with water and dried. The yield of 5-chlorobenzo[*b*]thiophene-3-carboxylic acid (I, R = Cl) was 1.6 g. (6%). Recrystallization from methanol gave m.p. 282-285°.

Anal. Calcd. for C₉H₆ClSO₂: C, 50.8; H, 2.37; Cl, 16.7; S, 15.1. Found: C, 50.6; H, 2.49; Cl, 16.6; S, 14.7.

5-Fluorobenzo[*b*]thiophene-3-carboxaldehyde (II, R = F) and 5-Fluorobenzo[*b*]thiophene-3-carboxylic Acid (I, R = F).

Procedure A was used for the preparation of these compounds. The 5-fluorobenzo[*b*]thiophene-3-carboxaldehyde (II, R = F), obtained in 76% crude yield, was recrystallized from 50% ethanol, m.p. 111-113°, ir (potassium bromide) 5.95 μ (C=O), nmr (deuteriochloroform) δ 8.36 (1H, s, C₂-H); 8.36 (1H, dd, C₄-H) J_{4,6} 2.5 Hz; J_{4,F} 9.5 Hz; 7.21 (1H, td, C₆-H) J_{4,6} 2.5 Hz; J_{6,F} 8.5 Hz; J_{6,7} 9 Hz; 7.79 (1H, dd, C₇-H) J_{6,7} 9 Hz; J_{7,F} 5 Hz; 10.08 (1H s, CHO).

Anal. Calcd. for C₉H₅FOS: C, 60.0; H, 2.80; F, 10.6; S, 17.8. Found: C, 59.7; H, 2.68; F, 10.6; S, 17.9.

Acidification with 6 *N* hydrochloric acid of the aqueous sodium carbonate solution of the above reaction, precipitated 5-fluorobenzo[*b*]thiophene-3-carboxylic acid (I, R = F), which was filtered, washed with water and dried. The yield was 16%. The product was recrystallized from ethanol, m.p. 259-262°.

Anal. Calcd. for C₉H₅FO₂S: C, 55.1; H, 2.57; F, 9.68; S, 16.3. Found: C, 55.1; H, 2.51; F, 9.92; S, 16.5.

Benzo[*b*]thiophene-3-carboxylic Acids (I).

B. The Reaction of II with 1 Molar Equivalent of *N*-Bromosuccinimide. 5-Chlorobenzo[*b*]thiophene-3-carboxylic Acid (I, R = Cl).

Five g. (0.025 mole) of crude II (R = Cl) obtained by Procedure A, and 4.2 g. (0.026 mole) of *N*-bromosuccinimide in 120 ml. of carbon tetrachloride was irradiated with a 500 W (G.E. Photospot) lamp, while heating on the steam bath under reflux for 1 hour. The reaction mixture was cooled and filtered, and the solvent was distilled off. The residue was heated, with stirring, on the steam bath in 45 ml. of 10% sodium carbonate solution. The reaction mixture was cooled, extracted with benzene and the sodium carbonate portion was acidified with 25 ml. of 6 *N* hydrochloric acid. The precipitated product was filtered, washed with water and dried. The yield of 5-chlorobenzo[*b*]thiophene-3-carboxylic acid (I, R = Cl) was 3.4 g. (64%), m.p. 282-285°.

5-Fluorobenzo[*b*]thiophene-3-carboxylic Acid (I, R = F).

When II (R = F) was used in Procedure B, the yield of 5-fluorobenzo[*b*]thiophene-3-carboxylic acid (I, R = F) was 68%. The product was recrystallized from ethanol, m.p. 259-262°.

Benzo[*b*]thiophene-3-carboxylic Acid (I, R = H).

This compound was prepared by Procedure B, using II (R = H) which was obtained by the procedure of Campaigne and Neiss (8). The yield of benzo[*b*]thiophene-3-carboxylic acid (I, R = H) was 69%, m.p. 168-170°. The product was recrystallized from benzene, m.p. 175-176°. Campaigne and Neiss reported m.p. 175-176°.

Anal. Calcd. for C₉H₆O₂S: C, 60.7; H, 3.40; S, 18.0. Found: C, 60.6; H, 3.49; S, 18.1.

C. Bromination of III (R = Cl) with 3 Molar Equivalents of *N*-bromosuccinimide.

Ten g. (0.053 mole) of III (R = Cl) and 24.3 g. (0.16 mole) of *N*-bromosuccinimide in 250 ml. of carbon tetrachloride was irradiated with a 500 W (G.E. Photospot) lamp, while under reflux on the steam bath for 2.5 hours. The mixture was cooled, filtered, and the solvent was distilled off on the steam bath. The residue in 275 ml. of 10% sodium carbonate solution was stirred and heated on the steam bath for 3 hours, cooled and extracted with benzene. The basic phase was acidified with 75 ml. of 6 *N* hydrochloric acid and the precipitated 3-carboxylic acid was filtered, washed with water and dried. The yield was 3.2 g. (28%), m.p. 278-281°. The benzene extracts were dried over magnesium sulfate, filtered and concentrated to give 12.8 g. of a brown oil. Gas chromatography of this oil indicated that incomplete hydrolysis had taken place. The oil was heated in 120 ml. of 2 *N* sodium hydroxide on the steam bath for 2.5 hours, cooled and extracted with benzene. Acidification of the alkaline portion with 6 *N* hydrochloric acid precipitated an additional 1.2 g. (11%) of I (R = Cl), m.p. 278-281°. The total yield of 5-chlorobenzo[*b*]thiophene-3-carboxylic acid (I, R = Cl) was 4.4 g. (39%). The crude aldehydic mixture obtained from benzene extractions weighed 5.6 g. (54%). Gas chromatography of this oil revealed a IV:I product mixture of 9:1.

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