Synthesis of 6-Aminobenzo[*b*]naphtho[2,1-*d*]thiophene

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6-Aminobenzo[*b*]naphtho[2,1-*d*]thiophene has been prepared by two different routes, one, a one-pot synthesis.

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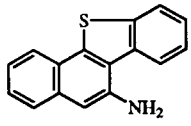
In our continued search for the presence of benzo[*b*]-naphtho[2,1-*d*]thiophenes in coal-derived products and shale oils [2] we now turn our attention to the aminobenzo-[*b*]naphtho[2,1-*d*]thiophenes.

The carcinogenic activity of the monomethylchrysenes [3] and of 6-aminochrysene [4] are adequately documented. We now report the synthesis of 6-aminobenzo[*b*]naphtho[2,1-*d*]thiophene (**1**) which has a structural resemblance



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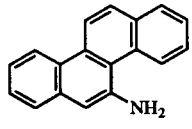
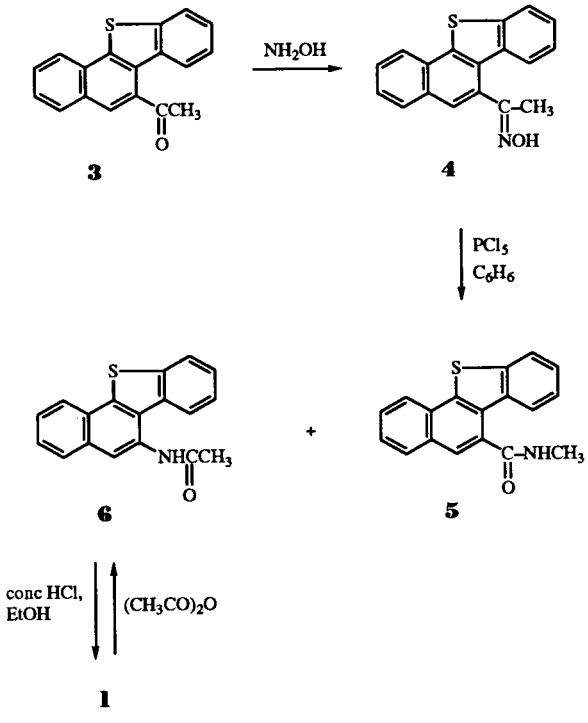


2

to 5-aminochrysene (**2**) [5]. Croisy, *et al* [6] have also been interested in benzo[*b*]naphtho[2,1-*d*]thiophene in their search for thiophene analogues of carcinogenic polycyclic hydrocarbons and their related biological properties [7]. The synthesis of **1** was accomplished by two different methods. The starting material for the synthesis of **1** is 6-acetylbenzo[*b*]naphtho[2,1-*d*]thiophene (**3**) [8]. Reaction of **3** with hydroxylamine afforded the oxime **4** which upon treatment with phosphorus pentachloride in benzene solution provided 6-acetylaminobenzo[*b*]naphtho[2,1-*d*]thiophene (**6**) contaminated with *N*-methylbenzo[*b*]naphtho-[2,1-*d*]thiophene-6-carboxamide (**5**) (seen only in the nmr spectrum). Refluxing crude **6** with a mixture containing 10 ml of concentrated hydrochloric acid in 100 ml of 95% ethanol afforded **1** in 46% yield from oxime **4**. Compound **1** could be converted into pure **6** upon allowing it to stand at room temperature with acetic anhydride (Scheme 1).

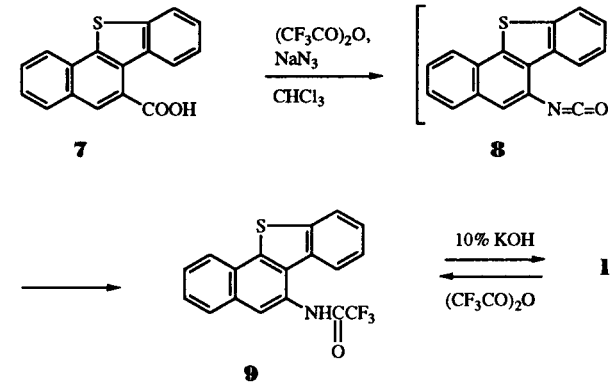
Scheme 1



3 **4** **6** **5** **1**

Compound **1** was also prepared from benzo[*b*]naphtho-[2,1-*d*]thiophene-6-carboxylic acid (**7**). Compound **7** was converted into **1** in a one pot reaction, thus **7** was allowed to react with trifluoroacetic anhydride and sodium azide in chloroform solution to afford the non-isolated intermediate **8** which upon long stirring deposited *N*-trifluoroacetylamidobenzo[*b*]naphtho[2,1-*d*]thiophene (**9**). Compound **9** contaminated with **8** upon hydrolysis with 10% potassium hydroxide provided the amine **1** in 48% yield from **7**. Characterization of **9** was accomplished by treatment of **1** with trifluoracetic anhydride at room temperature to afford a sample of **9** that could be purified (Scheme 2).

Scheme 2



7 **8** **9** **1**

In order to examine the proposed structural resemblance of 6-aminobenzo[*b*]naphtho[2,1-*d*]thiophene (**1**) to 5-aminochrysene (**2**), we have calculated the size and shape of **1** and **2** using the SYBYL force field at the de-

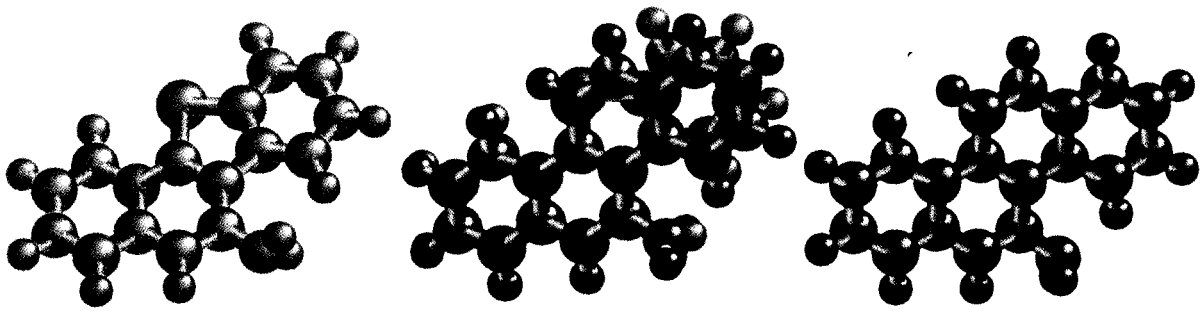


Figure 1 2 Superimposed upon 1 2

fault setting on a Sun 4/330 computer. A volume displacement calculation revealed that both structures are virtually identical in size; 198.6 Å^3 for **1** and 199.7 Å^3 for **2**. When structure **2** was superimposed on structure **1**, it was observed that the structures overlap in the naphthalene moiety (left side of Figure) but diverge (right side of Figure) as a result of the change in the geometry of the benzo[*b*]thiophene moiety. In the Figure, **2** (blue) is superimposed above the plane of **1** (orange) and the almost complete superimposition of **2** over **1** is easily apparent. The small change from the thiophene moiety *versus* the benzene moiety begins to become apparent with the greatest deviation being noted in the two right hand benzene rings. Furthermore in the case of **1**, the amino group minimizes with the amino protons pointing into the bay region, whereas in the case of **2**, the amino group minimizes with the lone pair of electrons pointing into the bay region. A search of the rotational barriers shows that the barrier to rotation around the C–N bond of **2** is greater than that of **1**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckman FT 100 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. The ^{1}H-nmr spectra were obtained on a JEOL FX90Q spectrometer in the solvent indicated with TMS as the internal standard. Chemical shifts are reported in ppm (δ) and J values are in Hz. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

6-Acetylbenzo[*b*]naphtho[2,1-*d*]thiophene Oxime (**4**).

A mixture of 6-acetylbenzo[*b*]naphtho[2,1-*d*]thiophene (**3**) (2.76 g, 10 mmoles), hydroxamine hydrochloride (1.4 g, 20 mmoles), pyridine (4 ml), and absolute ethanol (60 ml) was refluxed for 4 hours. After cooling, the reaction mixture was poured into an ice and water mixture (400 ml) and the precipitate was collected affording 2.42 g (8.3 mmoles, 83%) of colorless crystals. An analytical sample was recrystallized from benzene to give colorless needles, mp 170-172°; ir (potassium bromide): 3200 (broad, OH), 1368, 998, 946, 899, 750, 735 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}NOS \cdot 0.25H_2O$: C, 73.07; H, 4.60; N, 4.73. Found: C, 73.11; H, 4.73; N, 4.58.

6-Aminobenzo[*b*]naphtho[2,1-*d*]thiophene (**1**).

(a) Oxime **3** (2.91 g, 10 mmoles) was suspended in 40 ml of dry benzene and treated with 2.0 g of powdered phosphorus pentachloride. The reaction mixture was refluxed for 30 minutes. After evaporation of the benzene, the residue was washed with 100 ml of water and the solidified product was collected by filtration. The product is a mixture of 6-acetylaminobenzo[*b*]naphtho[2,1-*d*]thiophene (**6**) and *N*-methylbenzo[*b*]naphtho[2,1-*d*]thiophene-6-carboxamide (**5**) in a ratio of 3:1 from the ^{1}H-nmr spectrum. This mixture was refluxed with 100 ml of ethanol and 10 ml of concentrated hydrochloric acid for 24 hours. After cooling, 20 ml of concentrated ammonium hydroxide was added to the reaction mixture and stirred for 2 hours at room temperature. The tan solid that appeared was collected by filtration. This product was recrystallized from methanol to give 1.15 g (4.58 mmoles, 46%) of **1** as tan needles, mp 149-150°.

(b) To a cold (4°) swirling solution of 0.40 g (1.44 mmoles) of benzo[*b*]naphtho[2,1-*d*]thiophene-6-carboxylic acid (**7**), 3.2 ml of trifluoroacetic anhydride and 20 ml of chloroform was slowly added 0.19 g (2.8 mmoles) of sodium azide. This mixture was stirred in the cold for 35 minutes, during which time a gray precipitate appeared. The mixture was filtered and the gray precipitate thus collected was washed with water, a portion of the precipitate being water soluble. The gray material which remained is benzo[*b*]naphtho[2,1-*d*]thiophene-6-isocyanate (**8**). The organic solvent was removed from the filtrate above under reduced pressure, leaving a brown solid, mp 230-235°. This compound was identified as 6-trifluoroacetamidobenzo[*b*]naphtho[2,1-*d*]thiophene (**9**). The crude isocyanate **8** and the crude trifluoroacetamide **9** were combined and mixed with 50 ml of 70% ethanol and 0.3 g of potassium hydroxide. This mixture was refluxed for 4 hours, after which time it was poured over ice and allowed to stand overnight. The brown precipitate which appeared was collected, washed with water and dried to afford 0.22 g (0.88 mmole, 61%) of crude product **1**. This product was recrystallized from methanol to give 0.12 g (0.48 mmoles, 48%) of tan needles, mp 148-150°; ir potassium bromide: 3435, 3130 (NH_2), 1653, 1399, 1383, cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.10 (bs, 2H, NH_2), 7.05 (s, 1H, H-5), 7.36-7.79 (m, 6H, aromatic-H), 7.94-8.07 (m, 2H, H-4, H-7), 8.34-8.45 (m, 1H, H-1).

Anal. Calcd. for $C_{16}H_{11}NS$: C, 77.08; H, 4.45; N, 5.62; S, 12.86. Found: C, 76.89; H, 4.54; N, 5.54; S, 12.71.

6-Acetylaminobenzo[*b*]naphtho[2,1-*d*]thiophene (**6**).

A mixture of 0.125 g (0.5 mmole) of **1** and 0.5 ml of acetic anhydride was stirred at room temperature for 1 hour. The reaction mixture was poured into 50 ml of water and stirred for 2 hours. The precipitate that appeared was collected by filtration to give 0.14 g (0.48 mmole, 96%) of colorless crystals. An analytical sample was recrystallized from methanol to give colorless needles, mp 170-172°; ir (potassium bromide): 3255 (NH), 643 (CO), 1540, 879, 751, 723 cm^{-1}; ^1H nmr (deuteriochloroform + trifluoroacetic acid, 10:1): δ 2.09 (s, 3H, $COCH_3$), 7.56-8.20 (m, 8H, aromatic-H), 7.74 (s, 1H, H-5), 9.90 (bs, 1H, NH).

Anal. Calcd. for $C_{18}H_{13}ONS$: C, 74.20; H, 4.49; N, 4.81; S, 11.00. Found: C, 73.92; H, 4.57; N, 4.73; S, 11.11.

6-Trifluoroacetylaminobenzo[*b*]naphtho[2,1-*d*]thiophene (**9**).

A solution of 0.125 g (0.5 mmole) of **1** and 0.5 ml of trifluoroacetic anhydride in 10 ml of dichloromethane was stirred at room temperature for 2 hours. The reaction mixture was poured into 50 ml of water and stirred for 2 hours. The organic layer was separated and dried over magnesium sulfate. After removal of the solvent, the residue was recrystallized from methanol to give 0.142 g (0.41 mmole, 82%) of colorless crystals. An analytical sample was recrystallized from methanol to give colorless needles, mp 237-239°; ir (potassium bromide): 3281 (NH), 1707 (CO), 1550, 1170, 753 cm^{-1}.

Anal. Calcd. for $C_{18}H_{10}F_3NOS$: C, 62.60; H, 2.92; N, 4.06. Found: C, 62.50; H, 2.86; N, 3.98.

REFERENCES AND NOTES

[1] To whom correspondence should be directed at the Department of Chemistry, University of South Florida, Tampa, FL 33620-5250 USA.

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