Synthesis of *N*(3-Dimethylaminopropyl)-6-substituted Naphtho[2,1-*b*]thiophene-4-carboxamides

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A series of *N*-(3-dimethylaminopropyl)-6-substituted naphtho[2,1-*b*]thiophenes-4-carboxamides have been synthesized. 6-Substituted naphtho[2,1-*b*]thiophene-4-carboxylic acids were obtained upon oxidative-photocyclization of α-(2-thienyl)-β-arylacrylic acids. The naphtho[2,1-*b*]thiophene carboxylic acids were converted to the corresponding amides through their acid chlorides or, in one case, by use of 1,1-carbonyldiimidazole coupling of the amine and the acid.

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The relationship between structure of intercalators, their binding strength and the selectivity of their interactions with specific base pairs is fundamental to the understanding of small molecule nucleic acid interactions. Several factors influence intercalators' binding strength, including the shape and size of the planar aromatic ring and the electronic properties of the ring [2-4]. Factors that control their base-pair selectivity are not as well understood. Nevertheless, we have shown that it is possible to design intercalators which exhibit rather high A-T base-pair binding selectivity [5-7]. Since virtually all intercalators investigated to this time have shown G-C base pair specificity, our finding of systems which exhibit A-T selectvity is an important one which can lead to new understanding of specific base-pair interactions. The reported A-T specific intercalators included ones with the naphtho[2,1-*b*]thiophene system as the intercalating aromatic ring [5-7]. As part of a broad program of synthesis of intercalators [8-10], we have prepared a series of *N*-(3-dimethylaminopropyl) 6-substituted naphtho[2,1-*b*]thiophene-4-carboxamides.

The synthetic approach used to prepare the naphtho-[2,1-*b*]thiophenes outlined in Scheme 1 is one we have employed earlier [11,12]. The initial step in this approach to the naphtho[2,1-*b*]thiophene intercalators involves a modified Perkin condensation [13] between *ortho*-substituted benzaldehydes **1** and 2-thiopheneacetic acid **2** using triethylamine as the base in acetic anhydride as the solvent to form α-(2-thienyl)-β-arylacrylic acids (**3**). This condensation works well with most substituents (Table 1); however, with *ortho* halogens, particularly fluorine, the reaction conditions are such that condensation is rapidly followed by cyclization resulting in the formation of 3-aryl coumarins [14]. Consequently, 6-fluoronaphtho[2,1-*b*]thiophene-4-carboxylic acid (**4c**) had to be prepared by an indirect route. The α-(2-thienyl)-β-arylacrylic acids **3** formed by the Perkin condensation were directly subjected to oxidative-photocyclization without determination of which geometric isomer (or mixture of isomers) was obtained, since we had shown previously that irradiation of either isomer produces the naphtho[2,1-*b*]thiophene ring system [11a]. A number of naphtho[2,1-*b*]thiophenes [11,12] and a variety of other fused-ring thiophenes [15] have been synthesized by this method. Generally, the yields of the photooxidative reactions are good (60-70%) and are not particularly sensitive to variation of the substituent (Table 2).

Table 1

Physical Data for α-(2-Thienyl)-β-arylacrylic Acids

R	Yield (%)	Mp (°C)	Molecular Formula	Analysis C	Calcd. (Found) H
3a	65	185-186	$C_{14}H_{12}O_3S$	64.59 (64.69)	4.65 (4.69)
3b	39	114-115	$C_{14}H_{12}O_2S$	68.82 (68.75)	4.95 (5.01)
3d	31	120-121	$C_{13}H_9ClO_2S$	58.98 (59.08)	3.43 (3.44)
3e	44	107-108	$C_{13}H_9BrO_2S$	50.50 (50.41)	2.93 (2.96)
3f	25	145-146	$C_{14}H_9F_3O_2S$	56.37 (56.43)	3.04 (3.06)

Scheme 1

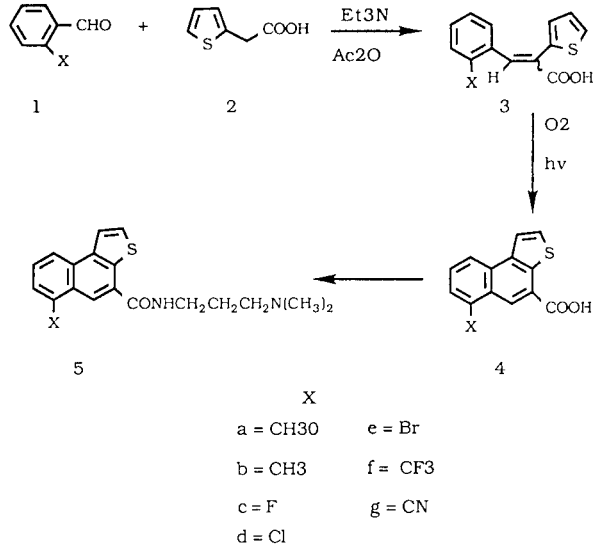

Table 2

Physical Data for 6-Substituted Naphtho[2,1-*b*]thiophene-4-carboxylic Acids **4** [a]

R	Yield (%)	Mp (°C)	Molecular Formula	Analysis Calcd. (Found) C	H	NMR [b] (Chemical shifts)
4a	75	273-275	$C_{14}H_{10}O_3S$	65.10 (65.15)	3.90 (3.92)	167.2, 156.4, 136.9, 135.4, 131.8, 130.1, 130.0, 122.4, 122.1, 121.4, 116.1, 105.3, 56.0
4b	63	278-280	$C_{14}H_{10}O_2S$	69.40 (69.36)	4.16 (4.19)	167.3, 137.7, 136.4, 134.7, 131.1, 130.1, 129.0, 128.9, 127.1, 124.7, 122.8, 122.4, 122.1, 19.5
4c	73	279-280	$C_{13}H_7FO_2S$	63.40 (63.38)	2.86 (2.95)	[c] 166.8, 159.2, 136.9, 135.8, 132.0, 131.1, 129.7, 123.9, 122.1, 120.4, 120.0, 119.7, 110.3
4d	41	323-325	$C_{13}H_7ClO_2S$	59.43 (59.42)	2.69 (2.74)	167.2, 137.9, 136.1, 132.9, 132.3, 131.7, 129.7, 127.5, 127.0, 124.9, 124.1, 124.0, 122.5
4e	47	329-330	$C_{13}H_7BrO_2$	50.83 (50.75)	2.30 (2.33)	166.9, 137.6, 135.7, 132.0, 131.3, 130.3, 129.8, 128.4, 126.5, 124.6, 124.3 123.7, 122.0
4f	74	295-296	$C_{14}H_7F_3O_2S$	56.75 (56.82)	2.38 (2.38)	[d] 166.5, 137.3, 135.2, 131.0, 130.9, 128.9, 127.3, 124.8, 124.7, 122.5, 121.7
4g	13	235-237	$C_{15}H_9NO_2S$	67.40 (67.25)	3.39 (3.45)	165.6, 137.0, 136.2, 131.9, 130.4, 130.3, 129.1, 128.5, 127.5, 124.4, 124.3, 120.6, 117.1, 111.3, 52.4

[a] Compound **4a** and **4d** were recrystallized from ethanol; **4b** from acetone, **4c** and **4e** from glacial acetic acid, **4f** from benzene. Compound **4g** was high melting and insoluble in all solvents used, so the data are for its methyl ester that was recrystallized from ethyl acetate. 13% is the overall yield of **4g** from *o*-tolunitrile, the starting material for preparation of *o*-cyanobenzaldehyde [16]. [b] Spectra for **4a-4f** are recorded in dimethylsulfoxide-d_6 and **4g** is recorded in chloroform-d. [c] 110.3 ($^2J_{C7F}$ = 19.7), 119.7 ($^2J_{C5aF}$ = 15.5), 120.0 ($^3J_{C5F}$ = 5.6), 120.4 ($^4J_{C9F}$ = 3.9), 123.9 ($^4J_{C1aF}$ = 1.5), 129.7 ($^3J_{C8F}$ = 8.9), 132.0 ($^3J_{C9aF}$ = 3.8), 136.9 ($^4J_{C4F}$ = 2.8), 159.2 ($^1J_{C6F}$ = 250.4). [Coupling constants are given in Hertz; superscripts correspond to number of bonds of coupling and subscripts correspond to carbon number (tentative assignment) and fluorine]. [d] Only intense carbon signals are reported; no effort was made to identify low intensity signals which resulted from coupling with CF_3 group.

Table 3

Physical Data for Compounds **5** [a]

R	Yield (%)	Mp (°C)	Molecular Formula	Analysis Calcd. (Found) C	H	NMR [b] (Chemical shifts)
5a	41	129-130	$C_{19}H_{22}N_2O_2S$	66.63 (66.65)	6.48 (6.50)	166.6, 156.5, 137.1, 136.0, 131.6, 130.0, 128.3, 125.8, 122.2, 121.0, 117.0, 116.2, 104.1, 59.9, 55.6, 45.4, 41.3, 24.8
5b	50	106-107	$C_{19}H_{22}N_2OS$	69.90 (69.64)	6.79 (6.88)	166.5, 137.5, 135.1, 134.8, 130.3, 129.6, 129.2, 127.3, 126.4, 126.1, 121.8, 120.6, 118.6, 59.8, 45.3, 41.0, 24.4, 19.8
5c	79	82-83	$C_{18}H_{19}FN_2OS$	65.43 (65.50)	5.80 (5.81)	[c] 166.2, 159.9, 137.0, 136.3, 131.8, 130.8, 127.9, 127.4, 120.7, 120.5, 119.6, 115.0, 109.5, 59.7, 45.2, 41.2, 24.8
5d	58	91-92	$C_{18}H_{19}ClN_2OS$	62.32 (62.23)	5.52 (5.77)	165.8, 137.2, 135.9, 132.8, 131.4, 130.8, 129.8, 127.6, 127.4, 125.8, 122.6, 120.5, 118.4, 60.2, 45.6, 41.7, 24.7
5e	31	97-98	$C_{18}H_{19}BrN_2OS$	55.24 (55.26)	4.89 (4.90)	165.9, 137.3, 136.1, 131.5, 130.9, 129.7, 129.0, 128.0, 127.8, 123.9, 123.5, 121.2, 120.4, 60.3, 45.7, 41.8, 24.9
5f	81	116-117	$C_{19}H_{19}F_3N_2OS$	59.98 (59.85)	5.03 (5.05)	[d] 166.4, 137.6, 136.0, 131.2, 131.1, 128.5, 128.3, 126.3, 126.2, 120.6, 118.0, 59.9, 45.0, 41.3, 24.6
5g	47	161-162	$C_{19}H_{19}N_3OS$	67.63 (67.55)	5.68 (5.71)	166.0, 137.9, 137.3, 132.7, 132.6, 130.5, 130.4, 129.7, 129.3, 127.2, 120.7, 119.0, 118.5, 111.6, 60.9, 45.8, 42.4, 24.7

[a] Compounds **5a-4d** were recrystallized from ethanol acetate. [b] Spectra for **5a-4g** were recorded in chloroform-d. [c] 109.5 ($^2J_{C7F}$ = 20.2), 115.0 ($^3J_{C5F}$ = 6.2), 119.6 ($^4J_{C9F}$ = 4.1), 120.6 ($^2J_{C5aF}$ = 15.4), 127.9 ($^3J_{C8F}$ = 9.0), 131.8 ($^3J_{C9aF}$ = 4.0), 137.0 ($^4J_{C4F}$ = 2.7), 159.9 ($^1J_{C6F}$ = 252.1). [Coupling constants are given in Hertz; superscripts correspond to number of bonds of coupling and subscripts correspond to carbon number (tentative assignment) and fluorine]. [d] Only intense carbon signals are reported; no effort was made to identify low intensity signals which resulted from coupling with CF_3 group.

All of the amides **5**, except **5a**, were prepared using the conventional approach of converting a carboxylic acid into its corresponding acid chloride followed by reaction with 3-dimethylaminopropylamine (Table 3). Earlier, we noted difficulty with this approach for a methoxy substituted compound and in the current series we failed to isolate **5a** employing the acid chloride route. The methoxy substituted amide **5a** was prepared in reasonable yields directly from the acid **4a** by using the 1,1-carbonyldiimidazole coupling method [17].

EXPERIMENTAL

Melting points were recorded on a Mel-Temp and/or a Thomas-Hoover Unimelt apparatus and all are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, Georgia. The nmr spectra were recorded in deuteriochloroform or DMSO-d_6 or deuterium oxide with Varian VXR 400, JEOL GX-270, or Varian EM360L spectrophotometers.

General Procedure for Preparation of 6-Substituted Naphtho[2,1-*b*]thiophene-4-carboxylic Acids (**4**).

The 6-methyl compound **4b** is used as a representative example for the reaction conditions for synthesis of 6-substituted naphtho[2,1-*b*]thiophene-4-carboxyclic acids. A mixture of *o*-methylbenzaldehyde (12.0 g, 0.1 mole), 2-thiopheneacetic acid (14.2 g, 0.1 mole), 16 ml of distilled triethylamine and 32 ml of acetic anhydride was refluxed for 12 hours. The mixture was poured into *ca.* 1 ℓ of water and made alkaline with potassium hydroxide. The alkaline solution was heated at a gentle boil with charcoal for *ca.* 1 hour, filtered, allowed to cool and acidified with concentrated hydrochloric acid, and the resulting solid was filtered and dried. The solid was recrystallized from ethanol to give 9.5 g (39%) of crystalline compound **3b**, mp 114-115°. The compound was used directly in the next step.

A solution of 1.2 g (5 mmoles) of α-(2-thienyl)-β-(*o*-methylphenyl)-acrylic acid and 0.07 g of iodine in 700 ml of ethanol was irradiated for 72 hours in a Rayonette reactor fitted with lamps that provided 2537 Å light. Air was bubbled through the solution during the irradiation period. The ethanol was removed under reduced pressure and the residue was washed with ether (3 x 100 ml). Recrystallization from acetone gave 0.77 g (63%) of a crystalline compound **4b**, mp, 278-280°.

General Procedure of the Synthesis of *N*-(3-Dimethylaminopropyl)-6-substituted Naphtho[2,1-*b*]thiophene-4-carboxamides **5**.

The synthesis of 6-methylnaphtho[2,1-*b*]thiophene **5b** is used as a typical example. A solution of the naphtho[2,1-*b*]thiophene-4-carboxylic acid **4b** (2.0 g, 8 mmoles) and distilled thionyl chloride (75 ml) was refluxed overnight. The excess thionyl chloride was distilled and the last traces of it were removed by codistillation with toluene. The resulting acid chloride was mixed with 30 ml of 3-dimethylaminopropylamine and refluxed for 5 hours. The reaction mixture was diluted with cold water and extracted with ether (3 x 100 ml). The combined ether extracts were washed with water (3 x 100 ml) and brine solution (1 x 100 ml). The ether solution was dried (magnesium sulfate). The solvent was removed under reduced pressure. The product was crystallized from ethyl acetate and pale yellow crystals (1.2 g, 50%) of **5b** were obtained, mp 106-107°.

Preparation of 6-Fluoronaphtho[2,1-*b*]thiophene-4-carboxylic acid (**4c**).

A mixture of 2-fluorobenzaldehyde (6 g, 50 mmoles), ethyl 2-thiopheneacetate (8.5 g, 50 mmoles), 8 ml of distilled triethylamine and 16 ml of acetic anhydride was refluxed overnight. The mixture was extracted with ethyl ether (3 x 100 ml), and the organic layer was washed with water, 10% aqueous sodium carbonate and water again. The organic layer was dried (magnesium sulfate) and the solvent was removed under reduced pressure. The residue was used directly in the oxidative photocyclization step by dissolving in 600 ml of ethanol containing 0.6 g of iodine and the solution was irradiated for 70 hours in a Rayonette reactor fitted with lamps which produced 2537 Å light. Air was allowed to bubble through the solution during irradiation. The ethanol was removed under reduced pressure and the crude cyclic ester was dissolved in ethanol (30 ml) to which 10 ml of 10% aqueous sodium hydroxide was added and the solution was held at reflux for 12 hours. Acidification with concentrated hydrochloric acid gave a pale brown solid (2.3 g) which was recrystallized from glacial acetic acid, mp, 279-280°.

Preparation of *N*-(3-Dimethylaminopropyl)-6-methoxynaphtho[2,1-*b*]thiophene-4-carboxamide (**5a**).

A mixture of 6-methoxynaphtho[2,1-*b*]thiophene-4-carboxylic acid (0.26 g, 1 mmole), 1,1-carbonyldiimidazole (0.24 g, 1.5 mmoles) in 2 ml of anhydrous *N,N*-dimethylformamide were stirred for 1 hour at room temperature. To the mixture was added 3-dimethylaminopropylamine (3.2 ml) and stirring was continued for 0.5 hour. The solvent was removed under reduced pressure and the residue was treated with 0.2 *M* sodium carbonate and extracted with methylene chloride (3 x 50 ml). The methylene chloride extracts were washed with water (3 x 50 ml) and brine solution (1 x 50 ml). The methylene chloride solution was dried (magnesium sulfate) and the solvent removed under reduced pressure to yield a solid which was recrystallized from ethyl acetate to yield 0.14 g, mp 129-130°.

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