Synthesis of Methyl 3-Amino-4-aryl(or methyl)sulfonyl-2-thiophenecarboxylates from 3-Alkoxy-2-aryl(or methyl)-sulfonylacrylonitriles

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The synthesis of a series of methyl 3-amino-4-aryl(or methyl)sulfonylthiophene-2-carboxylates by reaction of 3-alkoxy-2-aryl(or methyl)sulfonylacrylonitriles with methyl thioglycolate in the presence of triethylamine is described. Hydrolysis/decarboxylation of the ester at the 2-position and acylation of the resulting amine represents a convenient route to 4-arylsulfonyl-3-carboxamidothiophenes. Attempted acylation of a title aminothiophene under standard conditions was unsuccessful.

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As part of a program directed at the synthesis and antiviral evaluation of aminothiophene derivatives containing an *ortho*-substituted arylsulfonyl moiety, we recently required a convenient synthesis of a series of 4-arylsulfonyl-3-carboxamidothiophenes. Our search of the literature revealed that the general Fiesselmann and Gompper approaches [2] to thiophenes have been used to prepare a variety of 3-aminothiophenes that contain an electron-withdrawing group at the 4-position [*i.e.*, CN, CO_2R, SO_2R, $P(O)(OEt)_2$], along with an ester moiety at the 2-position [3-6]. As such compounds are potentially decarboxylated at the 2-position [7], this appeared to be an attractive route to the required intermediate 3-amino-4-arylsulfonylthiophenes. The only general syntheses of 3-amino-4-aryl(or alkyl)sulfonylthiophene-2-carboxylates to be reported, however, result in the incorporation of either an arylamino [4] or alkylsulfide [5] group at the 5-position. As our interest lies primarily in the analogous 5-unsubstituted, -alkyl, and -aryl derivatives, we thus required a synthetic route to such compounds.

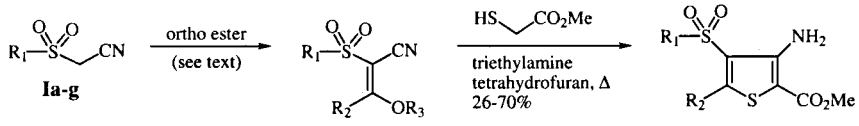
Herein, we describe a Fiesselmann-type synthesis of a series of methyl 3-amino-4-aryl(or methyl)sulfonylthiophene-2-carboxylates containing nonheteroatom substituents at the 5-position by reaction of 3-alkoxy-2-aryl(or methyl)sulfonylacrylonitriles with methyl thioglycolate in the presence of triethylamine. We also describe our preliminary work with these compounds directed towards the hydrolysis/decarboxylation of the ester moiety at the 2-position and acylation of the resulting 3-aminothiophene as a convenient route to 4-arylsulfonyl-3-carboxamidothiophenes.

Results and Discussion.

The reaction of 3-alkoxy-2-aryl(or alkyl)sulfonylacrylonitriles with bis-nucleophilic reagents (*i.e.*, hydrazine, hydroxylamine, thiourea, *etc.*) has previously led to a variety of aminoheterocycles (*i.e.*, pyrazoles, isoxazoles, and pyrimidines) containing an *ortho*-substituted aryl(or alkyl)sulfonyl moiety [8-11]. Considering this, we reasoned that the reaction of the same acrylonitriles with a thioglycolate in the presence of base would give the analogous thiophene-2-carboxylates, with the mercaptan and activated methylene serving as reacting nucleophiles.

As shown in Scheme 1, the reaction of acrylonitriles **IIa-l** with methyl thioglycolate (1.1 equivalents) in refluxing tetrahydrofuran for 2-5 hours using triethylamine (1.0

Scheme 1



Ia-g → **IIa-l** → **IIIa-l** (see Table for R_1 and R_2)

I	R_1	II	R_1	R_2	R_3
a	Ph	**a**	Ph	H	Et
b	4-Cl-Ph	**b**	4-Cl-Ph	H	Et
c	4-F-Ph	**c**	4-F-Ph	H	Et
d	4-Me-Ph	**d**	4-Me-Ph	H	Et
e	2-NO_2-Ph	**e**	2-NO_2-Ph	H	Et
f	2-CO_2Me-Ph	**f**	2-CO_2Me-Ph	H	Et
g	Me	**g**	4-Cl-Ph	Me	Me
		h	2-NO_2-Ph	Me	Me
		i	4-Cl-Ph	Et	Et
		j	4-Cl-Ph	Ph	Me
		k	Me	H	Et
		l	Me	Me	Me

equivalents) as base was found to give the title compounds in isolated yields ranging from 26-70%. As listed in the Table, substituents at the 5-position of these compounds include H, Me, Et, and Ph. Also illustrated in the Table is our extension of this reaction to the preparation of 4-methylsulfonyl analogues **IIIk-l** in addition to the targeted 4-arylsulfonyl derivatives **IIIa-j.**

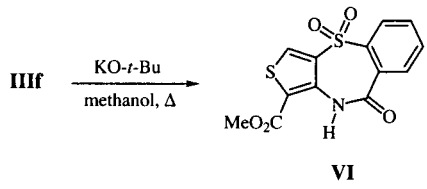
In all but one case, these compounds were readily obtained as essentially pure, crystalline solids by concentration of the reaction mixture and trituration of the crude residue with either aqueous or absolute methanol. As a single exception, methylsulfonyl derivative **IIIk** required a simple filtration through silica to remove a highly colored impurity which could not be removed otherwise. Recrystallization of each compound provided the analytical samples, which were characterized by ^1H nmr, ir, elemental analysis, and melting point (see the Table and Experimental).

Table

Data for Title Methyl 3-Amino-4-aryl(or methyl)sulfonylthiophene-2-carboxylates **IIIa-l**

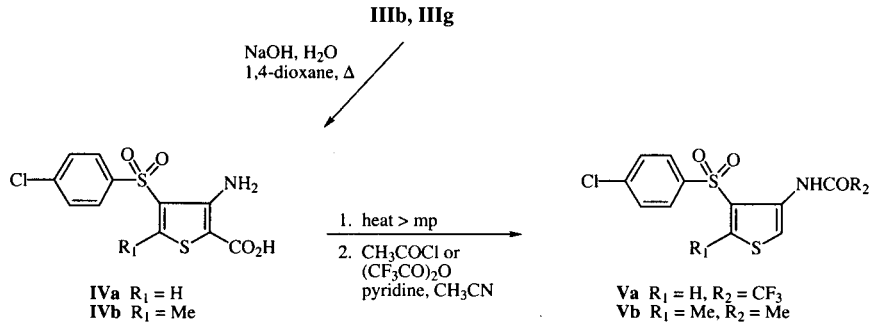
Compound No.	R_1	R_2	Reaction Time (hr)	Yield (%)	Mp (°) (recrystallization solvent)	Formula		Analysis (%) Calcd.	Found
IIIa	Ph	H	2	67	178-180 (methanol)	$C_{12}H_{11}NO_4S_2$	C	48.47	48.41
							H	3.73	3.71
							N	4.71	4.66
							S	21.56	21.65
IIIb	4-Cl-Ph	H	2	63	201-202 (acetone)	$C_{12}H_{10}ClNO_4S_2$	C	43.44	43.38
							H	3.04	3.03
							N	4.22	4.15
							S	19.33	19.43
IIIc	4-F-Ph	H	2	43	211-212 (acetone)	$C_{12}H_{10}FNO_4S_2$	C	45.70	45.82
							H	3.20	3.08
							N	4.44	4.39
							S	20.33	20.43
IIId	4-Me-Ph	H	2	52	182-183 (acetone)	$C_{13}H_{13}NO_4S_2$	C	50.15	49.98
							H	4.21	4.31
							N	4.50	4.45
							S	20.59	20.48
IIIe	2-NO_2-Ph	H	4	35	192-194 (EtOAc)	$C_{12}H_{10}N_2O_6S_2$	C	42.01	42.19
							H	2.94	2.93
							N	8.18	8.08
							S	18.73	18.82
IIIf	2-CO_2Me-Ph	H	2	50	146-147 (methanol)	$C_{14}H_{13}NO_6S_2$	C	47.31	47.26
							H	3.69	3.69
							N	3.94	3.87
							S	18.04	18.16
IIIg	4-Cl-Ph	Me	4	38	174-175 (acetone)	$C_{13}H_{12}ClNO_4S_2$	C	45.15	45.03
							H	3.50	3.42
							N	4.05	3.99
							S	18.54	18.71
IIIh	2-NO_2-Ph	Me	3	26	158-160 (methanol)	$C_{13}H_{12}N_2O_6S_2$	C	43.81	43.89
							H	3.40	3.35
							N	7.86	7.81
							S	17.99	17.90
IIIi	4-Cl-Ph	Et	5	54	142-144 (methanol)	$C_{14}H_{14}ClNO_4S_2$	C	46.73	46.74
							H	3.92	3.91
							N	3.89	3.83
							S	17.82	17.77
IIIj	4-Cl-Ph	Ph	2	40	149-150 (methanol)	$C_{18}H_{14}ClNO_4S_2$	C	53.00	52.84
							H	3.46	3.42
							N	3.43	3.39
							S	15.72	15.82
IIIk	Me	H	2	31	144-145.5 (methanol)	$C_7H_9NO_4S_2$	C	35.73	35.69
							H	3.86	3.87
							N	5.95	5.88
							S	27.25	27.34
IIIl	Me	Me	4	70	97-98 (methanol)	$C_8H_{11}NO_4S_2$	C	38.54	38.48
							H	4.45	4.43
							N	5.62	5.54
							S	25.72	25.59

As a note of interest, the use of potassium *t*-butoxide in methanol as base/solvent gave compound **IIIb** in much lower isolated yield compared to the triethylamine/tetrahydrofuran protocol, and thus the latter system was used to prepare the series. Also, it was found that the use of a catalytic amount of triethylamine (0.2 equivalent) resulted in a much slower reaction rate as observed by tlc, and thus a full equivalent of base was employed.



Equation 1.

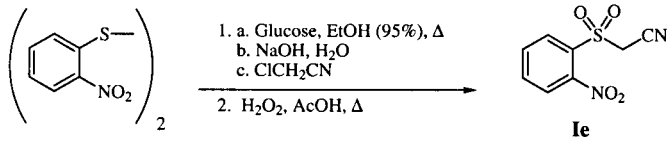
Scheme 2



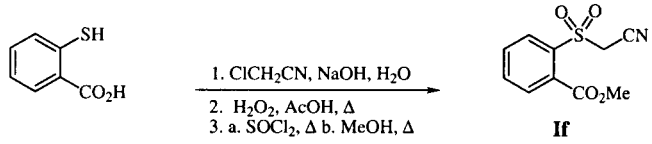
As shown in Scheme 2, title compounds **IIIb** and **IIIg** were subsequently hydrolyzed to the corresponding carboxylic acids **IVa-b** in high yield by treatment with aqueous sodium hydroxide in 1,4-dioxane at 100° for 4-5 hours. These acids were then readily decarboxylated by heating the neat samples above their melting points, and the intermediate amines were reacted directly following a bicarbonate wash with either trifluoroacetic anhydride (room temperature, overnight) or acetyl chloride (85°, 1 hour) in acetonitrile with pyridine as base to give trifluoroacetamide **Va** and acetamide **Vb** in 69% and 80% overall yield, respectively. Thus, based on the success of these two examples, the three step sequence of decarboxylation/acylation appears to represent a relatively facile process for the preparation of the targeted 4-arylsulfonyl-3-carboxamidothiophenes from the title thiophene-2-carboxylates.

In contrast to the success found with the acylation of the decarboxylated aminothiophenes, title aminothiophene **IIIb** failed to react with either acetyl chloride or trifluoroacetic anhydride under similar conditions, with starting material being recovered unchanged. Compound **IIIb** also failed to react with boiling acetic anhydride, with no appreciable amount of acetamide being formed according to tlc and infrared even after refluxing the neat mixture for 1 week. Thus, the presence of the two electron-withdrawing groups apparently makes this amine resistant to standard acylation conditions [12]. The hindered amine, however, did react intramolecularly with a nearby ester, as treatment of compound **IIIf** with potassium *t*-butoxide in refluxing methanol gave tricyclic **VI** [13] in 73% yield (Equation 1).

As starting materials for this work, the 3-alkoxy-2-aryl(or methyl)sulfonylacrylonitriles **IIa-l** were prepared according to general literature procedures by reaction of the appropriately substituted (arylsulfonyl)acetonitrile **Ia-f** or (methylsulfonyl)acetonitrile (**Ig**) with an *ortho* ester derivative in the presence of acetic anhydride/zinc chloride [10, 14], acetic anhydride alone [8], or acetic acid [8]. Acrylonitriles **IIa-d, g, i,** and **k** have previously been described [8, 11, 14], while **IIe-f, h, j,** and **l** represent novel compounds. It might be noted that the direct preparation of acrylonitrile **IIj** using trimethyl orthobenzoate represents a more convenient synthesis of a 3-phenyl substituted derivative than that previously described in the literature [10] which employs the hazardous diazomethane. Starting (arylsulfonyl)acetonitriles **Ia-d** [8, 15-16] and (methlysulfonyl)acetonitrile **Ig** [17] were either commercially available, (**Ia**) or readily prepared by adapting general literature procedures [8, 18], while the known 2-nitro- [19] and the novel 2-carbomethoxy-substituted (arylsulfonyl)acetonitriles **Ie-f** were prepared by novel methodology as shown in Equations 2-3.



Equation 2.



Equation 3.

In conclusion, we have described a convenient synthesis of 3-amino-4-aryl(or methyl)sulfonylthiophene-2-carboxylates containing non-heteroatom substituents at the 5-position. Preliminary work with these compounds indicates that the carboxylate can be easily removed, and that the resulting 3-aminothiophene reacts smoothly with two common acylating reagents. In contrast, the amine of the title compounds is much less reactive towards acylation, most likely due to the deactivation and/or steric demand of the two adjacent electron-withdrawing groups. The application of this chemistry to the synthesis of a diverse collection of 4-arylsulfonyl-3-carboxamidothiophenes for biological evaluation is currently underway, and the results of this work will be reported in due course.

EXPERIMENTAL

General analytical details are as previously described [20]. ^{1}H nmr spectra were recorded on a Brucker AM-300 spectrometer. Infrared spectra were recorded as KBr pellets unless otherwise indicated. Reaction temperatures given are indicative of the oil bath. Methyl thioglycolate (95%) was purchased from Aldrich and used as received. Tetrahydrofuran, acetonitrile, and triethylamine were routinely distilled from calcium hydride and stored over molecular sieves (4A). 2-Nitrophenyl disulfide was prepared according to a literature procedure [21], mp 197-198°, lit mp 192-195°.

(2-Nitrophenylsulfonyl)acetonitrile (**Ie**).

A finely ground mixture of 2-nitrophenyldisulfide (4.62 g, 0.015 mole) and glucose (3.12 g) was stirred well in 95% ethanol (75 ml) at 50-60° [22]. After 48 hours, the suspension was treated with sodium hydroxide (2.4 g, 0.06 mole) in water (7.5 ml) and stirring was continued at 60° for 2 hours. The dark yellow/brown mixture was then diluted with water (75 ml) (dissolving most of the solids), chilled for 1 hour, and filtered over celite. The resulting solution was treated with chloroacetonitrile (3.17 g, 0.042 mole) and stirred for 1 hour at room temperature to give a yellow solid which was collected, rinsed with water, and air dried (3.67 g). Recrystallization from ethanol (30-40 ml) gave (2-nitrophenylthio)acetonitrile as yellow needles (3.53 g, 60%), mp 116-117°, lit mp 117° [24].

A mixture of the above sulfide (2.62 g, 13.5 mmoles) and hydrogen peroxide (35%) (4.5 ml) in acetic acid (20 ml) was heated at 100° for 6 hours. The solution was then chilled to give the title compound as colorless needles, which were collected, rinsed with water, and air dried (2.72 g, 89%), mp 119-120°; lit mp 126-127° [19]; ir: ν 2250 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.64 (s, 2H, SO_2-CH_2), 7.86-7.97 (m, 3H, ArH), 8.31-8.34 (m, 1H, ArH); ms: (ei) m/z (relative intensity) 226 (M^+, 3.5), 186 (100), 92 (11), 76 (14), 64 (14). Recrystallization from ethanol did not change the melting point.

Methyl 2-(Cyanomethylsulfonyl)benzoate (**If**).

To a room-temperature solution of thiosalicylic acid (4.63 g, 0.03 mole) in aqueous sodium hydroxide (1*N*) (60 ml) was added in one portion chloroacetonitrile (2.38 g, 0.0315 mole) and the mixture was stirred at ambient temperature for 1 hour. The solution was then acidified with concentrated hydrochloric acid to give 2-(cyanomethylthio)benzoic acid as a solid which was collected rinsing with water and dried under vacuum to give a white powder (5.73 g, 99%), mp 201-202°, lit mp 195-198° [25].

To a suspension of the dried 2-(cyanomethylthio)benzoic acid (5.73 g, 0.03 mole) in acetic acid (50 ml) was added hydrogen peroxide (35%) (10 ml) and the mixture was stirred for 6 hours at 100° and then overnight at room temperature. The resulting solution was poured into a wide mouth dish and allowed to evaporate under a fume hood. The residue was suspended in water, collected, and air dried to give 2-(cyanomethylsulfonyl)-benzoic acid as a colorless crystalline solid (6.02 g, mp 77-83°, hydrate). Drying of the solid in a round-bottom flask under high vacuum for 1 hour while heating a few times with a heat gun (gentle fusing) gave the dehydrated product (5.60 g, 83%), mp 140-142°; ir: ν 3480 (OH), 3200-2200 (broad), 2245 (CN), 1675 (CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 5.32 (s, 2H, SO_2-CH_2), 7.83-7.96 (m, 3H, ArH), 8.09 (d, 1H, ArH).

A mixture of the dehydrated 2-(cyanomethylsulfonyl)benzoic acid (2.25 g, 0.01 mole) and thionyl chloride (4.2 g) was heated at 60° for 2 hours [26]. The pale yellow suspension was concentrated *in vacuo,* methanol (20 ml) was added, and heating was continued at 60° for 45 minutes. The solution was concentrated *in vacuo* to near dryness and diluted with saturated sodium bicarbonate solution to give an oil which solidified upon stirring and addition of ice. The solid was collected and recrystallized from methanol (15-20 ml) to give the title compound as colorless needles (1.84 g, 77%), mp 125-126°; ir: ν 2245 (CN), 1710 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.97 (s, 3H, OMe), 4.69 (s, 2H, SO_2-CH_2), 7.72-7.85 (m, 3H, ArH), 8.23-8.26 (m, 1H, ArH); ms: (ei) m/z (relative intensity) 239 (M^+, 10), 208 (50), 199 (100), 135 (52), 104 (48), 77 (60).

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85; S, 13.40. Found: C, 49.96; H, 3.85; N, 5.68; S, 13.17.

The following 3-alkoxy-2-arylsulfonylacrylonitriles **IIe-h** and **III** were prepared by reaction of the appropriate (phenylsulfonyl)acetonitrile with either triethyl orthoformate or trimethyl orthoacetate (5 equivalents), acetic anhydride (5 equivalents), and zinc chloride (0.15 equivalent) at 125-130° for 7-8 hours [8,10,14]. At the end of the reaction, the mixture was filtered, the lower boiling solvents were removed *in vacuo*, and the solution was poured into excess hexanes using an ether rinse to give the compound as a solid or oil. Compounds were further purified as described below or used directly as obtained.

3-Ethoxy-2-(2-nitrophenylsulfonyl)acrylonitrile (**IIe**).

Using the above procedure, an off-white crystalline solid was obtained (1.68 g, 85%), mp 92-93°. Recrystallization from ethyl acetate/hexanes gave a colorless crystalline solid, mp 93-95°; ir: ν 2210 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.49 (t, 3H, CH_3), 4.47 (q, 2H, CH_2), 7.75-7.83 (m, 3H, ArH), 8.03 (s, 1H, 3-H), 8.25-8.28 (m, 1H, ArH).

Anal. Calcd. for $C_{11}H_{10}N_2O_5S$: C, 46.80; H, 3.57; N, 9.93; S, 11.36. Found: C, 46.84; H, 3.47; N, 9.82; S, 11.48.

3-Ethoxy-2-[(2-methoxycarbonyl)phenylsulfonyl)]acrylonitrile (**IIf**).

Using the above procedure, an amber colored oil was obtained. Decanting and drying of the product in ethyl acetate (magnesium sulfate), followed by reconcentration (high vacuum) gave a viscous syrup (2.0 g, 90%), which was homogenous on tlc, and used without further purification; ir (neat film,

sodium chloride): ν 2210 (CN), 1725 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.46 (t, 3H, CH_3), 3.93 (s, 3H, OMe), 4.42 (q, 2H, CH_2), 7.61-7.69 (m, 3H, ArH), 8.03 (s, 1H, 3-H), 8.15-8.18 (m, 1H, ArH).

2-(4-Chlorophenylsulfonyl)-3-methoxy-3-methylacrylonitrile (**IIg**).

Using the above procedure, a light orange solid was obtained (1.84 g, 68%), mp 95-110° [27], which was a mixture of (*E*)- and (*Z*)-isomers as observed by tlc and ^1H nmr. Attempted purification by recrystallization from methanol or ethyl acetate/hexanes resulted in substantial degradation back to the (phenylsulfonyl)acetonitrile and thus this compound was used directly as obtained; ir: ν 2200 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.34 and 2.55 (2s, relative intensity 3.5:1, 3H, CH_3), 3.93 and 3.97 (2s, relative intensity 3.5:1, 3H, OMe), 7.48-7.54 (2d overlapping, 2H, ArH), 7.86-7.90 (2d overlapping, 2H, ArH).

2-(2-Nitrophenylsulfonyl)-3-methoxy-3-methylacrylonitrile (**IIh**).

This compound was prepared using 10 equivalents each of trimethyl orthoacetate and acetic anhydride due to precipitation of the product, which necessitated the use of more solvent. A reaction time of 24 hours at 110° was employed and the zinc chloride was omitted. Concentration and trituration with hexanes gave an orange/yellow solid, which was collected and recrystallized from ethyl acetate to yield a fluffy off-white solid (0.74 g, 72%) in two crops, mp 184-187°, as a mixture of (*E*)- and (*Z*)-isomers; ir: ν 2200 (CN) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.47 and 2.58 (2s, relative intensity 5:1, 3H, CH_3), 3.98 and 4.08 (2s, relative intensity 5:1, 3H, OMe), 7.92-8.20 (m, 4H, ArH).

Anal. Calcd. for $C_{11}H_{10}N_2O_5 \cdot 0.2H_2O$: C, 46.21; H, 3.67; N, 9.80; S, 11.22. Found: C, 46.10; H, 3.56; N, 9.65; S, 11.39.

3-Methoxy-3-methyl-2-methylsulfonylacrylonitrile (**III**).

This compound was prepared with a reaction time of 24 hours and without zinc chloride. Chromatography through a short silica plug eluting with ethyl acetate:hexanes (1:1) to remove residual starting material followed by ethyl acetate to remove product gave, after concentration and trituration with hexanes, a yellow crystalline solid. Recrystallization from a small volume of methanol gave a white crystalline solid, mp 107-112°, as a mixture of (*E*)- and (*Z*)-isomers (0.57 g, 38%); ir: ν 2200 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.45 and 2.55 (2s, relative intensity 2.75:1, 3H, CH_3), 3.10 and 3.12 (2s, relative intensity 2.75:1, 3H, SO_2Me), 4.02 and 4.07 (2s, relative intensity 1:2.75, 3H, OMe).

Anal. Calcd. for $C_6H_9NO_3S$: C, 41.13; H, 5.18; N, 7.99; S, 18.30. Found: C, 41.11; H, 5.24; N, 7.91; S, 18.42.

2-(4-Chlorophenylsulfonyl)-3-methoxy-3-phenylacrylonitrile (**IIj**).

A mixture of (4-chlorophenylsulfonyl)acetonitrile (**Ib**) (1.07 g, 5 mmoles), trimethyl orthobenzoate (2.28 g, 12.5 mmoles) and 4 drops of acetic acid was heated at 140° for 7 hours. The produced methanol was removed *in vacuo*, and the residue was triturated with hexanes to give a brown solid. Recrystallization from methanol (30 ml, followed by partial concentration) gave a white crystalline solid (0.845 g, 50%), mp 140-142°; ir: ν 2205 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H, OMe), 7.40-7.58 (m, 7H, ArH), 7.97-8.00 (dd, 2H, ArH).

Anal. Calcd. for $C_{16}H_{12}ClNO_3S$: C, 57.57; H, 3.63; N, 4.20; S, 9.61. Found: C, 57.67; H, 3.60; N, 4.16; S, 9.63.

General Procedure for the Synthesis of the Title Thiophene-2-carboxylates **IIIa-l.**

To a solution of the appropriate 3-alkoxy-2-aryl(or methyl)sulfonylacrylonitrile **IIa-l** (1.5-5.0 mmoles) in tetrahydrofuran (2-3 ml/mmole) was added methyl thioglycolate (1.1 equivalents) followed by triethylamine (1.0 equivalent). The mixture was heated under reflux at 75-80° (calcium sulfate guard tube) until tlc analysis (ethyl acetate/hexane mixtures) showed the reaction to be essentially complete (2-5 hours). Following concentration *in vacuo*, the usually dark red oily residue was triturated with aqueous or absolute methanol (see below) to precipitate the product as an orange/yellow to off-white solid which was collected and rinsed with a small amount of trituration solvent (yield, 26-70%). (Absolute methanol was generally employed when aqueous methanol had been found to give an impure product.) The product, which was practically homogeneous on tlc, was then recrystallized to give the analytical sample.

Methyl 3-Amino-4-phenylsulfonyl-2-thiophenecarboxylate (**IIIa**).

This compound was isolated following trituration with methanol; recrystallization gave a white crystalline solid; ir: ν 3465 and 3350 (NH_2), 1675 (CO), 1295 and 1140 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.74 (s, 3H, OMe), 6.56 (s, 2H, NH_2), 7.63-7.77 (m, 3H, ArH), 8.02 (dd, 2H, ArH), 8.66 (s, 1H, 5-H).

Methyl 3-Amino-4-(4-chlorophenylsulfonyl)-2-thiophenecarboxylate (**IIIb**).

This compound was isolated following trituration with methanol:water (2:1); recrystallization gave fine off-white/pale peach needles; ir: ν 3455 and 3345 (NH_2), 1675 (CO), 1290 and 1135 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.81 (s, 3H, OMe), 6.32 (br s, 2H, NH_2), 7.47 (d, 2H, ArH), 7.87 (d, 2H, ArH), 8.05 (s, 1H, 5-H).

Methyl 3-Amino-4-(4-fluorophenylsulfonyl)-2-thiophenecarboxylate (**IIIc**).

This compound was isolated following trituration with methanol:water (2:1); recrystallization gave white fluffy crystals; ir: ν 3465 and 3360 (NH_2), 1680 (CO), 1290 and 1140 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.81 (s, 3H, OMe), 6.31 (br s, 2H, NH_2), 7.15-7.21 (m, 2H, ArH), 7.93-7.98 (m, 2H, ArH), 8.05 (s, 1H, 5-H).

Methyl 3-Amino-4-(4-methylphenylsulfonyl)-2-thiophenecarboxylate (**IIId**).

This compound was isolated following trituration with methanol:water (2:1); recrystallization gave pale pink crystals; ir: ν 3460 and 3360 (NH_2), 1680 (CO), 1295 and 1140 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.39 (s, 3H, ArMe), 3.80 (s, 3H, OMe), 6.31 (br s, 2H, NH_2), 7.30 (d, 2H, ArH), 7.81 (d, 2H, ArH), 8.03 (s, 1H, 5-H).

Methyl 3-Amino-4-(2-nitrophenylsulfonyl)-2-thiophenecarboxylate (**IIIe**).

This compound was isolated following trituration with methanol; recrystallization gave pale yellow crystals; ir: ν 3460

and 3355 (NH_2), 1675 (CO), 1280 and 1135 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.77 (s, 3H, OMe), 6.58 (br s, 2H, NH_2), 7.93-8.03 (m, 2H, ArH), 8.06-8.10 (dd, 1H, ArH), 8.40-8.43 (dd, 1H, ArH), 8.60 (s, 1H, ArH).

Methyl 3-Amino-4-[(2-methoxycarbonyl)phenylsulfonyl]-2-thiophenecarboxylate (**IIIf**).

This compound was isolated following trituration with methanol:water (3:1); recrystallization gave pale orange/colorless scales; ir: ν 3475 and 3360 (NH_2), 1720 (CO), 1680 (CO), 1290 and 1140 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.80 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.42 (br s, 2H, NH_2), 7.54-7.64 (m, 3H, ArH), 7.99-8.02 (dd, 1H, ArH), 8.22 (s, 1H, 5-H).

Methyl 3-Amino-4-(4-chlorophenylsulfonyl)-5-methyl-2-thiophenecarboxylate (**IIIg**).

This compound was isolated following trituration with methanol; recrystallization gave a white fluffy solid; ir: ν 3460 and 3355 (NH_2), 1665 (CO), 1290, 1175, or 1130 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.58 (s, 3H, 5-Me), 3.79 (s, 3H, OMe), 6.65 (br s, 2H, NH_2), 7.46-7.49 (dd, 2H, ArH), 7.85-7.88 (dd, 2H, ArH).

Methyl 3-Amino-4-(2-nitrophenylsulfonyl)-5-methyl-2-thiophenecarboxylate (**IIIh**).

This compound was isolated following trituration with methanol:water (3:1); recrystallization gave yellow crystals; ir: ν 3475 and 3360 (NH_2), 1660 (CO), 1290 and 1180 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.51 (s, 3H, 5-Me), 3.80 (s, 3H, OMe), 6.52 (br s, 2H, NH_2), 7.76-7.79 (m, 2H, ArH), 7.84-7.87 (m, 1H, ArH), 8.20-8.23 (m, 1H, ArH).

Methyl 3-Amino-4-(4-chlorophenylsulfonyl)-5-ethyl-2-thiophenecarboxylate (**IIIi**).

This compound was isolated following trituration with methanol:water (3:1); recrystallization gave a white fluffy solid; ir: ν 3440 and 3335 (NH_2), 1675 (CO), 1285 and 1125 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_3), 3.06 (q, 2H, CH_2), 3.79 (s, 3H, OMe), 6.67 (br s, 2H, NH_2), 7.45-7.48 (dd, 2H, ArH), 7.85-7.88 (dd, 2H, ArH).

Methyl 3-Amino-4-(4-chlorophenylsulfonyl)-5-phenyl-2-thiophenecarboxylate (**IIIj**).

This compound was isolated following trituration with methanol; recrystallization gave colorless crystals; ir: ν 3460 and 3355 (NH_2), 1675 (CO), 1285 and 1135 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.82 (s, 3H, OMe), 6.87 (br s, 2H, NH_2), 7.19-7.46 (m, 9H, ArH).

Methyl 3-Amino-4-methylsulfonyl-2-thiophenecarboxylate (**IIIk**).

Before trituration, the dark oily residue was dissolved in a minimum amount of ethyl acetate and flushed through a short silica plug eluting with ethyl acetate/hexanes (1:1 to 3:2). The compound was then isolated by removal of the solvent and trituration of the residue with methanol:water (3:1); recrystallization gave light orange shears; ir: ν 3460 and 3350 (NH_2), 1660 (CO), 1285 and 1125 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.06 (s, 3H, SO_2Me), 3.84 (s, 3H, OMe), 6.20 (br s, 2H, NH_2), 8.03 (s, 1H, 5-H).

Methyl 3-Amino-5-methyl-4-methylsulfonyl-2-thiophenecarboxylate (**IIIl**).

This compound was isolated following trituration with methanol:water (3:1); recrystallization gave a white fluffy solid; ir: ν 3475 and 3365 (NH_2), 1680 (CO), 1290 and 1195 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.66 (s, 3H, 5-Me), 3.03 (s, 3H, SO_2Me), 3.81 (s, 3H, Me), 6.43 (br s, 2H, NH_2).

3-Amino-4-(4-chlorophenylsulfonyl)-2-thiophenecarboxylic Acid (**IVa**).

To a suspension of **IIIb** (0.50 g, 1.5 mmoles) in 1,4-dioxane (6 ml) was added 5*N* sodium hydroxide (2 ml) and the mixture was heated at 100° until tlc analysis (hexanes:ethyl acetate, 3:2) showed that no more starting material remained (4-5 hours). The mixture was then concentrated *in vacuo*, the solids were dissolved in water (5-6 ml), and the clear solution was acidified with concentrated hydrochloric acid/ice to give a white solid which was collected, rinsed well with water, and air dried (0.46 g, 97%). Recrystallization from methanol (50 ml, followed by partial concentration) gave a pale pink fluffy solid, mp 200-201° (with loss of CO_2); ir: ν 3470 and 3360 (NH_2), 1650 (CO), 1290, 1200, or 1145 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 6.49 (br s, 2H, NH_2), 7.74 (d, 2H, ArH), 8.02 (d, 2H, ArH), 8.62 (s, 1H, 5-H), 12.96 (br s, 1H, CO_2H).

Anal. Calcd. for $C_{11}H_8ClNO_4S_2$: C, 41.58; H, 2.54; N, 4.41; S, 20.18. Found: C, 41.67; H, 2.50; N, 4.36; S, 20.24.

3-Amino-4-(4-chlorophenylsulfonyl)-5-methyl-2-thiophenecarboxylic Acid (**IVb**).

Using the procedure described above and starting with **IIIg** (1.04 g, 3.0 mmoles), this compound was obtained in 92% yield. Recrystallization from methanol gave a white crystalline solid, mp 162-164° (with loss of carbon dioxide); ir: ν 3465 and 3355 (NH_2), 1650 (CO), 1290, 1190, or 1140 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.63 (s, 3H, 5-Me), 6.65 (br s, 2H, NH_2), 7.72-7.74 (dd, 2H, ArH), 7.99-8.02 (dd, 2H, ArH).

Anal. Calcd. for $C_{12}H_{10}ClNO_4S_2$: C, 43.44; H, 3.04; N, 4.22; S, 19.33. Found: C, 43.51; H, 3.03; N, 4.20; S, 19.42.

4-(4-Chlorophenylsulfonyl)-3-(trifluoroacetamido)thiophene (**Va**).

Compound **IVa** (0.24 g, 0.75 mmole) was placed in a 50 ml round-bottom and plunged into an oil-bath preheated to 210-215°. After 1-2 minutes, complete melting of the solid had occurred (facilitated by magnetic stirring) and the flask was removed from the heat and cooled under tepid water. The oily residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate, brine, and dried (magnesium sulfate). Following concentration, the amine was dissolved in dry acetonitrile (3 ml) and at ice-bath temperature was treated with pyridine (0.065 g, 0.82 mmole) followed by trifluroacetic anhydride (0.19 g, 0.90 mmole). After stirring at room temperature for 2 hours, additional trifluoroacetic anhydride (0.08 g) was added, and the mixture was stirred overnight. The resulting suspension was diluted with water (3 ml) and chilled, and the solid was collected, rinsed with water, and air dried (0.19 g, 69% overall). Recrystallization from 95% methanol gave an olive green/tan fluffy solid, mp 165-166°; ir: ν 3325 (NH), 1725 (CO), 1210, 1175, 1150, 1130, or 1080 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.52 (d, 2H, ArH), 7.81 (d, 2H, ArH), 8.07-8.10 (dd, 2H, 2-H and 5-H), 10.08 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_7ClF_3NO_3S_2$: C, 38.98; H, 1.91; N, 3.79; S, 17.34. Found: C, 39.11; H, 1.86; N, 3.77; S, 17.46.

3-Acetamido-4-(4-chlorophenylsulfonyl)-5-methylthiophene (**Vb**).

Starting with acid **IVb** (0.330 g, 1.0 mmole) and using the decarboxylation procedure described above (oil bath 185°), the intermediate amine was obtained as a yellow oil. This amine was dissolved in acetonitrile (4 ml) and treated with pyridine (0.08 g, 1.0 mmole) followed by acetyl chloride (0.09 g, 1.15 mmoles) and the solution was heated at 80-85° for 1 hour. The mixture was then concentrated to near dryness and diluted with water to give the acetamide as a light brown solid (0.264 g, 80% overall). Recrystallization from methanol gave tan crystals, mp 170-172°; ir: ν 3345 (NH), 1685 (CO), 1290, 1265, or 1130 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.21 (s, 3H, $COCH_3$), 2.55 (s, 3H, 5-CH_3), 7.47-7.50 (dd, 2H, ArH), 7.74-7.76 (dd, 2H, ArH), 7.84 (s, 1H, 2-H), 9.58 (br s, 1H, NH).

Anal. Calcd. for $C_{13}H_{12}ClNO_3S_2$: C, 47.34; H, 3.67; N, 4.25; S, 19.44. Found: C, 47.24; H, 3.63; N, 4.16; S, 19.51.

1-Methoxycarbonylthieno[3,4-*b*][1,4]benzothiazepin-9(10*H*)-one 4,4-Dioxide (**VI**).

To a suspension of **IIIf** (0.27 g, 0.76 mmole) in methanol (8 ml) was added potassium *t*-butoxide (0.102 g, 0.91 mmole) and the mixture was heated at 80-85° for 1 hour. A solution was quickly achieved followed by formation of a precipitate. The solvent was then removed *in vacuo,* and the remaining solid was treated with 1*N* hydrochloric acid (10 ml) and extracted with ethyl acetate (20 ml). The organic layer was separated, washed with brine, and dried (magnesium sulfate). Following concentration, the residue was triturated with a small amount of methanol to give a light pink crystalline solid (0.18 g, 73%). Recrystallization from methanol (30 ml, followed by partial concentration) gave fine white crystals, mp 226-227°; ir: ν 3305 (NH), 1685 (ridge, CO), 1655 (CO), 1315, 1265, 1215, 1190, 1155, or 1125 (SO_2) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.84 (s, 3H, OMe), 7.83-8.02 (m, 4H, ArH), 8.76 (s, 1H, 3-H), 10.74 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_9NO_5S_2$: C, 48.29; H, 2.81; N, 4.33; S, 19.83. Found: C, 48.32; H, 2.76; N, 4.30; S, 19.94.

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[27] Perez, *et al.* [10] also found a 3-methylacrylonitrile derivative to exist as a mixture of isomers with a similarly broad melting point.