Synthesis of Novel Heterocycles from 2-Amino-3-(cyanomethylsulfonyl)thiophene

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The synthesis and selected reactions of 2-amino-3-(cyanomethylsulfonyl)thiophene is reported. In particular, cyclization reaction of the versatile aminothiophene yielded a number of novel thieno[3,2-*b*][1,4]-thiazine 1,1-dioxides, as well as the analogous thieno[2,3-*e*][1,3,4]thiadiazine 4,4-dioxide. Reaction of the thienothiazine system with hydrazine was subsequently explored, which resulted in either ring-opening of the thiazine and formation of an aminopyrazole or solely ring cleavage depending on the thiazine substituent. Additionally, the synthesis of bis(2-amino-3-thienyl)sulfone and the corresponding bis-acetamide is described.

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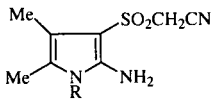
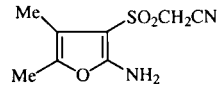
In previous reports, we have described the synthesis of substituted 2-amino-3-cyanomethylsulfonyl-4,5-dimethyl-pyrroles **I** [1] and the analogous furan **II** [2] *via* condensation of sulfonyldiacetonitrile with an α-aminoketone or acetoin, repectively. Through a variety of cyclization reactions between the activated methylene and the amino group, these compounds have served as immediate precursors to a number of interesting and readily-available bicyclic thiazines [2-3] and thiadiazines [4] for broad-screen biological evaluation. Our continued development of compounds of this type has led us now to report on our work with a thiophene analogue of **I** and **II**, namely 2-amino-3-(cyanomethylsulfonyl)thiophene (**III**).



I

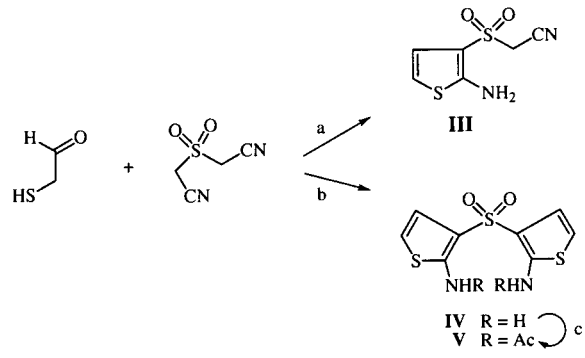


II

In 1965, Gewald first desribed the synthesis of 2-amino-thiophenes containing an electron-withdrawing group at the 3-postion through base-catalyzed condensation of an α-mercaptocarbonyl derivative with an activated acetonitrile [5]. Utilizing this methodolgy, we have prepared the title compound by reaction of sulfonyldiacetonitrile with mercaptoacetaldehyde [6] in ethanol using piperidine as base (Scheme 1). After stirring overnight at room temperature and purification by flash chromotography, the aminothiophene was obtained as a highly viscous syrup in consistantly high yields (90-95%). In contrast, attempted preparation of the analogous 4,5-dimethylthiophene, the direct thiophene analogue of **I** and **II**, *via* condensation of sulfonyldiacetonitrile with methyl ethyl ketone and sulfur again according to Gewald [7] was unsuccessful.

Interestingly, we found the choice of base in the preparation of **III** to be particularly critical, as the use of the more basic 1,8-diazabicyclo[5.4.0]undec-7-ene [8] gave a considerable amount of bis-condensation product **IV**, even with the use of 1 equivalent of the mercaptoaldehyde. On the other hand, the use of piperidine under nearly identical conditions resulted in selective formation of the mono-condensation product, with only trace amounts of IV formed as determined by nmr. As shown in Scheme 1, the bis-thiophene product was subsequently prepared in higher yield by reaction of sulfonyldiacetonitrile with 2 equivalents of the mercaptoaldehyde using triethylamine as base [9]. Bis-acetamide **V** was then obtained by reaction of **IV** with acetyl chloride and pyridine in refluxing tetrahydrofuran.

Scheme 1



(a) 1 Equivalent of the mercaptoaldehyde, piperidine, ethanol; (b) 2 Equivalents of the mercaptoaldehyde, triethylamine, ethanol; (c) Acetyl chloride, pyridine, tetrahydrofuran, Δ.

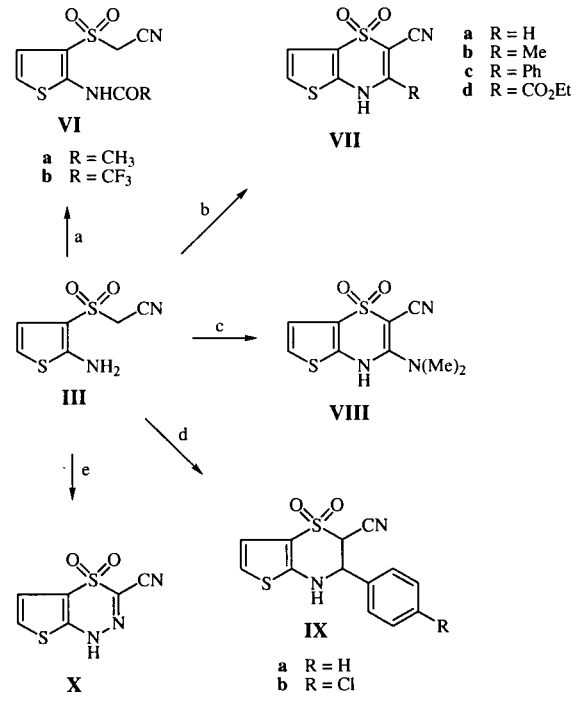
As shown in Scheme 2, aminothiophene **III** served as direct precursor to a number of new compounds, some in an analogous manner as previously reported for aminofuran **II** [2]. First, reaction of **III** with acetyl chloride (80°, 15 minutes) or trifluoroacetic anhydride (room temperature, overnight) in acetonitrile with pyridine as base readily gave acetamide **VIa** and trifluoroacetamide **VIb**, respectively.

Next, reaction of **III** neat with *ortho* esters at approximately 110° for 1-2.5 hours followed by heating with triethylamine in ethanol resulted in cyclization to various thieno[3,2-*b*]-[1,4]thiazine 1,1-dioxides. Thus, reaction with trimethyl orthoformate, trimethyl orthoacetate, trimethyl orthobenzoate, or ethyl triethoxyacetate led to thienothiazines **VIIa-d**, respectively. In a similar sequence, reaction of **III** with phosgene iminium chloride in dichloromethane at 40° for 1 hour followed by cyclization of the intermediate imino chloride with triethylamine gave (dimethylamino)thienothiazine **VIII**. Next, condensation of **III** with benzaldehyde or 4-chlorobenzaldehyde in ethanol at 90° using ammonium acetate as catalyst gave dihydrothienothiazines **IXa-b**. After recrystallization, the phenyl-unsubstituted compound was obtained almost selectively (>95%) as the *trans* diastereomer, while the 4-chlorophenyl derivative was obtained as an approximate 2:1 *cis:trans* diastereomeric mixture. Finally, treatment of **III** with sodium nitrite in acetic acid according to our conditions for the cyclization of pyrroles of type **I** [4] gave thieno[2,3-*e*][1,3,4]thiadiazine 4,4-dioxide **X** which upon review of *Chemical Abstracts* represents a novel ring system.

With 3-(ethoxycarbonyl)thienothiazine **VIId** in hand, we were interested in further elaboration of this compound to a pyridazine-containing tricyclic system *via* cyclization between the ester and nitrile moieties with hydrazine. This reaction in ethanol, however, resulted only in deprotonation of the starting material, with **VIId** recovered unchanged following acidification. To eliminate this acid/base chemistry, **VIId** was protected by *N*-methylation using sodium hydride and dimethyl sulfate to give **XI**. As shown in Scheme 3, reaction of this methylated derivative with hydrazine in ethanol at room temperature interestingly gave aminopyrazole **XII** rather than the expected tricyclic system. Thus, instead of attacking the ester, hydrazine apparently added *via* conjugate addition to the activated double bond, which resulted in elimination of the thiophenamine and opening of the thiazine. Intramolecular addition of the hydrazino moiety to the nitrile then finally gave the aminopyrazole.

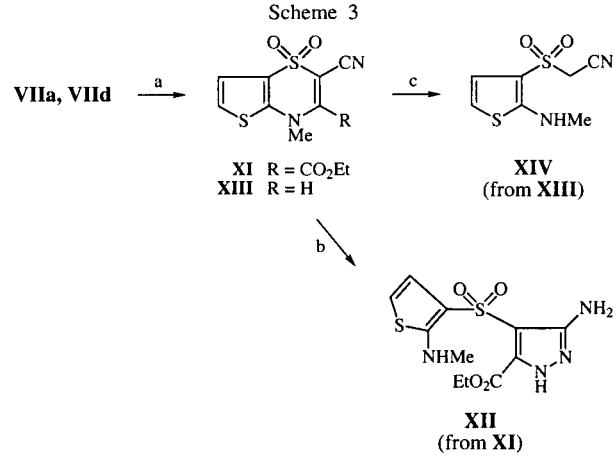
This pyrazole-forming reaction was subsequently extended to the 3-unsubstituted *N*-methylthienothiazine **XIII**, which was prepared from **VIIa** using potassium *t*-butoxide and dimethyl sulfate. In this case, reaction with hydrazine in ethanol proceeded only at elevated temperature (presumably due to insolubility) and led to cleavage of the thiazine ring with isolation of (*N*-methylamino)thiophene **XIV** (Scheme 3 again). Changing the solvent to dimethylformamide led to a reaction at room temperature, however, the ring-cleavage product was again obtained with no evidence of the pyrazole. Upon review of the literature, this result appears analogous to the cleavage of 2-arylsulfonyl-2-cyanovinyl ethers to the corresponding (arylsulfonyl)acetonitriles by heating with hydrazine [10]. Reaction of the other 3-substituted thienothiazines prepared here with hydrazine was not explored.

Scheme 2



(a) Acetyl chloride, pyridine, acetonitrile, Δ; or trifluoroacetic anhydride, pyridine, acetonitrile; (b) 1. $(MeO)_3CR$ (R = H, Me, or Ph) or $(EtO)_3CCO_2Et$, Δ 2. Triethylamine, ethanol, Δ; (c) 1. Phosgene iminium chloride, CH_2Cl_2, Δ 2. Triethylamine, (d) Benzaldehyde or 4-chlorobenzaldehyde, ammonium acetate, ethanol, Δ; (e) $NaNO_2$, AcOH.

Scheme 3



(a) NaH, $(CH_3)_2SO_4$, tetrahydrofuran/dimethylformamide (for **XI**); or $KOC(CH_3)_3$, $(CH_3)_2SO_4$, dimethylformamide (for **XIII**); (b) $NH_2NH_2 \cdot H_2O$, ethanol, RT; (c) $NH_2NH_2 \cdot H_2O$, ethanol, Δ.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus (open capillary) and are uncorrected. The nmr

and mass spectra were determined on a Brucker AM-300 or WH-400 spectrometer and a VG-70 SQ instrument, respectively. Infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique; where the presence of multiple intense ir absorptions made identification of the sulfone bands difficult, all peaks which are potentially ascribed to the sulfone are reported. Elemental analysis were performed by Atlantic Microlab, Inc., Norcross. Georgia; the presence of residual ethyl acetate in compounds **V** and **XIV** was confirmed by proton nmr. Thin-layer chromatograpy (tlc) was performed on Baker Si250F silica plates. Column chromatography was conducted on Fisher Selecto 60 (230-400 mesh) silica gel. Sulfonyldiacetonitrile was synthesized according to a literature procedure [11]. Ethyl triethoxyacetate was synthesized as a 66% mixture with diethyl oxalate following simple distillation and used as such [12]; the procedure described here for the synthesis of compound **VIId** gave only a trace of product when this mixture was substituted with pure diethyl oxalate.

2-Amino-3-(cyanomethylsulfonyl)thiophene (**III**).

A suspension of sulfonyldiacetonitrile (1.44 g, 10 mmoles), 1,4-dithiane-2,5-diol (0.80 g, 5.25 mmoles), and piperidine (0.43 g, 5 mmoles) in ethanol (50 ml) was stirred overnight (*ca.* 16 hours) at room temperature. The resulting orange solution was then filtered to clarify and the ethanol was removed *in vacuo*. The remaining oil was partitioned between hydrochloric acid (1 *N*) and ethyl acetate, and the organic layer was further washed with brine, dried (magnesium sulfate), and concentrated *in vacuo*. The oil was then dissolved in a minimum amount of ethyl acetate and flushed through a short silica plug eluting with ethyl acetate:hexanes (2:1) to give, following concentration *in vacuo*, a light orange viscous syrup (1.88 g, 93%); tlc R_f, ethyl acetate: hexanes (1:1), 0.76; ir: ν 3465 and 3360 (NH_2), 2250 (CN), 1305, 1280, 1240, 1160, 1135, 1100, cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 4.04 (s, 2H, CH_2, 5.68 (br s, 2H, NH_2), 6.36 and 6.86 (2d, 2H, 4-H and 5-H).

Anal. Calcd. for $C_6H_6N_2O_2S_2$: C, 35.63; H, 2.99; N, 13.85; S, 31.70. Found: C, 35.75; H, 2.96; N, 13.77; S, 31.75.

Bis(2-amino-3-thienyl)sulfone (**IV**).

A suspension of sulfonyldiacetonitrile (0.72 g, 5 mmoles), 1,4-dithiane-2,5-diol (0.80 g, 5.25 mmoles), and triethylamine (0.2 g, 2.0 mmoles) in ethanol (15 ml) was stirred at room temperature overnight. After removing about half of the ethanol *in vacuo*, ethyl acetate was added (dissolving the small amount of solid) and the solution was washed with hydrochloric acid (1*N*), brine and dried (magnesium sulfate). The solution was then concentrated partially (not allowing precipitation to begin) and flushed through a small silica plug eluting with ethyl acetate to give, following concentration *in vacuo*, a tan-colored pasty solid (0.90 g, 69%). An analytical sample recrystallized from methanol had mp 205-206°, with darkening >190°; ir: ν 3455 and 3350 (NH_2), 1275, 1245, 1125 cm^{-1}; ^1H nmr (400 MHz, dimethyl-d_6 sulfoxide): δ 6.35 and 6.76 (2d, 4H, thienyl hydrogens), 6.80 (s, 4H, 2 NH_2); ms :(ei) m/z 260 (M^+).

Anal. Calcd. for $C_8H_8N_2O_2S_3$: C, 36.90; H, 3.10; N, 10.76; S, 36.95. Found: C, 36.99; H, 3.12; N, 10.82; S, 36.86.

Bis(2-acetamido-3-thienyl)sulfone (**V**).

To a chilled solution of bis(2-amino-3-thienyl)sulfone (**IV**) (0.65 g, 2.5 mmoles) and pyridine (0.59 g, 7.5 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise acetyl chloride (0.59 g, 7.5 mmoles) and the mixture was heated at reflux for 20 minutes. The mixture was diluted with ethyl acetate/water and the organic layer was washed with brine and then dried (magnesium sulfate). After concentration *in vacuo*, the solid was boiled in ethanol (10-15 ml) and filtered hot to give a tan solid (0.41 g, 48%), mp 214-216° dec. The product was recrystallized from ethyl acetate:cyclohexane and then sucked dry on the filter paper (house vacuum) to give the analytical sample as tan crystalline flakes, mp 218-220° dec; ir: ν 3365 (NH), 1690 (CO), 1290, 1155, 1100 cm^{-1}; ^1H nmr (400 MHz, dimethyl-d_6 sulfoxide): δ 2.29 and 2.30 (2s, 6H, 2 $COCH_3$), 7.14 and 7.22 (2d, 4H, thienyl hydrogens), 10.36 (s, 2H, 2 NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_4S_3 \cdot 0.1CH_3CO_2C_2H_5$: C, 42.16; H, 3.65; N, 7.93; S, 27.23. Found: C, 42.27; H, 3.72; N, 7.80; S, 26.92.

2-Acetamido-3-(cyanomethylsulfonyl)thiophene (**VIa**)

To a chilled solution of 2-amino-3-(cyanomethylsulfonyl)-thiophene (**III**) (0.98 g, 4.85 mmoles) and pyridine (0.42 g, 5.33 mmoles) in acetonitrile (5 ml) was added dropwise acetyl chloride (0.57 g, 7.28 mmoles) and the mixture was heated at 80° for 15 minutes. The mixture was poured over ice to obtain an oil which solidified with stirring to give a tan solid (0.90 g, 76%), which was homogenous on tlc except for minor polar impurities at the origin. The product was dissolved in a minimum amount of ethyl acetate and flushed through a short silica plug eluting with ethyl acetate:hexanes (1:1) to give, following concentration *in vacuo* and recrystallization from methanol, light tan needles, mp 164-165°; tlc R_f, ethyl acetate:hexanes (1:1), 0.55; ir: ν 3360 (NH), 2250 (CN), 1695 (CO), 1300, 1220, 1165, 1115 cm^{-1}; ^1H nmr (400 MHz, dimethyl-d_6 sulfoxide): δ 2.24 (s, 3H, $COCH_3$), 5.21 (s, 2H, CH_2, 7.14 and 7.22 (2d, 2H, 4-H and 5-H), 10. 25 (s, 1H, NH).

Anal. Calcd. for $C_8H_8N_2O_3S_2$: C, 39.33; H, 3.30; N, 11.47; S, 26.25. Found: C, 39.47; H, 3.38; N, 11.39; S, 26.33.

2-Trifluoroacetamido-3-(cyanomethylsulfonyl)thiophene (**VIb**).

To a chilled solution of 2-amino-3-(cyanomethylsulfonyl)thiophene (**III**) (1.01 g, 5.0 mmoles) and pyridine (0.59 g, 7.5 mmoles) in acetonitrile (5 ml) was added dropwise trifluoroacetic anhydride (1.26 g, 6.0 mmoles) and the solution was stirred overnight at room temperature. The solution was then poured over ice to give an oil which solidified with stirring to give a tan solid (1.20 g, 81%). Recrystallization from methanol:water (10:1) gave fine tan needles, mp 143-144°; tlc R_f, ethyl acetate: hexanes (1:1), 0.70, ir: ν 3300 (NH), 2255 (CN), 1720 (CO), 1325, 1285, 1245, 1190, 1155, 1130, 1110 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 4.15 (s, 2H, CH_2, 7.18 and 7.26 (2d, 2H, 4-H and 5-H), 10.87 (br s, 1H, NH).

Anal. Calcd. for $C_8H_5F_3N_2O_3S_2$: C, 32.21; H, 1.69; N, 9.39; S, 21.50. Found: C, 32.17; H, 1.67; N, 9.34; S, 21.57.

The procedure given for the synthesis of **VIIa** was adapted for the preparation of **VIIb-d**.

2-Cyano-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIIa**).

A mixture of 2-amino-3-(cyanomethysulfonyl)thiophene (**III**) (0.81 g, 4.0 mmoles) and trimethyl orthoformate (1.6 g, 15 mmoles) was heated at 110° for 1 hour. After cooling, triethylamine (0.44 g, 4.4 mmoles) and ethanol (4 ml) were added and the mixture was refluxed for 1 hour. The majority of the solvent was then removed *in vacuo* and the mixture was diluted with sodium hydroxide (1*N*) and extracted with ethyl acetate. The

aqueous layer was then acidified with concentrated hydrochloric acid/ice to give a tan solid (0.64 g, 75%). Recrystallization from methanol:water (6:1) gave tan crystals, mp 302-303° dec, with darkening >250°; ir: ν 3210 (NH), 2205 (CN), 1315, 1245, 1100 cm^{-1}; ^1H nmr (400 MHz, dimethyl-d_6 sulfoxide): δ 7.42 and 7.48 (2d, 2H, 6-H and 7-H), 8.34 (s, 1H, 3-H), 12.90 (br s, 1H, NH).

Anal. Calcd. for $C_7H_4N_2O_2S_2$: C, 39.61; H, 1.90; N, 13.20; S, 30.21. Found: C, 39.64; H, 1.87; N, 13.14; S, 30.12.

2-Cyano-3-methyl-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIIb**).

This compound was prepared using trimethyl orthoacetate and was obtained as a tan solid (0.55 g, 55%). Recrystallization from methanol gave fine tan crystals, mp dec >290°; ir: ν 3215 (NH), 2200 (CN), 1260, 1230, 1120 cm^{-1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 2.41 (s, 3H, 3-CH_3), 7.38 and 7.44 (2d, 2H, 6-H and 7-H), 12.76 (br s, 1H, NH).

Anal. Calcd. for $C_8H_6N_2O_2S_2$: C, 42.46; H, 2.67; N, 12.38; S, 28.34. Found: C, 42.57; H, 2.69; N, 12.31; S, 28.34.

2-Cyano-3-phenyl-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIIc**).

This compound was prepared using trimethyl orthobenzoate (1.5 equivalents). Following acidification, the oily solid was extracted into ethyl acetate and the solution was washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to give a light brown solid (0.47 g, 33%), which was homogenous by tlc except for minor polar impurities at the origin. The solid was dissolved in a minimum amount of ethyl acetate spiked with methanol and flushed over a short silica plug eluting with ethyl acetate. The solution was then concentrated to *ca.* 10 ml and stored in the freezer to give the analytical sample as a tan crystalline solid, mp 304-305° dec, tlc R_f, ethyl acetate, 0.60; ir: ν 3220 (NH), 2205 (CN), 1250 and 1095 (SO_2) cm^{-1}; ^1H nmr (400 MHz, dimethyl-d_6 sulfoxide): δ 7.45 and 7.52 (2d, 2H, 6-H and 7-H), 7.62-7.77 (m, 5H, ArH), 13.01 (br s, 1H, NH).

Anal. Calcd. for $C_{13}H_8N_2O_2S_2$: C, 54.15; H, 2.80; N, 9.72; S, 22.24. Found: C, 54.22; H, 2.81; N, 9.66; S, 22.16.

2-Cyano-3-ethoxycarbonyl-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIId**).

This compound was prepared using ethyl triethoxyacetate (66%, 1.25 equivalents). After diluting with water (instead of sodium hydroxide) and extracting with ethyl acetate, the aqueous layer was acidified to give a brown/yellow solid (1.02 g, 66%), which was recrystallized from ethanol as fine golden needles, mp 248-250°; tlc R_f, ethyl acetate, 0.37; ir: ν 3280 (NH), 2200 (CN), 1715 (CO), 1305, 1280, 1210, 1120 cm^{-1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 1.36 (t, 3H, -CH_2-CH_3), 4.44 (q, 2H, -CH_2-CH_3), 7.43 and 7.55 (2d, 2H, 6-H and 7-H).

Anal. Calcd. for $C_{10}H_8N_2O_4S_2$: C, 42.24; H, 2.84; N, 9.86; S, 22.55. Found: C, 42.33; H, 2.79; N, 9.87; S, 22.50.

2-Cyano-3-dimethylamino-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIII**).

To a solution of 2-amino-3-(cyanomethylsulfonyl)thiophene (**III**) (0.61 g, 3.0 mmoles) in dichloromethane (15 ml) was added phosgene iminium chloride (Aldrich, tech. grade) (0.61 g, 3.75 mmoles) and the suspension was stirred at 40° for 1 hour. The reaction mixture was then diluted with dichloromethane (5 ml) and washed with saturated sodium bicarbonate solution, brine and dried (magnesium sulfate). Triethylamine (0.61 g, 6.0 mmoles) was then added and the solution was stirred overnight (*ca.* 22 hours) at room temperature. Extraction with sodium hydroxide (1*N*) followed by acidification of the aqueous layer with concentrated hydrochloric acid/ice gave a tan solid (0.41 g, 54%). Recrystallization from dimethylformamide:methanol gave tan powder-like needles, mp 294° dec, with darkening >250°; ir: ν 3200 (NH), 2185 (CN), 1280 and 1130 (300 cm^{-1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 3.16 (s, 6H, N-$(CH_3)_2$), 7.17 and 7.33 (2d, 2H, 6-H and 7-H), 11.63 (br s, 1H, NH).

Anal. Calcd. for $C_9H_9N_3O_2S_2$: C, 42.34; H, 3.55; N, 16.46; S, 25.12. Found: C, 42.48; H, 3.58; N, 16.38; S, 25.02.

2-Cyano-3,4-dihydro-3-phenyl-2*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**IXa**).

A mixture of 2-amino-3-(cyanomethylsulfonyl)thiophene (**III**) (1.01 g, 5.0 mmoles), benzaldehyde (0.58 g, 5.5 mmoles), and ammonium acetate (0.42 g, 5.5 mmoles) in ethanol (10 ml) was heated at 90° for 1.25 hours. The solution was then diluted with a few drops of water and stored in the freezer to give a yellow/orange solid (1.00 g, 69%). Recrystallization from methanol:water gave the analytical sample as a pale yellow solid, mp 232-234° dec; tlc R_f, ethyl acetate:hexanes (1:1), 0.64; ir: ν 3350 (NH), 2240 (CN, weak), 1300, 1285, 1120 cm^{-1}; ^1H nmr (400 MHz, dimethyl-d_6 sulfoxide) (*trans* diastereomer): δ 5.16 (d, J = 11.1 Hz, 1H, 2-H), 5.93 (d, J = 11.1 Hz, 1H, 3-H), 6.76 and 7.04 (2d, 2H, 6-H and 7-H), 7.48-7.68 (m, 5H, ArH), 8.65 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{10}N_2O_2S_2$: C, 53.77; H, 3.47; N, 9.65; S, 22.08. Found: C, 53.85; H, 3.46; N, 9.57; S, 22.03.

2-Cyano-3,4-dihydro-3-(4-chlorophenyl)-2*H*-thieno[3,2-*b*][1,4]-thiazine 1,1-Dioxide (**IXb**).

This compound was prepared according to the procedure for **IXa** using 4-chlorobenzaldehyde and diluting with a larger volume of water. The product (0.70 g, 50%) was recrystallized from methanol:water to give a yellow powder, mp 200-202°; tlc R_f, ethyl acetate:hexanes (2:3), 0.61; ir: ν 3360 and 3310 (NH), 2240 (CN, weak), 1295, 1160, 1100 cm^{-1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 5.26 (d, J = 10.4 Hz, 0.36H, 3-H), 5.37 (d, J = 2.5 Hz, 0.64H, 3-H), 5.71 (d, J = 2.4 Hz, 0.64H, 2-H), 5.95 (d, J = 10.7 Hz, 0.36H, 2-H), 6.77 and 6.83 (2d, 1H, thienyl-H), 7.04 and 7.06 (2d, 1H, thienyl-H), 7.56-7.71 (m, 4H, ArH), 8.67 and 8.76 (2s, 1H, NH).

Anal. Calcd. for $C_{13}H_9ClN_2O_2S_2$: C, 48.07; H, 2.79; N, 8.63; S, 19.74. Found: C, 48.15; H, 2.84; N, 8.53; S, 19.68.

3-Cyano-1*H*-thieno[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**X**).

To a solution of 2-amino-3-(cyanomethylsulfonyl)thiophene (**III**) (0.51 g, 2.52 mmoles) in acetic acid (10 ml) was added dropwise sodium nitrite (0.19 g, 2.77 mmoles) in water (1 ml). After stirring 30 minutes, the dark solution was diluted with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was allowed to slowly evaporated under a fume hood to give a dark purple/brown crystalline solid which was collected following trituration with water (0.30 g, 56%). A sample was dissolved in a minimum amount of hot ethanol, filtered, and diluted with water to give fine light brown prisms, mp 253-254° dec, with darkening >225°; ir: ν 3240 (NH), 2220 (CN), 1275, 1250, 1185, 1100 cm^{-1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): 7.62 and 7.71 (2d, 2H, 5-H and 6-H).

Anal. Calcd. for $C_6H_3N_3O_2S_2$: C, 33.80; H, 1.42; N, 19.71; S, 30.07. Found: C, 33.70; H, 1.45; N, 19.56; S, 30.16.

2-Cyano-3-ethoxycarbonyl-4-methyl-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**XI**).

To a suspension of **VIId** (0.43 g, 1.5 mmoles) in dry tetrahydrofuran (5 ml) was added sodium hydride (60%) (0.075 g, 1.875 mmoles). After stirring 5 minutes, dimethyl sulfate (0.28 g, 2.25 mmoles) was added followed by dimethylformamide (1 ml) and the mixture was heated under argon at 65° for 42 hours. Additional sodium hydride (0.02 g) and dimethyl sulfate (0.057 g) were then added and heating was continued for 2 hours. The tetrahydrofuran was then removed *in vacuo* and the mixture was diluted with water to give a yellow/orange solid. The product was dissolved in boiling ethanol (50 ml), filtered, and concentrated to about half the original volume. While hot, water (2 ml) was added and the solution was stored in the freezer to give fine orange needles (0.26 g, 58%), mp 206-208°; tlc R_f, ethyl acetate, 0.68; ir: ν 2210 (CN), 1745 (CO), 1280 and 1130 (SO_2) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 1.47 (t, 3H, -CH_2-CH_3), 3.64 (s, 3H, N-CH_3), 4.54 (q, 2H, -CH_2-CH_3); 7.19 and 7.42 (2d, 2H, 6-H and 7-H).

Anal. Calcd. for $C_{11}H_{10}N_2O_4S_2$: C, 44.28; H, 3.38; N, 9.39; S, 21.49. Found: C, 44.34; H, 3.37; N, 9.30; S, 21.38.

3(5)-Amino-5(3)-ethoxycarbonyl-4-[(2-methylamino-3-thienyl)-sulfonyl]pyrazole (**XII**).

To a suspension of **XI** (0.15 g, 0.5 mmoles) in ethanol (5 ml) was added hydrazine hydrate (0.075 g, 1.5 mmoles) and the mixture was stirred at room temperature overnight. A clear solution was achieved in *ca.* 20 minutes, followed by the gradual formation of a light-colored precipitate. The suspension was then chilled, and the product was collected and rinsed with a small amount of 50% aqueous ethanol to give a tan solid (0. 11 g, 66%). Recrystallization from methanol:water gave fine off-white prisms, mp 205°, with partial melting at 196-197°; tlc R_f, ethyl acetate, 0.65; ir: ν 3460, 3360, 3310, and 3210 (NH and NH_2), 1695 (CO), 1260, 1245, 1170, 1095 cm-^{1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 1.22 (t, 3H, -OCH_2CH_3), 2.84 (d, 3H, NH-CH_3, coalesces to singlet with deuterium oxide), 4.22 (t, 2H, -OCH_2CH_3), 6.21 (br s, 2H, NH_2, deuterium oxide exchangeable), 6.46 (d, 1H, thienyl-H), 6.92-6.97 (overlapping: q, 1H, N*H*CH_3, deuterium oxide-exchangeable; and d, 1H, thienyl-H); hrms: (fab$^+$) Calcd. for $C_{11}H_{14}N_4O_4S_2$: 330.0456. Found: 330.0448.

Anal. Calcd. for $C_{11}H_{14}N_4O_4S_2$: C, 39.99; H, 4.27; N, 16.96; S, 19.41. Found: C, 40.08; H, 4.30; N, 17.02; S, 19.31.

2-Cyano-4-methyl-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**XIII**).

To a solution of **VIIa** (0.42 g, 2.0 mmoles) in dry dimethylformamide (4 ml) was added potassium *t*-butoxide (0.25 g, 2.2 mmoles). After stirring 10 minutes, dimethyl sulfate (0.28 g, 2.2 mmoles) was added and the mixture was stirred overnight at room temperature and then poured over ice to give a tan solid. The product was dissolved in boiling methanol (60 ml), filtered, and concentrated on a hot plate until precipitation occurred. After storing in the freezer, a tan fluffy solid was collected (0.22 g, 49%), mp 255-257°; tlc R_f, ethyl acetate, 0.64; ir: ν 2200 (CN), 1260 and 1120 (300 cm^{-1}; ^1H nmr (300 MHz, dimethyl-d_6 sulfoxide): δ 3.69 (s, 3H, N-CH_3), 7.54 and 7.61 (2d, 2H, 6-H and 7-H), 8.42 (s, 1H, 3-H).

Anal. Calcd. for $C_8H_6N_2O_2S_2$: C, 42.46; H, 2.67; N, 12.38; S, 28.34. Found: C, 42.51; H, 2.66; N, 12.30; S, 28.26.

3-Cyanomethylsulfonyl-2-(methylamino)thiophene (**XIV**).

To a suspension of **XIII** (0.050 g, 0.22 mmole) in ethanol (3 ml) was added hydrazine hydrate (0.03 g, 0.6 mmoles) and the mixture was heated at 80° until solution was achieved (2-5 hours). The solution was diluted with ethyl acetate/water and the organic layer was washed with brine, dried (magnesium sulfate), and concentrated to give a light orange oil. Chromatography over silica (ethyl acetate:hexanes, 1:1) gave a pale pink oil (0.025 g, 52%) which was placed under high vacuum (0.5 mmHg) until it solidified to a soft tan solid (2-3 hours), mp 85-86°; tlc R_f, ethyl acetate:hexanes (1:1), 0.73; ir: ν 3390 (NH), 2250 (CN), 1285, 1140, 1095 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 2.97 (d, 3H, NHCH_3), 4.00 (s, 2H, CHO, 6.35 and 6.92 (2d, 2H, 4-H and 5-H), 6.60 (br s, 1H, NH).

Anal. Calcd. for $C_7H_8N_2O_2S_2$•0.1$CH_3CO_2C_2H_5$: C, 39.48; H, 3.94; N, 12.45; S, 28.49. Found: C, 39.11; H, 3.92; N, 12.40; S, 28.53.

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[8] 1,8-Diazabicylco[5.4.0]undec-7-ene is routinely used with success in our laboratory for the synthesis of 2-amino-3-(arylsulfonyl)-thiophenes (unpublished).

[9] The use of piperidine and 2 equivalents of mercaptoacetaldehyde also gave the bis-thiophene; however, triethylamine was found to give a cleaner and thus more readily purified product.

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