Synthesis and Derivatization of 4-Arylsulfonylthiophene- and furan-2-sulfonamides

George D. Hartman* and Wasyl Halczenko

Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

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Novel 4-arylsulfonylthiophene- and furan-2-sulfonamides are prepared from the 3-arylsulfonyl heterocycle *via* chlorosulfonation with chlorosulfonic acid/phosphorus pentachloride. Free radical bromination affords bromomethyl analogues that are precursors to amine derivatives of the parent thiophenesulfonamides. Instability of the furansulfonyl chlorides to free radical bromination necessitated a sequence employing bromomethyl group generation prior to chlorosulfonation. Demethylation of methoxyl substituted sulfonamides afforded phenols that underwent efficient mono- and bis-alkylation with Mannich reagents.

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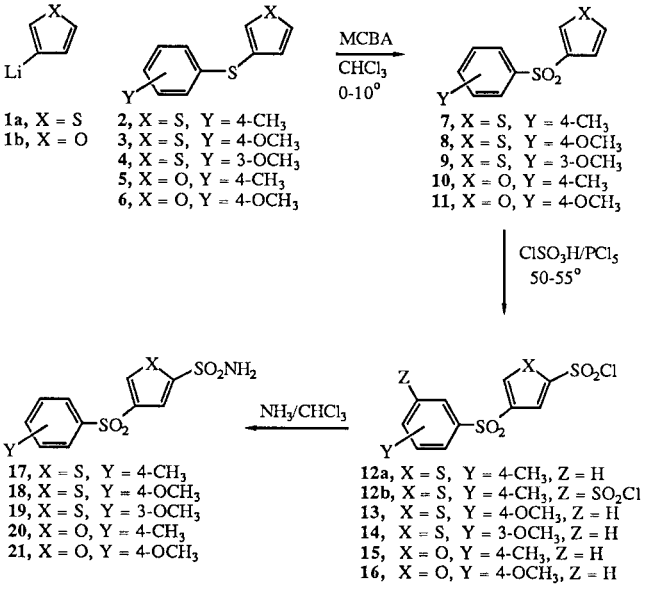
As described in the accompanying paper [1] aryl sulfonamides have been found to possess potent and varied biological activity. As a continuation of our program to prepare novel heterocyclic sulfonamides as ocular anti-hypertensive agents, we wish to report the synthesis of 4-arylsulfonylthiophene- and furan-2-sulfonamides. We also describe the conversion of the parent sulfonamides to various amine derivatives utilizing methodology which will have application to other heterocyclic systems.

Although good percedent exists for the preparation of 5-arylsulfonylthiophene-2-sulfonamides [2], there is little information on the corresponding 2,4-disubstituted compounds. Our general synthetic approach to this class of molecules is to functionalize C-2 *via* an electrophilic aromatic sulfonation of the heterocycle possessing the requisite electron-withdrawing group at C-4 [1]. The literature indicates that numerous electrophilic reactions, such as halogenation and nitration [3,4], proceed in this sense in a highly regioselective fashion. We report in the present work that chlorosulfonation of 4-arylsulfonylthiophenes and furans predictably and efficiently provides 2,4-disubstituted derivatives that are valuable for sulfonamide synthesis.

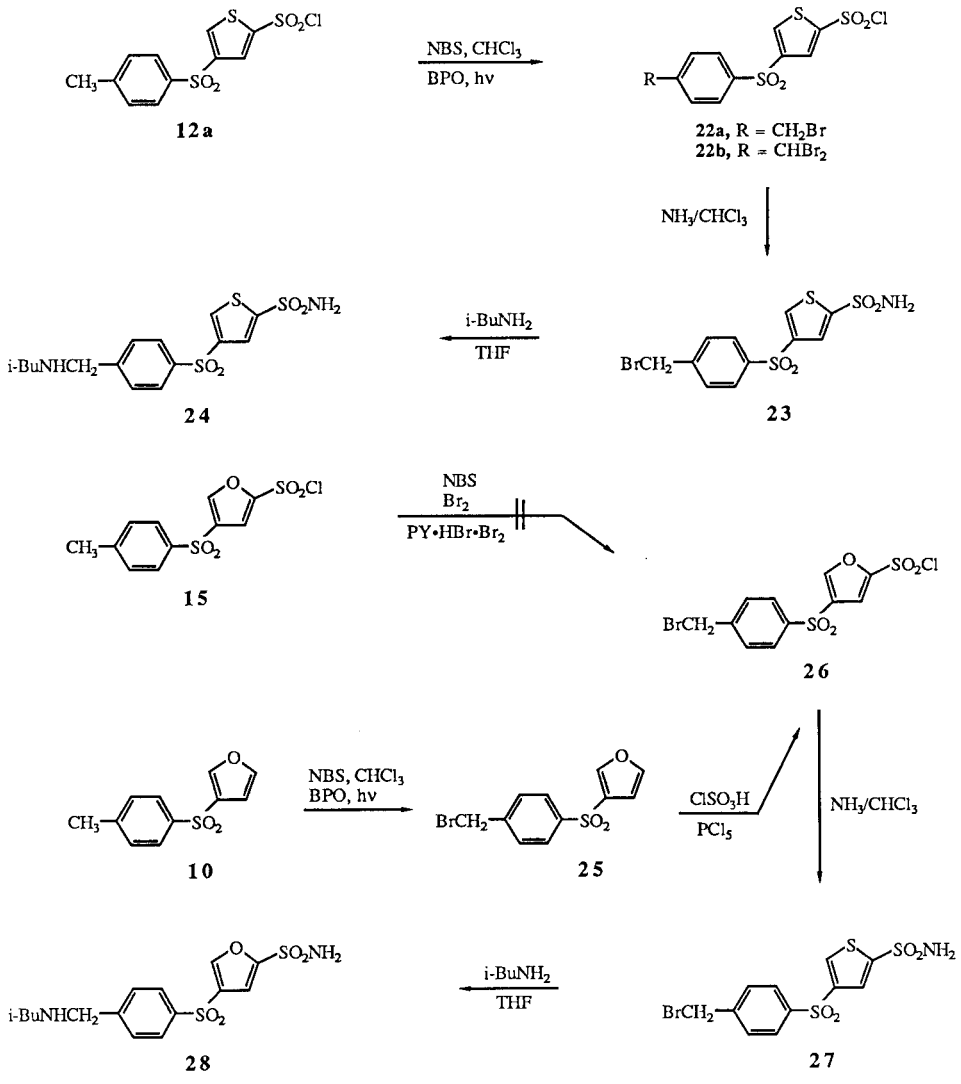
The synthetic sequence (Scheme I) begins with treatment of 3-lithiothiophene (**1a**) [5] or 3-lithiofuran (**1b**) with bis(4-methylphenyl) disulfide, bis(3-methoxyphenyl) disulfide or bis(4-methoxyphenyl) disulfide [6] to provide sulfides **2-6** in good yield. Oxidation of these sulfides to the sulfones **7-11** was readily accomplished by treatment with m-chloroperbenzoic acid at 0-10°. Treatment of **7-11** with a solution of chlorosulfonic acid/phosphorus pentachloride at 50-55° for 15-25 minutes provided the desired sulfonyl halides **12-16** in good yield. The outcome of the chlorosulfonation reaction was found to be critically dependent upon reaction conditions. If the reaction was run at higher temperatures or for longer periods the yield of desired acid halide was diminished due to decomposition or bis-chlorosulfonation. For example, when **7** was treated with chlorosulfonic acid/phosphorus pentachloride solution at 100° for 2 hours the major product was not the desired mono-adduct **12a**, but was the bis-chlorosulfonated compound **12b**. However, under the milder conditions described above, only mono-alkylated products are obtained in significant amounts. Conversion of the sulfonyl halides to the corresponding sulfonamides **17-21** was readily accomplished by treatment with ammonia in chloroform.

Scheme I



Functionalization of the benzylic methyl group of **12a** was carried out as previously described with the 4-aroyl analogues [1]. Treatment of a chloroform solution of **12a** (Scheme II) with *N*-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide under irradiation with a 200 watt sunlamp provided 4-[4-(bromomethyl)-phenylsulfonyl]thiophene-2-sulfonyl chloride (**22a**) in good yield. This reaction was monitored closely by tlc and nmr and was stopped at 80% of reaction, thus minimizing the formation of dibromo compound **22b**. Formation of **22b**

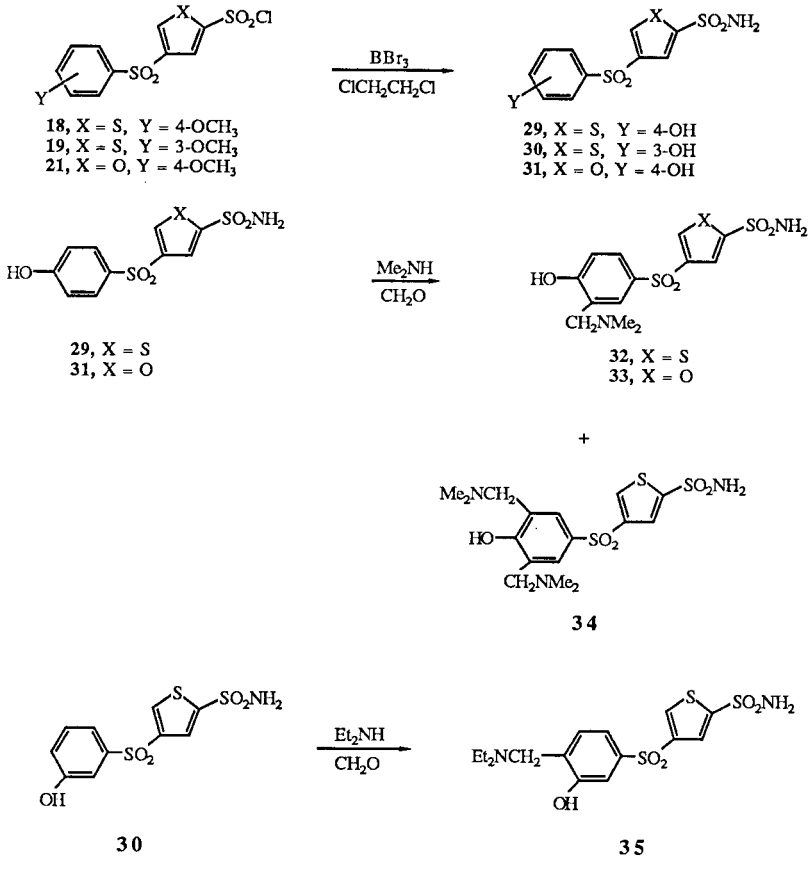
Scheme II



in the reaction mixture occurred in the present case to a much greater extent than with the corresponding 4-aroyl compounds [1], demonstrating the greater stabilization of the bromomethyl radical by the sulfone function, as compared to carbonyl. Since compound **22a** was unstable to silica gel chromatography, the crude bromination mixture, containing starting material, **22a**, and **22b** in a ratio of 1:4:1 was used directly in the next step. Ammonolysis of **22a** with ammonia in chloroform at 0-10° was closely monitored by tlc and was stopped as soon as all starting sulfonyl halide was consumed to provide 4-(4-bromomethylphenylsulfonyl)thiophene-2-sulfonamide **23**. Under these conditions ammonolysis proceeded in a regioselective fashion to provide the desired sulfonamide **23** in good yield. Unlike **22a**, sulfonamide **23** was chromatographed on silica gel to afford a homogenous solid in pure form. Treatment of **23** with *i*-butylamine provided the desired 4-[(4-i-butylaminomethyl)phenylsulfonyl]thiophene-2-sulfonamide (**24**).

Extension of the above sequence to compounds in the furan series proved to be problematic. To our surprise, treatment of 4-(4-methylphenylsulfonyl)furan-2-sulfonyl chloride (**15**) with NBS under the conditions described above resulted in rapid decomposition of starting material with only trace amounts of **26** formed. This conversion remained problematic despite numerous attempts with NBS, bromine, and pyridinium bromide perbromide under a variety of reaction conditions. Alternatively, **26** was prepared by conversion of **10** to **25** with NBS, followed by chlorosulfonation under our standard conditions. The stability of the furan nucleus of **10** to free radical bromination conditions which destroy the nucleus of **15** is intriguing. Apparently, the doubly deactivated furan ring of **26**, which would clearly be more stable than **15** toward simple

Scheme III



electrophilic reagents, is less stable toward the free radical conditions employed. Subsequent reaction of **26** with ammonia in chloroform at 0-10° provided **27** in a reaction that was noticeably faster than had occurred with the thiophene **22a**. As before, treatment of the bromomethyl sulfonamide with *i*-butylamine gave 4-[4-(i-butylaminomethyl)phenylsulfonyl]furan-2-sulfonamide (**28**).

In light of the contrasting reactivity found with aroylthiophenes and -furans [1] under Mannich [7] conditions, we chose to study the analogous reactivity of the present arylsulfonyl sulfonamides. Toward this goal we prepared the requisite phenols (Scheme III) of **18**, **19**, and **21** *via* boron tribromide demethylation. In this way phenolic sulfonamides **29**, **30**, and **31** were formed in 82%, 80% and 84% yields, respectively. Treatment of thiophenesulfonamide **29** with dimethylamine and formaldehyde resulted in smooth conversion to **32**, the adduct expected from electrophilic substitution *ortho* to the phenolic hydroxyl. A small amount (~10%) of the adduct **34** was present, suggesting that at longer reaction times, bisalkylation could become a major process.

In contrast to 4-aroylfurans which undergo ring cleavage [1] under standard Mannich conditions, sulfonamide **31** gave efficient alkylation in the desired sense to yield **33** in 66% yield, along with a small amount of the bis-adduct. Thus, 4-sulfonyl functionality appears to stabilize the furan nucleus, relative to the 4-acyl moiety, toward nucleophilic attack by amines on the sulfonamide carbon.

Finally, treatment of 3-methoxy substituted sulfonamide **30** with diethylamine and formaldehyde under standard Mannich conditions provided a single isomer **35** as the major product. The selective formation of **35** in preference to alkylation at the available *para* position, *i.e. ortho* to the sulfonyl group, demonstrates the *ortho* selectivity of the process [7].

In conclusion, the present methodology demonstrates efficient routes for the construction and elaboration of 4-arylsulfonylthiophene- and furan-2-sulfonamides. We anticipate that this approach will have broad utility for the synthesis of analogous heterocyclic systems.

EXPERIMENTAL

Melting points were determined in air employing a Thomas Hoover apparatus using a capillary tube and are uncorrected. Proton nmr spectra were obtained using a Varian T-60A or a

Nicolet NT-360 spectrometer. The elemental analyses were carried out by Dr. W. C. Randall and his staff. The mass spectra determinations were carried out by Dr. H. Ramjit and his staff using an LKB-9000S spectrometer at 70 eV. 3-Bromothiophene, 3-bromofuran, 4-methylbenzenethiol, 4-methoxybenzenethiol, and 3-methoxybenzenethiol were obtained from commercial sources and were used without purification.

3-(4-Methylphenylthio)thiophene (**2**).

To 67.6 g (0.415 mole) 3-bromothiophene in 225 mℓ ether cooled to -78° under nitrogen was added 0.415 moles of *n*-butyllithium (in hexane) dropwise at <-70°. After addition was complete the reaction mixture was stirred for 45 minutes at -78° to give a white suspension. Then 51.0 g (0.207 mole) of bis(4-methylphenyl) disulfide in 75 mℓ of ether was added dropwise at <-70°. The reaction mixture was then allowed to warm gradually to room temperature with stirring overnight.

The cooled reaction mixture was quenched with 250 mℓ of ice water and the organic phase was separated, washed with water, brine and dried. The solvent was removed *in vacuo* to provide 42.0 g (98%) of crude **2** as a yellow oil, R_f 0.5, silica gel eluted with 5% 2-propanol/hexane; ^{1}H nmr (deuteriochloroform): δ 2.33 (3H, s), 7.0-7.4 (7H, aromatic); ms: m/e 206.

Anal. Calcd. for $C_{11}H_{10}S_2$: C, 64.03; H, 4.89. Found: C, 64.11; H, 5.12.

3-(4-Methylphenylsulfonyl)thiophene (**7**).

To a solution of 20.6 g (0.1 mole) of **2** in 150 mℓ of chloroform cooled to 0-10° was added dropwise a solution of 43.0 g (0.25 mole) of *m*-chloroperbenzoic acid portionwise over 15 minutes with mechanical stirring. The resulting suspension was stirred at 0-10° for 1.5 hours at which time all starting sulfide was consumed. This suspension was then extracted with 2 x 75 mℓ portions of 1*N* sodium hydroxide solution, brine, and then dried. The solvent was removed *in vacuo* to give a dark oil that was triturated with 3:1 hexane/ethyl acetate to afford 18.6 g (78%) of **7** as a white solid, mp 128-132°; ^{1}H nmr (deuteriochloroform): δ 2.45 (3H, s), 7.30-7.43 (4H, m, aromatic), 7.90 (2H, d, J = 9 Hz), 8.12 (1H, d, J = 2 Hz); ms: m/e 238.

Anal. Calcd. for $C_{11}H_{10}S_2O_2$: C, 55.44; H, 4.23. Found: C, 55.28; H, 4.39.

4-(4-Methylphenylsulfonyl)thiophene-2-sulfonyl Chloride (**12a**).

To 1.22 g (10.5 mmoles) of chlorosulfonic acid under nitrogen was added 0.88 g (4.2 mmoles) of phosphorus pentachloride portionwise (caution, foaming) and the resulting solution was stirred at room temperature for 10 minutes. Then, 1.0 g (4.2 mmoles) of **7** was added in one portion and the resulting dark suspension was heated at 55° for 25 minutes during which time foaming occurred and subsided.

The reaction mixture was then poured onto ice and the resulting suspension was extracted with chloroform. The organic phase was filtered through a Celite pad, washed with brine and dried. The solvent was removed *in vacuo* to provide 1.3 g (93%) of nearly pure **12a** as a tan solid. This had R_f 0.7 on silca gel eluting with 10% 2-propanol/hexane, nearly identical to **7**, however the iodine stain of **12a** was much darker; **12a** had mp 118-120°; ^{1}H nmr (deuteriochloroform): δ 2.50 (3H, s), 7.42 (2H, d, J = 9 Hz), 7.90 (2H, d, J = 9 Hz), 8.00 (1H, d, J = 2 Hz), 8.41 (1H, d, J = 2 Hz); ms: m/e 336.

4-(4-Methylphenylsulfonyl)thiophene-2-sulfonamide (**17**).

A stream of ammonia gas was bubbled into a chloroform solution of 1.0 g (2.98 mmoles) of **12a**, cooled to 0-10°. The resulting suspension was then stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to give 0.75 g (80%) of pure **17** as a white solid, mp 164-166°; ^{1}H nmr (DMSO-d_6): δ 2.42 (3H, s), 7.40 (2H, d, J = 9 Hz), 7.71 (1H, d, J = 2 Hz), 7.84 (2H, d, J = 9 Hz), 8.53 (1H, d, J = 2 Hz); ms: m/e 317.

Anal. Calcd. for $C_{11}H_{11}NO_4S_3$: C, 41.62; H, 3.49; N, 4.41. Found: C, 41.77; H, 3.75; N, 4.40.

3-(4-Methoxyphenylthio)thiophene (**3**).

To a solution of 5.80 g (0.036 mmoles) of 3-bromothiophene in 75 mℓ of ether under nitrogen and cooled to -78° was added 0.036 mole of *n*-butyllithium (in hexane) dropwise at <-70°. The resulting white suspension was stirred at -78° for 45 minutes and then a solution of 4.96 g (0.018 mole) of bis(4-methoxyphenyl) disulfide in 25 mℓ of ether was added dropwise at <-70°. The reaction mixture was then allowed to gradually warm to room temperature with stirring overnight.

The cooled reaction mixture was quenched with 75 mℓ of water and the organic phase was separated, washed with brine and dried. The solvent was removed *in vacuo* to give 7.9 g (100%) crude **3** as an oil; ^{1}H nmr (deuteriochloroform): δ 3.81 (3H, s), 6.86 (2H, d, J = 7 Hz), 6.47 (1H, d, J = 6 Hz); ms: m/e 222.

3-(4-Methoxyphenylsulfonyl)thiophene (**8**).

To a solution of 7.9 g (0.036 mole) of **3** dissolved in 40 mℓ of chloroform and cooled to 0-10° was added 13.5 g (0.079 mole) of *m*-chloroperbenzoic acid portionwise over 10 minutes. This suspension was stirred at 0-10° for 2.0 hours and was then extracted with 2 x 50 mℓ of 1*N* sodium hydroxide solution, brine, and dried. The solvent was removed *in vacuo* to give a tan solid. This was purified by flash chromatography on silica gel eluting with 1% methanol/chloroform to give 7.3 g (80%) pure **8** as a white solid, mp 137-139°; ^{1}H nmr (deuteriochloroform): δ 3.90 (3H, s), 7.04 (2H, d, J = 8 Hz), 7.35 (1H, d, J = 6 Hz), 7.41 (1H, d, J = 6 Hz), 7.95 (2H, d, J = 8 Hz), 8.11 (1H, d, J = 2 Hz), ms: m/e 254.

4-(4-Methoxyphenylsulfonyl)thiophene-2-sulfonyl Chloride (**13**).

To a solution of 0.57 g (4.92 mmoles) of chlorosulfonic acid and 0.40 g (1.97 mmoles) of phosphorus pentachloride that had been stirred for 10 minutes under nitrogen was added 0.5 g (1.97 mmoles) of **8** in one portion. This suspension was stirred and heated at 55° for 15 minutes during which time significant foaming occurred and subsided. The reaction mixture was poured onto ice and extracted with chloroform. The organic phase was washed with brine, dried, and the solvent was removed *in vacuo* to give a yellow oil. This was purified by flash chromatography on silica gel eluting with 35% ethyl acetate/hexane to provide 0.94 g (54%) of pure **13** as a white solid, mp 92-95°; ^{1}H nmr (deuteriochloroform): δ 3.90 (3H, s), 7.05 (2H, d, J = 8 Hz), 7.92 (2H, d, J = 8 Hz), 8.02 (1H, d, J = 2 Hz), 8.42 (1H, d, J = 2 Hz), ms: m/e 352.

Anal. Calcd. for $C_{11}H_9ClS_3O_4$: C, 39.22; H, 2.69. Found: C, 39.55; H, 2.50.

4-(4-Methoxyphenylsulfonyl)thiophene-2-sulfonamide (**18**).

A stream of ammonia was bubbled into a solution of 6.0 g (0.019 moles) of **13** in 250 mℓ of chloroform at 0-10° for 10

minutes. The reaction mixture was then stirred at room temperature for 2 hours to consume all starting material. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to give 4.19 g (65%) of pure **18** as a white solid, mp 169-171°; ^{1}H nmr (DMSO-d_6): δ 3.92 (3H, s), 7.25 (2H, d, J = 9 Hz), 7.81 (1H, d, J = 2 Hz), 8.00 (2H, bs, SO_2NH_2), 8.04 (2H, d, J = 9 Hz), 8.70 (1H, d, J = 2 Hz), ms: m/e 333.

Anal. Calcd. for $C_{11}H_{11}NO_5S_3$: C, 39.63; H, 3.33; N, 4.23. Found: C, 39.94, H, 3.32, N, 4.07.

3-(3-Methoxyphenylthio)thiophene (**4**).

To a solution of 10.3 g (0.0615 mole) of 3-bromothiophene in 100 mℓ of ether under nitrogen cooled to -78° was added 0.0615 *n*-butyllithium (in hexane) dropwise at <-70°. The resulting pale yellow suspension was stirred at -78° for 45 minutes. Then a solution of 17.1 g (0.0615 mole) of bis(3-methoxyphenyl) disulfide in 30 mℓ of ether was added dropwise at <-70° and the reaction mixture was allowed to warm to room temperature with stirring overnight.

The cooled reaction mixture was quenched with 75 mℓ of water and the organic phase was separated and washed with brine and dried. The solvent was removed *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel eluting with 4% ethyl acetate/hexane to provide 8.4 g (62%) of **4** as an oil; ^{1}H nmr (deuteriochloroform): δ 3.75 (3H, s), 6.72 (3H, m), 7.05 (1H, d, J = 8 Hz), 7.16 (1H, t), 7.40 (2H, m); ms: m/e 222.

Anal. Calcd. for $C_{11}H_{10}S_2O$: C, 59.43; H, 4.53. Found: C, 59.18; H, 4.42.

3-(3-Methoxyphenylsulfonyl)thiophene (**9**).

To 1.0 g (4.5 mmoles) of **4** dissolved in 35 mℓ of chloroform cooled to 0-10° was added 1.81 g (10.0 mmoles) of *m*-chloroperbenzoic acid portionwise over 5 minutes. The reaction mixture was stirred at 0-10° for 2.0 hours at which time all starting material was consumed. The organic phase was washed with 2 x 35 mℓ of 1*N* sodium hydroxide solution, water, brine, and then dried. The solvent was removed *in vacuo* to afford 0.92 g (81%) of **9** as a white solid, mp 105-106°; ^{1}H nmr (deuteriochloroform): δ 3.88 (3H, s), 7.12 (1H, dd, J = 7, 1 Hz), 7.42 (5H, m), 8.12 (1H, d, J = 1 Hz), ms: m/e 254.

Anal. Calcd. for $C_{11}H_{10}S_2O_3$: C, 51.95; H, 3.96. Found: C, 52.22; H, 3.99.

4-(3-Methoxyphenylsulfonyl)thiophene-2-sulfonyl Chloride (**14**).

To a solution of 0.57 g (4.93 mmoles) of chlorosulfonic acid and 0.41 g (1.97 mmoles) of phosphorus pentachloride which had been stirred at room temperature for 10 minutes was added **9** in one portion. This mixture was stirred and heated at 55° for 20 minutes and the reaction mixture was then poured onto ice. This was extracted with chloroform and the organic phase was separated, washed with brine and dried. The solvent was removed *in vacuo* to give **14** as white solid, mp 240-245° dec; ^{1}H nmr (DMSO-d_6): δ 4.07 (3H, s), 7.40 (1H, s), 7.75 (2H, m), 8.0 (2H, m), 8.42 (1H, s), ms: m/e 352.

Anal. Calcd. for $C_{11}H_9ClS_3O_4$: C, 39.22; H, 2.69. Found: C, 39.01; H, 2.29.

4-(3-Methoxyphenylsulfonyl)thiophene-2-sulfonamide (**19**).

A stream of ammonia was bubbled into a solution of 3.0 g (8.5 mmoles) of **14** in 25 mℓ of chloroform at 0-10° for 10 minutes and the resulting solution was stirred at room temperature for 2.0 hours. The solvent was then removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to provide 2.34 g (83%) of **19** as a white solid, mp 112-113°; ^{1}H nmr (acetone-d_6): δ 3.84 (3H, s), 7.10 (2H, bs, SO_2NH_2), 7.25 (1H, m), 7.54 (3H, m), 7.81 (1H, d, J = 2 Hz), 7.57 (1H, d, J = 2 Hz), ms: m/e 333.

Anal. Calcd. for $C_{11}H_{11}NO_5S_3$: C, 39.63, H, 3.33, N, 4.20. Found: C, 39.72, H, 3.30, N, 4.00.

3-(4-Methylphenylthio)furan (**5**).

To a solution of 50.0 g (0.34 mole) of 3-bromofuran in 300 mℓ of ether cooled to -78° under nitrogen was added 0.34 mole of *n*-butyllithium (in hexane) dropwise at <-70°. The resulting brownish solution was stirred at -78° for 45 minutes and then a solution of 83.6 g (0.34 mole) of bis(4-methylphenyl) disulfide in 125 mℓ of ether was added dropwise at <-70°. The resulting mixture was allowed to gradually warm to room temperature with stirring overnight.

The cooled reaction mixture was quenched with 150 mℓ of water and the organic phase was washed with brine and dried. The solvent was removed and the resulting oil was taken up in hexane and passed through a silica gel pad to give a clear solution. The solvent was removed *in vacuo* to give 46.0 g (71%) of crude **5** as an oil; ^{1}H nmr (deuteriochloroform): δ 2.31 (3H, s), 6.42 (1H, d, J = 2 Hz), 7.05-7.20 (4H, m), 7.50 (1H, d, J = 2 Hz), 7.60 (1H, d, J = 2 Hz), ms: m/e 190.

3-(4-Methylphenylsulfonyl)furan (**10**).

To a solution of 4.6 g (0.024 mole) of **5** in 75 mℓ of chloroform at 0-10° was added 8.89 g (0.052 mole) of *m*-chloroperbenzoic acid portionwise over 10 minutes. The resulting suspension was stirred at 0-10° for 10 minutes and was then extracted with 2 x 50 mℓ of 1*N* sodium hydroxide solution. The organic phase was washed with brine, dried and the solvent removed *in vacuo* to give a dark oil. This was triturated with 20% ether/hexane to give 3.55 g (66%) of **10** as a white solid, mp 78-81°; ^{1}H nmr (deuteriochloroform): δ 2.44 (3H, s), 6.61 (1H, d, J = 2 Hz), 7.35 (2H, d, J = 8 Hz), 7.46 (1H, d, J = 2 Hz), 7.87 (2H, d, J = 8 Hz), 8.00 (1H, d, J = 2 Hz), ms: m/e 222.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54. Found: C, 59.67; H, 4.26.

4-(4-Methylphenylsulfonyl)furan-2-sulfonyl Chloride (**15**).

To a solution of 1.30 g (11.3 mmoles) of chlorosulfonic acid and 0.94 g (4.5 mmoles) of phosphorus pentachloride that had been stirred for 10 minutes was added 1.0 g (4.5 mmoles) of **10** in one portion. The resulting suspension was stirred and heated at 50° for 15 minutes during which time the mixture grew dark and foaming occurred. This was poured onto ice and extracted with chloroform. The organic phase was separated, washed with brine and dried. The solvent was removed *in vacuo* to give 0.79 g (55%) of **15** as a tan solid, mp 132-135°; ^{1}H nmr (deuteriochloroform): δ 2.48 (3H, s), 7.39 (1H, d, J = 1 Hz), 7.41 (2H, d, J = 8 Hz), 7.88 (2H, d, J = 8 Hz), 8.21 (1H, d, J = 1 Hz), ms: m/e 320.

4-(4-Methylphenylsulfonyl)furan-2-sulfonamide (**20**).

A steam of ammonia was bubbled into a solution of 1.50 g (4.69 mmoles) of **15** in 50 mℓ of chloroform cooled to 0-10° and the resulting suspension was stirred for 2 hours at room temperature. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to give 0.65 g (46%) of pure **20** as a white

solid, mp 184-186°; ^{1}H nmr (deuteriochloroform): δ 2.48 (3H, s), 5.09 (2H, bs, SO_2NH_2), 7.15 (1H, d, J = 1 Hz), 7.40 (2H, d, J = 8 Hz), 7.87 (2H, d, J = 8 Hz), 8.12 (1H, d, J = 1 Hz), ms: m/e 301.

Anal. Calcd. for $C_{11}H_{11}NO_5S_2$: C, 43.84, H, 3.68, N, 4.65. Found: C, 44.22, H, 3.84, N, 4.66.

3-(4-Methoxyphenylthio)furan (**6**).

To a solution of 5.20 g (0.036 mmoles) of 3-bromofuran in 60 mℓ of ether under nitrogen and cooled to -78° was added 0.036 mole of *n*-butyllithium (in hexane) dropwise at <-70°. This mixture was stirred at -78° for 45 minutes and then a solution of 9.92 g (0.036 mole) of bis(4-methoxyphenyl) disulfide in 40 mℓ of ether was added dropwise at <-70°. This mixture was stirred for 16 hours as the temperature rose to 20°.

The cooled reaction mixture was quenched with 50 mℓ of water and the organic phase was separated, washed with brine and dried. The solvent was removed *in vacuo* to provide 7.4 g (100%) of crude **6** as an oil; ^{1}H nmr (deuteriochloroform): δ 3.84 (3H, s), 6.38 (1H, d, J = 1 Hz), 6.85 (2H, d, J = 9 Hz), 7.28 (2H, d, J = 9 Hz), 7.45 (1H, d, J = 1 Hz), 7.53 (1H, d, J = 1 Hz), ms: m/e 206.

3-(4-Methoxyphenylsulfonyl)furan (**11**).

To a solution of 8.0 g (0.039 mole) of **6** in 75 mℓ of chloroform and cooled to 0-10° was added 17.1 g (0.1 mole) of *m*-chloroperbenzoic acid portionwise over 10 minutes. The resulting suspension was stirred at 0-10° for 2.0 hours and was extracted with 2 x 50 mℓ portions of 1*N* sodium hydroxide solution. The organic phase was washed with brine and dried. Ethyl acetate was added to make a 5% ethyl acetate solution and this was passed through a silica gel pad to afford a clear solution. The solvent was removed *in vacuo* and the residue was triturated with 5% 2-propanol/hexane to provide 4.11 g (44%) of **11** as a white solid; ^{1}H nmr (deuteriochloroform): δ 3.91 (3H, s), 6.60 (1H, d, J = 1 Hz), 7.03 (2H, d, J = 8 Hz), 7.45 (1H, d, J = 1 Hz), 7.90 (2H, d, J = 8 Hz), 8.00 (1H, d, J = 1 Hz), ms: m/e 238.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 55.45; H, 4.23. Found: C, 55.67; H, 4.20.

4-(4-Methoxyphenylsulfonyl)furan-2-sulfonyl Chloride (**16**).

To a solution of 1.2 g (0.01 mmole) of chlorosulfonic acid and 0.87 g (0.004 moles) of phosphorus pentachloride that had been stirred for 10 minutes under nitrogen was added 1.0 g (0.0042 mole) of **11** in one portion. The resulting mixture was stirred and heated at 50° for 15 minutes as the mixture darkened and foaming occurred. The reaction mixture was then poured onto ice and this was extracted with chloroform. The organic phase was separated, washed with brine and dried. The solvent was removed *in vacuo* to give a residue that was purified by flash chromatography on silica gel eluting with 35% ethyl acetate/hexane to give 0.45 g (32%) of pure **16** as a white solid, mp 146-148°; ^{1}H nmr (deuteriochloroform): δ 3.90 (3H, s), 7.07 (2H, d, J = 8 Hz), 7.35 (1H, d, J = 1 Hz), 7.85 (d, J = 8 Hz), 8.10 (1H, d, J = 1 Hz), ms: m/e 336.

Anal. Calcd. for $C_{11}H_9ClO_6S_2$: C, 39.23; H, 2.69. Found: C, 39.51; H, 2.61.

4-(4-Methoxyphenylsulfonyl)furan-2-sulfonamide (**21**).

A stream of ammonia gas was bubbled into a solution of 4.0 g (0.012 mole) of **16** in 150 mℓ of chloroform cooled to 0-10°. This mixture was then stirred at room temperature for 3.0 hours. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to provide 2.8 g (74%) of pure **21** as a white solid, mp 117-118°; ^{1}H nmr (DMSO-d_6): δ 3.90 (3H, s), 7.21 (2H, d, J = 8 Hz), 7.37 (1H, s), 8.02 (4H, m), 8.78 (1H, s), ms: m/e 317.

Anal. Calcd. for $C_{11}H_{11}NO_6S_2$: C, 41.63, H, 3.49, N, 4.41. Found: C, 41.26, H, 3.21, N, 4.41.

4-[4-(Bromomethyl)phenylsulfonyl]thiophene-2-sulfonyl Chloride (**22a**).

A solution of 18.0 g (0.054 mole) of **7**, 46.0 (0.258 mole) of *N*-bromosuccinimide and 20 mg of benzoyl peroxide in 300 ml of chloroform was heated at reflux and irradiated with a 200 watt sunlamp. The reaction mixture was closely monitored by nmr and the reaction was stopped (1 hour) when significant amounts of the dibromo product (C*H*Br_2, δ 6.65) began to appear. The cooled reaction mixture was washed with 2 x 300 ml of water, 150 ml of 5% sodium thiosulfate, brine, and was then dried. The solvent was removed to afford crude **22a** as an oil, which by nmr was 80% **22a**, 10% **7** and 10% **22b**; **22a** had ^{1}H nmr (deuteriochloroform): δ 4.51 (2H, s), 7.61 (2H, d, J = 8 Hz), 7.95 (2H, d, J = 8 Hz), 8.01 (1H, d, J = 2 Hz), 8.46 (1H, d, J = 2 Hz), ms: m/e 415.

4-[4-(Bromomethyl)phenylsulfonyl]thiophene-2-sulfonamide (**23**).

A stream of ammonia was bubbled into a cooled solution of 2.2 g (0.0053 mole) of **22a** in 35 mℓ of chloroform for 15 minutes and the resulting mixture was then stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 4% methanol/chloroform to give 1.2 g (57%) of **23** as an oil: ^{1}H nmr (deuteriochloroform): δ 4.50 (2H, s), 5.45 (2H, bs, SO_2NH_2), 7.57 (2H, d, J = 9 Hz), 7.85 (1H, d, J = 1 Hz), 7.95 (2H, d, J = 9 Hz), 8.28 (1H, d, J = 1 Hz), ms: m/e 396.

4-[4-(i-Butylaminomethyl)phenylsulfonyl]thiophene-2-sulfonamide (**24**).

A solution of 18.5 g (0.047 mole) of **23** and 22.08 g (0.30 mole) of *i*-butylamine in 100 mℓ of tetrahydrofuran was stirred at room temperature for 48 hours. The solvent and excess amine were removed at reduced pressure and the residue was taken up in 500 mℓ of ethyl acetate. This solution was washed with 3 x 50 mℓ portions of water, brine, and dried. The solvent was removed *in vacuo* to give an amber oil that was purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to give crude **24** as a gum. This was triturated with 20% hexane/ether to afford 5.4 g (30%) of **24** as a tan solid. This solid was dissolved in a mixture of 50 mℓ of ethanol/25 mℓ of methanol and then treated with ethanolic hydrogen chloride. Gradual dilution of the resulting solution with ether gave the hydrochloride salt of **24** as a white solid, mp 207-209°; ^{1}H nmr (DMSO-d_6): δ 1.06 (6H, d, J = 7 Hz), 2.11 (1H, m), 2.90 (2H, bs), 7.94 (3H, m), 8.08 (2H, s), 8.25 (2H, d), 8.86 (1H, s), ms: m/e 388.

Anal. Calcd. for $C_{15}H_{20}N_2O_4S_3$ HCl:C, 42.39; H, 4.98; N, 6.59. Found: C, 42.20; H, 4.92; N, 6.70.

3-(4-Bromomethylphenylsulfonyl)furan (**25**).

To a solution of 2.2 g (10 mmoles) **10**, 2.2 g (12.5 mmoles) of *N*-bromosuccinimide and 10 mg of benzoyl peroxide in 60 mℓ of carbon tetrachloride was heated at reflux and irradiated with a 200 watt sunlamp. This reaction was closely monitored by nmr and was stopped before the amount of dibromo compound became significant. At this point, generally 10-20% of starting

material remained. The cooled reaction mixture was extracted with 2 x 50 mℓ of water, 50 mℓ of 5% sodium thiosulfate solution, brine and then dried. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 20% ethyl acetate/hexane to give 1.36 g (45%) of **25** as a white solid, mp 78-80°; ^{1}H nmr (deuteriochloroform): δ 4.50 (2H, s), 6.62 (1H, d, J = 2 Hz), 7.48 (1H, d, J = 2 Hz), 7.58 (2H, d, J = 9 Hz), 7.95 (2H, d, J = 9 Hz), 8.07 (1H, d, J = 1 Hz), ms: m/e 301.

4-[4-(Bromomethyl)phenylsulfonyl]furan-2-sulfonylchloride (**26**).

To a solution of 0.96 g (8.3 mmoles) of chlorosulfonic acid and 0.86 g (4.13 mmoles) of phosphorus pentachloride that had been stirred for 10 minutes under nitrogen was added 0.5 g (1.66 mmoles) of **25** in one portion. The resulting mixture was stirred and heated at 55° for 15 minutes during which time the reaction mixture darkened and gas was evolved. The reaction mixture was poured onto ice and extracted with chloroform. The organic phase was separated, washed with brine and dried. This solution was passed through a silica gel pad and the solvent was then removed *in vacuo* to provide 0.41 (62%) of **26** as a tan solid; ^{1}H nmr (deuteriochloroform): δ 4.52 (2H, s), 7.38 (1H, d, J = 1 Hz), 7.60 (2H, d, J = 8 Hz), 7.91 (2H, d, J = 8 Hz), 8.18 (1H, d, J = 1 Hz), ms: m/e 399.

4-[4-(Bromomethyl)phenylsulfonyl]furan-2-sulfonamide (**27**).

A stream of ammonia was bubbled into a solution of 10.2 g (0.026 mole) of **26** cooled to 0-10° for 10 minutes. This mixture was then stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to provide 6.49 g (66%) of **27** as a viscous oil; ^{1}H nmr (DMSO-d_6): δ 4.55 (2H, s), 7.19 (1H, s), 7.50 (2H, d, J = 8 Hz), 7.80 (2H, bs, SO_2NH_2), 7.82 (2H, d, J = 8 Hz), 8.62 (1H, s); ms: m/e 380.

4-[4-(i-Butylaminomethyl)phenylsulfonyl]furan-2-sulfonamide (**28**).

A solution of 11.04 g (0.15 mole) of *i*-butylamine in 10 mℓ of tetrahydrofuran was added dropwise to a solution of 3.0 g (0.0079 mole) of **27** in 15 mℓ of tetrahydrofuran cooled to 0-10°. The resulting clear solution was then stirred at room temperature for 48 hours. The solvent and excess amine were removed *in vacuo* and the residue was taken up in 300 mℓ of ethyl acetate and washed with 2 x 50 mℓ portions of water, brine and dried. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 7% methanol/chloroform to give 1.4 g (48%) **28** as an oil. This was dissolved in ethanol and treated with ethanolic hydrogen chloride. The resulting solution was cooled and slowly diluted with ether to provide the hydrochloride salt of **28**, mp 190-205° dec; ^{1}H nmr (DMSO-d_6): δ 0.88 (6H, d, J = 7 Hz), 2.28 (2H, d, J = 6 Hz), 3.88 (2H, bs), 7.37 (1H, d, J = 2 Hz), 7.62 (2H, d, J = 8 Hz), 7.97 (2H, d, J = 8 Hz), 8.31 (2H, s, SO_2NH_2, 8.79 (1H, d, J = 2 Hz), ms: m/e 372.

Anal. Calcd. for $C_{15}H_{20}N_2O_5S_2$·HCl: C, 44.05; H, 5.18; N, 6.85. Found: C, 44.20; H, 5.07; N, 6.80.

4-(4-Hydroxyphenylsulfonyl)thiophene-2-sulfonamide (**29**).

To a suspension of 3.9 g (0.0117 mole) of **18** in 100 mℓ of 1,2-dichloroethane at room temperature was added 0.06 mole of boron tribromide (1*M* in dichloromethane) dropwise over 15 minutes. The reaction mixture became homogeneous for a short period and then a precipitate appeared. This was heated under nitrogen at reflux for 16 hours.

The cooled reaction mixture was carefully quenched by the dropwise addition of 50 mℓ of water and the resulting two phase mixture contained a tan solid. This was collected by filtration, washed with methylene chloride, and purified by flash chromatography on silica gel eluting with 8% methanol/chloroform to provide 3.05 g (82%) of pure **29** as a white solid, mp 192-194°; ^{1}H nmr (DMSO-d_6): δ 7.07 (2H, d, J = 9 Hz), 7.80 (1H, d, J = 2 Hz), 7.92 (2H, d, J = 9 Hz), 7.98 (2H, bs, SO_2NH_2), 8.67 (1H, d, J = 2 Hz); ms: m/e 319.

Anal. Calcd. for $C_{10}H_9NO_5S_3$: C, 37.60, H, 2.84, N, 4.39. Found: C, 37.29; H, 2.80; N, 4.23.

4-(3-Hydroxyphenylsulfonyl)thiophene-2-sulfonamide (**30**).

To a solution of 9.0 g (0.027 mole) **19** in 250 mℓ of methylene chloride at room temperature under nitrogen was added 0.135 mole of boron tribromide (1*M* in dichloromethane) dropwise over 15 minutes and the resulting mixture was heated at reflux for 16 hours.

The cooled reaction mixture was carefully quenched by the dropwise addition of 75 mℓ of water. The solid that appeared in this two-phase mixture was collected by filtration and purified by flash chromatography on silica gel eluting with 10% methanol/chloroform. This gave an oil that was triturated with cold methylene chloride to provide 6.95 g (80%) of pure **30** as a white solid, mp 144-146°; ^{1}H nmr (acetone-d_6): δ 7.18 (2H, m), 8.50 (4H, m), 7.79 (1H, d, J = 2 Hz), 8.58 (1H, d, J = 2 Hz); ms: m/e 319.

Anal. Calcd. for $C_{10}H_9NO_5S_3$: C, 37.61; H, 2.84; N, 4.39. Found: C, 37.54; H, 3.18; N, 4.36.

4-(4-Hydroxyphenylsulfonyl)furan-2-sulfonamide (**31**).

A solution of 2.0 g (0.0063 mole) of **21** and 0.03 mole of boron tribromide (1*M* in dichloromethane) in 1,2-dichloroethane was refluxed for 16 hours. The cooled reaction mixture was then carefully quenched by the dropwise addition of 75 mℓ of water and the solid that appeared in this two-phase mixture was collected and washed with methylene chloride. This solid was purified by flash chromatography on silica gel eluting with 10% methanol/chloroform to give 1.6 g (84%) of pure **31**, mp 174-176°; ^{1}H nmr (DMSO-d_6): δ 7.00 (2H, d, J = 9 Hz), 7.33 (1H, d, J = 2 Hz), 7.87 (2H, d, J = 9 Hz), 8.73 (1H, d, J = 2 Hz), ms: m/e 303.

Anal. Calcd. for $C_{10}H_9NO_6S_2$: C, 39.60; H, 2.99; N, 4.62. Found: C, 39.77; H, 2.93; N, 4.53.

4-[3-(Dimethylaminomethyl)-4-hydroxy]phenylsulfonylthiophene-2-sulfonamide (**32**).

A solution of 0.96 (3 mmoles) of **29**, 1.35 g (12.0 mmoles) of dimethylamine (40% aqueous solution), and 0.49 g (60 mmoles) of formaldehyde (37% aqueous solution) in 15 mℓ of ethanol was heated at reflux for 16 hours. The solvent was then removed *in vacuo* and the residue was acidified with 6*N* hydrochloric acid. This aqueous phase was washed with 2 x 50 mℓ portions of ethyl acetate and then basified with ammonium hydroxide (*p*H = 9). This was extracted with ethyl acetate and the organic phase was washed with brine, dried and the solvent stripped. The residue was purified by flash chromatography on silica gel eluting with 12% methanol/chloroform to give 0.67 g (59%) **32** as an oil. The hydrochloride salt of **32** was prepared by dissolving **32** in 10 mℓ of ethanol and treatment with ethanolic hydrogen chloride. This

was stripped to dryness and triturated with 10% ethanol/ether to provide pure hydrochloride salt of **32**, mp 75-80°; ^{1}H nmr of **32**; (2H, s), 6.95 (2H, d, J = 9 Hz), 7.62 (1H, d, J = 1 Hz), 7.79 (1H, dd, J = 6, 1 Hz), 7.83 (1H, d, J = 2 Hz), 8.25 (1H, d, J = 1 Hz), ms: m/e 376.

Anal. Calcd. for $C_{13}H_{16}N_2O_5S_3$·HCl: C, 37.81; H, 4.15; N, 6.79. Found: C, 37.68; H, 4.13; N, 6.50.

4-[3-(Dimethylaminomethyl)-4-hydroxy]phenylsulfonylfuran-2-sulfonamide (**33**).

A solution of 0.455 g (1.5 mmoles) of **31**, 0.68 g (60 mmoles) of dimethylamine (40% aqueous solution), and 0.24 g (3 mmoles) of formaldehyde (37% aqueous solution) in 10 mℓ of methanol was refluxed for 48 hours. The solvent was then removed *in vacuo* and the residue acidified with 6*N* hydrochloric acid. The aqueous phase was extracted with 2 x 35 mℓ of ethyl acetate and then basified (*p*H = 8) with ammonium hydroxide. This was extracted with ethyl acetate and the organic phase was washed with brine, dried and the solvent removed *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with 15% methanol/chloroform to give 0.39 g (66%) of **33** as a viscuous oil. This was treated with ethanolic hydrogen chloride and the resulting solution was diluted with ether to provide the hydrochloride salt of **33**; ^{1}H nmr of **33** free base (acetone-d_6): δ 1.33 (6H, t), 4.10 (2H, s), 7.09 (2H, d, J = 9 Hz), 7.40 (1H, d, J = 1 Hz), 7.95 (1H, d, J = 1 Hz), 8.05 (1H, dd, J = 6, 1 Hz), 8.14 (1H, d, J = 1 Hz); ms: m/e 360.

Anal. Calcd. for $C_{13}H_{16}N_2O_6S_2$ HCl: C, 39.34; H, 4.32; N, 7.06. Found: C, 39.70; H, 4.65; N, 6.83.

4-[4-(Diethylaminomethyl)-3-hydroxy]phenylsulfonylthiophene-2-sulfonamide (**35**).

A solution of 1.92 g (6.0 mmoles) of **30**, 1.76 g (24 mmoles) of diethylamine, and 0.97 g (12 mmoles) of formaldehyde (37% aqueous solution) in 20 mℓ of ethanol was heated at reflux for 48 hours. The solvent was then removed *in vacuo* and the residue was taken up in 200 mℓ of ethyl acetate and this washed with 3 x 25 mℓ of water, brine and dried. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to give 0.92 g (38%) of **35** as an oil. This oil was dissolved in ethanol and treated with ethanolic hydrogen chloride. Gradual dilution with ether provided the hydrochloride salt of **35** as a white solid, mp 190-198° dec, free base **35** had ^{1}H nmr (deuteriochloroform): δ 1.13 (6H, t), 2.56 (4H, q), 3.87 (2H, s), 7.65 (1H, d, J = 8 Hz), 7.41 (3H, bs), 7.48 (1H, d, J = 8 Hz), 7.87 (1H, d, J = 2 Hz), 8.25 (1H, d, J = 2 Hz); ms m/e 404.

Anal. Calcd. for $C_{15}H_{20}N_2O_5S_3$·HCl: C, 40.85; H, 4.80; N, 6.35. Found: C, 40.63; H, 4.80; N, 6.35.

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