Synthesis and Derivatization of Novel 4-Aroylthiophene- and furan-2-sulfonamides

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Received April 17, 1989

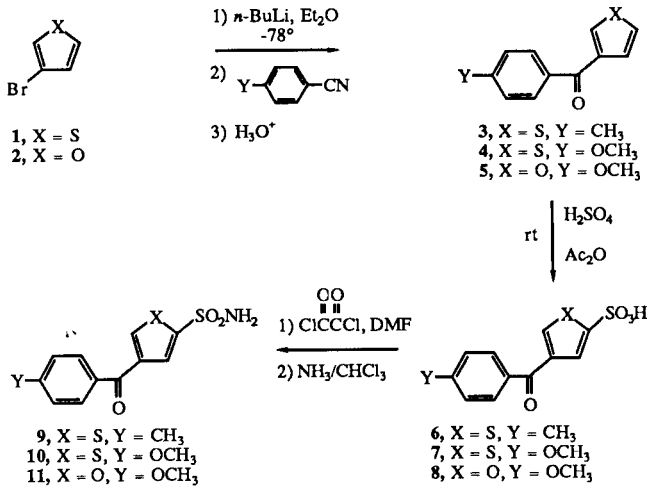
Sulfonation of 3-aroylthiophenes and furans with sulfuric acid in acetic anhydride regioselectively affords the corresponding 2,4-disubstituted heterocycle. Benzylamine derivatives of the parent sulfonamides are obtained either by Mannich reaction of aryl phenols, or *via* a sequence employing free radical bromination followed by selective ammonolysis. This methodology provides ready access to a wide variety of regioselectively-substituted heterocycles.

J. Heterocyclic Chem., **26**, 1793 (1989).

It is well recognized that the discovery of anti-bacterial phenylsulfonamides has revolutionized medical therapy for numerous pathologies [1]. Similarly, heterocyclic sulfonamides have proven of medicinal value, displaying unique and highly potent biological profiles [2-5]. Thus, there continues to be strong interest in new synthetic methods for the preparation of this latter class of compounds. As part of our program to prepare carbonic anhydrase inhibitors for use as topically effective ocular anti-hypertensive agents [6], we wish to report the synthesis of novel 4-aroylthiophene- and furan-2-sulfonamides, as well as the elaboration of the parent molecules to derivatives containing varied functionality.

Although ample literature precedent exits for the synthesis of 2,5-substituted heterocyclic sulfonamides [2-5], virtually no information is available on the corresponding 2,4-systems. These latter systems are attractive synthetic targets since they should possess the appropriate topology for good interaction at the catalytic site [7] of carbonic anhydrase, and should exhibit minimal potential for sensitization. We have found that 4-aroylthiophene-2-sulfonamides, and the corresponding furan compounds, are readily available by the method shown in Scheme I. In the case of the thiophenes, the initial step involves lithiation of 3-bromothiophene followed by treatment with the appropriate nitrile under standard conditions [8]. Acidic hydrolysis of the intermediate imines affords the ketones **3** and **4**, which are obtained in 83% and 52% yield, respectively. 3-Bromofuran (**2**) afforded **5** in similar fashion. Although exceptions have been noted in the literature [9], one expects that electrophilic aromatic substitution on a π-excessive heterocycle, such as thiophene or furan, possessing an electron withdrawing group at C-3 would afford predominately 2,4-disubstituted products [10,11]. Our initial attempts to functionalize in this manner involved treatment of **3** and **4** under chlorosulfonation conditions, *i.e.* chlorosulfonic acid/phosphorus pentachloride, as was previously used for 2-substituted heterocycles [5]. We found that **3**, **4** and **5**, as well as several other 3-aroyl heterocycles undergo rapid decomposition to intractable materials under these conditions. However, when **3-5** are treated under milder conditions, *e.g.* concentrated sulfuric acid/acetic anhydride [12], sulfonation of the thiophene or furan ring proceeds in high chemical yield with excellent regioselectivity for C-2 of the heterocycle. The resultant 4-aroyl-2-sulfonic acids **6-8** are isolated as either the acid or potassium salt depending upon work-up conditions.

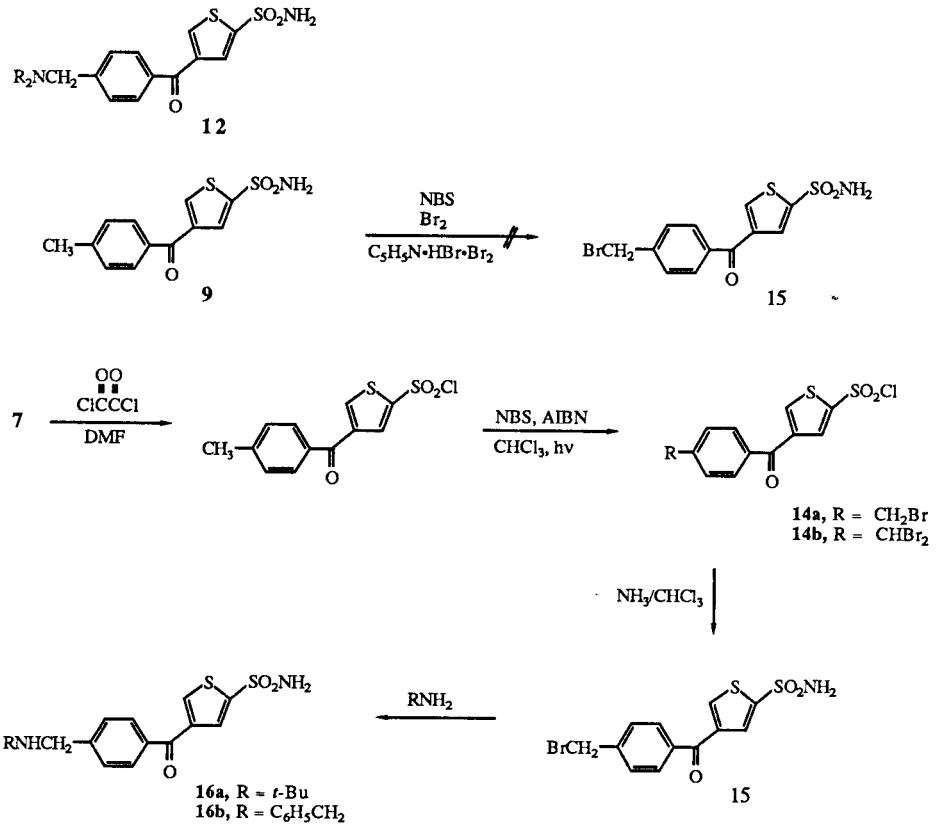
Scheme I



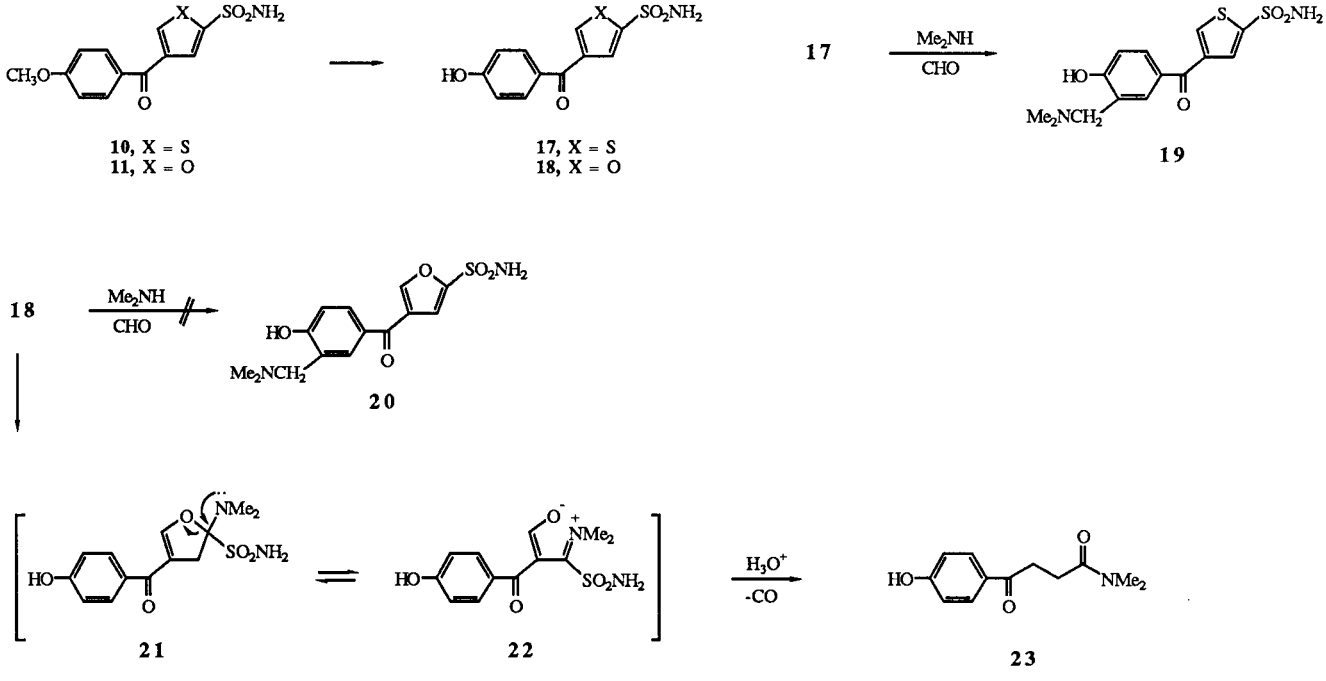
The parent sulfonic acids or potassium salts are converted to the corresponding acid chlorides with either thionyl chloride or, more conveniently, with oxalyl chloride in methylene chloride using dimethylformamide as catalyst. In each case the crude sulfonyl chloride intermediate was treated with ammonia in chloroform solution to provide the desired sulfonamides **9-11** in good yield.

In an effort to prepare water soluble analogs of these sulfonamides, attention was turned to the preparation of alkylamino derivatives, as given by **12** (Scheme II). Attemped bromination of sulfonamide **9** with either *N*-bromosuccinimide, pyridinium perbromide or bromine under a variety of reaction conditions gave only complex mixtures. However, treatment of sulfonyl chloride **13**, prepared from **7** by treatment with oxalyl chloride/DMF, with

Scheme II



Scheme III



N-bromosuccinimide in chloroform solution containing AIBN and irradiation with a 200 watt sunlamp gave smooth conversion to the desired bromomethyl compound **14a**. This reaction was closely monitored by nmr and tlc so that conversion was stopped at 80-90% of reaction to minimize the formation of the undesired dibromo product **14b**.

Although a small amount of **14a** could successfully be purified by flash chromatography on silica gel, similar attempts on a larger scale failed due to decomposition. Thus, in preparative runs, crude **14a** in chloroform solution at 0-10° was treated with ammonia. This reaction was closely monitored by tlc, and was stopped as soon as all **14a** was consumed. Under these conditions clean regioselective ammonolysis of the sulfonyl chloride group occurred to provide the desired sulfonamide **15** with no evidence of reaction at the benzylic bromide site. Reactions run for longer durations or at higher temperatures displayed products of bis-ammonolysis. Interestingly, treatment of **14a** with ammonium hydroxide, rather than ammonia in chloroform, gave a more complex reaction mixture that contained **15** in diminished yield. Treatment of **15** with isobutylamine or benzylamine afforded the expected products **16a** and **16b**, respectively, in good yield.

As described above, one of the goals of our synthetic work was to prepare compounds of varying polarities and water solubilities. Thus, methyl ethers **10** and **11** were treated with either 48% aqueous hydrobromic acid or boron tribromide to give the expected phenols **17** and **18**, respectively, in good yield (Scheme III). This conversion, which is problematic in the case of furans not functionalized with electron withdrawing groups such as sulfonamido that diminish the acid sensitivity of the nucleus, proceeded smoothly with **11**. Treatment of **17** with dimethylamine and formaldehyde under Mannich conditions [13] gave the expected amine **19** in 35% isolated yield. The modest yield is probably due to competing reactions involving formation of bis-alkylated phenol as well as to decomposition of **17**.

Treatment of furan sulfonamide **18** under Mannich conditions resulted in products derived from a completely different reaction pathway. In this case the major product was 3-(4-hydroxybenzoyl)propanamide (**23**), with only trace amounts of the expected amine **20** formed. Amide **23** probably arises from initial attack by dimethylamine on C-2 of the furan to afford intermediate **21**, which ultimately provides ring-opened species **22**. Hydrolysis of **22** with decarbonylation then provides the observed product **23**. The contrasting results of the Mannich reaction on **17** and **18** reflect the more electropositive nature of C-2 of the furan sulfonamide than of the thiophene, thus favoring nucleophilic attack at that position. The lower resonance energy [14] of the furan nucleus compared to thiophene would also favor attack in the sense described. The availability of γ-keto amides such as **23** *via* cleavage of 2,4-disubstituted furans, although not productive in the present context, is worthy of synthetic note. Also, unmasking of a protecting furan ring under basic conditions offers an intriguing conceptual alternative to the normal acidic hydrolytic methods [15].

In summary, the present work describes efficient methodology for the preparation of 4-aroylthiophene- and furan-2-sulfonamides *via* electrophilic aromatic sulfonation of 3-aroyl heterocycles. Subsequent functionalization using free radical bromination/amination and a demethylation/Mannich sequence provides novel, polar derivatives of the parent molecules.

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 an EM-390 or a Nicolet NT-360 spectrometer with tetramethyl silane as internal standard. Mass spectra were obtained on a LKB-9000S mass spectrometer at 70 eV. Elemental analyses were carried out by Dr. W. C. Randall and his staff and nmr spectra were determined by Dr. S. M. Pitzenberger and his staff. 3-Bromothiophene, 3-bromofuran, 4-methylbenzonitrile, 4-methoxybenzonitrile, and oxalyl chloride were purchased from Aldrich and *n*-butyllithium (in hexane) was purchased from Alfa. All were used without purification.

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

To a solution of 5.0 g (0.031 mole) of 3-bromothiophene in 20 ml of ether containing 5 ml of tetrahydrofuran cooled to −78° under nitrogen was added 0.031 mole of *n*-butyllithium (in hexane) dropwise at < −70°. This clear, pale yellow solution was stirred for 10 minutes and then 3.63 g (0.31 mole) 4-methylbenzonitrile in 5 ml of tetrahydrofuran was added dropwise at < −70°. The reaction mixture was stirred at −70° for 0.5 hours, −50° for 1.0 hour, and then allowed to rise to −10° over 1.5 hours as the color changed to deep sherry red.

The reaction mixture was quenched with 5 ml of water, 30 ml of 2*N* hydrochloric acid and the mixture extracted with 2 x 50 ml of ether. The acidic aqueous phase was then heated at reflux for 2 hours, cooled and extracted with 3 x 50 ml of ether. The combined organic phases were washed with brine, dried and the solvent removed *in vacuo* to give a dark oil. This was purified by flash chromatography on silica gel eluting with 5% 2-propanol/-hexane to give 0.5 g (83%) of pure **3** as a clear oil; ^{1}H nmr (deuteriochloroform): δ 2.50 (3H, s), 7.32 (1H, d, J = 10 Hz), 7.40 (1H, dd, J = 9, 1 Hz), 7.62 (1H, d, d, J = 9, 1 Hz), 7.80 (1H, d, J = 10 Hz), 7.95 (1H, d, J = 1 Hz).

Anal. Calcd. for $C_{12}H_{10}OS$: C, 71.26; H, 4.98. Found: C, 71.48; H, 5.15.

4-(4-Methylbenzoyl)thiophene-2-sulfonic Acid (**6**).

To 3.0 g (0.015 mole) of **3** in 25 ml of methylene chloride cooled to 0-10° was added 4.8 g (0.047 mole) of acetic anhydride followed by 1.9 g (0.016 mole) of sulfuric acid added dropwise. The resulting clear, dark solution was stirred at room temperature for 3 days and was then diluted with 50 ml of hexane. The resulting suspension was stirred in an ice bath for 0.5 hours and

was then filtered to provide **6** as a pale, brown solid, 2.4 g (57%); ^{1}H nmr (DMSO-d_6): δ 2.42 (3H, s), 7.40 (1H, d, J = 2 Hz), 7.43 (2H, d, J = 7 Hz), 7.74 (2H, d, J = 7 Hz), 8.13 (1H, d, J = 2 Hz).

4-(4-Methylbenzoyl)thiophene-2-sulfonamide (**9**).

To 2.2 g (0.0078 mole) of **6** suspended in 50 ml of ethyl acetate was added 1.97 g (0.0156 mole) of oxalyl chloride and then at 0-10° was added 1.46 g (0.020 mole) of *N,N*-dimethylformamide. The reaction mixture was then stirred at room temperature for 16 hours.

With cooling in an ice bath, the reaction mixture was quenched with 20 ml of water and the organic phase was then extracted with 3 x 20 ml of water. The organic phase was washed with brine, dried and the solvent was removed *in vacuo* to give the sulfonyl halide as a tan solid, R_f = 0.4 (5% isopropanol/hexane); ^{1}H nmr (deuteriochloroform): 300 MHz, δ 2.50 (3H, s), 7.35 (2H, d, J = 8 Hz), 7.75 (2H, d, J = 8 Hz), 8.29 (1H, d, J = 1 Hz), 8.35 (1H, d, J = 1 Hz). This solid was dissolved in 25 ml of chloroform and after cooling to 0-10° a stream of ammonia was passed into the solution. The addition was stopped after 10 minutes and after another 2 hours stirring at room temperature, all starting material was consumed. The solvent was removed *in vacuo* and the resulting solid (R_f 0.4) purified by flash chromatography on silica gel eluting with 5% methanol/chloroform to give 1.4 g (64%) of pure **9**, mp 175-177°; ^{1}H nmr (DMSO-d_6): δ 2.45 (3H, s), 7.38 (2H, d, J = 8 Hz), 7.77 (2H, d, J = 8 Hz), 7.86 (1H, d, J = 2 Hz), 8.45 (1H, d, J = 2 Hz).

Anal. Calcd. for $C_{12}H_{11}NO_3S_2$: C, 51.23; H, 3.94; N, 4.98. Found: C, 51.45; H, 4.01; N, 4.93.

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

To 0.026 mole *n*-butyllithium in 50 ml of ether at −78° under nitrogen was added a solution of 4.0 g (0.025 mole) of 3-bromothiophene in 100 ml of ether dropwise at < −70°. This was stirred at −78° for 45 minutes and then a solution of 3.46 g (0.026 mole) of 4-methoxybenzonitrile in 50 ml of ether was added dropwise at < −70°. The reaction mixture was stirred at −70° for 0.5 hour, −50° for 0.5 hour, and then allowed to warm to −10° over 2.0 hours. The mixture was quenched with 15 ml of water and 40 ml of ammonium chloride (2*N*). The acidic aqueous phase was separated, washed 3 x 30 ml of ether and then heated at reflux for 2.0 hours. The cooled solution was extracted with 3 x 60 ml of ether and the combined organic extracts were washed with brine. The solvent was removed *in vacuo* to give an oil that was triturated at 0-10° with petroleum ether to give **4** as a tan solid, 2.5 g (52%), mp 61-65°; ^{1}H nmr (deuteriochloroform): δ 3.82 (3H, s), 7.00 (2H, d, J = 8 Hz), 7.40 (1H, dd, J = 1 Hz), 7.60 (1H, dd, J = 7, 1 Hz), 7.85 (2H, d, J = 8 Hz), 7.87 (1H, d, J = 1 Hz).

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.33; H, 4.88.

4-(4-Methoxybenzoyl)thiophene-2-sulfonic Acid (**7**).

To a solution of 9.79 g (0.05 mole) **4** in 75 ml of methylene chloride cooled to 0-10° was added 15.3 g (0.15 mole) of acetic anhydride followed by 5.9 g (0.06 mole) of sulfuric acid added dropwise. The resulting dark solution was stirred at room temperature for 16 hours at which time a solid was present. This pale yellow solid was collected by filtration and was dried to give 9.16 g (61%) of crude **7**, mp 169-179°; ^{1}H nmr (DMSO-d_6): δ 3.90 (3H, s), 7.15 (2H, d, J = 8 Hz), 7.41 (1H, d, J = 2 Hz), 7.85 (2H, d, J = 8 Hz), 8.13 (1H, d, J = 2 Hz).

4-(4-Methoxybenzoyl)thiophene-2-sulfonamide (**10**).

A suspension of 2.98 g (0.01 mole) of **7** in 50 ml of thionyl chloride was refluxed for 1.5 hours to give a homogeneous solution. Excess thionyl chloride was removed *in vacuo* and the residue was decomposed with 20 ml of ice water and extracted with 2 x 40 ml of chloroform. The combined organic extracts were washed with brine, dried, and the solvent was removed *in vacuo* to give crude sulfonyl chloride as a yellow oil. This was taken up in 25 ml of acetone and treated at 0-10° with 10 ml of ammonium hydroxide. The solvent was removed *in vacuo* and the residue was extracted with chloroform. The organic extract was washed with brine, dried, and the solvent was removed *in vacuo* to give a yellow solid. This was triturated with ether to give 1.6 g (54%) of pure **10** as a white solid, mp 173-175°; ^{1}H nmr (DMSO-d_6): δ 3.90 (3H, s), 7.18 (2H, d, J = 9 Hz), 7.92 (6H, m), 8.49 (1H, s).

Anal. Calcd. for $C_{12}H_{11}NO_4S_2$: C, 48.47; H, 3.73; N, 4.71. Found: C, 48.60; H, 3.79; N, 4.77.

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

A solution of 3.0 g (0.01 moles) **10** in 75 ml of 48% aqueous hydrobromic acid was heated at reflux for 8 hours, at which time all starting material was consumed. The cooled reaction mixture was then poured into ice and stirred for 10 minutes. The violet colored solid that formed was collected by filtration and purified by flash chromatography on silica gel eluting with hexane (55)-ethyl acetate (45). This gave a solid that was triturated with methylene chloride to give 7.0 g (74%) of pure **17**, mp 189-191°; ^{1}H nmr (DMSO-d_6): δ 6.85 (2H, d, J = 8 Hz), 7.66 (2H, d, J = 8 Hz), 7.79 (1H, d, J = 2 Hz), 8.41 (1H, d, J = 2 Hz).

Anal. Calcd. for $C_{11}H_9NO_4S_2$: C, 46.63; H, 3.20. Found: C, 46.40; H, 3.54.

4-[(3-Dimethylaminomethyl-4-hydroxy)benzoyl]thiophene-2-sulfonamide (**19**).

A solution of 1.70 g (6 mmoles) of **17** and 2.71 g (24 mmoles) of dimethylamine and 0.73 g (9 mmoles) of formaldehyde (37% aqueous solution) in 15 ml of ethanol was heated at reflux for 16 hours. The cooled reaction mixture was filtered to remove a small amount of the crude bis-Mannich product. The filtrate solvent was removed *in vacuo* and the residue was flash chromatographed in silica gel eluting with chloroform (9)-methanol (1) to give 0.7 g (35%) of pure **19** as a pale yellow solid, mp 197-201°. This was suspended in 15 ml of ethanol and this treated with ethanolic hydrogen chloride to give a clear solution. This solution was gradually diluted with 15 ml of ether to provide after stirring at 0-10° for several hours, a hydrochloride of **19** as a white powder, mp 230-232°; ^{1}H nmr (DMSO-d_6): δ 2.33 (6H, s), 3.62 (2H, s), 6.95 (1H, d, J = 8 Hz), 7.74 (2H, bs), 7.90 (2H, bs), 8.42 (1H, s).

Anal. Calcd. for $C_{14}H_{17}ClN_2O_4S_2$: C, 44.61; H, 4.55; N, 7.43. Found: C, 44.90; H, 4.87; N, 7.39.

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

To 10.0 g (0.068 mole) of 3-bromofuran in 50 ml of ether cooled to −78° under nitrogen was added 0.068 mole of *n*-butyllithium dropwise at < −70°. The resulting solution was stirred at −78° for 45 minutes and then a solution of 9.98 g (0.075 mole) of 4-methoxylbenzonitrile in 15 ml of ether was added dropwise at < −70°. This was stirred at −78° for 1 hour and then was allowed to rise to −10° over 2 hours. During this period the original pale yellow suspension turned to an orange, homogeneous solution.

The reaction mixture was quenched with 30 ml of water and 100 ml of 2*N* hydrochloric acid. The aqueous phase was separated, washed with 2 x 50 ml of ether and was then heated at reflux for 2 hours. This cooled solution was extracted with 3 x 75 ml of ether and the combined organic extracts were washed with brine, and dried. The solvent was removed *in vacuo* to give an oil that was triturated at 0-10° with ligroin to give **6** as a white solid, 10.6 g (77%), mp 71-74°; ^{1}H nmr (deuteriochloroform): δ 3.78 (3H, s), 6.80 (1H, d, J = 1 Hz), 7.03 (2H, d, J = 7 Hz), 7.55 (1H, d, J = 1 Hz), 7.83 (2H, d, J = 8 Hz), 7.85 (1H, s).

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.60; H, 5.22.

4-(4-Methoxybenzoyl)furan-2-sulfonic Acid (**8**).

To a solution of 1.01 g (0.005 mole) of **5** in 75 ml of methylene chloride cooled to −10° was added 1.53 g (0.015 mole) of acetic anhydride followed by 0.59 g (0.006 mole) of sulfuric acid added dropwise. The resulting dark solution was then stirred at room temperature for 18 hours. The reaction mixture was filtered to give 1.07 g (76%) of crude **8** as a tan solid; ^{1}H nmr (acetone-d_6): δ 3.95 (3H, s), 7.20 (2H, d, J = 9 Hz), 7.28 (1H, d, J = 1 Hz), 8.04 (2H, d, J = 9 Hz), 8.32 (1H, d, J = 1 Hz).

4-(4-Methoxybenzoyl)furan-2-sulfonamide (**11**).

To a solution of 1.86 g (6.6 mmoles) of **8** in 25 ml of tetrahydrofuran cooled to 0-10° was added 3.17 g (25 mmoles) of oxalyl chloride followed by 2 ml of dimethylformamide dropwise. Spontaneous gas evolution occurred and the resulting mixture was stirred at room temperature for 16 hours. The solvent was then removed *in vacuo* and the residue was taken up in 300 ml of ether and this washed with 3 x 50 ml portions of water. The organic phase was washed with brine, dried, and the solvent was removed *in vacuo* to give the crude sulfonyl chloride as a yellow oil. This was purified by flash chromatography on silica gel eluting with hexane (4)-ethyl acetate (1) to give 0.93 g (49%) of pure sulfonyl chloride as a pale yellow solid; ^{1}H nmr (deuteriochloroform): δ 3.98 (3H, s), 7.08 (2H, d, J = 9 Hz), 7.69 (1H, d, J = 2 Hz).

This solid was taken up in chloroform and treated with a stream of gaseous ammonia for 10 minutes and the reaction mixture was then stirred at room temperature for 16 hours at which time all starting material was consumed. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with chloroform (9)-methanol (1) to provide 0.60 g (67%) of pure **11** as a white solid, mp 180-182.5°; ^{1}H nmr (DMSO-d_6): δ 3.98 (3H, s), 7.25 (2H, d, J = 9 Hz), 7.38 (1H, d, J = 1 Hz), 8.00 (2H, d, J = 9 Hz), 8.09 (2H, bs), 8.25 (1H, d, J = 1 Hz).

Anal. Calcd. for $C_{12}H_{11}NO_5S$: C, 51.24; H, 3.94; N, 4.98. Found: C, 51.20; H, 3.95; N, 4.94.

4-(4-Hydroxybenzoyl)furan-2-sulfonamide (**18**).

To a solution of 10.0 g (0.036 mole) of **11** in 150 ml of 1,2-dichloroethane at room temperature under nitrogen was added 0.178 mole of boron tribromide dropwise over 10 minutes. The reaction mixture grew dark with some precipitate and this was stirred at 85° for 16 hours.

The cooled reaction mixture was carefully quenched with 175 ml of water and the resulting suspension was filtered. The solid that was collected was air dried and then purified by flash chromatography on silica gel eluting with methanol (1)-chloroform (9) to give 4.4 g (46%) of **18** as a tan solid, mp 177-179° dec; ^{1}H nmr (acetone-d_6): δ 7.23 (2H, d, J = 7 Hz), 7.51 (1H, s), 8.13 (2H, d, J = 7 Hz), 8.60 (1H, s).

Anal. Calcd. for $C_{11}H_9NO_5S$: C, 49.44; H, 3.39, N, 5.24. Found: C, 49.40; H, 3.42; N, 5.22.

N,N-Dimethyl 3-(4-hydroxybenzoyl)propanamide (**23**).

A solution of 1.33 g (5 mmoles) of **18**, 2.25 g (20 mmoles) of dimethylamine, and 0.487 g (6 mmoles) of formaldehyde (40% aqueous solution) in 10 ml of ethanol was heated at reflux for 16 hours. The solvent was then removed *in vacuo* at room temperature and the residue dissolved in ethyl acetate and 6*N* hydrochloric acid solution. The aqueous phase was separated and extracted with 2 x 50 ml portions of ethyl acetate. The combined organic extracts were washed with brine, dried, and the solvent was removed *in vacuo* to provide 0.45 g (41%) of **23**; ^{1}H nmr (DMSO-d_6): δ 2.70 (2H, t, J = 7 Hz), 2.86 (3H, s), 3.09 (3H, s), 3.25 (2H, t, J = 7 Hz), 6.93 (2H, d, J = 5 Hz), 7.94 (2H, d, J = 5 Hz); ms: m/e 221.

4-(4-Bromomethylbenzoyl)thiophene-2-sulfonylchloride (**14a**).

A solution of 5.0 g (0.017 mole) of **13**, 5.9 g (0.033 mole) of *N*-bromosuccinimide, 10 mg of benzoyl peroxide in 100 ml of chloroform was heated at reflux and irradiated with a sunlamp (200 watt) for 0.5 hour. At this time almost all starting material was consumed. The cooled reaction mixture was extracted with 3 x 75 ml of water to remove the succinimide, 75 ml of 5% sodium thiosulfate, brine and was then dried. The solvent was removed *in vacuo* to give crude **14a** as an oil. A portion of this was purified by flash chromatography on silica gel eluting with 5% 2-propanol/hexane to give pure **14a** as a white solid, mp 140-145°; ^{1}H nmr (deuteriochloroform): δ 4.57 (2H, s), 7.60 (2H, d, J = 7 Hz), 7.85 (2H, d, J = 8 Hz), 8.30 (1H, d, J = 2 Hz), 8.38 (1H, d, J = 2 Hz). However, when large amounts of crude **14a** were chromatographed, recovered yields of pure product were very low due to the longer time on the column. In the preparative scale runs, crude **14a** was used directly in the next step. The dibromo compound **14b**, identified by the characteristic C*H*Br$_2$ absorption in the nmr at 6.70 ppm, was formed in 10% yield.

4-(4-Bromomethylbenzoyl)thiophene-2-sulfonamide (**15**).

To a solution of 5.0 g (0.013 mole) of crude **14a** in 75 ml of chloroform at 0-10° was added gaseous ammonia for 10 minutes and then this suspension was stirred at 0-10°. After 3 hours no more starting material remained so the solvent was stripped and the residue was purified by flash chromatography on silica gel eluting with 3% methanol/chloroform. A yield of 0.30 g (63%) of pure **15**, mp 172-180°, was obtained; ^{1}H nmr (DMSO-d_6): δ 4.81 (2H, s), 7.68 (2H, d, J = 7 Hz), 7.90 (5H, m), 8.50 (1H, d, J = 2 Hz).

4-(4-Isobutylaminomethylbenzoyl)thiophene-2-sulfonamide (**16a**).

A solution of 1.0 g (2.78 mmoles) of **15** and 2.2 g (30.2 mmoles) of isobutylamine in 15 ml of tetrahydrofuran was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue diluted with 40 ml of water and acidified with 6*N* hydrochloric acid. This solution was extracted with 3 x 30 ml of ethyl acetate to remove non-basic materials. The aqueous phase was made basic with ammonium hydroxide and the bright yellow solid that appeared was collected. The yield was 0.41 g (40%) of the free base. This was dissolved in ethanol and treated with ethanolic hydrogen chloride with stirring for 0.5 hour. The reaction mixture was then filtered to give the hydrochloride salt of **16a** as

a white solid, mp 235-237°; ^{1}H nmr (DMSO-d_6): δ 1.06 (6H, d, J = 7 Hz), 2.15 (1H, m), 4.42 (2H, bs), 7.83 (2H, m), 7.97 (3H, m), 8.55 (1H, s).

Anal. Calcd. for $C_{16}H_{20}N_2O_3S_2$.HCl: C, 49.41; H, 5.44; N, 7.20. Found: C, 49.50; H, 5.54; N, 7.19.

4-(4-Benzylaminomethylbenzoyl)thiophene-2-sulfonamide (**16b**).

A solution of 0.8 g (2.22 mmoles) of **15** and 1.47 g (20.1 mmoles) of benzylamine in 15 ml of tetrahydrofuran was stirred at room temperature for 16 hours. The solvent was removed on the rotary evaporator and excess benzylamine was removed at low pressure. The residue was taken up in 25 ml of water and acidified with 6*N* hydrochloric acid. This afforded a suspension which was filtered to provide 0.31 g (34%) of the hydrochloride salt of **16b**. This solid was purified by dissolving in hot ethanol, treatment of this with ethanolic hydrogen chloride and then collection of the solid resulting from cooling. This solid had mp 244-246° dec; ^{1}H nmr (DMSO-d_6): δ 4.23 (2H, bs), 4.35 (2H, bs), 7.53 (3H, m), 7.67 (2H, m), 7.88 (2H, d, J = 8 Hz), 7.98 (5H, m), 8.55 (1H, s), 9.95 (1H, bs).

Anal. Calcd. for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12. Found: C, 64.48; H, 5.33.

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