Preparation and Utility of Dianions from *N-tert*-Butylthiophene-2-sulfonamide

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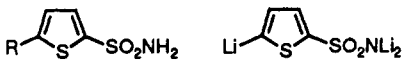
Received December 28, 1990

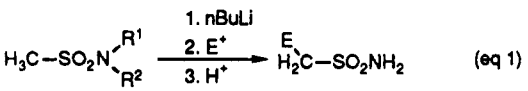
Metalation of *N-tert*-butylthiophene-2-sulfonamide with *n*-butyllithium occurs competitively at the 3- and 5-position of the thiophene ring. Equilibration of the initial mixture of carbanions or metalation with lithium diisopropylamide allows selective formation of the *N*,5-dilithiothiophenesulfonamide **7**. This dianion is useful for the preparation of a number of 5-substituted thiophene-2-sulfonamides.

As part of a program to develop a topically active carbonic anhydrase inhibitor for the treatment of glaucoma[1], a facile synthesis of 5-substituted thiophene-2-sulfonamides **1** was desired. One seemingly simple route to this



1 R= Acyl, alkyl **2**

end is the generation of an *N*,*N*,5-trilithiothiophenesulfonamide (**2**) and its subsequent reaction with electrophiles. However, a preliminary study showed that treatment of thiophene-2-sulfonamide with 3 equiv of *n*-butyllithium (*n*-BuLi) followed by addition of various electrophiles did not afford useful yields of products, possibly due to the insolubility of the polyanion **2**. A related attempt to prepare methanesulfonamide derivatives **5** via polymetalation of **3** and electrophilic substitution previously had been reported to fail.[2] As an alternative route

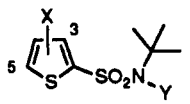


(eq 1)

3 (R^1= R^2= H) *no useful products* **5**

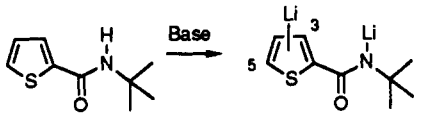
4 (R^1= *t*-Bu R^2= H) *efficient conversion*

to **5**, it was found that *N-tert*-butylmethanesulfonamide (**4**) could be converted to a dilithio derivative, which was well-behaved in reactions with electrophiles (E^+). The desired compounds were obtained by acid-catalyzed cleavage of the *tert*-butyl group. These findings suggested that the dianion **7** derived from *N-tert*-butylthiophene-2-sulfonamide **6** might be a useful intermediate in the synthesis of compounds of the general structure **1**.



6 X= Y= H
7 X= 5-Li Y= Li
11 X= 3-Li Y= Li

The viability of this approach depends on controlling the regiochemistry of the lithiation of **6**. Metalation of thiophene itself occurs exclusively at the position α to the heteroatom, and ample precedent is found for generating 5-lithiothiophenes bearing a variety of 2-substituents, including *N*,*N*-dialkyl sulfonamides.[3] However, two groups had reported[4] that alkyllithiums induce metalation at the 3-position of furans and thiophenes when these bear efficient directing groups for aromatic ortho lithiation in the 2-position. For example, Chadwick showed that deprotonation of *N-tert*-butylthiophene-2-carboxamide (**8**) with



(eq 2)

8 **9** 5-lithio **10** 3-lithio

Base = n-BuLi 9:10 = 0:100 Base = LDA 9:10 = 2:1

n-BuLi, in a variety of solvents, gave exclusively the 3-lithiothiophene **10**.[4a] Deprotonation of **8** with lithium diisopropylamide (LDA) partially reversed the metalation pattern, producing approximately a 2:1 mixture of 5- and 3-lithiation products **9** and **10**.[4a] Although the use of monoalkyl sulfonamides in ortho lithiation reactions is known,[5] the relative effectiveness of the *N-tert*-butyl sulfonamide group vis-a-vis the carboxamide in directing lithiation was unknown to us.[6]

Deuteration Studies. Deprotonation of **6** and quenching of the resulting carbanions with an excess of MeOD was carried out under a variety of conditions (Table I). The extent of deuterium incorporation was approximated by integration of the ^{1}H NMR spectrum, comparing the area of the resonance peak for the proton at C-4 with that of C-3 and C-5. This analysis assumes that deprotonation at C-4 does not occur. The data are estimated to be reliable to ±5%. A number of interesting trends appear in Table I. First, the rate of deprotonation of the 3-position of **6** with *n*-BuLi was only about twice that of the 5-position (entries 1–3). Thus, the directing effect of the anionic sulfonamide is not as pronounced as that of the anionic carboxamide.[4a] There was only a small difference between the deprotonation reaction in ether and THF. Prolonged reaction periods in THF at −10 °C gave increased amounts of the 5-lithio compound (entries 4, 5). Using less than a stoichiometric amount of *n*-BuLi (1.95 equiv) for the deprotonation increased the extent of isomerization to the 5-lithio species (entries 6–9). In addition, increasing the concentration of the reaction mixture increased the degree of isomerization (compare entries 6 and 7 with 8 and 9).

(1) For leading references, see: Graham, S. L.; Hoffman, J. M.; Gautheron, P.; Michelson, S. R.; Scholz, T. H.; Schwam, H.; Shepard, K. L.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Sugrue, M. F. *J. Med. Chem.* **1990**, *33*, 749.
(2) Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700.
(3) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1
(4) (a) Carpenter, A. J.; Chadwick, D. J. *J. Org. Chem.* **1985**, *50*, 4362. (b) Carpenter, A. J.; Chadwick, D. J. *J. Chem. Soc. Perkin Trans. 1* **1985**, 173. (c) Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. I. *Ibid.* **1982**, 1343. (d) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.
(5) (a) Lombardino, J. G. *J. Org. Chem.* **1971**, *36*, 1843. (b) Watanabe, H.; Gay, R.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900.
(6) Slocum and Jennings had suggested that the directing influences of the substituents $-SO_2NMe_2$, $-SO_2NHMe$, and $-CONHMe$ were roughly equal. However, the work cited above demonstrates that significant differences exist. Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.

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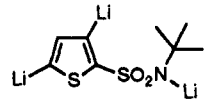
Table I. Metalation and Deuteration of 6

entry	base	equiv[c]	solvent,[d] ratio	final conc [6] (M)	temp (°C)	reaction time	deuterium content[e] 3-d_1	5-d_1	d_2	d_0
1	*n*-BuLi	2.0	THF/hex, 3.3:1	0.17	−70	60	55	45	0	0
2	*n*-BuLi	2.0	THF/hex, 3.3:1	0.17	−78	60	66	34	0	0
3	*n*-BuLi	2.0	Et_2O/hex, 3.3:1	0.17	0	15	68	32	0	0
4	*n*-BuLi	2.0	THF/hex, 1.7:1	0.29	−10	120	44	56	0	0
5	*n*-BuLi[a,b]	2.0	THF/hex, 1.7:1	0.29	−10	120	18	75	0	7
6	*n*-BuLi	1.95	THF/hex, 3.3:1	0.17	−10	120	42	49	0	9
7	*n*-BuLi[a]	1.95	THF/hex, 3.3:1	0.17	−10	120	19	70	0	11
8	*n*-BuLi	1.95	THF/hex, 1.7:1	0.29	−10	120	22	66	0	12
9	*n*-BuLi[a]	1.95	THF/hex, 1.7:1	0.29	−10	120	2	86	0	12
10	*n*-BuLi	3.0	THF/hex, 2.2:1	0.16	−10	60	28	19	53	0
11	*n*-BuLi	3.0	THF/hex, 2.2:1	0.16	−20	390	5	7	88	0
12	LDA	2.2	THF/hex, 1:1	0.36	−78	30	0	70	0	30
13	LDA	2.2	THF/hex, 1:1	0.36	−78	120	0	76	0	24
14	LDA	3.0	THF/hex, 1:1	0.24	−20	60	0	76	0	24

[a] Bipyridyl present at ~3 mol %. [b] Average of two experiments. [c] Molar equivalents of base. Base was added to a solution of **6** in the indicated solvent except for experiments using LDA where the inverse mode of addition was employed. Addition was performed at or below the indicated temperature, and the mixtures were then aged for the appropriate time. [d] Final solvent composition. [e] Deuterium incorporation determined by ^1H NMR integration of protons at C-3 and C-5 vs C-4.

While carrying out the deuteration studies, α,α'-bipyridyl was occasionally employed as an indicator[7] for the presence of organolithium compounds to ensure that the presence of adventitious water or other hydroxylic compounds did not complicate the interpretation of these experiments. *Surprisingly, the presence of the indicator appeared to be an important variable in the rate of isomerization of the thienyllithium reagents.* While α,α'-bipyridyl has little effect on the distribution of carbanions formed under conditions of kinetic control (entries 1, 2), an increase in the extent of isomerization (measured at 120 min) of **11** to **7** was observed when α,α'-bipyridyl was present (compare entries 4 and 5; 6 and 7; 8 and 9). This may represent a chelation-induced enhancement of carbanion reactivity due to reduction in its aggregation state.

Although it is tempting at first to conclude that *N*,5-dilithiothiophene **7** is thermodynamically more stable than **11**, our experiments do not unambiguously prove this point. The initially prepared carbanion mixtures were homogeneous, but during the equilibration process, **7** precipitated from solution. Thus, the observed equilibrium position may be driven entirely by the insolubility of **7**. The more rapid equilibration in the presence of 1.95 equiv of *n*-BuLi indicates that the proton exchange is more rapidly mediated by monoanionic *N*-lithio sulfonamide than by *N*,3,5-trilithiated thiophene **12**, although **12** will form slowly when **6** is treated with 3 equiv of *n*-BuLi (entries 10, 11).



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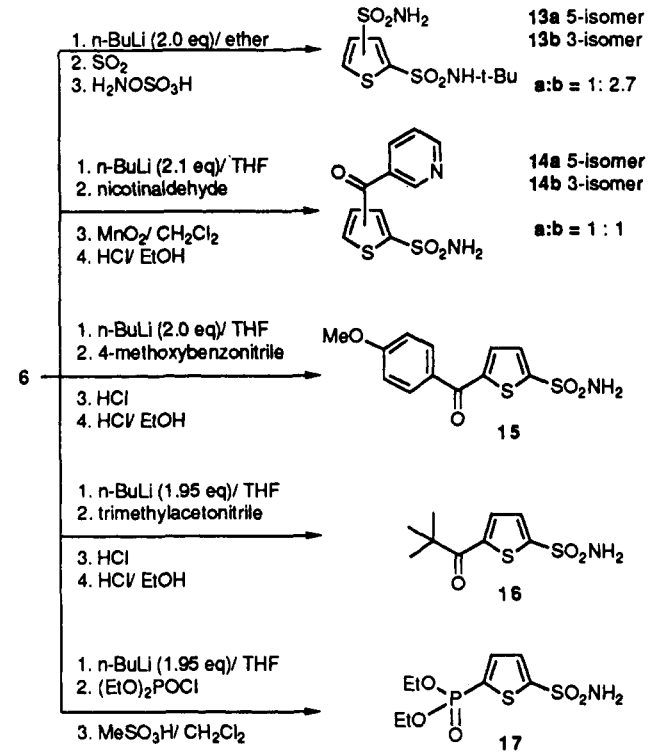
The ability to equilibrate the carbanions to the desired 5-lithio compound **7** solved in principle the synthetic problem that we were pursuing. However, the requirement to employ less than 2 equiv of *n*-BuLi in the deprotonation reaction makes certain the recovery of unreacted starting material. In addition, the dependence of successful equilibration on concentration and solubility phenomena made this process difficult to carry out with 100% reliability. The best method for the generation of **7** was deprotonation of **6** with LDA (entries 12–14). The low yield of deuterium incorporation in these experiments did not concern us in light of the work of Seebach, who showed that carbanion deuteration is frequently inefficient when secondary amines are present in the reaction mixture prior to quenching.[8] It is worth noting that LDA does not abstract the proton from the 3-position, even when present in significant excess (entry 14).

Scheme I. Reactions of Lithiated Thiophenes with Various Electrophiles

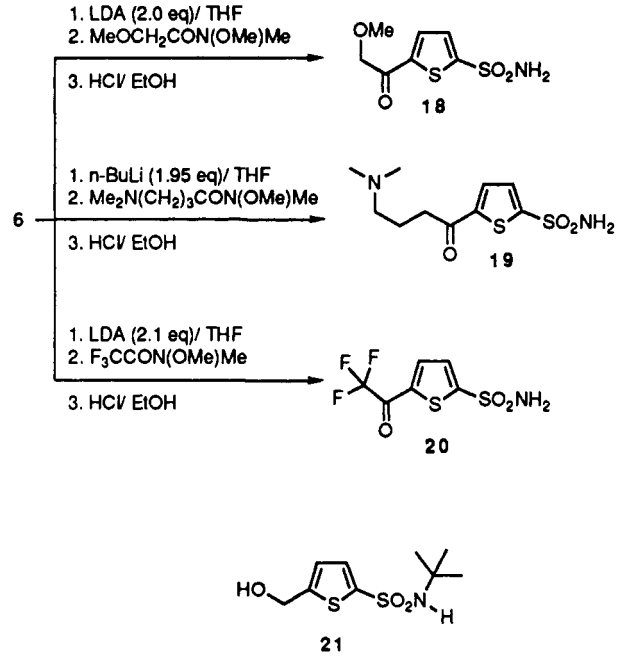


Derivatization Studies. The utility of the dianions **7** and **11** for the synthesis of substituted thiophene-2-sulfonamides is summarized in Schemes I and II. Under nonequilibrating conditions employing *n*-BuLi as base, mixtures of 5- and 3-substituted products such as **13a** and **13b** were obtained in ratios predictable from the deuteration studies. The preparation of **14a** and **14b** demon-

(7) (a) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin: Menlo Park, CA, 1972; pp 551–552. (b) Jorgensen, M. J. *Org. React.* **1970**, *18*, 1.

(8) (a) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (b) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

Scheme II. Reactions of Lithiated Thiophenes with *N*-Methoxy-*N*-methylamides



strated the feasibility of cleaving the *tert*-butyl group from the sulfonamide, establishing in full a methodology for the synthesis of the desired thiophene-2-sulfonamides. Under conditions where the carbanions were allowed to equilibrate (1.95 equiv of *n*-BuLi), 5-substituted derivatives **15–17** were almost exclusively obtained.

The synthesis of 5-acylated thiophenes **18–20** by the reaction of **7** with *N*-methoxy-*N*-methylamides[9] was also accomplished (Scheme II). Of some interest is the formation of the hydroxymethylated compound **21** in the reaction sequence leading to **18**. This product derives from base-induced generation of formaldehyde from the *N*-methoxy-*N*-methylamide and its subsequent reaction with **7**. A more detailed study of this process has been reported.[10]

Conclusions

This work establishes the relative efficiency of the *N*-alkylsulfamoyl group in promoting ortho metalation. In this regard, the rank order is as follows: $-CONH-t-Bu > -SO_2NH-t-Bu > -SO_2NMe_2$. The facile generation of the *N*,5-dianion **7** from *N*-*tert*-butylthiophene-2-sulfonamide **6** and its subsequent reaction with electrophiles provides a concise synthesis of 5-substituted thiophene-2-sulfonamides. Confirmation of the 2,5-substitution pattern in **13–20** was provided by the observation that these compounds were potent inhibitors of human carbonic anhydrase II.[11]

Experimental Section

N-*tert*-Butylthiophene-2-sulfonamide was prepared from 2-(chlorosulfonyl)thiophene (Aldrich Chemical Co.) and excess *tert*-butylamine. Other starting materials were obtained from commercial suppliers and used without further purification. Freshly opened bottles of tetrahydrofuran (THF, Fisher anhydrous grade) were serum stoppered and used without further purification except for deuteration studies where the solvent was distilled from sodium/benzophenone. Melting points were determined in open capillaries and are uncorrected. Elemental analyses were performed by Mr. J. Moreau of the Medicinal Chemistry Department.

Standard workup referred to in the experimental procedures involved the following: diluting the reaction mixture with ethyl acetate (EtOAc); washing sequentially with 10% HCl, 10% $NaHCO_3$, and brine; drying of the solution over anhydrous Na_2SO_4; and removing the solvent on a rotary evaporator. The general procedure for cleavage of the *tert*-butyl group from the sulfonamide involved dissolving the compound in 2:1 ethanol/concd HCl (30 mL/g) and heating at reflux for 6 h. The mixture was poured onto ice and worked up according to the standard procedure. Chromatography was carried out on silica gel eluting with methanol/chloroform gradients.

Deuteration studies were conducted as described in the footnotes to Table I.

***N*-*tert*-Butyl-5-sulfamoylthiophene-2-sulfonamide and *N*-*tert*-Butyl-3-sulfamoylthiophene-2-sulfonamide (13a and 13b).** A solution of **6** (1.00 g, 4.6 mmol) in 10 mL of dry ether with ~5 mg of α,α'-bipyridyl was treated with *n*-BuLi (6.0 mL, 1.56 M in hexane) at 0 °C. The mixture was stirred 1 h at room temperature and cooled to −78 °C. Sulfur dioxide gas was introduced just above the surface of the solution until the red color of the solution was discharged. Acetic acid (1 equiv) was added, and the mixture was warmed to room temperature and diluted with 20 mL ether. The hygroscopic sulfinic acid salt was isolated by filtration and aminated with hydroxylamine-*O*-sulfonic acid.[12] After workup and chromatography, two products were obtained. The less polar product (**13b**, 0.68 g) was recrystallized from *n*-butyl chloride (*n*-BuCl): mp 147–149 °C; ^1H NMR δ 7.91 (1 H, d, J = 5 Hz), 7.51 (1 H, d, J = 5 Hz), 6.70 (2 H, br s), 6.20 (1 H, br s), 1.30 (9 H, s). Anal. Calcd for $C_8H_{14}N_2O_4S_3$: C, 32.20; H, 4.73; N, 9.39. Found: C, 32.24; H, 4.73; N, 9.22.

The more polar isomer (**13a**, 0.25 g) was recrystallized (*n*-BuCl/acetone) to give 0.20 g of solid: mp 137–138 °C (lit.[13] mp 135–136 °C); ^1H NMR δ 7.52 (2 H, s), 7.05 (2 H, br s), 6.75 (1 H, br s), 1.30 (9 H, s). Found: C, 32.29; H, 4.75; N, 9.22.

5- and 3-(3-Pyridylcarbonyl)thiophene-2-sulfonamide (14a and 14b). A solution of **6** (2.30 g, 10.6 mmol) in 25 mL of THF was cooled to −50 °C, and *n*-BuLi (14 mL, 1.56 M in hexane) was added, maintaining the temperature <−40 °C. After addition, the mixture was warmed to −10 °C for 45 min and then cooled to −50 °C. Nicotinaldehyde (1 mL, 10.6 mmol) was added in a single portion, and the cooling bath was removed. After the mixture had reached 15 °C, acetic acid (1.3 mL, 23 mmol) and water (25 mL) were added. The product was isolated using the standard workup, deleting the 10% HCl wash, yielding 3.8 g of brown oil. Chromatography gave 3.1 g of a 1:1 mixture of products. The mixture (2.8 g) was dissolved in CH_2Cl_2, and 9.0 g MnO_2 was added. After 6 h, the manganese salts were removed by filtration through Celite and the filter cake was washed with EtOAc. The solution was given a standard workup and chromatographed. The less polar product was the 3-pyridoyl compound: ^1H NMR ($CDCl_3$) δ 9.02 (1 H, d, J = 1 Hz), 8.85 (1 H, dd, J = 4, 1 Hz), 8.14 (1 H, dt, J = 8, 1 Hz), 7.58 (1 H, d, J = 6 Hz), 7.48 (1 H, dd, J = 8, 4 Hz), 7.22 (1 H, d, J = 6 Hz), 5.90 (1 H, br s), 1.34 (9 H, s).

The spectrum of the other component, *N*-*tert*-butyl-5-(3-pyridoyl)thiophene-2-sulfonamide, which was not obtained in pure form, was assigned from the spectrum of the mixture by difference: ^1H NMR ($CDCl_3$) δ 9.10 (1 H, d, J = 1 Hz), 8.88 (1 H, dd, J = 4, 1 Hz), 8.18 (1 H, dt, J = 8, 1 Hz), 7.65 (1 H, d, J = 4 Hz), 7.57 (1 H, d, J = 4 Hz), 7.52 (1 H, dd, J = 8, 4 Hz), 5.20 (1 H, br s), 1.36 (9 H, s).

The *tert*-butyl group was cleaved using a mixture of the isomers (1.66 g) to afford 1.24 g of the sulfonamides, which were separated by chromatography. The less polar isomer **14b** weighing 0.32 g was not further characterized. The more polar isomer (**14a**, 0.64

(9) Weinreb, S. M.; Nahm, S. *Tetrahedron Lett.* **1981**, *22*, 3815.
(10) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269.
(11) (a) The IC_{50} values for the inhibition of human carbonic anhydrase II were determined by Mr. John Sondey of the Medicinal Chemistry Department, employing a previously described method.[11b] The values obtained were as follows (nM): **13a**, 3.4; **14a**, 0.9; **15**, 0.2; **16**, 4.3; **17**, 7.4; **18**, 5.8; **19**, 18; **20**, 13. (b) Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Lyle, P. A.; Schwam, H.; Varga, S. L.; Christy, M. E.; Randall, W. C.; Baldwin, J. J. *J. Med. Chem.* **1987**, *30*, 591. (c) The regiochemical assignment relies on the observation that ortho-substituted aromatic sulfonamides are poor inhibitors of carbonic anhydrase: King, R. W.; Burgen, A. S. V. *Proc R. Soc. London, B* **1976**, *193*, 107.
(12) Graham, S. L.; Scholz, T. H. *Synthesis* **1986**, 1031.
(13) Barnish, I. T.; Cross, P. E.; Dickinson, R. P. British Patent 1 516 024.

g) was recrystallized from THF/hexane to give 0.56 g of very fine granular material: mp 179–181 °C; ^{1}H NMR (acetone-d_6) δ 9.06 (1 H, d, J = 1 Hz), 8.86 (1 H, dd, J = 4, 1 Hz), 8.28 (1 H, dt, J = 8, 1 Hz), 7.77 (1 H, d, J = 4 Hz), 7.70 (1 H, d, J = 4 Hz), 7.63 (1 H, dd, J = 8, 4 Hz), 7.25 (2 H, br s). Anal. Calcd for $C_{10}H_8N_2O_3S_2$: C, 44.76; H, 3.00; N, 10.44. Found: C, 45.13; H, 3.05; N, 10.09.

5-(4-Methoxybenzoyl)thiophene-2-sulfonamide (15). A solution of **6** (1.00 g, 4.6 mmol) and 5 mg of α,α'-bipyridyl in 10 mL of THF was cooled to −50 °C, and *n*-BuLi (5.8 mL, 1.56 M in hexane) was added dropwise. The cooling bath was removed, and the reaction mixture was stirred at −10 to −15 °C for 40 min. *p*-Methoxybenzonitrile (0.62 g, 4.7 mmol) was added at −50 °C as a solution in 5 mL of THF, the mixture was allowed to warm to 10 °C over a 45-min period, and 15 mL of 10% HCl was added. After being stirred overnight, the mixture was worked up to give 1.63 g of a yellow semisolid, which was recrystallized from *n*-BuCl/hexane to afford 1.16 g (73%) of white solid, mp 120–124 °C.

Cleavage of the sulfonamide protecting group gave **15** as a yellow solid, mp 173–175 °C (lit.[14] 176–178 °C). The structure of the title compound was established by comparison to an authentic sample (TLC, ^{1}H NMR): ^{1}H NMR (DMSO) δ 8.0 (2 H, br s), 7.92 (2 H, d, J = 8 Hz), 7.72 (1 H, d, J = 4 Hz), 7.64 (1 H, d, J = 4 Hz), 7.14 (2 H, d, J = 8 Hz), 3.90 (3 H, s).

5-(2,2-Dimethylpropanoyl)thiophene-2-sulfonamide (16). A solution of **6** (2.36 g, 10.9 mmol) in 20 mL of THF was cooled to −30 °C, and *n*-BuLi (13.6 mL, 1.56 M in hexane) was added, maintaining the temperature ≤−20 °C. The mixture was warmed to −10 °C for 25 min and cooled to −30 °C, and trimethylacetonitrile (1.20 mL, 10.9 mmol) was added. The cooling bath was replaced with an ice bath, the mixture was stirred 1 h, and 50 mL of 10% HCl was added. After being stirred overnight, the mixture was worked up by the general method to give 3.49 g of a solid. The crude ^{1}H NMR showed a single 2,5-disubstituted thiophene: ($CDCl_3$) δ 7.65 (1 H, d, J = 4.2 Hz), 7.57 (1 H, d, J = 4.2 Hz), 4.95 (1 H, br s), 1.42 (9 H, s), 1.34 (9 H, s). The *tert*-butyl group was removed to give 2.16 g of solid, mp 128–132 °C. Recrystallization from aqueous ethanol gave 1.60 g of **16**: mp 130–134 °C; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.60 (1 H, d, J = 4.2 Hz), 7.52 (1 H, d, J = 4.2 Hz), 6.85 (2 H, br s), 1.34 (9 H, s). Anal. Calcd for $C_9H_{13}NO_3S_2$: C, 43.70; H, 5.30; N, 5.66. Found: C, 44.02; H, 5.49; N, 5.79.

5-(Diethoxyphosphoryl)thiophene-2-sulfonamide (17). Sulfonamide **6** (2.06 g, 9.4 mmol) was metalated as described in the preparation of **16**. The mixture was cooled to −70 °C, and diethyl chlorophosphate (1.36 mL, 9.4 mmol) was added over a 60-s period. The temperature rose to −55 °C during the addition. Stirring was continued 1 h at −70 °C, and 50 mL of saturated NH_4Cl solution was added. The mixture was worked up by the general method and evaporated to give 3.60 g of an oil. Chromatography (silica, 2:1 hexane/EtOAc followed by 10% methanol/chloroform) separated several minor components of the reaction mixture from the major product (1.67 g). This somewhat impure intermediate (1.60 g) was dissolved in 30 mL of CH_2Cl_2, 0.50 mL of methanesulfonic acid was added, and the mixture was refluxed for 18 h. After standard workup and chromatography, the major product (0.43 g) was recrystallized (EtOAc/hexane) to give 0.31 g of **17**: mp 97–99 °C; ^{1}H NMR (DMSO) δ 7.92 (2 H, br s), 7.64 (2 H, m), 4.07 (4 H, m), 1.27 (6 H, t, J = 7 Hz). Anal. Calcd for $C_8H_{14}NO_5PS_2$: C, 32.10; H, 4.71; N, 4.68. Found: C, 32.29; H, 4.87; N, 4.62.

5-(Methoxyacetyl)thiophene-2-sulfonamide (18) and *N-tert*-Butyl-5-(hydroxymethyl)thiophene-2-sulfonamide (21). A solution of diisopropylamine (6.7 mL, 48 mmol) in 30 mL of THF was cooled to −78 °C, and *n*-BuLi (30 mL, 1.56 M in hexane) was added dropwise. After 10 min, a solution of **6** (5.0 g, 23 mmol) in 30 mL of THF was added dropwise, and the resulting suspension was stirred 45 min at −78 °C. To this mixture was added *N*-methoxy-*N*-methylmethoxyacetamide (3.0 g, 23 mmol) dissolved in 10 mL of THF. The cooling bath was removed, and the mixture was allowed to warm to 0 °C and stirred at that temperature for 30 min. Standard workup, chromatography, and recrystallization (CCl_4) gave 3.25 g (49%) of *N-tert*-butyl-5-(methoxyacetyl)thiophene-2-sulfonamide: ^{1}H NMR ($CDCl_3$) δ 7.78 (1 H, d, J = 3.9 Hz), 7.62 (1 H, d, J = 3.9 Hz), 5.50 (1 H, br s), 4.52 (2 H, s), 3.52 (3 H, s), 1.32 (9 H, s). Further purification of several mixed fractions by chromatography on silica gel (20% EtOAc/hexane) gave 0.90 g (15%) of **21**: mp 74–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (1 H, d, J = 3.8 Hz), 6.90 (1 H, d of t, J = 3.7, 1.0 Hz), 4.85 (2 H, br d, J = 4.9 Hz), 4.75 (1 H, s), 2.38 (1 H, m), 1.29 (9 H, s). Anal. Calcd for $C_9H_{15}NO_3S_2$: C, 43.35; H, 6.06; N, 5.62. Found: C, 43.61; H, 6.31; N, 5.64.

Cleavage of the sulfonamide protecting group from *N-tert*-butyl-5-(methoxyacetyl)thiophene-2-sulfonamide gave 0.87 g of nearly pure **18** after chromatography. An analytical sample was prepared by recrystallization from methanol: mp 162–164.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (2 H, br s), 7.89 (1 H, d, J = 3.8 Hz), 7.60 (1 H, d, J = 3.8 Hz), 4.69 (2 H, s), 3.36 (3 H, s). Anal. Calcd for $C_7H_9NO_4S_2$: C, 35.73; H, 3.85; N, 5.95. Found: C, 35.85; H, 3.85; N, 5.85.

5-[4-(Dimethylamino)butanoyl]thiophene-2-sulfonamide (19). Carbonyldiimidazole (2.88 g, 17.7 mmol) was added to a suspension of 4-(dimethylamino)butyric acid hydrochloride (2.71 g, 16.1 mmol). After 10 min, gas evolution had ceased and *O,N*-dimethylhydroxylamine hydrochloride (1.72 g, 17.7 mmol) was added. After 2 h, the mixture was washed with 10% $NaHCO_3$ and brine, dried, and evaporated to afford 1.00 g *N*-methoxy-*N*-methyl-4-(dimethylamino)butyramide: ^{1}H NMR ($CDCl_3$) δ 3.70 (3 H, s), 3.20 (3 H, s), 2.45 (2 H, t, J = 8 Hz), 2.31 (2 H, t, J = 8 Hz), 2.24 (6 H, s), 1.80 (2 H, m).

Sulfonamide **6** (1.00 g, 4.56 mmol) was metalated as described in the preparation of **16**. The butyramide prepared previously (0.79 g, 9.4 mmol) was added over a 2-min period at −70 °C. The cooling bath was removed, the mixture was stirred at room temperature for 1 h, and 50 mL of saturated $NaHCO_3$ solution was added. A mixture of starting material and a single acylation product was obtained by EtOAc extraction. The basic product was extracted into 10% HCl. The aqueous solution was heated on a steam bath for 12 h, cooled, and saturated with NaCl. The solution was adjusted to pH 8 with NH_4OH and extracted repeatedly with EtOAc. The extracts were dried and evaporated to yield 0.41 g of white solid, which was recrystallized from CH_2Cl_2 to furnish 0.31 g **19**: ^{1}H NMR (acetone-d_6) δ 7.82 (1 H, d, J = 4 Hz), 7.61 (1 H, d, J = 4 Hz), 3.01 (2 H, t, J = 8 Hz), 2.30 (2 H, t, J = 8 Hz), 2.11 (6 H, s), 1.83 (2 H, m). This material was dissolved in methanol, concd HCl was added, and the methanol was evaporated. The hydrochloride of **19** was recrystallized from 95% ethanol, mp 205–213 °C. Anal. Calcd for $C_{10}H_{16}N_2O_3S_2$·HCl: C, 38.39; H, 5.48; N, 8.95. Found: C, 38.56; H, 5.78; N, 9.00.

5-(Trifluoroacetyl)thiophene-2-sulfonamide (20). A suspension of *O,N*-dimethylhydroxylamine hydrochloride (4.14 g, 42 mmol) in 20 mL of THF was cooled to 0 °C, and trifluoroacetic anhydride (6.0 mL, 42 mmol) was added over a 5-min period followed by pyridine (6.8 mL, 84 mmol) over a 2-min period. The mixture was allowed to warm to room temperature and worked up to give 4.8 g of *N*-methoxy-*N*-methyltrifluoroacetamide: ^{1}H NMR ($CDCl_3$) δ 3.80 (3 H, s), 3.30 (3 H, s).

Sulfonamide **6** (1.50 g, 6.8 mmol) was converted to **20** as described for the preparation of **18**, substituting the trifluoroacetamide prepared earlier (1.08 g, 6.8 mmol). Recrystallization from *n*-BuCl gave 0.76 g of **20**, mp 123–125 °C, which contained approximately 5% of thiophene-2-sulfonamide: ^{1}H NMR (acetone-d_6) δ 8.07 (1 H, m), 7.77 (1 H, d, J = 4 Hz), 7.38 (2 H, br s). Anal. Calcd for $C_6H_4F_3NO_3S_2$: C, 27.80; H, 1.56; N, 5.40. Found: C, 27.72; H, 1.45; N, 5.68.

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