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A Convenient Preparation of Heteroaryl Sulfonamides and Sulfonyl Fluorides from Heteroaryl Thiols

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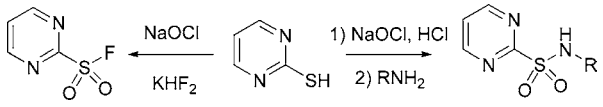

Heteroaromatic thiols may be oxidized to the sulfonyl chloride at low temperature (−25 °C) by using 3.3 equiv of aqueous sodium hypochlorite. The reaction is rapid, avoids the use of chlorine gas, and succeeds with substrates that have previously been found to afford little or none of the sulfonamide product with other procedures. The method allows the preparation of the sulfonyl fluorides, which are stable enough to be purified and stored, making them potentially useful monomers in parallel chemistry efforts.

Introduction

Sulfonamides play an important role in many medicinal chemistry analogue programs. During the course of some recent work, we wanted to prepare a number of heteroaryl sulfonamides. To prepare these analogues, we required access to the corresponding heteroaryl sulfonyl chlorides such as **1a**. Only a very small number of these compounds are commercially available due to their known instability.[1] An examination of the literature revealed that these compounds are generally prepared by the oxidation of the corresponding heteroaryl thiol such as **2a** with chlorine gas in the presence of aqueous hydrochloric acid. These conditions were first employed with a heteroaryl thiol in 1942,[2] and subsequent workers have generally used these conditions with little or no modification.[3] Unfortunately, as was indicated in the original papers and as subsequently confirmed by others, this procedure has preparative value only when the heterocycle is a pyridine. Other heterocycles, for example, pyrimidine, frequently afford yields of 10% or less, a result that we confirmed in our laboratories as well. In addition, it has been reported that the use of exactly 3 equiv of chlorine gas is required, although in the literature preparations little effort has been made to actually limit the amount of chlorine to 3 equiv.[4] Other conditions that have been used to effect this transformation include oxidation of the heteroaryl thiol by chloramines to afford the sulfenamide, followed by oxidation to the sulfonamide by mCPBA[5] or potassium permanganate.[6] The inadequate yield and lack of generality of these methods, coupled with the hazards associated with chlorine gas and chloramines, and the potential need to control the stoichiometry of a gaseous reagent, led us to examine other conditions for effecting the oxidation of **2a** to **1a** (Scheme 1). We reasoned

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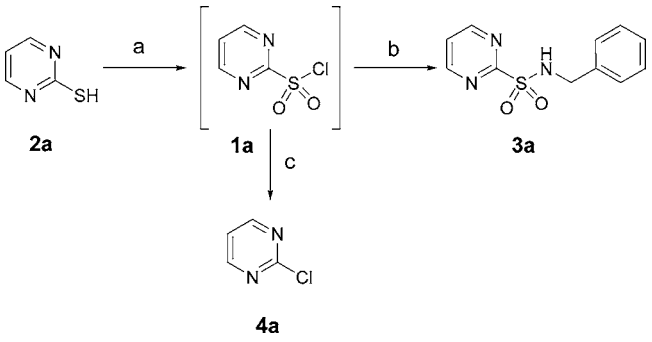
SCHEME 1. Oxidation of Heteroaryl Thiol to Heteroaryl Sulfonyl Chloride[a]



[a] Reagents and conditions: (a) Cl_2 or NaOCl, HCl; (b) $BnNH_2$ (excess); (c) HCl, prolonged standing or increased temperature.

that aqueous sodium hypochlorite, which is inexpensive and of easily determined molarity,[7] would provide an alternative oxidizing agent that would be more convenient to use and allow much greater control of reactant stoichiometry. We also anticipated that the use of a water−immiscible cosolvent such as dichloromethane would be beneficial by allowing extraction of the heteroaryl sulfonyl chloride as formed, thereby reducing the exposure of the heteroaryl sulfonyl chloride to the aqueous acid.

Such a process would have significant advantages: (a) the use of chlorine gas would be eliminated, resulting in a safer and much more convenient procedure, and (b) the stoichiometry of the oxidizing agent could be easily controlled, possibly resulting in higher yields by preventing decomposition of the heteroaryl sulfonyl chloride by excess chlorine or aqueous acid. In view of the known instability of heteroaryl sulfonyl chlorides, we elected to confirm their formation by trapping with an excess of benzylamine, followed by isolation of the *N*-benzyl sulfonamide.

Results and Discussion

A preliminary experiment, using commercial bleach as a source of sodium hypochlorite, showed that such a process was possible, affording a 67% yield of the pyrimidine sulfonamide **3a**. The reaction was run several times with 2-mercaptopyrimidine (**2a**) to identify optimal conditions. The yield of product was found to be dependent on four variables: (a) the temperature of the oxidation reaction, (b) the procedure used to separate the crude acid chloride, (c) the concentration of hydrochloric acid, and (d) the reaction cosolvent.

When the reaction was run at 5 to 10 °C (internal temperature, ice water bath), the yield of isolated **3a** averaged at 64%. At −10 to −5 °C internal temperature, the yield was almost quantitative. However, other substrates (for example, 4,6-dimethyl-2-mercaptopyrimidine, **2b**) afforded much less product at −10 to −5 °C internal temperature, yielding instead largely the heteroaryl chloride (**4b**) resulting from decomposition of the heteroaryl sulfonyl chloride. This difficulty was circumvented by carrying out the reaction at −30 to −25 °C internal temperature. In these cases it was necessary to include 25 wt % of calcium chloride in the aqueous phase to prevent freezing.[8]

Under these conditions, **2b** was transformed to **3b** in 77% crude yield and 64% yield following recrystallization. The addition of calcium chloride to both the aqueous acid and the sodium hypochlorite was necessary, otherwise the mixture began to freeze as the sodium hypochlorite solution was added. Addition of 25 wt % of anhydrous calcium chloride to the sodium hypochlorite solution caused decomposition of the hypochlorite, even with cooling in ice; therefore, calcium chloride hexahydrate was added to the bleach in a quantity sufficient to be equivalent to 25 wt % of anhydrous calcium chloride.

When the reaction was carried out on **2a** at 5 to 10 °C (internal temperature, ice water bath) and the dichloromethane layer was washed with saturated sodium bicarbonate solution prior to the trapping with benzylamine, the yield of **3a** was reduced to 25%. When brine was used in place of the sodium bicarbonate solution, the yield of **3a** was increased to 53%. However, as dichloromethane dissolves very little water, and the washing procedure appeared to provide no benefit, the washing of the crude sulfonyl chloride solution was omitted entirely. Instead, the crude sulfonyl chloride solution was separated from the aqueous phase in a separatory funnel precooled with ice water, and the dichloromethane layer was collected in a flask cooled in a dry ice−acetone bath. By this means further decomposition of the crude sulfonyl chloride was prevented and any aqueous phase entrained in the dichloromethane was immobilized by freezing.

When only the theoretical amount of HCl required by the reaction stoichiometry was used (6.6 mL of 1 M HCl, 2 equiv to NaOCl used) at 5 to 10 °C (internal temperature, ice water bath), the yield of **3a** decreased slightly to 50%. The use of ethyl acetate as cosolvent in the oxidation of **2a** resulted in a low recovery (30%) of **3a**. Not surprisingly, if the dichloromethane solution of **1a** was allowed to warm to room temperature, no **3a** was obtained on trapping with benzylamine.

This method was then applied to a variety of commercially available heteroaryl thiols (Table 1). As will be seen from the results in Table 1, certain heteroaryl thiols afforded reasonable yields of products at −10 to −5 °C (Method A), while other heteroaryl thiols required reaction at −30 to −25 °C (Method B) to afford acceptable yields of the sulfonamide products **3**. The limitations of the methods are apparent from Table 1 as well. The imidazole substrates **2i** and **2t** required chromatographic purification of the crude product mixtures and afforded a low purified yield of the desired sulfonamides. In the case of **2t**, the primary byproducts were identified as 2-chlorobenzimidazole and 2-hydroxybenzimidazole by comparison to commercial samples. The benzoxazole substrate **2r** and 4-mercaptoquinoline substrate **2j** failed at either temperature, affording only 2-chlorobenzoxazole (**4r**, identified by comparison to a commercial sample) and 4-chloro-7-(trifluoromethyl)quinoline (**4j**, identified by ^{1}H NMR and GC-MS), respectively. The 4-trifluoromethylpyrimidine **2s** returned only the disulfide upon reaction at either −25 or −5 °C. Predictably, the 4-hydroxypyrimidine substrate **2h** underwent simultaneous nuclear chlorination under the reaction conditions to afford product containing a 5-chloro-4-hydroxypyrimidine. However, we were pleased to find that certain substrates (**2a**, **2b**, **2c**, **2m**) that had been previously reported to give low yields[2b] gave much improved yields using this procedure.

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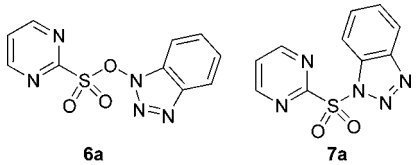
TABLE 1. Results of Conversion of Heteroaryl Thiols to Heteroaryl *N*-Benzyl Sulfonamides

entry	starting thiol	temp,[a] °C	product	yield,[b] %	mp, °C
1	2-mercaptopyrimidine (**2a**)	−5	**3a**	94	117−118
2	4,6-dimethyl-2-mercaptopyrimidine (**2b**)	−5	**3b**	19	129−130
3	4,6-dimethyl-2-mercaptopyrimidine (**2b**)	−25	**3b**	64	129−130[c]
4	5-mercapto-1-phenyl-1,2,3,4-tetrazole (**2c**)	−25[d]	**3c**	74[c]	129−131
5	2-mercapto-4-methylpyrimidine (**2d**)	−25[d]	**3d**	75[c]	103−105
6	2-mercaptobenzothiazole (**2e**)	−5	**3e**	90	129−130[e]
7	2-mercaptopyridine (**2f**)	−5	**3f**	98	102−103
8	methyl 2-mercaptonicotinate (**2g**)	−5	**3g**	53	97−98
9	4-hydroxy-2-mercapto-6-phenylpyrimidine (**2h**)	−5	**5**[f]	22	167−168
10	2-mercapto-1-methylimidazole (**2i**)	−25[d]	**3i**	9	109−110
11	2-mercapto-7-(trifluoromethyl)quinoline (**2j**)	−25[d]	**3j**	0	
12	2-mercaptoquinoline (**2k**)	−5	**3k**	80	106−107
13	3-cyano-4,6-dimethyl-2-mercaptopyridine (**2*l***)	−5	**3*l***	80	157−158
14	2-mercaptothiazole (**2m**)	−5	**3m**	93	98−99
15	methyl 6-mercaptonicotinate (**2n**)	−5	**3n**	57	115−116
16	3-mercapto-6-methoxypyridazine (**2o**)	−25[d]	**3o**	64	181−183
17	3-mercapto-5-methyl-4-phenyl-4*H*-1,2,4-triazole (**2p**)	−25[d]	**3p**	76	221−223
18	4-mercaptopyridine (**2q**)	−25[d]	**3q**	39	163−166
19	2-mercaptobenzoxazole (**2r**)	−25[d]	**3r**	0	
20	2-mercapto-4-trifluoromethylpyrimidine (**2s**)	−25[d]	**3s**	0	
21	2-mercaptobenzimidazole (**2t**)	−25[d]	**3t**	16	217−218

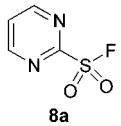
[a] Maximum internal reaction temperature during oxidation by NaOCl. [b] Unoptimized yield of analytically pure isolated product. [c] Literature mp 130.5−131 (see ref 16a). [d] Reaction was unsuccessful when carried out at −5 °C. [e] Literature mp 134 (see ref 16b). [f] Product was *N*-benzyl-4-hydroxy-5-chloro-6-phenylpyrimidine-2-sulfonamide.

Having identified a convenient oxidation and trapping procedure to prepare the desired heteroaryl sulfonamides, we turned our attention to the identification and preparation of stable heteroaryl sulfonyl derivatives that would serve as synthetic equivalents to the unstable sulfonyl chlorides. Such derivatives would be of great value in medicinal chemistry analogue programs and parallel synthesis. Arylsulfonyl 1-hydroxybenzotriazole esters have been described as reactive sulfonylating agents,[9] as have heteroaryl benzotriazole sulfonamides.[10] Aryl sulfonyl 4-nitrophenyl esters have also been described;[11] however, these appeared unsuitable for our purpose as they are known to react with amine nucleophiles by two pathways: (a) attack at the sulfonyl group to afford the sulfonamide and 4-nitrophenol and (b) attack at the 4-position of the nitrophenol to afford the sulfonic acid and a 4-nitroaniline derivative by an S_N2Ar mechanism.[12] Attempts to prepare either pyrimidine-2-sulfonic acid benzotriazol-1-yl ester (**6**) or 1-(pyrimidine-2-sulfonyl)-1*H*-benzotriazole (**7**) from dichloromethane solutions of **1a** were entirely unsuccessful, affording only 2-chloropyrimidine.



6a

7a



8a

We therefore turned our attention to the preparation of 2-pyrimidinyl sulfonyl fluoride (**8a**).[13] We were pleased to find that we could obtain a nearly quantitative yield of the sulfonyl fluoride at −10 to −5 °C using bleach as the oxidizing agent in the presence of a tetralkylammonium salt. The identity of **8a** was confirmed by ^1H, ^{13}C, and ^{19}F NMR, IR, elemental analysis, and conversion to **3a** by reaction with excess benzylamine in CH_2Cl_2 at room temperature. We found that the inclusion of a quaternary ammonium salt was crucial to obtain good yields of the sulfonyl fluoride. With use of 2-mercaptobenzothiazole (**2e**) as a model, tetrabutylammonium ion and tetraethylammonium ion gave approximately a 2:1 ratio of the sulfonyl fluoride to combined other products as judged by examination of the ^1H NMR spectra of the crude reaction products. Not surprisingly, the tetraethylammonium ion was more easily washed out of the crude sulfonyl fluoride product with water. Benzyltrimethylammonium ion was less satisfactory, affording approximately a 1:1 ratio of the sulfonyl fluoride to combined other products as judged by examination of the ^1H NMR spectrum of the crude reaction product. Somewhat surprisingly, the use of a methanol−water mixture as reaction solvent generally gave poor results in all cases, with the crude reaction products consisting largely of disulfide and some **4**.[14] We therefore applied the biphasic oxidation method to some commercially available heteroaryl thiols (Table 2).

We found that in general the reaction afforded good yields (>80%) of the heteroaryl sulfonyl fluorides following removal of the tetraalkylammonium salt by washing with water. Further purification, to remove the last traces of tetraalkylammonium salt in order to afford analytically pure samples, was more difficult. Not surprisingly, the heteroaryl sulfonyl fluorides were

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TABLE 2. Results of Conversion of Heteroaryl Thiols to Heteroaryl Sulfonyl Fluorides

entry	starting thiol	product	yield,[a] %	mp, °C
1	2-mercaptopyrimidine (**2a**)	**8a**	73	58−60[b]
2	4,6-dimethyl-2-mercaptopyrimidine (**2b**)	**8b**	79	57−58[c]
3	2-mercaptobenzothiazole (**2e**)	**8e**	42	95−96
4	2-mercaptopyridine (**2f**)	**8f**	70	25−28[d]
5	2-mercaptoquinoline (**2k**)	**8k**	49	76−77
6	3-mercapto-6-methoxypyridazine (**2o**)	**8o**	73	55−57[e]

[a] Unoptimized yield of analytically pure isolated product. [b] Literature mp 57 °C (see ref 13). [c] Literature mp 58 °C (see ref 13). [d] Product purified by Kugelrohr distillation (oven temperature 125 °C, pressure 2 Torr). [e] See ref 16c.

decomposed upon attempted chromatography on silica or alumina. Distillation proved successful for sufficiently low molecular weight compounds (**8f**). Recrystallization from ethanol or 2-propanol afforded analytically pure samples of crystalline products, but the relatively high solubility of the products in these solvents resulted in low recovery of the products.

In summary, we have developed a general method for the preparation of heteroaryl sulfonamides from the readily available heteroaryl thiols by oxidation at lower temperatures than previously employed and immediate trapping of the unstable intermediate heteroaryl sulfonyl chloride with the desired amine. The reaction uses readily available reagents, allows easy control of stoichiometry, and avoids the use of chlorine gas. The reaction conditions may be modified to afford the heteroaryl sulfonyl fluorides, which are stable enough to isolate and store, yet reactive enough toward amines to afford the corresponding heteroaryl sulfonamides. These features make the heteroaryl sulfonyl fluorides potentially useful fragments to consider in a parallel medicinal chemistry effort. We hope that these procedures may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

Experimental Section

All oxidation reactions involving sodium hypochlorite were carried with rapid continuous magnetic stirring in Erlenmeyer flasks open to the atmosphere. Sodium hypochlorite was commercial "ultra" laundry bleach containing a stated concentration of 6% NaOCl. The actual concentration of hypochlorite was determined by iodometric titration. Hydrochloric acid (ca. 1 M) containing 25 wt % of calcium chloride was prepared by dissolving 125 g of anhydrous calcium chloride in 350 mL of water and cooling to room temperature. Once the solution had cooled, 42 mL of concentrated hydrochloric acid was added and the solution was diluted to 500 mL with water. Methyl 2-mercaptonicotinate (**2g**) and methyl 6-mercaptonicotinate (**2n**) were prepared by literature procedures.[15]

Titration of Sodium Hypochlorite. Potassium iodide (2 g) and 3 mL of glacial HOAc were dissolved in 50 mL of H_2O in an Erlenmeyer flask. An accurately measured volume (3 mL) of hypochlorite solution was added by pipet and the liberated iodine was titrated with 0.100 N standardized sodium thiosulfate solution, adding a few milliliters of starch solution as the endpoint was approached. Each milliliter of 0.100 N sodium thiosulfate required is equivalent to 3.722 mg of NaOCl.

Procedure A: Preparation of Heteroaryl Sulfonamides at −10 to −5 °C. *N*-Benzyl Pyrimidine-2-sulfonamide (3a). 2-Mercaptopyrimidine (**2a**, 0.561 g, 5 mmol) was stirred in a mixture of 25 mL of CH_2Cl_2 and 25 mL of 1 M HCl in a 125-mL Erlenmeyer flask for 10 min at −10 to −5 °C (internal temperature). Cold (5 °C) sodium hypochlorite (6% solution, 0.68 M, 26 mL, 18 mmol, 3.3 equiv) was added dropwise with *very rapid* stirring, maintaining the internal temperature at −10 to −5 °C. The mixture was stirred for 15 min at −10 to −5 °C (internal temperature) after the addition was completed. The mixture was transferred to a separatory funnel (pre-cooled with ice water) and the CH_2Cl_2 layer was rapidly separated and collected in a clean 125-mL Erlenmeyer flask cooled in a dry ice−acetone bath. Benzylamine (1.4 mL, 12.5 mmol) was added with stirring, whereupon the CH_2Cl_2 layer became a white suspension. The flask was removed to an ice-water bath and the suspension was stirred for 30 min at 0 °C. The suspension was then washed with 1 M phosphoric acid (all solids dissolved at once), then with water and brine. Drying (Na_2SO_4) and concentration afforded 1.171 g (94%) of **3a** as a fine white powder, mp 117−118 °C. ^{1}H NMR ($CDCl_3$) δ 8.87 (d, J = 5 Hz, 2 H), 7.46 (t, J = 5 Hz, 1 H), 7.28 (m, 5 H), 5.14 (br t, 1 H), 4.41 (d, J = 6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 136.5, 129.0, 128.2, 123.3, 48.4. APCI MS: m/z 250 $(M + H)^+$. Anal. Calcd for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86. Found: C, 52.71; H, 4.40; N, 16.71.

Procedure B: Preparation of Heteroaryl Sulfonamides at −30 to −25 °C. *N*-Benzyl 4,6-dimethylpyrimidine-2-sulfonamide (3b): 4,6-Dimethyl-2-mercaptopyrimidine (**2b**, 0.701 g, 5 mmol) was stirred in a mixture of 25 mL of CH_2Cl_2 and 25 mL of 1 M HCl (25 wt % $CaCl_2$) in a 125-mL Erlenmeyer flask for 10 min at −30 to −25 °C (internal temperature, maintained by intermittent cooling with a dry ice−acetone bath). Calcium chloride 6-hydrate (19 g) was dissolved in sodium hypochlorite (6% solution, 0.74 M, 24 mL, 18 mmol, 3.3 equiv), and the resulting clear solution was added dropwise with *very rapid* stirring, maintaining the internal temperature at −30 to −25 °C. The mixture was stirred for 15 min at −30 to −25 °C (internal temperature) after the addition was completed. The mixture was diluted with 25 mL of ice water and transferred to a separatory funnel (pre-cooled with ice water). The CH_2Cl_2 layer was rapidly separated and collected in a clean 125-mL Erlenmeyer flask cooled in a dry ice−acetone bath. Benzylamine (1.4 mL, 12.5 mmol) was added with stirring, whereupon the CH_2Cl_2 layer became a white suspension. The flask was removed to an ice-water bath and the suspension was stirred for 30 min at 0 °C. The suspension was then washed with 1 M phosphoric acid, then with water and brine. Drying (Na_2SO_4) and concentration afforded 1.060 g of **3b** as a fine white powder. ^{1}H NMR indicated the presence of about 5% of 2-chloro-4,6-dimethylpyrimidine. Recrystallization from 2-propanol gave 0.885 g (64%) of **3b** as white crystals, mp 129−130 °C. ^{1}H NMR ($CDCl_3$) δ 7.29−7.20 (m, 5 H), 7.11 (s, 1 H), 5.24 (br t, 1 H), 4.37 (d, J = 6 Hz, 2 H), 2.54 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.2, 165.3, 136.7, 128.8, 128.3, 128.2, 128.1, 122.4, 48.4, 24.1. APCI MS: m/z 278 (M +

(14) Oxidation of **2a**, **2b**, and **2d** with Cl_2 in MeOH−H_2O−KHF_2 has been reported to proceed in good yield; see ref 13. Oxidation of **2o** under similar conditions has been reported; see: Turck, A.; Ple, N.; Pollet, P.; Queguiner, G. *J. Heterocycl. Chem.* **1998**, *35*, 429. These procedures use chlorine gas in large excess as the oxidant. Presumably the use of hypochlorite in stochiometeric amounts is unsatisfactory under the MeOH−H_2O conditions due to competing oxidation of MeOH by hypochlorite.

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$H)^+$. Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.28; H, 5.23; N, 15.13.

Procedure C: Preparation of Heteroaryl Sulfonyl Fluorides. Pyrimidine-2-sulfonyl Fluoride (8a): 2-Mercaptopyrimidine (**2a**, 2.803 g, 25 mmol) was stirred in a mixture of 100 mL of CH_2Cl_2 and 100 mL of water containing 19.55 g (250 mmol) of KHF_2 and 8.48 g (25 mmol) of Bu_4NHSO_4 in a 500-mL polypropylene Erlenmeyer flask for 30 min at 0 to −5 °C (internal temperature). Cold (5 °C) sodium hypochlorite (6% solution, 0.68 M, 130 mL, 90 mmol, 3.6 equiv) was added dropwise with *very rapid* stirring, maintaining the internal temperature at 0 to −5 °C. The mixture was stirred for 10 min at 0 to −5 °C (internal temperature) after the addition was completed. The CH_2Cl_2 phase was separated, washed with water and brine, dried (Na_2SO_4), and concentrated. The residual oil (5.241 g) was dissolved in Et_2O and washed twice with water to remove the Bu_4N salt, then dried (Na_2SO_4) and concentrated to afford 3.210 g (79%) of **8a** as an oil that crystallized quickly. Recrystallization from EtOH gave 0.442 g (11%) of **8a** as white crystals, mp 58−60 °C. ^{1}H NMR ($CDCl_3$) δ 9.03 (d, 2 H), 7.71 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 159.4, 125.5; ^{19}F NMR ($CDCl_3$) Φ* −180.8; IR 1570, 1415, 1383, 1241, 1157 cm^{-1}. EI MS: *m*/*z* 162 (M^+). Anal. Calcd for $C_4H_3FN_2O_2S$: C, 29.63; H, 1.86; N, 17.28; F 11.72. Found: C, 29.67; H, 1.87; N, 17.07; F 11.53.

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Supporting Information Available: General experimental procedures and ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, MS data, and elemental analyses for compounds **3c**−**3g**, **3i**, **3k**−**3q**, **3t**, **5**, **8b**, **8e**, **8f**, **8k**, **8o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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