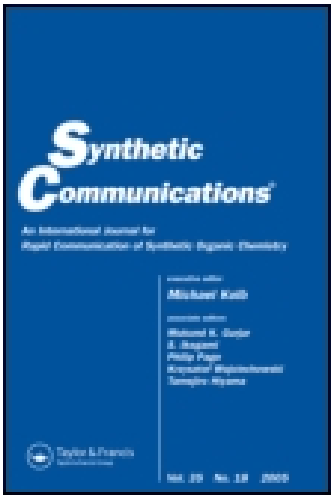

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Practical Synthesis of 4-Fluoro-2-(methylthio)benzylamine and the Corresponding Sulfone and Sulfonamide

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Practical Synthesis of 4-Fluoro-2-(methylthio)benzylamine and the Corresponding Sulfone and Sulfonamide

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Abstract: Practical syntheses of 4-fluoro-2-(methylthio)benzylamine 1 and the corresponding 2-methylsulfonyl analog **2** are reported. The methylthio moiety was introduced regioselectively by two methods. In the first method, metallation of 4-fluoro-2-bromobenzoic acid, followed by treatment with dimethyl disulfide resulted in an easily isolated intermediate, which was suitable for further elaboration to the benzylamine **1**. In the second method, selective nucleophilic aromatic substitution of 2,4-difluorobenzonitrile with methanethiolate was explored, and a mechanistic rationale was offered for solvent effects on regioselectivity. Optimized conditions furnished the key 4-fluoro-2-(methylthio)benzonitrile for further functionalization to the 2-methylsulfonyl-4-fluorobenzylamine **2**. In addition, the analogous sulfonamide 3 was prepared in a straightforward manner from 5-fluoro-2-methylbenzenesulfonyl chloride.

Keywords: lithiation, nucleophilic aromatic substitution, sulfonamide, sulfone, thiol

INTRODUCTION

In the course of our research on HIV-1 integrase inhibitors, we became interested in preparing 4-fluoro-2-(methylthio)benzylamine **1**, the corresponding sulfone **2**, and dimethylsulfonamide **3**.[1] Although 2-(methylthio)benzylamine and 2-methylsulfonylbenzylamine are commercially available, preparations of the 4-fluoro derivatives have not been reported in the literature.

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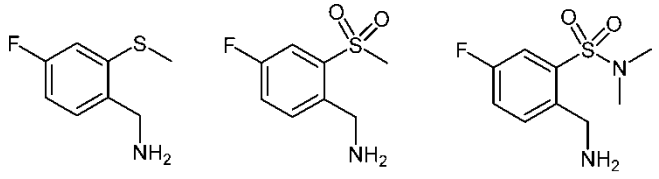
We report here two complementary approaches for preparation of **1** and **2** and an efficient synthesis of **3**.

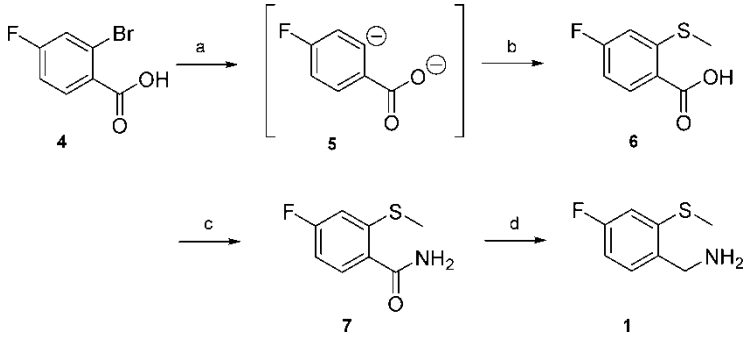


1 **2** **3**

RESULTS AND DISCUSSION

We proposed that reaction of the dianion **5** derived from commercially available 2-bromo-4-fluorobenzoic acid **4** with a CH_3S^+ synthon would provide the key 4-fluoro-2-(methylthio)benzoic acid intermediate **6**, which would be suitable for further elaboration to the corresponding benzylamine **1** (Scheme 1).[2] Indeed, successive treatment of 2-bromo-4-fluorobenzoic acid **4** with methylmagnesium chloride at 0°C in THF[3] followed by lithiation with *n*-butyllithium and addition of dimethyl disulfide at −78°C provided 4-fluoro-2-(methylthio)-benzoic acid **6** in 80% isolated yield (Scheme 1). Treatment of the acid **6** with ammonium chloride and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in the presence of 1-hydroxy-7-azabenzotriazole (HOAt) in DMF produced quantitatively the corresponding 4-fluoro-2-(methylthio)benzamide **7**. Lithium aluminum hydride reduction of the amide **7** in ether afforded the benzylamine **1** as a crystalline solid in an overall isolated yield of 63% from commercially available starting material **4** without the need for chromatography.

It appeared that we could prepare the sulfone **2** from the sulfide intermediate **7**. As such, amide **7** was oxidized to the corresponding 4-fluoro-2-(methylsulfonyl)benzamide with *m*-CPBA in methylene chloride. Although



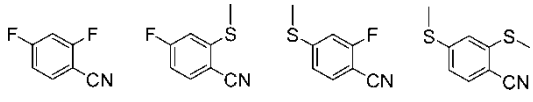
4 **5** **6** **7** **1**

Scheme 1. Reagents and conditions: a) MeMgCl (1.1 equiv), THF, 0°C; *n*-BuLi (2.2 equiv) −78°C; below −65°C, 1 h; b) CH_3SSCH_3 (6 equiv), −78°C, 10 min; 0°C 2 h; c) NH_4Cl (2 equiv), EDC (2 equiv), HOAt (2 equiv), Hunig's base (4 equiv), DMF, rt. 4 h; d) 6 suspended in ether, LAH, 0°C to rt.

it is well established that under appropriate conditions an amide could be selectively reduced to the corresponding amine in the presence of a sulfone functional group,[4] the crystalline 4-fluoro-2-(methylsulfonyl)-benzamide was found to be too insoluble in solvents amenable for reduction. To circumvent this problem, an alternative route was investigated. It was anticipated that regioselective nucleophilic displacement of the 2-fluoro group from the commercially available 2,4-difluorobenzonitrile **8** with methanethiolate would furnish the key 4-fluoro-2-(methylthio)benzonitrile **9** for further functionalization.[5] Reactions of 2-4-difluoro-benzonitrile (0.7 mmol) and sodium methanethiolate (1.0 equiv) in various solvents (0.35 M) under nitrogen in sealed tubes were set up in parallel. The reaction mixtures were stirred at room temperature for 16 h. The effects of different solvents on rate and regioselectivity of this substitution reaction are summarized in Table 1 as percentages of starting material remaining and products generated in the reaction mixtures.

In acetone, the product distribution between the 2-, 4-, and disubstituted products **9**, **10**, and **11** was in the ratio of ~2:1:0.1, respectively (Table 1, entry 1). In DMF, the selectivity between 2- and 4-substitution improved to a ratio of ~3:1, but the amount of disubstituted product **11** formed was more than that of the desired regioisomer **9** (entry 2). A slight exotherm was noted in the DMF and DMSO reactions. A similar distribution was seen with DMSO

Table 1. Effect of solvent and temperature on product distribution[a]



Entry	Solvent	Temp.	8	9	10	11
1	Acetone	rt	10 ± 1.5%*	61 ± 0.6%	26 ± 0.6%	3 ± 1.1%
2	DMF	rt	34 ± 3.2%	26 ± 4.2%	8 ± 1.0%	32 ± 1.7%
3	DMSO	rt	30 ± 2.3%	33 ± 4.0%	7 ± 0.6%	30 ± 2.3%
4	THF	rt	12 ± 1.0%	77 ± 0.0%	10 ± 0.6%	1 ± 0.0%
5	Toluene	rt	24 ± 3.5%	74 ± 3.0%	2 ± 0.6%	0 ± 0.0%
6	Toluene	60°C	9 ± 3.5%	89 ± 3.5%	2 ± 0.6%	0 ± 0.0%

[a]Product distribution was determined by integration of a reverse-phase HPLC chromatogram (UV absorbance at 215 uM) of filtered reaction mixtures. Toluene co-elutes with the di-substituted product and because the 2,4-difluorobenzonitrile **8** is volatile, analysis of reaction mixtures in Table 1, entries 5 and 6, was performed in two parts. HPLC of the filtered reaction gave the ratio of remaining starting material to desired product **9**. The toluene was then removed on a rotovap without heating and pumped on in vacuo, which also removed starting material **8**. HPLC of this residue showed the ratio of **9** to **10** and **11**. Normalizing each component to compound **9** gave the reported percentages. Identity of each component was confirmed by purification and ^{1}H NMR characterization. The ratios reported are averages of three independent experiments under the same conditions. These are further substantiated with ^{1}H NMR spectra of the crude product mixture from DMF.

(entry 3). With THF, a less polar solvent, selection for **9** versus **10** was about 8:1 but with no significant quantity of disubstituted product **11** generated (entry 4). With toluene, the least polar solvent in the study, selection for **9** versus **10** improved to 37:1, and no disubstituted product **11** was observed (entry 5). However, the rate of consumption of starting material was slower in toluene than in THF.

We reasoned that there is an intrinsic difference in energy associated with the transition states **12** and **13** that favors formation of the 2- *versus* the 4-substitution products, **9** and **10**, respectively, in polar, nonprotic solvents such as acetone, DMF, and DMSO (Fig. 1).[5] Nonpolar solvents such as THF and toluene may further bias against transition state **13** with charge separation. For the same reason, formation of disubstituted product **11** from 2-substituted **9** may be slower than that from 4-substituted **10** under these conditions. This could reinforce selectivity against formation of the disubstituted product **11** as observed when THF or toluene was used in the reaction. The reaction was further optimized using toluene as the solvent. Heating the reaction at 60°C resulted in most of the starting material being consumed after 16 h and further improvement in the product distribution for **9**, **10**, and **11** of 45:1:0. This reaction scaled well from 0.1 g to 5 g in a sealed flask.

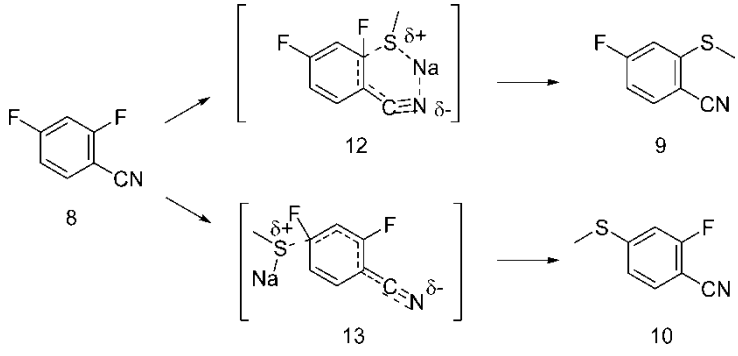
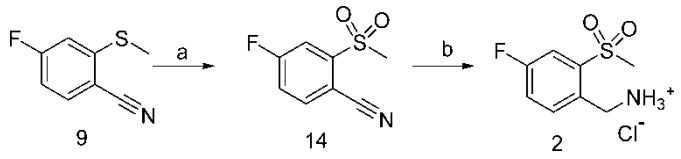


Figure 1. Mechanistic rationale for observed regioselectivity.

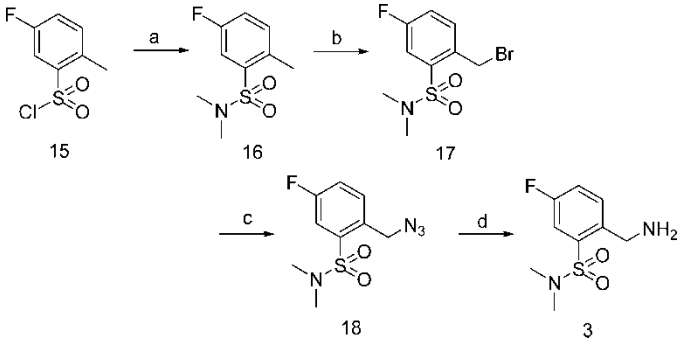
Oxidation of the 4-fluoro-2-(methylthio)benzonitrile **9** with *m*-chloroperoxybenzoic acid in methylene chloride at room temperature followed by purification via recrystallization from methanol gave 2-methylsulfonyl-4-fluorobenzonitrile **14** in 86% isolated yield (Scheme 2). The nitrile **14** was hydrogenated with 10% Pd/C in ethanolic hydrogen chloride to give 2-methylsulfonyl-4-fluorobenzylamine **2** as the hydrochloride salt, with an overall yield of **41**% in three steps from commercially available 2,4-difluorobenzonitrile **8**.

Scheme 3 outlines the preparation of sulfonamide **3**. Reaction of the commercially available 5-fluoro-2-methylbenzenesulfonyl chloride **15** with dimethylamine in THF provided the corresponding 5-fluoro-*N,N*,2-trimethylbenzenesulfonamide **16**. Sequential bromination of **16** with *N*-bromosuccinimide



Scheme 2. Reagents and conditions: a) MCPBA (2.2 equiv), CH_2Cl_2, rt, 16 h; b) H_2 (50 psi), EtOH–conc. HCl, 5 : 1 v/v, 10% Pd/C.

followed by conversion to the corresponding azide **17** and catalytic hydrogenation with 5% Pd/C in ethanol produced the required 1-(aminomethyl)-5-fluoro-*N,N*-dimethyl-benzenesulfonamide **3** as yellow oil with an overall yield of 34% from **15**.



Scheme 3. Reagents and conditions: a) excess dimethylamine gas, THF, rt, 1 h; b) NBS (1.1 equiv), CCl_4, 77°C, 16 h; c) sodium azide (2.5 equiv), DMF, rt, 1 h; d) H_2, 5% Pd/C, EtOH, rt, 1 h.

In summary, practical syntheses of 4-fluoro-2-(methylthio)benzylamine **1** and the corresponding 2-methylsulfonyl analog **2** were established. The methylthio moiety was introduced via either a regioselective lithiation or a selective nucleophilic aromatic substitution. The analogous sulfonamide **3** was prepared from 5-fluoro-2-methylbenzenesulfonyl chloride using standard chemical transformations.

EXPERIMENTAL

4-Fluoro-2-(methylthio)benzoic Acid (6)

To a cold (0°C) solution of 2-bromo-4-fluorobenzoic acid (**4**) (15.0 g, 68.5 mmol) in anhydrous THF (150 mL) under argon, a solution of methylmagnesium chloride (26 mL, 75.3 mmol, 2.9 M) in THF was added

over 5 min. The reaction temperature was maintained below 10°C throughout the addition. After the resulting solution was cooled to −78°C, a solution of *n*-butyllithium (60.3 mL, 150.7 mmol, 2.5 M) in hexanes was added over 10 min. The reaction temperature was kept below −65°C during the addition. The reaction mixture was stirred at −78°C for 1 h. Complete formation of the bis-anion was confirmed by quenching an aliquot in methanol, evaporating the mixture, partitioning the crude between acidic water and chloroform, and observing the NMR spectrum of the organic layer (^{1}H NMR 4-fluorobenzoic acid ($CDCl_3$, 400 MHz) δ 8.13 (m, 2H), 7.15 (t, $J = 8.6$ Hz, 2H)). A cold (−78°C) solution of dimethyl disulfide (38.7 g, 410.9 mmol) in anhydrous THF (20 mL) was added via cannula. The resulting mixture was stirred for 10 min, warmed to 0°C, and stirred for 2 h. The course of the reaction was followed by quenching aliquots in MeOH and observing the NMR ratio between 4-fluorobenzoic acid and the product. Warming the reaction to room temperature gave complete conversion. The salt of the product precipitated from the reaction and was collected by filtration. This solid was suspended in a mixture of ethyl acetate (400 mL) and water (400 mL) and acidified with 12 N HCl to pH < 1. The aqueous portion was separated and extracted with ethyl acetate (4 × 500 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to a small volume in vacuo. The desired product crystallized and was filtered and dried in vacuo to afford 10.2 g (80% yield) of the title compound.

^{1}H NMR (*d*-DMSO, 400 MHz) δ 7.98 (1H, dd, $J = 8.8$, 6.4 Hz), 7.15 (1H, d, $J = 10.8$ Hz), 7.05 (1H, dd, $J = 8.8$, 6.4 Hz), 2.41 (3H, bs) ppm. EI HRMS exact mass calcd. for $C_8H_7FO_2S$ 186.0151 (M); found 186.0151.

4-Fluoro-2-(methylthio)benzamide (7)

To a solution of 4-fluoro-2-(methylthio)benzoic acid (**6**) (8.1 g, 43.6 mmol) in degassed anhydrous DMF (100 mL) under nitrogen, ammonium chloride (4.7 g, 87.2 mmol), 1-hydroxy-7-azabenzotriazole (11.9 g, 87.2 mmol), *N*-[3-(dimethylamino)propyl]-*N*'-ethylcarbodiimide hydrochloride (16.7 g, 87.2 mmol), and *N,N,*-diisopropylethylamine (30.4 mL, 174.4 mmol) were added successively. The resultant mixture was stirred at rt for 4 h and concentrated under vacuum. The residual oil was partitioned between methylene chloride (800 mL) and 5% aqueous HCl (400 mL). The organic extract was washed with saturated aqueous sodium bicarbonate (400 mL) and then with brine (400 mL). The organic solution was dried over Na_2SO_4, filtered, and reduced to a small volume in vacuo. The resulting crystalline solids were filtered and dried in vacuo to afford 8.0 g (99% yield) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (1H, dd, $J = 8.4$, 5.9 Hz), 7.00 (1H, dd, $J = 9.9$, 2.4 Hz), 6.88 (1H, dd, $J = 8.4$, 2.4 Hz), 2.48 (3H, s) ppm.

APCI HRMS exact mass calcd. for C_8H_8FNOS 186.0783 (MH^+); found 186.0365.

4-Fluoro-2-(methylthio)benzylamine (1)

A solution of lithium aluminum hydride (199.2 mL, 1.0 M in diethyl ether) was added dropwise to a cold (0°C) suspension of 4-fluoro-2-(methylthio)benzamide (7) (12.3 g, 66.4 mmol) in anhydrous diethyl ether (500 mL) under nitrogen over 5 min. The reaction mixture was stirred at rt for 16 h. The product mixture was cooled to 0°C and treated successively with water (7.5 mL), 15% aqueous NaOH solution (7.5 mL), and water (23 mL). The suspension was filtered through a pad of Celite® and washed with diethyl ether. The filtrate was washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residual brown oil turned into a crystalline solid upon standing to afford 9.0 g (79% yield) of the title product.

^{1}H NMR (*d*-DMSO, 400 MHz) δ 7.43 (1H, t, $J = 7.0$ Hz), 7.03 (1H, dd, $J = 10.0$, 2.4 Hz), 6.94 (1H, ddd, $J = 8.8$, 6.4, 2.4 Hz), 3.64 (2H, s), 2.50 (3H, s) ppm. APCI HRMS exact mass calcd. for $C_8H_{10}FNS$ 172.0591 (MH^+); found 172.0566.

4-Fluoro-2-(methylthio)benzonitrile (9)

To a stirred suspension of sodium methanethiolate (2.54 g, 36 mmol) in anhydrous toluene (50 mL) under an atmosphere of nitrogen in a sealed flask (350 mL), a solution of 2,4-difluorobenzonitrile (**8**) (5.0 g, 36 mmol) in toluene (100 mL) was added by cannula. The flask was sealed, and the mixture was heated at 60°C for 16 h. The resulting reaction mixture was filtered and concentrated in vacuo, and the residue was partitioned between methylene chloride (400 mL) and water (400 mL). The organic extract was washed with brine (400 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residual solid was concentrated three times from acetonitrile and pumped on for 2 h in vacuo to remove the remaining starting material. The desired 4-fluoro-2-(methylthio)benzonitrile (4.3 g) was obtained in 71% yield. The resulting purity of the desired product was 97% by HPLC. Further purification at this scale was found to be more effective after oxidation to the corresponding sulfone (**10**).

Note: When this reaction was run in an unsealed vessel, we observed that the rate of reaction was significantly slower, although regioselectivity remained the same.

Compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (1H, dd, $J = 8.5$, 5.6 Hz), 6.95 (1H, dd, $J = 9.4$, 2.4 Hz), 6.88 (1H, dt, $J = 8.2$, 2.4 Hz), 2.54 (3H, s) ppm. EI HRMS exact mass calcd. for C_8H_6FNS 167.0203 (MH^+); found 167.0205.

Compound **10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (1H, dd, J = 8.2, 6.8 Hz), 7.03 (1H, dd, J= 8.4, 1.8 Hz), 6.97 (1H, dt, J = 8.2, 1.8 Hz), 2.50 (3H, s) ppm. Compound **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (1H, d, J = 8.2 Hz), 7.07 (1H, d, J = 1.7 Hz), 6.98 (1H, dd, J= 8.2, 1.7 Hz), 2.54 (3H, s), 2.50 (3H, s) ppm.

2-Methylsulfonyl-4-fluorobenzonitrile (14)

To a solution of the mixture of 4-fluoro-2-(methylthio)benzonitrile (**9**) and 2-fluoro-4-(methylthio)benzonitrile (**10**) (5.6 g, 33.5 mmol) in methylene chloride (50 mL), 3-chloroperoxybenzoic acid (19.3 g, 67.0 mmol, 60% by weight) was added. The reaction mixture was stirred at room temperature for 16 h. The organic extract was washed with saturated aqueous sodium bicarbonate solution (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Crystallization of the residue from methanol provided pure 2-methylsulfonyl-4-fluorobenzonitrile (**14**) as a white crystalline solid (5.6 g, 86% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (1H, dd, J = 8.5, 4.8 Hz), 7.90 (1H, dd, J = 7.7, 2.4 Hz), 7.45 (1H, ddd, J = 8.5, 7.2, 2.4 Hz), 3.28 (3H, s) ppm. EI HRMS exact mass calcd. for $C_8H_6FNSO_2$ 199.0103 (MH^+); found 199.0103.

4-Fluoro-2-(methylsulfonyl)benzylamine Hydrogen Chloride (2)

A mixture of 2-methylsulfonyl-4-fluorobenzonitrile (**14**) (5.6 g, 28.11 mmol), 10% Pd/C (1 g), and 12 N HCl (10 mL) in ethanol (50 mL) in a Parr vessel was shaken at rt under an atmosphere of hydrogen (50 psi) for 16 h. A ratio of 50:50 starting material to desired product was observed. The mixture was filtered through a bed of Celite® and concentrated slightly. Additional 10% Pd/C (1 g) and 12 N HCl (10 mL) were added, and the reaction was again put under H_2 (50 psi) and shaken for 16 h. The completed reaction was filtered through Celite® and concentrated to afford 3.8 g (67% yield) of the desired material as a white crystalline solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (1H, dd, J = 8.2, 2.7 Hz), 7.74 (1H, dd, J = 8.5, 5.0 Hz), 7.57 (1H, dt, J = 8.2, 2.7 Hz), 4.45 (2H, s), 3.27 (3H, s) ppm. EI HRMS exact mass calcd. for $C_8H_{10}FNO_2S$ 203.0410 (MH^+); found 203.0416. C, H, N calcd. for $C_8H_{10}FNO_2S$ 1.1 HCl C, 39.49%; H, 4.6%; N, 5.76%; found C, 39.50%; H, 4.34%; N, 5.56%.

5-Fluoro-*N,N*,2-trimethylbenzenesulfonamide (15)

A solution of 5-fluoro-2-methyl-benzenesulfonyl chloride **14** (5.0 g, 24.0 mmol, Lancaster) in THF (100 mL) was saturated with dimethylamine

gas and stirred at room temperature for 1 h. The ammonium chloride salts were removed by filtration, and the filtrate was concentrated under vacuum. The residual oil was subjected to column chromatography on silica gel (110 g), eluting with a gradient of 90% hexanes/10% ethyl to 75% hexanes/25% ethyl acetate over 40 min. Collection and concentration of appropriate fractions afforded 5.2 g (99% yield) of the desired material.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (1H, dd, $J = 8.6$, 2.8 Hz), 7.29 (1H, dd, $J = 8.4$, 2.8 Hz), 7.16 (1H, m), 2.93 (6H, s), and 2.59 (3H, s) ppm. LCMS calcd. for $C_9H_{12}FNO_2S$ 218.1 (MH^+); found 218.0.

2-(Bromomethyl)-5-fluoro-*N,N*-dimethylbenzenesulfonamide (16)

A mixture of 5-fluoro-*N,N*,2-trimethylbenzenesulfonamide (**15**) (5.2 g, 24.0 mmol) and *N*-bromosuccinimide (4.69 g, 26.4 mmol) in dry CCl_4 (100 mL) was refluxed overnight under nitrogen. After the reaction was allowed to cool to room temperature, the succinimide by-product was removed by filtration. The filtrate was concentrated, and the residue was subjected to column chromatography on silica gel (110 g), eluting with a gradient of 100% hexanes to 80% hexanes/20% ethyl acetate over 40 min. Collection and concentration of appropriate fractions afforded 4.3 g (60% yield) of desired product (**16**).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (2H, m), 7.31 (1H, m), 4.87 (2H, s), and 2.88 (6H, s) ppm. LCMS calcd. for $C_9H_{11}BrFNO_2S$ 297.1 (MH^+); found 297.0.

2-(Azidomethyl)-5-fluoro-*N,N*-dimethylbenzenesulfonamide (17)

A solution of 2-(bromomethyl)-5-fluoro-*N,N*-dimethylbenzenesulfonamide (**16**) and sodium azide (2.36 g, 36.3 mmol) in DMF (100 mL) was stirred at rt under nitrogen for 1 h. The product mixture was filtered, and the filtrate, was concentrated under vacuum. The residual brown oil was subjected to column chromatography on silica gel (110 g), eluting with a gradient of 100% hexanes to 80% hexanes/20% ethyl acetate over 40 min. Collection and concentration of appropriate fractions afforded the desired material (**17**).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (2H, m), 7.32 (1H, m), 4.79 (2H, s), and 2.85 (6H, s) ppm.

2-(Aminomethyl)-5-fluoro-*N,N*-dimethylbenzenesulfonamide (3)

A mixture of the 2-(azidomethyl)-5-fluoro-*N,N*-dimethylbenzenesulfonamide (3.57 g, 13.8 mmol) and 5% Pd/C (890 mg) in absolute ethanol (100 mL) was

stirred under a hydrogen gas balloon at rt for 1 h. The reaction mixture was filtered through a bed of Celite®. The filtrate was concentrated in vacuo to a yellow oil, which was subjected to preparative reverse-phase chromatography (Waters Deltapak, 3 serial (10 × 40-mm I.D.) column cartridges, C18, 15 μm pore size) eluting with 5–65% acetonitrile/water gradient (0.1% TFA at 30 mL/min) over 30 min. The appropriate fractions were collected and concentrated under vacuum. The residue was partitioned between ethyl acetate (100 mL) and 10% sodium bicarbonate (100 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 2.15 g (67% yield) of the desired product (**3**).

^{1}H NMR (*d*-DMSO, 400 MHz) δ 8.24 (2H, bs), 7.75 (2H, m), 7.67 (1H, dd, $J = 8.6$, 2.5 Hz), 4.34 (2H, s) and 2.78 (6H, s) ppm.

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