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Synthesis of isomeric fluoronitrobenzene-sulfonyl chlorides

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ABSTRACT

The synthesis of five hitherto unknown isomeric fluoronitrobenzenesulfonyl chlorides is described. The compounds are prepared from difluoronitrobenzenes by a two-step procedure. In the first step the starting compounds undergo a regioselective reaction with phenylmethanethiol giving rise to the corresponding thioethers. The oxidative cleavage of the latter with chlorine results in the sulfonyl chlorides in good yields. One example of a threefold sequential functionalization of 2-fluoro-6-nitrobenzenesulfonyl chloride showing the synthetic utility of the title compounds is provided.

1. Introduction

The synthesis of functional organic compounds for different applications largely relies on laborious approaches involving an extensive usage of protecting groups. Nowadays inventive chemoselective routes to the construction of complex molecules are becoming a better alternative because they shorten the length of multistep syntheses by excluding protecting groups and, as a consequence, lead to increased overall yields of the target compounds.[1] It is also of importance for both high-throughput chemistry and fragment-based drug design to have building blocks capable of consecutive linking of two or more fragments in chemically and stereochemically predefined manners.[2] In this context fluoronitrobenzenesulfonyl chlorides shown in Figure 1 are attractive building blocks. They contain three selectively addressable functional groups, which could be employed in a variety of synthetic transformations involving acylation, arylation, and nitro-group reduction with options for follow up chemistry. Despite the apparent synthetic potential of the fluoronitrobenzenesulfonyl chlorides their chemistry has been little explored. Up to the present the synthesis of only five (compounds **1**,[3] **2**,[3] **3**,[4] **6**,[5] and **9**[5]) out of ten possible isomers depicted in Figure 1 was described. Moreover, there are only a few reports showing the synthetic utility of the known fluoronitrobenzene-sulfonyl chlorides. For example, stepwise derivatizations of compound **3** were successfully used in the

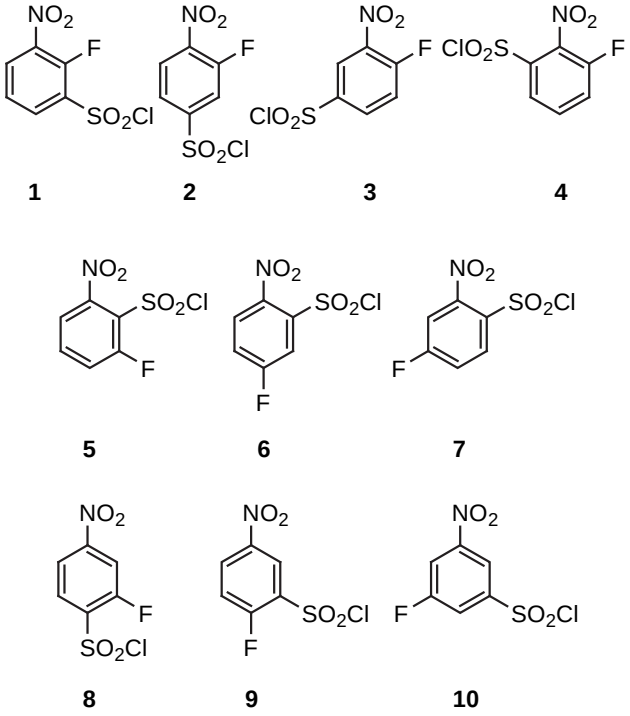

Figure 1. Constitutional isomers of fluoronitrobenzene-sulfonyl chloride.

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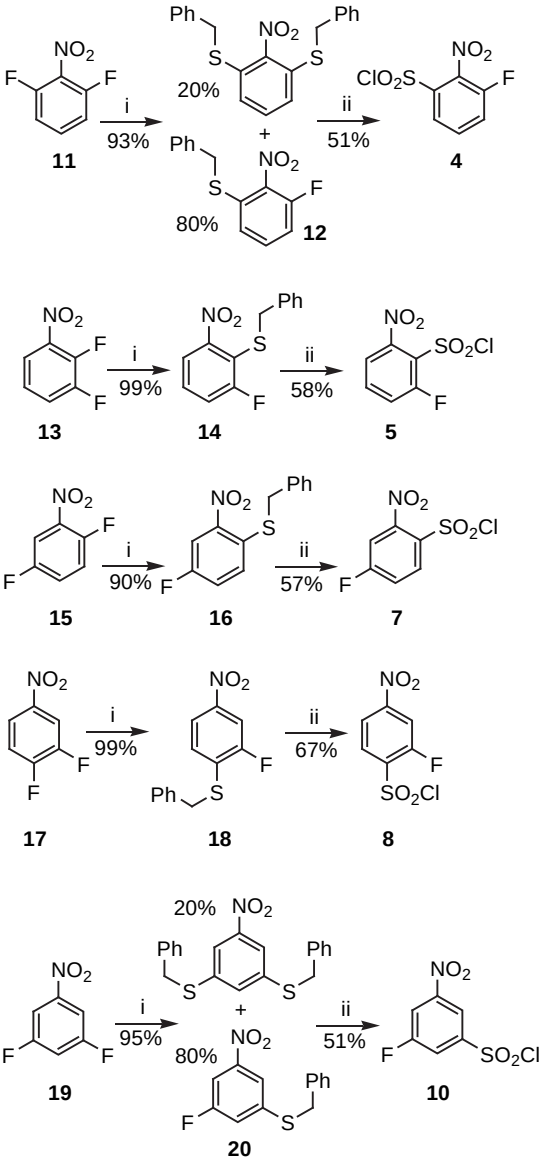
synthesis of biologically active compounds modulating protein/protein interactions,[6] lead compounds for potentiators of cancer chemotherapy,[7] and inhibitors of nuclear enzymes.[8] Compound **9** was shown to be a handy building block in the synthesis of drug-like substances[9] and some functionalized organofluorine species.[10] Many more ways to use the fluoronitrobenzenesulfonyl chlorides can be envisaged.

For example, since these are isomers they can be used for the preparation of isosteric sets of biologically potent compounds. Synthesis of new functional branched macromolecular assemblies, such as dendrimers and hyperbranched polymers is another perspective to use these compounds. For example, the fluoronitrobenzenesulfonyl chlorides can be employed as core units for attaching dendrons of up to three different types or, alternatively, they can be used as branching units in repetitive steps of reduction and sulfonylation in divergent synthesis of functionalized dendrimers (for structural examples see Ref. 11). Therefore, having the complete set of isomers (Fig. 1) available on a multi-gram scale would stimulate progress in medicinal chemistry and materials science. Given this synthetic potential it is of importance to develop methods for the preparation of new isomeric fluoronitrobenzenesulfonyl chlorides. It is also advantageous to simplify the synthesis of the existing isomers.

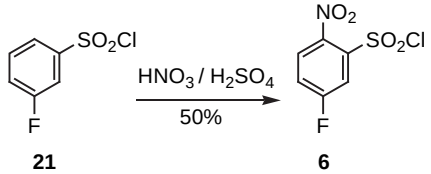
In this contribution we described the synthesis of five hitherto unknown isomeric fluoronitrobenzenesulfonyl chlorides and an optimized route to one previously reported structure. We also disclose one example of sequential transformations of the three functional groups demonstrating the synthetic utility of the title compounds.

2. Results and discussion

The synthesis of the five new isomeric fluoronitrobenzenesulfonyl chlorides is summarized in Scheme 1. The rationale for the selected synthetic strategy was as follows. First, the starting benzene derivatives must be readily accessible on a multi-gram scale. Second, to minimize number of synthetic steps the starting compounds should bear two functional groups, which are present in the product while the third group should be introduced in a most straightforward way. We considered several options to approach the target compounds: (i) electrophilic reactions including the sulfochlorination of nitrofluorobenzenes, and the nitration of fluorobenzenesulfonyl chlorides, (ii) nucleophilic reactions, such as displacements of nitro- and fluoro-groups in fluorodinitrobenzenes and difluoronitrobenzenes, respectively. From structural considerations of the target species in Scheme 1 the sulfochlorination with chlorosulfonic acid was discarded from the list because the nitro-group would prevent the electrophilic attack at the required positions. Although the nitration is a more aggressive electrophilic process it seemed of little use for the preparation of the new isomeric fluoronitrosulfonyl chlorides on account of an unfovarable *meta*-location of fluorine with regard to the nitro-group in compounds **5**, **7**, **8**, and **10**. A nitration of *m*-fluoronitrobenzenesulfonyl chloride **21** (Scheme 2) gave rise to the known 5-fluoro-2-nitrobenzenesulfonyl chloride **6**[5] while no traces of compound **4** were isolated. Notably, the nitration of **21** shown in Scheme 2 simplifies considerably the published five-step synthesis of **6**. Analysis of the literature shows that the nucleophilic aromatic displacement of the nitro-group with *S*-, *N*-, and *F*-nucleophiles occurs only in highly activated substances, such as trinitrobenzene and its derivatives.[12] Nucleophilic displacement of the fluorine also requires the presence of strong electron withdrawing groups in the aromatic ring. The widely used 1-fluoro-2,4-dinitrobenzene (Sanger reagent)[13] reacts with many nucleophiles in the presence of a base under very mild conditions. A simultaneous presence of nitro- and sulfo-groups in the fluoroaromatic ring is also known to activate the C_{ar}–F bond.[6,14] Our attention was drawn by a recent report[14] in which a selective nucleophilic displacement of one fluorine in a resin-bound 4,5-difluoro-2-nitrobenzamide with an *S*-nucleophile was described. The ability of the nitro-group to selectively activate one out of the two C_{ar}–F bonds in the aromatic ring prompted us to investigate nucleophilic displacement of the fluorine in readily available difluoronitrobenzenes. As illustrated in Scheme 1, the treatment of a difluoronitrobenzene with an equimolar amount of phenylmethanethiol in the presence of potassium carbonate leads to a clean regioselective substitution of one fluorine. Only in the case of com-



Scheme 1. Synthesis of new isomeric fluoronitrobenzenesulfonyl chlorides. Reagents and conditions: (i) phenylmethanethiol, K_2CO_3, DMF; (ii) Cl_2, H_2O, 5 °C.

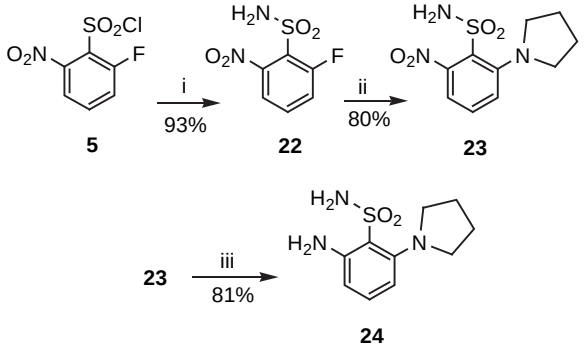


Scheme 2. A simplified route to fluoronitrosulfonyl chloride **6**.

pounds **11** and **19** partial disubstitution took place. The latter observation can be explained by the fact that introduction of one thioether unit into **11** and **19** increases electron density in *ortho*- and *para*-positions while *meta*-located CF groups remain largely unaffected. Consequently, intermediates **12** and **20** compete to some degree with their parent difluoronitrobenzenes in the nucleophilic substitution of fluorine.

However, as will be shown below the latter mixtures can be used in the following synthetic step without purification. The obtained fluoronitrophenylbenzylthioether intermediates can undergo oxidative cleavage with chlorine resulting in the corresponding sulfonyl chlorides. However, the use of glacial acetic acid as solvent in the available experimental procedure[15] was not suitable for our purpose on account of the poor solubility of the obtained thioethers. We have found that saturating a rigorously stirred emulsion consisting of equal volumes of water and a dichloromethane solution of a thioether with chlorine readily gives the desired sulfonyl chloride. The latter is isolated by extraction. Although, thioethers **12** and **20** used for the preparation of sulfonyl chlorides **4** and **10**, respectively, were contaminated by 20% with the disubstituted byproducts, the raw sulfonyl chlorides were successfully purified by distillation in vacuum. The compounds can be additionally purified by recrystallization from hexane. The structure and the high purity of the new isomeric fluoronitrobenzenesulfonyl chlorides were confirmed by means of ^{1}H, ^{13}C, and ^{19}F NMR, LC/MS, and elemental analysis.

To illustrate the synthetic utility of the new compounds a threefold sequential chemoselective functional group transformation of compound **5** was undertaken. As shown in Scheme 3, in the first step the chlorosulfo-group of **5** readily reacts with aqueous ammonia giving rise to the corresponding sulfonamide **22**. The latter undergoes substitution of the fluorine by the reaction with pyrrolidine in refluxed ethanol producing aminosulfonamide **23**. Finally, the nitro-group of the compound **23** is reduced yielding aniline **24** that can undergo a variety of further synthetic transformations.



Scheme 3. Reagents and conditions: (i) aqueous ammonia, dioxane, room temperature; (ii) pyrrolidine, ethanol, reflux; (iii) iron powder, ammonium chloride, ethanol/water, reflux.

3. Conclusions

To conclude, we have developed a convenient synthetic procedure for a multi-gram scale preparation of six isomeric fluoronitrobenzene-sulfonyl chlorides of which five have not been described before. We have also shown that the three functional groups in these compounds can be addressed consecutively with no need for protecting groups exemplifying their synthetic potential for many applications. Presently our attention is focused on the preparation of other halonitrobenzenesulfonyl chlorides that could be employed in a metal-mediated cross-coupling chemistry.

4. Experimental details

4.1. General

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker Avance DRX 500 spectrometer with TMS as an internal standard. Melting points were measured with a Büchi melting point apparatus. HPLC-MS analyses were done on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)). IR spectra were recorded on a Perkin–Elmer Spectrum BX II FT-IR spectrometer. Difluoronitrobenzenes **11**, **15**, **17**, and **19** were purchased from commercial sources. 2,3-Difluoronitrobenzene **13** was prepared from commercially available 2,3-difluoroaniline by the published procedure.[16]

*4.1.1. 3-Fluoro-2-nitrobenzenesulfonyl chloride (**4**).* To a solution of 1,3-difluoro-2-nitrobenzene **11** (30 g, 189 mM) in DMF (200 mL) potassium carbonate (27.6 g, 200 mM) was added. Then to the stirred mixture phenylmethanethiol (23.4 g, 189 mM) was added dropwise. During the addition the temperature of the reaction mixture was kept below 20 °C. Upon the addition the reaction mixture was allowed to stir for 2 h at room temperature. Then the mixture was filtered and the filtrate was evaporated to give red oil in a yield of 46 g (93%). The ^{1}H NMR analysis of the crude product revealed that the target thioether **12** was contaminated by ca. 20% of the disubstituted byproduct. This mixture was dissolved in 200 mL of dichloromethane. To the solution deionized water (200 mL) was added. The chlorine was bubbled slowly into the stirred reaction mixture. The reaction course was monitored by TLC. The organic layer of the resulting mixture was separated and washed with a saturated water solution of $Na_2S_2O_3$. The organic layer was dried over $MgSO_4$ and evaporated in vacuum to give a viscous residue. The residue was subjected to a vacuum distillation giving rise to 21 g (51%) of **4** that crystallized upon standing. Yellowish crystals; mp 51–52 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (m, 1H, Ar–H_{para}), 7.83–7.87 (m, 1H, Ar–H_{meta}), 8.03 (d, 1H, $^{3}J_{H,H}$=7.5 Hz, Ar–H_{ortho}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.9 (s, *C*H–C–S), 125.0 (s, *C*H–CH–C–S), 125.1 (d, $^{2}J_{C,F}$=4 Hz, *C*H–C–F), 132.9 (d, $^{2}J_{C,F}$=8 Hz, *C*–N), 136.0 (*C*-S), 153.8 (d, $^{1}J_{C,F}$=263 Hz, *C*-F); ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.23; IR: 3106 (CH), 1549 (NO_2), 1266, 1179 (SO_2) cm^{-1}; elemental analysis: calcd for $C_6H_3ClFNO_4S$: C, 30.08; H, 1.26; Cl, 14.80; N, 5.85; S, 13.38. Found: C, 30.18; H, 1.20; Cl, 14.66; N, 5.67; S, 13.53.

*4.1.2. 2-Fluoro-6-nitrobenzenesulfonyl chloride (**5**).* The reaction conditions for the first step are identical with those used for the preparation of **4**. 30.4 g (190 mM) of 1,2-difluoro-3-nitrobenzene **13**, 200 mL of DMF, 27.6 g (200 mM) of potassium carbonate, and 23.6 g (190 mM) of phenylmethanethiol were used in the reaction. The yield of the target 2-(benzylsulfanyl)-1-fluoro-3-nitrobenzene **14** was 50.6 g (99%). No traces of a disubstitution product were detected by NMR and LC/MS. Brownish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (s, 2H, Ph–CH_2), 7.21–7.28 (m, 6H, Ar–*H*), 7.32–7.37 (m, 1H, Ar–*H*), 7.49 (d, $^{3}J_{H,H}$=7.5 Hz, 1H, Ar–$H_{ortho\text{-}NO2}$,); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.5 (d, $^{4}J_{C,F}$=8 Hz, *C*H_2), 118.5 (d, $^{2}J_{C,F}$=23 Hz, *C*-S), 119.5 (d, $^{2}J_{C,F}$=25 Hz, *C*H–C–F), 120.7 (d, $^{4}J_{C,F}$=4 Hz, *C*H–C–N), 127.6, 128.6, 129.0, 129.4 (d, $^{3}J_{C,F}$=9 Hz, *C*H–CH–C–F), 136.4 (s, *C*–N), 162.8 (d, $^{1}J_{C,F}$=250 Hz, *C*–F); ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.48; MS (EI): m/z (%)=263.0 (100) $[M]^{+}$. To a solution of **14** (50 g, 190 mM) in dichloromethane (200 mL) deionized water (200 mL) was added. The chlorine was bubbled slowly into the stirred reaction mixture. The reaction course was monitored by TLC. The organic layer of the mixture was separated and washed with a saturated water solution of $Na_2S_2O_3$. Upon drying over $MgSO_4$ the solvent was removed under reduced pressure. The viscous colorless residue crystallized upon standing. The crude product was transferred into a glass filter, washed with ethanol (25 mL), and dried in vacuum. Yield 27 g (58%); colorless crystals, mp 91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, $^{3}J_{H,H}$=7.5 Hz, Ar–$H_{ortho\text{-}NO2}$), 7.60 (d, 1H, $^{3}J_{H,H}$=7.5 Hz, Ar–$H_{meta\text{-}NO2}$), 7.92–7.96 (m, 1H, Ar–$H_{para\text{-}NO2}$); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 119.8 (d, $^4J_{C,F}$=4 Hz, *C*H–C–N), 121.3 (d, $^2J_{C,F}$=23 Hz, *C*–S), 124.2 (d, $^2J_{C,F}$=15 Hz, *C*H–C–F), 138.2 (d, $^3J_{C,F}$=10 Hz, *C*H–CH–C-F), 148.53 (s, *C*–N), 159.1 (d, $^1J_{C,F}$=269 Hz, *C*–F); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.38; elemental analysis: calcd for $C_6H_3ClFNO_4S$: C, 30.08; H, 1.26; Cl, 14.80; N, 5.85; S, 13.38. Found: C, 30.33; H, 1.14; Cl, 14.61; N, 6.07; S, 13.41.

*4.1.3. 5-Fluoro-2-nitrobenzenesulfonyl chloride (**6**).* A stirred mixture of a concentrated nitric acid (13 mL, ρ=1.5 g/mL) and a concentrated sulfuric acid (26 mL, ρ=1.83 g/mL) was cooled on an ice bath below 5 °C. Then to the stirred mixture 3-fluorobenzenesulfonyl chloride (9.75 g, 50 mM) was carefully added over a 30 min period keeping the temperature of the reaction mixture below 5 °C. Upon the addition the reaction mixture was allowed to stir for 2 h at 0–5 °C and then for 4 h at room temperature. The reaction mixture was carefully poured onto ice (ca. 200 g) and extracted with diethyl ether (3×100 mL). The joined organic layers were washed with water and dried over Na_2SO_4. Then the solvent was removed under reduced pressure and the crude product was recrystallized from hexane to give 6 g (50%) of **6**. The analytical data of **6** are in full agreement with the published ones.[5] ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.74 ppm.

*4.1.4. 4-Fluoro-2-nitrobenzenesulfonyl chloride (**7**).* The reaction conditions for the first step are identical with those used for the preparation of **4**. 5 g (31 mM) of 1,4-difluoro-2-nitrobenzene **15**, 50 mL of DMF, 8 g (58 mM) of potassium carbonate, and 3.9 g (31 mM) of phenylmethanethiol were used in the reaction. The yield of the 1-(benzylsulfanyl)-4-fluoro-2-nitrobenzene **16** was 7.4 g (90%). No traces of a disubstitution product were detected by NMR and LC/MS. Yellowish crystalline solid; mp 104 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.37 (s, 2H, Ph–CH_2), 7.29–7.43 (m, 5H, Ar–*H*), 7.67–7.68 (m, 1H, Ar–*H*), 7.77–7.79 (m, 1H, Ar–*H*), 8.08 (d, $^3J_{C,F}$=5 Hz, 1H, Ar–$H_{ortho\text{-}NO2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.9 (CH_2), 113.4 (d, $^2J_{C,F}$=27 Hz, *C*H–C–N), 122.3 (d, $^2J_{C,F}$=22 Hz, *C*H–C–F), 128.0, 129.1 (s, *C*–S), 129.7, 130.6 (d, $^3J_{C,F}$=6 Hz, *C*H–C–S), 132.2, 136.1, 145.7 (d, $^3J_{C,F}$=9 Hz, *C*–N), 159.3 (d, $^1J_{C,F}$=246 Hz, *C*–F); ^{19}F NMR (376 MHz, DMSO-d_6) δ −102.69; elemental analysis: calcd for $C_{13}H_{10}FNO_2S$: C, 59.30; H, 3.83; N, 5.32; S, 12.18. Found: C, 59.32; H, 3.75; N, 5.19; S, 12.34. Compound **16** (59.5 g) was dissolved in dichloromethane (500 mL). Deionized water (300 mL) was added to the solution. The chlorine was bubbled slowly into the stirred reaction mixture. The reaction course was monitored by TLC. The organic layer of the mixture was separated and washed with a saturated water solution of $Na_2S_2O_3$. Upon drying over $MgSO_4$ the solvent was removed under reduced pressure and the residue was distilled at 2 mm collecting the fraction with bp 150–155 °C. The liquid product obtained in a yield of 31 g (57%) crystallized upon standing. Yellow crystals; mp 45–47 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.65 (m, 2H, Ar–*H*), 8.32 (m, 1H, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 113.8 (d, $^2J_{C,F}$=28 Hz, *C*H–C–N), 120.1 (d, $^2J_{C,F}$=22 Hz, *C*H–C–F), 132.1 (d, $^4J_{C,F}$=4 Hz, *C*–S), 133.4 (d, $^3J_{C,F}$=10 Hz, *C*H–C–S), 143.8 (*C*–N), 166.0 (d, $^1J_{C,F}$=266 Hz, *C*–F); ^{19}F NMR (376 MHz, $CDCl_3$) δ −95.99; elemental analysis: calcd for $C_6H_3ClFNO_4S$: C, 30.08; H, 1.26; Cl, 14.80; N, 5.85; S, 13.38. Found: C, 30.18; H, 1.20; Cl, 14.66; N, 5.67; S, 13.53.

*4.1.5. 2-Fluoro-4-nitrobenzenesulfonyl chloride (**8**).* The conditions of the reaction of 1,2-difluoro-4-nitrobenzene **17** with phenylmethanethiol are analogous to those used to prepare **4** and **7**. 30.5 g (191 mM) of **17**, 200 mL of DMF, 55.2 g (400 mM) of potassium carbonate, and 23.8 g (191 mM) of phenylmethanethiol were used in the reaction to yield 50.4 g (99%) of **18**. No traces of a disubstitution product were detected by NMR and LC/MS. Yellowish crystalline solid; mp 126 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.46 (s, 2H, Ph–CH_2), 7.28 (t, $^3J_{H,H}$=7.5 Hz, 1H, Ar–*H*), 7.33–7.36 (m, 3H, Ar–*H*), 7.46 (d, $^3J_{H,H}$=7.5 Hz, 2H), 7.69–7.72 (m, 1H), 8.04–8.08 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.29; elemental analysis: Calcd for $C_{13}H_{10}FNO_2S$: C, 59.30; H, 3.83; N, 5.32; S, 12.18. Found: C, 59.06; H, 3.68; N, 5.15; S, 12.29. Compound **18** ((50.4 g, 192 mM)) was suspended in formic acid (400 mL). The chlorine was bubbled slowly into the stirred suspension. The reaction course was monitored by TLC taking small portions of the reaction mixture into water and extracting with chloroform. Then the reaction mixture was poured into 2 L of deionized water and extracted with chloroform. The organic layer was separated, washed with water, and saturated water solutions of $Na_2S_2O_3$ and Na_2CO_3. Upon drying over $MgSO_4$ the chloroform was removed under reduced pressure and the crude product distilled at 2 mm (bp 145–152 °C). The liquid product crystallized upon standing affording 24.4 g (67%) of **8** as a yellow crystalline solid. Mp 70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23–8.29 (m, 3H, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.2 (d, $^2J_{C,F}$=26 Hz, *C*H–C–F), 119.8 (s, *C*H–C–N), 133.4 (d, $^3J_{C,F}$=5 Hz), 130.8 (s, *C*H–C–S), 136.6 (d, $^2J_{C,F}$=13 Hz, *C*–S), 152.7 (d, $^3J_{C,F}$=9 Hz, *C*–N), 158.6 (d, $^1J_{C,F}$=267 Hz, *C*–F); ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.49; elemental analysis: Calcd for $C_6H_3ClFNO_4S$: C, 30.08; H, 1.26; Cl, 14.80; N, 5.85; S 13.38. Found C, 29.87; H, 1.40; Cl, 14.70; N, 5.61; S, 13.33.

*4.1.6. 3-Fluoro-5-nitrobenzenesulfonyl chloride (**10**).* The conditions of the reaction of 1,3-difluoro-5-nitrobenzene **19** with phenylmethanethiol are analogous to those used to prepare **4**, **7**, and **8**. 51 g of **19**, 300 mL of DMF, 69.5 g of potassium carbonate, and 39.8 g of phenylmethanethiol were used in the reaction. The crude product was isolated in the form of yellow oil. According to its ^{1}H and ^{19}F NMR spectra it contained ca. 20% of a disubstituted byproduct. The crude product was used in the next step without purification. The crude **20** (166 g, 630 mM) was dissolved in methylene chloride (200 mL). To the solution deionized water (200 mL) was added. The chlorine was bubbled slowly into the stirred reaction mixture. The reaction course was monitored by TLC. The organic layer of the mixture was separated and washed with a saturated water solution of $Na_2S_2O_3$. Upon drying over $MgSO_4$ the solvent was removed under reduced pressure and the residue was distilled at 2 mm. A fraction with bp 136–138 °C was collected in a yield of 76 g (51%). Yellow oil crystallized upon standing. Mp 46 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12–8.14 (m, 1H), 8.35–8.36 (m, 1H), 8.7 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 117.9 (d, $^2J_{C,F}$=27 Hz, F–C–CH–C–N), 118.2 (d, $^4J_{C,F}$=6 Hz, N–CH–C–S), 120.3 (d, $^2J_{C,F}$=26 Hz, F–C–CH–C–S), 146.4 (d, $^3J_{C,F}$=7 Hz, *C*–S), 149.5 (d, $^3J_{C,F}$=5 Hz, *C*–N), 162.2 (d, $^1J_{C,F}$=260 Hz, *C*–F); ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.93; IR: 3104, 3092 (CH), 1546 (NO_2), 1254, 1172 (SO_2) cm^{-1}; elemental analysis: calcd for $C_6H_3ClFNO_4S$: C, 30.08; H, 1.26; Cl, 14.80; N, 5.85; S, 13.38. Found: C, 30.12; H, 1.16; Cl, 14.68; N, 5.63; S, 13.57.

*4.1.7. 2-Fluoro-6-nitrobenzenesulfonamide (**22**).* 2-Fluoro-6-nitrobenzenesulfonyl chloride (**5**) (10 g, 42 mM) was dissolved in dioxane (50 mL). Concentrated aqueous ammonia solution (20 mL) was added dropwise to the stirred solution of **5** at 0 °C. The reaction mixture was allowed to stir for 2 h slowly reaching room temperature. Then the solvent was removed under reduced pressure and the solid residue was triturated with deionized water (50 mL) and filtered affording upon drying 8.5 g (93%) of **22**. Colorless crystalline solid; mp 164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.75 (m, 2H, Ar–*H*), 7.84–7.88 (m, 1H, Ar–*H*), 8.29 (s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 119.9 (d, $^4J_{C,F}$=4 Hz, *C*H–C–N), 120.7 (d, $^2J_{C,F}$=23 Hz, *C*H–C–F), 124.5 (d, $^3J_{C,F}$=8 Hz, *C*H–CH–C–F), 136.6 (d, $^2J_{C,F}$=10 Hz, *C*-S), 148.8 (s, *C*-N), 158.5 (d, $^1J_{C,F}$=257 Hz, *C*–F); elemental analysis: calcd for $C_6H_5FN_2O_4S$: C, 32.73; H, 2.29; N, 12.72; S, 14.56. Found: C, 32.58; H, 2.20; N, 12.54; S, 14.74.

*4.1.8. 2-Nitro-6-pyrrolidin-1-ylbenzenesulfonamide (**23**).* Compound **22** (6.7 g, 30 mM) and pyrrolidine (5 g, 70 mM) were dissolved in ethanol (50 mL). The mixture was refluxed for 5 h and then the solvent was removed under reduced pressure. The residue was triturated

with water (50 mL) and the precipitated reddish crystalline solid was filtered and dried in vacuum. Yield 6.6 g (80%); mp 152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (m, 4H, NCH_2–CH_2), 3.41 (m, 4H, N–CH_2), 7.21–7.23 (m, 2H), 7.26–7.43 (br 2H, NH_2), 7.47 (t,$^3J_{H,H}$=7 Hz, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.6, 53.4, 114.5, 122.7, 123.5, 132.2, 150.8, 152.6; elemental analysis: calcd for $C_{10}H_{13}N_3O_4S$: C, 44.27; H, 4.83; N, 15.49; S, 11.82. Found: C, 44.05; H, 4.88; N, 15.25; S, 11.82.

*4.1.9. 2-Amino-6-pyrrolidin-1-ylbenzenesulfonamide (**24**).* To a solution of compound **23** (0.5 g, 1.8 mmol) in 95% ethanol (20 mL) iron powder (0.5 g, 9 mmol) and ammonium chloride (0.5 g, 9 mmol) were added. The reaction mixture was stirred for 1 h at reflux. The stirred mixture was allowed to cool down to room temperature and then sodium carbonate (2 g) and activated charcoal (2 g) were added. Upon filtration the solvent was removed under reduced pressure and the crude product was crystallized from ethanol/water affording 0.35 g (81%) of the target amine. Mp 146 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.87 (br s, **4** H, NCH_2–CH_2), 3.35 (br s, 4H, N–CH_2), 6.20 (s, 2H, Ar–NH_2) 6.63 (m, 2H, Ar–H), 7.05 (s. 2H, S–NH_2), 7.16 (br s, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 54.9, 111.3, 114.9, 122.3, 132.8, 147.6, 151.6; elemental analysis: calcd for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.41; S, 13.29. Found: C, 49.65; H, 6.51; N, 17.29; S, 13.43.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.036.

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