Nitro-Sulfinate Reductive Coupling to Access (Hetero)aryl Sulfonamides

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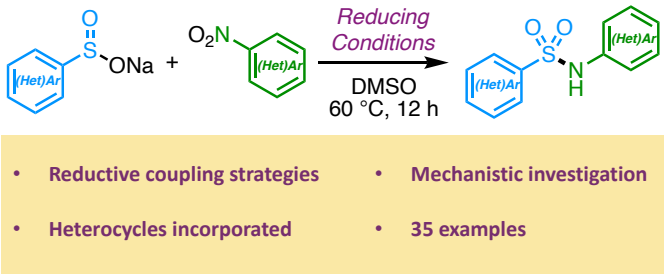
ABSTRACT: A method to assemble (hetero)aryl sulfonamides *via* the reductive coupling of aryl sulfinates and nitroarenes is reported. Various reducing conditions with sodium bisulfite and with or without tin(II) chloride in DMSO were developed using an ultrasound bath to improve reaction homogeneity and mixing. A range of (hetero)aryl sulfonamides bearing a selection of functional groups were prepared and the mechanism of the transformation was investigated. These investigations have led us to propose the formation of nitrosoarene intermediates, which were established *via* an independent molecular coupling strategy.



Introduction. Aryl sulfonamides, and particularly their heteroaryl counterparts, feature commonly in active pharmaceutical ingredients (APIs) and agrochemical agents.[1] Their importance is exhibited in compounds such as those used in the treatment of human immunodeficiency viruses (Tipranavir), rheumatoid arthritis (Sulfasalazine), high blood pressure (Bosentan), bacterial infections (Sulfamethazole) and cancer (Dabrafenib) among others (Figure 1).[1b] In spite of their noticeable absence in natural products,[2] sulfonamides were reported in 2018 to be present in over 8% of all APIs, largely due to their advantageous properties pertaining to metabolic stability, improved physicochemical characteristics and even their tendency to form crystalline solids, which aids work-up.[3] As a consequence, numerous methods for the synthesis of sulfonamides have emerged over the years,[4] yet even the most common and versatile procedures – such as the base promoted coupling of sulfonyl chlorides with amines[4v] – is not without challenges. These can include reactivity issues with electron-withdrawn (hetero)arylamines, functional group incompatibilities, solubility issues and instability in either component, and even high toxicity of the coupling partners.[3,4v,5] Furthermore, the chemical space accessible using this approach is limited by the lack of commercially available sulfonyl chlorides and routes to prepare them, in particular their alkyl, alkenyl and heteroaryl counterparts.[4a,g,6]

For these reasons, synthetic chemists have expanded the tools available for the assembly of these useful entities. Indeed, an alternative S-N bond-forming strategy that has emerged is nitro-sulfinate reductive coupling (Scheme 1). This approach involves the direct coupling of nitroarenes and (typically) aryl sulfinates under reducing conditions.[7] By employing a reductive coupling of

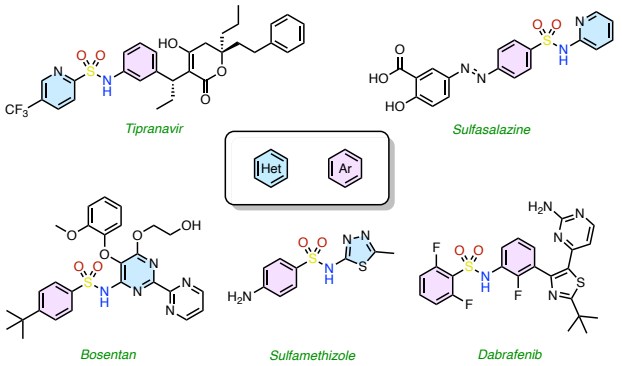
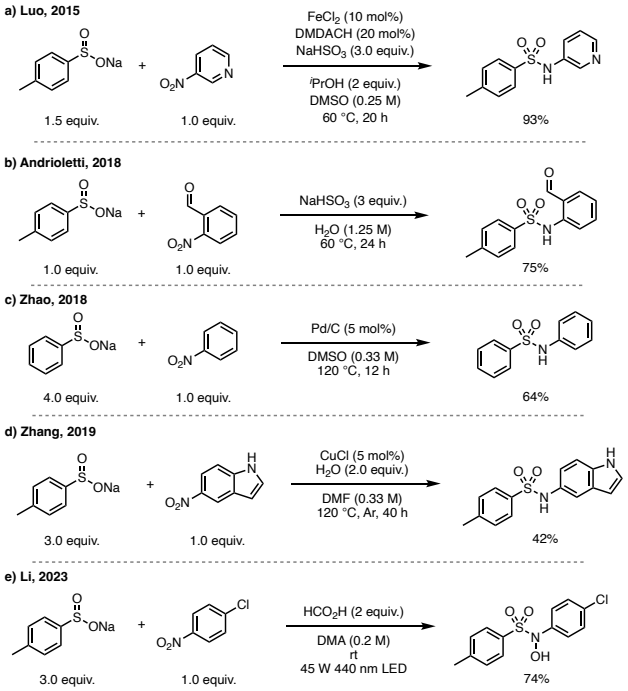


Figure 1. Drugs containing (hetero)aryl sulfonamides.

otherwise mutually inert, readily available functional groups, there are opportunities to overcome some of the limitations associated with other sulfonamide preparations. Furthermore, nitroarenes and sodium sulfinate salts are widely available and/or readily preparable, are typically stable solids and are among the most common intermediates.[8] Direct coupling of these fragments bypasses the need to first prepare mutually reactive intermediates. Despite these potential advantages, nitro-sulfinate reductive couplings have so far shown practical limitations by requiring heat and/or transition metal catalysts, large stoichiometric excesses of one coupling partner and functional group limitations, in particular with respect to aromatic heterocycles.[7] Indeed, previous methods are limited to 2- or 3-nitropyridines and indoles as nitroheteroarene substrates.[7a,c,e,f,h]

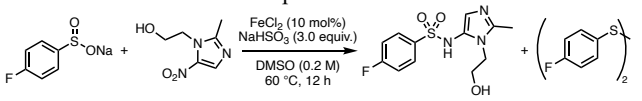


Scheme 1a-e. Previously reported nitro-sulfinate reductive coupling strategies as alternative S-N bond-forming reactions.

Aware of these limitations, we became interested in this area and in particular the work of Luo in 2015, who showed that aryl sulfinates could be coupled with readily available nitroarenes to give the corresponding sulfonamides under reducing conditions in the presence of a catalytic quantity of $FeCl_2$ and a diamine ligand.[7a] Here we report the development of new procedures facilitating the preparation of (hetero)aromatic sulfonamide compounds of pharmaceutical relevance.

Results and Discussion. To begin our work, a reaction optimization study was conducted using sodium 4-fluorobenzenesulfinate (**1a**) and nitroimidazole **2a** as coupling partners under the original Luo conditions (Table 1).[7a] The reaction proved to be capricious and failed to deliver the desired sulfonamide **3a** reliably (entry 1). However, variations on the procedure proved interesting. Without the addition of $FeCl_2$, the reaction gave **3a** in 62% yield by ^{19}F NMR (entry 2). It was also observed that 21% of **1a** was converted to homocoupling by-product **4a**. The further removal of half the sodium bisulfite led to a reduced 35% conversion of **2a** to **3a** and also a reduction in the formation of **4a** (entry 3). Increasing the excess of sodium bisulfite to 4.5 equivalents then produced **3a** in essentially quantitative conversion, with 17% of **1a** converted to **4a** (entry 4). Interestingly, removing $FeCl_2$ and exchanging $NaHSO_3$ for $SnCl_2$ also produced **3a** in 34% yield (entry 5), though unreacted *N*-sulfonyl hydroxylamine intermediate was observed.

Table 1. Reaction condition optimization.

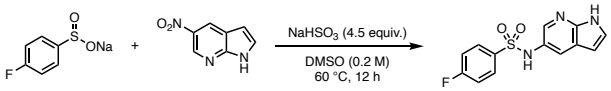


entry	deviation from conditions	conversion 2a to 3a (%)[a]	conversion 1a to 4a (%)[a]
1	none	50	21
2	No $FeCl_2$	62	21
3	No $FeCl_2$, 1.5 equiv. $NaHSO_3$	35	13
4	No $FeCl_2$, 4.5 equiv. $NaHSO_3$	Quant.	17
5	No $FeCl_2$ 3.0 equiv. $SnCl_2$ instead of $NaHSO_3$	34[b]	0

Reaction conditions: 0.2 mmol, 2.0 equiv. sodium 4-fluorobenzenesulfinate (**1a**), 1.0 equiv. metronidazole (**2a**), 3.0 equiv. sodium bisulfite, 10 mol% $FeCl_2$ in 1 mL DMSO (0.2 M). [a]Conversion determined using ^{19}F NMR and an internal standard. [b]Unconverted *N*-sulfonyl hydroxylamine intermediate observed.

With these new conditions in hand, the reaction was repeated on a 0.5 mmol scale. Unexpectedly, gelling of the reaction mixture was observed to such an extent that the reaction mixture ceased to stir effectively. This created reproducibility issues between the 0.2 mmol and 0.5 mmol scale reactions. Recognising that this mass-transfer problem could be even more significant on ever larger scales, we decided to investigate alternative methods of stirring the reaction mixture to improve reaction homogeneity. This approach was adopted instead of simply diluting the reaction mixture further owing to product isolation difficulties from large volumes of DMSO.

Table 2. Investigating alternative modes of mixing.



entry	stirring method	scale (mmol)	conversion to 3b (%)
1	Conical stirring bar (800 rpm)	0.2	Quant.
2	Conical stirring bar (1100 rpm)	0.5	30%
3	Eppendorf Thermo-Mixer	0.5	63%
4	Ultrasonic Bath	0.5	70%

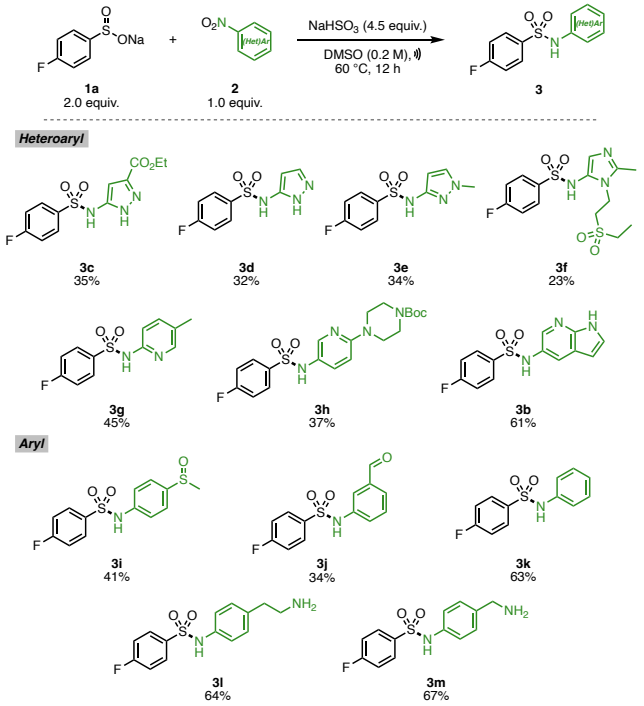
Reaction conditions: 2.0 equiv. sodium 4-fluorobenzenesulfinate (**1a**), 1.0 equiv. 5-nitro-7-azaindole (**2b**), 4.5 equiv. sodium bisulfite in 1 mL DMSO (0.2 M). [a]Conversion determined using ^{19}F NMR and an internal standard.

The gel formation was particularly pronounced during the attempted coupling of **1a** with 5-nitro-7-azaindole (**2b**) and so the investigation began with these substrates (Table 2). On a 0.2 mmol scale, sulfonamide **3b** was obtained in quantitative conversion. However, when scaled to 0.5 mmol, **3b** was obtained in a meagre 30% yield. By recording a repeat of the 0.5 mmol reaction with a camera,[9] we noticed a non-homogeneous mixture formed with insolubilized solid material accumulating at the bottom of the reaction vessel. By employing an Eppendorf ThermoMixer to act as the stirrer mantle, more vigorous stirring was achieved. Indeed, a significantly improved yield of 63% of **3b** was achieved, despite the observation of an accumulated slurry at the base of the vessel. To address this, the reaction was again repeated in an ultrasonic bath,[10] whereby gel aggregation was prevented and **3b** was obtained in 70% yield. During the optimization process, reactions were associated with a mild unpleasant odor, possibly due to the reduction of DMSO to dimethylsulfide to a small extent. However, DMSO proved to be the best solvent investigated for this reaction.

With new conditions and set-up for the reaction, a substrate scope was then established, beginning with varying the nitro(hetero)arene component (Table 3). Pleasingly, both *N*-substituted as well as *N*-

H-nitropyrazoles were well tolerated, giving **3c**, **3d** and **3e** in 35%, 32% and 34% yields respectively. Other nitro-substituted azoles and azines were also suitable substrates. Tinidazole (**2f**) was directly converted to sulfonamide **3f** in 23% yield. 2- and 3-substituted pyridines **3g** and **3h** were prepared in 45% and 37% yields respectively, whilst **3b** was isolated in 61% yield. Nitroarenes bearing various functional groups were generally well tolerated. Sulfoxide **3i** was prepared in 41% yield. Aldehyde **3j** was isolated in 34% yield, which would otherwise encounter preparative issues using more conventional methods. Sulfonamide **3k** was isolated in 63% yield. Interestingly, amines **3l** and **3m** were also isolated in 64% and 67% yields respectively, which would otherwise encounter selectivity issues if prepared by direct sulfonyl chloride-amine condensations.[11] One class of substrate found to be unsuited to the reaction conditions was chloro-substituted nitroarenes, which instead of reacting in the desired reductive coupling fashion, underwent S_NAr-based reactivity with the sodium 4-fluorobenzenesulfinate nucleophile to form sulfones (see ESI).[12]

Table 3. Nitro(hetero)arene scope investigation.

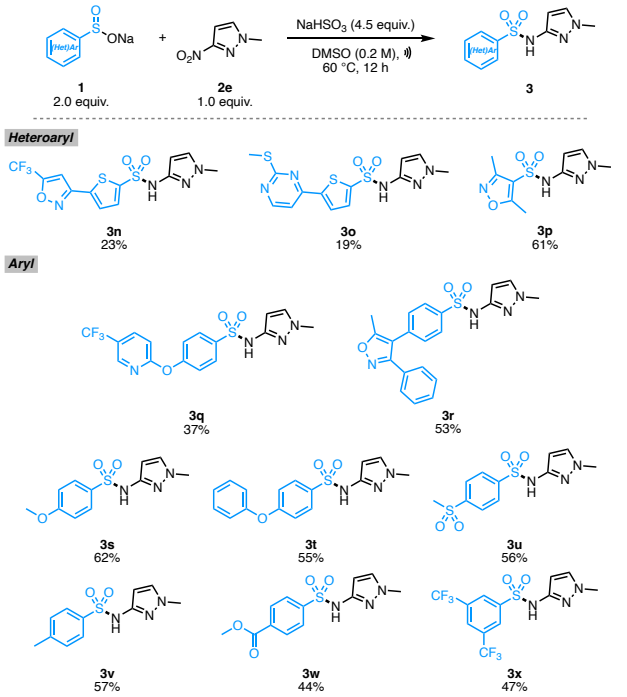


Reaction conditions: 0.5 mmol, 2.0 equiv. sodium 4-fluorobenzenesulfinate (**1a**), 1.0 equiv. nitro(hetero)arene (**2**), 4.5 equiv. sodium bisulfite in DMSO.

Whilst investigating the scope of the reaction, we observed that the polar nature of many of the sulfonamides prepared resulted in some loss into the aqueous phase during the extraction process of the work-up. Previous methods employed similar aqueous work-ups to remove DMSO from the reaction mixture and were likely to be well-suited to the compounds being investigated as they were relatively non-polar.[7a] As an alternative to aqueous extraction, Kugelrohr distillation was employed to remove DMSO from the crude reaction mixture. This enabled us to isolate comparatively polar compounds such as **3l** and **3m** in good yields by chromatography with the DMSO removed.

Next, we moved on to investigate the sodium (hetero)aryl sulfinate section of the scope (Table 4). The sodium sulfinates in this instance were prepared by the aqueous sodium sulfite-mediated reduction of corresponding sulfonyl chlorides.[13] Using 1-methyl-3-nitropyrazole (**2e**) as the nitroarene, a selection of sodium aryl sulfinates were investigated. Firstly, sodium heteroaryl sulfinates delivered sulfonamides with varying success. Thiophene sulfonamides **3n** and **3o** were isolated in modest 23% and 19% yields respectively. Isoxazole **3p**, however, was isolated in 61% yield. In addition to heterocycles directly attached to the sulfonamide group, other heterocycles were tolerated as appendages to S-aryl sulfonamides, including pyrimidine (**3o**) and pyridine (**3q**). Further to these, S-aryl sulfonamides bearing various substituents were also obtained. Electron donating groups were well tolerated with **3s** and **3t** isolated in 62% and 55% yields respectively. Sulfone and methyl substituted aryl sulfonamides **3u** and **3v** were isolated in 56% and 57% yields. Sodium aryl sulfinates bearing electron withdrawing groups also delivered their corresponding sulfonamides (**3w** and **3x**) in moderate yields.

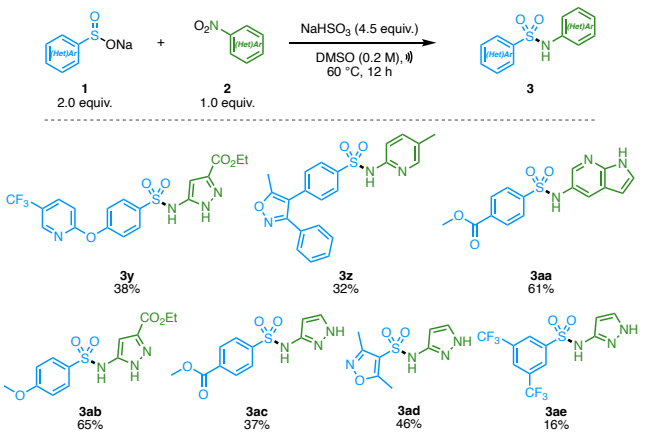
Table 4. Sodium (hetero)aryl sulfinate scope investigation.



Reaction conditions: 0.5 mmol, 2.0 equiv. sodium (hetero)aryl sulfinate (**1**), 1.0 equiv. 1-methyl-3-nitropyrazole (**2e**), 4.5 equiv. sodium bisulfite in DMSO.

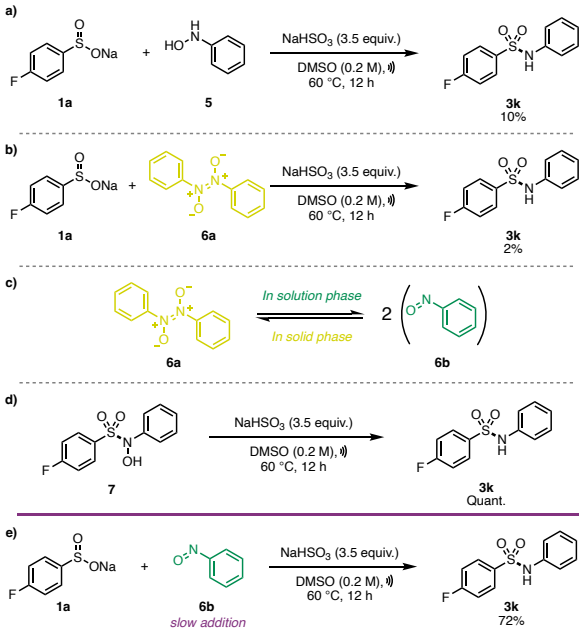
Having demonstrated that various aromatic heterocycles bearing a range of appendages were amenable to the reductive coupling conditions, we anticipated that a suitable reductive coupling methodology could find applications in drug discovery as well as route scouting towards sulfonamide targets. Having addressed methods to improve the reliability of scaling the nitro-sulfinate reductive coupling, we envisioned that a library of drug-like sulfonamides could be generated from the corresponding sodium (hetero)aryl sulfinates and nitro(hetero)arenes.[14] The building blocks containing toxicophoric and highly reactive groups were excluded.[15] Initially, the library was enumerated automatically in DataWarrior to generate 144 (12 x 12) virtual compounds.[16] Of this library, seven members (**3y-3ae**) were prepared in the laboratory using the aforementioned reductive coupling strategy (Table 5).

Table 5. Drug-like sulfonamides.



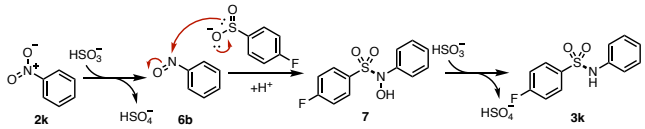
Reaction conditions: 0.5 mmol, 2.0 equiv. sodium (hetero)aryl sulfinate (**1**), 1.0 equiv. 1-methyl-3-nitropyrazole (**2e**), 4.5 equiv. sodium bisulfite in DMSO.

Previous investigations into the mechanisms of nitro-sulfinate reductive couplings had not provided conclusive evidence for key proposed intermediates during the reaction, with the exception of the formation of *N*-hydroxyl sulfonamide intermediates, which can be isolated during incomplete reductions.[7a,e] We then began our own preliminary set of control experiments (Scheme 2, see ESI for full details). Under the reaction conditions, we envisioned that potential intermediates would be *N*-arylhydroxylamines (**5**) or nitrosoarenes (**6**), as was previously suggested by Luo before they concluded otherwise as a result of their own control experiments.[7a] This is because these intermediates are known to be formed during the bisulfite-mediated reduction of nitroarenes, as in the Piria reaction.[17] As was consistent with Luo, when we subjected each of these intermediates directly into the standard reaction conditions with **1a**, we observed the formation of only small amounts of sulfonamide **3k** (Scheme 2a and 2b).[7a] However, we were not convinced that this ruled out the formation of either **5** or **6b** as intermediates for two reasons. Firstly, *C*-nitroso compounds typically exist as azobenzene dioxide dimers (**6a**) in the solid state (though can be isolated as green solid monomers upon sublimation) and so the proposed electrophilic nitroso species **6b** is only formed upon dissociation of the dimer, which is often achieved in solution (Scheme 2c).[18] Indeed, this equilibrium needs to be carefully controlled to use nitroso compounds effectively in synthesis.[19] As a result, we speculated that addition of solid dimer **6a** in one go may prevent the reaction from proceeding due to lack of dimer dissociation, as monomeric **6b** was the intermediate in the reaction. Secondly, *C*-nitroso arenes are known to react with sodium aryl sulfinates to form *N*-sulfonyl hydroxylamines, such as **7**.[20] Indeed, we had isolated *N*-sulfonyl hydroxylamines during the optimization of the reaction when insufficient quantities of reducing agent were added. We also demonstrated that pure **7** could be reduced under the reaction conditions to **3k** in quantitative yield (Scheme 2d). This is consistent with other works, where *N*-sulfonyl hydroxylamines have been shown to reduce to the corresponding sulfonamide with sodium bisulfite.[7a] With this information at hand, a 0.2 M solution of **6b** in *d*6-DMSO was prepared. This solution was shown by ^{1}H NMR to be in the monomeric form and was also the characteristic deep blue-green colour typical of *C*-nitroso monomers (see ESI). This solution was then added slowly over the period of one hour to a reaction mixture containing **1a** and sodium bisulfite in *d*6-DMSO heated at 60 °C (Scheme 2e). Gratifyingly, sulfonamide **3k** was observed to form in 72% yield by ^{19}F NMR. We see this as supporting evidence for potential formation of the nitrosoarene monomer (**6b**) as a key intermediate in the reaction.



Scheme 2 a) Control experiment using *N*-phenyl hydroxylamine (**5**), b) control experiment using azobenzene dioxide (**6a**), c) dissolution-influenced equilibrium of azobenzene dioxide **6a** and nitrosobenzene (**6b**), d) sodium bisulfite mediated reduction of *N*-sulfonyl hydroxylamine **7**, e) control experiment using a slowly added solution of nitrosobenzene (**6b**).

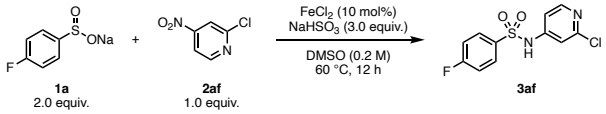
With these control experiments, we suggest that the reaction proceeds *via* nitrosoarene and *N*-sulfonyl hydroxylamine intermediates (Scheme 3). Firstly, the nitroarene starting material (**2k**) undergoes a 2-electron reduction, in an analogous fashion to the Piria reaction,[17] to a nitroso monomer intermediate (**6**), which upon electrophilic interception of the sodium aryl sulfinate nucleophile (**1a**) and protonation, forms an *N*-sulfonyl hydroxylamine (**7**). Subsequent 2-electron reduction of this species then produces the desired sulfonamide **3k**. Further studies into the mechanism are needed however, to confirm whether the reaction proceeds *via* **7** or its conjugate base under these reaction conditions.



Scheme 3. Proposed reaction mechanism.

With additional insight into the mechanism of the sodium bisulfite-mediated reductive coupling reaction, we reasoned that a wider range of nitroarenes may become viable substrates with the choice of other reducing agents as the first step of the proposed mechanism requires direct reduction of the nitroarene to the nitrosoarene. After a quick screen with alternative reducing agents for previously sluggish/unreactive substrates such as **2af**, we found that a combination of sodium bisulfite and tin(II) chloride was successfully able to convert them (entry 2, Table 6). For example, sodium 4-fluorobenzenesulfinate (**1a**) was reductively coupled with nitroheteroarene **2af** in 81% conversion.

Table 6. Alternative reducing agent investigation.

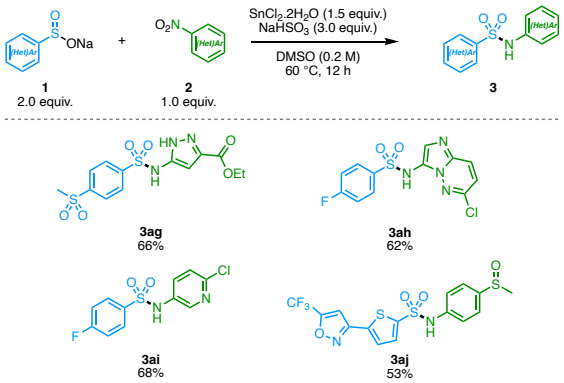


entry	deviation from conditions	conversion to 3af (%)[a]
1	none	1
2	1.5 equiv. $SnCl_2$ added	81
3	No $FeCl_2$, 1.5 equiv. $SnCl_2$ added	Quant.
4	No $FeCl_2$, 1.5 equiv. $SnCl_2$ added, 1.5 equiv. $NaHSO_3$	89[b]

Reaction conditions: 0.2 mmol, 2.0 equiv. sodium 4-fluorobenzenesulfinate (**1a**), 1.0 equiv. nitroarene **2a**f, 3.0 equiv. sodium bisulfite, in DMSO (0.2 M). [a]Conversion determined using ^{19}F NMR and an internal standard. [b]Unconverted *N*-sulfonyl hydroxylamine intermediate observed.

After a brief optimisation we found that 1.5 equivalents of tin(II) chloride and 3 equivalents of sodium bisulfite produced **3af** in quantitative conversion (entry 3). Interestingly, both reducing agents were required to achieve full conversion. Reduction in the quantity of sodium bisulfite resulted in incomplete conversion of the *N*-sulfonyl hydroxylamine intermediate (entry 4). With these new conditions we prepared a small selection of sulfonamides, many of which were sluggish under the original conditions, including **3ag-3aj** in moderate to very good yields (Table 7). Not only this, but arenes that previously underwent S_NAr solely with sodium bisulfite as the reducing agent, instead selectively formed the desired sulfonamide with the new tin(II) chloride-sodium bisulfite conditions (**3af**, **3ah** and **3ai**). These results indicate that the selection of particular reducing agents may enable the activation of a much wider range of nitroheteroarenes for the reductive coupling strategy to sulfonamides.

Table 7. Substrates prepared using $SnCl_2$ as a co-reducing agent.



Reaction conditions: 0.5 mmol, 2.0 equiv. sodium (hetero)aryl sulfinate (**1**), 1.0 equiv. nitro(hetero)arene (**2**), 1.5 equiv. sodium bisulfite, 1.5 equiv. $SnCl_2.2H_2O$ in DMSO.

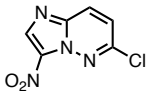
In summary, we have established a method for the reductive coupling of various nitro-heteroarenes with aryl sulfinates using sodium bisulfite with and without $SnCl_2$ to afford the corresponding sulfonamides. The ready availability and stability of the initial building blocks provides a useful alternative to conventional sulfonamide preparations and in particular, for the generation of heteroaryl derivatives.

Experimental Section

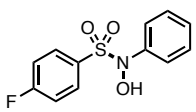
General Information. All procedures below were conducted under an inert nitrogen atmosphere unless stated otherwise. Reagents not prepared were supplied by Sigma-Aldrich, Alfa Aesar, Acros Organics, TCI, and Fluorochem and were used as received. Extra dry DMSO was purchased from Acros Organics and used for all reductive coupling reactions. Reactions carried out on a 0.5 mmol scale were done in a Fisher Scientific FB15051 ultrasonic bath. Work-up solvents were obtained from commercial sources and distilled prior to use. Petroleum ether refers to the fractions of petrol collected between 40 and 60 °C bp. Automated flash column chromatography was performed using a Teledyne ISCO CombiFlash® NextGen 100 system with single-use disposable silica columns of the appropriate size (SiliaSep Flash Cartridges 12 or 25 g 40–60 µm ISO04/012). Thin-layer chromatography (TLC) analysis was carried out using silica gel 60 F254 precoated glass-backed plates and visualized under UV light (254 nm) or with permanganate stains. ^1H NMR, $^{13}C\{^1H\}$ NMR, and $^{19}F\{^1H\}$ NMR were obtained using a Bruker AV400 (Avance 400 MHz) spectrometer. ^1H NMR Chemical shifts (δ) are referenced to residual $CHCl_3$ (7.26 ppm) and DMSO (2.50 ppm & 3.33 ppm) in the unit of parts per million (ppm). $^{13}C\{^1H\}$ NMR Chemical shifts (δ) are referenced to residual $CDCl_3$ (77.5 ppm) and DMSO-d_6 (39.5 ppm). Coupling constants *J* are quoted in the unit of hertz (Hz). Proton and carbon multiplicity are recorded as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m), and broad (br). ^1H NMR signals are reported to two decimal places, $^{13}C\{^1H\}$ NMR signals to one decimal place, and $^{19}F\{^1H\}$ NMR signals to one decimal place. All compounds examined were dried *in vacuo* to remove residual solvents. High-resolution mass spectra (HRMS) were obtained on a Waters Xevo G2-S bench-top quadrupole time of flight (QTOF) spectrometer. Infrared spectra were recorded neat on a Bruker Alpha II Fourier transform infrared (FTIR) spectrometer with a universal attenuated total reflection (ATR) sampling accessory, and selected peaks were reported. The following abbreviations are used when describing the data: w (weak), m (medium), s (strong). Melting points were uncorrected and recorded using one-end closed glass capillaries supplied by Marienfeld Superior on a Stuart Scientific melting point apparatus.

Preparation of Starting Materials:

All sodium aryl sulfinates were prepared according to literature procedure.[13]



6-Chloro-3-nitroimidazo[1,2-b]pyridazine (**2ah**). Compound was prepared according to a literature procedure.[21] 6-Chloro-imidazo[1,2-b]pyridazine (2.48 g, 15.8 mmol) was dissolved in 98% H_2SO_4 (30 mL) and cooled (0 °C). Concentrated HNO_3 (5 mL) was added dropwise over 10 minutes with vigorous stirring. After stirring at 0 °C for 30 minutes, the solution was warmed to room temperature and stirred for a further 4 hours. The reaction mixture was then poured onto ice (100 g) neutralized with 50% aqueous NaOH (50 mL) and then extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water (2 x 100 mL), brine (100 mL), then dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to produce **2ah** as a yellow crystalline solid (2.99 g, 95%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.12 (d, J = 9.5 Hz, 1H), 7.46 (d, J = 9.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.3, 139.4, 136.5, 128.4, 124.0. m.p. 208 – 210 °C. HRMS: m/z calculated for $C_6H_4N_4O_2Cl^+$, 199.0017 $[M+H]^+$. Found m/z 199.0018, Δ = 0.3 ppm. Data was consistent with that in the literature.[21]



*4-Fluoro-N-hydroxy-N-phenylbenzenesulfonamide (**7**).* Compound was prepared according to a literature procedure.[22] A mixture of phenylhydroxylamine (109 mg, 1.0 mmol), $NaHCO_3$ (200 mg, 1.2 mmol), 4-fluorobenzenesulfonyl chloride (464 mg, 1.2 mmol) in THF (10 mL) was stirred at room temperature for 2 h. Water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4,

filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc in petroleum ether) to give **7** as beige solid (79 mg, 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 7.53 – 7.44 (m, 2H), 7.43 – 7.34 (m, 2H), 7.34 – 7.21 (m, 3H), 7.11 – 7.02 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 165.22 (d, J = 253.2 Hz), 142.4, 132.2 (d, J = 10.0 Hz), 128.6 (d, J = 3.0 Hz), 128.4, 127.2, 122.7, 116.1 (d, J = 23.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −105.1. m.p. 138 – 139 °C. ν_{max} 3346, 1344, 1148 cm^{-1}. HRMS: m/z calculated for $C_{12}H_{11}NO_3SF^+$, 268.0444 $[M+H]^+$. Found m/z 268.0433, Δ = -4.1 ppm. Data was consistent with that in the literature.[22]

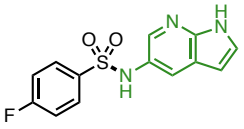
General Procedures for the Synthesis of Sulfonamides:

General Procedure 1. A mixture of sodium arylsulfinate (1.0 mmol, 2.0 equiv.), nitroarene (0.5 mmol, 1.0 equiv.), and $NaHSO_3$ (234 mg, 2.25 mmol, 3.5 equiv.) in DMSO (2.5 mL, 0.2 M) was allowed to react in an ultrasonic water bath at 60 °C for 12 h. After cooling to room temperature, water (25 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give the product.

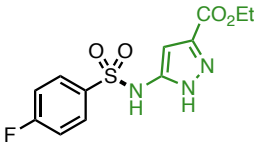
General Procedure 2. A mixture of sodium arylsulfinate (1.0 mmol, 2.0 equiv.), nitroarene hydrochloride (0.5 mmol, 1.0 equiv.), and $NaHSO_3$ (234 mg, 2.25 mmol, 3.5 equiv.) in DMSO (2.5 mL, 0.2 M) was allowed to react in an ultrasonic water bath at 60 °C for 12 h. The reaction was cooled down to room temperature. The DMSO was removed by Kugelrohr distillation (60 °C − 80 °C, 0.1 mbar, 3 h). The crude product was purified by flash column chromatography to give the product as a free amine.

General Procedure 3. To a 10 mL microwave vial was added a stirrer bar, nitroarene (0.4 mmol, 1.0 equiv.), aryl sulfinate (0.8 mmol, 2.0 equiv.), tin chloride (0.6 mmol, 1.5 equiv.) and sodium bisulfite (0.6 mmol, 1.5 equiv.). The vial was then sealed, evacuated and back-filled with nitrogen (×3). Dry DMSO (2 mL, 0.2 M) was then added and the reaction mixture stirred vigorously (>800 rpm) for 5 minutes. The mixture was then heated to 60 °C in an oil bath with vigorous stirring for 16 hours. As the reaction reached a constant temperature, all components became solubilised. After 16 hours, the reaction mixture was cooled to room temperature before being diluted with DCM (30 mL) and water (30 mL). The layers were separated and the organic phase washed with water (2 × 30 mL), then brine (30 mL) before being dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was then purified by column chromatography to yield the desired sulfonamide.

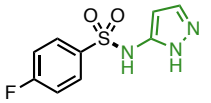
Characterization of Products



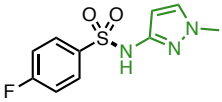
*4-Fluoro-N-(1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide (**3b**).* Following General Procedure 1. Purification by flash column chromatography (50 – 80% EtOAc in petroleum ether) yielded **3b** as a white solid (88 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 10.02 (s, 1H), 7.83 – 7.78 (m, 1H), 7.72 – 7.64 (m, 2H), 7.61 – 7.56 (m, 1H), 7.45 – 7.40 (m, 1H), 7.37 – 7.29 (m, 2H), 6.36 (dd, J = 3.4, 1.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.2 (d, J = 251.4 Hz), 146.5, 138.8, 135.5 (d, J = 3.0 Hz), 129.8 (d, J = 9.6 Hz), 127.4, 126.2, 123.2, 119.4, 116.4 (d, J = 22.7 Hz), 100.0. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −107.2. m.p. 183 – 185 °C. ν_{max} 1333, 1166 cm^{-1}. HRMS: m/z calculated for $C_{13}H_{11}N_3O_2SF^+$, 292.0556 $[M+H]^+$. Found m/z 292.0561, Δ = 1.7 ppm.



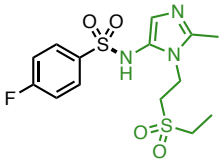
*Ethyl 5-((4-fluorophenyl)sulfonamido)-1H-pyrazole-3-carboxylate (**3c**).* Following General Procedure 1. Purification by flash column chromatography (30 – 50% EtOAc in petroleum ether) yielded **3c** as a white solid (55 mg, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.61 (s, 1H), 10.76 (s, 1H), 7.82 (dd, J = 8.7, 5.2 Hz, 2H), 7.46 – 7.35 (m, 2H), 6.46 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.3 (d, J = 251.6 Hz), 158.5, 146.2, 136.3, 133.8, 129.7 (d, J = 9.7 Hz), 116.4 (d, J = 22.5 Hz), 100.3, 60.9, 14.1. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −107.1. m.p. 175 – 177 °C. ν_{max} 1703, 1356, 1138 cm^{-1}. HRMS: m/z calculated for $C_{12}H_{13}N_3O_4SF^+$, 314.0611 $[M+H]^+$. Found m/z 314.0613, Δ = -0.6 ppm.



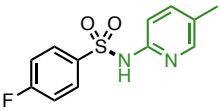
*4-Fluoro-N-(1H-pyrazol-3-yl)benzenesulfonamide (**3d**).*Following General Procedure 1. Purification by flash column chromatography (30 – 90% EtOAc in petroleum ether) yielded **3d** as a white solid (38 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 10.42 (s, 1H), 7.91 – 7.76 (m, 2H), 7.63 – 7.49 (m, 1H), 7.46 – 7.32 (m, 2H), 6.02 – 5.88 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.19 (d, J = 251.0 Hz), 136.6, 129.73 (d, J = 9.6 Hz), 129.5, 116.16 (d, J = 22.9 Hz), 97.2, one quaternary carbon not visible. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −107.6. ν_{max} 3323, 1352, 1149 cm^{-1}. HRMS: m/z calculated for $C_9H_9N_3O_2SF^+$, 242.0400 $[M+H]^+$. Found m/z 242.0407, Δ = 2.9 ppm.



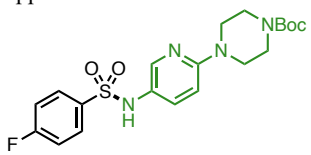
*4-Fluoro-N-(1-methyl-1H-pyrazol-3-yl)benzenesulfonamide (**3e**).* Following General Procedure 1. Purification by flash column chromatography (20 – 90% EtOAc in petroleum ether) yielded **3e** as a white solid (43 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 7.87 – 7.79 (m, 2H), 7.49 (d, J = 2.3 Hz, 1H), 7.44 – 7.35 (m, 2H), 5.91 (d, J = 2.3 Hz, 1H), 3.63 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.2 (d, J = 251.1 Hz), 145.0, 136.5 (d, J = 3.0 Hz), 131.8, 129.7 (d, J = 9.5 Hz), 116.2 (d, J = 22.9 Hz), 97.3, 38.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −106.5. m.p. 150 – 151 °C. ν_{max} 1325, 1169 cm^{-1}. HRMS: m/z calculated for $C_{10}H_{11}N_3O_2SF^+$, 256.0556 $[M+H]^+$. Found m/z 256.0568, Δ = 4.7 ppm.



*N-(1-(2-(Ethylsulfonyl)ethyl)-2-methyl-1H-imidazol-5-yl)-4-fluorobenzenesulfonamide (**3f**).* Following General Procedure 1. Purification by flash column chromatography (0 – 2% MeOH in EtOAc) yielded **3f** as a brown solid (44 mg, 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.79 (m, 2H), 7.46 – 7.32 (m, 2H), 5.92 (s, 1H), 4.19 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 7.2 Hz, 2H), 3.10 (q, J = 7.4 Hz, 2H), 2.20 (s, 3H), 1.19 (t, J = 7.4 Hz, 3H), exchangeable proton not visible. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.1 (d, J = 250.5 Hz), 143.4, 139.89, 139.86, 129.1 (d, J = 9.5 Hz), 116.3 (d, J = 22.6 Hz), 111.9, 48.7, 46.9, 35.7, 12.9, 5.8. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −107.9. m.p. 119 – 121 °C. ν_{max} 1128 cm^{-1}. HRMS: m/z calculated for $C_{14}H_{19}N_3O_4FS_2^+$, 376.0801 $[M+H]^+$. Found m/z 376.0810, Δ = 2.4 ppm.

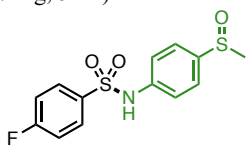


4-Fluoro-N-(5-methylpyridin-2-yl)benzenesulfonamide ***(3g)***. Following General Procedure 1. Purification by flash column chromatography (40% EtOAc in petroleum ether) yielded **3g** as a white solid (60 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.87 (m, 2H), 7.87 – 7.82 (m, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.09 (d, J = 8.8 Hz, 1H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.7 (d, J = 253.2 Hz), 154.0, 144.7, 138.4 (d, J = 3.3 Hz), 138.3, 129.5 (d, J = 9.1 Hz), 124.0, 116.2 (d, J = 22.4 Hz), 115.2, 17.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −108.5. m.p. 196 – 198 °C. ν_{max} 1355, 1137 cm^{-1}. HRMS: m/z calculated for $C_{12}H_{12}N_2O_2FS^+$, 267.0604 [M+H]$^+$. Found m/z 267.0605, Δ = 0.4 ppm.

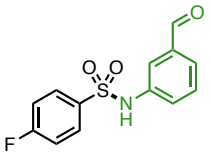


Tert-butyl 4-(5-((4-fluorophenyl)sulfonamido)pyridin-2-yl)piperazine-1-carboxylate ***(3h)***. Following General Procedure 1. Purification by flash column chromatography (30 – 40% EtOAc in petroleum ether) yielded **3h** as a yellow solid (81 mg, 37%).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.77 – 7.66 (m, 3H), 7.46 – 7.34 (m, 2H), 7.20 (dd, J = 9.1, 2.8 Hz, 1H), 6.74 (d, J = 9.1 Hz, 1H), 3.41 – 3.34 (m, 8H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.30 (d, J = 255.3 Hz), 157.9, 154.9, 144.8, 135.7, 135.08 (d, J = 3.3 Hz), 130.17 (d, J = 9.4 Hz), 122.8, 116.42 (d, J = 22.6 Hz), 107.1, 80.3, 45.1, 42.8, 28.5. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −107.2. m.p. 79 – 80 °C. ν_{max} 1660, 1364, 1153 cm^{-1}. HRMS: m/z calculated for $C_{20}H_{26}N_4O_4SF^+$, 437.1659 [M+H]$^+$. Found m/z 437.1653, Δ = -1.4 ppm.

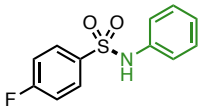
*Reaction was repeated on 1.0 mmol scale to produce **3h** as a white crystalline solid (237 mg, 54%)



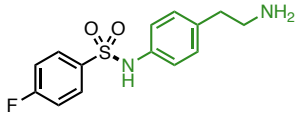
4-Fluoro-N-(4-(methylsulfinyl)phenyl)benzenesulfonamide ***(3i)***. Following General Procedure 1. Purification by flash column chromatography (0 – 4.5% MeOH in CH_2Cl_2) yielded as a pale yellow oil (64 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.82 (m, 2H), 7.60 – 7.51 (m, 2H), 7.45 – 7.36 (m, 2H), 7.31 – 7.24 (m, 2H), 2.66 (s, 3H), exchangeable proton not visible. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.4 (d, J = 251.9 Hz), 140.9, 140.0, 135.7 (d, J = 3.0 Hz), 129.8 (d, J = 9.7 Hz), 125.1, 119.8, 116.7 (d, J = 22.9 Hz), 43.0. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −106.5. ν_{max} 1335, 1153, 1010 cm^{-1}. HRMS: m/z calculated for $C_{13}H_{13}NO_3FS_2^+$, 314.0321 [M+H]$^+$. Found m/314.0333, Δ = 3.8 ppm.



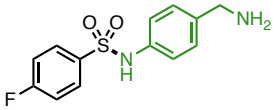
4-Fluoro-N-(3-formylphenyl)benzenesulfonamide ***(3j)***. Following General Procedure 1. Purification by flash column chromatography (0 – 30% EtOAc in petroleum ether) yielded **3j** as a colorless oil (48 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.88 – 7.79 (m, 2H), 7.63 – 7.57 (m, 2H), 7.52 – 7.46 (m, 1H), 7.43 – 7.35 (m, 3H), exchangeable proton not visible. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 192.8, 164.5 (d, J = 251.9 Hz), 138.5, 137.1, 135.6 (d, J = 2.6 Hz), 130.3, 129.8 (d, J = 9.6 Hz), 126.2, 125.7, 119.3, 116.7 (d, J = 22.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −106.5. ν_{max} 1688, 1332, 1150 cm^{-1}. HRMS: m/z calculated for $C_{13}H_{11}NO_3FS^+$, 280.0444 [M+H]$^+$. Found m/z 280.0445, Δ = 0.4 ppm. Data consistent with that available in the literature.[23]



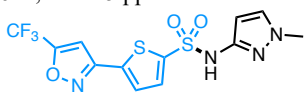
4-Fluoro-N-phenylbenzenesulfonamide ***(3k)***. Following General Procedure 1. Purification by flash column chromatography (0 – 50% EtOAc in petroleum ether) yielded **3k** as a colorless oil (79 mg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.85 – 7.74 (m, 2H), 7.43 – 7.32 (m, 2H), 7.27 – 7.17 (m, 2H), 7.14 – 6.97 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.3 (d, J = 251.7 Hz), 137.5, 135.8 (d, J = 3.0 Hz), 129.7 (d, J = 9.6 Hz), 129.2, 124.3, 120.3, 116.4 (d, J = 22.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −107.0. ν_{max} 1341, 1150 cm^{-1}. HRMS: m/z calculated for $C_{12}H_{11}NO_2FS^+$, 252.0495 [M+H]$^+$. Found m/z 252.0489, Δ = -2.4 ppm. Data consistent with that in the literature.[7a]



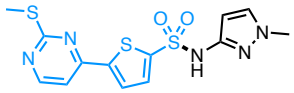
N-(4-(2-Aminoethyl)phenyl)-4-fluorobenzenesulfonamide ***(3l)***. Following General Procedure 2. Purification by flash column chromatography (0 – 10% MeOH, 1% NH_4OH in CH_2Cl_2) yielded **3l** as a beige solid (95 mg, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 – 7.71 (m, 2H), 7.35 – 7.26 (m, 2H), 7.00 – 6.94 (m, 2H), 6.93 – 6.87 (m, 2H), 2.78 – 2.70 (m, 2H), 2.59 – 2.52 (m, 2H), exchangeable protons not visible. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.7 (d, J = 249.5 Hz), 139.3, 138.5 (d, J = 2.8 Hz), 133.0, 129.4 (d, J = 9.4 Hz), 129.1, 120.6, 115.9 (d, J = 22.5 Hz), 42.6, 37.1. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −109.1. m.p. 159 – 161 °C. ν_{max} 1292, 1110 cm^{-1}. HRMS: m/z calculated for $C_{14}H_{16}N_2O_2FS^+$, 295.0917 [M+H]$^+$. Found m/z 295.0927, Δ = 3.4 ppm.



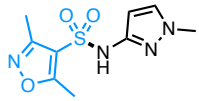
N-(4-(Aminomethyl)phenyl)-4-fluorobenzenesulfonamide ***(3m)***. Following General Procedure 2. Purification by flash column chromatography (0 – 10% MeOH, 1% NH_4OH in CH_2Cl_2) yielded **3m** as a beige solid (93 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 – 7.72 (m, 2H), 7.35 – 7.27 (m, 2H), 7.15 – 7.09 (m, 2H), 6.98 – 6.90 (m, 2H), 3.65 (s, 2H), exchangeable protons not visible. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.69 (d, J = 249.7 Hz), 139.6, 138.10 (d, J = 3.1 Hz), 135.0, 129.4 (d, J = 9.4 Hz), 128.1, 120.4, 115.9 (d, J = 22.3 Hz), 44.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −108.9. m.p. 151 – 153 °C. ν_{max} 1335, 1153, 1010 cm^{-1}. HRMS: m/z calculated for $C_{13}H_{12}N_2O_2SF^+$, 279.0604 [M+H]$^+$. Found m/z 279.0611, Δ = 2.5 ppm.



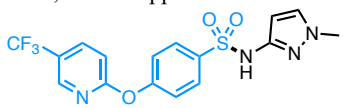
N-(1-methyl-1H-pyrazol-3-yl)-5-(5-(trifluoromethyl)isoxazol-3-yl)thiophene-2-sulfonamide ***(3n)***. Following General Procedure 1. Purification by flash column chromatography (0 – 50% EtOAc in in petroleum ether) yielded **3n** as a pale yellow solid (45 mg, 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 – 8.10 (m, 1H), 7.83 (d, J = 4.0 Hz, 1H), 7.67 (d, J = 4.0 Hz, 1H), 7.56 (d, J = 2.3 Hz, 1H), 6.01 (d, J = 2.3 Hz, 1H), 3.68 (s, 3H), exchangeable proton not visible. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 157.8 (q, J = 42.4 Hz), 157.5, 144.5, 143.5, 132.9, 132.6, 132.0, 130.6, 117.6 (q, J = 270.3 Hz), 105.9 (q, J = 1.9 Hz), 97.8, 38.6; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −65.2. m.p. 130 – 132 °C. ν_{max} 1364, 1157 cm^{-1}. HRMS: m/z calculated for $C_{12}H_{10}N_4O_3S_2F_3^+$, 379.0146 [M+H]$^+$. Found m/z 379.0157, Δ = 2.9 ppm.



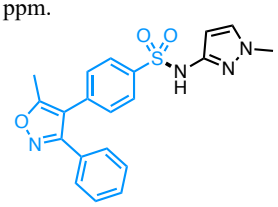
*N-(1-methyl-1H-pyrazol-3-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide (**3o**).* Following General Procedure 1. Purification by flash column chromatography (0 – 55% EtOAc in petroleum ether) yielded **3o** as a yellow solid (36 mg, 19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.69 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 4.1 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.61 (d, J = 4.1 Hz, 1H), 7.55 (d, J = 2.3 Hz, 1H), 6.00 (d, J = 2.3 Hz, 1H), 3.67 (s, 3H), 2.54 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 171.8, 158.8, 157.2, 146.6, 144.6, 144.1, 132.9, 131.9, 128.6, 111.2, 97.6, 38.5, 13.5. m.p. 166 – 169 °C. ν_{max} 1350, 1163 cm^{-1}. HRMS: m/z calculated for $C_{13}H_{14}N_5O_2S_3^+$, 368.0310 $[M+H]^+$. Found m/z 368.0326, Δ = 4.3 ppm.



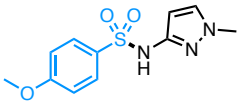
*3,5-Dimethyl-N-(1-methyl-1H-pyrazol-3-yl)isoxazole-4-sulfonamide (**3p**).* Following General Procedure 1. Purification by flash column chromatography (50 – 100% EtOAc in petroleum ether) yielded **3p** as a white solid (79 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 2.4 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 3.88 (s, 3H), 2.49 (s, 3H), 2.18 (s, 3H), exchangeable proton not visible. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.8, 157.7, 145.4, 132.2, 115.8, 98.1, 39.2, 12.8, 10.7. m.p. 117 – 119 °C. ν_{max} 1355, 1125 cm^{-1}. HRMS: m/z calculated for $C_9H_{13}N_4O_3S^+$, 257.0708 $[M+H]^+$. Found m/z 257.0707, Δ = -0.4 ppm.



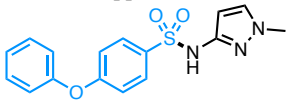
*N-(1-methyl-1H-pyrazol-3-yl)-4-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzene sulfonamide (**3q**).* Following General Procedure 1. Purification by flash column chromatography (100% $CHCl_3$ → 0 – 50% EtOAc in petroleum ether) yielded **3q** as a pale yellow solid (74 mg, 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.64 – 8.56 (m, 1H), 8.28 (dd, J = 8.7, 2.6 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.51 (d, J = 2.3 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.37 – 7.31 (m, 1H), 5.97 (d, J = 2.3 Hz, 1H), 3.66 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.7, 156.2, 145.3 (q, J = 4.5 Hz), 145.2, 138.0 (q, J = 3.3 Hz), 136.9, 131.8, 128.8, 123.8 (q, J = 271.5 Hz), 122.0, 121.1 (q, J = 32.8 Hz), 112.5, 97.1, 38.5. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ −61.1. m.p. 53 – 54 °C. ν_{max} 1357, 1155 cm^{-1}. HRMS: m/z calculated for $C_{16}H_{14}N_4O_3F_3S^+$, 399.0739 $[M+H]^+$. Found m/z 399.0756, Δ = 4.3 ppm.



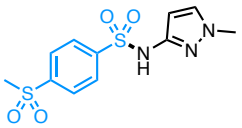
*N-(1-Methyl-1H-pyrazol-3-yl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (**3r**).* Following General Procedure 1. Purification by flash column chromatography (0 – 70% EtOAc in petroleum ether) yielded **3r** as a white solid (104 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.80 – 7.75 (m, 2H), 7.51 (d, J = 2.3 Hz, 1H), 7.49 – 7.35 (m, 5H), 7.33 – 7.27 (m, 2H), 5.90 (d, J = 2.3 Hz, 1H), 3.65 (s, 3H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.7, 160.7, 145.0, 139.4, 134.2, 131.8, 130.1, 129.9, 128.8, 128.3, 128.2, 127.2, 114.2, 97.6, 38.5, 11.4. m.p. 185 – 187 °C. ν_{max} 1356, 1161 cm^{-1}. HRMS: m/z calculated for $C_{20}H_{19}N_4O_3S^+$, 395.1178 $[M+H]^+$. Found m/z 395.1196, Δ = 4.6 ppm.



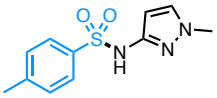
*4-Methoxy-N-(1-methyl-1H-pyrazol-3-yl)benzenesulfonamide (**3s**).* Following General Procedure 1. Purification by flash column chromatography (30 – 55% EtOAc in petroleum ether) yielded **3s** as a white solid (82 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.76 – 7.63 (m, 2H), 7.46 (d, J = 2.3 Hz, 1H), 7.13 – 6.98 (m, 2H), 5.89 (d, J = 2.3 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.3, 145.5, 131.9, 131.7, 128.9, 114.2, 97.0, 55.7, 38.4. m.p. 118 – 120 °C. ν_{max} 1352, 1152 cm^{-1}. HRMS: m/z calculated for $C_{11}H_{14}N_3O_3S^+$, 268.0756 $[M+H]^+$. Found m/z 268.0766, Δ = 3.7 ppm.



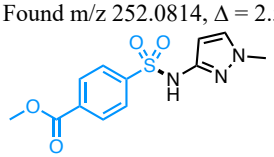
*N-(1-methyl-1H-pyrazol-3-yl)-4-phenoxybenzenesulfonamide (**3t**).* Following General Procedure 1. Purification by flash column chromatography (0 – 40% EtOAc in petroleum ether) yielded **3t** as a white solid (90 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 2H), 7.42 – 7.32 (m, 2H), 7.22 – 7.15 (m, 2H), 7.07 – 6.98 (m, 2H), 6.94 – 6.86 (m, 2H), 6.24 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7, 155.3, 146.5, 133.3, 131.9, 130.3, 129.3, 125.0, 120.4, 117.6, 97.7, 39.1. m.p. 137 – 139 °C. ν_{max} 1357, 1153 cm^{-1}. HRMS: m/z calculated for $C_{16}H_{16}N_3O_3S^+$, 330.0912 $[M+H]^+$. Found m/z 330.0920, Δ = 2.4 ppm.



*N-(1-methyl-1H-pyrazol-3-yl)-4-(methylsulfonyl)benzenesulfonamide (**3u**).* Following General Procedure 1. Purification by flash column chromatography (0 – 70% EtOAc in petroleum ether) yielded **3u** as a white solid (89 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 8.17 – 8.07 (m, 2H), 8.07 – 7.96 (m, 2H), 7.52 (d, J = 2.3 Hz, 1H), 5.95 (d, J = 2.3 Hz, 1H), 3.64 (s, 3H), 3.29 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 144.7, 144.5, 144.2, 131.9, 128.0, 127.7, 97.5, 43.1, 38.5. m.p. 213 – 215 °C. ν_{max} 1308, 1166 cm^{-1}. HRMS: m/z calculated for $C_{11}H_{14}N_3O_4S_2^+$, 316.0426 $[M+H]^+$. Found m/z 316.0416, Δ = -3.2 ppm.

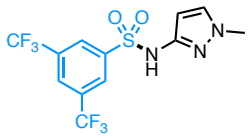


*4-Methyl-N-(1-methyl-1H-pyrazol-3-yl)benzenesulfonamide (**3v**).* Following General Procedure 1. Purification by flash column chromatography (100% $CHCl_3$ → 0 – 50% EtOAc in petroleum ether) yielded **3v** as a white solid (71 mg, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 7.69 – 7.59 (m, 2H), 7.46 (d, J = 2.3 Hz, 1H), 7.38 – 7.27 (m, 2H), 5.89 (d, J = 2.3 Hz, 1H), 3.62 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 145.3, 142.9, 137.3, 131.6, 129.5, 126.7, 97.0, 38.4, 21.0. m.p. 122 – 124 °C. ν_{max} 1354, 1160 cm^{-1}. HRMS: m/z calculated for $C_{11}H_{14}N_3O_2S^+$, 252.0807 $[M+H]^+$. Found m/z 252.0814, Δ = 2.5 ppm.

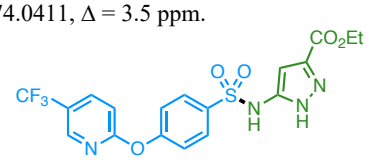


*Methyl 4-(N-(1-methyl-1H-pyrazol-3-yl)sulfamoyl)benzoate (**3w**).* Following General Procedure 1. Purification by flash column chromatography (50 – 70% EtOAc in petroleum ether) yielded **3w** as a white solid (64 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.15 – 8.05 (m, 2H), 7.94 – 7.84 (m, 2H), 7.49 (d, J = 2.3 Hz, 1H), 5.92 (d, J = 2.3 Hz, 1H), 3.87 (s, 3H), 3.63 (s, 3H);

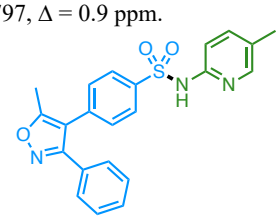
$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 165.2, 144.7, 144.1, 133.1, 131.8, 129.9, 127.2, 97.5, 52.6, 38.5. m.p. 188 – 190 °C. ν_{max} 1722, 1355, 1163 cm^{-1}. HRMS: m/z calculated for $C_{12}H_{14}N_3O_4S^+$, 296.0705 $[M+H]^+$. Found m/z 296.0710, Δ = 1.7 ppm.



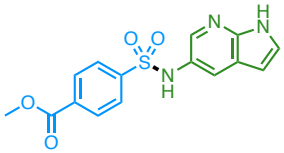
*N-(1-methyl-1H-pyrazol-3-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide (**3x**).* Following General Procedure 1. Purification by flash column chromatography (20 – 80% EtOAc in petroleum ether) yielded **3x** as a pale yellow solid (87 mg, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 8.55 – 8.45 (m, 1H), 8.37 – 8.25 (m, 2H), 7.56 (d, J = 2.3 Hz, 1H), 5.99 (d, J = 2.3 Hz, 1H), 3.64 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 144.1, 142.6, 132.2, 131.1 (q, J = 33.9 Hz), 127.6 – 127.3 (m), 126.9 – 126.8 (m), 122.6 (q, J = 273.8 Hz), 98.5, 38.5. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ −62.6. m.p. 156 – 158 °C. ν_{max} 1360, 1162 cm^{-1}. HRMS: m/z calculated for $C_{12}H_{10}N_3O_2F_6S^+$, 374.0398 $[M+H]^+$. Found m/z 374.0411, Δ = 3.5 ppm.



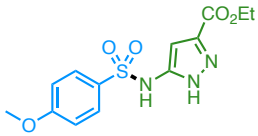
*Ethyl 5-((4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)sulfonamido)-1H-pyrazole-3-carboxylate (**3y**).* Following General Procedure 1. Purification by flash column chromatography (50 – 70% EtOAc in petroleum ether) yielded **3y** as a white solid (86 mg, 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.64 (s, 1H), 10.81 (s, 1H), 8.71 – 8.47 (m, 1H), 8.28 (dd, J = 8.7, 2.7 Hz, 1H), 7.90 – 7.79 (m, 2H), 7.46 – 7.28 (m, 3H), 6.50 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 164.7, 156.4, 145.4 (q, J = 4.2 Hz), 138.1 (q, J = 3.1 Hz), 136.6, 133.9, 129.0, 128.8, 123.8 (q, J = 271.7 Hz), 122.2, 121.2 (q, J = 32.7 Hz), 112.6, 104.8, 100.2, 61.0, 14.1. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ −60.7. m.p. 151 – 153 °C. ν_{max} 1702, 1323, 1159 cm^{-1}. HRMS: m/z calculated for $C_{18}H_{16}N_4O_5SF_3^+$, 457.0793 $[M+H]^+$. Found m/z 457.0797, Δ = 0.9 ppm.



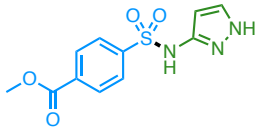
*4-(5-Methyl-3-phenylisoxazol-4-yl)-N-(5-methylpyridin-2-yl)benzenesulfonamide (**3z**).* Following General Procedure 1. Purification by flash column chromatography (0 – 60% EtOAc in petroleum ether) yielded **3z** as a white solid (65 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 – 7.80 (m, 3H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 – 7.32 (m, 5H), 7.32 – 7.25 (m, 2H), 7.13 (d, J = 8.8 Hz, 1H), 2.44 (s, 3H), 2.15 (s, 3H), exchangeable proton not visible. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 167.3, 161.2, 154.0, 144.6, 141.5, 138.2, 134.5, 130.2, 129.8, 128.8, 128.7, 128.6, 127.2, 124.0, 115.4, 114.7, 17.4, 11.9. m.p. 217 – 219 °C. ν_{max} 1361, 1141cm^{-1}. HRMS: m/z calculated for $C_{22}H_{20}N_3O_3S^+$, 406.1225 $[M+H]^+$. Found m/z 406.1231, Δ = 1.5 ppm.



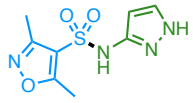
*Methyl 4-(N-(1H-pyrrolo[2,3-b]pyridin-5-yl)sulfamoyl)benzoate (**3aa**).* Following General Procedure 1. Purification by flash column chromatography (50 – 70% EtOAc in petroleum ether) yielded **3aa** as an orange solid (102 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 10.20 (s, 1H), 8.09 – 8.03 (m, 2H), 7.83 – 7.81 (m, 1H), 7.80 – 7.76 (m, 2H), 7.63 – 7.58 (m, 1H), 7.47 – 7.41 (m, 1H), 6.39 (dd, J = 3.4, 1.8 Hz, 1H), 3.85 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 165.1, 146.5, 143.2, 138.9, 133.1, 130.0, 127.5, 127.2, 125.9, 123.4, 119.4, 100.0, 52.6. m.p. 188 – 190 °C. ν_{max} 1725, 1333, 1160 cm^{-1}. HRMS: m/z calculated for $C_{15}H_{14}N_3O_4S^+$, 332.0705 $[M+H]^+$. Found m/z 332.0710, Δ = 1.5 ppm.



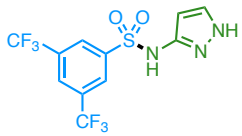
*Ethyl 5-((4-methoxyphenyl)sulfonamido)-1H-pyrazole-3-carboxylate (**3ab**).* Following General Procedure 1. Purification by flash column chromatography (40 – 80% EtOAc in petroleum ether) yielded **3ab** as a white solid (104 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.55 (s, 1H), 10.58 (s, 1H), 7.79 – 7.59 (m, 2H), 7.21 – 6.98 (m, 2H), 6.43 (s, 1H), 4.26 (q, J = 7.0 Hz, 2H), 3.81 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 162.5, 158.6, 146.7, 133.7, 131.6, 128.9, 114.4, 100.0, 61.0, 55.7, 14.1. m.p. 129 – 131 °C. ν_{max} 1722, 1341, 1159 cm^{-1}. HRMS: m/z calculated for $C_{13}H_{16}N_3O_5S^+$, 326.0811 $[M+H]^+$. Found m/z 326.0824, Δ = 4.0 ppm.



*Methyl 4-(N-(1H-pyrazol-3-yl)sulfamoyl)benzoate (**3ac**).* Following General Procedure 1. Purification by flash column chromatography (50 – 80% EtOAc in petroleum ether) yielded **3ac** as a white solid (53 mg, 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 10.59 (s, 1H), 8.16 – 8.04 (m, 2H), 7.96 – 7.84 (m, 2H), 7.61 – 7.49 (m, 1H), 6.02 – 5.88 (m, 1H), 3.87 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 165.2, 145.2, 144.2, 133.1, 129.8, 129.6, 127.2, 97.4, 52.6. m.p. 214 – 216 °C. ν_{max} 1725, 1333, 1160 cm^{-1}. HRMS: m/z calculated for $C_{15}H_{14}N_3O_4S^+$, 332.0705 $[M+H]^+$. Found m/z 332.0710, Δ = 1.5 ppm.

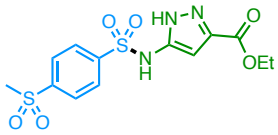


*3,5-Dimethyl-N-(1H-pyrazol-3-yl)isoxazole-4-sulfonamide (**3ad**).* Following General Procedure 1. Purification by flash column chromatography (50 – 100% EtOAc in petroleum ether) yielded **3ad** as a white solid (56 mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 10.49 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 5.98 (d, J = 2.4 Hz, 1H), 2.44 (s, 3H), 2.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 173.0, 157.5, 144.7, 129.8, 116.0, 98.3, 12.2, 10.3. m.p. 165 – 167 °C. ν_{max} 1348, 1178 cm^{-1}. HRMS: m/z calculated for $C_8H_{11}N_4O_3S^+$, 243.0552 $[M+H]^+$. Found m/z 243.0546, Δ = -2.5 ppm.

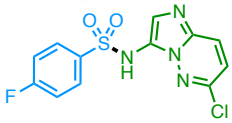


*N-(1H-Pyrazol-3-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide (**3ae**).* Following General Procedure 1. Purification by flash column chromatography (30 – 40% EtOAc in petroleum ether) yielded **3ae** (29 mg, 16%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.75 (s, 1H), 8.47 (s, 1H), 8.31 (s, 2H), 7.61 (d, J = 2.4 Hz, 1H), 6.03 (d, J = 2.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 144.7, 142.9, 131.2 (q, J = 33.9 Hz), 130.0, 127.5 – 127.3 (m), 127.0 – 126.7 (m), 122.6 (q, J = 273.5 Hz), 98.2. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ −62.5. m.p. 216 – 218 °C.

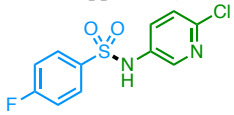
ν_{max} 1358, 1156 cm^{-1}. HRMS: m/z calculated for $C_{11}H_8N_3O_2SF_6^+$, 360.0241 $[M+H]^+$. Found m/z 360.0236, Δ = -1.4 ppm.



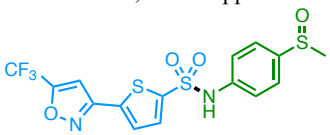
*Ethyl 5-((4-(methylsulfonyl)phenyl)sulfonamido)-1H-pyrazole-3-carboxylate (**3ag**).* Following General Procedure 3 on a 0.2 mmol scale. Flash column chromatography (5% MeOH in DCM) afforded **3ag** as a white crystalline solid (24.5 mg, 66%). ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 13.67 (s, 1H), 11.04 (s, 1H), 8.19 – 8.08 (m, 2H), 8.02 (app d, *J* = 8.2 Hz, 2H), 6.50 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.29 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, *d*$_6$-DMSO) δ 158.4, 158.0, 145.8, 144.4, 133.9, 128.1, 127.7, 100.5, 61.0, 43.0, 14.1. m.p. 138 – 140 °C. IR: ν_{max} 3118, 2921, 2851, 1708, 1562, 1536, 1235 cm^{-1}. HRMS: m/z calculated for $C_{13}H_{16}N_3O_6S_2^+$, 374.0475 $[M+H]^+$. Found m/z 374.0457, Δ = -4.8 ppm. Rf (5% MeOH in DCM) = 0.28.



*N-(6-Chloroimidazo[1,2-b]pyridazin-3-yl)-4-fluorobenzenesulfonamide (**3ah**).* Following General Procedure 3 on a 0.5 mmol scale. Flash column chromatography (0-5% MeOH in DCM) afforded **3ah** as a white crystalline solid (102 mg, 62%). ^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ 7.93 (d, *J* = 9.5 Hz, 1H), 7.80 (ddd, *J* = 10.1, 5.1, 2.6 Hz, 2H), 7.62 (s, 1H), 7.23 – 7.17 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, MeOD-*d*$_4$) δ 166.8 (d, *J* = 253.3 Hz), 148.9, 138.1 (d, *J* = 3.2 Hz), 137.2, 131.3 (d, *J* = 9.6 Hz), 131.1, 128.4, 124.6, 121.1, 117.1 (d, *J* = 23.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, MeOD-*d*$_4$) δ -107.5. m.p. 200 – 206 °C. IR: ν_{max} 3097, 1175, 1126, 1080 cm^{-1}. HRMS: m/z calculated for $C_{12}H_9ClFN_4O_2S^+$, 327.0113 $[M+H]^+$. Found m/z 327.0104, Δ = -3.0 ppm. R_f (5% MeOH in DCM) = 0.19



*N-(6-Chloropyridin-3-yl)-4-fluorobenzenesulfonamide (**3ai**).* Following General Procedure 3 on a 0.2 mmol scale. Flash column chromatography (20% EtOAc in petroleum ether) afforded **3ai** as a white crystalline solid (39.0 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 2.6 Hz, 1H), 7.79 (ddd, *J* = 9.9, 5.0, 2.6 Hz, 2H), 7.73 (s, 1H), 7.60 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.19 – 7.11 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.7 (d, *J* = 256.9 Hz), 148.1, 142.9, 134.5 (d, *J* = 3.3 Hz), 132.6, 132.6, 130.1 (d, *J* = 9.5 Hz), 125.0, 116.9 (d, *J* = 22.8 Hz). m.p. 137 – 139 °C. IR: ν_{max} 3109, 2890, 1589, 1494, 1458, 1325, 1171, 1155, 1088 cm^{-1}. HRMS: m/z calculated for $C_{11}H_9ClFN_2O_2S^+$, 287.0052 $[M+H]^+$. Found m/z 287.0052, Δ = 0.1 ppm.



*N-(4-(Methylsulfinyl)phenyl)-5-(5-(trifluoromethyl)isoxazol-3-yl)thiophene-2-sulfonamide (**3aj**).*Following General Procedure 3 on a 0.2 mmol scale. Flash column chromatography (0 – 2% MeOH in DCM) afforded **3aj** as a white crystalline solid (93 mg, 53%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 11.11 (s, 1H), 8.12 (q, *J* = 1.0 Hz, 1H), 7.84 (d, *J* = 4.0 Hz, 1H), 7.76 (d, *J* = 4.0 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.39 – 7.31 (m, 2H), 2.68 (s, 3H).^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 157.7 (q, J = 42.2 Hz), 157.4, 142.6, 141.5, 139.6, 133.4, 133.2, 130.8, 125.2, 120.3, 117.6 (q, J = 270.2 Hz), 106.0, 43.01. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -63.2. m.p. 222 – 224 °C. IR: ν_{max} 3134, 3098, 3046, 2924, 2867, 1338, 1316, 1151 cm^{-1}. HRMS: m/z calculated for $C_{15}H_{11}F_3N_2O_4S_3^+$, 436.9906 $[M+H]^+$. Found m/z 436.9897, Δ = -2.0 ppm.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website and contains details of experimental set-up, optimization data and NMR spectra. The data underlying this study are available in the published article and its Supporting Information.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest(s) other than WJ, PM, ELF and DCB are employees and stockholders of Pfizer Inc.

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REFERENCES

(1) a) Smith, D. A.; Jones, R. M. The sulfonamide group as a structural alert: A distorted story? *Curr. Opin. Drug Discov. Devel.* **2008,** *11,* 72 – 79; b) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem. (Z)* **2018,** *376,* 5.

(2) Petkowski, J. J.; Bains, W.; Seager, S. Natural Products Containing a Nitrogen–Sulfur Bond. *J. Nat. Prod.* **2018**, *81,* 423 – 446.
(3) a) Zhao, C.; Rakesh, K. P.; Ravidar, L.; Fang, W.-Y.; Qin, H.-L. Pharmaceutical and medicinal significance of sulfur (S^{VI})-Containing motifs for drug discovery: A critical review. *Eur. J. Med. Chem.* **2018**, *162,* 679–734; b) Kalgutkar, A. S.; Jones, R.; Sawant, A. in *Metabolism, Pharmacokinetics and Toxicity of Functional Groups: Impact of the Building Blocks of Medicinal Chemistry on ADMET*; Smith, D. A., Ed.; Royal Society of Chemistry: Cambridge, UK, **2010**, 210 – 274.
(4) For examples of multicomponent reactions, see: a) DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. Synthesis of Aryl Sulfonamides *via* Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids. *J. Am. Chem. Soc.* **2013**, *135*, 10638 – 10641; b) Chen, Y.; Murray, P. R. D.; Davies, A. T.; Willis, M. C. Direct Copper-Catalyzed Three-Component Synthesis of Sulfonamides *J. Am. Chem. Soc.* **2018**, *140*, 8781 – 8787; c) Bajohr, J.; Diallo, A. G.; Whyte, A.; Gaillard, S.; Renaud, J.-L. Lautens, M. Palladium-Catalyzed Domino Heck/Sulfination: Synthesis of Sulfonylated Hetero- and Carbocyclic Scaffolds Using DABCO-Bis(sulfur dioxide). *Org. Lett.* **2021**, *23*, 2797 – 2801; d) Pedersen, P. S.; Blakemore, D. C.; Chinigo, G. M.; Knauber, T.; MacMillan, D. W. C. One-Pot Synthesis of Sulfonamides from Unactivated Acids and Amines *via* Aromatic Decarboxylative Halosulfonylation. *J. Am. Chem. Soc.* **2023**, *145*, 21189 – 21196; e) Zhang, M.; Liu, L.; Wang, B.; Yang, Y.; Liu, Y.; Wang, Z.; Wang, Q. Direct Synthesis of Sulfonamides *via* Synergetic Photoredox and Copper Catalysis. *ACS Catal.* **2023**, *13*, 11580 – 11588. For examples of S-N bond formation towards sulfonamides, see: f) Caddick, S.; Wilden, J. D.; Judd, D. B. Direct Synthesis of Sulfonamides and Activated Sulfonate Esters from Sulfonic Acids. *J. Am. Chem. Soc.* **2004**, *126*, 1024 – 1025; g) Wright, S. W.; Hallstrom, K. N. A Convenient Preparation of Heteroaryl Sulfonamides and Sulfonyl Fluorides from Heteroaryl Thiols. *J. Org. Chem.* **2006**, *71*, 1080 – 1084; h) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. Direct Conversion of Thiols to Sulfonyl Chlorides and Sulfonamides. *J. Org. Chem.* **2009**, *74*, 9287 – 9291; i) Taniguchi, N. Copper-Catalyzed Formation of Sulfur-Nitrogen Bonds by Dehydrocoupling of Thiols with Amines. *Eur. J. Org. Chem.* **2010**, *2010*, 2670 – 2673; j) Tang, X.; Huang, L.; Qi, C.; Wu, X.; Wu, W.; Jiang, H. Copper-catalyzed sulfonamides formation from sodium sulfinates and amines. *Chem. Commun.* **2013**, *49*, 6102 – 6104; k) Pan, X.; Gao, J.; Liu, J.; Lai, J.; Jiang, H.; Yuan, G. Synthesis of sulfonamides *via* I_2-mediated reaction of sodium sulfinates with amines in an aqueous medium at room temperature. *Green Chem.* **2015**, *17*, 1400 – 1403; l) Jiang, J.; Zeng, S.; Chen, D.; Cheng, C.; Deng, W.; Xiang, J. Synthesis of *N*-arylsulfonamides *via* Fe-promoted reaction of sulfonyl halides with nitroarenes in an aqueous medium. *Org. Biomol. Chem.* **2018**, *16*, 5016 – 5020. For examples of C-N bond formation towards sulfonamides, see: m) Burton, G.; Cao, P.; Li, G.; Rivero, R. Palladium-Catalyzed Intermolecular Coupling of Aryl Chlorides and Sulfonamides under Microwave Irradiation. *Org. Lett.* **2003**, *5*, 4373 – 4376; n) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. Copper-catalyzed cross-coupling of sulfonamides with aryl iodides and bromides facilitated by amino acid ligands. *Tetrahedron Lett.* **2005**, *46*, 7295 – 7298; o) Baffoe, J.; Hoe, M. Y.; Touré, B. B. Copper-Mediated *N*-Heteroarylation of Primary Sulfonamides: Synthesis of Mono-*N*-heteroaryl Sulfonamides. *Org. Lett.* **2010**, *12*, 1532 – 1535; p) Rosen, B. R.; Ruble, J. C.; Beauchamp, T. J.; Navarro, A. Mild Pd-Catalyzed *N*-Arylation of Methanesulfonamide and Related Nucleophiles: Avoiding Potentially Genotoxic Reagents and Byproducts. *Org. Lett.* **2011**, *13*, 2564 – 2567; q) Shekhar, S.; Dunn, T. B.; Kotecki, B. J.; Montavon, D. K.; Cullen, S. C. A General Method for Palladium-Catalyzed Reactions of Primary Sulfonamides with Aryl Nonaflates. *J. Org. Chem.* **2011**, *76*, 4552 – 4563; r) Zheng, Q.-Z.; Liang, Y.-F.; Qin, C.; Jiao, N. Ru(II)-catalyzed intermolecular C-H amidation of weakly coordinating ketones. *Chem. Commun.* **2013**, *49*, 5654 – 5656; s) Bhanuchandra, M.; Yadav, M. R.; Rit, R. K.; Kuram, M. R.; Sahoo, A. K. Ru(II)-catalyzed intermolecular *ortho*-C-H amidation of aromatic ketones with sulfonyl azides. *Chem. Commun.* **2013**, *49*, 5225 – 5227; t) Cao, X.; Bai, Y.; Xie, Y.; Deng, G.-J. Palladium-catalyzed arylation of aryl sulfonamides with cyclohexanones. *J. Mol. Catal. A Chem.* **2014**, *383*, 94 – 100; u) Kim, T.; McCarver, S. J.; Lee, C.; MacMillan, D. W. C. Sulfonamidation of Aryl and Heteroaryl Halides through Photosensitized Nickel Catalysis. *Angew. Chem. Int. Ed.* **2018**, *57*, 3488 – 3492. For reviews, see: v) Anderson, K. K. *Comprehensive Organic Chemistry*; Pergamon Press: Oxford, **1979**, 331– 350; w) Das, T. C.; Quadri, S. A.; Farooqui, M. Recent advances in synthesis of sulfonamides : A review. *J. Chem. Biol. Interfaces* **2018**, *8,* 194 – 204; x) Mulina, O. M.; Ilovaisky, A. I.; Terent'ev, A. O. Oxidative Coupling with S-N Bond Formation. *Eur. J. Org. Chem.* **2018**, *2018*, 4648 – 4672; y) Joseph, D.; Idris, M. A.; Chen, J.; Lee, S. Recent Advances in the Catalytic Synthesis of Arylsulfonyl Compounds. *ACS Catal.* **2021**, *11*, 4169 – 4204.
(5) Skipper, P. L.; Kim, M.; Sun, H.-L. P.; Wogan, G. N.; Tannenbaum, S. R. Monocyclic aromatic amines as potential human carcinogens: old is new again. *Carcinogenesis* **2010**, *31,* 50 – 58.
(6) Iakovenko, R. O.; Chrenko, D.; Kristek, J.; Desmedt, E.; Zálešák, F.; Vleeschouwer, F. D.; Pospíšil, J. Heteroaryl sulfonamide synthesis: scope and limitations. *Org. Biomol. Chem.* **2022**, *20*, 3154 – 3159.
(7) For selected examples, see: a) Zhang, W.; Xie, J.; Rao, B.; Luo, M. Iron-Catalyzed *N*-Arylsulfonamide Formation through Directly Using Nitroarenes as Nitrogen Sources. *J. Org. Chem.* **2015,** *80,* 3504 – 3511; b) Eid, N.; Karamé, I.; Andrioletti, B. Straightforward and Sustainable Synthesis of Sulfonamides in Water under Mild Conditions. *Eur. J. Org. Chem.* **2018**, *2018*, 5016 – 5022; c) Li, X.; Chen, F.; Lu, G. P. Fe-based metal-organic frameworks for the synthesis of *N*-arylsulfonamides *via* the reactions of sodium arylsulfinates or arylsulfonyl chlorides with nitroarenes in water. *Tetrahedron Lett.* **2018,** *59,* 4226 – 4230; d) Yang, B.; Lian, C.; Yue, G.; Liu, D.; Wei, L.; Ding, Y.; Zhao, X. Synthesis of *N*-arylsulfonamides through a Pd-catalyzed reduction coupling reaction of nitroarenes with sodium arylsulfinates. *Org. Biomol. Chem.* **2018,** *16,* 8150 – 8154; e) Liu, S.; Chen, R.; Zhang, J. Copper-Catalyzed Redox Coupling of Nitroarenes with Sodium Sulfinates. *Molecules* **2019,** *24,* 1407 – 1418; f) Lasso, J. D. ; Castillo-Pazos, D. J. ; Sim, M. ; Barroso-Flores, J. ; Li, C.-J. EDA mediated S-N bond coupling of nitroarenes and sodium sulfinate salts. *Chem. Sci.* **2023**, *14*, 525 – 532. For multicomponent examples, see: g) Chen, K.; Chen, W.; Han, B.; Chen, W.; Liu, M.; Wu, H. Sequential C-S and S-N Coupling Approach to Sulfonamides. *Org. Lett.* **2020**, *22,* 1841 – 1845; h) Marset, X.; Torregrosa-Crespo, J.; Martínez-Espinosa, R. M.; Guillena, G.; Ramón, D. J. Multicomponent

synthesis of sulfonamides from triarylbismuthines, nitro compounds and sodium metabisulfite in deep eutectic solvents. *Green Chem.* **2019**, *21*, 4127 – 4132; i) Wang, X.; Yang, M.; Kuang, Y.; Liu, J. B.; Fan, X.; Wu, J. Copper-catalyzed synthesis of sulfonamides from nitroarenes *via* the insertion of sulfur dioxide. *Chem. Commun.* **2020,** *56,* 3437 – 3440; j) Li, Y.; Wang, M.; Jiang, X. Straightforward Sulfonamidation *via* Metabisulfite-Mediated Cross Coupling of Nitroarenes and Boronic Acids under Transition-Metal-Free Conditions. *Chin. J. Chem.* **2020,** *38,* 1521 – 1525. For a review, see: k) Xia, J.; Zhang, K.; Mahmood, E. A. Methods for the synthesis of *N*-aryl sulfonamides from nitroarenes: an overview. *J. Sulfur Chem.* **2021**, *42*, 692 – 710.

(8) Reddy, R. J.; Kumari, A. H. Synthesis and applications of sodium sulfinates (RSO_2Na): a powerful building block for the synthesis of organosulfur compounds. *RSC Advances* **2021**, *11,* 9130 – 9221.

(9) Ley, S. V.; Ingham, R. J.; O'Brien, M.; Browne, D. L. Camera-enabled techniques for organic synthesis. *Beilstein J. Org. Chem.* **2013,** *9,* 1051 – 1072.

(10) Gharat, N. N.; Rathod, V. K. *Ultrasound-assisted organic synthesis. In Green sustainable process for chemical and environmental engineering and scienc*e **2020,** 1 – 41. Elsevier.

(11) a) Ulman, A.; Urankar, E. Novel Synthesis of 4-[Alkyl(aryl)sulfonyl]benzaldehydes: Alkyl(aryl)sulfinate Anion as a Nucleophile in Aromatic Substitutions. *J. Org. Chem.* **1989,** *54,* 4691 – 4692; b) Yuan, Y. Q.; Guo, S. R. A Mild and Efficient Synthesis of Aryl Sulfones from Aryl Chlorides and Sulfinic Acid Salts Using Microwave Heating. *Synlett* **2011,** *18,* 2750 – 2756.

(12) Maloney, K. M.; Kuethe, J. T.; Linn, K. A Practical, One-Pot Synthesis of Sulfonylated Pyridines. *Org. Lett.* **2013**, *13*, 102 – 105.

(13) Shen, Q.; Wu, J.; Zhao, Q. CN107033046A.

(14) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. Biology-Oriented Synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 10800 – 10826.

(15) Konteatis, Z. What makes a good fragment in fragment-based drug discovery? *Expert Opin. Drug Discov.* **2021,** *16,* 723 – 726.

(16) López-López, E.; Naveja, J. J.; Medina-Franco, J. L. DataWarrior: an evaluation of the open-source drug discovery tool. *Expert Opin. Drug Discov.* **2019,** *14,* 335 – 341.

(17) a) Hunter, W. H.; Sprung, M. M. The Piria Reaction. I. The Over-All Reaction. *J. Am. Chem. Soc.* **1931,** *53,*1432 – 1443; b) Lauer, W. M.; Sprung, M. M.; Langkammerer, C. M. The Piria Reaction. III. Mechanism Studies. *J. Am. Chem. Soc.* **1936,** *58,* 225 – 228; c) Benson, G. A.; Spillane, W. J. Sulfamic Acid and Its *N*-Substituted Derivatives. *Chem. Rev.* **1980,** *80,* 151 – 186.

(18) Beaudoin, D.; Wuest, J. D. Dimerization of Aromatic *C*-Nitroso Compounds. *Chem. Rev.* **2016**, *116*, 258 – 286.

(19) Yamamoto, H.; Momiyama, N. Rich chemistry of nitroso compounds. *Chem. Commun.* **2005**, 3514 – 3525.

(20) Conte, M. L.; Carroll, K. S. Chemoselective Ligation of Sulfinic Acids with Aryl-Nitroso Compounds. *Angew. Chem. Int. Ed.* **2012**, *51*, 6502 – 6505.

(21) Fabio, P. F.; Lanzilotti, A. E.; Lang Jr, S. A. Synthesis of carbon-14 and deuterium labeled 3-nitro-6-propoxyimidazo[1,2-b]pyridazine – An antiparasitic agent. *J. Label. Compd. Radiopharm.* **1978**, *15*, 407 – 412.

(22) Zhu, X.; Wei, J.; Hu, C.; Xiao, Q.; Cai, L.; Wang, H.; Xie, Y.; Sheng, R. Difluorocarbene-Induced Ring Opening of Tetrahydrofuran with $TMSCF_2Br$ for Difluoromethoxybutylation of *N*-aryl-*N*-hydroxylamines. *Eur. J. Org. Chem.* **2022**, *2022*, e202200629.

(23) Ding, Z.; Ma, M.; Zhong, C.; Wang, S.; Fu, Z.; Hou, Y.; Liu, Y.; Zhong, L.; Chu, Y.; Li, F.; Song, C.; Wang, Y.; Yang, J.; Li, W. Development of novel phenoxy-diketopiperazine-type plinabulin derivatives as potent antimicrotubule agents based on the co-crystal structure. *Bioorg. Med. Chem.* **2020**, *28*, 115186.