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ARTICLE

SO_2F_2 mediated transforming pyrozolones to pyrazolyl fluorosulfates

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The construction of a class of novel *N*-heterocyclic molecules containing both pyrazole and fluorosulfate functionalities was achieved through the reactions of pyrazolones with SO_2F_2 in good to excellent yields. The fluorosulfate moieties were utilized as versatile building blocks in Suzuki coupling reaction and SuFEx click chemistry.

Functionalized pyrazoles as core motifs are present in numerous biologically active molecules with wide applications in pharmaceuticals, agrochemicals, and other functional materials.[1] Many pyrazole derivatives have been successfully developed as drugs or drug candidates for the treatment of a variety of diseases (figure 1).[2] Among various type of pyrazoles, pyrazolones have been particularly recognized as an outstanding scaffolds for the discovery and development of new drugs since Knorr and Filehne developed phenazone, the very first antipyretic and analgesic in 1883.[3] Because of the great pharmaceutical importance of pyrazole moieties, development of efficient and reliable methods to synthesize pyrazole-containing scaffolds continues to be of great significance, and therefore, extensive investigations have been performed.[4]

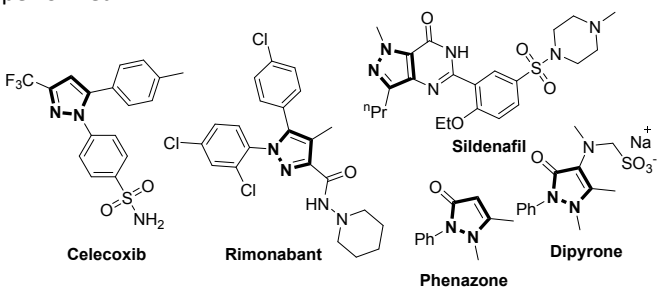

Figure 1. Representative drugs containing pyrazole moieties

On the other hand, arylfluorosulfates as the phenolic derivatives were reported in the early 1930s,[5] however, studies on this functionality (-OSO_2F) were very limited in the past decades, mainly due to the lack of applicable methods for their preparation. Recently, the Sharpless group discovered a mild and robust procedure of using phenols and SO_2F_2 [6] under base conditions to obtain a series of arylfluorosulfates compounds,[7] which further spurred comprehensive studies of arylfluorosulfates in chemical synthesis and transformation,[8] medicinal chemistry and biological chemistry.[9] Compared with sulfonyl fluoride group (R-SO_2F),[10] the lower intrinsic reactivity of the fluorosulfate (R-OSO_2F) assured the reduced off-target labeling in a cellular context and largely had no influence on human proteome, what's more, its higher chemical stability was found to be valuable for the design of targeted covalent drugs (Figure 2). Therefore, the screening of libraries of chemically diverse fluorosulfates play an extremely important role in drug modification and discovery.[9h] Based on the significance of both pyrazole and fluorosulfate, finding a portal to assembly of molecules bearing both pyrazole and fluorosulfate moieties would unquestionably increase the chance of identifying drug candidates as well as lead compounds optimization.[11]

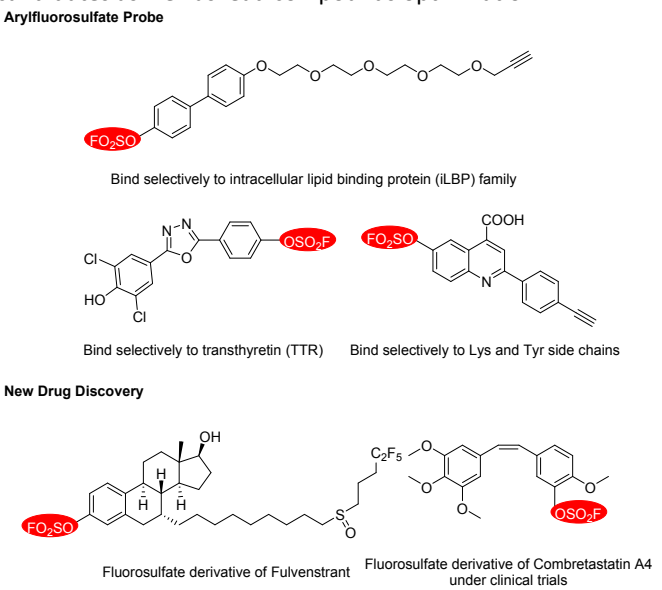

Figure 2. Application of arylfluorosulfate in fluorescent probe and drug discovery

However, nowadays nearly all fluorosulfates are derived from their phenolic compounds, which has unfortunately limited the diversifying and accessing to new fluorosulfates. Considering that pyrazolones can be readily transformed into their enol forms under appropriate conditions, we envision that the hydroxy group of the newly formed enols would have the

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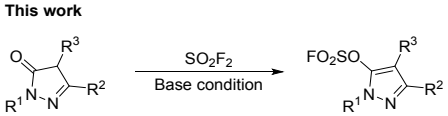
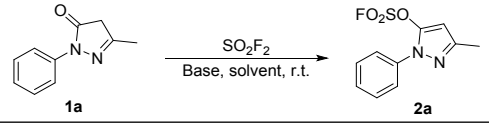
nucleophilic ability to react with SO_2F_2 by the promotion of bases to provide a portal to a new class of fluorosulfates. Herein, we described the development of a new method for accessing a library of pyrazole-containing fluorosulfates heterocycles though the reaction of pyrazolones with SO_2F_2 under very mild condition (Scheme 1).



Scheme 1. Base promoted fluorosulfation of pyrazolone.

We initially chose 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **1a** as model substrate to test feasibility of formation of fluorosulfate **2a** (Table 1). After screening a large variety of conditions, we were delighted to find that, a moderate yield of 46% was obtained when 3.0 equivalents of Et_3N was used as base in the solvent of DCM at room temperature (entry 1). Organic bases were found to be more efficient in this transformation than inorganic bases. The use of *N, N*-diisopropylethylamine (DIPEA) provided the desired product **2a** in 95% yield (entry 2) while most inorganic bases were found to be ineffective for promotion of this reaction (entry 3 and 4, more details see SI) which could be attributed to their poor solubilities in organic solvents. A slight decreasing of the yield (85%, entry 5) was detected when the loading of DIPEA was reduced to 1.0 equivalent. The use of 1.5 equivalent of DIPEA was found to be the best option (entry 6). The use of other solvents such as DMSO and H_2O (entry 7 and 8) were found to be significant less effective than the use of DCM. Control experiments indicated that no product was generated without the assistance of base (entry 9).

Table 1. Optimization of the reaction conditions. [a]



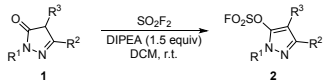
1a **2a**

Entry	Base (X equiv.)	Solvent	Yield (%) [b]
1	Et_3N (3.0)	DCM	46
2	DIPEA (3.0)	DCM	95
3	$NaHCO_3$ (3.0)	DCM	21
4	Cs_2CO_3 (3.0)	DCM	29
5	DIPEA (1.0)	DCM	85
6	DIPEA (1.5)	DCM	93
7	DIPEA (1.5)	DMSO	70
8	DIPEA (1.5)	H_2O	46
9	-	DCM	n.d.

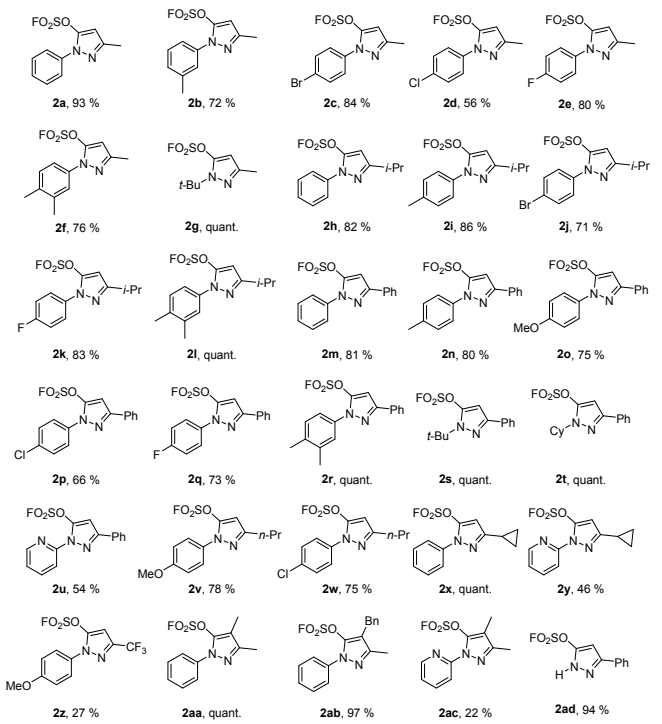
[a] Reaction conditions: **1a** (0.1 mmol), base (0.3 mmol, 3 equiv.) and DCM (1.5 mL) were mixed in a tube with a SO_2F_2 balloon and reacted at room temperature for 10 h. [b] The yield was determined by HPLC using pure **2a** as the external standard. [$t_{\mathbf{2a}}$ = 8.020 min, λ_{max} = 241.7 nm, methanol / water = 70 : 30 (v / v)].

Under the optimal conditions (Table 1, entry 6), various pyrazolones, including 2,5-disubstituted and 2,4,5-trisubstituted ones, were examined for the construction of the corresponding fluorosulfates (Table 2). 2-Aryl or alkyl substituted pyrazolones were all successfully transformed into their corresponding fluorosulfates in nearly quantitative yields. Both electron-donating and electron-withdrawing groups on 2-position of phenyl rings were well compatible with this protocol (**2i** and **2k**, **2o** and **2q**). Bis-substitutions on phenyl (**1f** and **1l**) were also smoothly transformed to the corresponding fluorosulfate products (**2f** and **2l**) in good and quantitative yields, respectively. Heteroaryl substituted substrates on 2-position such as **1u** and **1y** produced their products **2u** and **2y** in relatively lower yields (54% and 46% respectively) which could probably be attributed to the strong electron-deficient property of pyridine motif. Different substitutions on 5-position of pyrazolones were also examined for their feasibility of fluorosulfation. Phenyl, methyl, propyl, isopropyl, cyclopropyl groups (**1m**, **1b**, **1v**, **1h**, **1x**) were also compatible to this reaction to provide their corresponding products (**2m**, **2b**, **2v**, **2h**, **2x**) smoothly with satisfactory yields. However, strong electron-withdrawing group of CF_3 substituted pyrazolone **1z** significantly affected the product yield, which could be considered because of the weak stability and nucleophilicity of enol intermediates. Pyrazolones with an additional substitution on 4-position (**1aa** and **1ab**) were also smoothly transformed to their corresponding fluorosulfates with excellent yields (**2aa** and **2ab**). Non-protected pyrazolone **1ad** was also tolerable to this condition providing a satisfactory 94% yield of product **2ad**.

Table 2. Substrate scope studies [a]



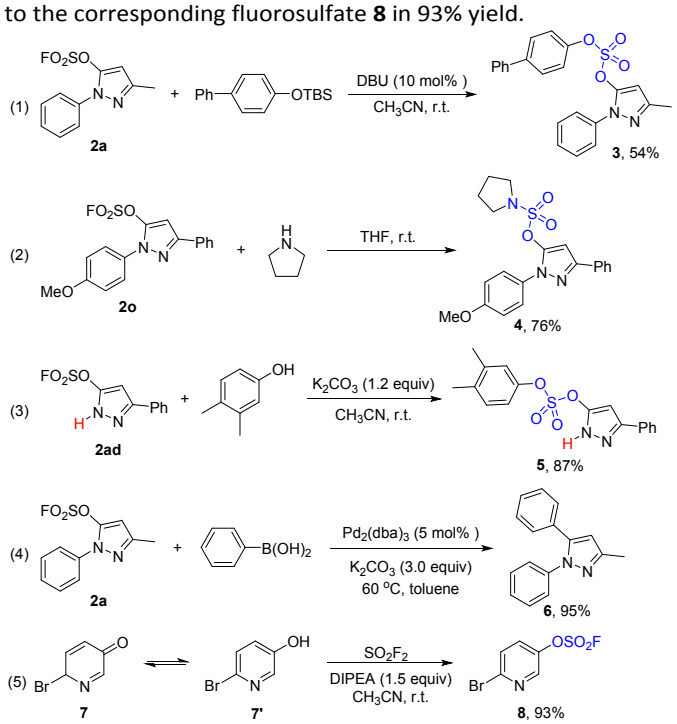
1 **2**



[a] Reaction conditions: **1** (1.0 mmol), DIPEA (1.5 equiv., 194 mg) and DCM (5 mL) were mixed in a tube with a SO_2F_2 balloon and reacted at room temperature for 5-10h.

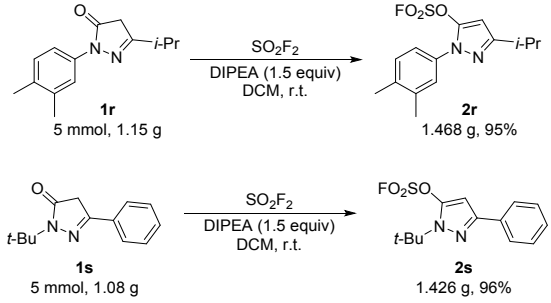
The fluorosulfate (-OSO_2F) unit was regarded as both a good leaving group and a robust connector in SuFEx chemistry. The utilization of the new pyrazole-containing fluorosulfates for further chemical transformations (Scheme 2) was also achieved. In the presence of 10 mol % of 1,8-diazabicycloundec-7-ene (DBU), SuFEx reaction of **2a** with the *tert*-butyldimethylsilyl (TBS) ether of phenol in acetonitrile afforded the desired sulfonate **3** in 54% isolated yield. Similarly, sulfamide **4** was also generated

in 76% yield when pyrrolidine was used as SuFEx coupling partner in THF. The fluorosulfate **2ad** generated from the non-protected pyrazolone was also smoothly transformed into the corresponding sulfonate **5** after SuFEx click reaction with 3,4-dimethylphenol. Aryl fluorosulfates were reported to undergo Suzuki-Miyaura reaction with boronic acids,[12] interestingly, fluorosulfate-containing pyrazole **2a** was applied to the Suzuki reaction using the $Pd_2(dba)_3$ catalysis to provide the desired product **6** in 95% isolated yield. What's more, the tautomerization of pyridone **7** was also successfully converted to the corresponding fluorosulfate **8** in 93% yield.



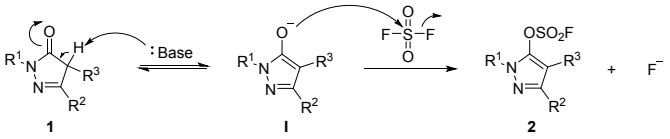
Scheme 2. SuFEx chemistry and Suzuki-Miyaura reaction of the new fluorosulfates

To further demonstrate the practicality of this method, a couple of 5.0 mmol scale reactions were carried out using pyrazolones **1r** and **1s**. Notably, the efficiencies of the grams-scale reactions were not decreased (Scheme 3) to obtain their corresponding products **2r** and **2s** in 95% and 96% yields, respectively.



Scheme 3. Gram-scale synthesis.

A more detailed mechanism was proposed and illustrated in Scheme 4. Initially, starting material pyrazolone **1** was transformed into its enol form **I** under base condition (which was in equilibrium with its own ketone). Subsequently, SO_2F_2 was attacked by the enol oxygen to generate the product **2** with the release of fluoride anion. Because of the aromaticity and aromatic character of the products, the transformation of non-aromatic pyrazolone **1** to the fluorosulfated pyrazolone **2** is theoretically favoured.



Scheme 4. Proposed mechanism.

Conclusions

In conclusion, a method providing a portal to a class of novel fluorosulfate-containing pyrazoles heterocycles was developed through the reactions of corresponding pyrazolones with SO_2F_2 featuring a wide substrate scope and broad functional group compatibility. The fluorosulfate moieties (-OSO_2F) served as both SuFEx coupling partner and leaving group in SuFEx chemistry and Suzuki reaction. This class of heterocycles have great potential to be used as covalent probes and inhibitors for the discovery of novel therapeutics. Further studies of these scaffolds in chemical biology and drug discovery are ongoing in our laboratory.

Experimental section

General procedure for synthesis of pyrazolone derivatives 1

1g, **1s**, **1t**, **1ab** were prepared according to the literature,[13] others were prepared according to the literature.[14]All homemade starting materials are identical to those reported regarding the ^1H and ^{13}C NMR and melting points (if applicable).

General procedure for synthesis of compound 2

An oven-dried reaction tube (20 mL) was charged with pyrazolone **1** (1 mmol), DIPEA (1.5 mmol), 5 mL DCM and a SO_2F_2 balloon. The mixture was stirred at room temperature for 5-10 h with monitoring by TLC. After the reaction was completed, the solution was concentrated to dryness and the residue was purified through silica gel chromatography using a mixture of ethyl acetate and PE to afford the desired products **2**.

General procedure for synthesis of compound 3

An oven-dried reaction tube (20 mL) was charged with 3-methyl-1-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2a**, 0.5 mmol, 128 mg), ([1,1'-biphenyl]-4-yloxy)(tert-butyl)dimethylsilane (0.6 mmol, 171 mg), DBU (10 mol%, 7.6 mg) and CH_3CN (3 mL), the mixture was reacted at room temperature for 1 h with monitoring by TLC. After the reaction was completed, the solution was concentrated to dryness and purified through silica gel chromatography using 5 % EtOAc / PE to afford the desired products **3** in 54 % yield (110 mg).

General procedure for synthesis of compound 4

An oven-dried reaction tube (20 mL) was charged with 1-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2o**, 0.5 mmol, 174 mg), pyrrolidine (0.6 mmol, 42.6 mg) and THF (3 mL), the mixture was reacted at room temperature for overnight with monitoring by TLC. After the reaction was completed, the solution was concentrated to dryness and purified through silica gel chromatography using 40 % DCM / PE to afford the desired products **4** in 76 % yield (153 mg).

General procedure for synthesis of compound 5

An oven-dried reaction tube (20 mL) was charged with 3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2ad**, 0.5 mmol, 121 mg), 3,4-dimethylphenol (0.6 mmol, 73.2 mg) and THF (3 mL), the mixture was reacted at room temperature for overnight with monitoring by TLC. After the reaction was completed, the solution was concentrated to dryness and purified through silica gel chromatography using a mixture of Et_3N / EtOAc / PE (1/20/100) to afford the desired products **5** in 87 % yield (150 mg).

General procedure for synthesis of compound 6

An oven-dried reaction tube (20 mL) was charged with phenylboronic acid (1.5 mmol, 183 mg), $Pd_2(dba)_3$ (45 mg, 5 mol%), K_2CO_3 (3 mmol, 414 mg) and 3-methyl-1-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2a**, 1 mmol, 256 mg), the reaction tube was then capped with a rubber septum and placed under a nitrogen atmosphere (through a needle attached to a vacuum manifold). 5 mL toluene was then added using syringes. The resulting mixture was stirred at 60 °C for overnight with monitoring by TLC. After the reaction was completed, the solution was concentrated to dryness and purified through silica gel chromatography using 10 % EtOAc / PE to afford the desired products **6** in 95 % yield (223 mg).

General procedure for synthesis of compound 8

An oven-dried reaction tube (20 mL) was charged with 6-bromopyridin-3-ol **7'** (1 mmol, 173 mg), DIPEA (1.5 mmol), 5 mL DCM and a SO_2F_2 balloon. The mixture was stirred at room temperature for 3 h with monitoring by TLC. After the reaction was completed, the solution was concentrated to dryness and the residue was purified through silica gel chromatography using 20 % EtOAc / PE to afford the desired products **8** in 93 % yield (238 mg).

3-Methyl-1-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2a**). Colorless liquid, 238 mg, 93 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.47 (m, 4H), 7.40 (t, *J* = 7.2 Hz, 1H), 6.22 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4 (s), 141.3 (s), 136.8 (s), 129.6 (s), 128.5 (s), 123.5 (s), 96.2 (s), 14.7 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.6 (s, 1F). ESI-MS HRMS calculated for $C_{10}H_{10}FN_2O_3S$ $[M+H]^+$ 257.0391, found 257.0390.

3-Methyl-1-(m-tolyl)-1H-pyrazol-5-yl sulfurofluoridate (**2b**). Colorless liquid, 194 mg, 72 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.30-7.29 (m, 1H), 7.22-7.20 (m, 1H), 6.20 (s, 1H), 2.41 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2 (s), 141.2 (s), 139.8 (s), 136.7 (s), 129.28 (s), 129.27 (s), 124.2 (s), 120.4 (s), 96.0 (s), 21.5 (s), 14.6 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.6 (s, 1F). ESI-MS HRMS calculated for $C_{11}H_{12}FN_2O_3S$ $[M+H]^+$ 271.0547, found 271.0543.

1-(4-Bromophenyl)-3-methyl-1H-pyrazol-5-yl sulfurofluoridate (**2c**). Colorless liquid, 281 mg, 84 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 8.9 Hz, 2H), 6.22 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8 (s), 141.3 (s), 135.9 (s), 132.8 (s), 124.7 (s), 122.1 (s), 96.6 (s), 14.7 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.7 (s, 1F). ESI-MS HRMS calculated for $C_{10}H_9BrFN_2O_3S$ $[M+H]^+$ 334.9496, found 334.9494.

1-(4-Chlorophenyl)-3-methyl-1H-pyrazol-5-yl sulfurofluoridate (**2d**). Yellow liquid, 162 mg, 56 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.45 (m, 4H), 6.22 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7 (s), 141.3 (s), 135.3 (s), 134.2 (s), 129.8 (s), 124.5 (s), 96.5 (s), 14.6 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.7 (s, 1F). ESI-MS HRMS calculated for $C_{10}H_9ClFN_2O_3S$ $[M+H]^+$ 291.0001, found 291.0001.

1-(4-Fluorophenyl)-3-methyl-1H-pyrazol-5-yl sulfurofluoridate (**2e**). Yellow liquid, 219 mg, 80 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.20-7.16 (m, 2H), 6.21 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, *J* = 249.0 Hz), 149.5 (s), 141.3 (s), 132.9 (d, *J* = 3.1 Hz), 125.6 (d, *J* = 8.7 Hz), 116.6 (d, *J* = 23.1 Hz), 96.2 (s), 14.6 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.5 (s, 1F), -112.38 – -112.43 (m, 1F). ESI-MS HRMS calculated for $C_{10}H_9F_2N_2O_3S$ $[M+H]^+$ 275.0296, found 275.0295.

1-(3,4-Dimethylphenyl)-3-methyl-1H-pyrazol-5-yl sulfurofluoridate (**2f**). Yellow liquid, 217 mg, 76 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.21 (m, 2H), 6.18 (s, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0 (s), 141.2 (s), 138.2 (s), 137.3 (s), 134.5 (s), 130.5 (s), 124.8 (s), 120.8 (s), 95.8 (s), 19.9 (s), 19.6 (s), 14.6 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.5 (s, 1F). ESI-MS HRMS calculated for $C_{12}H_{14}FN_2O_3S$ $[M+H]^+$ 285.0704, found 285.0704.

1-(*Tert*-butyl)-3-methyl-1H-pyrazol-5-yl sulfurofluoridate (**2g**). Yellow liquid, 236 mg, quant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 2.22 (s, 3H), 1.60 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9 (s), 141.6 (s), 94.7 (s), 60.6 (s), 29.4 (s), 14.5 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.3 (s, 1F). ESI-MS HRMS calculated for $C_8H_{14}FN_2O_3S$ $[M+H]^+$ 237.0704, found 237.0702.

3-Isopropyl-1-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2h**). Yellow liquid, 233 mg, 82 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 6.24 (s, 1H), 3.02 (hept, *J* = 6.9 Hz, 1H), 1.32 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4 (s), 141.1 (s), 137.0 (s), 129.6 (s), 128.4 (s), 123.6 (s), 93.5 (s), 28.8 (s), 22.4 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.5 (s, 1F). ESI-MS HRMS calculated for $C_{12}H_{14}FN_2O_3S$ $[M+H]^+$ 285.0704, found 285.0701.

3-Isopropyl-1-(*p*-tolyl)-1H-pyrazol-5-yl sulfurofluoridate (**2i**). Yellow liquid, 257 mg, 86 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.22 (s, 1H), 3.01 (hept, *J* = 7.0 Hz, 1H), 2.40 (s, 3H), 1.31 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (s), 161.3 (s), 159.5 (s), 141.1 (s), 133.0 (d, *J* = 3.1 Hz), 125.6 (d, *J* = 8.7 Hz), 116.6 (d, *J* = 23.1 Hz), 93.5 (s), 28.8 (s), 22.3 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.5 (s, 1F). ESI-MS HRMS calculated for $C_{13}H_{16}FN_2O_3S$ $[M+H]^+$ 299.0860, found 299.0860.

1-(4-Bromophenyl)-3-isopropyl-1H-pyrazol-5-yl sulfurofluoridate (**2j**). Yellow liquid, 256 mg, 71 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.24 (s, 1H), 3.00 (hept, *J* = 7.1 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8 (s), 141.1 (s), 136.0 (s), 132.8 (s), 124.8 (s), 122.0 (s), 94.0 (s), 28.9 (s), 22.3 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.7 (s, 1F). ESI-MS HRMS calculated for $C_{12}H_{13}BrFN_2O_3S$ $[M+H]^+$ 362.9809, found 362.9807.

1-(4-Fluorophenyl)-3-isopropyl-1H-pyrazol-5-yl sulfurofluoridate (**2k**). Green liquid, 252 mg, 83 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.20-7.16 (m, 2H), 6.23 (s, 1H), 3.00 (hept, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (s), 141.0 (s), 138.5 (s), 134.5 (s), 130.1 (s), 123.5 (s), 93.2 (s), 28.8 (s), 22.4 (s), 21.2 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.5 (s, 1F), -112.57 - -112.62 (m, 1F). ESI-MS HRMS calculated for $C_{12}H_{13}F_2N_2O_3S$ $[M+H]^+$ 303.0609, found 303.0608.

1-(3,4-Dimethylphenyl)-3-isopropyl-1H-pyrazol-5-yl sulfurofluoridate (**2l**). Yellow liquid, 312 mg, quant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.22 (s, 2H), 6.21 (s, 1H), 3.01 (m, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 1.31 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (s), 141.0 (s), 138.2 (s), 137.2 (s), 134.7 (s), 130.5 (s), 124.9 (s), 120.9 (s), 93.1 (s), 28.8 (s), 22.5 (s), 20.0 (s), 19.6 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.5 (s, 1F). ESI-MS HRMS calculated for $C_{14}H_{18}FN_2O_3S$ $[M+H]^+$ 313.1017, found 313.1017.

1,3-Diphenyl-1H-pyrazol-5-yl sulfurofluoridate (**2m**). White solid, 259 mg, 81 %. Mp 56-57 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.1 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 3H), 7.39 (t, *J* = 7.3 Hz, 1H), 6.73 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4 (s), 142.0 (s), 136.9 (s), 132.1 (s), 129.7 (s), 129.1 (s), 128.9 (s), 128.8 (s), 125.7 (s), 123.7 (s), 93.9 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.9 (s, 1F). ESI-MS HRMS calculated for $C_{15}H_{12}FN_2O_3S$ $[M+H]^+$ 319.0547, found 319.0545.

3-Phenyl-1-(*p*-tolyl)-1H-pyrazol-5-yl sulfurofluoridate (**2n**). White solid, 264 mg, 80 %. Mp 84-85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.71 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1 (s), 141.9 (s), 139.0 (s), 134.4 (s), 132.2 (s), 130.2 (s), 129.0 (s), 128.9 (s), 125.7 (s), 123.7 (s), 93.6 (s), 21.3 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.9 (s, 1F). ESI-MS HRMS calculated for $C_{16}H_{14}FN_2O_3S$ $[M+H]^+$ 333.0704, found 333.0703.

1-(4-Methoxyphenyl)-3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2o**). White solid, 260 mg, 75 %. Mp 79-80 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.1 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.70 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 (s), 151.0 (s), 141.9 (s), 132.2 (s), 129.8 (s), 128.92 (s), 128.89 (s), 125.7 (s), 125.5 (s), 114.8 (s), 93.4 (s), 55.7 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.8 (s, 1F). ESI-MS HRMS calculated for $C_{16}H_{14}FN_2O_4S$ $[M+H]^+$ 349.0653, found 349.0651.

1-(4-Chlorophenyl)-3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2p**). Yellow liquid, 234 mg, 66 %. Mp 50-51 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.45 (t, *J* = 7.98 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 6.73 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7 (s), 141.9 (s), 135.4 (s), 134.6 (s), 131.8 (s), 129.9 (s), 129.2 (s), 129.0 (s), 125.7 (s), 124.7 (s), 94.2 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 40.1 (s, 1F). ESI-MS HRMS calculated for $C_{15}H_{11}ClFN_2O_3S$ $[M+H]^+$ 353.0157, found 353.0157.

1-(4-Fluorophenyl)-3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2q**). White solid, 246 mg, 73 %. Mp 59-61 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.3 Hz, 2H), 7.62-7.59 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 8.5 Hz, 2H), 6.72 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 (d, *J* = 249.4 Hz), 151.5 (s), 142.0 (s), 133.0 (d, *J* = 3.1 Hz), 131.9 (s), 129.2 (s), 129.0 (s), 125.8 (d, *J* = 8.8 Hz), 125.7 (s), 116.7 (d, *J* = 23.2 Hz), 93.9 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.9 (s, 1F), -111.86 – -111.92 (m, 1F). ESI-MS HRMS calculated for $C_{15}H_{11}F_2N_2O_3S$ $[M+H]^+$ 337.0453, found 337.0452.

1-(3,4-Dimethylphenyl)-3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2r**). Yellow solid, 346 mg, quant. Mp 58-59 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.40-7.36 (m, 2H), 7.32-7.30 (m, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 6.70 (s, 1H), 2.35 (s, 3H) 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0 (s), 141.9 (s), 138.3 (s), 137.7 (s), 134.5 (s), 132.2 (s), 130.6 (s), 128.93 (s), 128.90 (s) ,125.7 (s), 125.0 (s), 121.1 (s), 93.5 (s), 20.0 (s), 19.7 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.9 (s, 1F). ESI-MS HRMS calculated for $C_{17}H_{16}FN_2O_3S$ $[M+H]^+$ 347.0860, found 347.0859.

1-(*T*ert-butyl)-3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2s**). Yellow liquid, 298 mg, quant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.53 (s, 1H), 1.70 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0 (s), 142.3 (s), 132.8 (s), 128.7 (s), 128.3 (s), 125.3 (s), 92.4 (s), 61.4 (s), 29.4 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.7 (s, 1F). ESI-

MS HRMS calculated for $C_{13}H_{16}FN_2O_3S$ $[M+H]^+$ 299.0860, found 299.0860.

1-Cyclohexyl-3-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2t**). Yellow liquid, 324 mg, quant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 6.51 (s, 1H), 4.17 (m, 1H), 2.08-2.02 (m, 4H), 1.98-1.95 (m, 2H), 1.78-1.76 (m, 1H), 1.51-1.42 (m, 2H), 1.38-1.32 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8 (s), 141.1 (s), 132.9 (s), 128.7 (s), 128.4 (s), 125.4 (s), 91.5 (s), 57.9 (s), 32.5 (s), 25.5 (s), 25.1 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 37.8 (s, 1F). ESI-MS HRMS calculated for $C_{15}H_{18}FN_2O_3S$ $[M+H]^+$ 325.1017, found 325.1014.

3-Phenyl-1-(pyridin-2-yl)-1H-pyrazol-5-yl sulfurofluoridate (**2u**). White solid, 172 mg, 54 %. Mp 80-81 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.6 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.90-7.87 (m, 3H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 6.1 Hz, 1H), 6.74 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4 (s), 151.3 (s), 148.3 (s), 142.7 (s), 138.9 (s), 131.8 (s), 129.3 (s), 129.0 (s), 125.9 (s), 122.6 (s), 115.4 (s), 96.4 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 42.3 (s, 1F). ESI-MS HRMS calculated for $C_{14}H_{11}FN_3O_3S$ $[M+H]^+$ 320.0500, found 320.0457.

1-(4-Methoxyphenyl)-3-propyl-1H-pyrazol-5-yl sulfurofluoridate (**2v**). Yellow liquid, 241 mg, 78 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.18 (s, 1H), 3.84 (s, 3H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.71 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (s), 153.5 (s), 141.1 (s), 129.8 (s), 125.4 (s), 114.7 (s), 94.7 (s), 55.7 (s), 31.2 (s), 22.5 (s), 13.9 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.4 (s, 1F). ESI-MS HRMS calculated for $C_{13}H_{16}FN_2O_4S$ $[M+H]^+$ 315.0809, found 315.0807.

1-(4-Chlorophenyl)-3-propyl-1H-pyrazol-5-yl sulfurofluoridate (**2w**). Yellow liquid, 238 mg, 75 %.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.45 (m, 4H), 6.23 (s, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 1.71 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2 (s), 141.2 (s), 135.4 (s), 134.2 (s), 129.8 (s), 124.5 (s), 95.6 (s), 31.2 (s), 22.4 (s), 13.9 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.7 (s, 1F). ESI-MS HRMS calculated for $C_{12}H_{13}ClFN_2O_3S$ $[M+H]^+$ 319.0314, found 319.0313.

3-Cyclopropyl-1-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2x**). Yellow liquid, 282 mg, quant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.47 (m, 4H), 7.39 (t, *J* = 7.2 Hz, 1H), 6.09 (s, 1H), 1.97 (m, 1H), 1.00-0.98 (m, 2H), 0.84-0.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6 (s), 141.1 (s), 136.9 (s), 129.6 (s), 128.4 (s), 123.5 (s), 93.4 (s), 10.0 (s), 8.2 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 39.6 (s, 1F). ESI-MS HRMS calculated for $C_{12}H_{12}FN_2O_3S$ $[M+H]^+$ 283.0547, found 283.0546.

3-Cyclopropyl-1-(pyridin-2-yl)-1H-pyrazol-5-yl sulfurofluoridate (**2y**). White solid, 130 mg, 46 %. Mp 44-45 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.7 Hz, 1H), 7.83-7.78 (m, 2H), 7.23 (t, *J* = 5.8 Hz, 1H), 6.10 (s, 1H), 1.97 (hept, *J* = 4.8 Hz, 1H), 1.02-0.98 (m, 2H), 0.86-0.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9 (s), 151.1 (s), 148.2 (s), 141.9 (s), 138.7 (s), 122.2 (s), 115.1 (s), 95.9 (s), 10.0 (s), 8.3 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 42.0 (s, 1F). ESI-MS HRMS calculated for $C_{11}H_{11}FN_3O_3S$ $[M+H]^+$ 284.0500, found 284.0499.

1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl sulfurofluoridate (**2z**). Yellow liquid, 92 mg, 27 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.67 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7 (s), 142.2 (q, *J* = 40.0 Hz), 141.6 (s), 128.7 (s), 125.9 (s), 120.3 (q, *J* = 269.4 Hz), 115.0 (s), 94.9 (s), 55.8 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 40.7 (s, 1F), -63.3 (s, 1F). ESI-MS HRMS calculated for $C_{11}H_9F_4N_2O_4S$ $[M+H]^+$ 341.0214, found 341.0213.

3,4-Dimethyl-1-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2aa**). Colorless liquid, 270 mg, quant. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.46 (m, 4H), 7.37 (t, *J* = 7.2 Hz, 1H), 2.28 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9 (s), 138.7 (s), 137.3 (s), 129.6 (s), 128.1 (s), 123.2 (s), 105.7 (s), 12.9 (s), 7.0 (d, *J* = 1.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ 42.0 (s, 1F). ESI-MS HRMS calculated for $C_{11}H_{12}FN_2O_3S$ $[M+H]^+$ 271.0547, found 271.0546.

4-Benzyl-3-methyl-1-phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2ab**). Yellow liquid, 336 mg, 97 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 9.4 Hz, 2H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.27-7.22 (m, 3H), 3.90 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1 (s), 139.0 (s), 138.1 (s), 137.1 (s), 129.6 (s), 128.8 (s), 128.30 (s), 128.27 (s), 126.7 (s), 123.3 (s), 108.9 (s), 28.2 (s), 13.3 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 42.6 (s, 1F). ESI-MS HRMS calculated for $C_{17}H_{16}FN_2O_3S$ $[M+H]^+$347.0860, found 347.0860.

3,4-Dimethyl-1-(pyridin-2-yl)-1H-pyrazol-5-yl sulfurofluoridate (**2ac**). Yellow liquid, 60 mg, 22 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.6 Hz, 1H), 7.81-7.77 (m, 2H), 7.20-7.18 (m, 1H), 2.27 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4 (s), 149.5 (s), 148.0 (s), 139.5 (s), 138.7 (s), 121.8 (s), 114.3 (s), 107.6 (s), 13.0 (s), 6.7 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 46.1 (s, 1F). ESI-MS HRMS calculated for $C_{10}H_{11}FN_3O_3S$ $[M+H]^+$ 272.0500, found 272.0500.

3-Phenyl-1H-pyrazol-5-yl sulfurofluoridate (**2ad**). white solid, 227 mg, 94 %. Mp 129-120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.33 (s, 1H), 7.58 (d, *J* = 7.1 Hz, 2H), 7.50-7.45 (m, 3H), 6.45 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2 (s), 145.9 (s), 130.1 (s), 129.5 (s), 127.9 (s), 125.7 (s), 92.8 (s).^{19}F NMR (471 MHz, $CDCl_3$) δ 39.2 (s, 1F). ESI-MS HRMS calculated for $C_9H_8FN_2O_3S$ $[M+H]^+$ 243.0234, found 243.0234.

[1,1'-Biphenyl]-4-yl (3-methyl-1-phenyl-1H-pyrazol-5-yl) sulfate (**3**). White solid, 110 mg, 54 %. Mp 101-103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (t, *J* = 8.8 Hz, 6H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.41-7.37 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.27 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5 (s),

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149.2 (s), 142.6 (s), 141.4 (s), 139.5 (s), 137.3 (s), 129.3 (s), 129.1 (s), 128.8 (s), 128.1 (s), 127.8 (s), 127.2 (s), 123.4 (s), 121.2 (s), 95.6 (s), 14.6 (s). ESI-MS HRMS calculated for $C_{22}H_{19}N_2O_4S$ $[M+H]^+$ 407.1060, found 407.1060.

1-(4-Methoxyphenyl)-3-phenyl-1H-pyrazol-5-yl pyrrolidine-1-sulfonate (**4**). Yellow liquid, 153 mg, 76 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.3 Hz, 2H), 7.60 (d, *J* = 8.9 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.64 (s, 1H), 3.86 (s, 3H), 3.23 (t, *J* = 6.7 Hz, 4H), 1.77 (t, *J* = 6.7 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (s), 150.8 (s), 144.5 (s), 133.0 (s), 131.0 (s), 128.8 (s), 128.4 (s), 125.6 (s), 125.2 (s), 114.4 (s), 93.6 (s), 55.7 (s), 49.5 (s), 25.7 (s). ESI-MS HRMS calculated for $C_{14}H_{18}N_3O_3S$ $[M+H]^+$ 308.1063, found 308.1062.

3,4-Dimethylphenyl (3-phenyl-1H-pyrazol-5-yl) sulfate (**5**). White solid, 150 mg, 87 %, Mp 91-93 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.25 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.44-7.38 (m, 3H), 7.17-7.13 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.49 (s, 1H), 2.21 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3 (s), 148.6 (s), 145.3 (s), 138.9 (s), 136.6 (s), 130.9 (s), 129.6 (s), 129.4 (s), 128.3 (s), 125.6 (s), 122.2 (s), 118.5 (s), 93.2 (s), 20.0 (s), 19.3 (s). ESI-MS HRMS calculated for $C_{17}H_{17}N_2O_4S$ $[M+H]^+$ 345.0904, found 345.0904.

3-Methyl-1,5-diphenyl-1H-pyrazole (**6**).[15] Yellow liquid, 223 mg, 95 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 10H), 6.32 (s, 1H), 2.40 (s, 3H).

6-Bromopyridin-3-yl sulfurofluoridate (**8**).[12b] Colorless liquid, 238 mg, 93 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 3.6 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.43 (dd, *J* = 8.1, 4.7 Hz, 1H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 42.6 (s).

Conflicts of interest

There are no conflicts to declare.

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