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Selective Access to Heterocyclic Sulfonamides and Sulfonyl Fluorides via a Parallel Medicinal Chemistry Enabled Method

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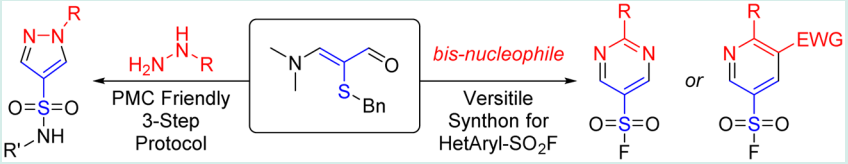
Supporting Information



ABSTRACT: A sulfur-functionalized aminoacrolein derivative is used for the efficient and selective synthesis of heterocyclic sulfonyl chlorides, sulfonyl fluorides, and sulfonamides. The development of a 3-step parallel medicinal chemistry (PMC) protocol for the synthesis of pyrazole-4-sulfonamides effectively demonstrates the utility of this reagent. This reactivity was expanded to provide rapid access to other heterocyclic sulfonyl fluorides, including pyrimidines and pyridines, whose corresponding sulfonyl chlorides lack suitable chemical stability.

KEYWORDS: *heterocyclic sulfonamides, sulfonyl fluorides, 3-step PMC protocol, rapid access*

Sulfonamides hold a privileged role in drug discovery efforts due in part to the unique electronic and conformational properties they impart on compounds.[1] Though various conditions exist for the synthesis of sulfonamides,[2] including Pd-catalyzed coupling reactions[3] and electrophilic amination reactions of sulfinate salts,[4] the vast majority of sulfonamide syntheses are accomplished by the reaction of an amine with a sulfonyl chloride. This strategic bond disconnection necessitates robust methods for the synthesis of the requisite sulfonyl halide. Therefore, we view the efficient and general access of varied classes of sulfonyl chlorides as a valuable goal, applicable to numerous drug discovery projects.

In particular, recent project work required a means to generate 1-substituted pyrazole-4-sulfonyl chlorides (of type **5**) in order to rapidly assess the structure-activity-relationship (SAR) around this particular sulfonamide motif. Initial attempts at synthesizing this class of chlorides focused on direct Friedel–Crafts sulfonylation of *N*-substituted pyrazoles by heating in chlorosulfonic acid[5] (Figure 1, A). Substrates bearing a variety of *N*-substituents were examined to assess the generality of this method for synthesizing sulfonyl chlorides with broad chemical diversity. In exploring this chemistry, we often observed formation of varying mixtures of regioisomeric sulfonyl chlorides (eg., **2a** and **2b**) as a function of the *N*-substituent, along with low overall yield. Isolation of the desired sulfonyl chloride or the resulting sulfonamide was made more difficult by the inability to distinguish the regioisomeric byproducts during isolation by mass-triggered reverse phase HPLC purification. Furthermore, we were limited to using preformed *N*-substituted pyrazoles as starting materials, which were of relatively limited supply in the corporate monomer store.

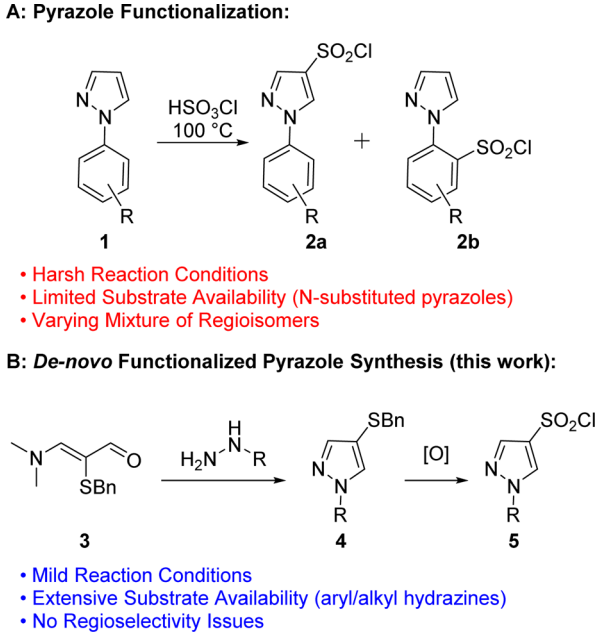


Figure 1. Synthesis of pyrazole-4-sulfonyl chlorides.

An alternative strategy was sought in which the de novo synthesis of a pyrazole ring bearing appropriate functionality would alleviate any potential regioselectivity issues and avoid the harsh reaction conditions associated with pyrazole

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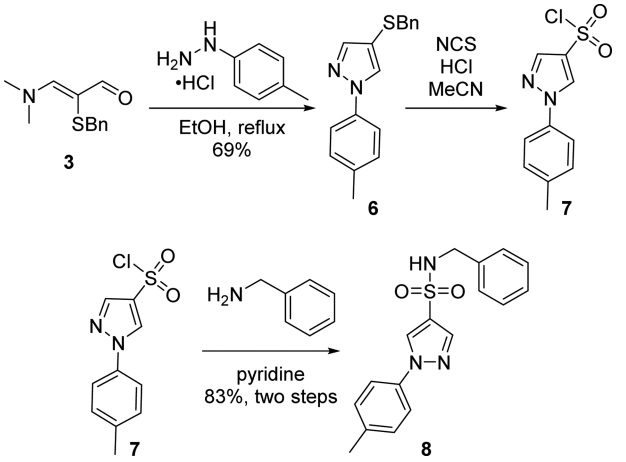
functionalization. Herein, we present a realization of this strategy by the identification of a bis-electrophilic reagent which contains a low-valent sulfur functionality, allowing for the synthesis of pyrazoles via a condensation reaction with readily available hydrazines (Figure 1B).

We identified the aminoacrolein derivative **3**[6] as an appropriate reagent for the formation of pyrazole-4-thioethers. The use of **3** allows for incorporation of the required sulfur substitution from the initial pyrazole synthesis.[7] As a result, the problems encountered with later-stage heterocycle functionalization are obviated. Furthermore, rich literature precedent exists for the oxidative conversion of low-valent sulfur precursors to sulfonyl chlorides under mild reaction conditions.[8] We identified the benzyl thioether[9] as an appropriate synthetic handle to allow for the generation of the desired sulfonyl chloride (Scheme 1).

Scheme 1. Development of Selective Pyrazole-4-sulfonamide Synthesis

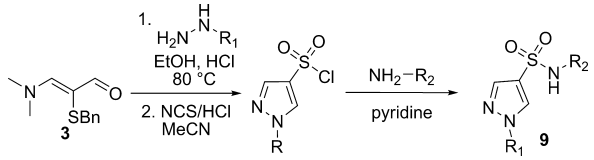


Thioether **3** is a shelf stable and odorless solid, easily accessible in multigram quantities by the reaction of *N,N*-dimethylamino acrolein with benzyl sulfenyl bromide, generated in situ from dibenzyl disulfide and bromine. Demonstration of the desired reactivity began with condensation of *p*-tolylhydrazine·HCl with **3**. Refluxing in ethanol smoothly provided the functionalized pyrazole **6**. It was found that the oxidation of **6** was effected by treatment with a preformed solution of *N*-chlorosuccinimide and HCl in MeCN.[10] Clean conversion to the sulfonyl chloride **7** was observed after simple aqueous workup. The only byproducts identifiable by ^{1}H NMR analysis were the expected: succinimide and benzyl chloride. Treatment of the crude mixture with a representative amine in pyridine cleanly provided the desired sulfonamide **8** in 83% yield over two steps (Scheme 1).

The ability to rapidly probe the SAR of a particular chemical series by means of library or parallel medicinal chemistry (PMC) enabled synthesis is an important tool in drug discovery.[11] The high overall yield and the clean reaction profiles of the transformations involved suggested this procedure would translate well into a PMC mode. To demonstrate this, a library using 13 structurally varied hydrazines, each crossed with an alkyl and aryl amine template, was run with conditions essentially identical to those developed for the standard reaction protocol. The isolated yields of final targets for this library are presented in Table 1.

The three-step procedure was run without purification of intermediates, and products were isolated by means of mass-triggered semiautomated HPLC purification. It is important to note that, unlike for the reactions run in Scheme 1, the

Table 1. PMC Synthesis of Pyrazole-4-sulfonamides[a]



	Diversity reagents 1: **10**	Diversity reagents 2: **11** {1}	**11** {2}
1	**10** {1}	**9** {1,1}: 37%	**9** {1,2}: 71%
2	**10** {2}	**9** {2,1}: 25%	**9** {2,2}: 52%
3	**10** {3}	**9** {3,1}: 48%	**9** {3,2}: 11%
4	**10** {4}	**9** {4,1}: 11%	**9** {4,2}: 0%
5	**10** {5}	**9** {5,1}: 47%	**9** {5,2}: 65%
6	**10** {6}	**9** {6,1}: 47%	**9** {6,2}: 30%
7	**10** {7}	**9** {7,1}: 56%	**9** {7,2}: 66%
8	**10** {8}	**9** {8,1}: 0%	**9** {8,2}: 10%
9	**10** {9}	**9** {9,1}: 57%	**9** {9,2}: 72%
10	**10** {10}	**9** {10,1}: 37%	**9** {10,2}: 74%
11	**10** {11}	**9** {11,1}: 4.5%	**9** {11,2}: 0%
12	**10** {12}	**9** {12,1}: 38%	**9** {12,2}: 56%
13	**10** {13}	**9** {13,1}: 43%	**9** {13,2}: 73%

[a]Isolated yield given after three steps. General conditions: Step 1, HCl omitted when hydrazine was available as HCl salt, 0.20 M, 80 °C, 2 h; step 2, 0.15 M, 0 °C to rt, 1.5 h; step 3, 0.1 M, rt, 12 h.

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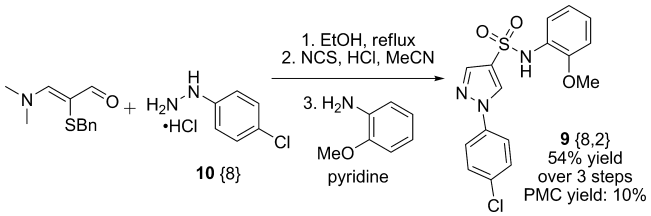
operations involved with running these 26 reactions in parallel are optimized with overall success rate, as opposed to individual chemical yields, in mind. As a result, it is common that workup, isolation, and purification processes lead to sub optimal isolated yields, but provide sufficient quantities of final targets for biological screening in drug discovery programs. This is typical of PMC enabled chemical syntheses, which strive to make numerous compounds quickly instead of fewer compounds in maximal yield. This distinction is represented in the occasionally low and variable yields observed for even structurally related hydrazines in Table 1.

The data presented in Table 1 do demonstrate a more critical result for PMC syntheses: high monomer success rate, defined as number of final targets isolated divided by the number of monomers submitted to the library. Under these conditions, the desired pyrazole-4-sulfonamides were recovered with high overall success rates: 85% for the aryl amine and a 92% for the alkyl amine template (Table 1).[12] The protocol was effective for electron-deficient (Table 1, entry 6) and electron-rich (Table 1, entry 2) aryl hydrazines, as well as alkyl hydrazines (Table 1, entries 1 and 3) including those with sterically hindered α-branching (Table 1, entries 7, 9, 12, and 13). The high success rate for both amine types along with the structural variety accessible via the hydrazine monomers makes this PMC protocol particularly valuable, allowing for variation in two vectors from a central pyrazole core in only three chemical steps.[13] In addition, the relatively mild nature of the reaction conditions make this protocol applicable to more heavily functionalized and pharmaceutically relevant hydrazines and amines which are stable to the acidic oxidation procedure.

We sought to demonstrate that the low yields observed for some substrates were likely attributable to the working realities of PMC synthesis discussed above. A poorly performing example was selected from Table 1 and repeated using techniques associated with typical batch-style synthetic laboratory execution (Scheme 2). To this end, the 3-step

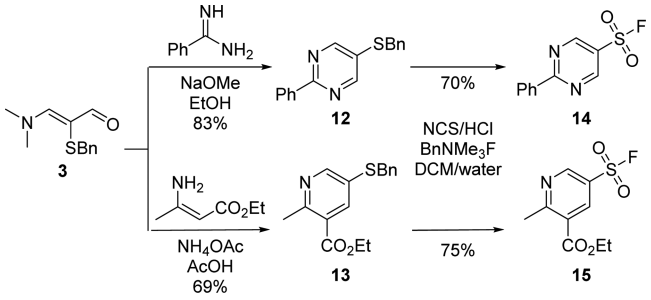
Scheme 2. Improvement of PMC Yield Using Standard Synthetic Techniques



conversion of hydrazine **10**{*8*} to sulfonamide **9**{*8,2*} was conducted without purification of any intermediates, and final chromatographic isolation afforded **9**{*8,2*} in 54% overall yield after three steps. This clearly demonstrates that the 10% yield observed in the library synthesis of **9**{*8,2*} (Table 1, entry 8) is not due to a lack of robustness or reproducibility of the synthetic route.

Beyond the synthesis of pyrazoles, we recognized that **3** may be suitable for the synthesis of a wide range of sulfur-functionalized heterocycles. With this in mind, we explored the condensation of bis-electrophile **3** with other bis-nucleophiles, including amidines and amino-acrylates.[14] We were delighted to find that these reactions cleanly afforded functionalized pyrimidine (**12**) and pyridine (**13**), respectively (Scheme 3). Given the instability of many electron-deficient heterocyclic

Scheme 3. Synthesis of Heterocyclic Sulfonyl Fluorides



sulfonyl chlorides,[15] we opted to investigate the oxidative cleavage of these intermediates for the synthesis of the more chemically stable sulfonyl fluorides.[16,17] The solvent for the oxidation was switched from MeCN to DCM due to decreased solubility of these thioethers. Optimization then required identification of a viable fluoride source. The use of KHF_2 was evaluated under various phase-transfer conditions, but provided low yields of the desired sulfonyl fluoride. Ultimately the more organic soluble benzyl trimethylammonium fluoride was found to give the best conversion to the sulfonyl fluoride. Exposure of a solution of thioether and fluoride source in DCM with a minimal amount of water to a preformed mixture of oxidant cleanly and rapidly afforded full conversion to the isolable sulfonyl fluorides (**14**, **15**).[18,19]

In conclusion, we have demonstrated the utility of **3** as a valuable synthon for the selective generation of heterocycles bearing appropriate functionality for facile conversion to sulfonyl chlorides, sulfonyl fluorides and sulfonamides. The power of this method is demonstrated by its use in a three-step PMC protocol affording sulfonamide products of possible value in drug discovery programs, with high success rates from readily available and diverse hydrazine monomers. Furthermore, rapid access to pyrimidyl and pyridyl sulfonyl fluorides promises potential entry into chemical space not accessible via the corresponding sulfonyl chlorides because of inherent instability

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00120.

Full experimental, characterization data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PMC, parallel medicinal chemistry; SAR, structure−activity-relationship; HPLC, high pressure liquid chromatography; MeCN, acetonitrile; DCM, dichloromethane

■ REFERENCES

(1) (a) Brameld, K. A.; Kuhn, B.; Reuter, D. C.; Stahl, M. Small Molecule Conformational Preferences Derived from Crystal Structure Data. A Medicinal Chemistry Focused Analysis. *J. Chem. Inf. Model.* **2008**, *48*, 1−24. (b) Chang, C.-P.; Wu, C.-H.; Song, J.-S.; Chou, M.-C.; Wong, Y.-C.; Lin, Y.; Yeh, Y.-K.; Sadani, A. A.; Ou, M.-H.; Chen, K.-H.; Chen, P.-H.; Kuo, P.-C.; Tseng, C.-T.; Chang, K.-H.; Tseng, S.-L.; Chao, Y.-S.; Hung, M.-S.; Shia, K.-S. Discovery of 1-(2,4-Dichlorophenyl)-*N*-(piperidin-1-yl)-4-((pyrrolidine-1-sulfonamido)-methyl)-5-(5-((4-(trifluoromethyl)phenyl)ethynyl)thiophene-2-yl)-1*H*-pyrazole-3-carboxamide as a Novel Peripherally Restricted Cannabinoid-1 Receptor Antagonist with Significant Weight-Loss Efficacy in Diet-Induced Obese Mice. *J. Med. Chem.* **2013**, *56*, 9920−9933.

(2) (a) Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. A New Route to Sulfonamides via Intermolecular Radical Addition to Pentafluorophenyl Vinylsulfonate and Subsequent Aminolysis. *Org. Lett.* **2002**, *4*, 2549−2551. (b) 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. (c) Ruano, J. L. C.; Parra, A.; Yuste, F.; Mastranzo, V. M. Mild and General Method for the Synthesis of Sulfonamides. *Synthesis* **2008**, *2008*, 311−319. (d) Moon, S.-Y.; Nam, J.; Rathwell, K.; Kim, W.-S. Copper-Catalyzed Chan-Lam Coupling between Sulfonyl Azides and Boronic Acids at Room Temperature. *Org. Lett.* **2014**, *16*, 338−341.

(3) (a) Rosen, B. R.; Ruble, J. C.; Beauchamp, T. J.; Navarro, A. Mild Pd-Catalyzed *N*-Arylation of Methanesulfonamide and Related Nucleophiles: Avoiding Potentially Genotoxic Reagens and By-products. *Org. Lett.* **2011**, *13*, 2564−2567.

(4) (a) Baskin, J. M.; Wang, Z. A Mild, Convenient Synthesis of Sulfinic Acid Salts and Sulfonamides from Alkyl and Aryl Halides. *Tetrahedron Lett.* **2002**, *43*, 8479−8483. (b) Deeming, A. S.; Russell, C. J.; Willis, M. C. Combining Organometallic Reagents, the Sulfur Dioxide Surrogate DABSO, and Amines: A One-Pot Preparation of Sulfonamides, Amenable to Array Synthesis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1168−1171. (c) Johnson, M. G.; Gribble, M. W., Jr.; Houze, J. B.; Paras, N. A. Convenient Route to Secondary Sulfinates: Application to the Stereospecific Synthesis of α-*C*-Chiral Sulfonamides. *Org. Lett.* **2014**, *16*, 6248−6251.

(5) Markwalder, J. A.; Arnone, M. R.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Chang, C.-H.; Cox, S. S.; Czerniak, P. M.; Dean, C. L.; Deleniak, D.; Grafstrom, R.; Harrison, B. A.; Kaltenbach, R. F., III; Nugiel, D. A.; Rossi, K. A.; Sherk, S. R.; Sisk, L. M.; Stouten, P.; Trainor, G. L.; Worland, P.; Seitz, S. P. Synthesis and Biological Evaluation of 1-Aryl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one Inhibitors of Cyclin-Dependent Kinases. *J. Med. Chem.* **2004**, *47*, 5894−5911.

(6) For the synthesis of **3** and its use as a precursor for vinamidinium salts, see: Matthews, D. P. Synthesis of N-[3-(dimethylamino)-2-(substituted thio)-2-propenylidene]-N-methylmethanaminium salts via 2-(alkylthio)- and 2-(arylthio)-3-(dimethylamino)acroleins. *J. Org. Chem.* **1984**, *49*, 2823−2824.

(7) The use of 2-bromo-3-(dimethylamino)acrolein was also considered to synthesize the 4-Br-pyrazole followed by a thio-coupling reaction. This route was not pursued due to the increased step count, see: Fraley, M. E.; Rubino, R. S.; Hoffman, W. F.; Hambaugh, S. R.; Arrington, K. L.; Hungate, R. W.; Bilodeau, M. T.; Tebben, A. J.; Rutledge, R. Z.; Kendall, R. L.; McFall, R. C.; Huckle, W. R.; Coll, K. E.; Thomas, K. A. Optimization of a Pyrazole[1,5-*a*]pyrimidine Class of KDR Kinase Inhibitors: Improvements in Physical Properties Enhance Cellular Activity and Phamacokinetics. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3537−3541.

(8) For selected examples of oxidations of other low-valent sulfur precursors, see: (a) 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. (b) Woolven, H.; González-Rodriguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. DABCO-*Bis*(sulfur dioxide), DABSO, as a Convenient Source of Sulfur Dioxide for Organic Synthesis: Utility in Sulfonamide and Sulfamide Preparation. *Org. Lett.* **2011**, *13*, 4876−4878. (c) Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Masciti, V.; Toste, F. D. Application of Fundamental Organometallic Chemistry to the Development of a Gold-Catalyzed Synthesis of Sulfinate Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 4404−4407.

(9) For a selective example of the oxidative cleavage of benzyl thioethers, see: Wang, M.; Gao, M.; Miller, K. D.; Sledge, G. W.; Zheng, Q.-H. [11C]GSK2126458 and [18F]GSK2126458, The First Radiosynthesis of New Potential PET Agents for Imaging of PI3K and mTOR in Cancers. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1569−1574.

(10) We found that treatment of a solution of HCl in MeCN with NCS rapidly formed a homogenous yellow solution, presumably because of the formation of Cl_2, see: Mahajan, T.; Kuman, L.; Dwivedi, K.; Agarwal, D. D. Efficient and Facile Chlorination of Industrially-Important Aromatic Compounds using NaCl/*p*-TsOH/NCS in Aqueous Media. *Ind. Eng. Chem. Res.* **2012**, *51*, 3881−3886.

(11) For an example of strategic use of parallel medicinal chemistry in a drug discovery program, see: Claffey, M. M.; Helal, C. J.; Verhoest, P. R.; Kang, Z.; Fors, K. S.; Jung, S.; Zhong, J.; Bundesmann, M. W.; Hou, X.; Liu, S.; Kleiman, R. J.; Vanase-Frawley, M.; Schmidt, A. W.; Menniti, F.; Schmidt, C. J.; Hoffman, W. E.; Hajos, M.; McDowell, L.; O'Connor, R. E.; MacDougall-Murphy, M.; Fonseca, K. R.; Becker, S. L.; Nelson, F. R.; Liras, S. Application of Structure-Based Drug Design and Parallel Chemistry ot Identify Selective, Brain Penetrant, In Vivo Active Phosphodiesterase 9A Inhibitors. *J. Med. Chem.* **2012**, *55*, 9055−9068.

(12) No quality controls were run on the purity of the hydrazines that were ordered from the internal chemical file prior to library execution. However, for those hydrazines that failed to afford products for both amines used, samples were ordered retrospectively and they were found to have decomposed during storage. These false-negative results are neither reported in the table nor calculated into the library success rate.

(13) For selected examples of pyrazole syntheses in parallel, see: (a) Vickerstaffe, E.; Warrington, B. H.; Ladlow, M.; Ley, S. V. Fully Automated Polymer-Assisted Synthesis of 1,5-Biaryl Pyrazoles. *J. Comb. Chem.* **2004**, *6*, 332−339. (b) Sidique, S.; Ardecky, R.; Su, Y.; Narisawa, S.; Brown, B.; Millán, J. L.; Sergienko, E.; Cosford, N. D. P. Design and Synthesis of Pyrazole Derivatives as Potent and Selective Inhibitors of Tissue-Nonspecific Alkaline Phophatase (TNAP). *Bioorg. Med. Chem. Lett.* **2009**, *19*, 222−225. (c) Ma, W.; Peterson, B.; Kelson, A.; Laborde, E. Efficient Synthesis of Trisubstituted Pyrazoles and Isoxazoles Using a Traceless "Catch and Release" Solid-Phase Strategy. *J. Comb. Chem.* **2009**, *11*, 697−703. (d) Pendri, A.; Dodd, D. S.; Chen, J.; Cvijic, M. E.; Kang, L.; Baska, R. A.; Carlson, K. E.; Burford, N. T.; Sun, C.; Ewing, W. R.; Gerritz, S. W. Solid Phase Synthesis of 1,5-Diarylpyrazole-4-carboxamides: Discovery of Antagonists of the CB-1 Receptor. *ACS Comb. Sci.* **2012**, *14*, 197−204.

(14) An insightful reviewer asked for the same reaction sequence to be demonstrated using hydroxylamine to generate isoxazole-4-sulfonyl fluoride. Despite condensation of **3** with hydroxylamine hydrochloride proceeding smoothing to afford the thioether, no desired sulfonyl fluoride could be isolated after oxidation. Crude ^{1}H NMR analysis indicated successful oxidative cleavage; however, multiple attempts at purification and isolation failed.

(15) Johnson, T. B.; Sprague, J. M. A New Method for the Preparation of Alkyl Sulfonyl Chlorides. *J. Am. Chem. Soc.* **1936**, *58*, 1348−1352.

DOI: 10.1021/acscombsci.5b00120
ACS Comb. Sci. XXXX, XXX, XXX−XXX

(16) For a review on the stability and reactivity of sulfonyl fluorides, see: Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry. *Angew. Chem., Int. Ed.* **2014**, *36*, 9430−9448.
(17) For the use of sulfonyl fluorides in the parallel synthesis of sulfonamides, see: Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Pipko, S. E.; Konovets, A. I.; Sadkova, I. V.; Tolmachev, A. Sulfonyl Fluorides as Alternative to Sulfonyl Chlorides in Parallel Synthesis of Aliphatic Sulfonamides. *ACS Comb. Sci.* **2014**, *16*, 192−197.
(18) For a selected example of the synthesis of pyridine-3-sulfonyl chlorides, see: Hogan, P. J.; Cox, B. G. Aqueous Process Chemistry: The Preparation of Aryl Sulfonyl Chlorides. *Org. Process Res. Dev.* **2009**, *13*, 875−879.
(19) For a selected example of the preparation and use of a pyrimidyl sulfonyl chloride, see: Gerard, G.; Rojas de la Parra, V.; Lauwers, A. Phenyl- and benzylthiazolypiperazine derivatives for the treatment of neurodegenerative diseases and their preparation. WO 2009/019295 A2, Feb 12, 2009.

DOI: 10.1021/acscombsci.5b00120
ACS Comb. Sci. XXXX, XXX, XXX−XXX