OL | Organic Letters

Letter

SuFEx Activation with Ca(NTf$_2$)$_2$: A Unified Strategy to Access Sulfamides, Sulfamates, and Sulfonamides from S(VI) Fluorides

Subham Mahapatra,[§] Cristian P. Woroch,[§] Todd W. Butler, Sabrina N. Carneiro, Sabrina C. Kwan, Samuel R. Khasnavis, Junha Gu, Jason K. Dutra, Beth C. Vetelino, Justin Bellenger, Christopher W. am Ende,* and Nicholas D. Ball*

Read Online

ACCESS | Metrics & More | Article Recommendations | SI Supporting Information

ABSTRACT: A method to activate sulfamoyl fluorides, fluorosulfates, and sulfonyl fluorides with calcium triflimide and DABCO for SuFEx with amines is described. The reaction was applied to a diverse set of sulfamides, sulfamates, and sulfonamides at room temperature under mild conditions. Additionally, we highlight this transformation to parallel medicinal chemistry to generate a broad array of nitrogen-based S(VI) compounds.

Sulfamoyl fluorides ● = NR^{1}R^2 → *Sulfamides*
Fluorosulfates ● = OAr → *Sulfamates*
Sulfonyl fluorides ● = Ar → *Sulfonamides*
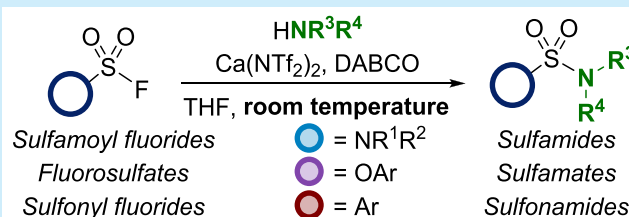
■ Single-set of reaction conditions
■ Mild, room temperature transformation
■ Parallel medicinal chemistry exemplified
■ >130 structurally diverse compounds prepared

Interest in sulfur(VI) fluorides has grown immensely since Sharpless and co-workers introduced the concept of sulfur−fluoride exchange (SuFEx) chemistry in 2014.[1,2] For example, SuFEx has been applied extensively in chemical biology and medicinal chemistry with application toward protein labeling, protease inhibition, and drug target discovery.[3] In polymer chemistry, sulfur(VI) fluorides have been employed to generate novel polysulfates and polysulfonates, materials that have unique properties with promising applications.[1,4,5] Furthermore, advancements in fluorosulfurylation chemistry and the development of new reagents to install the −SO$_2$F group have spurred additional exploration into these functional groups.[6−12] However, employment of sulfur(VI) fluorides as synthetic precursors toward nitrogen-based sulfonylated compounds is underdeveloped.[1,13−18]

Nitrogenous sulfur(VI) compounds are well represented among small molecule drugs. For example, sulfonamides make up 25% of all sulfur-based FDA approved drugs, with therapeutic applications for multiple indications (Figure 1A).[19]
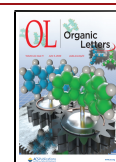
Sulfamides and sulfamates are also valuable motifs; however, they are comparatively underexplored, despite their presence in a multitude of biologically active compounds.[20] The most common approach to nitrogen-based sulfur(VI) compounds relies on the isolation or in situ generation of sulfur(VI) chlorides, such as sulfonyl chlorides (−SO$_2$Cl), chlorosulfates (−OSO$_2$Cl), and sulfamoyl chlorides (−NSO$_2$Cl).[1,21] Although widely used, there are several challenges with their application. While some sulfonyl chlorides are commercially available, the synthesis of sulfonyl chlorides with more complex

architectures can be challenging due to the harsh synthetic conditions required to access these compounds and their inherent instability.[21b] Moreover, in the presence of nucleophiles, S(VI) chlorides can undergo competing addition to the chlorine or sulfur atom, dehydrochlorination, and hydrolysis (Figure 1B).[1,21−23]

In contrast, the corresponding S(VI) fluorides have remarkable hydrolytic, redox, and thermal stability, rendering them attractive alternatives to S(VI) chlorides.[21] Despite innovation in their synthesis, there are still barriers to the broader application of S(VI) fluorides in organic chemistry. A key challenge is the reduced reactivity at the sulfur center compared to other S(VI) halides.[1] Furthermore, the canonical S(VI) fluorides—sulfonyl fluorides (−SO$_2$F), fluorosulfates (−OSO$_2$F), and sulfamoyl fluorides (−NSO$_2$F)—have considerably different reactivity at the sulfur center due to the reduced electrophilicity of the sulfur atom as the C−S bond is replaced with more resonance-donating atoms. Notably, disubstituted sulfamoyl fluorides require forcing conditions to undergo sulfur-fluoride exchange,[24] limiting a common method toward their application in SuFEx chemistry.[25]

A. Representative Sulfamide, Sulfamate and Sulfonamide Containing Biologically Active Compounds

Antibacterial
[Sulfafurazole]

Ethinylestradiol Analogue

PPAR-α agonist

B. S(VI) Chloride Approach to Sulfamide, Sulfamates and Sulfonamides

- Variable yielding
- Competing attack of Nu at chloride
- Challenges with accessing and instability of some S(VI) chlorides

C. This work: A Unified Strategy to S(VI) Fluoride Activation

HNR³R⁴

Ca(NTf₂)₂, DABCO

THF, room temperature

Sulfamides
Sulfamates
Sulfonamides

Sulfamoyl fluoride ⬤ = NR¹R²
Fluorosulfate ⬤ = OAr
Sulfonyl fluoride ⬤ = Ar

- Mild, room temperature transformation
- Single-set of reaction conditions
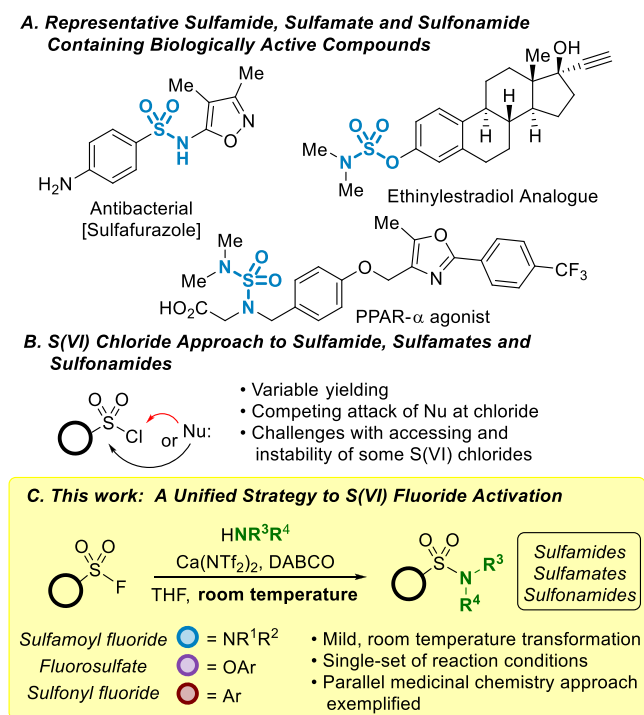- Parallel medicinal chemistry approach exemplified

Figure 1. (A) Biologically active nitrogenous S(VI) compounds; (B) S(VI) chloride-based approach to synthesize sulfonamides, sulfamates, and sulfamides; (C) our room-temperature method using Ca(NTf₂)₂ and DABCO to synthesize sulfamides, sulfamates, and sulfonamides from S(VI) fluorides.

We recently reported a Ca(NTf₂)₂-mediated activation of sulfonyl fluorides to generate sulfonamides[13] and envisioned a similar Lewis acid approach could be employed to activate less reactive sulfamoyl fluorides and fluorosulfates to access sulfamides and sulfamates, respectively. To date, a unified approach to enable SuFEx chemistry across a broader array of S(VI) fluorides does not exist, limiting their adoption as synthetic precursors. Herein, we report a high-yielding, unified method to access sulfamides, sulfamates, and sulfonamides through the room-temperature activation of sulfamoyl fluorides, fluorosulfates, and sulfonyl fluorides with calcium triflimide and DABCO (Figure 1C).

Applying our previously reported method utilizing excess amine in *tert*-amylOH generated sulfamide **3** in 70% yield

(Table 1, entry 1); however, sulfamoyl fluoride **1** was not fully consumed in the reaction, and additional heating at 60 °C for 48 h did not further improve the conversion. Increasing the temperature and equivalents of Ca(NTf₂)₂ improved the yield, although the reactions still did not fully consume sulfamoyl fluoride **1** (entries 2 and 3). We identified that increasing the concentration to 1 M had a marked effect, affording a 96% yield of sulfamide **3**, with full consumption of starting material (**1**) in only 2 h (entry 4).
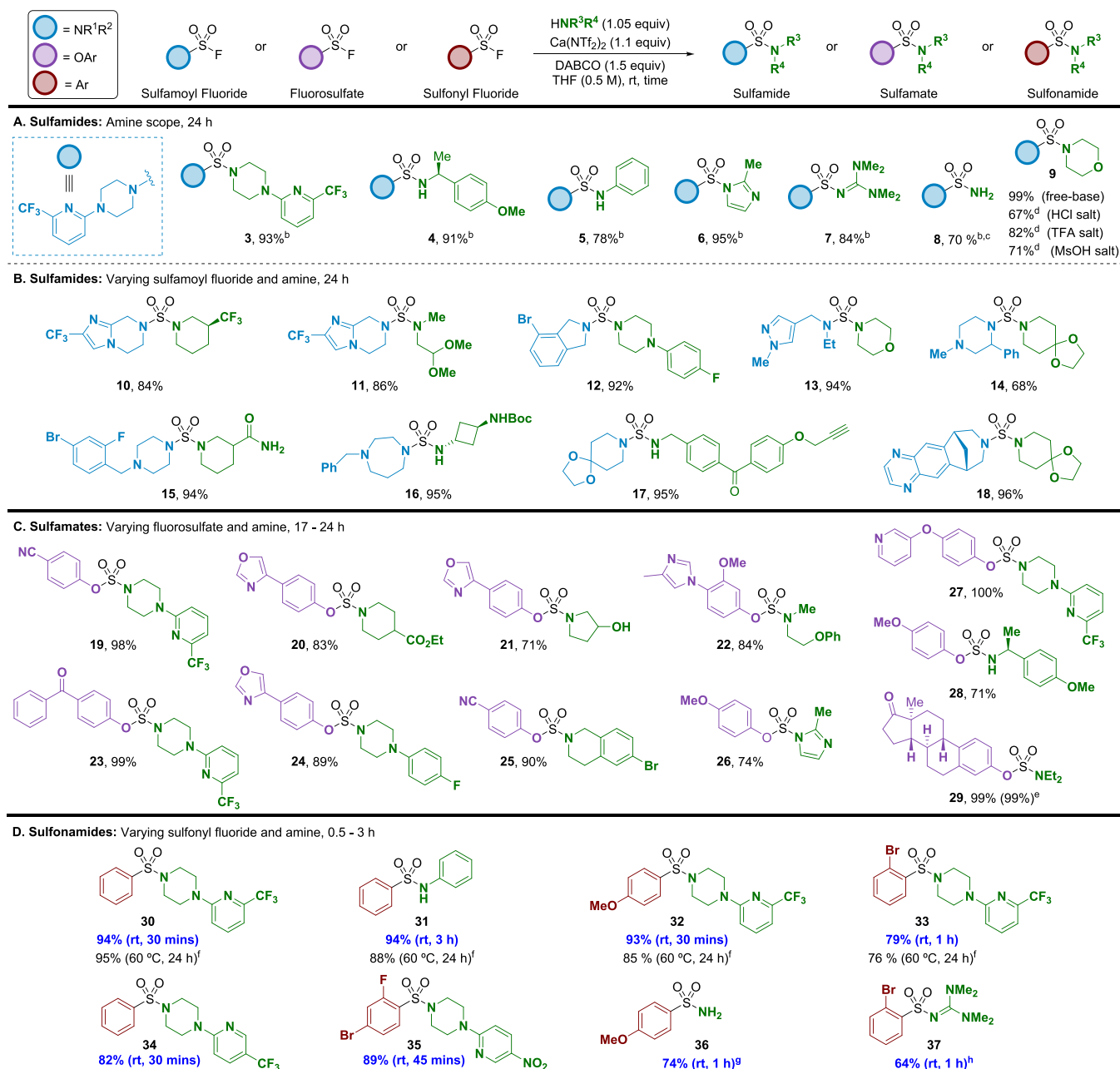
We next explored the amine nucleophile and found that decreasing the equivalents (2 equiv → 1.05 equiv of amine **2**, entry 5) required the addition of a base to drive the reaction to completion (e.g., DIPEA or DABCO, entries 6 and 7). With DIPEA, the yield varied depending on the bottle of *tert*-amylOH employed. We surmised that this could be a result of varying amounts of water present in the solvent. Indeed, the addition of 5% water (by volume) significantly decreased the yield from 95% to 54% (entry 6). Notably, when DABCO was employed, the inclusion of 5% water in the reaction had a minimal effect, yielding 88% yield of the desired sulfamide **3** (entry 7). This result led us to hypothesize that DABCO may have an expanded role, beyond acting solely as a base in the reaction, and led us to investigate additional reaction parameters.[1,26,27]

Toward this end, we explored the effect of various bases, solvents, and Lewis acids on the transformation (see the Supporting Information (SI) for details). DABCO proved exceptional as compared to other bases explored. With DABCO, we no longer observed a preference for an alcoholic solvent, the requirement for high concentration was less pronounced, and the reaction proceeded at room temperature when using THF as a solvent (entry 8). Evaluating a selected set of Lewis acids further established Ca(NTf₂)₂ as particularly effective across a variety of substrates (vide infra). In our screen we found that 0.55 equiv of Ca(NTf₂)₂, and calcium triflate Ca(OTf)₂ could generate sulfamide **3** in good yields, although in both cases the reactions required higher temperatures and were not as general across different amine substrates. Lower equivalents of Ca(NTf₂)₂ resulted in significantly reduced yield of **3** precluding catalysis (see the SI for details). Further decreasing the equivalents of Ca(NTf₂)₂ led to incomplete conversion to **3**. It is noteworthy that in the absence of calcium the reaction does not proceed (entry 9).

Table 1. Optimization Studies[a]

entry	amine **2** (equiv)	Ca(NTf₂)₂ (equiv)	base (equiv)	solvent (conc, M)	temp (°C)	time (h)	yield (%)
1	2	1		*t*-amylOH (0.2)	60	24	70
2	2	1		*t*-amylOH (0.2)	90	24	89
3	2	1.1		*t*-amylOH (0.2)	100	24	92
4	2	1.1		*t*-amylOH (1.0)	90	2	96
5	1.05	1.1		*t*-amylOH (1.0)	90	2	52
6	1.05	1.1	DIPEA (1.5)	*t*-amylOH (1.0)	90	2	95 (54)[b]
7	1.05	1.1	DABCO (1.5)	*t*-amylOH (1.0)	90	2	96 (88)[b]
8	1.05	1.1	DABCO (1.5)	THF (0.5)	rt	24	93
9	1.05	0	DABCO (1.5)	THF (0.5)	rt	24	NR[c]

[a]Reaction scale: sulfamoyl fluoride **1** (0.35 mmol, 1.0 equiv). [b]Reaction was performed in the presence of 5% water by volume. [c]No reaction.

Scheme 1. Scope of Sulfamide, Sulfamate, and Sulfonamide Formation[a]

We next investigated the generality of the sulfamide preparation by exploring a diverse set of amine nucleophiles with sulfamoyl fluoride **1** (Scheme 1A). Primary and secondary amines, as well as weaker amine nucleophiles such as aniline, methylimidazole and tetramethyl guanidine, readily underwent SuFEx to produce sulfamides (**3–7**). Ammonia was also a competent nucleophile, generating sulfamide **8** with a free amino group. In addition, amine salts (i.e., HCl, TFA, and MsOH) of morpholine were tolerated, giving sulfamide **9**, albeit with a reduction in yield compared to the free base. To further evaluate the versatility of the reaction, we paired a diverse array of sulfamoyl fluorides with various amines

(Scheme 1B, **10–18**). The reaction was compatible with a broad range of functional groups (e.g., primary amide, halides, alkyne, etc.) and acid sensitive functionality (e.g., Boc and acetal protecting groups), as well as multiple heterocyclic motifs.

Fluorosulfates pose additional challenges, as multiple reaction pathways can be envisioned upon reaction with amine nucleophiles (Figure 2).[3b] Indeed, 4-cyanophenyl fluorosulfate in the presence of DABCO and amine **2** (excluding Ca(NTf₂)₂) resulted in significant side-product formation, including products outlined in Figure 2 (see the SI for details). Remarkably, inclusion of Ca(NTf₂)₂ into the
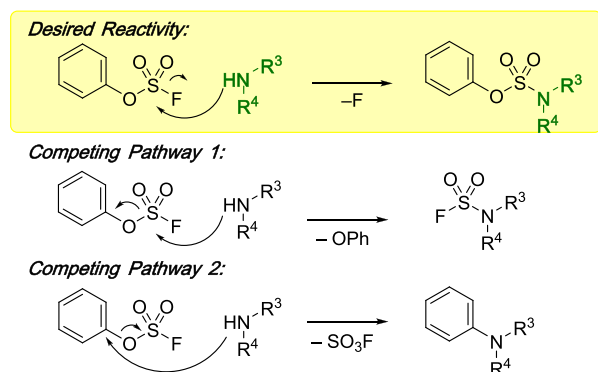
Figure 2. Possible modes of fluorosulfate reactivity with amines.

reaction mixture completely rescued the transformation, affording sulfamate **19** in 98% yield. A structurally diverse set of sulfamates were synthesized with secondary amines and phenolic fluorosulfates in excellent yield (Scheme 1C, **19**–**29**). Notably, the reaction was run on a 1.2 mmol scale with the synthesis of estrone-derived sulfamate **29** in near-quantitative yield. Utilizing a primary amine with the electron-poor 4-benzoylphenyl fluorosulfate resulted in elimination of the phenol (see the SI for details);[24] however, on a more electron-rich substrate (i.e., 4-methoxyfluorosulfate) the desired product **28** could be isolated with only a minor amount of side product formation.

Our previous work demonstrated the conversion of sulfonyl fluorides to sulfonamides using Ca(NTf$_2$)$_2$ with various amines; however, the reaction required elevated temperature (60 °C) and long reaction time (24 h). Applying the new Ca(NTf$_2$)$_2$/DABCO combination had an exceptional effect: phenylsulfonyl fluoride undergoes the SuFEx reaction to form sulfonamide **30** in 94% yield *in less than 30 min at room temperature* (Scheme 1D). Encouraged by these results, we revisited a series of amine nucleophiles and sulfonyl fluorides for comparison. In all cases, comparable or improved yields were obtained, along with a dramatic increase in reaction rate, at a lower reaction temperature (i.e., sulfonamides **30**–**33**). Further scope was exemplified by varying the electronics on the sulfonyl fluoride, amine, and highlighting the use of both ammonia and tetramethyl guanidine nucleophiles (**34**–**37**). In addition, to probe the mechanism of this reaction, we conducted NMR (^{1}H and ^{19}F) and LCMS studies and propose a SuFEx mechanism that first involves Ca/DABCO activation of the S(VI) fluoride to form an activated *N*-sulfonyl-DABCO salt, that in the presence of an amine undergoes product formation (see the SI for details).[27]

Parallel medicinal chemistry (PMC) is frequently used in drug discovery to rapidly expand SAR and optimize lead compound properties. PMC-enabled chemistry should be tolerant of a wide range of functional groups and have relatively simple reaction setup and purification. This is to facilitate the use of a plate-based (e.g., 96-well or greater) format, automated liquid handling equipment, and HPLC purification of final products, with the goal of generating numerous compounds in a more efficient manner than in singleton or batch format. To explore the utility of our Ca(NTf$_2$)$_2$/DABCO reaction conditions in PMC, we selected three S(VI) fluoride templates (sulfonyl fluoride **38**, fluorosulfate **39**, and sulfamoyl fluoride **1**) and a diverse set of amine monomers (Scheme 2; see the SI for the full set of

Scheme 2. PMC of S(VI) Fluorides with Amines
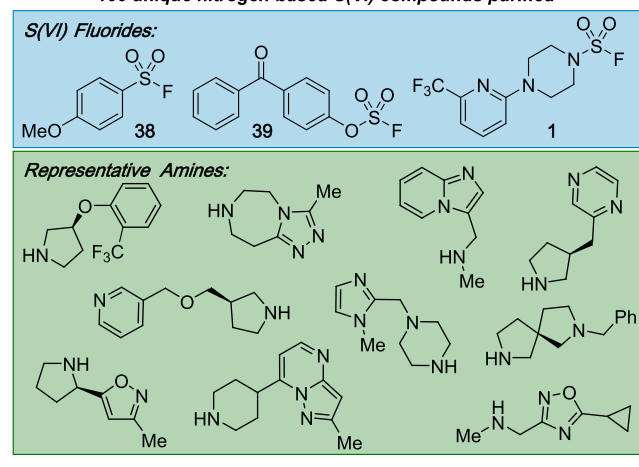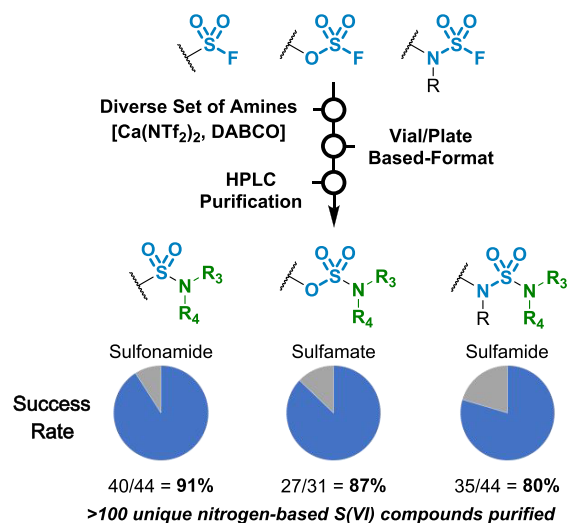
amines). Our protocol successfully translated to PMC format, generating >100 unique nitrogen-based S(VI) compounds with high overall success rate and purity across three classes of nitrogen-based S(VI) compounds (i.e., sulfonamide 40/44, sulfamate 27/31, and sulfamides 35/44 compounds). These results highlight the application of this robust transformation to a diverse set of functional groups and heterocycles.

In conclusion, we have developed a unified Ca(NTf$_2$)$_2$/DABCO-mediated method that activates S(VI) fluorides, with considerably different reactivity, toward SuFEx with amines. The reaction proceeds at room temperature, a diverse array of sulfamides, sulfamates, and sulfonamides can be readily prepared, and application to parallel medicinal chemistry is exemplified. We anticipate the introduction of this Ca(NTf$_2$)$_2$/DABCO SuFEx method will further solidify S(VI) fluorides as privileged S(VI) synthons in synthetic chemistry.[28]

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01397.

General methods, LC−MS traces, procedures, NMR spectra (PDF)

Pure lab results (XLSX)

■ AUTHOR INFORMATION

Corresponding Authors

Nicholas D. Ball − *Department of Chemistry, Pomona College, Claremont, California 91711, United States;* ⊙ orcid.org/0000-0002-6816-1113; Email: nicholas.ball@pomona.edu

Christopher W. am Ende − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States;* ⊙ orcid.org/0000-0001-8832-9641; Email: christopher.amende@pfizer.com

Authors

Subham Mahapatra − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States*

Cristian P. Woroch − *Department of Chemistry, Pomona College, Claremont, California 91711, United States*

Todd W. Butler − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States*

Sabrina N. Carneiro − *Department of Chemistry, Pomona College, Claremont, California 91711, United States*

Sabrina C. Kwan − *Department of Chemistry, Pomona College, Claremont, California 91711, United States*

Samuel R. Khasnavis − *Department of Chemistry, Pomona College, Claremont, California 91711, United States*

Junha Gu − *Department of Chemistry, Pomona College, Claremont, California 91711, United States*

Jason K. Dutra − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States*

Beth C. Vetelino − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States*

Justin Bellenger − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.0c01397

Author Contributions

This work was performed in collaboration between the Ball laboratory at Pomona College and Pfizer, Inc.

Author Contributions

§S.M. and C.W.P are co-first authors.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) 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**, *53*, 9430−9448.

(2) For representative reviews on sulfur−fluoride exchange, see: (a) Abdul Fattah, T.; Saeed, A.; Albericio, F. Recent advances towards sulfur (VI) fluoride exchange (SuFEx) click chemistry. *J. Fluorine Chem.* **2018**, *213*, 87−112. (b) Revathi, L.; Ravindar, L.; Leng, J.; Rakesh, K. P.; Qin, H.-L. Synthesis and Chemical Transformations of Fluorosulfates. *Asian J. Org. Chem.* **2018**, *7*, 662−682. (c) Chinthakindi, P. K.; Arvidsson, P. I. More Than Click Reagents? *Eur. J. Org. Chem.* **2018**, *2018*, 3648−3666. (d) Barrow, A. S.; Smedley, C. J.; Zheng, Q.; Li, S.; Dong, J.; Moses, J. E. The growing applications of SuFEx click chemistry. *Chem. Soc. Rev.* **2019**, *48*, 4731−4758.

(3) (a) Narayanan, A.; Jones, L. H. Sulfonyl fluorides as privileged warheads in chemical biology. *Chem. Sci.* **2015**, *6*, 2650−2659. (b) Jones, L. H. Emerging Utility of Fluorosulfate Chemical Probes. *ACS Med. Chem. Lett.* **2018**, *9*, 584−586.

(4) Wang, H.; Zhou, F.; Ren, G.; Zheng, Q.; Chen, H.; Gao, B.; Klivansky, L.; Liu, Y.; Wu, B.; Xu, Q.; Lu, J.; Sharpless, K. B.; Wu, P. SuFEx-Based Polysulfonate Formation from Ethenesulfonyl Fluoride-Amine Adducts. *Angew. Chem., Int. Ed.* **2017**, *56*, 11203−11208.

(5) Gao, B.; Zhang, L.; Zheng, Q.; Zhou, F.; Klivansky, L. M.; Lu, J.; Liu, Y.; Dong, J.; Wu, P.; Sharpless, K. B. Bifluoride-catalysed sulfur(VI) fluoride exchange reaction for the synthesis of polysulfates and polysulfonates. *Nat. Chem.* **2017**, *9*, 1083−1088.

(6) Veryser, C.; Demaerel, J.; Bieliūnas, V.; Gilles, P.; De Borggraeve, W. M. Ex-Situ Generation of Sulfuryl Fluoride for the Synthesis of Aryl Fluorosulfates. *Org. Lett.* **2017**, *19*, 5244−5247.

(7) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. One-pot palladium-catalyzed synthesis of sulfonyl fluorides from aryl bromides. *Chem. Sci.* **2017**, *8*, 1233−1237.

(8) Tribby, A. L.; Rodríguez, I.; Shariffudin, S.; Ball, N. D. Pd-Catalyzed Conversion of Aryl Iodides to Sulfonyl Fluorides Using SO$_2$ Surrogate DABSO and Selectfluor. *J. Org. Chem.* **2017**, *82*, 2294−2299.

(9) Zhou, H.; Mukherjee, P.; Liu, R.; Evrard, E.; Wang, D.; Humphrey, J. M.; Butler, T. W.; Hoth, L. R.; Sperry, J. B.; Sakata, S. K.; Helal, C. J.; am Ende, C. W. Introduction of a Crystalline, Shelf-Stable Reagent for the Synthesis of Sulfur(VI) Fluorides. *Org. Lett.* **2018**, *20*, 812−815.

(10) Laudadio, G.; de A Bartolomeu, A.; Verwijlen, L. M. H. M.; Cao, Y.; de Oliveira, K. T.; Noël, T. Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride. *J. Am. Chem. Soc.* **2019**, *141*, 11832−11836.

(11) Lee, C.; Ball, N. D.; Sammis, G. M. One-pot fluorosulfurylation of Grignard reagents using sulfuryl fluoride. *Chem. Commun.* **2019**, *55*, 14753−14756.

(12) Pérez-Palau, M.; Cornella, J. Synthesis of Sulfonyl Fluorides from Sulfonamides. *Eur. J. Org. Chem.* **2020**, *2020*, 2497−2500.

(13) Mukherjee, P.; Woroch, C. P.; Cleary, L.; Rusznak, M.; Franzese, R. W.; Reese, M. R.; Tucker, J. W.; Humphrey, J. M.; Etuk, S. M.; Kwan, S. C.; am Ende, C. W.; Ball, N. D. Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides. *Org. Lett.* **2018**, *20*, 3943−3947.

(14) Guo, T.; Meng, G.; Zhan, X.; Yang, Q.; Ma, T.; Xu, L.; Sharpless, K. B.; Dong, J. A New Portal to SuFEx Click Chemistry: A Stable Fluorosulfuryl Imidazolium Salt Emerging as an "F−SO$_2$+" Donor of Unprecedented Reactivity, Selectivity, and Scope. *Angew. Chem., Int. Ed.* **2018**, *57*, 2605−2610.

(15) Thomas, J.; Fokin, V. V. Regioselective Synthesis of Fluorosulfonyl 1,2,3-Triazoles from Bromovinylsulfonyl Fluoride. *Org. Lett.* **2018**, *20*, 3749−3752.

(16) Liu, J.; Wang, S.-M.; Qin, H.-L. Installation of sulfonyl fluorides onto primary amides. *Beilstein J. Org. Chem.* **2019**, *15*, 1907−1912.

(17) Liu, F.; Wang, H.; Li, S.; Bare, G. A. L.; Chen, X.; Wang, C.; Moses, J. E.; Wu, P.; Sharpless, K. B. Biocompatible SuFEx Click Chemistry: Thionyl Tetrafluoride (SOF$_4$)-Derived Connective Hubs

for Bioconjugation to DNA and Proteins. *Angew. Chem., Int. Ed.* **2019**, *58*, 8029−8033.

(18) Zhang, S.; Xiong, H.; Lu, F.; Ma, F.; Gu, Y.; Ma, P.; Xu, H.; Yang, G. Synthesis of *N*-Acyl Sulfamates from Fluorosulfonates and Potassium Trimethylsilyloxyl Imidates. *J. Org. Chem.* **2019**, *84*, 15380−15388.

(19) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Topics in Current Chemistry Topics in Curr. Chem.* **2019**, *376*, 1−34.

(20) (a) Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. Sulfamates and their therapeutic potential. *Med. Res. Rev.* **2005**, *25*, 186−228. (b) Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. Therapeutic applications of sulfamates. *Expert Opin. Ther. Pat.* **2004**, *14*, 1273−1308. (c) Spillane, W.; Malaubier, J.-B. Sulfamic Acid and Its *N*- and *O*-Substituted Derivatives. *Chem. Rev.* **2014**, *114*, 2507−2586.

(21) (a) Wright, S. W.; Hallstrom, K. N. Sulfonamides and Sulfonyl Fluorides from Heteroaryl Thiols. *J. Org. Chem.* **2006**, *71*, 1080−1084. (b) 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.

(22) Gaulton, A.; Bellis, L. J.; Bento, A. P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; Al-Lazikani, B.; Overington, J. P. ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* **2012**, *40*, D1100−D1107.

(23) Spillane, W. J.; McHugh, F. A.; Burke, P. O. Elimination mechanisms in the anilinolysis of sulfamoyl chlorides in chloroform and acetonitrile. *J. Chem. Soc., Perkin Trans. 2* **1998**, *2*, 13−18.

(24) Monosubstituted sulfamoyl fluorides are more reactive because of their ability to go through the sulfenium intermediate (see the SI for details and the following reference): Edwards, D. R.; Wolfenden, R. Proton-in-Flight Mechanism for the Spontaneous Hydrolysis of *N*-Methyl *O*-Phenyl Sulfamate: Implications for the Design of Steroid Sulfatase Inhibitors. *J. Org. Chem.* **2012**, *77*, 4450−4453.

(25) Employing the Sharpless MgO conditions (ref 1) with sulfamoyl fluoride **1** and amine **2** gave sulfamide **3** in 45% yield (see the SI for details).

(26) Gembus, V.; Marsais, F.; Levacher, V. An Efficient Organo-catalyzed Interconversion of Silyl Ethers to Tosylates Using DBU and *p*-Toluenesulfonyl Fluoride. *Synlett* **2008**, *2008*, 1463−1466.

(27) For examples of DABCO addition to sulfonyl chlorides, see: (a) Hartung, J.; Hünig, S.; Kneuer, R.; Schwarz, M.; Wenner. 1,4-Diazabicyclo[2.2.2]octane (DABCO) − an Efficient Reagent in the Synthesis of Alkyl Tosylates or Sulfenates. *Synthesis* **1997**, *1997*, 1433−1438. (b) Fu, Y.; Xu, Q.-S.; Li, Q.-Z.; Li, M.-P.; Shi, C.-Z.; Du, Z. Sulfonylation of 1,4-Diazabicyclo[2.2.2]octane: Charge-Transfer Complex Triggered C−N Bond Cleavage. *ChemistryOpen* **2019**, *8*, 127−131.

(28) A previous version of this manuscript was published as a preprint: Mahapatra, S.; Woroch, C. P.; Butler, T. W.; Carneiro, S. N.; Kwan, S. C.; Khasnavis, S. R.; Gu, J.; Dutra, J. K.; Vetelino, B. C.; Bellenger, J.; am Ende, C. W.; Ball, N. D. SuFEx Activation with Ca(NTf$_2$)$_2$: A Unified Strategy to Access Sulfamides, Sulfamates and Sulfonamides from S(VI) Fluorides. *ChemRxiv* **2020**, ver. 1. (accessed 2020-05-21).