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Introduction of a Crystalline, Shelf-Stable Reagent for the Synthesis of Sulfur(VI) Fluorides

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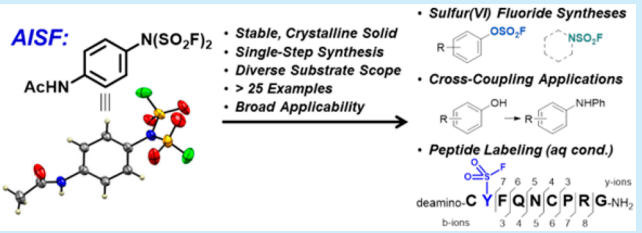
Supporting Information

ABSTRACT: The design, synthesis, and application of [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF), a shelf-stable, crystalline reagent for the synthesis of sulfur(VI) fluorides, is described. The utility of AISF is demonstrated in the synthesis of a diverse array of aryl fluorosulfates and sulfamoyl fluorides under mild conditions. Additionally, a single-step preparation of AISF was developed that installed the bis(fluorosulfonyl)imide group on acetanilide utilizing an oxidative C−H functionalization protocol.



Fluorosulfates have been utilized in a myriad of applications, extending from chemical biology[1] to polymer chemistry.[2] The seminal report by Sharpless and co-workers which describes the principles of sulfur(VI) fluoride exchange (SuFEx) chemistry extols the virtues of the sulfur(VI) hub and has established a foundation for numerous research endeavors, further demonstrating the utility of fluorosulfates.[2a] For example, a clickable aryl fluorosulfate chemical biology probe was shown to selectively modify a conserved tyrosine residue of the intracellular lipid binding protein (iLBP) family.[1c] In cross-coupling applications, the aryl fluorosulfate is an effective electrophile in a variety of transition-metal-catalyzed transformations including Negishi,[3] Suzuki,[4] Sonogashira,[4c,5] Stille,[3,6] Buchwald−Hartwig amination,[7] and carbonylation[8] chemistries. Recently, the Sanford laboratory developed a deoxyfluorination procedure that utilizes the intermediacy of a fluorosulfate to assemble aryl fluorides from phenols.[9] In addition, the corresponding nitrogen variant, the sulfamoyl fluoride, is a particularly stable, yet effective, synthetic precursor to substituted sulfamides.[2a]

The current state-of-the-art method to synthesize fluorosulfates and sulfamoyl fluorides relies on the use of sulfuryl fluoride gas (Figure 1A).[10] However, the additional safety precautions and specialized equipment required when working with a toxic gas have impeded broad adoption of this reagent. Alternatively, the use of 1,1′-sulfonyldiimidazole (SDI) as a precursor to sulfuryl fluoride gas was recently reported.[11] This protocol relies on the ex situ generation of sulfuryl fluoride gas and a specialized two-chamber reactor which pressurizes as sulfuryl fluoride gas is generated. Therefore, an easily manipulated, solid reagent that directly installs the $-SO_2F$ group would facilitate the synthesis of these valuable functional groups. Additionally, during the review process for this manuscript, a new azolium triflate reagent to synthesize sulfur(VI) fluorides was disclosed by Sharpless, Dong, and co-workers; however, preparation of this reagent requires the

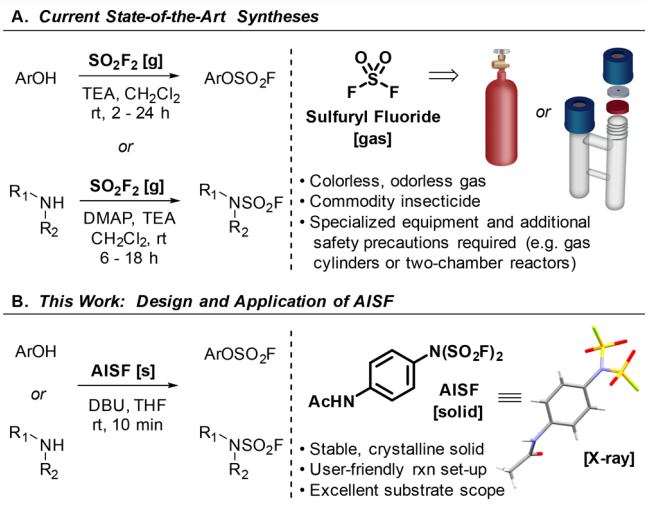


Figure 1. (A) Synthesis of fluorosulfates and sulfamoyl fluorides using sulfuryl fluoride gas. (B) Design and application of AISF, a solid reagent for the synthesis sulfur(VI) fluorides.

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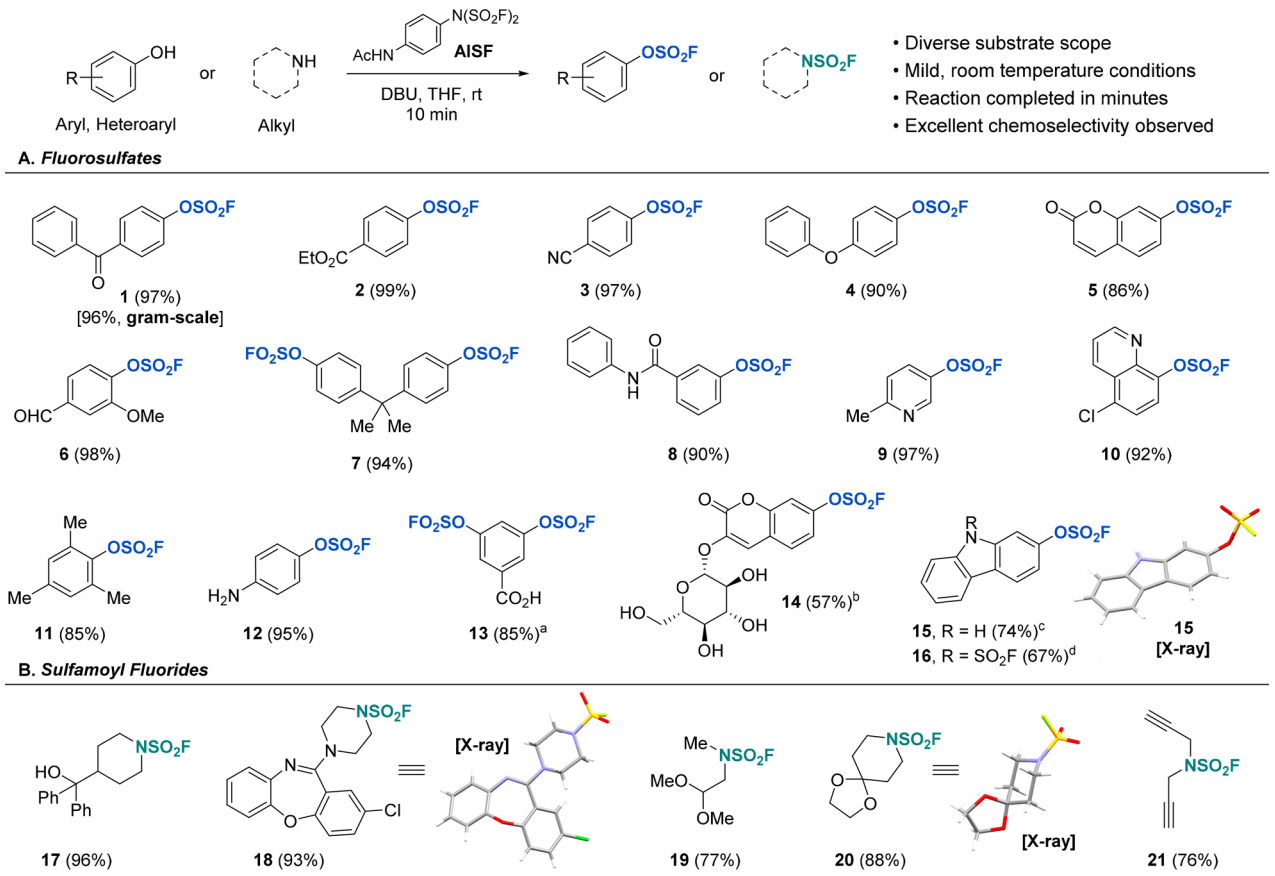


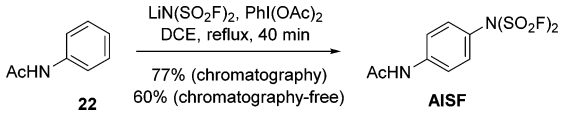
Figure 2. Substrate scope for the synthesis of fluorosulfates and sulfamoyl fluorides using AISF. Reaction conditions: phenol or amine (1 equiv), AISF (1.2 equiv), DBU (2.2 equiv) in THF (0.2 M) at rt, 10 min. An average of two independent experiments was used to calculate the reported yields. Key: (a) AISF (3.2 equiv), DBU (4.2 equiv); (b) AISF (1.2 equiv), Cs_2CO_3 (2.2 equiv), DMSO (0.2 M); (c) AISF (1.04 equiv), DBU (2.2 equiv) in THF (0.2 M) at 0 °C; (d) AISF (2.2 equiv), DBU (4.4 equiv), THF (0.2 M) at rt.

use of sulfuryl fluoride gas and the reagent is reported to be hygroscopic, requiring storage at 4 °C or in a desiccator to minimize reagent decomposition.[12] Toward this end, we report the invention of AISF ([4-(Acetylamino)phenyl]-ImidodiSulfuryl diFluoride), a convenient, shelf-stable, crystalline reagent for the synthesis of fluorosulfates and sulfamoyl fluorides (Figure 1B and Figure 2).

In designing a solid reagent to install the $-SO_2F$ group, we required three key attributes: (1) the reagent must demonstrate comparable or improved reactivity to sulfuryl fluoride gas; (2) it must be a crystalline, shelf-stable and easily manipulated solid; and (3) it must be readily accessible on decagram scale from commercially available starting materials. We were inspired by the solid alternatives of triflic anhydride (e.g., *N*-phenyltriflimide,[13] Comin's reagent,[14] trifluoromethanesulfonic imidazolide,[15] and 4-nitrophenyltriflate)[16] and explored multiple structural variations of these reagents for the potential to transfer an $-SO_2F$ group. Ultimately, the stable, crystalline solid AISF was identified as a reagent that fulfilled the aforementioned criteria.

A synthesis of AISF was developed that directly installed the bis(fluorosulfonyl)imide through an iodine(III)-promoted oxidative C−H functionalization of acetanilide (**22**, Scheme 1).[17] AISF was isolated as a white, crystalline, free-flowing solid (yield = 77%, >400 g prepared, mp 141.0−143.1 °C, dec), with X-ray crystallography providing unambiguous structural confirmation (Figure 1B). The reagent is easily manipulated in an open atmosphere and is stable at ambient temperature either as

Scheme 1. Synthesis of AISF through an Oxidative C−H Functionalization of Acetanilide (22)



a solid or in solution (THF-d_6), with no measurable decomposition over a prolonged period of time (>1 month, Supplementary Figure S3). Differential scanning calorimetry (DSC) indicated low thermal potential (319 J/g, Supplementary Figure S5) for the decomposition of AISF, which occurs subsequent to the reagent's melt at approximately 140 °C and is consistent with the lack of high energy functional groups within the molecule. Further evaluation through differential accelerating rate calorimetry (DARC) revealed an accompanying pressure increase associated with the exotherm (Supplementary Figure S6), and therefore, to prevent reagent decomposition, it is recommended to avoid heating AISF beyond approximately 140 °C. To facilitate the scale-up of AISF, a chromatography-free protocol was also developed and showcased on decagram scale (see the Supporting Information).

We found that reaction of phenols with AISF occurs rapidly in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to produce the desired fluorosulfates in high yield (Figure 2A).[18] The reaction is unaffected by the presence of electron-withdrawing or -donating substituents on the phenol and is

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tolerant of heterocycles as well as sterically encumbered substrates. AISF can also be used in the presence of reactive functional groups (i.e., aniline, carboxylic acid, 1° and 2° alcohols), generating the desired fluorosulfates (**12**–**14**) in good yields. Careful control of stoichiometry is also easily accomplished with the solid reagent. This is exemplified by the monofunctionalization of 2-hydroxycarbazole to generate fluorosulfate **15** when 1 equiv of AISF is employed (structure confirmed by X-ray crystallography, Figure 2A). Alternatively, the addition of greater than 2 equiv of AISF in the reaction affords the corresponding bis-functionalized product **16**.

Synthesis of sulfamoyl fluorides was also achieved using AISF (Figure 2B). Subjecting amines to the same reaction conditions identified for the synthesis of fluorosulfates from phenols (DBU, THF, 10 min) produced the corresponding sulfamoyl fluorides (**17**–**21**) in good yield. It is noteworthy that these reactions do not require the addition of the activating agents DMAP or DABCO, as reported with sulfuryl fluoride gas[2a] and similar to what was observed with the azolium triflate reagent.[12]

We next evaluated the single-flask cross-coupling of phenols via the intermediacy of the AISF-derived fluorosulfate (Figure 3A). Subjecting phenol **23** to modified Buchwald–Hartwig

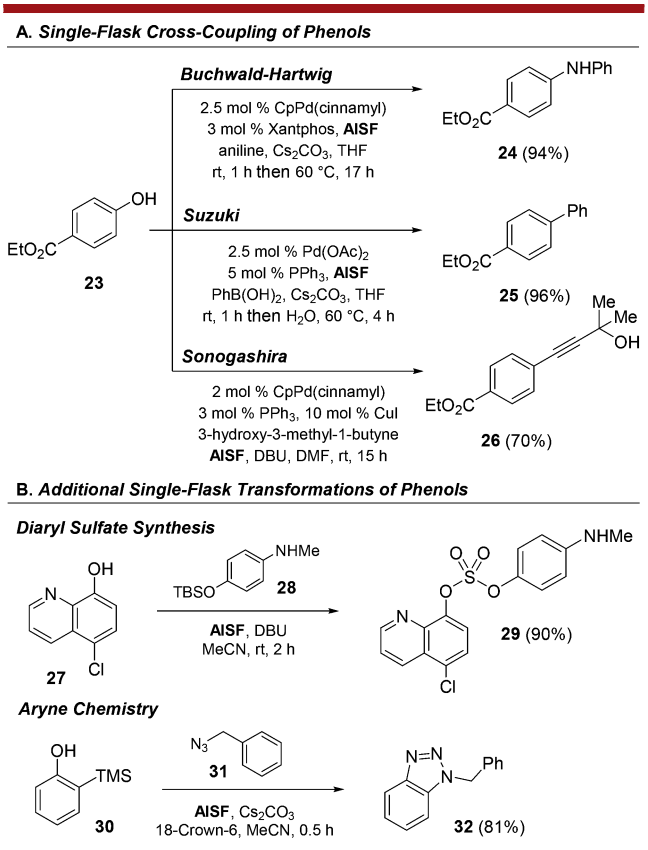

Figure 3. Single-flask reactions of phenols via the intermediacy of AISF-generated fluorosulfates.

amination conditions[7b] in the presence of AISF afforded the corresponding aniline product **24** in excellent yield (94%). Similar results were also observed with both modified Suzuki[4b] and Sonogashira[5] cross-couplings generating biaryl **25** and alkyne **26**, respectively. These reactions highlight the chemoselectivity of AISF, as the reagent was inert to the catalyst, ligand and nucleophiles present in the reaction mixtures.[19] Additional single-vessel phenol transformations were demonstrated in the preparation of diaryl sulfate **29**[2a] and in the aryne chemistry to access triazole **32**,[20] further demonstrating the broad utility of AISF (Figure 3B).

Incorporation of the fluorosulfate group into a peptide or protein imparts a reactive handle for further modification or to assist in the investigation of binding events such as protein–ligand or protein–protein interactions (PPIs). Therefore, to evaluate the capacity of AISF to chemoselectively label a tyrosine residue under biologically relevant conditions, we explored the modification of the peptidic macrocycle desmopressin in an aqueous environment (Figure 4). Thus,

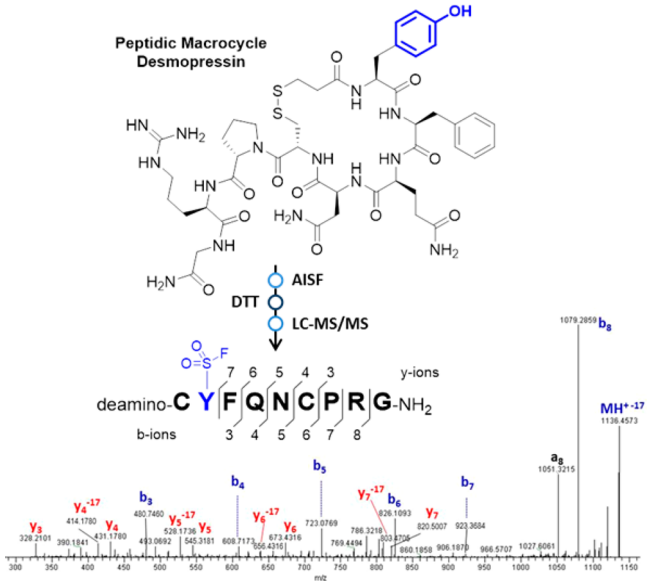

Figure 4. Selective modification of the tyrosine residue on the peptidic macrocycle desmopressin with AISF in pH 8.6, 0.1 M Tris buffer/KF:DMSO (1:1) followed by treatment with DTT (5 mM). Reduced, fluorosulfate-modified desmopressin (deamino-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-dArg-Gly-NH_2, **33**) was analyzed by LC–MS/MS.

addition of AISF to a pH 8.6 Tris buffer/DMSO solution (1:1) containing potassium fluoride and desmopressin resulted in the successful labeling of the peptide with a single $-SO_2F$ group, despite the presence of multiple potentially reactive amino acids and functional groups (i.e., Tyr, Arg, Gln, Asn, disulfide bond). The site of modification was established by reduction of the disulfide with dithiothreitol (DTT) and then analysis by liquid chromatography (LC)–mass spectrometry (MS) utilizing a LTQ Orbitrap XL spectrometer. In the tandem mass spectrum, detection of the $-SO_2F$-modified b_3 ion, in combination with the lack of modification of the y_7 ion, is consistent with selective conversion of the tyrosine residue to the corresponding aryl fluorosulfate. It is noteworthy that at pH 8.6, potassium fluoride (KF) additive was necessary for conversion of the tyrosine residue to the fluorosulfate. This is attributed to an alternative reaction pathway in which KF reacts with AISF to generate sulfuryl fluoride in situ as the reactive species (see Supplementary Figure S12 for ^{19}F NMR experiments). Alternatively, at pH 10, and presumably with the tyrosine phenol deprotonated in solution, KF is not required and the tyrosine residue is modified through reaction with AISF without generating sulfuryl fluoride (Supplementary Figure S10). The capacity of AISF to possess dual reactivity modes, namely through direct functionalization of phenols and

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amines, or to serve as an in situ precursor to sulfuryl fluoride, expands the utility of the AISF reagent.

In conclusion, we have designed and synthesized a novel, crystalline, and bench-stable reagent for the installation of the $-SO_2F$ group. AISF boasts exceptional reactivity with a wide array of phenol and amine nucleophiles, as demonstrated by the rapid conversion to fluorosulfates and sulfamoyl fluorides under mild reaction conditions. Furthermore, AISF is compatible with other potentially reactive functional groups and reagents as exemplified in several one-flask transformations of phenols and the selective functionalization of a tyrosine residue on a peptidic macrocycle under aqueous conditions. We anticipate the user-friendliness, broad applicability, and ease of preparation of AISF will facilitate further exploration into the value of fluorosulfates and sulfamoyl fluorides by others.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03950.

Full experimental details and procedures; ^{1}H, ^{13}C, and ^{19}F NMR spectra; supporting figures and data (PDF)

Accession Codes

CCDC 1812516−1812519 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

This work was performed as a collaboration between BioDuro and Pfizer.

The authors declare the following competing financial interest(s): H.Z., R.L., and D.W. are employees at BioDuro. P.M., E.E., J.M.H., T.W.B., L.R.H., J.B.S., S.K.S., C.J.H., and C.W.A. are employees at Pfizer, Inc.

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(18) Additional base and solvent combinations were also effective in converting phenols to fluorosulfates and amines to sulfamoyl fluorides in the presence of AISF. Refer to the Supporting Information for selected examples.

(19) For the Suzuki coupling, water was added after generation of the fluorosulfate.

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