Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride

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Supporting Information

ABSTRACT: Sulfonyl fluorides are valuable synthetic motifs for a variety of applications, among which sulfur(VI) fluoride exchange-based “click chemistry” is currently the most prominent. Consequently, the development of novel and efficient synthetic methods to access these functional groups is of great interest. Herein, we report a mild and environmentally benign electrochemical approach to prepare sulfonyl fluorides using thiols or disulfides, as widely available starting materials, in combination with KF, as an inexpensive, abundant and safe fluoride source. No additional oxidants nor additional catalysts are required and, due to mild reaction conditions, the reaction displays a broad substrate scope, including a variety of alkyl, benzylic, aryl and heteroaryl thiols or disulfides.

Arguably, sulfonyl fluorides can be considered a “privileged moiety” in chemistry, as they can be adopted in a wide variety of applications. This can be attributed to the unique balance between reactivity and stability of these functional groups, which is in sharp contrast with analogous sulfonyl chlorides (Figure 1A).1 Hence, sulfonyl fluorides have been used in chemical biology as covalent protein modifiers, strong protease inhibitors and activity-based probes.2 In addition, sulfonyl fluorides have been successfully applied as fluorinating reagents,3 18F radiolabeling agents4 and have been engaged in other useful transformations,5 including polymerizations.6 However, the breakthrough application for sulfonyl fluorides is the realization of their utility as stable and robust sulfonyl precursors using sulfur(VI) fluoride exchange “click chemistry” (SuFEx).1,7

Due to their evident value, efficient syntheses of sulfonyl fluorides starting from abundant starting materials are highly desired. The classical strategy to access these functional groups involves a chloride/fluoride exchange of sulfonyl chlorides using fluoride salts (Figure 1B).8 However, sulfonyl chlorides are not widely available and need to be prepared from the corresponding thiols using a combination of oxidizing and chlorinating reagents.9 In order to avoid toxic and unstable sulfonyl chlorides, new synthetic methods have been developed using alternative starting materials, including sulfonyl hydrazides10 or sodium sulfonates.10 Also palladium-based cross-coupling strategies have been developed which utilize ary
reagents, such as Selectfluor and N-fluorodibenzenesulfonimide. Kirihara et al. reported a method to transform disulfides and thiols into sulfonyl fluorides using Selectfluor and refluxing conditions. Despite the synthetic value of these approaches, the use of costly and atom-inefficient fluoride sources limits their practicality to small scale applications.

It is, however, evident that the development of a synthetic method which directly uses commodity chemicals, such as thiols and metal alkali fluorides, would be particularly useful given the broad availability and the low cost of these starting materials.

Even so, it is immediately clear that a number of challenges need to be overcome to develop such a hitherto elusive transformation. First, fluoride is poorly soluble in organic solvents and is hardly reactive in its solvated form in aqueous media. Second, combining nucleophilic fluorine reagents with thiols to establish a single S-F bond appears unlikely. Nevertheless, based on our recent success in the electrochemical synthesis of sulfonamides, we speculated that the union of these stubborn starting materials would not only be plausible using electrochemical activation but would also facilitate the subsequent oxidation to sulfonyl fluoride via anodic oxidation. Herein, we report the discovery and optimization of an electrochemical method which meets these design criteria. The method utilizes KF as a readily available, safe and cost-efficient fluoride source. Moreover, anodic oxidation allows to avoid stoichiometric amounts of oxidants and enables the direct use of thiols or disulfides as convenient and widely available starting materials.

Initial experiments on a representative thiol, 2-mercapto-4,6-dimethylpyrimidine, revealed that the combination of 5 equiv of KF, 1 equiv of pyridine in a CH3CN/1 M HCl biphasic reaction mixture using inexpensive graphite/stainless steel electrodes is highly effective, providing the targeted sulfonyl fluoride in 74% isolated yield (Figure 1C, Entry 1). Tetra-n-butylammonium fluoride and other alkali fluorides, such as NaF and CsF, are less effective (see Supporting Information). Selectfluor, an electrophilic fluorine source, is equally potent as KF, but was not further considered due to the unfavorable price difference (KF 8 $/mol vs Selectfluor 407 $/mol). We surmise that KF functions partially as an electrolyte, as the total amount can be lowered when supporting electrolytes are added (see Supporting Information). However, given the low cost of KF in comparison to these supporting electrolytes, we opted to keep a higher concentration of KF. In the absence of acid or at lower concentrations, decreased yields are observed.

Figure 2. Synthesis of sulfonyl fluorides. Substrate scope for the electrochemical sulfonyl fluoride synthesis. Reported yields are isolated and reproduced at least two times. Yields between [brackets] are those referring to 19F NMR yields calculated with PhCF3 as internal standard. Reaction conditions (Entry 1): thiol (2 mmol) or disulfide (1 mmol), KF (5 equiv), pyridine (1 equiv), CH3CN/1 M HCl (20 mL, 1:1 v/v), C anode/Fe cathode, 20 mA (4.1 mA/cm²). *3.2 V applied potential. **4.0 V applied potential. †Isolated as a phenyl sulfonate derivative through reaction with phenol. ¶Scale-up reaction conditions: thiophenol (10 mmol), KF (5 equiv), pyridine (1 equiv), CH3CN/1 M HCl (40 mL, 1:1 v/v), C anode/Fe cathode, 3.2 V applied potential.
The addition of one equivalent of pyridine is beneficial (Figure 1C, Entry 5), and is speculated to function as an electron mediator or as a phase transfer catalyst. The reaction was confirmed to be electrochemically driven (Figure 1C, Entry 6).

With the optimal conditions in hand, we next turned our attention to examine the generality of this electrochemical transformation. As shown in Figure 2, a wide variety of structurally and electronically distinct thiols can be transformed into the corresponding sulfonyl fluorides. First, with a diverse set of thiophenols, it was determined that substrates bearing electron-neutral (1−5), -donating (6, 7) and -withdrawing substituents (8−10) were all compatible with the reaction conditions; the yields were ranging from 37 to 99%. Due to the volatility of some products, isolated yields were in some cases lower than observed with 19F nuclear magnetic resonance (NMR). This could be partially avoided by converting the obtained volatile sulfonyl fluoride in situ to the corresponding sulfonate through reaction with phenol (e.g., 1). The electrochemical reaction is not particularly sensitive to sterical hindrance as ortho-substituted thiophenols displayed similar yields to unsubstituted variants (1 versus 4). Also, halogenated thiophenols (11−13) were suitable reaction partners, providing opportunities to further functionalize the formed sulfonyl fluorides using cross-coupling chemistry.

Protected amines (14), previously unreactive in our electrochemical sulfonamide chemistry, were tolerated under the current reaction conditions. Heterocyclic thiols (15−17), which are among the most widely used moieties in pharmaceutical and agrochemical syntheses, were also effective. Notably, compound 15 is also known as PyFluor, an effective deoxyfluorination reagent reported by Doyle and co-workers.3 We next examined a variety of different primary and secondary aliphatic thiol substrates, including methanethiol (18),

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Figure 3. Mechanistic investigation of the electrochemical sulfonyl fluoride synthesis. (A) 19F NMR Kinetic batch experiment (see Supporting Information). (B) Kinetic experiment carried out in an electrochemical microreactor (gas chromatography flame ionization detector, see Supporting Information). (C) Toroidal vortices in segmented flow result in enhanced mass transport to and from the electrodes. (D) Fluorination step experiments and radical trapping experiments. Gas chromatography yield (biphenyl as internal standard). (E) Proposed mechanism.
corresponding disulfide transformation. Experiments revealed a rapid conversion of 4-proteinogenic amino acid building blocks, providing opportunities for the preparation of new non-proteinogenic amino acid building blocks.

To obtain insights into the underlying mechanism, a number of additional experiments were carried out (Figure 3). Kinetic experiments revealed a rapid conversion of 4-(trifluoromethyl)thiophenol via anodic oxidation to the corresponding disulfide within 45 min (Figure 3A). Next, the disulfide intermediate is consumed and the corresponding sulfonyl fluoride is formed. The pseudo-zero-order behavior suggests that mass transfer limitations from the bulk to the electrode surface occur during the batch electrochemical transformation.

Indeed, when the reaction is carried out in an electrochemical microflow reactor with a small interelectrode gap (250 μm), full conversion is observed in only 5 min reaction time (Figure 3B). The reduced reaction times observed in flow can be attributed to (i) the increased electrode surface-to-volume ratio, (ii) a high interfacial area between the organic and the aqueous phase and (iii) an intensified mass transport to and from the electrodes due to multiphase fluid patterns (Figure 3C).

Oxidation of the disulfide results in the formation of a radical cation, which can react further with nucleophilic fluoride to yield the corresponding sulfonyl fluoride (Figure 3E). At this point, we still wondered whether a nucleophilic or electrophilic fluorination, with an in situ generated 1-fluoro-pyridinium reagent, was operative under these reaction conditions. Hence, we carried out the reaction in the presence of 1-fluoro-pyridinium tetrafluoroborate and observed only traces of product formation (Figure 3D). In contrast, using either HCl-pyridine or HClEt3N in combination with KF allowed us to isolate the corresponding sulfonyl fluoride in good yields, indicating the presence of a nucleophilic fluorination. Adding (2,2,6,6-tetramethylpiperidin-1-yl)oxyl or benzoquinone to and from the electrodes due to multiphase fluid patterns (Figure 3C).

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b06126.

Data and materials availability: additional optimization, mechanistic data, experimental procedures and analytical data (1H, 19F and 13C NMR, high resolution mass spectrometry) for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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