Acid-Mediated Imidazole-to-Fluorine Exchange for the Synthesis of Sulfonyl and Sulfonimidoyl Fluorides

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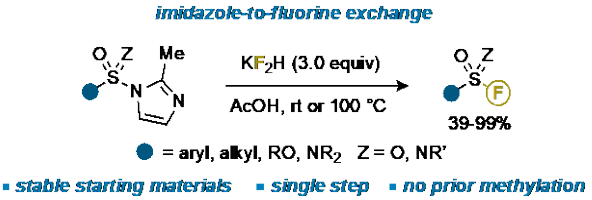


ABSTRACT: Sulfur(VI) fluoride motifs are important entities in organic chemistry. Typically, their syntheses involve the corresponding chlorides, which are often difficult to prepare and characterized by a poor storability due to the inherently weak S–Cl bond. Here, a single-step procedure for the preparation of sulfur(VI) fluorides starting from sulfonyl imidazoles as stable S(VI) reservoirs is described. By using a simple combination of AcOH and potassium bifluoride (KF_2H), an imidazole-to-fluorine exchange furnishes a variety of sulfonyl, sulfonimidoyl, sulfoxyl and sulfamoyl fluorides in good to excellent yields.

Sulfur(VI) fluorides have become important entities in organic chemistry (Scheme 1A). The strong, polarized nature of the S–F bond makes such compounds thermally and hydrolytically highly stable.[1] For example, in contrast to other S^{VI}–X structures (with X = Cl or higher halogens), sulfonyl fluorides have no propensity to undergo reduction and are uniquely electrophilic at sulfur.[2] However, in a thermodynamic stabilization environment (i.e. in a protic solvent or by capture with an organosilane) the fluoro substituent becomes an excellent leaving group and fluoride is easily expelled under mild conditions.[1a,3] This class of nucleophilic substitutions is coined as Sulfur(VI)–Fluoride Exchange (SuFEx) chemistry[4] and has found many applications in materials chemistry and chemical biology.[5]

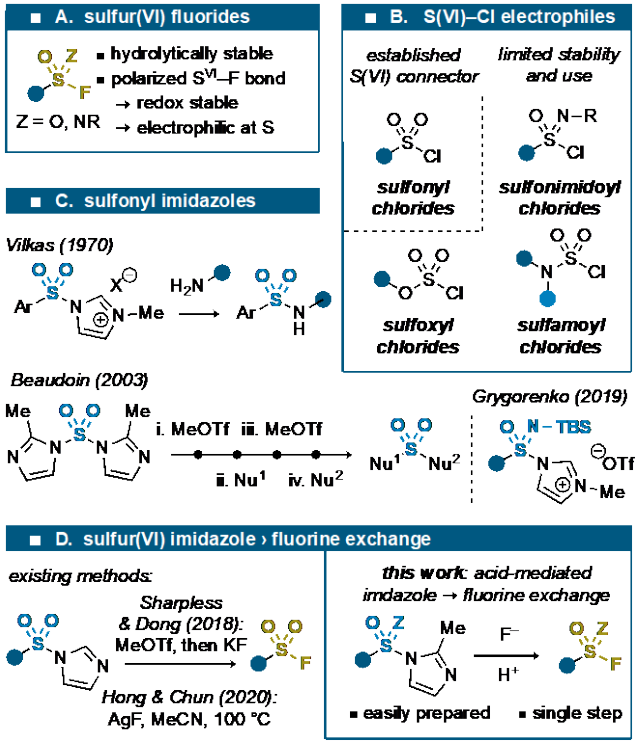
Sulfur(VI) fluorides are typically prepared from the corresponding chlorides by means of a halogen exchange.[6] Various fluoride sources have proven to be applicable in these reactions, with KF/18-crown-6, AgF, and KF_2H being the most frequently used reagents.[1a,6a,7] While sulfonyl chlorides behave relatively well in such transformations, their aza analogs, sulfonimidoyl chlorides, are more difficult to convert due to their higher tendency to reductively collapse.[8] Finally, sulfoxyl and sulfamoyl chlorides are not easily prepared as the parent SO_2Cl_2 has a BDE (S–Cl) of only 46 kcal·mol^{-1} leading to [Cl^+] species instead of undergoing fluoride exchange (Scheme 1B).[9]

As sulfonyl chlorides, sulfonyl imidazoles are stable sulfur(VI) compounds with a leaving group, and as such, they are synthons of [RSO_2^+]. Often crystalline by nature, these azole-based sulfur derivatives show no propensity to undergo reduction or hydrolysis. This behavior is particularly pronounced for 2-substituted imidazoles.[10,11]

Vilkas and others showed that sulfonyl imidazolium reagents were very effective sulfur(VI) precursors, forming sulfonamides or sulfonate esters upon nucleophilic attack (Scheme 1C).[12-18] Subsequent work by Beaudoin and others extended this chemistry to sulfonyl units with two connected heteroatoms.[11] By repeating the methylation/substitution steps, they rendered 1,1'-sulfonyldiimidazole (SO_2Im_2) into a universal building block for the preparation of unsymmetrical sulfamides and sulfamates (Scheme 1C). Kluge[15] and later Grygorenko[17] developed a synthetic platform to various sulfonimidamides and imidosulfuric diamides, wherein the methylated sulfonimidoyl imidazole played the key role as a stable electrophilic precursor (Scheme 1C). Several of these authors have noted the convenience of working with the sulfonyl imidazolium reagent in comparison to the corresponding S^{VI}–Cl electrophile.[15,16]

Recognizing the robust nature of S(VI) imidazoles and the high potential of the respective imidazolium salts, Sharpless, Dong and co-workers introduced [$MeImSO_2F$]OTf as a solid equivalent of gaseous SO_2F_2 (Scheme 1D).[10] Treatment

Scheme 1. Chemistry of Sulfonyl Fluorides and Sulfonyl Imidazoles

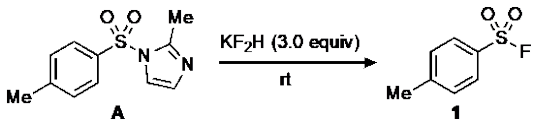


of that salt with KF generated the desired gas, which reacted further with heteroatomic nucleophiles. Hong, Chun and coworkers prepared sulfoxyl imidazoles from SO_2Im_2 and directly transformed them to the corresponding fluorosulfates using AgF at elevated temperatures.[19]

Those results convinced us that an easy to execute single-step procedure with inexpensive reagents being applicable to all classes of S(VI) imidazoles would be a valuable addition to the preparative toolbox for synthesizing SuFEx electrophiles. We hypothesized that the sulfonyl-bound imidazole retained enough Lewis-basic character to allow protonation by a sufficiently strong acid. Nucleophilic substitution with fluoride would then displace the imidazole from the highly destabilized sulfonyl imidazolium salt. A precedent for this scenario was found in the acid-mediated *ex situ* synthesis of SO_2F_2 from SO_2Im_2 by De Borggraeve and coworkers.[20] The generality of this approach has, however, not yet been demonstrated.

To explore the acid-mediated imidazole-fluorine exchange, 1-(*p*-toluenesulfonyl)-2-methylimidazole **A** was chosen as representative starting material (Table 1).[21] Initially, a combination of KF_2H (3 equiv) and TFA (1 equiv) was used as fluoride and proton source, respectively. In various aprotic solvents, the reaction was slow and full conversion of **A** to **1** took >4 h (Table 1, entry 1; for details and the full optimization study, see the SI). In methanol with 3 equiv of TFA, **A** reacted faster (45 min), but now, a series of solvolysis products were detected (Table 1, entry 2). Other carboxylic acids were less effective (Table 1, entry 3). Finally, acetic acid (as solvent and proton donor) proved optimal, and now full

Table 1. Selected Results from the Optimization Study[a]



entry	conditions	time to full conv. of **A**[b]
1	aprotic solvent + TFA (1 equiv)	>4 h
2	MeOH + TFA (3.0 equiv)	45 min[c]
3	MeOH + other carboxylic acids	4 h
4	in AcOH	1.5 h

[a]For further details, see the SI. [b]As monitored by TLC. [c]Solvolysis products were observed.

conversion of **A** to **1** occurred in 1.5 h (Table 1, entry 4). After filtration through silica gel and removal of all volatiles by evaporation, **1** was isolated in 98% yield.

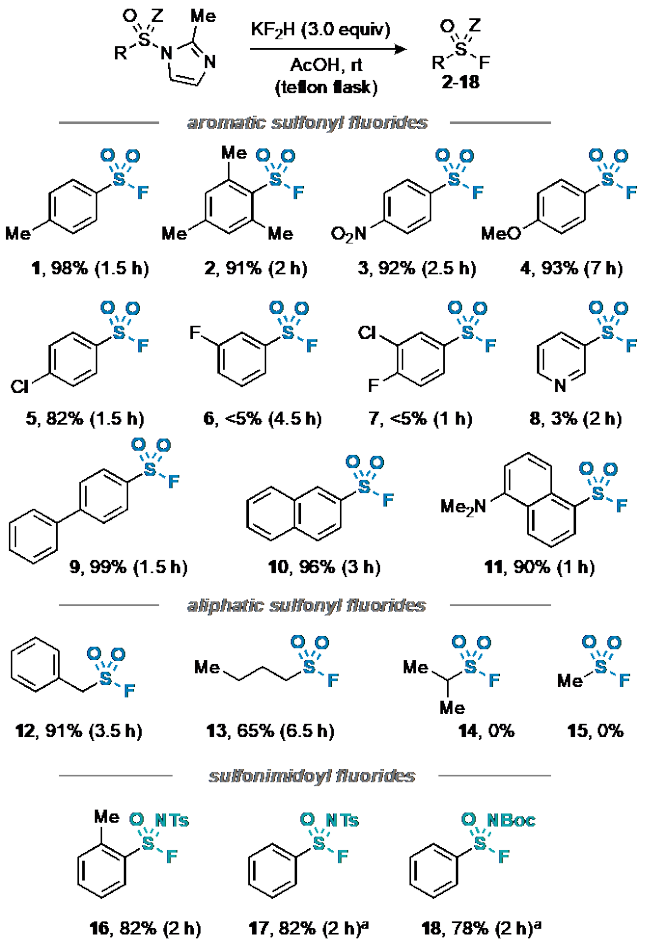
With these optimized conditions in hand, the reaction scope was explored (Scheme 2). First, substituted arylsulfonyl fluorides **2**-**11** were targeted. With the exceptions of compounds **6**-**8**, all products were obtained in high yields (82-99%). Purification by chromatography was unnecessary. In general, stereoelectronic effects appeared to be of low relevance. The unsatisfying results for products **6**-**8** were attributed to an exceptionally high volatility (of **6**-**8**) and a reduced reactivity due to protonation of the Lewis-basic pyridine nitrogen (for **8**). Aliphatic substrates reacted too, although they led to mixed results. Thus, while sulfonyl fluorides **12** and **13** were obtained in yields of 91% and 65%, respectively, isopropyl- and methyl-containing compounds **14** and **15** remained inaccessible. Also on those cases, the high product volatility is assumed to be the decisive reaction parameter. Sulfonimidoyl imidazoles performed equally well leading to sulfonimidoyl fluorides **16**-**18** in yields ranging from 78% (**18**) to 82% (**16** and **17**). Notably, the acid-labile *N*-Boc protective group remained intact under reaction conditions.

In none of the described sulfur(VI) fluoride syntheses (Scheme 2), hydrolysis or reduction, which are common problems in direct fluorinations of sulfonimidoyl chlorides, was observed.

Next, applications of heteroatom-substituted sulfonyl imidazoles were investigated (Scheme 3). As phenoxy and secondary amino groups are known to form strong bonds with S(VI) centers, the attention was focused on the corresponding sulfoxyl and sulfamoyl 2-methylimidazoles. Those compounds were also of interest, as they could directly be prepared from sulfonyl di-(2-methylimidazole) as universal building block (Scheme 1C).

When applying the optimized conditions for the conversion of sulfoxyl imidazole to their corresponding fluorides was very sluggish. However, when the temperature was increased to 100 °C, most transformations were complete within a few hours (Scheme 3). Halo-substituted arylsulfoxyl fluorides **19**-**21** were formed in good yields (64-88%). Electron-donating substituents on the arene

Scheme 2. Transformations of S(VI) Imidazoles to Sulfonyl and Sulfonimidoyl Fluorides (1 Mmol Scale)

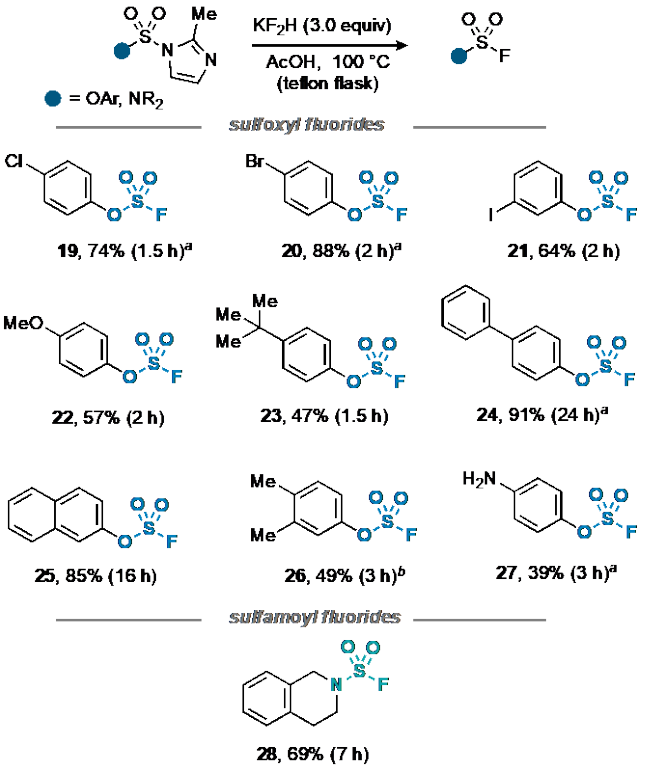


[a]Performed on a 0.5 mmol scale.

appeared to hamper the reaction as indicated by the lower yields for products **22** (57%), **23** (47%), and **26** (49%). Substrates with more extended aryl moieties needed a longer reaction time for achieving high yields (**24**: 91% after 24 h and **25**: 85% after 16 h). Of note is the reaction leading to aniline derivate **27**, which was obtained in 39%, which indicated that also Lewis-basic substrates could be converted. Finally, starting from the corresponding sulfamoyl imidazole led to fluoride **28** in 69% yield under the same conditions.

In conclusion, we developed a method for the conversion of sulfur(VI) imidazoles to their corresponding fluorides by using a combination of AcOH and KF_2H. The protocol is operationally simple and provides products in high purity without the need of column chromatography. The starting materials are bench-stable and easy to store. Besides sulfonyl derivatives with C–S bonds, a variety of other S(VI)–imidazoles reacts well too, leading to fluorides with sulfonimidoyl, sulfoxyl and sulfamoyl groups. All of these SuFEx handles can thus be accessed in a one-method-fits-all manner, and we are convinced that this approach will find broad application in future work directed to the synthesis of clickable linkers.

Scheme 3. Transformations of Aryloxysulfonyl and Sulfamoyl Imidazoles to the Corresponding Fluorides (1 Mmol Scale)



[a]Performed on a 0.5 mmol scale. [b]Performed on a 0.47 mmol scale.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

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

Experimental procedures, characterization data, NMR spectra for new compounds (PDF)

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21. The choice for 2-methylimidazole rather than imidazole was deduced from ref. 11. In comparing the two, the 2-methylated derivative gave consistently higher substitution yields.