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Synthesis of Sulfonyl Fluorides from Sulfonamides

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Abstract: A simple and practical synthesis of sulfonyl fluorides from sulfonamides is reported. The method capitalizes on the formation of the sulfonyl chloride by virtue of the reaction of Pyry-BF$_4$ and MgCl$_2$, and subsequent *in situ* conversion to the more robust and stable sulfonyl fluoride by the presence of KF. The mild conditions and high chemoselectivity of the protocol enables late-stage formation of sulfonyl fluorides from densely functionalized molecules.

The synthesis of complex organic molecules bearing sulfonyl fluorides in their structure has gained tremendous momentum due to their successful activity in the field of chemical biology.[1],[2] Due to its unique chemical properties, several sulfonyl fluorides have been utilized as warheads in chemical biology to target aminoacid residues and act as activity-based probes (Figure 1).[3]
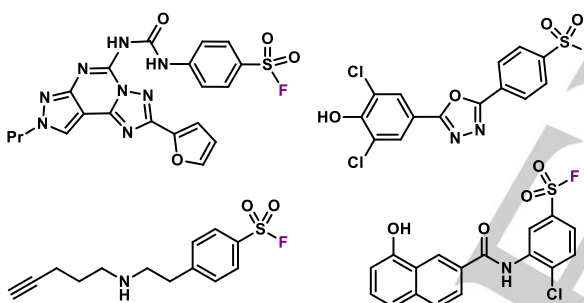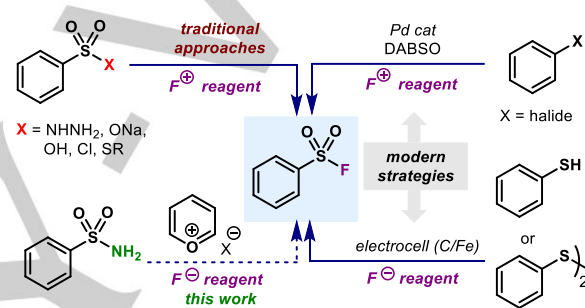

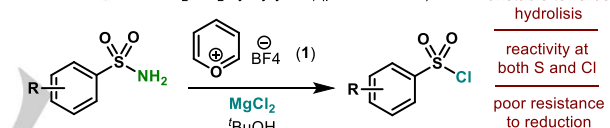**Figure 1.** Examples of functionalized arylsulfonyl fluorides as activity-based probes.

Numerous synthetic approaches to sulfonyl fluorides are available in the literature, starting from a myriad of different starting materials.[4] Early syntheses can be found from the sulfonyl hydrazide,[5] thiosulfonate,[6] sulfonyl chloride,[2],[7] sulfonic acids,[8] sulfonate salts[9] among others (Figure 2A).[10] However, most of these traditional methods are restricted in terms of functional group compatibility and synthetic steps are required to obtain the starting materials. In more recent approaches, Willis and Bagley[11] and Ball[12] independently addressed these issues and reported elegant Pd-catalyzed strategies for the synthesis of sulfonyl fluorides using simple and readily available aryl halides as starting materials, DABSO (solid SO$_2$ surrogate) and an electrophilic fluorinating agent. Recently, Noël and co-workers have also provided a new electrochemical-based method to convert aryl- and alkylthiols and disulfides into the corresponding high-valent S(VI) fluoride compounds.[13] Although these represent tremendous advances for the synthesis of highly functionalized sulfonyl fluorides, methods to forge the S–F bond from alternative starting materials would truly expand the palette of opportunities in this field. In this

regard, we realized that methods to convert primary sulfonamides into the corresponding sulfonyl fluoride are virtually non-existant. Based on the vast number of biologically relevant compounds bearing sulfonamides and the growing interest in their modification in drug discovery programs,[14] we envisaged that a method to convert sulfonamides into sulfonyl fluorides would be highly beneficial.

Figure 2. (**A**) Overview of the synthetic methods to obtain sulfonyl fluorides. (**B**) Synthesis of sulfonyl chlorides through activation of sulfonamides.

We have recently reported on the use of Pyry-BF$_4$ (**1**), as a highly chemoselective reagent for the modification of amino groups.[15] One particular application is the selective activation of sulfonamides by Pyry-BF$_4$ (**1**) thus converting them into the corresponding sulfonyl chloride in the presence of MgCl$_2$ (Figure 2B).[16] Although great electrophiles, sulfonyl chlorides suffer from high instability and fast hydrolysis rates, which results in troublesome isolation procedures.[2] Herein, we present a strategy which enables the conversion of aryl- and alkylsulfonamides into more robust, bench-stable sulfonyl fluorides in one operation. The simplicity of operation and the robustness of the method combined with the high chemoselectivity profile enabled the preparation of sulfonyl fluorides in late-stage contexts, which is demonstrated in the modification of six different biologically relevant compounds.

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**Table 1.** Optimization of the reaction conditions.

entry	deviation from above	yield of 3 (%)[a]
1	none	**97% (76%)[b]**
2	w/o MgCl₂	18%
3	w/o KF	< 5%
4	w/o 1	< 5%
5	w/o H₂O quench	< 5%
6	4 equiv. KF	50%
7	5 equiv. KF	67%
8	6 equiv. KHF₂ instead of KF	93%

[a] Yield determined by ^{1}H and ^{19}F NMR using 4-fluoroanisole as internal standard. [b] Yield of isolated pure material.

Our investigations started by exploring the modification of simple benzensulfonamide (**2**), in the presence of Pyry-BF₄ (**1**) and MgCl₂. After optimization of the reaction parameters, it was found that the addition of KF (6.0 equiv.) in MeCN at 60 °C followed by an aqueous quench at 25 °C afforded clean formation of benzenesulfonyl fluoride (**3**) in excellent yields as judged by ^{1}H and ^{19}F NMR (Table 1, entry 1, 97%). The presence of all the reagents was necessary for the reaction to proceed (entries 2-5). These control experiments suggest the formation of the sulfonyl chloride and *in situ* conversion to the sulfonyl fluoride when KF is solubilized by the H₂O in the quench. Remarkably, this transformation proceeds in the same reaction flask without isolation of any of the intermediates. This is in contrast to previously reported methods where purification of the corresponding sulfonyl chlorides is required followed by a fluoride source in combination with 18-crown to successfully undergo nucleophilic displacement of the chloride.[2],[7] A decrease on the amount of KF resulted in much lower yields of **3** (entries 6 and 7). The replacement of KF by KHF₂ afforded similar yields of **3**, suggesting that similar species might be involved in solution when using both KHF₂ and KF (entry 8).

With the optimized conditions in hand, we performed a preliminary scope of the substitution pattern on the aryl group (Figure 3, top). Gratifyingly, the presence of π-extended systems (**4**) or electron-donating groups (**5-8**) did not influence the reactivity and excellent yields of sulfonyl fluoride were obtained. Halogenated groups in the aryl ring such as trifluoromethyl (**9**), bromo (**10**) and chloro (**11** and **12**) posed no difficulties. The presence of electron-withdrawing groups such as nitro (**13**) or ester (**14**) also boded well with these conditions. Interestingly, sulfonamides bearing a free hydroxyl group (**15**) or having a protected aniline with Fmoc (**16**) were both successfully converted to the corresponding sulfonyl fluoride. Unfortunately, free amino groups or anilines protected with Boc did not afford the desired product (**17** and **18**). In the former, direct reaction of the Ar–NH₂ with **1** occurs thus capturing the pyrylium reagent; in the latter case, fluoride-induced deprotection of the Boc group is most likely the reason for the lack of S–F formation. Free carboxylic acids did not engage in sulfonyl fluoride formation (**19**). The conversion of alkylsulfonamides was also explored; as

shown in Figure 3 (bottom), primary and secondary alkyl sulfonamides smoothly reacted to afford the alkylsulfonyl fluoride (**20-22**). On the other hand, sulfonamides bearing tertiary groups such as *tert*-butyl were not amenable for reaction with this protocol (**23**).
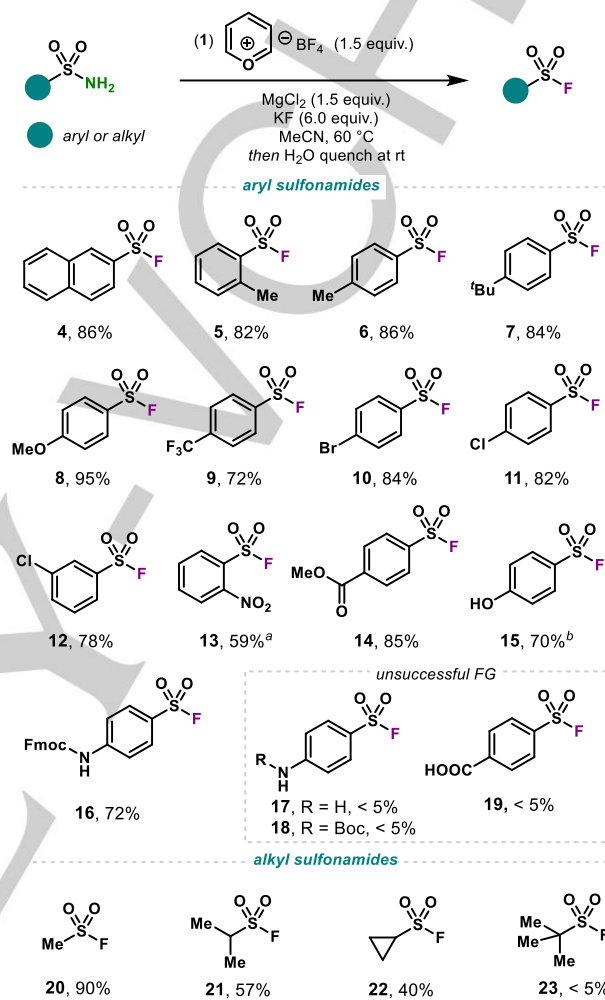
Figure 3. Scope of simple aryl and alkylsulfonamides in the pyrylium mediated sulfonyl fluoride formation. Reaction conditions: sulfonamide (0.25 mmol, 1.0 equiv.), **1** (1.5 equiv.), MgCl₂ (1.5 equiv.) and KF (6.0 equiv.) in MeCN (1.2 mL) at 60 °C for 2 h; then H₂O (1.0 mL) was added and stirred for 1 h at 25 °C. Yields of isolated pure material. [a] Using 2.0 equiv. of **1** and MgCl₂ at 100 °C for 3 h. [b] Using 2.0 equiv. of **1**.

Due to the high chemoselectivity profile of **1** towards amino groups, we sought out to explore the formation of sulfonyl fluorides in late-stage contexts. Hence, a variety of complex sulfonamides bearing different functionalities were tested (Figure 4). For example, sulfonamide bearing a cyano group and a benzoate moiety afforded clean formation of the sulfonyl fluoride (**24**, 90%). The presence of heterocycles such as pyridine bearing a chloride handle did not affect the reactivity and the sulfonyl fluoride was obtained in high yields (**25**, 83%). Benzamides containing bioisosteres of MeO such as the trifluoromethoxy group (OCF₃) also engaged in sulfonyl fluoride formation in good yields (**26**, 70%). Urea-derivatives boded well

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with this protocol as exemplified by the high yield of **27** (90%). As aforementioned, primary sulfonamides are widely present in biologically active compounds[17] and as a result, the chemical libraries of pharmaceutical and agrochemical industries contain substantial amounts of compounds bearing this scaffold.[14] Hence, we concurred to capitalize on this functionality for biologically active sulfonamide-bearing compounds to forge the corresponding sulfonyl fluoride. In this regard, a glibencamide precursor bearing an amide engaged in sulfonyl fluoride formation in high yields (**28**, 80%). Despite the presence of a nucleophilic tertiary amine, the antipsychotic (±)-sulpiride smoothly afforded the corresponding sulfonyl fluoride in good yields (**29**, 69%). Celecoxib, a pyrazole-bearing drug featuring a trifluoromethyl group afforded excellent yields of sulfonyl fluoride (**30**, 90%). The presence of a secondary amine and a furan did not pose any complications and a benzylated furosemide derivative successfully delivered **31** in 54% yield. Herbicide oryzalin, which contains two nitro groups and a tertiary amine also afforded the sulfonyl fluoride albeit in lower yields (**32**, 32%). Finally, hydrochlorothiazide, a cyclic secondary sulfonamide bearing an unprotected secondary amine in its core also reacted and afforded acceptable yields of **33** (43%).
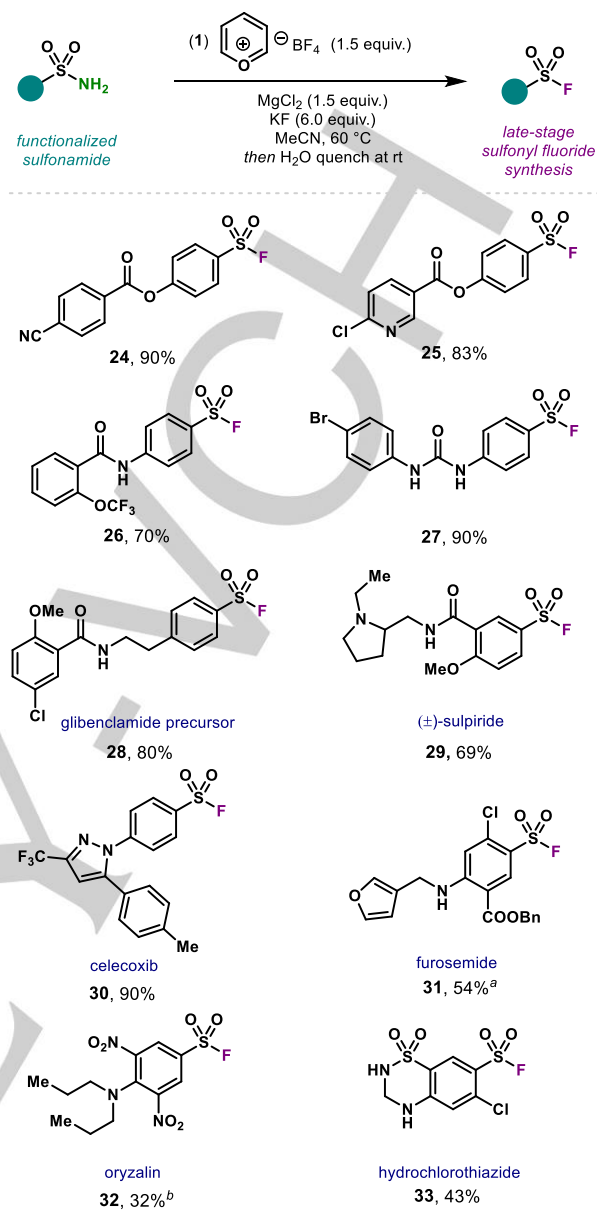
Figure 4. Functionalization of densely functionalized sulfonamides. Reaction conditions as reported in Figure 3. [a] Reaction carried out in ᵗBuOH and quenched with MeCN:H$_2$O mixture; [b] Using 4.0 equiv. of **1** at 100 °C.

In conclusion, we have developed a practical, straightforward and simple method to convert primary sulfonamides into important sulfonyl fluorides. The method capitalizes on the use of a pyrylium salt (Pyry-BF$_4$, **1**) in combination with MgCl$_2$ and KF. The high chemoselectivity of the protocol permitted the formation of sulfonyl fluorides in late-stage contexts for complex and densely functionalized molecules. We believe this method could find rapid adoption in the chemical biology arena thus providing new avenues in the identification of drug candidates and expanding the synthetic methods for the synthesis of aminoacid targeting warheads
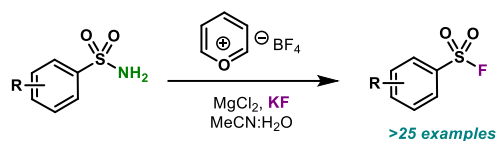
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Keywords: pyrylium • sulfonamides • sulfonyl fluorides • late-stage modification • fluorine

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