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One-pot fluorosulfurylation of Grignard reagents using sulfonyl fluoride†

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Herein, we report a new method for the one-pot syntheses of sulfonyl fluorides. Addition of an alkyl, aryl, or heteroaryl Grignard to a solution of sulfonyl fluoride at ambient temperature affords the desired sulfonyl fluorides in 18–78% yield. Furthermore, this method is applicable for *in situ* sequential reactions, whereby the Grignard reagent can be converted to the corresponding diarylsulfone, sulfonate ester, or sulfonamide in a one-pot process.

Sulfur(vi) fluorides are an important class of biomedical compounds and synthetic precursors.^{1,2} Compared to other S(vi) halides, the strong S–F bond in sulfur(vi) fluoride infers unique chemical properties, including hydrolytic stability,^{3–5} resistance to reduction,^{6,7} and chemoselective reactivity at the sulfur center.^{1,8,9} As a result, the installation of the SO₂F group in organic molecules allows for a diversity of reactivity and applications.¹⁰ Sulfonyl fluorides –RSO₂F– are of particular interest due to studies demonstrating their use as protease inhibitors¹¹ and pharmaceuticals.^{12,13} Furthermore, the advent of sulfur-fluoride exchange (SuFEx) chemistry has led to numerous applications, ranging from ¹⁸F radiolabeling agents,¹⁴ fluorinating agents,¹² chemical probes for bioconjugation,^{15,16} and synthetic precursors for other sulfur(vi) compounds,¹⁷ including sulfones,¹⁸ sulfonate esters,¹⁹ and sulfonamides.^{19–22}

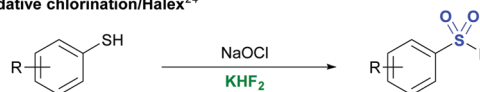
The utility of sulfonyl fluorides has necessitated new, efficient methods for their synthesis. Sulfonyl fluorides are traditionally synthesized using either a Halex reaction from the corresponding sulfonyl chloride (Scheme 1A),^{1,23} or oxidative chlorination of thiols followed by a Halex reaction (Scheme 1B).^{24,25} These methods require the isolation or *in situ* formation of a sulfonyl chloride, necessitating the use of aryl diazonium salts,²⁶ strong acids, or oxidants.^{27,28} These reagents are incompatible with

numerous functional groups, precluding their use in late-stage functionalization. Furthermore, there are operational challenges with these methods as the sulfonyl chlorides are reactive, and are thus susceptible to rapid, undesired processes including: hydrolysis, elimination of chloride in the presence of base, or nucleophilic addition to the chlorine atom.^{1,10} To address these issues, several groups have developed strategies that circumvent the formation of sulfonyl chlorides in sulfonyl fluoride synthesis.^{29–32} For example, the Ball and Willis groups have recently demonstrated

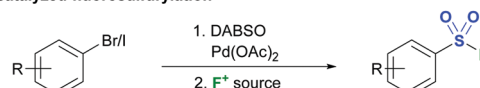
A) Chloride/fluoride exchange^{1, 23}



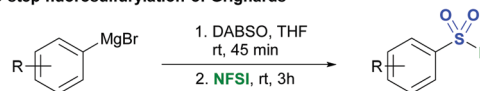
B) Oxidative chlorination/Halex²⁴



C) Pd-catalyzed fluorosulfurylation^{19,33}



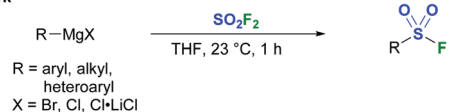
D) Two-step fluorosulfurylation of Grignards³³



E) Incorporation from arynes³⁵



This work



Scheme 1 Strategies for the syntheses of sulfonyl fluorides.

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the one-pot conversion of aryl halides, or vinyl triflates, to aryl sulfonyl fluorides using 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) and electrophilic fluorine reagents (Scheme 1C and D).^{19,33,34} Kim and coworkers also recently demonstrated that sulfonyl fluorides can be accessed from aryne intermediates (Scheme 1E).³⁵ While obviating the need to generate sulfonyl chlorides, certain challenges remain, such as extended reaction times, limited substrate scope, and the use of expensive sulfonylation agents.

We hypothesized that we may be able to access sulfonyl fluorides in a one-pot process through the addition of Grignard reagents to sulfuryl fluoride (SO_2F_2). To the best of our knowledge, there are no examples of the syntheses of sulfonyl fluorides using Grignard reagents and sulfuryl fluoride. Manufactured by Dow and used for over 50 years as a fumigant, SO_2F_2 ^{36,37} has been successfully employed to synthesize stable fluorosulfates (ROSO_2F) and sulfamoyl fluorides ($\text{NR}_2\text{SO}_2\text{F}$).^{1,36–38} Furthermore, the gas can readily be generated *ex situ* in the desired amount through the addition of trifluoroacetic acid (TFA) to 1,1-sulfonyldiimidazole (SDI) and potassium fluoride (KF).³⁶ Additionally, Grignard reagents are commercially accessible or readily prepared from the corresponding halides. Therefore, the direct installation of sulfonyl fluorides from the corresponding Grignards³⁹ without the need for transition metal catalysts, oxidants, low temperatures, or specialized sulfonylation/fluorination reagents³³ would represent a considerable advance in sulfur-fluoride exchange chemistry.

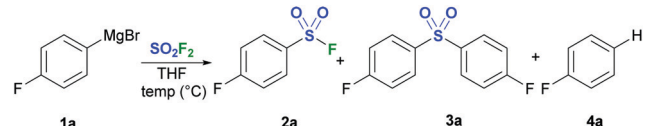
Investigations into the direct fluorosulfonylation of Grignard reagents began by bubbling *ex situ* generated sulfuryl fluoride⁴⁰ through a solution of *para*-fluorophenyl magnesium bromide (**1a**) in THF (Table 1). In under five minutes, sulfonyl fluoride **2a** was obtained in modest yield along with diaryl sulfone (**3a**) and fluorobenzene **4a**, the majority of which likely results from

quenching the remaining Grignard at the end of the reaction (Table 1, entry 1).⁴¹ While decreasing the reaction temperature led to no observed diaryl sulfone (**3a**), the rate of formation of the desired product also decreased with a concomitant increase in the amount of fluorobenzene **4a** (Table 1, entry 2). Increasing the reaction temperature to 40 °C to drive the reaction forward only afforded the desired product (**2a**) in 30% yield (Table 1, entry 3), with an increase in the amount of the diaryl sulfone (**3a**). To minimize the amount of diaryl sulfone (**3a**) formation, the addition protocol was reversed so that the Grignard reagent was slowly added to a THF solution of sulfuryl fluoride (Table 1, entry 4). This change in the addition order had the desired effect, and led to an increase in the amount of sulfonyl fluoride **2a** relative to diaryl sulfone **3a**. The yield was further improved by increasing the size of the reaction vessel, which increases the surface area of the gas/liquid interface (entry 5). Increasing the amount of sulfuryl fluoride improved the reaction yield, regardless of the size of the reaction vessel (entries 6 and 7). Further increasing the amount of sulfuryl fluoride beyond 6.1 equivalents had minimal impact on the reaction (entry 8), so we chose 4.6 equivalents for further investigations (entry 7).

With optimized conditions in hand, we next examined the scope of this new reaction with substituted phenylmagnesium bromide reagents (Table 2). Substrates with *para*-F or Cl substitution led to 78% and 59% yields of the sulfonyl fluorides **2a** and **2b**, respectively. However, electron poor bis(trifluoromethyl) derivative **1c** was not an effective substrate for our new method, affording **2c** in only 18% isolated yield, with the corresponding sulfone as the major product. Phenyl magnesium bromide, and alkyl-substituted phenyl derivatives were successfully fluorosulfonylated to give **2d–2h** in good isolated yields regardless of the steric congestion close to the nucleophilic center. Substrates with stronger electron-donating substituents were also effective in this fluorosulfonylation reaction, affording the desired products **2i–2k** in 64–70% isolated yields. Biphenyl derivative **2l** and naphthyl substrate **2m** were converted to the corresponding sulfonyl fluorides in 64% and 67% yield, respectively. While methylsulfonyl fluoride (**2n**) was only formed in moderate yield, less volatile octylsulfonyl fluoride (**2o**) was isolated in 64% isolated yield.

Investigations next turned to the preparation of heteroaryl sulfonyl fluoride derivatives, with a focus on thiophene and benzothiophene derivatives as they are important classes of synthetic intermediates^{42,43} and PET imaging precursors¹⁴ (Table 3). Unsubstituted thiophene derivative **5a** was an effective substrate for the reaction, affording fluorosulfonylated product **6a** in 59% isolated yield. Methyl-substituted thiophene Grignard reagents **5b** and **5c** were also viable, although the yield decreased when the methyl group was adjacent to the nucleophilic center (**6c**). Further increasing the sterics from a methyl group (**6c**) to an octyl group (**6d**) led to a decrease in the yield from 48% to 32%. Chloride-substitution was also tolerated, affording **6e** in 48% yield. Benzothiophene derivative **5f** was an effective substrate, providing **6f** in 50% isolated yield. As Grignard **5g** (X = Br) is challenging to synthesize under standard conditions, it was prepared under the conditions described by Knochel.⁴⁴ Treatment of this Grignard (**5**, X = Cl-LiCl) under our

Table 1 Optimization of the reaction conditions^a



Entry	Temp. (°C)	Solvent/reaction vessel (v/v; mL)	SO_2F_2^c (equiv.)	Yield ^b (%)		
				2a	3a	4a
1 ^d	23	3/4	3.1	45	10	35
2 ^d	0	3/4	3.1	25	0	75
3 ^d	40	3/4	3.1	30	15	40
4 ^e	23	3/4	3.1	53	8	31
5 ^e	23	3/20	3.1	59	6	29
6 ^e	23	3/20	4.6	66	2	30
7 ^e	23	3/20	4.6	78	6	10
8 ^e	23	3/20	6.1	77	6	11

^a Reaction conditions: **1a** (1 equiv.) on 0.29 mmol scale. ^b The yields were determined by ¹⁹F NMR using trifluorotoluene as the internal standard. ^c SO_2F_2 gas was generated *ex situ* from the addition of TFA to SDI/KF; equivalents of SO_2F_2 was adjusted by increasing the equivalents of SDI, KF and TFA in a 1:2.7:7.5 molar ratio. ^d SO_2F_2 was bubbled into a THF solution of the Grignard reagent for 30 min. ^e The Grignard reagent was added into a 0.1 M SO_2F_2 solution in THF and stirred for 1 h.

derivatives was more sensitive to the steric environment adjacent to the nucleophile (**6c** and **6d**). Compared to all existing fluorosulfurylation protocols, this method is the first that allows for sequential reactions, providing a one-pot process to convert Grignard reagents to asymmetric diaryl sulfones, sulfonate esters, and sulfonamides.

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Conflicts of interest

There are no conflicts to declare.

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