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Sulfur fluoride exchange with carbon pronucleophiles

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Aryl alkyl sulfones are an important class of compounds in drug discovery; thus, new methods toward their synthesis are desirable. A general sulfur fluoride exchange (SuFEx) method to couple aryl sulfonyl fluorides with alkyl carbon pronucleophiles to make aryl alkyl sulfones is described. The reaction was applied to a diverse set of pronucleophiles, including esters, amides, heteroarenes, nitriles, sulfones, sulfoxides, and sulfonamides, at room temperature under mild conditions. We highlight the application of this transformation in parallel medicinal chemistry for the high-throughput generation of a broad array of aryl alkyl sulfones. Lastly, we apply this method to the late-state SuFEx derivatization of a complex sulfonyl fluoride template.

Introduction

Sulfones are sulfur(vi) compounds representing over 8% of all sulfur-containing FDA-approved drugs.¹ A subset of these compounds are aryl alkyl sulfones, with applications ranging from COX-2 inhibitors to anti-cancer agents (Fig. 1). Traditionally, synthetic routes to aryl alkyl sulfones proceed by adding nucleophilic aryl or alkyl sulfonates or thiols to halogenated carbon electrophiles (Fig. 2a).^{2–8} Potential limitations of this approach include the need for pre-functionalized carbon electrophiles, the limited structural diversity available for aryl sulfonates, and the functional group incompatibility of oxidative conditions required when using thiols.⁹ Alternatively, strategies that use sulfur electrophiles and carbon nucleophiles to access aryl alkyl sulfones are underexplored.^{10,11} Direct coupling of aryl S(vi) halides with alkyl carbon pronucleophiles offers two diverse handles to access aryl alkyl sulfones and obviates the need to generate pre-activated carbon electrophiles. Incorporating sp³ carbon fragments (Fsp³) is one way to improve key physical properties of drug molecules, including solubility.¹² Thus, robust methods to incorporate sp³ carbon centers into sulfones are highly attractive.

Since the re-introduction of S(vi) fluoride chemistry by Sharpless in 2014, innovations in the field have pushed the frontiers of material science, chemical biology, and synthesis.¹³ New methods in preparing sulfonyl fluorides in conjunction with sulfur fluoride exchange (SuFEx) chemistry have

demonstrated that sulfonyl fluorides are viable synthetic precursors for sulfonylation chemistry.^{14–17} Most approaches for carbon nucleophile addition to sulfonyl fluorides rely on aryl organoboronic acids,¹⁸ aryl organomagnesium reagents,¹⁹ or styrene reagents.²⁰ Comparatively, there are limited instances of SuFEx involving sulfonyl fluorides and alkyl nucleophiles.²¹ Examples reacting aryl sulfonyl fluorides and alkyl carbon pronucleophiles are limited to allylic malonates and a few esters (Fig. 2b),^{22–25} despite other pronucleophiles having pK_a values in a similar range (Fig. 2c).²⁶ Notably, few examples of SuFEx with alkyl esters can be found in the literature, and these reactions must be run at low temperatures (Fig. 2b).^{22–24}

The tempered reactivity of aryl sulfonyl fluorides improves their compatibility with Brønsted bases relative to their sulfonyl chloride congeners.²⁷ We reasoned that the improved stability

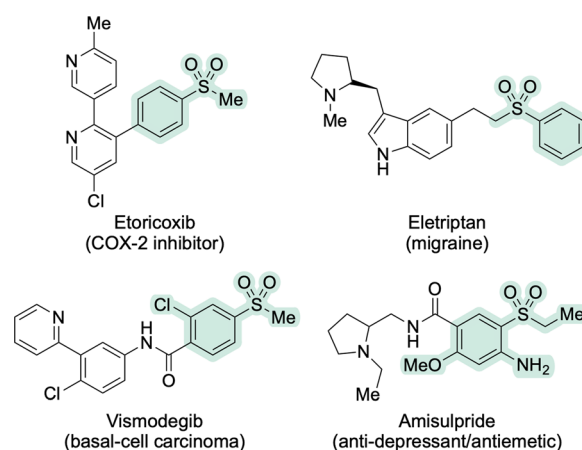


Fig. 1 Aryl alkyl sulfone-based drug compounds.

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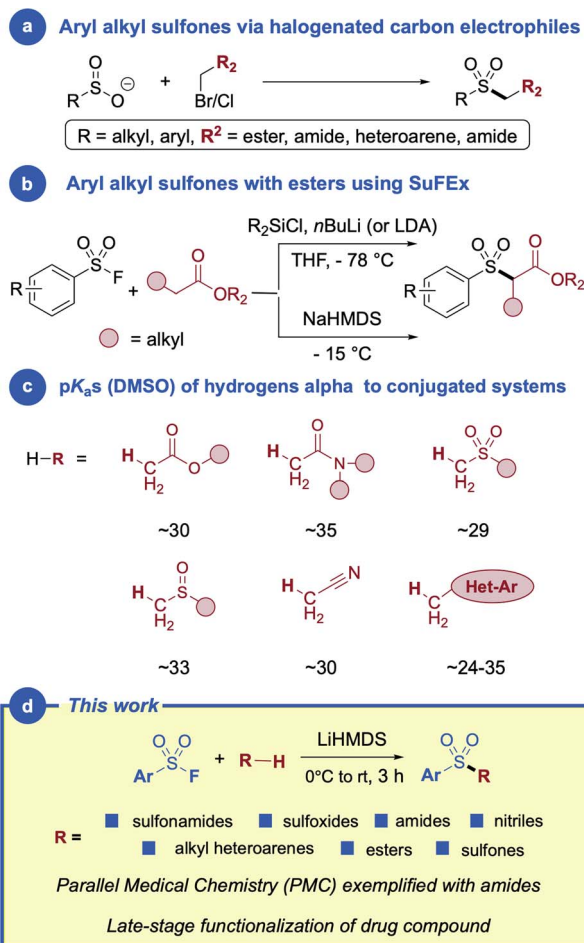


Fig. 2 Strategies to synthesize aryl alkyl sulfones.

Table 1 Optimization studies^a

| Entry | Solvent | Base | Yield (%) |
|-------|---------|--------|-----------|
| 1 | DME | LiHMDS | 77 |
| 2 | DME | NaHMDS | 27 |
| 3 | DME | KHMDS | 48 |
| 4 | DME | LiOtBu | 0 |
| 5 | DME | KOtBu | 0 |
| 6 | Toluene | LiHMDS | 67 |
| 7 | DMF | LiHMDS | 58 |
| 8 | 2-MeTHF | LiHMDS | 64 |
| 9 | Dioxane | LiHMDS | 61 |
| 10 | DMPU | LiHMDS | 54 |

^a Reaction conditions: benzenesulfonyl fluoride **1** (0.25 mmol, 1 equiv.), methyl ester **2a** (0.375 mmol, 1.5 equiv.), solvent (0.25 M) at 0 °C, and base (0.50 mmol, 2 equiv.) 0 °C to r.t., 3 h. LC-MS detected products, and yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

of sulfonyl fluorides could be leveraged to expand the scope of carbon pronucleophiles coupling partners, thereby introducing new molecular architectures previously inaccessible using SuFEx chemistry. Herein, we describe a unified set of reaction conditions using LiHMDS, which effectively facilitates the addition of various carbon pronucleophiles to aryl sulfonyl fluorides under mild conditions. Aryl alkyl sulfones are readily accessed from alkyl esters, amides, sulfones, sulfoxides, sulfonamides, heteroarenes, and nitriles. Next, we demonstrate the robustness of this protocol in parallel medicinal chemistry experiments to create a library of amide-based sulfones. Lastly, late-stage functionalization of a drug-like compound is shown with several pronucleophiles under these reaction conditions (Fig. 2d).

Results and discussion

We first subjected benzenesulfonyl fluoride **1** and methyl ester **2a** to LiHMDS in 1,2-dimethoxyethane (DME). Fortunately, α -sulfone ester **3a** was formed in 77% yield by ¹H NMR spectroscopy (Table 1 and entry 1). In DME, other bases, including KHMDS, NaHMDS, LiOtBu, and KOtBu, gave significantly reduced yields of **3a** (Table 1 and entries 2–5). With LiHMDS demonstrated as an efficient base, we screened several other solvents and determined DME was the optimal solvent explored. Notably, subjecting benzenesulfonyl chloride to the reaction conditions did not result in any detectable formation of **3a** by LC-MS.

With optimized SuFEx conditions in hand, we next wanted to explore if we could induce decarboxylative conditions to convert α -sulfone ester **3a** to aryl alkyl sulfone **4a**. While there

Table 2 Synthesis of α -sulfone ester **3a** and decarboxylation studies^a

| Entry | Base | Equiv. | Yield of 4a (%) |
|-------|--------------|--------|------------------------|
| 1 | DABCO | 10 | 97 |
| 2 | LiOH | 2 | 97 |
| 3 | Quinuclidine | 2 | 72 |
| 4 | Quinuclidine | 3 | 90 |
| 5 | TBD | 2 | 92 |

^a Reaction conditions: **3a** (0.20 mmol, 1 equiv.), DME (0.80 mL, 0.25 M), and base (0.40–2.0 mmol), 100 °C, 16 h. LC-MS detected products, and yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.



are a few examples of SuFEx using sulfonyl fluorides and esters to form α -sulfone esters,^{22–25} cases that demonstrate decarboxylation of these products to form aryl alkyl sulfones are limited to heteroaryl α -sulfone esters or α -monofluorinated sulfones.^{28–30} First, sulfone ester **3a** was isolated using the SuFEx reaction conditions in 55% isolated yield (Table 2). Next, we screened a series of bases to promote decarboxylation of **3a** to form aryl alkyl sulfone **4a**. DABCO (10 equiv.) provided sulfone **4a** with a 97% yield (Table 2 and entry 1).³¹ Other bases, including LiOH, TBD, and quinuclidine, were effective for decarboxylation, providing **4a** in 72% to 97% yield with only 2 to 3 equiv. of base.

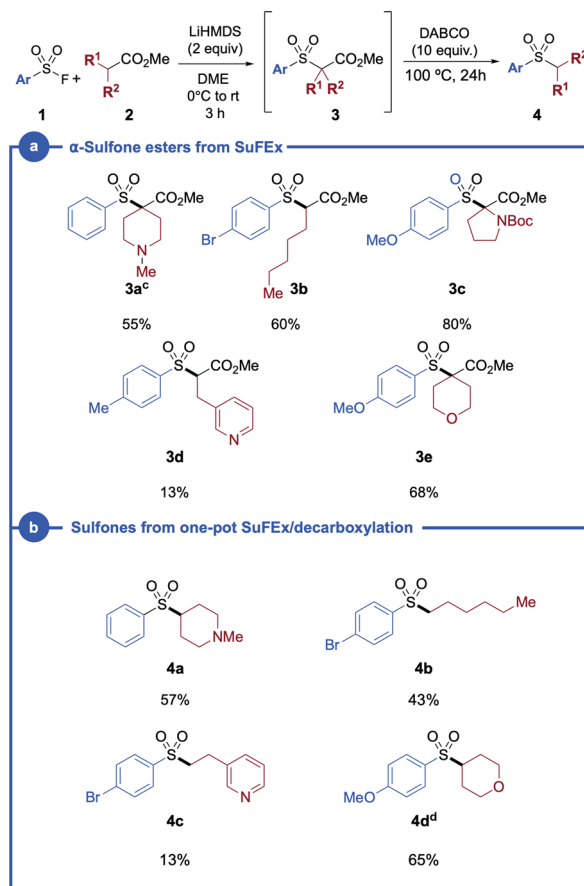
Next, we investigated the scope of SuFEx of sulfonyl fluorides with esters. Gratifyingly, cyclic and acyclic esters successfully underwent SuFEx to form α -sulfone esters **3a–3e** in 13–68% yields (Table 3). With the α -sulfone esters in hand, we wanted to demonstrate a one-pot SuFEx/decarboxylation to form aryl alkyl sulfones. Although several bases were effective for the decarboxylation of the isolated ester intermediate, we found DABCO and quinuclidine were the most compatible for a one-pot process.³² Using these conditions, aryl alkyl sulfones **4a–4d** were successfully prepared in 13–65% yield. Notably, the

decarboxylated sulfone yields mirrored that of the isolated α -sulfone esters (Table 3). This is consistent with the observation that decarboxylation from α -sulfone esters to aryl alkyl sulfones is nearly quantitative (Table 2).

Other classes of organic compounds possess suitably acidic alpha hydrogens and could serve as carbon pronucleophiles for SuFEx (Fig. 2c). We envisioned that these carbon pronucleophiles could be utilized to expand the scope of architectures accessible *via* SuFEx. Sulfones with amide moieties – amido-sulfones – have shown promise as protein inhibitors and have antihyperglycemic activity.^{33,34} Gratifyingly, cyclic and acyclic amides successfully underwent SuFEx to generate amidosulfones **5a–5j** in 16–76% yields (Table 4). SuFEx was successful with amides with electron-rich (**5c**) and tertiary substitution (**5f**) at the alpha carbon. The reaction is also tolerant to amides with alkene and free amine functional groups, forming amidosulfones **5d** and **5e** in 76% and 51% yields, respectively. The reaction works with aryl sulfonyl fluorides bearing halogen groups (**5c–5f**) and *ortho*-substitution (**5e–5f**), with no evidence of competing halide substitution.

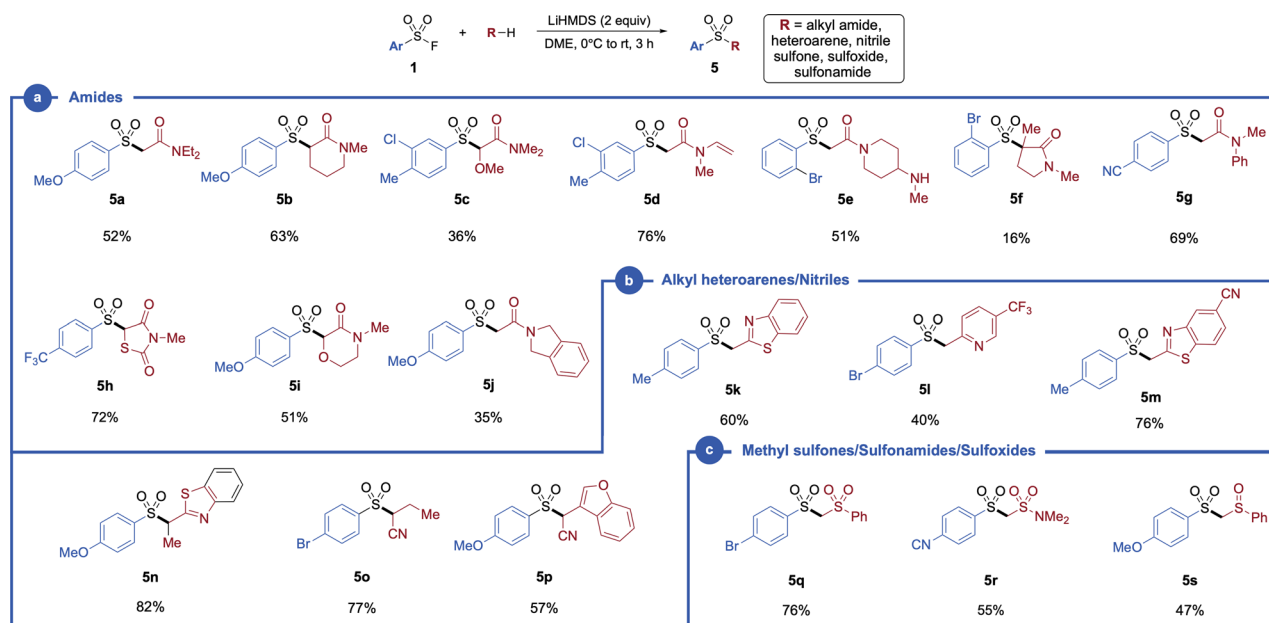
In addition to amides, alkyl heteroarenes were also demonstrated to be effective pronucleophiles for SuFEx. Aryl alkyl

Table 3 LiHMDS-mediated SuFEx with esters^{a,b}



^a Isolated yields. ^b Reaction conditions: part A (SuFEx), ArSO₂F (1.0 mmol, 1 equiv.), methyl ester (2.0 mmol, 2 equiv.), DME (3.33 mL) and LiHMDS (1 M in THF, 1.0–2.0 mmol, 2 equiv.), 0 °C to r.t., 3 h. Part B (one pot SuFEx/decarboxylation), SuFEx conditions then DABCO (10 mmol, 10 equiv.), 100 °C for 24 h. ^c Reaction was run on a 1 g scale. ^d Reaction was run with quinuclidine (3.0 mmol, 3 equiv.).



Table 4 LiHMDS-mediated SuFEx with carbon pronucleophiles^{a,b}

^a Reaction conditions: ArSO₂F (0.50–1.0 mmol, 1 equiv.), pronucleophile (1.0–2.0 mmol, 1–2 equiv.), DME (0.3 M), and LiHMDS (1 M in THF, 1.0–2.0 mmol, 2 equiv.), 0 °C to r.t., 3 h. ^b Isolated yields.

sulfones derived from alkyl benzothiazole and pyridine (**5k–5n**) pronucleophiles were synthesized in 40% to 82% yields (Table 4). Nitriles were also compatible pronucleophiles, providing **5o** and **5p** in 77% and 57% yield, respectively (Table 4). Lastly, under our conditions, methyl sulfones, sulfonamides, and sulfoxides were successful SuFEx pronucleophiles, providing **5q–5s** in 47–76% yield (Table 4). This is the first account of amides, heteroarenes, oxidized sulfur species, and nitriles serving as carbon pronucleophiles in SuFEx chemistry.

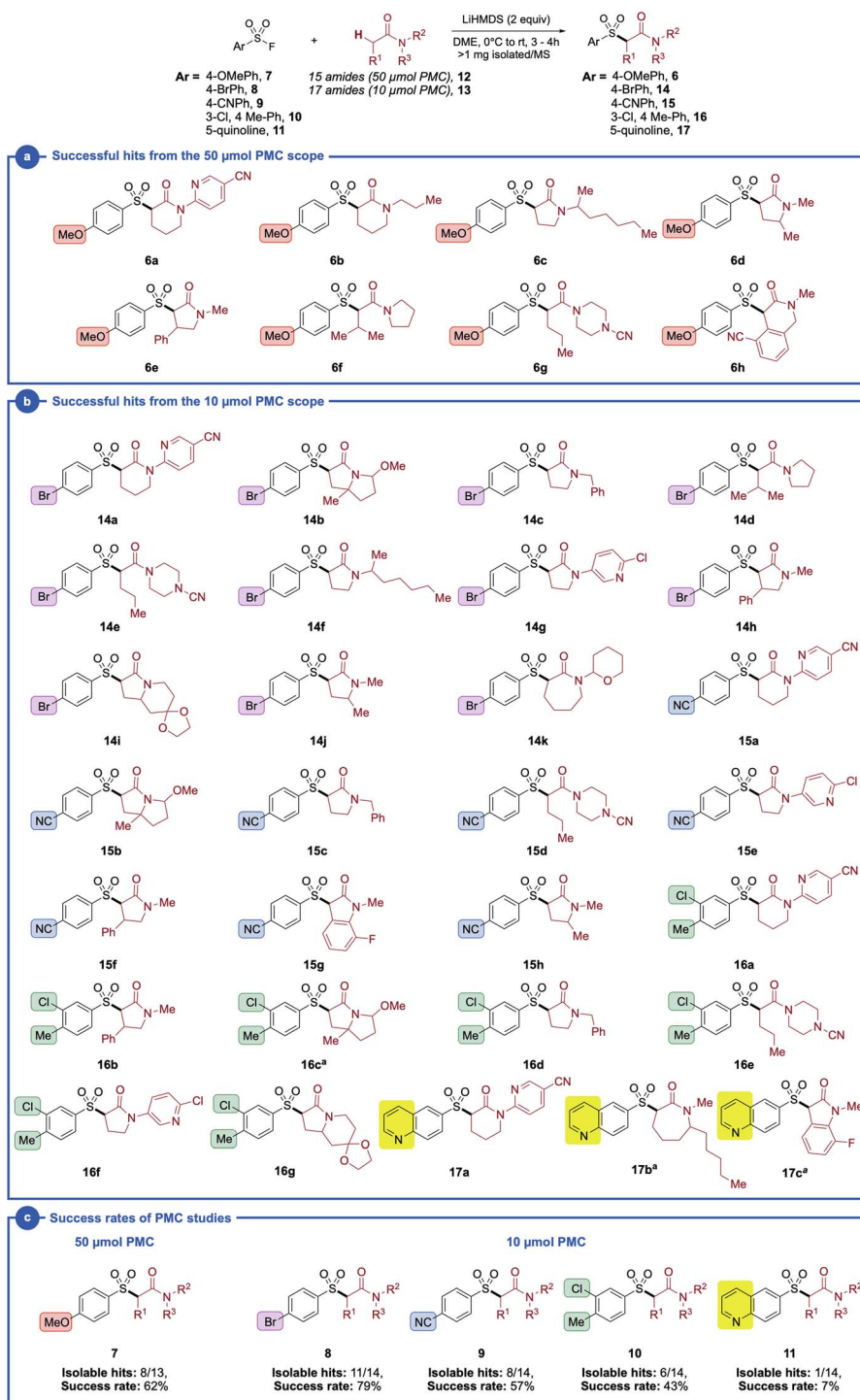
Parallel medicinal chemistry (PMC) is an effective tool used in drug discovery to rapidly generate compound libraries for structure–activity relationships (SAR) and identification of lead compounds. Often conducted on the micromole scale, the reactions used for PMC require functional group tolerance and a simple reaction setup. Additionally, PMC processes employ automated liquid handling, HPLC purification of the final product, and analytical techniques for product identification, which facilitate the efficient synthesis of numerous compounds in a parallel or single manner.

To investigate our LiHMDS-mediated SuFEx reaction for PMC, we decided to leverage the vast amide catalog at Pfizer to demonstrate the scope of amides as pronucleophile coupling partners. To assess how well our reaction conditions translated to PMC, we started on a traditional 50 μmol scale using 4-methoxybenzene sulfonyl fluoride as a SuFEx coupling partner. Amides were chosen based on the following criteria: (1) their success rate in screens of other PMC campaigns, (2) compatibility with LiHMDS, (3) avoidance of other acidic hydrogens that could compete with the desired reaction, and

(4) their availability in the Pfizer catalog. A successful hit required product detection by LC/MS and >0.3 mg of isolable product.³⁵ Using a set of 15 amides, our protocol produced amidosulfones **13a–13h** with a favorable 62% success rate (Table 5, see SI). Encouraged by these results, we next conducted a broader PMC study with 17 amides and four model sulfonyl fluorides featuring halogens (Br/Cl) and electron-withdrawing groups (CN) on the aryl group as well as a heteroarene (quinoline). Notably, this PMC screen was conducted on a 10 μmol scale, with the smaller scale testing the method's robustness. Overall, 29 products were detected and isolated from the screen (Table 5). 4-Bromobenzene sulfonyl fluoride had the most successful hit rate, with 11 out of 14 amides (79%) providing products **14a–14k**. Success rates decreased using 4-cyano (57%) and 3-chloro-4-methyl (43%) substituted sulfonyl fluorides (see SI). Quinoline-6-sulfonyl fluoride was the least successful SuFEx substrate with only one isolable product (7%). Notably, three products, **16c**, **17b** and **17c**, were detected by LC/MS; however, the amount of material present was insufficient to isolate. These compounds were not counted in the success rate (Table 5). All isolable products were characterized by LC/MS, and details regarding successful and unsuccessful hits can be found in the SI.

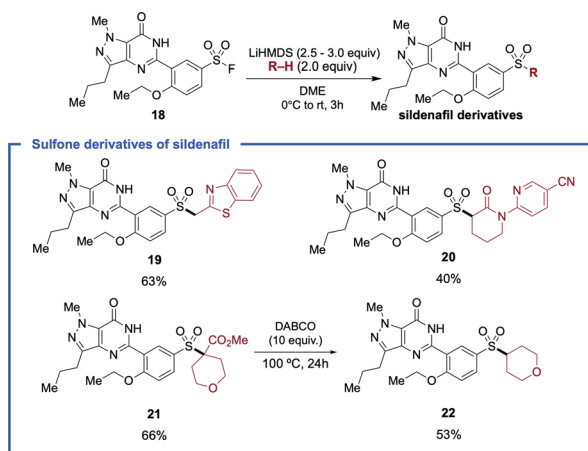
Lastly, we demonstrated this method in the late-stage functionalization of a complex target. First, we synthesized a sulfonyl fluoride derivative of sildenafil (**18**).³⁶ This template was successfully derivatized with a methyl benzothiazole, an alkyl amide, and a methyl ester to give products **19–22** in 40–66% yields (Table 6). Under our DABCO decarboxylation



Table 5 PMC studies of sulfonyl fluorides with amide pronucleophiles^{a,b}

^a Reaction conditions: for 50 μmol PMC, a stock solution of **7** (50 μmol, 1 equiv. per reaction) in DME (170 μL, per reaction) was added to 75 μmol of pre-weighed monomer (1.5 equiv.) and cooled to 7 °C. Next, a stock solution of LiHMDS (100 μmol, 2 equiv., per reaction) in THF (100 μL per reaction) was added, r.t. for 4 h. For 10 μmol PMC, a stock solution of ArSO₂F monomers (10 μmol, 1 equiv., per reaction) in DME (59 μL, per reaction) was added to 75 μmol of pre-weighed monomer (1.5 equiv.) at 7 °C. Next, a stock solution of LiHMDS (20 μmol, 2 equiv., per reaction) in DME (20 μL per reaction) was added, r.t. for 3 h. ^b A trace amount of product was detected by LC/MS, but levels were too low for isolation.



Table 6 Sulfone derivatives of sildenafil^{a,b}

^a Reaction conditions: for SuFEX; **19–21** (0.10 mmol, 1 equiv.), pronucleophile (0.20 mmol, 2 equiv.), DME (3.3 mL) at 0 °C, then LiHMDS (1 M in THF, 2.5–3.0 mmol, 2 equiv.), 0 °C to r.t., 3 h. For decarboxylation (**22**); α -sulfone ester **21** (0.029 mmol, 1 equiv.), DABCO (0.29 mmol, 10 equiv), DME (0.19 mL), 100 °C, 24 h. ^b Isolated yields.

conditions, **21** could be converted to sulfone **22** in 53% yield. Notably, the acidic N–H bond in the sildenafil scaffold does not interfere with this reaction.

Conclusions

In conclusion, we have developed and optimized a SuFEX method to make aryl alkyl sulfones from a range of pronucleophiles and aryl sulfonyl fluorides. Alkyl esters, amides, heteroarenes, nitriles, sulfoxides, sulfones, and sulfonamides were demonstrated as compatible pronucleophiles. The method was successfully applied to parallel medicinal chemistry experiments, generating a diverse set of amidosulfones. Lastly, the late-stage functionalization of a sildenafil sulfonyl fluoride derivative **18** was exemplified using a methyl heteroarene, amide, and ester. This method provides a convenient and general approach to access aryl alkyl sulfones and establishes carbon pronucleophiles as viable nucleophilic partners for SuFEX.

Author contributions

Investigation and data curation: J. R. N., M. D. T., N. J. B., T. R. P., A. D. R. and N. D. B.; methodology and formal analysis: all authors; conceptualization: all authors; project administration: T. R. P., A. D. R., C. W. A., and N. D. B.; writing – original draft: N. D. B.; writing review & editing; all authors; resources: C. W. A., T. R. P., A. D. R. and N. D. B.

Conflicts of interest

N. J. B. C. W. A., T. R. P., and A. D. R. are employees of Pfizer Inc.

Data availability

The data supporting the article have been included as a part of the SI.

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