Radiosynthesis of $[^{18}F]$ArylSCF$_2$H Using Aryl Boronic Acids, S-(Chlorofluoromethyl)benzenesulfonothioate and $[^{18}F]$Fluoride

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Herein, we report a mild and practical protocol for the copper-catalyzed chlorofluoromethylthiolation of (hetero)aryl boronic acids with the novel reagent PhSO$_2$SCFClH. The resulting products are amenable to halogen-exchange $^{18}$F-fluorination with cyclotron-produced $[^{18}F]$fluoride affording $[^{18}F]$ArSCF$_2$H. This process highlights the combined value of reagent development and (hetero)aryl boron precursors for radiochemistry by adding the $[^{18}F]$SCF$_2$H group to the list of $^{18}$F-motifs within reach for positron emission tomography studies.

Keywords: chlorofluoromethylthiolation, boron reagent, PET, fluorine, radiolabeling

Introduction

As a noninvasive and highly sensitive imaging technique, positron emission tomography (PET) is an indispensable tool within the field of nuclear imaging and medicinal chemistry.$^{1-3}$ An important aspect contributing to the success of PET is the availability of methodologies for the incorporation of radioisotopes into (bio)molecules of interest.$^{15}$ Among the radionuclides available, fluorine-18 is one of the most widely used isotopes due to its advantageous properties ($t_{1/2}=109.7$ min, positron energy of 0.63 MeV).$^{6,7}$ As a result, the demand for structurally complex $^{18}$F-labeled tracers continues to grow.$^8$ In recent years, numerous methods that allow broader access to $^{18}$F-labeled (hetero)aryl and alkyl fluorides,$^9$ as well as new $^{18}$F-motifs including $[^{18}F]$CF$_3$,$^{18-22}$ $[^{18}F]$CF$_2$H,$^{23-26}$ $[^{18}F]$OCF$_3$,$^{27}$ $[^{18}F]$OCF$_2$H,$^{27}$ and $[^{18}F]$SCF$_3$,$^{27-31}$ have emerged. Methods for the preparation of structurally diverse $[^{18}F]$ArSCF$_2$H have not been reported despite studies reporting that the difluoromethylthio group can be beneficial for pharmacokinetic and physicochemical properties such as metabolic stability, thermodynamic stability, and lipophilicity.$^{32-35}$ Several pharmaceutical drugs contain a difluoromethylthio group, for example, β-lactamaserasistant oxcephalosporin, the antibiotic floxofe sodium,$^{36}$ as well as the pesticide pyriprole and the broad-spectrum paddy herbicide pyrimisulfan.$^{37}$ Methods allowing access to $[^{18}F]$ArSCF$_2$H could therefore...
enable PET studies aimed at facilitating drug discovery, for example, biodistribution studies. To this end, we decided to develop a mild and practical approach for the preparation of $[^{18}F]$ArSCF$_2$H from ArSCFClH and cyclotron-produced $[^{18}F]f$luoride. Our proposed strategy required an efficient method to access chlorofluoromethylthiolated (hetero)arenes that would be subsequently subjected to halogen-exchange (halex) $^{18}F$-fluorination. Boron reagents are highly versatile precursors for divergent $^{18}F$-radiofluorination with the most recent example consisting of a two-step process to transform aryl boron pinacol esters into structurally complex $[^{18}F]$ArSCF$_3$ via the corresponding ArSCF$_2$Br intermediates (Figure 1a).$^{38,39}$ A logical step was therefore to convert aryl boron reagents into ArSCFClH followed by halex $^{18}F$-fluorination to access $[^{18}F]$ArSCF$_2$H (Figure 1b).

Figure 1 | (a) Boron reagents for $^{18}F$-radiochemistry. (b) Proposed approach toward $[^{18}F]$ArSCF$_2$H.

### Experimental Section

#### General information

$^1$H NMR and $^{13}$C NMR spectra were recorded on 400 and 500 MHz spectrometer and are calibrated using residual undeuterated solvent (CHCl$_3$ at 7.26 ppm $^1$H NMR, 77.16 ppm $^{13}$C NMR). $^{19}$F NMR was recorded on 400 MHz spectrometer (CFCI$_3$ as an external standard and low field is positive). Chemical shifts ($\delta$) are reported in ppm, and coupling constants ($J$) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR yield was determined by $^{19}$F NMR using benzotrifluoride as an internal standard before working up the reaction. Flash column chromatography was carried out using 300–400 mesh silica gel at medium pressure.

#### Materials

All reagents were received from commercial sources. Solvents were freshly dried and degassed according to the purification handbook *Purification of Laboratory Chemicals* before use. All olefins or aryl boronic acids were used from commercial suppliers or prepared using standard literature procedures.

#### Preparation of benzyl(chlorofluoromethyl)thioether

Into a 500 mL three-necked flask equipped with a magnetic stirring bar and a reflux condenser hexane (200 mL) was added. The solvent was stirred at room temperature, then CFCI$_3$H gas was bubbled into the solution for a period of 1.5 h (600 mmol, determined by $^{19}$F NMR spectroscopy using PhCF$_3$H as an internal standard). (Caution: Use a balloon to contain tail gas in order to avoid environmental pollution.) Then NaOH (400 mmol, 16.0 g), PhCH$_2$SH (100 mmol, 12.4 g), tris-(2-(2-methoxyethoxy)ethyl)amine (8.0 mmol, 2.5 g) were added, and the reaction was stirred at 60 °C for 4 h. The mixture was filtered, and the solvent was evaporated under vacuum. The organic layer was further purified by reduced pressure distillation to give benzyl(chlorofluoromethyl)thioether.
as a colorless liquid (4.0 g, 21%). 1H NMR (400 MHz, CDCl3, δ): 7.42–7.28 (m, 5H), 6.91 (d, J = 55.2 Hz, 1H), 4.09 (dt, J = 33.9, 7.4 Hz, 2H); 13C NMR (376 MHz, CDCl3, δ): −103.16 (d, J = 55.1 Hz); 19F NMR (376 MHz, CDCl3, δ): 135.74, 129.18, 128.98, 127.89, 103.45 (d, J = 280.0 Hz), 35.09 ppm. IR (KBr): νmax = 3031, 141, 240. HRMS (EI): calcd for C7H6O2FClS2, 239.9482; found, 239.9483.

**Preparation of S-(chlorofluoromethyl) benzenesulfonothioate 1**

A solution of chlorine in CHCl₃ (23.0 mL, 1.50 mmol/mL) was placed into a three-neck round-bottom flask equipped with a stirring bar. The mixture was cooled to −5 °C, and benzyl(chlorofluoromethyl)thioether (6.60 g, 35.0 mmol) was added. The reaction was stirred at room temperature for 0.5 h. Sodium benzenesulfonate (11.5 g, 70.0 mmol) was added quickly at −5 °C, and the reaction was stirred for another 2 h at room temperature. The resulting precipitate was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel [eluent: ethyl acetate/petroleum ether (1/10), Rf = 0.7] to give S-(chlorofluoromethyl)benzenesulfonothioate 1 as a colorless oil. 1H NMR (400 MHz, CDCl3, δ): 7.93 (d, J = 7.8 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.63–7.41 (m, 3H); 13C NMR (376 MHz, CDCl3, δ): −102.74 (d, J = 56.1 Hz); 19F NMR (376 MHz, CDCl3, δ): 145.06, 134.79, 129.74, 127.23 (d, J = 0.9 Hz), 103.36 (d, J = 289.2 Hz) ppm. IR (KBr): νmax = 1449, 1347, 1148, 1079, 1024, 782, 715 cm⁻¹. MS (EI); calcd for C₇H₆O₂FClS₂, 239.9482; found, 239.9483.

**General procedure for copper-catalyzed coupling of aryl boronic acids and reagent 1**

Aryl boronic acids (0.9 mmol, 1.8 equiv), CuSO₄ (8.0 mg, 0.050 mmol, 10 mol %), NaHCO₃ (63.0 mg, 0.750 mmol, 1.50 equiv) were placed into an oven-dried Schlenk tube that was equipped with a stirring bar under an atmosphere of argon. About 5 mL of absolute methanol and reagent 1 (120 mg, 0.500 mmol, 1.00 equiv) was added into the Schlenk tube. The reaction was stirred at room temperature for 2 h. About 15.0 mL of distilled water was added and extracted with Et₂O. The organic phase was separated and washed twice with 10.0 mL of saturated brines. The separated organic phase was dried over anhydrous MgSO₄, filtered through a short plug of Celite and concentrated under vacuum. The residue was purified by flash chromatography on silica gel.

**General experimental details for radiochemistry**

18F-Fluoride was produced by Alliance Medical (Sutton, UK) via the 18O(p,n)18F reaction and delivered as 18F-fluoride in 18O-water. Radiosynthesis and azeotropic drying were performed on a NanoTek automated microfluidic device (HPLC instrument, Advion). Radio-Thin-layer chromatographies (TLC) were performed on Merck Kieselgel 60 F254 plates. Analyses were performed using a plastic scintillator/Photomultiplier tube (PMT) detector. High-performance liquid chromatography (HPLC) analyses were performed with a Dionex Ultimate 3000 dual-channel HPLC system equipped with shared autosampler, parallel UV-detectors, and LabLogic NaI/PMT-radiodetectors with Flow-RAM analog output (LabLogic Systems, Inc, Tampa, FL, USA). All 18F-radiolabeled compounds were characterized by comparing the radio-HPLC trace with the HPLC UV-trace of an authentic reference sample. Each 18F-radiolabeled compound was characterized by comparing the radio-HPLC to the HPLC UV-trace of the authentic 18F-reference. Radiochemical yields (RCYs) were calculated using radio-TLC and radiochemical purity (RCP). All RCYs were given as non-decay corrected yields.

**General procedure for the generation of the [18F]KF/K222 complex**

[18F]Fluoride was separated from 18O-enriched water using an anion-exchange cartridge (Chromatix PS-HCO₃) and redisolved in acetonitrile (200 μL) and dried in anhydrous acetonitrile (500–1000 μL).

**General procedure for the 18F-fluorination of arylSCHFCl**

To a Vial containing AgOTf (21 mg, 0.080 mmol) and a magnetic stirrer bar was added [18F]KF/K222 (∼30 MBq) in MeCN (∼30 μL). The MeCN was removed by heating (100 °C) the vial under a stream of N₂. Upon cooling of the Vial, a solution of precursor (0.04 mmol) in 1,2-dichloroethane (300 μL) was added by syringe. The sealed vial was allowed to stir for 20 min at 60 °C. The reaction was quenched by addition of EtOH/H₂O (9:1, 500 μL). An aliquot was removed for analysis by radio-TLC and HPLC for radiochemical conversion (RCC) and product identity. Analysis was performed with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1 mL/min.

**Results and Discussion**

Considering the few methods available to install the -SCFClH group onto (hetero)arenes, all requiring multi-step syntheses and starting from the corresponding...
Our first objective was to design and prepare a new reagent enabling direct (hetero)aryl-SCFClH bond construction. This would allow for a more facile installation of this motif in a late-stage functionalization context. Inspired by our previous studies leading to the novel reagents PhSO2SCF2H and PhSO2SCH2F, we envisaged that PhSO2SCFClH, an electrophilic chlorofluoromethylthiolation reagent, would be ideal to transfer the chlorofluoromethylthio group via metal-catalyzed cross-coupling with (hetero)aryl boron

**Scheme 1** | Copper-catalyzed chlorofluoromethylthiolation of (hetero)aryl boronic acids. Standard conditions: Aryl boronic acid (0.90 mmol), PhSO2SCFClH (0.50 mmol), CuSO4 (10 mol %), NaHCO3 (0.75 mmol), MeOH (5.0 mL, 0.1 M), room temperature, 12 h. Isolated yields. "Yields were determined by quantitative 19F NMR spectroscopy using α,α,α-trifluorotoluene as the internal standard.

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precursors. To this end, PhSO₂SCFClH 1 was synthesized in two steps (eq 1).a

\[ \text{BnSH} + \text{CFCl}_2H \xrightarrow{\text{NaOH/TDA-1, Hexane, 60 °C, 4 h, 21%}} \text{BnSCFClH} \]

(1) Cl₂/CHCl₃, –5 °C, 0.5 h
(2) PhSO₂Na, rt, 2.0 h
85% yield (8.2 g scale)

With reagent 1 in hand, we examined its suitability for coupling with (hetero)aryl boronic acids. 4-Biphenylboronic acid was chosen as a model substrate for investigations. The optimal conditions to generate the chlorofluoromethylthiolated product 2a consisted of reacting 4-biphenylboronic acid and reagent 1 in methanol in the presence of CuSO₄ (10 mol %) and NaHCO₃ (1.5 equiv). This process afforded 2a in 98% yield after 12 h at room temperature. Other Cu(II) salts such as Cu(OAc)₂ or CuBr₂ led to a dramatic decrease in yields. NaHCO₃ as a base was vital for the reaction to proceed since reactions using other bases such as Na₂CO₃ and Li₂CO₃ gave lower yields, and K₂CO₃ was ineffective. All tested solvents other than MeOH did not lead to product formation. Notably, conducting the reaction with excess reagent 1 afforded 2a in low yield.¹ With the optimal conditions for the copper-catalyzed chlorofluoromethylthiolation of aryl boronic acids in hand, we investigated the tolerance of the reaction to functional groups. As illustrated in Scheme 1, electron-rich and electron-poor aryl boronic acids reacted with PhSO₂SCFClH 1 to give the desired chlorofluoromethylthiolated arenes in high isolated yields. Oxygen or sulfur-containing heteroaryl boronic acids were amenable to coupling (2w–ac and 2ae), but pyridinyl boronic acid 2ac or pyrazolyl boronic acid 2ad was not compatible, likely due to the presence of the metal-coordinating nitrogen atom. A wide variety of common functional groups were tolerated, including ester (2f–h), enolizable ketone (2l), aldehyde (2j), halogens such as fluorne (2k), chlorine (2l), bromine (2m), or iodine (2n), alkene (2o), nitro (2p and 2q), and thiocarbon (2r). To investigate the scalability of the reaction, (4-(ethoxycarbonyl)phenyl) boronic acid (5.0 mmol) and thiianthen-7-y1boronic acid (6.0 mmol) were coupled with reagent 1 affording 1.21 g of 2g and 1.70 g of 2aa, respectively. Furthermore, the method was found to be readily applicable for the preparation of chlorofluoromethylthio-substituted derivatives of natural products such as pterostilbene 2af, diacetone-d-glucose 2ag, estrone 2ah, and the two lipid-lowering agents fenofibrate 2ai clofibrate 2ai. Finally, an advanced intermediate of the anti-type-II diabetes drug canagliflozin 2ak and an intermediate for the synthesis of dronedarone 2al, a drug used for the treatment of arrhythmia,² were isolated in 78% and 64% yield, respectively. This novel method represents a significant improvement in comparison with known multistep synthetic routes, which are limited to a single example.⁴⁰–⁴³

Having developed a general method for the preparation of ArSCFClH, we investigated the halogen-exchange reaction with widely used [¹⁸F]KF/K₂₂₂ (Scheme 2). Successful implementation of this protocol would allow access to a novel radiofluorinated motif, thereby expanding the toolbox of reactions available to radiochemists for the design of new probes. Previously, a single example of halogen exchange for the preparation of a [¹⁸F]-labeled difluoromethylthio-substituted heteroarene, which was a precursor for the radiosynthesis of an [¹⁸F]-difluoromethylation reagent in high molar activity, has been reported.²⁶ Building on our previous work for the radiosynthesis of [¹⁸F]arylSCF₃, [¹⁸F]arylOCF₃, and [¹⁸F]arylOCF₂H, a selection of chlorofluoromethylthiolated arenes was reacted with [¹⁸F]KF/K₂₂₂ in the presence of AgOTf (2.0 equiv) in 1,2-dichloroethane at 60 °C for 20 min. The [¹⁸F]-labeled difluoromethylthio-substituted (hetero)arenes were obtained in good RCYs⁴⁹,b and RCP (Scheme 2, 3a–h). For instance, reactions of 2t and 2x under standard conditions gave corresponding [¹⁸F]ArSCF₂H 3a and 3b in 81% and 72% RCY, respectively (3a and 3b). In the absence of AgOTf, product 3b was obtained in 8% RCY, indicating the importance of halogenophilic Ag(I) for this transformation.⁵ This study identified lower-performing substrates; for example, reaction of chlorofluoromethylthiolated carbazole 2ae afforded [¹⁸F]ArSCF₂H 3k in 10% RCY. Next, we subjected structurally complicated chlorofluoromethylthiolated drug-like molecules, including clofibrate, fenofibrate, estrone, and advanced intermediates of canagliflozin and dronedarone, to our standard reaction conditions. Successful labeling of these molecules was observed with RCYs ranging from 15 to 72%. For example, the method offered [¹⁸F]-analogs of fenofibrate and clofibrate in 51% and 72% RCY, respectively 3l and 3m. Using 4.6 GBq of [¹⁸F]fluoride, we obtained 3h with a molar activity (Aₘ) of 0.12 GBq/µmol, a result consistent with other Ag-mediated halogen-exchange [¹⁸F]-fluorinations.⁶
Conclusion

We have developed a mild and practical approach for the preparation of structurally diverse $^{[18F]}$ArSCF$_2$H. To the best of our knowledge, this represents the first general route to these $^{[18F]}$-labeled compounds, with the added benefit of using easily accessible aryl boron reagents. The success in accessing structurally diverse $^{[18F]}$ArSCF$_2$H was based on two critical elements: (1) the design and synthesis of the first electrophilic chlorofluoromethylthiolating reagent PhSO$_2$SCFClH 1, and (2) the development of a robust copper-catalyzed coupling reaction that converts (hetero)aryl boronic acids into chlorofluoromethylthiolated (hetero)arenes. This work expands the radiochemical space by introduction of $^{[18F]}$ArSCF$_2$H as a new $^{18F}$-labeled functional group.

Currently, application of this novel $^{18F}$-radiochemistry on a broad range of translational applications is underway in our laboratory.

Footnotes

a For details, see the Supporting Information.

b Radiochemistry nomenclature was used using the following guidelines.

c For a single example of halex $^{18F}$-fluorination carried out in the absence of Ag(I) to access $^{[18F]}$2-benzothiazolyl-SCF$_2$H, see ref 26.

Supporting Information

Supporting Information is available.

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Conflict of Interest
There are no conflicts to declare.

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