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# $^{18}$F-Fluoroform: a $^{18}$F-trifluoromethylating agent for the synthesis of $SCF_2{}^{18}F$-aromatic derivatives

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**Herein the synthesis of various $SCF_2{}^{18}F$-containing derivatives is reported by a transition metal-free process. By using $HCF_2{}^{18}F$, readily generated from a bench-stable difluoromethyl sulfonium salt, various aromatic disulfides were easily converted into the desired radiolabelled trifluoromethylthiolated compounds in the presence of a base. This protocol allowed the formation of the $SCF_2{}^{18}F$-containing aromatic derivatives in good to excellent radiochemical yields. This process was also extended to the corresponding selenium derivative.**

Positron emission tomography (PET) is one of the leading imaging tools used in clinic and research. [1] PET is based on the use of radioactive isotopes that are capable of $\beta^+$-decay (positron emission). Positrons interact with electrons in the media, giving rise to a pair of $\gamma$-rays that are emitted in the opposite directions and are detected by a PET scanner. Pairs of simultaneously detected $\gamma$-rays are used to build up a 3D image of the radionuclide distribution in the analyzed object. The choice of a particular radioactive isotope depends on the specific application. [1a] Generally, nuclei that emit low-energy positrons are preferred since they offer better resolution. Therefore, short and efficient synthesis of radiolabeled probes and the typical interaction time with a biological target are key parameters to take in consideration. $^{18}$F is one of the most frequently used isotopes for PET. It has a convenient half-life of 109.7 minutes that allows using small quantities of the radionuclide but is still long enough to use it for the synthesis of complex small molecules. For example, $^{18}$F-FDG (2-$^{18}$F-fluoro-2-deoxy-D-glucose) is the most widely used PET tracer for the diagnosis of cancer since it is absorbed by the proliferating tumor cells.[2] Worth to mention that numerous $^{18}$F-labelled molecules have been also synthesized and used in the studies of various biological processes.[1c,d] As a consequence, important efforts and significant results in the blossoming $^{18}$F radiochemistry research field have been reported within the last thirty years. However, these recent advances are mainly restricted to the development of new approaches to radiotracers bearing a single fluorine-18 atom (either an aliphatic or aromatic derivative), and $^{18}$F-trifluoromethylated compounds.[3] Therefore, the quest for the design of original radiolabeled fluorinated groups is of high interest. In this context, a lot of efforts has been devoted towards the trifluroromethylthio group ($SCF_3$), an emergent fluorinated moiety, which appears as promising for pharmaceuticals and agrochemicals.[4] Hence, nowadays efficient synthetic methodologies have been reported for the introduction of the non-radiolabeled $SCF_3$ moiety, mostly in aromatic series. In contrast, to the best of our knowledge, only two articles dealing with the $^{18}$F-trifluoromethylthiolation were published in 2015 by the research groups of Gouverneur[5] as well as Liang and Xiao[6] (Scheme 1). Gouverneur and co-workers developed a silver(I) triflate-mediated halex $^{18}$F-fluorination of bromodifluoromethylthio aromatic derivatives leading to the expected $^{18}$F-trifluoromethylthiolated aromatic compounds in low to excellent radiochemical yields. A complementary approach based on an *in situ* generated difluorocarbene was depicted by the group of Liang and Xiao. Indeed, the first $^{18}$F-trifluoromethylthiolation of benzylic, allylic and aliphatic electrophiles (ie. R-X) using difluoromethylenephosphobetaine, elemental sulphur and $^{18}$F-fluoride furnished the corresponding $^{18}$F-trifluoromethyl thiolated derivatives in moderate to very good radiochemical yields.

In a preliminary work, we reported an efficient method for the preparation of a well-defined radiolabeled trifluoromethylcopper ($CuCF_2{}^{18}F$) from $HCF_2{}^{18}F$, allowing us to prepare $^{18}$F-trifluoromethylated aromatic compounds from arylboronic acids at room temperature.[7] In that sequence, the efficient generation of $HCF_2{}^{18}F$ under mild conditions was carried out from $^{18}$F-fluoride and the bench-stable crystalline (difluoromethyl)(mesityl)(phenyl) sulfonium salt **1**. Continuing our ongoing research program devoted to the use of this radiolabeled reagent, we investigated its application toward the synthesis of other $^{18}$F-radiolabeled aromatic compounds under simple reaction conditions. Indeed, we depicted herein the reaction of $HCF_2{}^{18}F$ with readily available disulfides in the presence of a base to build up $SCF_2{}^{18}F$-containing aromatic molecules.[8]

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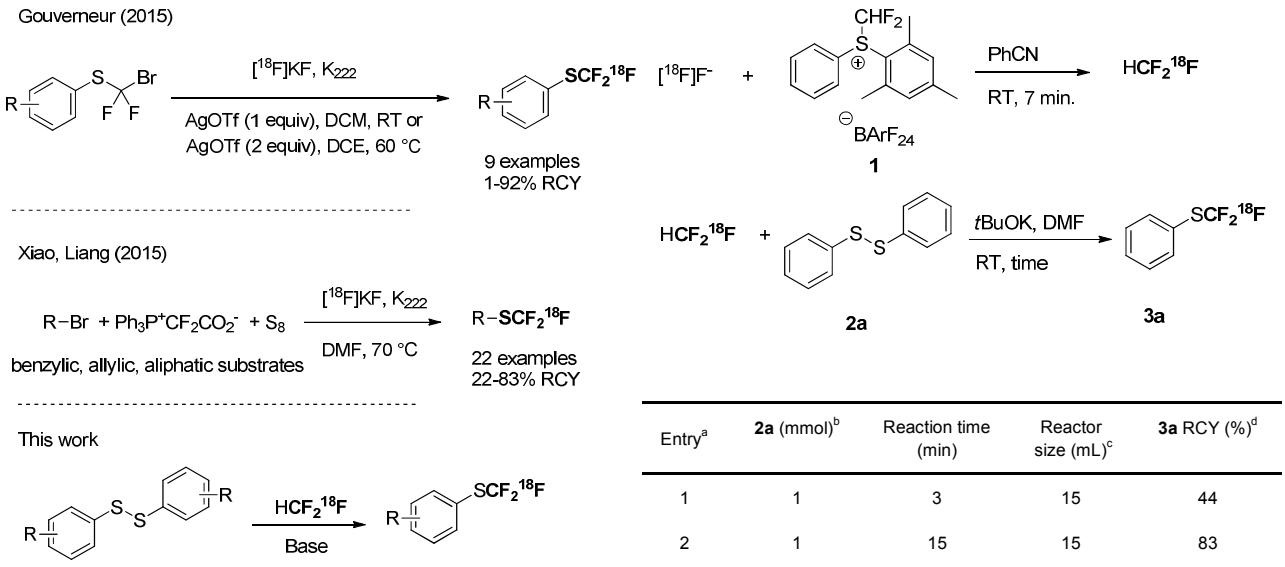


**Scheme 1.** State of the art of the $^{18}$F-trifluoromethylthiolation reaction.

At the outset of our optimization studies,1,2-diphenyl disulfane **2a** was chosen as an electrophile. The radiochemical synthesis of $SCF_2{}^{18}F$-containing aromatic derivatives was achieved using a semi-automated module.[9] $^{18}$F-Fluoride anions previously produced and dried according to the usual procedure[10] were solubilized in PhCN and the resulting solution was then transferred onto neat **1**[11] to generate the radiolabeled fluoroform: $HCF_2{}^{18}F$.[12] This latter, was then pulled out using a flow of $N_2$ and trapped in a solution of *t*BuOK and 1,2-diphenyl disulfane **2a** in DMF. With 0.07 mmol of the precursor **1** and a reaction time of 3 minutes, $PhSCF_2{}^{18}F$ **3a** was obtained in an encouraging 44% radiochemical yield (RCY, Table 1, entry 1). Increasing the reaction time to 15 minutes resulted in a 84% RCY (Table 1, entry 2). We next examined the importance of the stoichiometry between **2a** and **1**. With a 7:1 ratio, we observed an important decrease of the RCY to 40% (Table 1, entry 3). Finally, we turned our attention to the reactor size in order to minimize the volume of the gas phase. Replacing a 15 mL reactor by a 8 mL one did not improve the reaction outcome and a similar 84% RCY of $PhSCF_2{}^{18}F$ **3a** was obtained (Table 1, entry 4).

**Table 1.** Optimization of $^{18}$F-trifluorothiomethylation from **1**.

| Entry[a] | **2a** (mmol)[b] | Reaction time (min) | Reactor size (mL)[c] | **3a** RCY (%)[d] |
|---|---|---|---|---|
| 1 | 1 | 3 | 15 | 44 |
| 2 | 1 | 15 | 15 | 83 |
| 3 | 0.5 | 15 | 15 | 40 |
| 4 | 1 | 15 | 8 | 84 |

[a] For each entry, $[^{18}F]KF/K_{222}$ was obtained after elution of a QMA carbonate cartridge with a $K_2CO_3/K_{222}$ solution in $CH_3CN$ and water. [b] Each experiment was carried out using 0.07 mmol of **1**, PhCN (1 mL), *t*BuOK (1 equiv relatively to **2a**), DMF (0.5M). [c] See Supporting information for details. [d] Calculated from the activity of $HCF_2{}^{18}F$. One experiment for each entry has been carried out. Radiochemical yield was calculated from the activities of organic and aqueous layers.

Then, these optimized conditions were successfully applied to a large panel of disulfides and one diselenide (Scheme 2). 1,2-Diphenyl disulfane **2a** gave the corresponding product **3a** in a very good 73% RCY and an excellent radiochemical purity (> 99%). Electron rich aryldisulfide derivatives led to the expected radiolabeled products (Scheme 2, **3b**, **3f** and **3g**) in good to high RCY (58 to 74%). It is noteworthy that functional groups such as ester, halogen and nitrile are compatible with the reaction conditions (Scheme 2, **3h**, **3c-e, 3i**) leading to good RCY (61-68%) except for **3h** (45% RCY and 82% radiochemical purity). Interestingly 1,2-di(pyridin-2-yl) disulfane was also a suitable substrate in this process (Table 2, entry 10) providing **3j** in 45% RCY. Finally, this protocol has been applied to 1,2-diphenyl diselane (Table 2, entry 11) leading for the first time to the corresponding $^{18}$F-trifluoromethylselenoarene **3k** in a very good RCY and an excellent radiochemical purity. Unfortunately, application of this $^{18}$F-trifluoromethylthiolation sequence to 1,2-dibenzyl sulfane or bis(dodecylthio)-methane failed.

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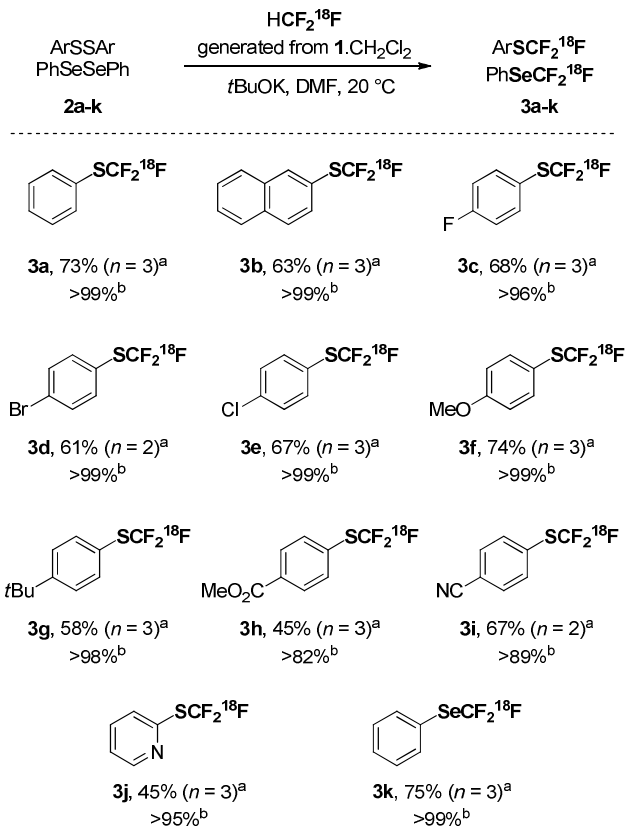
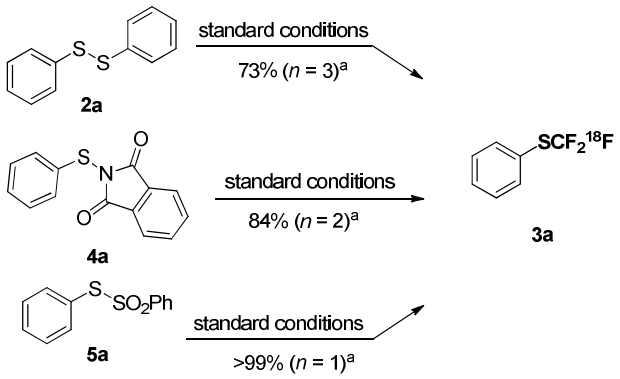



**Scheme 2.** Scope for the $^{18}$F-trifluoromethylthiolation of disulfane and diselane derivatives. Reactions were performed on a 1 mmol scale of substrate **2**. Reaction conditions: 0.07 mmol of **1**, PhCN (1 mL), *t*BuOK (1 equiv relatively to **2a**), DMF (0.5M). [a] Radiochemical yields were calculated from the activities of organic and aqueous layers. Average of n experiments. [b] The radiochemical purity was determined by radio-HPLC of the crude organic layer.

The specific activity observed for the $^{18}$F-trifluoromethylthiolated arenes prepared with our process (0.38 GBq.μmol$^{-1}$ for **3e**) is in agreement with the ones reported by Gouverneur[5] (0.17 GBq.μmol$^{-1}$) as well as Xiao and Liang[6] (0.78 GBq.μmol$^{-1}$); this range of specific activity is compatible with most applications in PET.

We next examined the possibility to use different sulfur-containing derivatives as precursors containing either a phthalimide group or a sulfone moiety as a leaving group (Scheme 3). We were pleased to observe that when 2-(phenylthio)isoindoline-1,3-dione **4a** was reacted under the same optimized reaction conditions as reported for **2a**, $^{18}$F-phenyl(trifluoromethyl)sulfane **3a** was obtained in very good 84 % RCY and excellent radiochemical purity (> 96%). A similar reactivity was observed when the *S*-phenyl benzenesulfonothioate **5a** was reacted, furnishing **3a** in quantitative RCY and excellent radiochemical purity. These results clearly demonstrated the efficiency and the potential of this protocol using various starting materials. This constitutes a real asset from a synthetic point of view and opens new synthetic strategies to access the final target.




**Scheme 3.** $^{18}$F-trifluoromethylthiolation of different sulfur-containing derivatives as precursors. Reactions were performed on 1mmol scale of substrate. Reaction conditions: 0.07 mmol of **1**, PhCN (1 mL), *t*BuOK (1 equiv relatively to **2a, 4a** or **5a**), DMF (0.5M). [a] Radiochemical yields were calculated from the activities of organic and aqueous layers. Average of n experiments.

## Conclusions

We have developed an efficient transition metal- free radiolabeled trifluoromethylthiolation reaction of aromatic derivatives using disulfides as starting materials. This approach showcased a very interesting application of the well-defined preparation of $HCF_2{}^{18}F$ as a radiolabeling agent[12] for the synthesis of radiolabeled trifluoromethylthiolated arenes in good to excellent RCY and radiochemical purities. The whole sequence is rapid (<25 minutes), operates at room temperature from easy accessible starting materials. Therefore, this methodology opens new doors towards the radiolabeling of $CF_3S$-containing biologically active targets.

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## Notes and references

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