Ring-Closing Synthesis of Dibenzothiophene Sulfonium Salts and Their Use as Leaving Groups for Aromatic $^{18}$F-Fluorination

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Supporting Information

ABSTRACT: Herein, we report a novel intramolecular ring-closing reaction of biaryl thioethers that give access to highly functionalized dibenzothiophene sulfonium salts under mild conditions. The resulting precursors react regioselectively with $[^{18}$F$]$fluoride to give $[^{18}$F$]$fluoroarenes in predictable radiochemical yields. The strategy expands the available radiochemical space and provides superior labeling efficiency for clinically relevant PET tracers.

INTRODUCTION

Fluorine-18 is uniquely suited for imaging with positron emission tomography (PET) due to its favorable half-life (110 min) and high-efficiency, low-energy positron emission (97% $^{+/0}$, $E_{\text{mean}} = 0.250$ keV). The versatile properties of C–F bonds and their widespread use in medicinal chemistry further contribute to the appeal of fluorine-18 for diagnostic imaging and pharmaceutical research. Yet, incorporation of $[^{18}$F$]$fluoride into biologically active molecules is often difficult, if not impossible, to achieve. Nucleophilic $S_N$2 and $S_N$Ar substitution reactions with $[^{18}$F$]$fluoride remain the most widely used strategies for labeling, as they are technically simple and robust. However, target compounds are rarely suitable for this approach, and radiotracers are therefore typically modified with fluorinated aliphatic side chains, or highly activated aromatic groups, to allow labeling to take place. Since the development of $S_N$2 reactions with $[^{18}$F$]$fluoride more than 30 years ago, continuous efforts have been made to expand the radiochemical space. Recent chemical insights have re-invigorated the field and led to the discovery of several innovative strategies for radiofluorination. New types of precursors, including aryl boronic acids and esters, preformed PdIV or NiII complexes, N-aryl sydnone, uronium salts, iodonium ylides, and aryl-sulfonium salts, now allow direct fluorination of aromatic ring systems that until recently were beyond reach. While these methods certainly have expanded the radiochemical space, their impact on clinical PET remains limited. This reflects the difficulties in preparing highly complex precursors for labeling, shortcomings of the radiochemical reactions, and, for metal-based methods, concerns about toxicity.

We have previously reported that triarylsulfonium salts allow direct $[^{18}$F$]$-fluorination of small molecule drug-like compounds containing non-activated and electron-deficient aromatic rings. The appeal of this approach is the ability to label a broad range of bioactive molecules under conditions that mirror conventional substitution reactions with $[^{18}$F$]$fluoride. However, few reactions are available to form aryl-sulfonium salts, and access to the precursors for labeling depends on protection strategies to enable selective S-arylation of thioethers in the presence of other reactive functional groups. Here we report that dibenzothiophene sulfonium salts can be accessed through intramolecular cyclization of biaryl thioethers under mild conditions. The strategy overcomes the synthetic limitations of triarylsulfonium salts and provides a flexible platform for the design of leaving groups for aromatic $^{18}$F- fluorination (Figure 1).

Dibenzothiophene sulfonium salts have previously been obtained through activation of aromatic sulfoxides with

Figure 1. Dibenzothiophene sulfonium salts as leaving groups for aromatic $^{18}$F-fluorination. A: coupling of a biaryl building block with the structure of interest; B: ring-closing to form the dibenzothiophene sulfonium salt precursor; C: $^{18}$F-fluorination. X = Br, I.

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trifluoromethanesulfonic acid, or trifluoromethanesulfonic anhydride, to form highly reactive Pummerer-type intermediates that trigger intramolecular cyclization.\textsuperscript{17–19} We envisaged that direct $S$-activation of thioethers with a source of electrophilic halogen, e.g. N-chlorosuccinimide (NCS),\textsuperscript{20,21} could provide a more concise and flexible synthetic route to the target compounds.

**RESULTS AND DISCUSSION**

During initial studies with the unsubstituted biaryl thioether 1a, we found that treatment with NCS and silver triflate afforded the target dibenzothiophene sulfonium salt 2a, albeit in poor yield (Table 1). To investigate the influence of electron-donating groups on the ring-closing reaction, a small library of biaryl thioethers was prepared. Introduction of methyl groups to rings A and B, as for 1b, had a marginal impact on the cyclization yield. However, addition of a tert-butyl substituent on ring A to give 1c substantially increased the reactivity (14% and 56% for 2b and 2c, respectively). Finally, decoration of ring system A with methoxy groups, as for 1d and 1e, allowed highly efficient ring-closure, with formation of 2d and 2e in 82% and 79% yield, respectively. The sulfonium triflate salts were obtained as stable, non-hygroscopic solids and could readily be purified by liquid/liquid extraction and column chromatography on silica gel.

**Table 1. Synthesis and Labeling of Dibenzothiophene Sulfonium Salts 2a–e**

| Substitution Pattern | Cyclization Yield (%$^{[18F]}$PhF) | RCY (%)$^a$ |
|----------------------|-------------------------------------|-------------|
| R$^1$ | R$^2$ | R$^3$ | R$^4$ | Compd | Side product |
| H | H | H | H | 1a/2a | 8 | 45 ± 3 | 6 ± 1 |
| H | CH$_3$ | CH$_3$ | CH$_3$ | 1b/2b | 14 | 30 ± 5 | 2 ± 1 |
| fBu | H | CH$_3$ | CH$_3$ | 1c/2c | 56 | 31 ± 2 | 4 ± 1 |
| OCH$_3$ | OCH$_3$ | OCH$_3$ | OCH$_3$ | 1d/2d | 82 | 34 ± 9 | 23 ± 3 |
| OCH$_3$ | OCH$_3$ | CH$_3$ | CH$_3$ | 1e/2e | 79 | 29 ± 3 | 5 ± 1 |

$^a$Conditions: (i) NCS, AgOTf, 1,4-dioxane, reflux, 2 h, 96%; (ii) 3,5-dimethoxyphenylboronic acid, PEPPSI-IPr, K$_2$CO$_3$, toluene/water, reflux, 2 h, 95%; (iii) 3,5-dimethoxyphenylboronic acid, Pd(OAc)$_2$, K$_2$CO$_3$, toluene, reflux, 2 h, 93%; (iv) NaH, THF, 0 °C, 30 min, b) dimethylthiocarbamoyl chloride, 70 °C, 16 h, 89%; (v) n-Hex, 290 °C, 3 h, 97%; (vi) iBuOK, Pd$_2$(dba)$_3$, DPEPhos (bis(2-diphenylphosphino)phenyl) ether), toluene, reflux, X = Br, I.

| Isolated yield. $^b$As determined by radio-HPLC; experiments were carried out in triplicate.

Dibenzothiophene sulfonium salts can potentially react with $^{[18F]}$fluorobenzene with ipso-attack at any of the three $S$-substituted carbons, resulting in either release of the desired $^{[18F]}$fluorinated arene, or side product formation by opening of the heterocyclic ring system (red vs blue positions, respectively, Scheme on Table 1). To assess the reactivity profile of this novel class of leaving groups, the labeling efficiency of compounds 2a–e with $^{[18F]}$fluoride was investigated (Table 1). The radiochemical reactions were carried out with 5 mg precursor in dimethylsulfoxide (DMSO) at 110 °C for 15 min. The unsubstituted analog 2a afforded $^{[18F]}$fluorobenzene in 45 ± 3% radiochemical yield (RCY) as determined by radio-high-performance liquid chromatography (radio-HPLC), whereas the more electron-rich precursors 2b–e gave RCYs in the range of 29–34%. High regioselectivity in favor of $^{[18F]}$fluorobenzene formation was observed for all cases, with the exception of precursor 2d. In the latter case, introduction of an electron donating methyl substituent on ring B, to give precursor 2e, restored regioselectivity. Of the compounds investigated, sulfonium salt 2e offered the optimal balance between cyclization yield, reactivity with $^{[18F]}$fluoride and regioselectivity of the labeling reaction.

To allow direct incorporation of the optimized biaryl thiol moiety 1e into complex structures (Figure 1, Step A), we designed the two building blocks 5a-b and optimized their synthesis on multigram scale (Scheme 1A). Briefly, 5a was obtained in two steps, starting with the Pd-catalyzed coupling of 2-bromo-1-iodo-4-methylbenzene 3 with 2-ethylhexyl-3-mercaptopropionate, Xantphos, Et$_3$N, toluene, reflux, 0.5 h, 93%; (ii) 3,5-dimethoxyphenylboronic acid, PEPPSI-IPr, K$_2$CO$_3$, toluene/water, reflux, 2 h, 95%; (iii) 3,5-dimethoxyphenylboronic acid, Pd(OAc)$_2$, iPr$_2$NH, water, reflux, 24 h, 93%; (iv) a) NaH, THF, 0 °C–RT, 30 min, b) dimethylthiocarbamoyl chloride, 70 °C, 16 h, 89%; (v) n-Hex, 290 °C, 3 h, 97%; (vi) iBuOK, Pd$_2$(dba)$_3$, DPEPhos (bis(2-diphenylphosphino)phenyl) ether), toluene, reflux, X = Br, I.
step in the sequence was a Newman–Kwart rearrangement under thermal conditions,23,24 which provided 5b in 80% overall yield. Although the building blocks 5a–b underwent rapid deprotection under basic conditions (Scheme 1B), we were not able to isolate the corresponding thiol in synthetically useful yields, as 9 rapidly oxidized to form the corresponding disulfide. To circumvent this problem, we developed a one-pot procedure for deprotection of 5a–b and subsequent Pd-mediated coupling of 9 with aryl halides in situ (Scheme 1B) by combining previously reported methods for the individual steps.22,25 This provided a flexible, concise, and high-yielding route to install the biaryl thioether moiety. Conveniently, the strategy also avoids the need to handle any foul smelling compounds which otherwise can be problematic with organosulfur chemistry.

While the synthesis of 5a is shorter and higher yielding than the route to 5b, deprotection of 5a results in the formation of 2-ethylhexyl acrylate as a byproduct, which can give rise to side products and complicate purification. The building block 5b offers several advantages over 5a in that it is a crystalline solid and the carbamothioate protecting group simplifies purification and handling. However, the high temperature required for the Newman–Kwart rearrangement makes this transformation non-trivial, and deprotection of 5b requires excess potassium tert-butoxide, which may compromise base-sensitive functional groups.

With a method in hand to couple the biaryl thiol moiety with functionalized aryls, we optimized the conditions for the cyclization reaction to give the target dibenzothiophene sulfonium salts. To ultimately allow labeling of the PET tracer 3-[[18 F]fluoro-5-(pyridin-3-ylethynyl)benzonitrile ([18F]FPEB),26,27 the thioether 10a was prepared (2 steps from 5a, 65% overall yield). Attempted cyclization by treatment of 10a with NCS and silver triflate gave a disappointing 6% yield of the corresponding sulfonium salt 11a, as determined by HPLC (Table 2, entry 1). A comparable yield was obtained with NCS in the presence of lanthanum(III) triflate, whereas bismuth(III) triflate greatly increased the reactivity and provided 11a in 48% yield (Table 2, entries 2 and 3). Changing the solvent from 1,4-dioxane to acetonitrile (MeCN) further increased the yield to 79%. Remarkably, under these conditions, thioether 10a cyclized almost instantly at ambient temperature to give the target sulfonium salt 11a in 65% analytical yield (Table 2, entry 5) (Method A). When these conditions were applied on a preparative scale, 11a was obtained in 82% yield. As bismuth(III) triflate can liberate trifluoromethanesulfonic acid,28 we hypothesized that the ring-closing reaction was promoted by formation of a superelectrophile through Bronsted acid activation of NCS (Scheme 2).29,30 Consistent with this, trifluoromethanesulfonic acid in combination with NCS also mediated rapid cyclization of 10a at room temperature (Table 2, entry 8).

Table 2. Optimization of the Ring-Closing Reaction

| entry | Cl− source | additive | solvent | temp (°C) | time (h) | HPLC yield (%) |
|-------|------------|----------|---------|-----------|----------|----------------|
| 1     | NCS        | AgOTf    | 1,4-dioxane | 100       | 2.5      | 6              |
| 2     | NCS        | La(OTf)3 | 1,4-dioxane | 100       | 2.5      | 7              |
| 3     | NCS        | Bi(OTf)3 | 1,4-dioxane | 100       | 2.5      | 48             |
| 4     | NCS        | Bi(OTf)3 | MeCN     | 80        | 2.5      | 79             |
| 5     | NCS        | Bi(OTf)3 | MeCN     | 20        | 15       | 65             |
| 6     | NCS        | Bi(OTf)3 | MeCN     | 20        | 15       | 0              |
| 7     | NCS        | —        | MeCN     | 20        | 15       | 0              |
| 8     | NCS        | Ti(OH)   | MeCN     | 20        | 15       | 58             |
| 9     | Ca(OCl)2   | acetate/ | acetone/ | 20        | 15       | 43             |

Aqueous acetate buffer, 1 M, pH 4.

On the basis of these findings, we propose the following mechanism for the ring-closing reaction: protonation of NCS triggers attack of chlorine on the thioether group to give an intermediate chlorosulfonium salt, which subsequently rearranges through an intramolecular S$_{E2}$Ar reaction to yield the target dibenzothiophene sulfonium salt (Scheme 2).

To allow cyclization under neutral conditions, we explored alternative sources of electrophilic chlorine. Several hypochlorite salts mediated ring-closing of the thioether 10a; however, yields varied considerably, and chlorination of the dimethoxy-substituted aromatic group became a prominent side reaction (results not shown). Eventually, we found that calcium hypochlorite, in an acetate-buffered (pH 4) water–acetonitrile solvent system,31 reacted cleanly with 10a to give the target sulfonium salt 11a in 43% yield within 15 min at room temperature (Table 2, entry 9) (Method B). The latter system is appealing, as it is exceptionally mild and relies exclusively on low-toxicity, biocompatible components.

To investigate the scope of the ring-closing reaction, we prepared a library of biaryl thioethers (Table 3). The compounds 10b–k were obtained by Pd-mediated coupling of the building block 5a with the respective aryl bromides or iodides (see Supporting Information (SI)). When treated with NCS and bismuth(III) triflate (Method A), the thioethers 10b–i rapidly cyclized (5 min to 2 h) under ambient conditions...
Dibenzothiophene Sulfonium Salts as Precursors

Experiments were carried out in room temperature, open to air) to give the target sulfonium salts 11b–k in 54% and 72% yields, respectively.

The dibenzothiophene sulfonium salts 11b–k were subsequently used to investigate the scope of aromatic 18F-fluorination (Table 3). To allow direct comparison, the radiochemical reactions were carried out using the non-optimized conditions described above. The least reactive of the compounds, the tolyl salt 11b, afforded 4-[18F]fluorotoluene in a modest 2% RCY (Table 3, entry 1). However, the regioisomer 11c reacted to give 3-[18F]fluorobenzene, a fragment of the PET tracer [11C]UCB-J,2 in 43 ± 5% RCY. Notably, 3-[18F]fluoropyridine, which is difficult to label with many other strategies, was formed in 65 ± 5% RCY. The sterically hindered tert-butyl ester 11i proved highly reactive and gave [18F]12i in 84 ± 5% RCY. However, labeling of 11e and 11h was problematic under these conditions due to decomposition and side product formation. When the temperature was reduced from 110 to 80 °C, 11e readily reacted to give [18F]-1,2,3-trifluorobenzene, a fragment of the PET tracer [11C]UCB-J,2 in 43 ± 5% RCY. In the case of 11h, the reaction proceeded cleanly at 75 °C to give 4-[18F]fluorobenzaldehyde, a well-established prosthetic labeling group,7 in 71% RCY.

Table 3. Scope Study for Aromatic 18F-Fluorination Using Dibenzothiophene Sulfonium Salts as Precursors

| Entry | Ar                  | Cyclization yield (%) | RCY (%) |
|-------|---------------------|-----------------------|---------|
| 1     | CH₃                 | 11b                   | 94 ± 4  |
| 2     | CH₃                 | 11c                   | 90 ± 5  |
| 3     | OCH₃                | 11d                   | 90 ± 5  |
| 4     | F                   | 11e                   | 60 ± 5  |
| 5     | Br                  | 11f                   | 86 ± 5  |
| 6     | CF₃                 | 11g                   | 74 ± 7  |
| 7     | CHO                 | 11h                   | 67 ± 5  |
| 8     | CO₂Bu               | 11i                   | 51 ± 5  |
| 9     | N                  | 11j                   | 54 ± 5  |
| 10    | N                  | 11k                   | 72 ± 3  |

*Conditions: (i) Method A: NCS, Bi(OTf)₃, MeCN, RT, 5 min–2 h or Method B: Ca(OCl)₂, acetate buffer pH 4, acetone, 0 °C–RT, 15 min; (ii) [18F]fluoride, K₂₂₂/KHCO₃, DMSO, 110 °C, 15 min. As determined by radio-HPLC. Experiments were carried out in triplicate. Method A was used. Method B was used. Labeling at 80 °C. Labeling at 75 °C.
above that of Ia.37 This low barrier, compared to the barriers for product formation (vide infra), suggests that the Curtin−Hammett principle will be applicable and that the relative rates of product formation will be determined by the energies of the transition states leading to product, rather than by the relative populations of conformers Ia and IIa.

From intermediate Ia, two possible routes for the formation of fluorobenzene and dibenzothiophene 14 were considered: a stepwise SNAr mechanism proceeding through a Meisenheimer complex, and a concerted process which could be viewed either as a direct nucleophilic aromatic substitution or as a reductive elimination from sulfur. After extensive searching, no local minimum corresponding to a Meisenheimer complex could be located; instead a concerted mechanism, passing through a single transition state TS-IVa, was identified. Similar concerted mechanisms have been determined in computational studies of nucleophilic aromatic fluorinations of iodonium(III) ylides and diaryliodonium salts,12,38 aryl fluorosulfonates,39 and phenoluronium adducts.10

Analogous transition states TS-Va and TS-VIa could be located, connecting conformation IIa of the sulfonium fluoride salt 13a to biaryls 15 and 16, respectively. These transition states were found 6.6 and 29.2 kJ mol−1, respectively, higher in energy than TS-IVa, in accord with the good selectivity for attack on the phenyl group seen experimentally.

Several other dibenzo thiophenium fluorides 13b−k, corresponding to the triflates 11b−k, were modeled to examine any correlation between calculated activation energies and experimental reactivity. Ground-state conformations and transition states for fluoride attack on each of the three aromatic rings were identified. Due to the difficulty in calculating a meaningful energy for the solvated fluoride ion, the fluoride salts 13a−k were taken as the zero-energy baseline for each of these calculations (Table S5, SI). High correlation (R² = 0.98) was observed between calculated activation energy for attack on the isolated aromatic ring and RCY (Figure S13, SI); i.e., compounds with low calculated activation energy gave high RCYs. Moreover, the value of ΔΔG (i.e., the difference between attack on the isolated ring and the dibenzothiophene) increased with decreasing activation energy. This is consistent with the increased regioselectivity observed experimentally for activated substrates. Interestingly, the labeling yields also correlate with the Hammett substituent constant σ (R² = 0.97) and 19F chemical shifts (R² = 0.83) of the non-radioactive reference compounds (Figures S14 and S15, SI). While we have not measured the rates of the labeling reactions, the strong correlation of RCYs with the Hammett substitution constant nonetheless provides a valuable tool to predict the outcome of radiochemical reactions. For substrates decorated with complex functional groups, 19F NMR chemical shifts provide a convenient alternative to determine the suitability of the labeling reaction.

With the aim to demonstrate practicability of the method, we prepared the sulfonium salt precursors of five biologically active compounds, which were subsequently labeled with fluorine-18 (Figure 3). The thioether 10a was used to optimize cyclization conditions (vide supra) and provided the dibenzothiophene sulfonium salt precursor 11a for labeling of [18F]FPEB. This PET tracer, which has been used clinically for imaging of metabotropic glutamate 5 receptors, was particularly pertinent, as our previous attempts at preparing the corresponding triarylsulfonium salt had failed. Using the optimized ring-closing
reaction conditions (Method A), the labeling precursor 11a was obtained in 82% yield. The resulting white crystalline solid proved stable upon storage at ambient temperature over the course of 3 years (Figure S2, SI). Attempted labeling of 11a under the conditions used for the model compounds 11b–k resulted in formation of a radioactive side product, likely due to hydrolysis of the nitrile group (Table S1, SI). The side product was practically eliminated by reducing the temperature and shortening the reaction time. Further optimization revealed that the precursor load could be lowered to 1 mg, and the solvent changed to MeCN, without a significant effect on the RCY. In DMSO, the reaction proceeded at 50 °C (1 mg precursor, 5 min) to give \([^{18}F]\)FPEB 12a in 75% RCY as determined by HPLC. An identical RCY was obtained in MeCN at 80 °C. Under these conditions (1 mg precursor, MeCN, 80 °C, 5 min), hands-on labeling afforded \([^{18}F]\)FPEB 12a in 55 ± 3% decay-corrected (d.c.) RCY (43 ± 2% non-decay-corrected (n.d.c.), Figure 3). The molar activity was 13–20 GBq mmol⁻¹, reflecting the low levels of activity used for labeling (2 GBq) due to local constraints.

The high reactivity of 11a, combined with its ease of synthesis and suitability for long-term storage, demonstrate clear advantages over other labeling strategies reported for this tracer. For example, \(^{18}\)F-fluorination of the corresponding spirocyclic iodonium ylide precursor was recently reported to give \([^{18}F]\)FPEB in 20% n.d.c. RCY, whereas copper-mediated labeling of a boronic ester precursor afforded the tracer in a modest 13% n.d.c. RCY.\(^{5,40}\) As the reaction takes place under conditions that mirror nucleophilic substitution reactions with \([^{18}F]\)fluoride, the radiosynthesis can readily be automated using conventional equipment and established sequences for trapping and release of \([^{18}F]\)fluoride, labeling, and purification.

With this proof of concept established, we applied the method for labeling of the nitroimidazole \([^{18}F]\)12l, a novel candidate tracer for imaging of hypoxia (Figure 3). The sulfonium salt precursor 11l was obtained in 67% yield (Method A) from the corresponding biaryl thioether 10l. Labeling with \([^{18}F]\)fluoride (DMSO, 110 °C, 15 min, non-optimized) afforded the target tracer \([^{18}F]\)12l in 32 ± 3 d.c. RCY. The 3-[\(^{18}\)F]fluoropyridine 12m (\([^{18}F]\)P3BZA) has recently shown promise for imaging of melanoma in patients with metastatic disease; however, the reported radiosynthesis is low yielding.\(^{41}\) Initial attempts to synthesize the dibenzothiophene sulfonium salt precursor 3-[\(^{18}\)F]fluorodeprenyl \([^{18}F]\)P3BZA 11m (Method B) were unsuccessful (<10% yield) when the 2-(diethylamino)ethyl amide side chain was in place. We therefore resolved to cyclize the corresponding ethyl amide (method B, 54% yield, SI) and subsequently installed the side chain to give 11m (92% yield). Labeling proceeded cleanly to provide \([^{18}F]\)P3BZA 12m in 52 ± 5 d.c. RCY (DMSO, 110 °C, 15 min, non-optimized), a substantial improvement on the 12 ± 4% RCY reported for the corresponding bromide precursor.\(^{41}\) To further evaluate the scope of the pH-buffered cyclization method, we chose the 2-[\(^{18}\)F]fluoropyridine 12n (2-[\(^{18}\)F]fluoro-H-11ONH) as the next target. Gratifyingly, cyclization proceeded smoothly and provided the Boc-protected precursor 11n in 72% yield (Method B). \(^{18}\)F-fluorination of 11n (DMSO, 110 °C, 15 min, non-optimized) followed by Boc deprotection afforded \([^{18}F]\)12n in 41 ± 3 d.c. RCY.

Finally, we applied the labeling strategy for development of 3-[\(^{18}\)F]fluorodeprenyl 12o as a monoamine oxidase B (MAO-B) PET tracer. MAO-B is highly expressed in glial cells and is up-regulated in a number of neurodegenerative diseases.\(^{1,6,42}\) \([^{1}\text{C}]\)-deprenyl was reported as a MAO-B-selective PET tracer more than 30 years ago, yet attempted development of fluorine-18-labeled analogs has so far been unsuccessful, and no other MAO-B-selective ligand has found clinical use for PET imaging. To explore the potential for direct aromatic fluorination of deprenyl, we prepared the corresponding biaryl thioether 10o (3 steps from 5b, 56% overall yield). Cyclization of 10o proceeded...
smoothly to give the corresponding dibenzothiophene sulfoxonium salt 110 in 73% yield (Method A). Subsequent labeling of 110 with fluorine-18 (DMSO, 150 °C, 15 min, non-optimized) afforded 3-[18F]fluorodeprenyl in 32 ± 2% d.c. RCY, with a molar activity of 17–30 GBq mmol^-1 (starting from 2 GBq of [18F]fluoride). Autoradiography with [18F]120 in human post-mortem brain sections of a case with Alzheimer’s disease (Figure 4) revealed tracer binding consistent with the expected distribution of MAO-B. The specificity of the signal was confirmed by blocking with the parent compound L-deprenyl. Further development of [18F]120 as a MAO-B-selective PET tracer is outside the scope of this study and will be reported elsewhere.

■ CONCLUSIONS

In summary, we have developed dibenzothiophene sulfoxonium salts as a novel class of leaving groups for aromatic 18F-fluorination. Intramolecular cyclization of biaryl thioethers gave access to a diverse set of functionalized sulfoxonium salts under mild conditions. Non-activated and electron-poor substrates reacted regioselectively with [18F]fluoride and gave experimental radiochemical yields that correlated closely with theoretical DFT calculations. The strategy broadens the available radiochemical space and brings the added advantage of superior labeling efficiency for clinically relevant tracers, as exemplified by direct 18F-fluorination of 3-[18F]fluorodeprenyl, [18F]FPEB, and [18F]P3BZA.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06730.

Experimental procedures, spectral and analytical data, and radio-HPLC traces (PDF)
Computational results (ZIP)

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Notes

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