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HPLC-free *in situ* ^{18}F-fluoromethylation of bioactive molecules by azidation and MTBD scavenging

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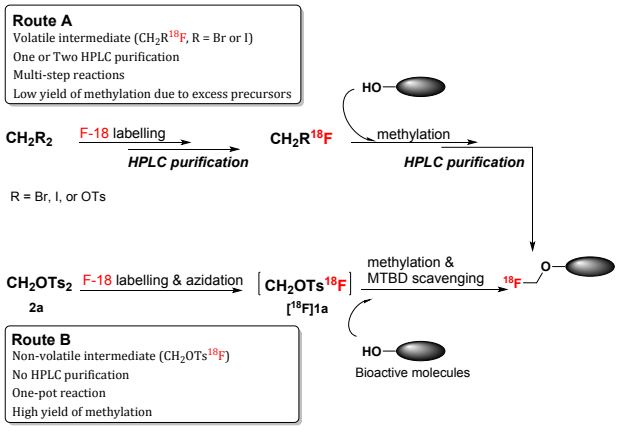
Sequential usage of azide and MTBD, which generates pure [^{18}F]fluoromethyl tosylate and scavenges unreacted desmethyl precursors, provided an efficient HPLC-free strategy for the radiosynthesis of ^{18}F-fluoromethylated compounds with high radiochemical yields and purity. This *in situ* ^{18}F-fluoromethylation can serve as a facile and efficient tool for the development of radiopharmaceuticals.

Positron emission tomography (PET) is an important nuclear imaging modality that provides useful preclinical and clinical information on the *in vivo* biodistribution of radioligand, diagnosis of disease, and monitoring of treatment response.[1] ^{18}F is the most preferred positron emitting radionuclide for PET imaging because of its ideal physical properties (half-life ($t_{1/2}$) = 109.7 min).[2] There are two major approaches to prepare ^{18}F-labelled ligands, namely, direct[3-5] and indirect approaches.[6] In contrast to the limitations of direct fluorination, which include complex syntheses of precursors and metal catalysts,[3a, 5] the indirect method offers numerous advantages, such as easily accessible prosthetic molecules, well-established radio-labelling procedures, reliable radiochemical yields (RCYs), and high adaptability to various ^{18}F-labelled probes. In particular, some radioligands such as [^{18}F]fluorocholine,[7] *S*-[^{18}F]fluoroalkylated diarylguanidines,[8] and most of the ^{18}F-labelled proteins and peptides can only be obtained *via* the indirect approach. Among the various prosthetic groups for radiofluorination, ^{18}F-fluoromethylation induces the least structural modification in parent bioactive molecules, thereby minimising the influence on the chemical and biological properties of the radioligands. In addition, ^{18}F-fluoromethyl group is a credible alternative to ^{11}C-methyl group, allowing radiochemists to overcome the limitations arising due to the short half-life of carbon-11 ($t_{1/2}$ = 20.3 min) and hence, expediting the development of new radiopharmaceuticals. Today, ^{18}F-fluoromethyl bifunctional molecules have been employed on numerous probes.[7-12] To reduce the defluorination caused by C–H bond cleavage and hence, enhance the *in vivo* stability of probes, some deuterated ^{18}F-fluoromethyl labelling agents were also developed and utilised.[13-15]

[^{18}F]Fluoromethyl bromide is the representative prosthetic group for ^{18}F-fluoromethylation, but its high volatility (boiling point = 9 °C) makes it difficult to be used for further alkylation of bioactive molecules on an automated platform. The relatively non-volatile [^{18}F]fluoromethyl tosylate ([^{18}F]**1a**) was introduced as an alternative, and it exhibited comparable labelling efficiency.[16] However, the excess precursor of **1a**, *bis*(tosyloxy)methane (**2a**), inevitably remained in the reaction mixture. If not separated by HPLC, it led to serious interferences (low RCYs, by-products, etc.) in the next step involving the ^{18}F-fluoromethylation of *O*-desmethyl arenes. Therefore, to obtain a good yield of the PET tracer, it was necessary to carry out two HPLC purifications, one for the prosthetic group and one for the final product, in order to obtain a PET tracer in good yield.

Scheme 1. *O*-^{18}F-fluoromethylation on bioactive molecules using a previously reported method (Route A)[16] and the method used in the present work (Route B).



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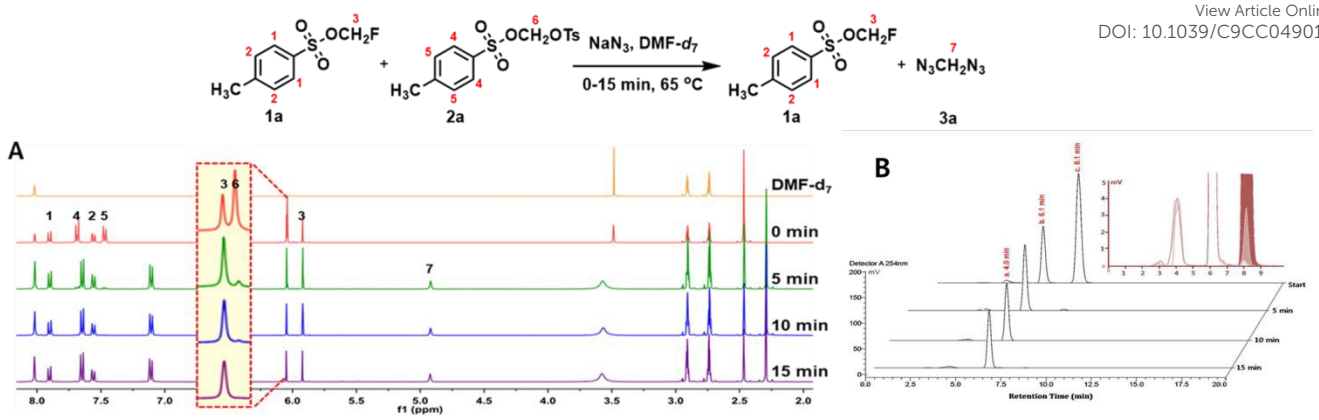


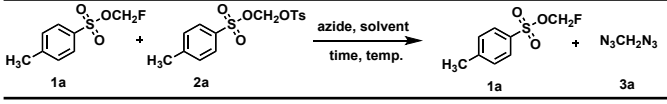
Figure 1. (A) ^{1}H NMR spectra of (top to bottom) DMF-d_7 solvent only, reaction mixture of **1a** and **2a** during azidation at 0 min, 5 min, 10 min, and 15 min. Signals 1–3 are from **1a**, and signals 4–6 are from **2a**. The reaction was performed with equimolar amounts of **1a** and **2a** in the presence of NaN_3 at 65 °C. (B) HPLC profiles of the mixture of **1a** and **2a** during the azidation at 0, 5, 10, and 15 min. Identification of system peak (a, T_R = 4.0 min), peak for **1a** (b, T_R = 6.1 min), and peak for **2a** (c, T_R = 8.1 min).

However, the two consecutive HPLC purifications complicate the routine automation (Route A, Scheme 1).

In this work, we demonstrate the *in situ* azidation using an azide reagent to remove excess **2a**; the azide reagent, however, does not attack the ^{18}F-labelled prosthetic group, [^{18}F]**1a**. Although the azidation of alkyl tosylates is well known, sensitivity and selectivity of azides towards mono- and di-tosylates are still not investigated. The selective azidation of the ditosylate precursor allows quantitative methylation with [^{18}F]**1a**. The [^{18}F]fluoromethylated bioactive compound is generated by the complete scavenging of the excess desmethyl precursors with 7-methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene (MTBD) (Route B in Scheme 1). Notably, the ^{18}F-labelled bioactive molecule is obtained without any HPLC purification.

Figure 1A shows the azidation in equimolar amounts (4.9 µmol) of **1a** and **2a** in *N*,*N*-dimethylformamide-d_7 (DMF-d_7, 0.3 mL) with NaN_3. Equimolar mixture of mono- and di-tosylates (**1a** and **2a**) was heated at 65 °C in the presence of NaN_3 (12.3 µmol). The progress of the reaction at 0, 5, 10, and 15 min was monitored by ^{1}H NMR and HPLC. In the ^{1}H NMR spectra, signals from benzene (signals 1–2 for **1a**, signals 4–5 for **2a**) and methyl groups (signals 3, 6, and 7 for **1a**, **2a**, and diazidomethane (**3a**), respectively) allow the identification of different compounds. It is evident from the ^{13}C NMR spectra (Supplementary Figure (SF) 2) that the chemical shift of CH_2 in **2a** was 87.8 ppm while the same in **1a** was observed at a higher field (98.0 ppm). This suggests that the electron density on the methyl group was relatively higher in **1a** compared with that in **2a**. Therefore, in the competitive azidation between **1a** and **2a**, an azide anion is expected to attack the more electron-deficient carbon in **2a**. From the early stages of the reaction, **2a** was rapidly consumed by the azide, and an equivalent amount of **3a** (signal 7) was produced in 5 min, as evident from the ^{1}H NMR spectra (Figure 1A). The chemical shift of CH_2 (6.04 ppm, signal 6) in **2a** changed to 4.94 ppm in 15 min. Besides, the monomer substituted intermediate, azidomethyl tosylate, could not be observed by NMR spectroscopy. This phenomenon is similar to that observed in Hassner's and Banert's experiment using alkyl halides[17-18] and can be attributed to the much faster second displacement on the monomer intermediate than the first tosylate displacement. To our surprise, **1a** maintained excellent stability under the reaction conditions of ^{1}H NMR up to 15 min. Quantitative HPLC measurement was employed to obtain the calibration curve from known amounts of **1a** and **2a** (Figure 1B). The amounts of **1a** and **2a** remaining at a particular time point were calculated. At 5 min, the reaction mixture contained at least 94.2% **1a**, showing its excellent stability and outstanding tolerance towards attack by the azide. Even after 40 min and 90 min, the reaction mixture contained more than 90.5% and 81% **1a**, respectively. In contrast, over 96.1% **2a** was converted into **3a** within 10 min, while more than 99.9% **2a** was converted in 40 min (SF 1B).

Table 1 Azidation at 65 °C for 10 min using various azide reagents[a]



Entry	Azide source	Solvent	Conversion of **2a** (%)[b]	Stability of **1a** (%)[c]
1	NaN_3	DMF	96.1 ± 2.4	91.9 ± 1.7
2	LiN_3	DMF	91.0 ± 3.8	94.7 ± 1.2
3	KN_3	DMF	>99.5	91.0 ± 4.5
4	KN_3	DMA	>99.5 (>99.5)[d]	94.2 ± 3.9 (94.6 ± 2.8)[d]
5[e]	KN_3	DMA	>99.5	62.0 ± 3.9
6	nBu_4NN_3	DMF	98.6 ± 1.3	93.6 ± 0.9
7	nBu_4NN_3	DMA	98.9 ± 0.9	93.4 ± 2.0
8[f]	nBu_4NN_3	DMA	>99.5	94.0 ± 4.2
9	nBu_4NN_3	DMSO	91.0 ± 2.1	89.9 ± 3.3
10	nBu_4NN_3	CH_3CN	84.2 ± 4.5 (86.0 ± 3.6)[d]	98.6 ± 1.3 (98.8 ± 1.6)[d]
11[g]	nBu_4NN_3	CH_3CN	>99.5	96.3 ± 3.1
12	nBu_4NN_3	THF	>99.5	86.2 ± 1.7
13	nBu_4NN_3	Benzene	>99.5	87.6 ± 2.0
14	nBu_4NN_3	1,4-dioxane	93.1 ± 3.2	98.1 ± 1.6
15	nBu_4NN_3	*t*-BuOH	43.2 ± 5.6	97.1 ± 2.3
16	nBu_4NN_3	MeOH	53.9 ± 2.0	90.1 ± 1.2

[a]The reaction (n > 3) was carried out with 2.5 equiv. of azides (12.3 µmol) relative to the reactants (4.9 µmol, **1a** and **2a**) in 0.3 mL of solvents (DMF, DMA (*N*,*N*-dimethylacetamide), DMSO (dimethyl sulfoxide), THF (tetrahydrofuran), or CH_3CN (acetonitrile). [b]% Conversion is calculated as the difference between the initial amount of

2a added to the reaction and the amount of **2a** remaining in the reaction mixture after 10 min, as determined by HPLC. [c]Amount of **1a** remaining after azidation was calculated from HPLC using the calibration curve of **1a**. [d]Results of deuterated compounds (**1b** and **2b**). [e]Reaction was conducted at 100 °C for 5 min. [f]Azide (24.5 μmol). [g]Azide (73.5 μmol) at 80 °C for 5 min.

Next, the influences of different azide reagents, solvents, and reaction temperatures were explored to maximise the elimination of **2a** and minimise the loss of **1a** (Table 1). We performed the azidation at 65 °C for 10 min using different azide reagents (12.3 μmol) in an equimolar mixture (4.9 μmol) of **1a** and **2a** in DMF (0.3 mL). KN_3 resulted in the highest yield of **3a** in DMF (Entries 1–3 and 6), though it also slightly affected the stability of **1a**. The loss of **1a** was recovered by changing the solvent to DMA or using the deuterated analogue **1b** (Entry 4). Reaction with two-fold equivalents of azides also did not result in any significant loss of **1a** (Entry 8). However, **1a** underwent decomposition at high temperature (Entry 5). Although nBu$_4$NN$_3$ is significantly more soluble in organic solvents compared with other azides, the complete conversion of **2a** into **3a** could not be achieved (Entry 9–10).

To our delight, this limitation could be overcome by a six-fold increase in the concentration of nBu$_4$NN$_3$ (Entry 11). In non-polar solvents such as benzene and 1,4-dioxane, nBu$_3$NN$_3$ had a remarkable reactivity (Entries 13 and 14) with **2a**. However, the stability of **1a** in benzene was reduced by more than 10%, as compared with that in polar aprotic solvents. Interestingly, in polar protic solvents such as *t*-butanol and methanol, the tendency for azidation was weak (Entries 15 and 16). Although **1a** was very stable in these solvents, merely half of **2a** participated in the azide substitution.

With the optimal conditions in hand (Entry 11), we proceeded for the radiolabelling reaction. [^{18}F]Fluoromethyl tosylate analogues ([^{18}F]**1a**-**b**) were prepared from *bis*(tosyloxy)methane analogues (**2a**-**b**) *via* nucleophilic aliphatic substitution (Table 2). The isolated RCYs were 77.0 ± 6.4% for [^{18}F]**1a** and 78.9 ± 4.2% for [^{18}F]**1b** (decay corrected) based on the HPLC analysis. Besides, a by-product, tosyl [^{18}F]fluoride, was formed with **1a** during fluorination,[16a] and the ratio of [^{18}F]**1a** to tosyl [^{18}F]fluoride was 72:28 (SF 9). Before azidation, the amount of the remaining **2a** and **2b** were calculated to be 1.3 ± 0.3 and 1.4 ± 0.3 μmol, respectively. During azidation, nBu$_4$NN$_3$ (84.4 μmol) was added to convert **2a**-**b** to **3a**-**b** in 5 min, and no precursors (**2a**-**b**) were detected in the chromatogram. The radio-TLC analysis indicated that [^{18}F]**1a**-**b** was highly stable with 99% [^{18}F]**1a**-**b** remaining in the mixture after azidation. This was in agreement with the results in Table 1 (Entry 11) and indicated that the optimal condition for non-radioactive reactions could be adapted for radiolabelling reactions. Remarkably, tosyl [^{18}F]fluoride was reduced after azidation. This could be because of the substitution of fluoride with azide via a S_N2 reaction. The measurement of radio-TLC (SF 3) showed that the amount of free ^{18}F increased while that of tosyl [^{18}F]fluoride decreased after azidation, thus verifying our assumption. Moreover, in the further *O*- or *N*-alkylation reaction, the remaining tosyl [^{18}F]fluoride continued to decompose completely under basic conditions, as confirmed by TLC (SF 4B) and HPLC (SF 9-11). Also, to confirm the levels of azide impurities, the reaction mixture and the eluent from the cartridge were examined by ^{1}H NMR spectroscopy and an ion chromatography (SF 12 and S Table 1). These analyses showed only trace amounts of nBu$_4$NN$_3$ in the final product solution (16 μg and 1.1 μg, respectively) which are below the reported rodent median lethal dose (LD_{50} = 27 mg/kg for rats).

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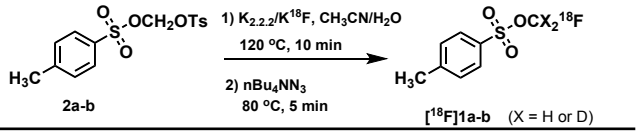
Molar activities (A_M) of [^{18}F]**1** and [^{18}F]**2** by starting with ^{18}F (222 MBq) after azidation were 96.5 and 85.4 GBq/μmol, respectively, while those without azidation were 96.8 and 85.8 GBq/μmol, respectively. Similar values under the two conditions indicated that the reaction with azide did not affect their molar activities.

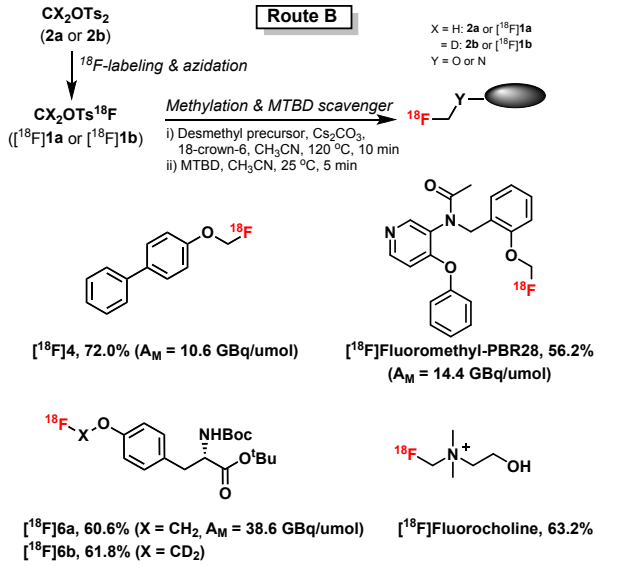
Table 2 Radiofluorination and azidation of **2a-b**[a]



	Results
RCY (%)[b]	77.0 ± 6.4 (78.9 ± 4.2)[c]
Unreacted **2a-b**	1.3 ± 0.3 μmol (1.4 ± 0.3 μmol)[c]
Stability of [^{18}F]**1a-b** (%)[d]	99.4 ± 0.5 (99.6 ± 0.3)[b]
Unreacted **2a-b** after azidation (%)	Not detected[e]

[a]The synthetic details describe in ref. 19. [b]The [^{18}F]**1a** (or [^{18}F]**1b**) fraction was measured by gamma counter, and the radiochemical yield (RCY, decay corrected) was calculated. HPLC condition describes in Supporting Information (Experimental Section). [c]For deuterated [^{18}F]fluoromethyl tosylate ([^{18}F]**1b**). [d]Stability of [^{18}F]**1a-b** was measured by comparing of radio-TLC yields between before and after azidation (SF 3, n = 5). [e]See SF 9.

Scheme 2 Synthesis of ^{18}F-fluoromethyl compounds using the current method.



With the optimised ^{18}F-labelling and methylation protocols in hand, the *in situ* *O*-^{18}F-fluoromethylation of 4-phenylphenol was achieved at a RCY of 72.0% (Scheme 2). Due to the absence of **2a**, as confirmed by HPLC, a much purer [^{18}F]**1** (in Route B) allowed the quantitative *O*-alkylation of [^{18}F]**1** to give

[^{18}F]**4**. However, using the conventional method (Route A), the RCY of [^{18}F]**4** dramatically dropped to 27.8% (decay corrected) in the presence of a relatively large amount of **2a** (SF 4A). Additionally, synthesis *via* Route A required HPLC purification to obtain [^{18}F]**4**, while Route B enabled the isolation of [^{18}F]**4** using a C-18 Sep-Pak cartridge. For some reported radioligands, e.g., [^{18}F]fluoromethy-PBR28, protected [^{18}F]fluoromethyl-tyrosine, and [^{18}F]fluorocholine, we passed the mixture after azidation through Accell CM cartridge, to remove the unreacted azide ions. Scheme 2 shows the highly pure [^{18}F]**1a**-**b** obtained after azidation, which has an excellent reactivity towards the bioactive precursors (desmethyl PBR28 and desmethyl protected tyrosine (**5**)). It forms the desired products in good RCYs (56.2–72.0%). After ^{18}F-labelling, the reaction mixture was treated with MTBD to capture the unreacted desmethyl precursor *via* forming an ion salt (SF 5).[19] HPLC was used to monitor the reaction progress, and less than 1.8% precursor (**5**) of protected [^{18}F]fluoromethyl-tyrosine ([^{18}F]**6a**) remained after 3 min of the reaction. Complete capture of **5** was confirmed by HPLC after treating them with MTBD for 5 min (SF 10). The obtained mixture could be simply separated by passing it through silica and light C18 cartridges to give pure [^{18}F]fluoromethy-PBR28 or [^{18}F]**6a**, without the assistance of HPLC (SF 6, 7 and 10). This is because MTBD, precursor-MTBD ion salt, and **3a** were totally captured by silica cartridges. In case of [^{18}F]fluorocholine, the precursor was isolated by employing the Accell CM plus short cartridge instead of MTBD.

In conclusion, we demonstrated for the first time a highly selective, one-pot azidation reaction that occurs on *bis*(tosyloxy)methane analogues (**2a**-**b**) but not on fluoromethyl tosylate analogues (**1a**-**b**). Taking advantage of the selective azidation, pure [^{18}F]**1** could be obtained without the aid of HPLC. The *in situ* ^{18}F-fluoromethylation of bioactive molecules with [^{18}F]**1** promises to provide better RCYs and purities for ^{18}F probes. Moreover, MTBD, a scavenger for phenol moieties, can capture unreacted precursors, allowing an HPLC-free purification to give the final product. This new protocol suggests that [^{18}F]**1** can be extensively utilised for the development of ^{18}F-labelled radiopharmaceuticals as well as for the automated synthesis of ^{18}F probes.

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Conflicts of interest

The authors declare no conflict of interest.

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19 To a reaction vial containing $K_{2.2.2}$/$K^{18}F$ (45 MBq), **2a** or **2b** (2 mg, 5.6 μmol), H_2O (20 μL), and CH_3CN (0.75 mL) were added and then heated at 120 °C for 10 min. The reaction mixture was treated with nBu$_4$NN$_3$ (24 mg, 84.4 μmol) at 80 °C for 5 min and then was penetrated into Accell CM plus short cartridge to provide [^{18}F]**1a**. In the presence of Cs_2CO_3 (3 equiv.) and 18-crown-6 (4 equiv.), the reaction mixture including [^{18}F]**1a** was reacted with the desmetyl precursor (1 mg, 1 equiv.) at 120 °C for 10 min. After cooling the reaction vial, MTBD (20 μL) was treated and the mixture was stirred at 25 °C for 5 min. The reaction mixture was consecutively passed through silica and C18 Sep-Pak cartridges to provide the product.

