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Research Article

Use of 1,8-*bis*-(dimethylamino)-naphthalene/$H^{18}F$ complex as new radiofluorinating agent

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Summary

Radiopharmaceuticals containing an ^{18}F label are of increasing interest due to their utilization in PET imaging. However, the bottleneck in these applications is the limited methods available for introduction of this radionuclide into biologically interesting molecules. In this work, we have evaluated a new radiofluorination method based on the properties of the complex between 1,8-(dimethylamino)-naphthalene (**PS**) and [^{18}F]–HF. The results obtained on various model substrates suggest that, in some limited cases, this new procedure can be regarded as a possible alternative to the traditional nucleophilic route using K_{222}/K_2CO_3 in CH_3CN. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: proton sponge; nucleophilic fluorination; [^{18}F]fluoride; PET

Introduction

Positron emission tomography (PET) has earned increasing interest in the biomedical field due to its ability to provide high-resolution molecular imaging of various organs *in vivo*. The methodology introduces a β^+-emitting radionuclide into a molecule of known pharmacological and metabolic fates and quantitatively detects such radiolabelled molecule *in vivo* with temporal information.

A large number of β^+-emitting nuclides are known, but only a few are used for this purpose; ^{11}C ($t_{1/2} = 20.4\,\text{min}$), ^{15}O ($t_{1/2} = 2\,\text{min}$), ^{13}N ($t_{1/2} = 10\,\text{min}$) and ^{18}F ($t_{1/2} = 109.7\,\text{min}$) are widely employed radionuclides because they offer mimetic or quasi-mimetic labelling. If a longer synthetic pathway or longer PET

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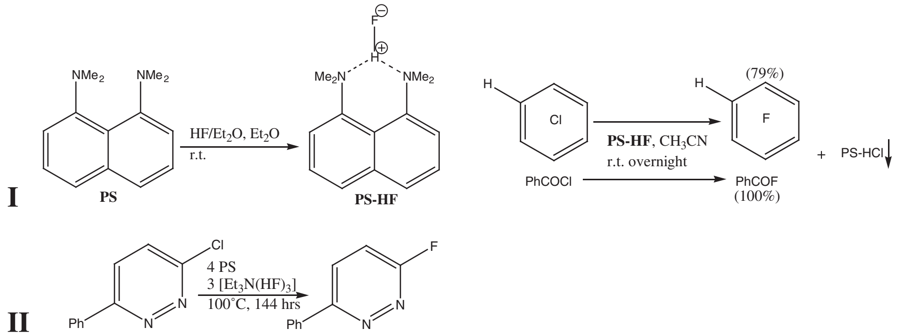


Figure 1. Previous reactions involving the use of PS/HF (I: Chambers, II: Darabantu)

acquisition time is required, ^{18}F is the nuclide of choice because of its longer half-life. A large and increasing variety of radiopharmaceuticals containing ^{18}F have been found to be useful in PET imaging; this leads to the increasing importance of the development of new introductory routes for this nuclide in interesting molecular contexts. ^{18}F can be produced by a biomedical cyclotron as carrier-added $[^{18}F]$–F_2 or as no-carrier-added $[^{18}F]$–HF_{aq}. $[^{18}F]$–F_2, or reagents directly derived from it, can effect labelling reactions by electrophilic substitution (S_E) whereas, nucleophilic substitution (S_N) employs the complex $K_{222}/K^{18}F$ (derived from $[^{18}F]$–HF_{aq}) in polar organic solvents (generally acetonitrile or DMSO). This nucleophilic reaction is preferable for many reasons such as higher specific activity and ease of handling. In this work, we have studied the use of the complex between 1,8-*bis*(dimethylamino)-naphthalene (Proton Sponge, (**PS**)) and $H^{18}F$ as a new nucleophilic radiofluorinating agent.

The use of the non-radioactive **PS/HF** complex has been previously reported by Chambers[1] and Darabantu[2] as a useful mild fluorinating agent capable of aromatic nucleophilic substitution (S_NAr) of chlorine atoms bound to *di*- and *tri*-azine moieties. The **PS/HF** complex could be synthesized separately or *in situ* using either ethereal solution of HF (Chambers) or the complex $Et_3N \cdot (3HF)$ (Darabantu) (Figure 1). The yields reported for the fluorinated products were generally high for most of the substrates, but required long ($\gg 2$ h) reaction times, not suitable for a radiosynthesis.

We report the *in situ* synthesis of **$[^{18}F]$–PS/HF** from an aqueous solutions of $H^{18}F$ and the resulting reactions with a variety of substrates.

Results and discussion

Non-radioactive test reactions

In order to test the feasibility of these fluorinating methods, we have first studied the reactivity of the **PS/HF** complex, produced *in situ* from a 48% HF_{aq} solution, towards various halogenated aromatics and heteroaromatic substrates.

Table 1. GC-MS yields of non-radioactive test reactions

	Substrate	Thermal 2 h	Thermal 20 h	MW
1	2-chloropyrimidine	1.4	3.5	5.4
2	2-chloro-3-nitropyridine	4	22.1	8.4
3	5-chloro-1-phenyl-1H-tetrazole	13	33.7	Trace
4	4-chloro-3-nitrotoluene	3.5	3.5	3.4

In the first set of experiments, a 0.5 mmol scale was used and all the reagents were added in equimolar amounts in a 1 ml V-vial. The excess water was evaporated under Ar by azeotropic distillation. CH_3CN was added and the solutions stirred and heated at 100°C while samples, taken at 2 and 20 h, were analyzed by GC–MS.

Ionic liquids, a class of chemical salts in which either the cation or anion is an organic charged molecule, have interesting physical properties such as high polarity, high conductivity and high boiling point.[3] These compounds have been used as co-solvents for fluoride substitution reactions on some aliphatic substrates.[4] We have tested a 2:1 solution of 1-pentyl-3-methylimidazolinium bromide (**PMIMBr**) and CH_3CN as solvent in a microwave (MW) procedure employing 0.2 mmol of reagent, HF_{aq} and **PS** in an open 7 ml glass tube. Pulsed MW irradiation (10 cycles of {5 s ON, 15 s OFF}) was employed to avoid overheating.

Fluorinated products (calculated on the basis of the GC-MS peaks of the starting substrates) were only detected for four compounds (Table 1) that are activated to S_NAr. No fluorination was observed using aromatic chlorides not activated to S_NAr, as well as various aromatic bromides and iodides.

Solubility of [^{18}F]–PS/HF

In the previous literature, the **PS/HF** complex was reported as an acetonitrile soluble fluoride source.[1,2] We have used radioactive ^{18}F to assess the claimed solubility of this fluorinating system. For this purpose, irradiated water (100 μl) was added to various quantities of **PS**. After azeotropic distillation, the vial was washed with 0.6 ml of CH_3CN. The recovered acetonitrile solution was assayed for radioactivity content and compared to the total radioactivity present in the vial. These data showed that the radioactivity recovered by this procedure was related to the quantity of **PS** in a linear fashion, requiring approximately 80 mg of **PS** in order to recover 50% of the ^{18}F in solution. These results show that the complex **PS/HF** is not highly soluble in acetonitrile, at least at tracer levels.

Nucleophilic incorporation methods

After some initial experiments to settle issues such as the amount of substrate, amount of **PS** and length of reaction, we selected three compounds (**2**, **3**, and

2,3,4,5,6-pentamethylbenzyl 4-fluoro-3-nitrobenzoate [**6**]) to conduct comparison radiofluoride incorporation reactions. The evaluated parameters were: heating method (either MW or thermal), proportion of water, and comparison of **PS/HF** *versus* K_{222}/K_2CO_3. In all procedures using **PS**, irradiated water was added to the melted base at 100°C. Substrates were added in 50 µl of solvent.

Procedures **A1** and **A2** employed **PS** (8 mg) with substrate (3 mg) in 50 µl of solvent under thermal heating (100°C, 30 min). A1 used only 5 µl of irradiated water and no drying procedure was done prior addition of the substrate in CH_3CN. A2 used 100 µl of irradiated water, which was azeotropically evaporated under an Ar stream prior addition of the substrate dissolved in 10% water in CH_3CN. These two methods would evaluate the effects of quantity of irradiated water used and drying process on radiochemical incorporation.

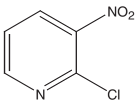
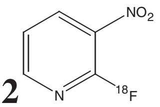
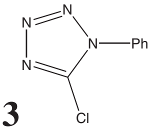
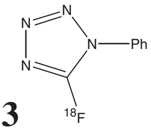
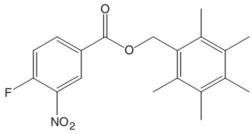
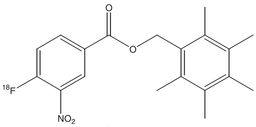
Procedure **B1** was designed to evaluate the effect of ionic liquids on the radiochemical yield (RCY). Procedure **A2** was followed, except that the substrate was added in 50 µl of a 1:1 solution of CH_3CN and 1-ethyl-3-methylimidazolium triflate (**EMIMTfO**). Procedure **B2**, designed to evaluate MW heating, followed the procedure **B1** except that heating was conducted by MW (200 W, 10 cycles of {5 s ON, 15 s OFF}).

Procedure **C** provided the comparison to the established K_{222}/K_2CO_3 method. The vial was charged with K_{222} (6 µmol) and K_2CO_3 (3 µmol), irradiated water was added, and CH_3CN-assisted azeotropic drying was conducted. Substrate (3 mg) was added in acetonitrile (50 µl) and the reaction heated thermally (100°C, 30 min). Procedure **D** shows the effect of having no nucleophilic assistance. Irradiated water was placed into a vial, evaporated with the assistance of CH_3CN, and substrate was added in CH_3CN. After thermal heating (100°C, 30 min), the solution was assayed for RCY.

The radiochemical yields obtained for all procedures are shown in Table 2. For these three substrates, **A1** provides the best decay corrected RCY and does not require azeotropic distillation, but has the drawback of allowing the use of only 5 µl of radioactive water and, hence, limited radioactivity. Pre-concentration of aqueous ^{18}F, as in **A2**, allowed use of more radioactivity and provided similar RCY for **2** and **6**. Interestingly, the addition of a 10% of water in the reaction solvent (CH_3CN) is optimal in these methods: if water is not added to the vessel, no substitution reaction occurs on **2**, **3** and **6** (data not shown).

Recently, Kim and co-workers[5] have shown the successful use of ionic liquids in radiofluorination reactions. In procedures **B1** and **B2**, we investigated the effect of using an ionic liquid, ethyl-1-methyl-imidazolium triflate (**EMIMTfO**), as co-solvent with CH_3CN, using both a thermal and a microwave heating method. As it can be seen from Table 2, the addition of **EMIMTfO** lowered the yields with all the substrates studied, especially when using a microwave irradiation.

Table 2. Substrates, yields and comparison of radiofluorination procedures

Substrates	Products	Procedures (RCY% ± STD)[a]					
		A1	**A2**	**B1**	**B2**	**C**	**D**
 **2**	 **^{18}F-2**	30±8	30±7	18±5	10±4	8±2	0
 **3**	 **^{18}F-3**	71±7	35±8	22±5	0	0	0
 **6**	 **^{18}F-6**	88±10	70±7	65±9	28±7	80±9	5±4

[a] Yields are HPLC-recovered and based on the total ^{18}F activity; all the numbers are averaged on a minimum of three experiments.

In order to compare the data obtained from these procedures involving the use of **PS**, we did some experiments using a traditional K_{222}/K_2CO_3 in CH_3CN[6] approach (**C**) and one without adding any activating agent to the irradiated water (**D**). The yields reported show that the **PS** method can give comparable or better results than the Kryptofix method with the three reported substrates: the difference is particularly large in the case of **2** and **3**. Moreover, it seems that these new procedures are very mild since the only radioactive peaks present in the radio-chromatograms (not reported) are the one of the product and the one for unreacted fluoride, while with the traditional method, a number of other radioactive peaks can be detected.

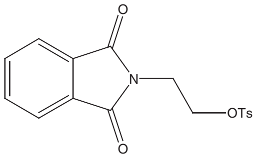
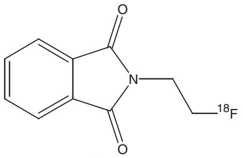
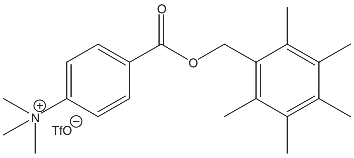
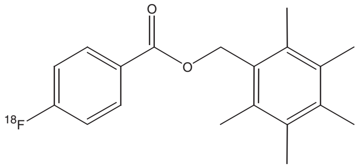
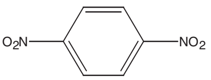
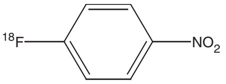
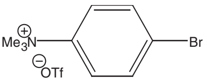
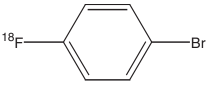
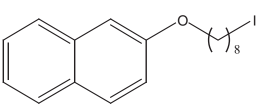
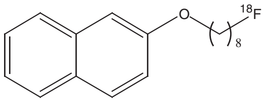
We have applied these methods to other model compounds (Table 3). Aromatic NO_2 and NMe_3^+ leaving groups are not displaceable with **A1** (substrate **8**–**10**). Aliphatic tosylates are also poor substrates but alkyl iodide is somewhat better (cf. substrate **7**–**11**).

Experimental

General

Chemistry: Ionic liquid **EMIMTfO** was purchased from Fluka Chemicals and K_{222} from EM Science. Ionic liquid **PMIMBr** was synthetized by a literature procedure.[7] Compounds **6**,[10] **7**, **F-7**,[8] **8**[9] and **10**[10] were synthetized according to literature methods. All other chemicals (solvents, reagents unless indicated)

Table 3. Substrates and yields in procedures utilizing PS compared to $K_{222}/K_2CO_3/CH_3CN$ method

Substrates	Products	PS[a]	K_{222}/K_2CO_3[a]
 **7**	 **^{18}F-7**	**A1**, 2	72[b]
 **8**	 **^{18}F-8**	**A1**, 0	**C**, 62
 **9**	 **^{18}F-9**	**A1**, 0	**C**, 19
 **10**	 **^{18}F-10**	**A1**, 0	**C**, 0
 **11**	 **^{18}F-11**	**A2**, 10	**C**, 27

[a] The yields are HPLC-recovered and are based on the total ^{18}F activity.
[b] Optimized literature data[8].

were purchased from Aldrich (analytical grade when available) and were used without purification unless otherwise stated. **PS** was generally used without purification; in case of visible oxidation (brown color), it can be recrystallized from cold pentane. Analytical TLC was run on pre-coated Silica Gel 60 F_{245} plates (Merck) and the results read under UV light ($\lambda = 254\,\mathrm{nm}$). ^{1}H and ^{13}C-NMR were run on a Varian Gemini 2000 using TMS as internal standard and 200 MHz for ^{1}H and 50 MHz for ^{13}C. GC-MS analysis were conducted using a Thermo Finnegan Trace-GC/Trace DSQ system equipped with a DB5 Restek column (15 m × 0.25 mm; coating 0.25 μm thin) and a EI ion source (200°C).

Radiochemistry: ^{18}F aqueous solutions were prepared by a ^{18}O(p,n)^{18}F reaction in a GE PETrace cyclotron using a 1.8 ml target of 95% enriched water irradiated by a 14.1 MeV beam at 20–25 μA for 60–90 min.

The HPLC system consisted of 2 Gilson pumps (Model 305 and 306), a Gilson high-pressure mixer, a Rheodyne injector and an analytical C-18 column (Phenomenex Luna, 250 × 4.6 mm, 5 μm); chromatograms were obtained using a Gilson Model 151 UV–VIS detector and a Bioscan radioactivity detector. All the analysis were done using varying composition H_2O/CH_3CN eluent systems and the radioactive fractions were collected and assayed for radioactivity in a Capintec Dose calibrator.

Chemistry

***PS-HF** fluorination test reactions, thermal:* 0.5 mmol of **PS** (107 mg), 48% HF_{aq} (18.5 μl) and 0.5 mmol of substrates were added in a 1 ml V-vial and azeotropically dried with 200 μl of CH_3CN (100°C, Ar stream). The vial was capped after addition of 50 μl of CH_3CN and heated (100°C, heating block) without stirring for 20 h. Samples were taken at 2 and 20 h and analyzed by GC-MS.

***PS-HF** fluorination test reactions, microwave*: 0.2 mmol of **PS** (42.8 mg), 48% HF_{aq} (7.4 μl) and 0.2 mmol of substrates were added in a 7 ml test tube together with 100 μl of **PMIMBr** and 50 μl of CH_3CN. Microwave irradiation was conducted using a pulsed heating at 200 W: 10 cycles of {5 s ON, 15 s OFF}. The final mixture was extracted with 1 ml of Et_2O and analyzed by GC-MS.

Synthesis of 2-fluoro-3-nitropyridine **F-2**: 2-chloro-3-nitropyridine (0.635 g, 4 mmol), **PS** (1.822 g, 8 mmol) and $Et_3N \cdot 3HF$ (3.9 ml, 24 mmol) were placed in a 5 ml V-vial and heated at 90°C under vigorous stirring for 4 days. After cooling, the residue was extracted with 10 ml of CH_2Cl_2 and the organic phase washed with 3 portions of water. The crude product (65% of fluoro-product and 35% of unreacted chloro-compound by GC-MS) was purified by flash chromatography (AcOEt/Hexane = 2/1 + 5% MeOH; $R_f = 0.24$) affording 0.340 g of yellow oil (60% yield). GC-MS: > 99% purity; *m/z*: 142, 112, 96, 76, 69. ^{1}H-NMR ($CDCl_3$): (δ ppm, *J* Hz) 8.65–8.60 (2H, m), 7.57 (1H, dd, 8.0, 4.8); ^{13}C-NMR ($CDCl_3$): 155.6 (d, $J = 248$ Hz), 153.3, 153.0, 137.3, 122.8.

Synthesis of 5-fluoro-1-phenyl-1H-tetrazole **F-3**: 5-chloro-1-phenyl-1*H*-tetrazole (0.541 g, 3 mmol), **PS** (0.642 g, 3 mmol) and $Et_3N \cdot 3HF$ (1.5 ml, 9.3 mmol) were placed in a 5 ml V-vial and heated at 90°C under vigorous stirring for 5 days. After cooling, the reaction vessel was washed with 10 ml of CH_3CN; the solid remained was discarded and the solution (> 98% of fluoro-product by GC-MS) evaporated and purified by flash chromatography ($CHCl_3$, $R_f = 0.6$) affording 0.364 g of white crystals (74% yield). GC-MS: > 99% purity; *m/z*: 164, 136, 116, 109, 85, 64. ^{1}H-NMR ($CDCl_3$): 7.69–7.58 (5H, m); ^{13}C-NMR ($CDCl_3$): 137.5 (d, $J = 290$ Hz), 131.9, 130.4, 124.7, 121.9.

Synthesis of 1,8-ditosyloctane **12**: In a 150 ml round bottom flask, 1,8-octanediol (6.66 g, 45.6 mmol) was dissolved in 50 ml of pyridine; the solution was cooled to 0°C and then tosyl chloride (26.8 g, 140.6 mmol) was added. The mixture was stirred at 0°C for 30 min and then stored in a refrigerator overnight. The solution was then poured into ice water and the white solid precipitate filtered and dried affording 13.6 g of pure product (66% yield based on the diol). MS (FAB^+) *m/z*: 455. ^{1}H-NMR ($CDCl_3$): (δ ppm, *J* Hz) 7.79 (4H, d, 8.2), 7.35 (4H, d, 8.2), 4.01 (4H, t, 6.8), 2.46 (6H, s), 1.61 (6H, b), 1.21 (6H, bm); ^{13}C-NMR ($CDCl_3$): 144.8, 133.2, 130.0, 128.0, 70.7, 28.8, 28.7, 25.2, 21.7.

Synthesis of 2-(8-tosyloctyloxy)-naphthalene **13**: In a 10 ml round flask, *β*-naphthol (0.130 g, 0.9 mmol) was dissolved in 4 ml of CH_3CN and 1 ml of 1.52 M Bu_4NOH was added as base; compound **12** (0.520 g, 1.52 mmol), dissolved in 4 ml of CH_3CN, was added to the solution in five portions. The solution was stirred overnight at room temperature. A white precipitate formed that was identified as the undesired product resulting from dimerization of two naphthol unit through the octyl bridge. Hence, the solution was filtered, the filtrated concentrated and purified using flash chromatography (75/20/5 = Hexane/$CHCl_3$/EtOAc, $R_f = 0.43$) obtaining 0.163 g (0.38 mmol) of a yellow oil (42% yield). This compound was crystallized from cold CH_3CN containing a few drops of water yielding pale yellow crystals. MS (FAB^+) *m/z*: 427. ^{1}H-NMR ($CDCl_3$): (δ ppm, *J* Hz) 7.76 (5H, m), 7.33 (4H, m), 7.13 (2H, m), 4.04 (4H, dd, 6.4, 12.8), 2.44 (3H, s), 1.82 (2H, m), 1.64 (2H, m), 1.30 (8H, b); ^{13}C-NMR ($CDCl_3$): 157.2, 144.8, 134.8, 133.5, 130.0, 129.5, 129.1, 128.1, 127.8, 126.9, 126.5, 123.7, 119.2, 106.8, 70.8, 68.1, 29.4, 29.2, 26.2, 25.5, 21.8.

Synthesis of 2-(8-iodooctyloxy)-naphthalene **11**: Compound **13** (0.148 g, 0.35 mmol) was placed in a 25 ml round bottom reaction flask and dissolved in 10 ml of acetone; NaI (0.065 g, 0.43 mmol) was added. The solution was heated under gentle reflux with magnetic stirring overnight. The solvent was evaporated and the residue partitioned between CH_2Cl_2/H_2O; the evaporation of the organic solvent gives 0.041 g (31% yield) of **11**. GC-MS: 93% purity; *m/z*: 382, 157, 144, 127, 115, 69. ^{1}H-NMR ($CDCl_3$): (δ ppm, *J* Hz) 7.73 (3H, m), 7.35 (2H, m), 7.16 (2H, m), 4.07 (2H, t, 6.4), 3.19 (2H, t, 6.8), 1.84 (4H, m), 1.38 (8H, b); ^{13}C-NMR ($CDCl_3$): 157.3, 134.8, 129.5, 129.1, 127.8, 126.9, 126.5, 123.7, 119.2, 106.8, 68.1, 33.7, 30.6, 29.4, 28.7, 26.24.

Synthesis of 2-(8-fluorooctyloxy)-naphthalene **F-11**: Compound **13** (0.163 g, 0.38 mmol) was placed in a 25 ml round bottom reaction flask and dissolved in 5 ml of acetonitrile; Me_4NHF_2 (0.170 g, 1.5 mmol) was added. The solution was heated to reflux under magnetic stirring for 2 h. The solvent was evaporated and the residue partitioned between CH_2Cl_2/H_2O. Evaporation of the organic solvent gives 0.057 g (55% yield) of **F-11**. GC-MS: >99% purity;

m/*z*: 274, 254, 157, 144, 127, 115, 69 ^{1}H-NMR (CDCl$_3$): (δ ppm, *J* Hz) 7.81 (3H, m), 7.36 (3H, m), 7.15 (1H, m), 4.42 (2H, dt, 6.4, 47.8), 4.07 (2H, *t*, 6.4), 1.75 (3H, m), 1.35 (9H, b); ^{13}C-NMR (CDCl$_3$): 156.5, 134.3, 129.2, 128.3, 127.4, 126.6, 126.3, 123.4, 118.7, 106.6, 83.7 (d, $J = 160$ Hz), 67.4, 29.9, 29.6, 28.6, 25.4, 24.7, 24.6

Radiochemistry

Solubility test (general procedure): Various quantities of **PS** (from 0.5 to 80 mg) were melted at 100°C in a V-vial; 100 μl of [^{18}F]–F^-_{aq} were added and azeotropic distillation was conducted with five portions of 100 μl of CH$_3$CN (100°C, Ar stream). 50 μl of CH$_3$CN were added and the vessel cooled down; the content of the vial and a 600 μl CH$_3$CN rinse were transferred, assayed for radioactivity and compared to the total radioactivity.

Radiolabelling procedures

Procedure A1: **PS** (8 ± 1 mg) was melted at 100°C in a 1 ml V-vial; to that, [^{18}F]–F^-_{aq} (5 μl), substrate (3 ± 0.5 mg) and 50 μl of CH$_3$CN were added. The reaction vessel was then closed and heated (100°C, heating block) without stirring for 30 min. After cooling, the content of the vial and a 600 μl CH$_3$CN rinse were transferred, assayed for radioactivity and analyzed by Radio-HPLC.

Procedure A2: [^{18}F]–F^-_{aq} (100 μl) was added to 8 ± 1 mg of **PS** melted at 100°C in a 1 ml V-vial. Azeotropic distillation conducted with five portions of 100 μl of CH$_3$CN (100°C, Ar stream) was followed by the addition of 3 ± 0.5 mg of substrate and of 50 μl of 10% H$_2$O in CH$_3$CN as solvent. The reaction was heated in a closed vessel for 30 min without stirring (100°C, heating block); after cooling, the content of the vial and a 600 μl CH$_3$CN rinse were transferred, assayed for radioactivity and analyzed by Radio-HPLC.

Procedure B1: [^{18}F]–F^-_{aq} (100 μl) was added to 8 ± 1 mg of **PS** melted at 100°C in a 1 ml V-vial. Azeotropic distillation conducted with five portions of 100 μl of CH$_3$CN (100°C, Ar stream) was followed by the addition of 3 ± 0.5 mg of substrate and of 50 μl of a 1:1 mixture of CH$_3$CN and 1-ethyl-3-methylimidazolinium triflate (**EMIMTfO**) as solvent. The reaction was heated in a closed vessel for 30 min without stirring (100°C, heating block). After cooling, the content of the vial and a 600 μl CH$_3$CN rinse were transferred, assayed for radioactivity and analyzed by Radio-HPLC.

Procedure B2: [^{18}F]–F^-_{aq} (100 μl) was added to 8 ± 1 mg of **PS** melted at 100°C in a 1 ml V-vial. Azeotropic distillation conducted with five portions of 100 μl of CH$_3$CN (100°C, Ar stream) was followed by the addition of 3 ± 0.5 mg of substrate and of 50 μl of a 1:1 solution of CH$_3$CN and 1-ethyl-3-methylimidazolinium triflate (**EMIMTfO**) as solvent. The reaction was heated by microwave irradiation: 10 cycles of {5 s ON, 15 s OFF} at 200 W. After cooling, the content of the vial and a 600 μl CH_3CN rinse were transferred, assayed for radioactivity and analyzed by Radio-HPLC.

Procedure using C: K_{222} (2.26 mg, 6 μmol) in acetonitrile (30 μl) and of K_2CO_3 (0.415 mg, 3 μmol) in water (15 μl) were added to a 1 ml V-vial. $[^{18}F]$–F^-_{aq} (100 μl) was added and azeotropically dried with five portions of 100 μl of CH_3CN (100°C, Ar stream); the addition of 3 ± 0.5 mg of substrate and of 50 μl of CH_3CN followed. The reaction was heated in a closed vessel for 30 min without stirring (100°C, heating block); after cooling, the content of the vial and a 600 μl CH_3CN rinse were transferred, assayed for radioactivity and analyzed by Radio-HPLC.

Procedure using D: $[^{18}F]$–F^-_{aq} (100 μl) was added and azeotropically dried with five portions of 100 μl of CH_3CN (100°C, Ar stream). 3 ± 0.5 mg of substrate and 50 μl of CH_3CN were added and the vessel closed and heated (100°C, heating block) for 30 min without stirring. After cooling, the content of the vial and a 600 μl CH_3CN rinse were transferred, assayed for radioactivity and analyzed by Radio-HPLC.

Conclusion

A new method for $[^{18}F]$radiofluorination utilizing **PS** has been studied and developed. This procedure allows ^{18}F incorporation through halogen exchange (F, Cl, I are reported) that is comparable or even superior to the traditional K_{222}/K_2CO_3 in CH_3CN procedure for some of the model compounds reported. The best reaction conditions require as solvent 10% H_2O in CH_3CN, since radiofluorination does not occur from an azeotropically dried medium. It is clear from solubility studies that the reactivity of this system is not due to the better availability of the fluoride ion in pure acetonitrile, as proposed in the previous literature. The procedure works best on strongly deactivated aromatic rings while substrates not activated to S_NAr do not seem to be amenable for fluorine exchange. For aliphatic substitutions, displacement proceeds better with iodide than tosylate as leaving group. Although **PS/HF** may be rather limited in scope, it may be an alternative to more established methods in some cases.

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