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Neither azeotropic drying, nor base nor other additives: a minimalist approach to ^{18}F -labeling

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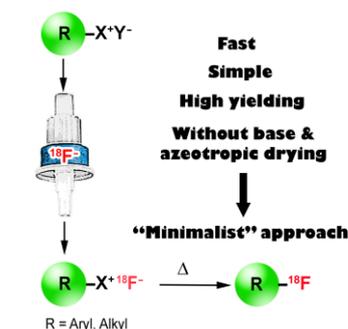
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A novel, efficient, time-saving and reliable radiolabeling procedure via nucleophilic substitution with ^{18}F fluoride is described. Different radiolabeled aliphatic and aromatic compounds were prepared in high radiochemical yields simply by the heating of quaternary anilinium, diaryliodonium and triarylsulfonium ^{18}F fluorides in suitable solvents. The latter were obtained via direct elution of $^{18}\text{F}^{-}$ from an anion exchange resin with alcoholic solutions of onium precursors. Neither azeotropic evaporation of water, nor a base, nor any other additives like kryptands or crown ethers were necessary. Due to its simplicity this method

should be highly suitable for automated radiosyntheses, especially in microfluidic devices.

Introduction

Positron emission tomography (PET) offers quantitative real time 3D-visualization of physiological and pathological processes in vivo by means of probes labeled with β^{+} -emitting nuclides (PET-nuclides). Among PET-nuclides fluorine-18 (^{18}F) is the most widely used since it is easily accessible in > 50 GBq quantities from H_2^{18}O via the high-yielding $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction. Furthermore, ^{18}F exhibits a low β^{+} -energy [$E(\beta^{+}) = 630 \text{ keV}$, 97%] resulting in PET images with high spatial resolution.¹ In addition, the half-life of ^{18}F (109.8 min) enables multistep radiosynthesis and allows distribution of the radiolabeled tracers to regional medical centers.

Although numerous methods of ^{18}F -labeling have been developed, the vast majority of radiofluorinated compounds are prepared via aliphatic and aromatic nucleophilic substitution reactions with $^{18}\text{F}^{-}$.² In accordance with the production route, ^{18}F fluoride is obtained in a H_2^{18}O solution (1–3 mL). Owing to tenacious hydration, water significantly diminishes the nucleophilicity of $^{18}\text{F}^{-}$. To remove the bulk of the water, $^{18}\text{F}^{-}$ is usually trapped on an anion-exchange resin³ and then eluted with an aqueous solution of K_2CO_3 . Thereafter, 2.2.2-cryptand (K2.2.2) in acetonitrile is added and the water is removed by time-consuming (7–15 min) repetitive azeotropic drying with acetonitrile. K2.2.2 captures K^{+} , and consequently increases the nucleophilicity of $^{18}\text{F}^{-}$ by means of charge separation. To

prepare the radiofluorinated compound, the dried residue of $[\text{K}2.2.2\text{K}^{+}]^{18}\text{F}^{-}$ is usually taken up in a solution of the precursor in a polar aprotic solvent and heated for a short period of time. The precursor should contain a suitable leaving group for nucleophilic substitution with ^{18}F fluoride. Instead of K_2CO_3 , other basic salts such as KHCO_3 or $\text{K}_2\text{C}_2\text{O}_4/\text{K}_2\text{CO}_3$ in combination with cryptand or Cs^{+} or tetraalkylammonium carbonates or bicarbonates without cryptand can be used.⁴ For more demanding radiofluorinations radiolabeling can be substantially hampered by adsorption of $^{18}\text{F}^{-}$ onto the vessel walls (up to > 50%).

A plethora of methods describing the production of highly reactive ^{18}F fluoride without the use of azeotropic drying were reported. However, all of them suffer from significant limitations.

Lemaire et al.⁵ avoided azeotropic drying by applying solutions of phosphazene superbases like P_2Et in MeCN containing water for almost quantitative elution of $^{18}\text{F}^{-}$ from the anion exchange resin. The eluate was added to a solution of the appropriate labeling precursor (up to 40 mg) and BTMG (2-tert-butyl-1,1,3,3-tetramethylguanidine) as an additional base in anhydrous MeCN. Several radiofluorinated compounds were successfully prepared by heating of the resulting mixture for a short time. However, the extremely strong basic conditions raise the question whether this reaction milieu is compatible with the majority of precursors for radiofluorination.

Additionally, this method demands high amounts of P₂Et and BTMG which are known to be highly toxic.

Aerts et al.⁶ avoided azeotropic drying by using water-wettable macroporous copolymers loaded with a long alkyl chain quaternary ammonium carbonate to directly recover [¹⁸F]fluoride from [¹⁸O]H₂O. [¹⁸F]Fluoride was eluted with MeCN in the form of *n*-tetradecyltrimethylammonium [¹⁸F]fluoride together with *n*-tetradecyltrimethylammonium carbonate.

This eluate was directly used for ¹⁸F-nucleophilic substitutions. This method was disadvantageous with respect to the need of high precursor amounts (15–40 mg) as well as in a majority of cases of high amounts of an additional base (K₂CO₃/K₂.2.2 or Et₄NHCO₃) to achieve high radiochemical yields.

Wessmann et al.⁷ used highly concentrated KOH/K₂.2.2 in anhydrous MeCN to efficiently elute [¹⁸F]fluoride from an anion exchange resin. An efficient ¹⁸F-incorporation via nucleophilic aliphatic substitution was demonstrated using small aliquots of ¹⁸F⁻ eluate. In upscaling experiments high amounts of radiolabeling precursors were to be applied to achieve an acceptable level of radiochemical conversion (RCC).⁸

Quite recently, Chun et al.⁸ published radiofluorination of diaryliodonium tosylates under organic-aqueous (up to 28% water) and cryptand-free conditions using K₂CO₃ as a base. Their method allowed to obtain moderate yields of ¹⁸F-labeled compounds directly using the irradiated [¹⁸O]water without the need of azeotropic drying and cryptand addition. Unfortunately, the narrow scope significantly confines the practical utility of this method. Only (4-methoxyphenyl)aryliodonium salts containing selected strong electron-withdrawing groups: CN, CO₂R and CO(4-EWGAr) in 2- or 4-position to iodine, could be radiolabeled yielding the corresponding [¹⁸F]fluorobenzonitriles, [¹⁸F]fluorobenzoates and [¹⁸F]fluorobenzophenones in moderate RCYs. Furthermore, the relatively low concentration of ¹⁸F⁻ in irradiated [¹⁸O]H₂O limits the accessible amounts of ¹⁸F-labeled compounds, especially using microfluidic devices (reaction volume < 50 μL).

Usually, basic salts are used to elute [¹⁸F]fluoride from an anion-exchange resin. At the same time, it can be quantitatively recovered by using neutral salts (e.g. isotonic saline). On the other hand trimethylammonium and aryliodonium salts are widely used as precursors for the preparation of radiofluorinated aromatic compounds. These onium salts which are highly soluble in organic solvents could, we thought, be used directly to elute [¹⁸F]fluoride from the anion-exchange resin. Furthermore, we examined if the resulting onium [¹⁸F]fluoride salts could be directly converted into ¹⁸F-labeled compounds without addition of a base or any other ingredients under “minimalist” conditions.

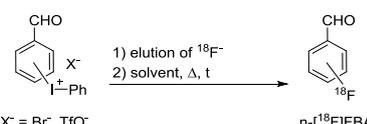
Results and discussion

Initial Experiments

Radiofluorinated fluorobenzaldehydes (2-, 3- and 4-[¹⁸F]FBA) were chosen as model compounds. They serve as versatile

building blocks for different radiosyntheses.⁹ First, the elution of [¹⁸F]fluoride from an anion exchange resin with iodonium [¹⁸F]FBA precursors in anhydrous DMF or DMSO was examined (Table 1). With (3- and 4-formylphenyl)phenyliodonium triflates radioactivity recovery amounted up to 30% (in the case of bromides up to 20%). The precursor eluate was directly heated for 10–15 min.

Table 1. Preparation of [¹⁸F]fluorobenzaldehydes using iodonium precursors without azeotropic drying and any additives.^a



entry	LG ⁺ X ⁻	n ^b	solvent	temperature [°C], time [min]	elution yield of [¹⁸ F] [%]	RCC [%] ^c
1	TfO ⁻	2	95% DMF	130, 10	30	2
2 ^d	TfO ⁻	3	DMSO	130, 10	30	22
3	Br ⁻	3	DMF	160, 10	6	34
4	Br ⁻	3	95% DMF	160, 15	30	5
5	Br ⁻	4	DMSO	90, 10	20	51
6	TfO ⁻	4	90% DMF	160, 15	55	51

^a ¹⁸F⁻ (200–500 MBq) was eluted from a QMA cartridge with a solution of the iodonium precursor in the corresponding solvent (5 mg in 500 μL). The resulting solution was heated at T °C for t min; ^b n – substitution position; ^c H₂O (4 mL) was added to quench the reaction and completely solubilize surface-adsorbed ¹⁸F⁻ and RCC determined by radio-HPLC; ^d with 20 mg precursor. Each experiment was carried out at least in triplicates. Standard deviation of RCC did not exceed 20% of its mean value.

Afterwards, an excess of water was added to quench the reaction and, most importantly, completely solubilize surface-adsorbed ¹⁸F⁻.¹⁰ Formation of 3-[¹⁸F]FBA and 4-[¹⁸F]FBA in RCCs up to 22 and 51%, respectively, was observed (determined by HPLC). Unreacted ¹⁸F⁻ was the only impurity observed in the case of (*para*-formylphenyl)phenyliodonium salt precursors. In the case of *meta*-substituted salts formation of [¹⁸F]fluorobenzene was also observed. In contrast to other nucleophilic ¹⁸F-substitutions, the radiofluorination reactions of diaryliodonium salts tolerate the presence of water well.⁸ Consequently, water was added to the corresponding solvent to improve the elution yield of ¹⁸F⁻. When (*para*-formylphenyl)phenyliodonium triflate in 90% DMF was used for elution, the radioactivity recovery amounted to 55% and 4-

[^{18}F]FBA was obtained in radiochemical conversions (RCCs) of up to 51% within 15 min.¹¹

Elution of $^{18}\text{F}^-$ with onium salts

The elution of $^{18}\text{F}^-$ with onium salts in aprotic solvents like DMF or DMSO was rather ineffective (recovery < 60%). However, after some pilot experiments we found that the elution of $^{18}\text{F}^-$ with onium salts in various alcohols was much more effective (Figure 1). Especially, with solutions of these salts in MeOH or EtOH the total recovered radioactivity averaged 90–98%. Elution with precursors in higher alcohols was less efficient. In particular, low-boiling methanol not only enabled elution of more than 95% of initially applied [^{18}F]fluoride but could also be completely removed at 70–80 °C within 2–3 min without the need for azeotropic drying. Radioactivity loss during the evaporation step was negligible (< 2%).

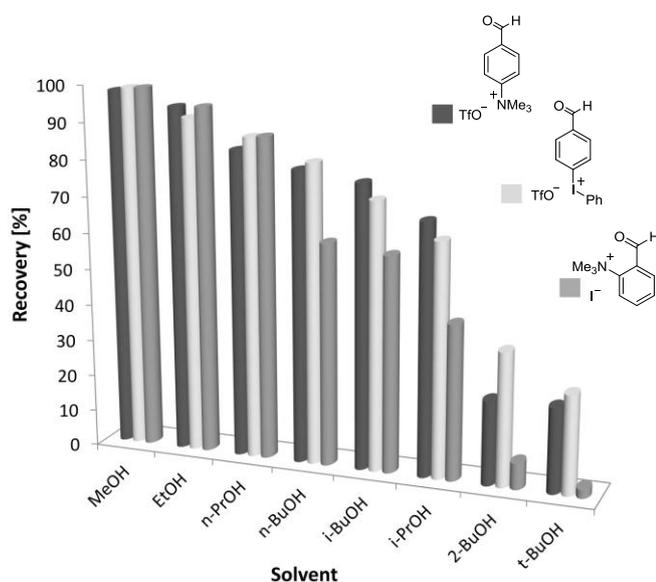


Figure 1. Recovery yield for the elution of $^{18}\text{F}^-$ from a QMA cartridge with onium salts in anhydrous alcohols.

With regard to radiosynthesis in microfluidic devices, we studied the dependence of [^{18}F]fluoride elution yield on behalf of the precursor amount (Table 2). The elution yield of $^{18}\text{F}^-$ exceeded 85% with only 0.1 mg precursor in the case of the basic bicarbonate salt. Radioactivity recovery of more than 75% was reached using only 0.3–0.5 mg of non-basic iodide, triflate or perchlorate precursors.

[^{18}F]Fluorobenzaldehydes

Once a reliable method for the elution of [^{18}F]fluoride had been established, we focused on the preparation of [^{18}F]FBAs and an optimization of the radiosynthesis with respect to precursor, reaction solvent and temperature (Table 3).¹¹ In the case of 2- and 4-[^{18}F]FBA, the best RCCs were achieved with *N,N,N*-

trimethylanilinium precursors. The counter-ion of the precursor salt significantly influenced radiolabeling. From the corresponding perchlorates in DMSO highest RCCs of 80% and 90% for 2- and 4-[^{18}F]FBA were achieved within 10 min, at 130 and 150 °C respectively. With bicarbonate or iodide salts, 2- and 4-[^{18}F]FBA were obtained in good to excellent RCCs (up to 68% and 87%, respectively) at 80 °C. In all cases, [^{18}F]fluoride was the only radioactive impurity detected after quenching the reaction mixture with an excess of H_2O . Reproducibility and scalability were excellent.

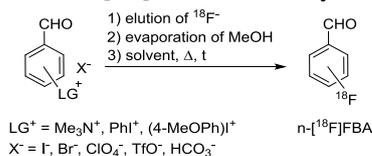
Table 2. Elution of $^{18}\text{F}^-$ from a QMA cartridge with different amounts of onium salts.^a

entry	amount [mg]	Recovery of $^{18}\text{F}^-$ [%]			
		$\text{Me}_3\text{N}^+\text{HCO}_3^-$	$\text{Me}_3\text{N}^+\text{ClO}_4^-$	Ph^+TFO^-	Ph^+I^-
1	10	99	-	-	-
2	8	-	98	-	-
3	5	99	-	99	98
4	2.5	99	-	97	92
5	1	-	96	-	-
6	0.7	-	89	-	-
7	0.5	97	78	80	84
8	0.3	-	-	68	82
9	0.1	85	44	65	76

^a Target [^{18}O]water was passed through an anion exchange resin. The cartridge was washed with anhydrous MeOH and $^{18}\text{F}^-$ was eluted by a solution of the corresponding precursor in MeOH (500 μL).

Thus, 4-[^{18}F]FBA was prepared in 65–75% RCY from 43–47 GBq [^{18}F]fluoride ($n = 20$, non-decay corrected) with > 99% radiochemical purity (RP) within 23 min using the bicarbonate precursor. Unreacted [^{18}F]fluoride was removed by SPE. By comparison, using the conventional $\text{K}_2\text{CO}_3/\text{K}_2.2.2$ protocol, 2- and 4-[^{18}F]FBA could be obtained best in RCYs of 30–55%. Furthermore, a concurrent formation of labeled side-products (5–25%) was observed. In addition very short reaction times and a narrow temperature range (60–120 s at 90 ± 5 °C) had to be applied to obtain reasonable RCCs and RCPs of 2-[^{18}F]FBA since 2-[^{18}F]FBA was unstable under basic reaction conditions. In contrast, use of the perchlorate precursor under “minimalist”

conditions yielded 2-[¹⁸F]FBA in high RCCs of 63–80% within a broad temperature/reaction and

Table 3. Preparation of [¹⁸F]fluorobenzaldehydes^a

entry	n ^b	LG ⁺ X ⁻	solvent	temperature [°C], time [min]	RCC [%] ^c
1	4	Me ₃ N ⁺ I ⁻	DMSO	80, 10	75(65) ^d
2	4	Me ₃ N ⁺ HCO ₃ ⁻	DMSO	80, 10	87
3	4	Me ₃ N ⁺ ClO ₄ ⁻	DMSO	150, 10	90
4	4	Me ₃ N ⁺ TfO ⁻	DMF	115, 10	63
5 ^e	4	Me ₃ N ⁺ TfO ⁻	DMSO	80, 10	40–65
6	2	Me ₃ N ⁺ HCO ₃ ⁻	MeCN	80, 10	68
7	2	Me ₃ N ⁺ I ⁻	DMSO	80, 10	62(62) ^d
8	2	Me ₃ N ⁺ TfO ⁻	DMSO	130, 15	64(46) ^d
9 ^e	2	Me ₃ N ⁺ TfO ⁻	DMSO	80, 1–2	30–46
10	2	Me ₃ N ⁺ ClO ₄ ⁻	DMSO	80–200, 10–15	63–80
11	3	Me ₃ N ⁺ I ⁻	sulfolane	200, 10	6
12	3	(4-MeOPh)I ⁺ ClO ₄ ⁻	DMSO	150, 10	40
13 ^f	3	PhI ⁺ Br ⁻	DMF	130, 10	45

^a ¹⁸F⁻ was eluted from a QMA cartridge with precursor (5–8 mg) in MeOH, methanol was evaporated under He flow (Ar/N₂ can be used instead) at 70–80 °C, the residue was dissolved in the appropriate solvent and the resulting solution heated at T °C for t min; ^bn – substitution position; ^cH₂O (4 mL) was added to quench the reaction and solubilize surface-adsorbed ¹⁸F⁻ and RCC determined by radio-HPLC; ^dRCC with 2 mg precursor in 100 μL solvent; ^eK₂.2.2/K₂CO₃ protocol; ^fCsHCO₃/TEMPO protocol.^{7b} Each experiment was carried out at least in triplicates. If standard deviation of RCC exceeded 20% of its mean value the range of RCC is given. TEMPO – 2,2,4,4-tetramethylpiperidine-*N*-oxyl.

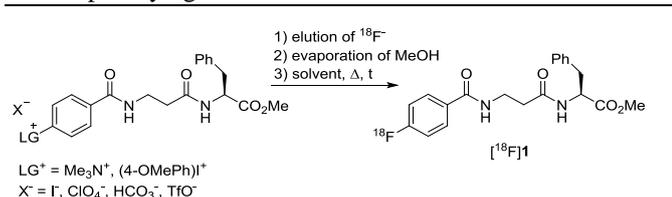
time range (8–15 min at 80–200 °C). The dependence of RCC on precursor amount was briefly examined. RCCs of 2- and 4-[¹⁸F]FBA obtained from 2 mg of *N,N,N*-trimethylanilinium iodide salts were similar to those obtained from 5 mg precursor (Table 3, entries 1 and 7; given in parentheses). In case of other onium salts RCCs were lower (Table 3, entry 8; given in parentheses; see also Table S4, entries 3, 10, 15 and Table S5 entries 3, 5, 8; given in parentheses in the Supporting Information).¹¹ Consequently, all further experiments were carried out with a precursor amounts of 5–8 mg.

As with 2- and 4-isomers, 3-[¹⁸F]FBA could be prepared from the corresponding *N,N,N*-trimethylanilinium salts. However, due to the weaker activating effect of the carbonyl group at the *meta*-position, RCCs were low (no more than 6%) even under harsh reaction conditions (Table 3). Using (4-methoxyphenyl)iodonium salt precursors, 3-[¹⁸F]FBA could be prepared in moderate RCCs of up to 40%, which were comparable to those obtained under conventional radiofluorination conditions.^{11,12} Again ¹⁸F⁻ was the only radioactive impurity which could be detected.

¹⁸F-Labeled model peptide [¹⁸F]1

To further explore the scope of the novel radiofluorination procedure, its applicability was tested for several practically relevant radiosyntheses. First, we studied the feasibility of the *n.c.a* one-step preparation of ¹⁸F-benzoylated peptides via direct aromatic nucleophilic radiofluorination.¹³ In all radiosyntheses published so far additional electron withdrawing groups, such as CN, CF₃ have to be used in order to increase the reactivity of the trimethylammonium or nitro leaving group and ensure acceptable labeling yields. These hydrophobic groups could noticeably increase the overall lipophilicity of the radiolabeled conjugates (especially in the case of short peptides) and, consequently, unfavourably affect their biodistribution. We studied whether direct ¹⁸F-peptide labeling could be also carried out without an additional activating group. 4-[¹⁸F]Fluorobenzoyl-βAla-Phe-OMe [¹⁸F]1 was chosen as a model peptide. Initially, different *N,N,N*-trimethylammonium peptide precursors were investigated (Table 4). Using the conventional K₂CO₃/K₂.2.2 radiofluorination procedure, no formation of [¹⁸F]1 was observed (entry 3, 4), whereas preparation of [¹⁸F]1 under “minimalist” conditions led to the desired radiolabeled conjugate as a single product in RCCs of up to 30%. Application of the corresponding (4-methoxyphenyl)iodonium iodide precursor allowed reaction time to be reduced from 15 to 10 min and raised RCC to 56%. This almost neutral reaction conditions are comparable to or even milder as those described in the literature for the preparation of radiolabeled bombesin analogs and RGD peptides using additional activating groups (DMSO, K₂.2.2/K₂CO₃ or Cs₂CO₃, 70–130 °C, 4–15 min).¹³ The scope and limitations of the application of radiofluorination under “minimalist” conditions for the one-step ¹⁸F-labeling of more complicated peptides are left to be investigated in further studies.

Table 4. Preparation of [^{18}F]1 from onium precursors without azeotropic drying and addition of a base.^a



entry	LG ⁺ X ⁻	solvent	temperature [°C], time [min]	RCC [%] ^b
1	Me ₃ N ⁺ HCO ₃ ⁻	sulfolane	130, 15	30
2	Me ₃ N ⁺ HCO ₃ ⁻	DMSO	200, 15	29
3 ^c	Me ₃ N ⁺ TfO ⁻	DMSO	130, 30	0
4 ^c	Me ₃ N ⁺ T	sulfolane	200, 15	0
5	(4-MeOPh) ⁺ F ⁻	DMSO	130, 10	56
6 ^d	(4-MeOPh) ⁺ F ⁻	DMSO	120, 10	56

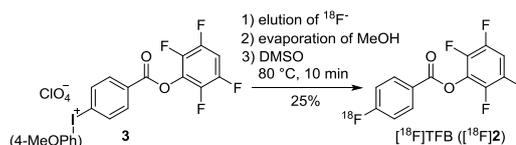
^a $^{18}\text{F}^-$ was eluted from a QMA cartridge with precursor in MeOH, MeOH was evaporated under He flow at 70–80 °C, the residue was dissolved in the appropriate solvent and the resulting solution heated at T °C for t min; ^bH₂O (4 mL) was added to quench the reaction and solubilize surface-adsorbed $^{18}\text{F}^-$ and RCC determined by radio-HPLC; ^cK₂.2.2/K₂CO₃ protocol; ^dCsHCO₃/TEMPO protocol; Each experiment was carried out at least in triplicates. Standard deviation of RCC did not exceed 10% of its mean value.

^{18}F -Labeled active ester [^{18}F]2

The novel radiofluorination method was applied for the preparation of ^{18}F -labeled active ester, 2,3,5,6-tetrafluorophenyl 4- ^{18}F fluorobenzoate ([^{18}F]TFB, [^{18}F]2) (Scheme 1) which is the carbo-analog of 2,3,5,6-tetrafluorophenyl 6- ^{18}F fluoronicotinate ([^{18}F]F-Py-Tfp).¹⁴ [^{18}F]TFB is a novel amine-reactive prosthetic group which can be used for labeling of peptides and proteins similar to well known *N*-succinimidyl 4- ^{18}F fluorobenzoate ([^{18}F]SFB).¹⁵ However, all published radiosyntheses of [^{18}F]SFB using the K₂.2.2/K₂CO₃ protocol for radiofluorination consist of time-consuming and demanding procedures comprising 2–3 reaction and multiple operation steps.¹⁶ In contrast, [^{18}F]F-Py-Tfp can be prepared in good yield via direct radiofluorination of the respective pyridine-2-*N,N,N*-trimethylammonium precursor using less basic TBAHCO₃ or KHCO₃/K₂.2.2. Unfortunately, formation of [^{18}F]F-Py-Tfp is accompanied by the concurrent formation of 2,3,5,6-tetrafluorophenyl 6-(2,3,5,6-tetrafluorophenoxy)-nicotinate

which should be completely separated from the radiolabeled active ester best by HPLC.

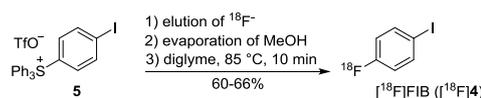
Under “minimalist” conditions the radiolabeled active ester [^{18}F]2 was successfully prepared from the corresponding iodonium precursor **3** in one step in a fair 24% RCC. Under conventional K₂.2.2/K₂CO₃ conditions an extensive decomposition of **3** was observed and only trace amounts of [^{18}F]2 (< 1%) could be detected in the reaction mixture.



Scheme 1. Synthesis of the ^{18}F -labeled active ester [^{18}F]2 under “minimalist” conditions.

Radiolabeling of sulfonium salt **5**

Recently, triarylsulfonium salts have been proposed as precursors for radiofluorination of aromatic compounds.¹⁷ 1- ^{18}F fluoro-4-iodobenzene ([^{18}F]FIB, [^{18}F]4), a valuable building block for radiolabeling via transition metal-catalyzed cross-coupling reactions, was prepared from commercially available (4-iodophenyl)diphenylsulfonium triflate (**5**) (Scheme 2).¹⁸ As with anilinium and iodonium salts, almost complete $^{18}\text{F}^-$ recovery from the anion exchange cartridge was achieved with sulfonium salt **5** in MeOH. [^{18}F]4 was prepared under “minimalist” conditions in 60–66% RCC using diglyme as a solvent at 85 °C for 10 min. Concurrent formation of [^{18}F]fluorobenzene (20–25%) was observed. By using K₂CO₃/K₂.2.2 [^{18}F]FIB was obtained in RCCs of up to 40–50%.

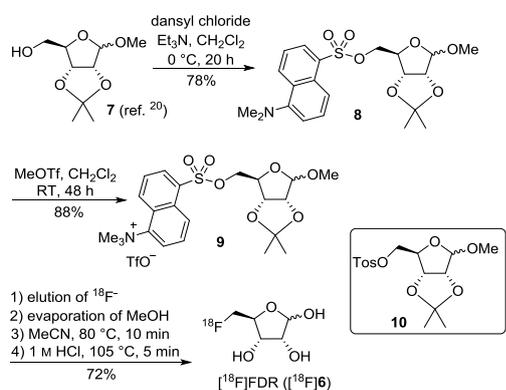


Scheme 2. Preparation of [^{18}F]FIB from sulfonium precursor **5** under “minimalist” conditions.

Aliphatic ^{18}F -labeling – preparation of [^{18}F]FDR

Finally, the novel radiolabeling procedure was used for the synthesis of 5- ^{18}F fluoro-D-ribose ([^{18}F]FDR, [^{18}F]6) (Scheme 3). [^{18}F]FDR is a hydrophilic prosthetic group for radiolabeling of biopolymers via oxime ligation.^{19,20} First, the onium group-containing precursor for radiolabeling has to be prepared. To this end, protected D-ribose **7**²⁰ was converted to the intermediate dansyl sulfonate ester **8** which in turn was treated with methyl triflate to give the desired precursor **9** with a 54% yield over two steps (Scheme 3). [^{18}F]Fluoride was eluted from the solid support with **9** in MeOH almost quantitatively. After MeOH removal, MeCN was added and the resulting solution was heated at 80 °C for 10 min. Deprotection of the labeled intermediate was accomplished by addition of 1 N HCl and heating at 105 °C for 5 min. [^{18}F]FDR was obtained in 72% RCC. By comparison using the conventional

$K_2CO_3/K2.2.2$ protocol [^{18}F]6 was prepared from the corresponding tosylate precursor 10²⁰ in 58% RCC.



Scheme 3. Preparation of [^{18}F]FDR.

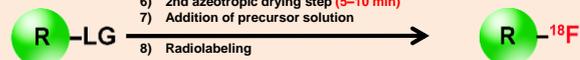
Conclusion

In all nucleophilic radiosyntheses with $^{18}F^-$ published to date, a base often in combination with a cryptand or crown-ether has been used. We demonstrated for the first time that application of these ingredients is dispensable and in some cases even counterproductive. ^{18}F -Labeled compounds could be efficiently prepared using only [^{18}F]fluoride and onium salt precursors. The radiolabeling method based on this finding consists of direct elution of [^{18}F]fluoride with alcoholic solutions of precursors bearing a quaternary ammonium, diaryliodonium or triarylsulfonium functionality followed by heating of the resulting [^{18}F]fluoride salt in a suitable solvent. A comparison between conventional $K_2CO_3/K2.2.2$ and the novel radiofluorination method is shown in Fig. 2. The versatility and the exceptionally wide scope of the novel radiofluorination procedure were demonstrated by the preparation of several useful ^{18}F -labeled prosthetic groups and by the one-step preparation of a radiolabeled model peptide. Labeling yields were comparable to or in many cases even better than those achieved with the classical $K2.2.2/K_2CO_3$ method. Importantly, our novel method eliminates the need, not only for a base or other additives but also for time-consuming azeotropic evaporation steps. Besides, it enables the synthesis of base-sensitive radiotracers and the use of base-sensitive precursors. Moreover, due to its simplicity and the fact that all starting materials and products are soluble in organic solvents, the novel procedure should be well-suited for automated radiosyntheses, especially in microfluidic devices.

$K_2CO_3/K2.2.2$ method

- 1) $^{18}F^-$ Fixation
- 2) Elution of $^{18}F^-$ with $K_2CO_3/K2.2.2$
- 3) Addition of MeCN
- 4) 1st azeotropic drying step (10–20 min)
- 5) Addition of MeCN
- 6) 2nd azeotropic drying step (5–10 min)
- 7) Addition of precursor solution
- 8) Radiolabeling

Ready for Radiolabeling after at least 15 min



„Minimalist“ method (this work)

- 1) $^{18}F^-$ Fixation
- 2) Resin flushed with MeOH (<1 min)
- 3) $^{18}F^-$ elution with onium precursor in MeOH
- 4) Evaporation of MeOH (2 min)
- 5) Addition of solvent
- 6) Radiolabeling

Ready for Radiolabeling within 3 min



- ✓ Versatility (S_NAr and S_N2)
- ✓ Shorter preparation time
- ✓ Less operation steps
- ✓ W/o base and any additives
- ✓ W/o azeotropic drying
- ✓ Better or comparable RCY and RCP
- ✓ Compatible with base sensitive precursors/ ^{18}F -labeled products

Figure 2. Comparison between conventional $K_2CO_3/K2.2.2$ and “minimalist” radiofluorination method.

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Notes and references

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§ Radiochemical conversion (RCC) refers to the amount of radiofluoride which is transformed to the desired ^{18}F -labeled compound. It was determined by radio-HPLC. Radiochemical yield (RCY) refers to the isolated yield of radiochemically and chemically pure radiolabeled compound.

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