Preliminary evaluation of two recently developed evaporation-free [^{18}F]fluorination methods on aromatic precursors

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Objectives

The utility of [^{18}F]fluorinated aromatic compounds for PET imaging has often been highlighted over the past few years. Unfortunately, the difficulty to make the C_{Ar}-F bond is also well known.

With that in mind, we hereby explore the potential of two recently developed evaporation-free [^{18}F]fluorination methods (namely the Organic Bases method (OB)[1] and the "C_{14}" method[2]) on a collection of aromatic precursors, and compare their efficiency with classical fluorination techniques.

This study also provides a general idea of what fluorination method is best for each type of precursor.

[^{18}F]fluorobenzonitrile ([^{18}F]FBN) and [^{18}F]ethyl-fluorobenzoate ([^{18}F]FBZ) were chosen as preliminary target compounds, as they are both convenient synthons for various PET radiotracers (Fig. 1).

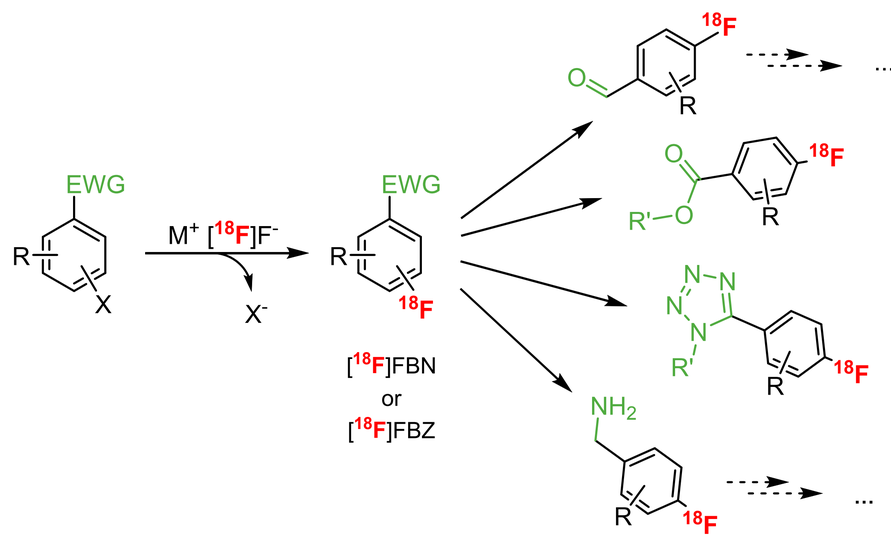
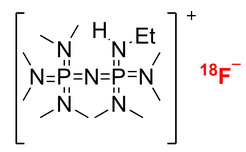


Fig. 1. Nucleophilic radiofluorination of aromatic compounds (general scheme) and subsequent possible paths[3-5] towards radiolabelled prosthetic groups.
X = -$NMe_3^+OTf^-$, -NO_2, -Cl, -Br, -I, -S(=O)-Ar, -I(Ar)(OTf)
EWG = Electron-Withdrawing Group (-CN or -CO_2Et)

Methods

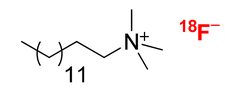
Evaporation-free fluorination methods

ORGANIC BASES (OB)



M⁺:Phosphazenium
Preparation time : 2 min

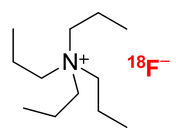
C_{14}



M⁺: n-tetradecyl-trimethylammonium
Preparation time : 7 min

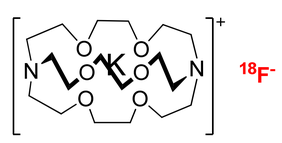
Classical fluorination methods

TPAF



M^+ : tetrapropylammonium
Preparation time : 7 min

K_2CO_3/KRYPTOFIX



M^+: K_{222}^+
Preparation time : 7 min

Results & discussion

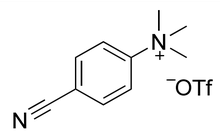
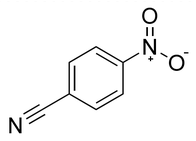
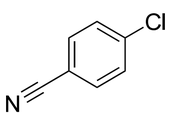
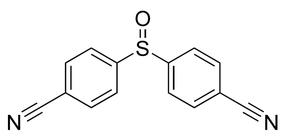
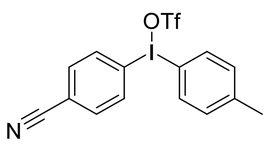
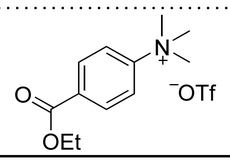
Precursor	Entry	Method (solvent, T(°C), time(min))[a]	Synthesis duration[b]	RCY (%)	Main Product
	1	**OB (ACN, 90, 5)**	•	**99**	4-[18F]FBN
	2	C_{14} (ACN, 120, 10)	•••	99	
	3	K_{222} (DMF, 140, 5)	••	91	
	4	TPAF (DMF, 120, 5)	••	95	
	5	OB (ACN, 140, 15)	••	61	4-[18F]FBN
	6	C_{14} (ACN, 140, 10)	•••	93	
	7	K_{222} (DMSO, 140, 10)	•••	84	
	8	TPAF (DMF, 120, 5)	••	89	
	9	OB (ACN, 140, 15)	•••	4	4-[18F]FBN
	10	C_{14} (ACN, 140, 10)	•••	5	
	11	K_{222} (DMF, 140, 10)	•••	15	
	12	TPAF (DMF, 120, 5)	••	30	
	13	OB (ACN, 140, 10)	••	4	4-[18F]FBN
	14	C_{14} (ACN, 140, 10)	•••	51	
	15	K_{222} (DMF, 140, 10)	•••	68	
	16	TPAF (ACN, 120, 5)	••	63	
	17	OB (ACN, 140, 5)[c]	•	42	4-[18F]FBN
	18	C_{14} (ACN, 140, 10)[c]	•••	6	
	19	K_{222} (DMF, 120, 5)[c]	••	35	
	20	TPAF (DMF, 140, 5)[c]	••	18	
	21	OB (ACN, 120, 10)	••	81 (8)[d]	4-[18F]FBZ
	22	C_{14} (ACN, 140, 10)	•••	79 (7)[d]	
	23	K_{222} (DMF, 120, 15)	••••	77 (9)[d]	
	24	TEAF (DMSO, 120, 10)	•••	70 (13)[d]	

Table 1. Radiofluorination of *para*-substituted aromatic precursors.

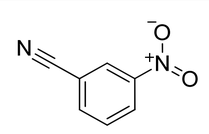
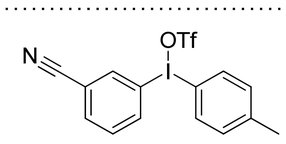
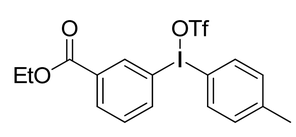
Precursor	Entry	Method (solvent, T(°C), time(min))[a]	Synthesis duration[b]	RCY (%)	Main Product
	25	OB (ACN, 140, 15)	•••	5	3-[18F]FBN
	26	C_{14} (ACN, 140, 10)	•••	6	
	27	K_{222} (DMSO, 140, 10)	•••	40	
	28	TPAF (DMF, 140, 5)	••	57	
	29	OB (ACN, 140, 5)[c]	•	9	3-[18F]FBN
	30	C_{14} (ACN, 120, 5)[c]	••	12	
	31	K_{222} (DMF, 120, 5)[c]	••	51	
	32	TPAF (DMF, 120, 5)[c]	••	12	
	33	OB (ACN, 140, 5)[c]	•	7	3-[18F]FBZ
	34	C_{14} (ACN, 120, 5)[c]	••	14	
	35	K_{222} (DMSO, 120, 5)[c]	••	72	
	36	TPAF (DMF, 140, 5)[c]	••	4	

Table 2. Radiofluorination of *meta*-substituted aromatic precursors.

Tables. Radiofluorination of various [^{18}F]FBN and [^{18}F]FBZ precursors with four radiofluorination methods, using 1-10mCi of no-carrier-added [^{18}F]fluoride in a 3mL glass reactor. All given RCYs were determined by radio-TLC and corrected for decay and adsorption. n ≥ 2 for each labelling.
[a]: conditions for the best RCYs.
[b]: fluorination reagent preparation + labelling duration. • = 7min; ••= 12min; •••=17min; •••• =22min.
[c]: plus 2 eq. TEMPO
[d]: % volatile by-products.

The efficiencies of the OB and C_{14} techniques were compared to those of the well-known Kryptofix and TPAF methods on [^{18}F]FBN and [^{18}F]FBZ precursors bearing various leaving groups.

The aim of this work was also to establish if the new OB and C_{14} techniques were realistically implementable on high-activity aromatic [^{18}F]fluorinations. Therefore, all the labellings were carried out under automation-friendly conditions (conventional heating, below 140°C & for labelling times shorter than 15min).

Our preliminary results reveal the interesting potential of the BO and C_{14} techniques in the field of aromatic radiofluorination. The most interesting results are shown in **Table 1**, and demonstrate that the efficiency of the OB and C_{14} methods is often comparable or better than that of the classical [^{18}F]fluorination methods (**Table 1**, entries 1, 2, 6, 17, 21, 22).

However, as can be seen in **Table 2**, the OB and C_{14} labelling techniques seem to be less efficient on *meta*-substituted derivatives. More experiments shall determine if this trend is to be generalized to all meta-substituted derivatives, or to less deactivated aromatic rings in general.

Achievements/ Advantages brought by the OB & C_{14} radiofluorination methods

OB:
- -Fast [^{18}F]fluoride preparation → shorter overall synthesis duration
- -Unprecedented, quantitative RCY for the synthesis of 4-[^{18}F]FBN, at low T° and for a short reaction time (**Table 1**, entry 1)

C_{14}:
- -Limited basicity of the reaction medium (softer reaction conditions, better tolerated by basic-sensitive functions)

OB & C_{14}:
- - Good efficiency towards aromatic precursors
- - Evaporation-free [^{18}F]fluoride preparation → implementable on microfluidic devices

Conclusion

In addition to being practical from both chemical and technical points of view, the OB and C_{14} radiofluorination methods have shown very interesting abilities towards aromatic radiofluorination. These techniques are therefore interesting and viable alternatives to more classical ones, such as the K_{222} or TPAF methods. They could be used to enhance the radiosynthesis yields of existing PET radiotracers, or to develop new radiosyntheses on microfluidic devices. The new OB and C_{14} radiofluorination methods shall be further tested to determine if their usefulness can be extended to the labelling of electron-deficient aromatic rings.

Acknowledgements
We gratefully acknowledge the FRS-FNRS for the FRIA grant supporting this project.

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[1] C. F. Lemaire et al., *Angew. Chem. Int. Ed.* **2010**, *49*, 3161. [2] J. Aerts et al., *Tetrahedron Lett.* **2010**, *51*, 64. [3] I. Koslowski, J. Mercer, F. Wuest, *Org. Biomol. Chem.* **2010**, *8*, 4730.
[4] J. de M. Muñoz et al., *Tetrahedron Lett.* **2011**, *52*, 6058. [5] V. Aureggi, G. Sedelmeier, *Angew. Chem. Int. Ed.* **2007**, *46*, 8440.