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2-Bromo-6-[18F]fluoropyridine: two-step fluorine-18 radiolabelling via transition metal-mediated chemistry†

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Novel radiolabelling methods are important for the development of new tracers for positron emission tomography. Direct nucleophilic fluorination of aromatic rings with [18F]fluoride is limited to activated substrates, restricting the application of this approach. Inspired by transition metal-mediated transformations, a fluorine-18 synthon was prepared to supplement the radiolabelling methods available for molecules unsuitable for direct labelling. 2-Bromo-6-[18F]fluoropyridine (denoted [18F]1) was prepared in high yield, and palladium-mediated cross-coupling reactions were exemplified. High incorporation of fluoride and efficient cross-coupling reactions demonstrate that compound [18F]1 holds promise as a new synthon for construction of fluorine-18-labelled molecules via transition metal-mediated reactions.

Keywords: PET; fluorine-18; synthon; 2-Fluoropyridine; palladium; cross-coupling

Introduction

Positron emission tomography (PET) is a valuable imaging technique for monitoring physiological processes *in vivo* in a non-invasive manner, using concentrations of radiolabelled compounds that do not cause a pharmacological response.[1] The most widely available isotope for PET imaging is fluorine-18, which has a half life of 109.7 min and is readily produced as aqueous fluoride from a cyclotron. Although the moderate half life is ideal for patient scanning without excessive radiation burden, it presents a challenge for the radiochemist to prepare and purify [18F]fluorine-labelled imaging agents within a short window.

Molecules of interest for PET imaging commonly feature the fluorine radiolabel as a fluoroaromatic group. Direct nucleophilic [18F]fluorination of aromatic ring systems requires the presence of electron withdrawing substituents, and harsh reaction conditions are employed for efficient incorporation.[2] Multistage synthon approaches provide an alternative in which an activated precursor is radiolabelled and subsequently incorporated into the molecule of interest. Popular synthons include 4-[18F]fluorobenzaldehyde and *N*-succinimidyl-4-[18F]fluorobenzoate. However, these synthons are limited to labelling molecules with a reactive nucleophile for conjugation, and their purification from by-products can be difficult.[3] Novel methods of radiolabelling aromatic systems with [18F]fluoride are therefore of interest.

This article describes the synthesis and transition metal-mediated reactions of the novel synthon 2-bromo-6-[18F]fluoropyridine. Transition metal-mediated approaches have often been reported in carbon-11 radiosyntheses ($t_{1/2} = 20$ min, β^+) to selectively assemble reaction components in good yield; however, relatively few examples exist for [18F]fluorine radiolabelling.[1] Notably, palladium-mediated reactions of [18F]fluorobromo benzene and [18F]fluoroiodobenzene have been reported, but these synthons have not been widely adopted as they are either prepared in moderate yield from the symmetrical dihalobenzene or from iodonium salts, which require complex precursor syntheses, and can be prone to side reactions.[4–6] [18F]Fluorinated heteroaromatics such as [18F]fluoropyridines have become more prevalent as the heteroatom can be used to tune a potential PET tracer's pharmacokinetic profile. In some cases, heteroaromatics are more amenable to a direct radiolabelling approach, although the presence of electron withdrawing groups is preferred.[7]

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Inspired by the range of transformations possible using transition metal cross-coupling, we developed 2-bromo-6-[^{18}F]fluoropyridine and here report its synthesis and characterisation.

Synthon

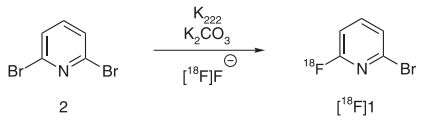
2-Bromo-6-[^{18}F]fluoropyridine, [^{18}F]**1**, was prepared from 2,6-dibromopyridine **2** by nucleophilic aromatic fluorination with [^{18}F]fluoride dried in the presence of the phase transfer agent Kryptofix-222 and potassium carbonate. (Scheme 1). 2,6-Dibromopyridine **2** is appropriate for both fluoride substitution and oxidative addition reactions, and the symmetrical precursor was selected to avoid potential mixtures of products. Furthermore, **2** is commercially available as a crystalline solid and has no special storage requirements.

Various solvents and reaction conditions were screened, and the resulting [^{18}F]**1** was purified by semi-preparative HPLC, (Table 1). All reactions were performed manually using starting [^{18}F]fluoride activity of 74–222 MBq. Crude reaction mixtures were analysed by HPLC with UV and radio-detection. Under all conditions tested, only two radioactive species were present, identified as [^{18}F]fluoride and [^{18}F]**1** as verified by co-injection of [^{19}F]**1** standard. After HPLC purification, non-decay-corrected isolated yields of [^{18}F]**1** of up to 53% (79% corrected for decay) were obtained. Complete removal of **2** was observed after HPLC purification. As an alternative purification method, [^{18}F]**1** was passed through a silica Sep-Pak cartridge. Using cartridge purification, compound **2** was not separated from [^{18}F]**1**, but this was not detrimental to the subsequent coupling reaction. Cartridge purification was therefore pursued to minimise the total reaction time.

Coupling reactions

Cross-coupling reactions

With [^{18}F]**1** in hand, palladium-mediated cross-coupling reactions were exemplified by the Buchwald–Hartwig amination and Suzuki coupling, (Scheme 2). The coupling efficiency for each reaction using [^{18}F]**1** after silica cartridge purification is displayed in Table 2. Radiolabelled products were verified by co-injection of a conventionally characterised [^{19}F] standard, (see Supplementary Information).



Scheme 1. Preparation of 2-bromo-6-[^{18}F]fluoropyridine, [^{18}F]1.

Table 1. Summary of radiolabelling conditions for [^{18}F]**1**

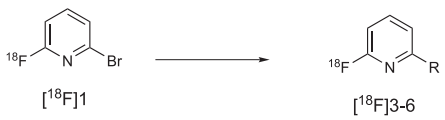
Mass of **2** (mg)	Solvent (0.2 mL)	Temp °C*	Yield (decay corrected) %	Synthesis time (min)
5.0	DMF	120	42(68)	74
2.0	DMF	120	42(64)	65
2.0	MeCN	100	43(67)	70
2.0	NMP	100	18(28)	74
2.0	DMF	100	53(79)	64
2.0	THF	100	5(7)	68
1.0	MeCN	100	40(60)	67

*Each reaction was heated for 10 min. Yields given are of HPLC purified, isolated [^{18}F]**1** calculated from aqueous [^{18}F] fluoride. Decay corrected yields are given in brackets.

Buchwald–Hartwig amination was successfully used to prepare electron-rich [^{18}F]fluoropyridyl compounds. Reaction of [^{18}F]**1**, [Pd_2dba_3], BINAP and sodium *t*-butoxide with benzylamine or *N*-benzylpiperazine yielded *N*-benzyl-6-[^{18}F]fluoropyridin-2-amine (denoted [^{18}F]**3**) and 1-benzyl-4-(6-[^{18}F]fluoropyridin-2-yl) piperazine (denoted [^{18}F]**4**), respectively, (Table 2 and Scheme 2). Preliminary experiments showed that pre-mixing the [Pd_2dba_3] and BINAP prior to addition to [^{18}F]**1**, purging of the reaction headspace with N_2, as well as keeping solvent volume to a minimum were all beneficial to the rate of reaction. The use of a great excess of the amine (~100-fold, with respect to [Pd_2dba_3]) was critical to drive conversion to the desired product.

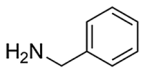
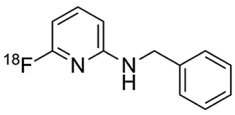
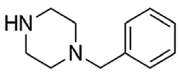
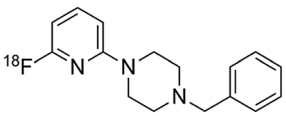
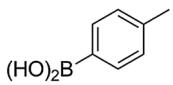
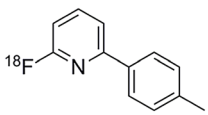
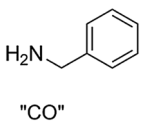
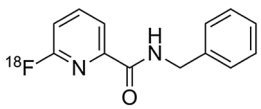
Various solvents were tested to establish the optimum conditions for the Buchwald–Hartwig reaction. In anhydrous MeCN, compound [^{18}F]**3** was formed with a 60% conversion from [^{18}F]**1** after 15 min at 100 °C. Under the same conditions, the coupling reaction to form [^{18}F]**4** showed 49% conversion after 25 min; presumably, steric effects around the nitrogen hindered the formation of the [^{18}F]FPy-Pd(II)-amine complex in the reaction cycle. For both amine substrates (after dilution with H_2O for HPLC analysis), the balance of the radioactivity was found at the solvent front, with no [^{18}F]**1** remaining. Attempts to increase the conversion by using the higher boiling solvents NMP, DMF or toluene did not improve the reaction yields, although the rate of consumption of [^{18}F]**1** was increased; after 5 min in MeCN/NMP, all [^{18}F]**1** was consumed, and [^{18}F]**3** was formed in 53%. No desired product was observed when the reaction was attempted in DMF. As expected, omission of the palladium catalyst resulted in the displacement of [^{18}F]fluoride from [^{18}F]**1**, and all radioactivity was found at the solvent front by analytical HPLC.

The Suzuki reaction was used to prepare a further model electron-rich [^{18}F]fluoropyridine. [^{18}F]**1**, and *p*-tolylboronic acid reacted in the presence of sodium carbonate and [$Pd(PPh_3)_4$] in MeCN/H_2O. Excellent conversion to 2-[^{18}F]fluoro-6-(*p*-tolyl) pyridine [^{18}F]**5** of 98% was found after 5 min. Unlike the Buchwald–Hartwig aminations, this reaction was relatively insensitive to volume; comparable yields of 98% and 95% were recorded with total reaction volumes of 0.35 mL and 0.65 mL, respectively. Product [^{18}F]**5** was isolated to assess the end of synthesis yield from [^{18}F]fluoride. The reaction was diluted in H_2O and passed through a filter before loading to a semi-preparative HPLC system. Use of aqueous-miscible MeCN as the reaction medium facilitated the purification by standard reverse-phase HPLC on C18 stationary phase, using a MeCN/H_2O gradient method. The major UV-active components (including 2-bromo-6-(*p*-tolyl)pyridine) were easily separated from [^{18}F]**5**, which was isolated in 22 ± 6% ($n = 4$) non-decay-corrected yield from starting [^{18}F]fluoride activity. The total



Scheme 2. Cross-coupling reactions of [^{18}F]1.

Table 2. Summary of cross-coupling reactions described by Scheme 2

Substrate	Product	Product	Temp (°C)	Time (min)	Reagents	Solvent	Yield* (%)
		[^{18}F]**3**	100	15	Pd_2dba_3 (±)BINAP NaO^tBu	MeCN	60
		[^{18}F]**3**	100	15	Pd_2dba_3 NaO^tBu (No BINAP)	MeCN	0
		[^{18}F]**3**	100	15	Pd_2dba_3 BINAP (No NaO^tBu)	MeCN	0
		[^{18}F]**3**	100	15	NaO^tBu	MeCN	0
		[^{18}F]**3**	130	5	Pd_2dba_3 (±)BINAP NaO^tBu	MeCN/NMP (1:3)	53
		[^{18}F]**4**	100	25	Pd_2dba_3 (±)BINAP NaO^tBu	MeCN	49
		[^{18}F]**4**	150	15	Pd_2dba_3 (±)BINAP NaO^tBu	MeCN/ toluene	45
		[^{18}F]**4**	110	15	Pd_2dba_3 (±)BINAP NaO^tBu	DMF	0
		[^{18}F]**5**	100	5	$Pd(PPh_3)_4$ Na_2CO_3	MeCN/H_2O (0.35 mL)	98
		[^{18}F]**5**	100	5	$Pd(PPh_3)_4$ Na_2CO_3	MeCN/H_2O (0.65 mL)	95
		[^{18}F]**6**	100	30	Pd(II)OAc_2 $Mo(CO)_6$ DBU	THF	70

DBU, diazabicycloundecene.
*Reactions were performed using silica cartridge purified [^{18}F]**1**. Yield refers to the percentage of product from radio-HPLC analysis. 'CO' source is $Mo(CO)_6$/DBU.

synthesis time was approximately 90 min. Further optimisation and shortened reaction time may be achieved once translated to an automated platform.

Multicomponent aminocarbonylation

Multicomponent reactions provide an elegant solution to the preparation of many carbon-11 radiotracers. Such multicomponent reactions have scarcely been considered for fluorine-18, and the first examples have been reported recently.[8] Here, compounds [^{18}F]**1**, benzylamine and CO were selectively assembled to form *N*-benzyl-6-fluoropicolinamide (denoted [^{18}F]**6**) using [$Pd(OAc)_2$] as the palladium mediator. $Mo(CO)_6$ was chosen as a convenient solid source of CO, where CO is released when heated after addition of diazabicycloundecene.[9] Using silica cartridge purified [^{18}F]**1**, the aminocarbonylation reaction in THF yielded [^{18}F]**6** in 70% after 30 min heating at 100 °C. It is notable that under these conditions, the competing Buchwald–Hartwig amination product was absent, indicating efficient insertion of CO in the reaction cycle.

Conclusions

We have successfully demonstrated that the novel synthon 2-bromo-6-[^{18}F]fluoropyridine [^{18}F]**1** can be prepared in high yield and used in palladium-mediated reactions to prepare electron-rich 2-[^{18}F]fluoropyridines. The possibility of using this synthon in multicomponent reactions was also demonstrated. We envisage that this synthon can widely applied in the wealth of known transition metal-mediated cross-coupling reactions and provides a novel method to add to the fluorine-18 radiochemistry toolkit for the development of new PET imaging agents.

Acknowledgments

We would like to acknowledge I. Khan for the contributions in planning this project and the cyclotron operators at Hammersmith Imanet for the provision of [^{18}F]fluoride. We disclose that this work is the subject of a patent application.

Conflict of Interest

The authors did not report any conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website