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Short Communication

Synthesis of ^{18}F-arenes from spirocyclic iodonium(III) ylides via continuous-flow microfluidics

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ABSTRACT

Spirocyclic hypervalent iodine(III) ylides have proven to be synthetically versatile precursors for efficient radiolabelling of a diverse range of non-activated (hetero)arenes, highly functionalised small molecules, building blocks and radiopharmaceuticals from [^{18}F]fluoride ion. Herein, we report the implementation of these reactions onto a continuous-flow microfluidic platform, thereby offering an alterative and automated synthetic procedure of a radiopharmaceutical, 3-[^{18}F]fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile ([^{18}F]FPEB) and a routinely used building block for click-radiochemistry, 4-[^{18}F]fluorobenzyl azide. This new protocol was applied to the synthesis of [^{18}F]FPEB (radiochemical conversion (RCC) = 68 ± 5%) and 4-[^{18}F]fluorobenzyl azide (RCC = 68 ± 5%; isolated radiochemical yield = 24 ± 0%). We anticipate that the high throughput microfluidic platform will accelerate the discovery and applications of ^{18}F-labelled building blocks and labelled compounds prepared by iodonium ylide precursors as well as the production of radiotracers for preclinical imaging studies.

1. Introduction

Positron Emission Tomography (PET) is an established molecular imaging technique that has applications in clinical diagnosis and drug development, especially in combination with anatomical imaging techniques including computed tomography and magnetic resonance imaging. Fluorine-18 (^{18}F) [1] is widely regarded as the foremost radionuclide for PET due to the significant use of ^{19}F in drug design [2], as well as a favourable decay profile (97% β^+ decay to ^{18}O). Furthermore, its relatively long half-life ($t_{½}$ = 109.8 min) enables imaging timeframes and multi-centre trials [3], which are not possible with other common radionuclides, such as carbon-11 (^{11}C [$t_{½}$ = 20.3 min]). Radiometals that are used for PET imaging purposes can have longer half-lives (e.g., ^{64}Cu [$t_{½}$ = 12.7 h] and ^{89}Zr [$t_{½}$ = 78.4 h]), however these are generally not suitable for small molecule drugs without change to their parent structures, as they require high-affinity chelators for complexation.

Continuous-flow microfluidic technology can offer significant advantages for the synthesis of PET radiotracers, including increased reproducibility, faster reaction kinetics and rapid reaction optimisation [4]. There have been over 50 reported syntheses of labelled compounds for PET that exploit the advantages of continuous-flow microfluidics [5]. Recently, continuous-flow microfluidics was used for the preparation of [^{18}F]FPEB [6], [^{18}F]T807 [7], and [^{18}F]FMISO [8] for human use, whilst [^{18}F]Fallypride [9] has comparably been prepared using a micro-reactor.

We recently reported a novel procedure for the ^{18}F-fluorination of hypervalent iodonium(III) ylides to give ^{18}F-arenes from ^{18}F-fluoride [10], that provided efficient regiospecific labelling for a diverse scope of non-activated functionalised (hetero)arenes. These include electron-donating motifs, which have typically been difficult to label with preceding hypervalent iodine(III) mechanisms, as well as highly functionalised molecules and PET radiopharmaceuticals. This approach has recently been extended to the automated production of 3-[^{18}F]fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile ([^{18}F]FPEB) in a good radiochemical yield (15–25%, formulated and ready for injection, n = 3) and validated for human use, utilising a commercial radiosynthesis module [11].

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The goal of the work presented herein was to demonstrate a translation of our spirocyclic iodonium(III) ylide methodology onto a continuous-flow microfluidic platform and utilise the high throughput advantages held by this technology over both manual and other automated protocols. This work aims to enable rapid radiochemistry optimisation and synthesis of labelled compounds for preclinical research.

As proof of concept, our goals were: (1) to confirm that the iodonium ylide precursors can be suitably translated to a commercial continuous flow reactor system with a model substrate; (2) to synthesise and isolate ^{18}F-fluorobenzyl azide, a building block for high throughput click chemistry and (3) to synthesise a radiopharmaceutical, with [^{18}F]FPEB as a model compound, which was previously a challenge to synthesise for preclinical or clinical work.

2. Results and discussion

2.1. Synthesis of model ^{18}F-labelled substrates via iodonium ylide precursors and continuous flow microfluidics

A commercial continuous-flow microfluidic platform (NanoTek®; Advion, Inc.) [12] was utilised for this study. A model biphenyl iodonium ylide precursor was explored for initial proof-of-concept and reaction optimisation using tetraethylammonium [^{18}F]fluoride ([^{18}F]TEAF) as the ^{18}F-fluoride source, formed by the elution of ^{18}F-fluoride from an anion exchange cartridge with a solution of tetraethylammonium bicarbonate (TEAB). The precursor, 6,10-dioxaspiro[4.5]decane-7,9-dion-[1,1′-biphenyl-4-iodonium] ylide (**1**) was reacted with [^{18}F]TEAF to form 4-[^{18}F]fluorobiphenyl (**2**), and was chosen for this study to allow for a direct comparison of incorporation of ^{18}F-fluoride based on our previous manual synthesis [10]. The initial conditions, translated from our previous approach (8 mg/mL **1**, 12 mg/mL [^{18}F]TEAF/TEAB, DMF, RCC = 85%) [10], were subjected to a temperature range (130–220 °C) using a 4 m (32 μL) reactor, into which the [^{18}F]TEAF/TEAB (Pump 3 [P3]) and substrate solutions (Pump 1 [P1]) were introduced in a 1:1 (P1:P3) ratio. This immediately showed that an automated approach could match the RCCs from a manual approach and consequently a more exhaustive optimisation of the reaction conditions was rapidly performed. A comparison of DMF, DMSO and CH_3CN (Fig. 1A) showed DMF to be the preferred solvent, though intriguingly CH_3CN performed better at $T \geq 200$ °C, at which a drop in conversion was observed in all other solvents. In comparison, CH_3CN was dismissed early in the manual methodology as it had led to relatively low conversion with this substrate and reaction condition ($9 \pm 8\%$, $n = 3$) [10] when compared with both DMF and DMSO. We attributed the lower yield to the lower boiling point of CH_3CN as the limiting factor.

A study of five different flow rates through the reactor (20–100 μL/min) showed that there was no significant change in the conversion, with a slight increase at slower rates being annulled by the increased time for the reaction and respective decay of activity (Fig. 1B). Both the precursor loading and base ([^{18}F]TEAF/TEAB) loading were optimised consecutively using DMF as the solvent. It was found that increasing the precursor loading to 16 mg/mL improved the incorporation of fluoride into **2** across the temperature range and the drop in conversion, which had been seen when $T > 190$ °C, was no longer observed (Fig. 1C).

Decreasing the loading of [^{18}F]TEAF/TEAB in the system increased the RCC at lower temperature, although a reduction in conversion was observed once the temperature exceeded 160 °C. Increasing the base loading decreased the conversions across the temperature range 140–220 °C (Fig. 1D). The effect of the base loading with a series of other ylides has been observed by us and a mechanistic study will be published elsewhere.

Final optimised conditions for the radiofluorination of **1** (16 mg/mL **1**, 12 mg/mL [^{18}F]TEAF/TEAB, DMF, 60 μL/min, P1:P3 1:1, 4 m (32 μL) reactor) gave excellent incorporation of ^{18}F-fluoride ($95 \pm 1\%$, $T = 200$ °C, $n = 4$) (Scheme 1), and offers an improvement on the RCC established by the manual procedure (85%) [10].

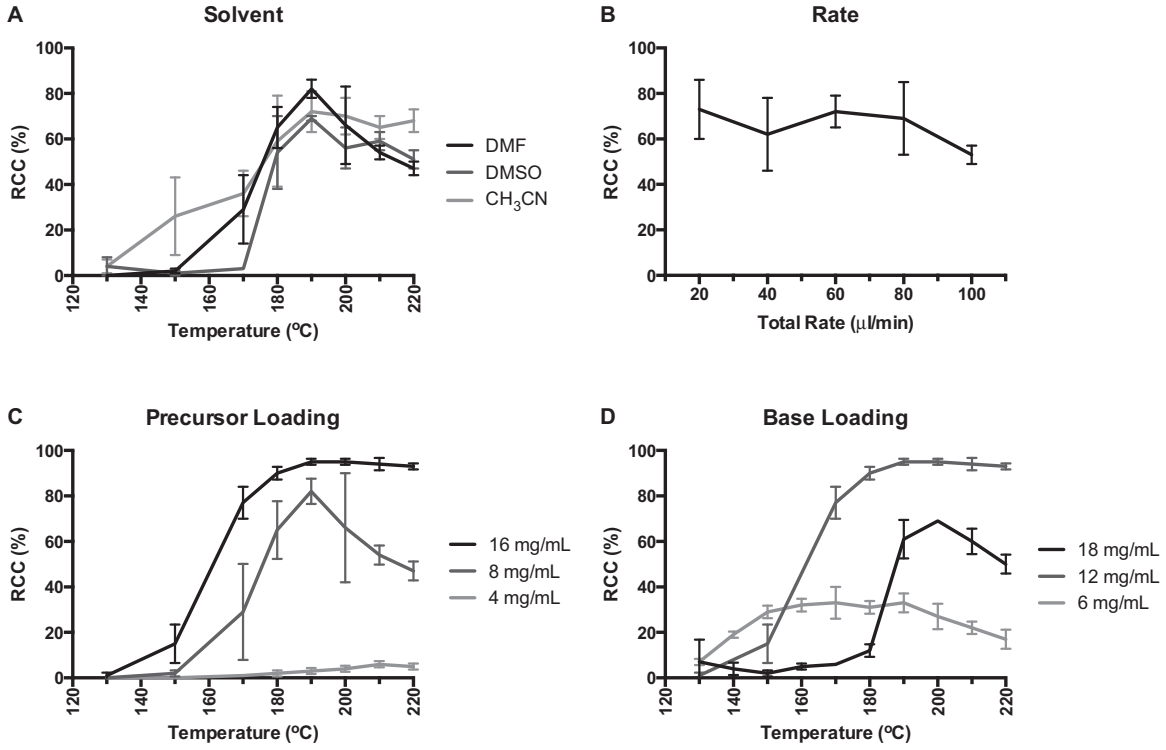

Fig. 1. Optimisation plots for radiolabelling of 4-[^{18}F]fluorobiphenyl (**2**). Conditions ($n = 2$, 4 m reactor): (A) 8 mg/mL **1**, 12 mg/mL [^{18}F]TEAF/TEAB, 60 μL/min; (B) 8 mg/mL **1**, 12 mg/mL [^{18}F]TEAF/TEAB, DMF, 190 °C; (C) 12 mg/mL [^{18}F]TEAF/TEAB, DMF, 60 μL/min; (D) 16 mg/mL **1**, DMF, 60 μL/min. Incorporation yield, as radiochemical conversion (RCC), and product identity were determined by radioTLC and radioHPLC, respectively.