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Radical fluoroarylation in radiochemical synthesis

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Abstract

In this study, we report on the radical [^{18}F]fluoroarylation of different olefins using 4-[^{18}F]fluorobenzenediazonium ions to provide a new route to radiopharmaceuticals containing a deactivated, 4-[^{18}F]fluoro substituted phenyl group. This new methodology was shown to be well suited for the synthesis of ^{18}F-labelled stilbenes. Stilbene **7** is now accessible within 80 min in 30–45% overall radiochemical yield starting from [^{18}F]fluoride.

Positron emission tomography (PET) is a powerful non-invasive method for the imaging and quantification of physiological and biochemical processes in vivo.

The wide scope of physiological targets of interest suitable for diagnosis, planning and monitoring of therapeutic interventions by means of imaging has led to an increasing search for new radiopharmaceuticals. Due to its broad availability, its low positron energy ($E_{max} = 635$ keV) and half-life ($t_{1/2} = 109.7$ min),[1,2] no-carrier-added (n.c.a.) fluorine-18 is the most commonly used PET isotope. Although favoured by these advantages, chemical synthesis and incorporation of fluorine-18 into the target molecule in reasonable overall reaction times (ideally less than 2 h) often remains the key obstacle for the development of new radiopharmaceuticals.

In this study, we report on the radical [^{18}F]fluoroarylation of different olefins using 4-[^{18}F]fluorobenzenediazonium ions to provide a new route to radiopharmaceuticals containing a deactivated, 4-[^{18}F]fluoro substituted phenyl group.

Although well known for short reaction times, radical chemistry has rarely been used for the synthesis of ^{18}F-labelled radiopharmaceuticals. For example a photochemically induced thiodediazonation reaction has been applied for the synthesis of ^{18}F-labelled *S*-aryl-cysteine.[3] Inspired by our recent work on reactions involving aryl radicals and arenediazonium salts,[4,5] we decided to evaluate the applicability of the reductive Meerwein arylation for radiochemical syntheses.[6] In this way, the incorporation of radioactivity would be achieved by the addition of a 4-[^{18}F]fluorophenyl radical to a carbon-carbon double bond of a suitable precursor molecule. For optimization, we first reacted 4-fluorobenzenediazonium tetrafluoroborate **1** with arecoline **2** under various conditions (see Supplementary data). Commercially available titanium(III)-chloride in dilute hydrochloric acid is known to be a suitable reductant for arenediazonium salts.[5,6] Due to the basic nitrogen atom in the structure of arecoline (and the other substrates described below), no additional co-solvent is necessary to reach high concentrations of the olefinic substrate in the reaction mixture. To ensure complete conversion of the arenediazonium salt at reasonable excess of titanium(III) and in reaction times of less than 20 min, we raised the reaction temperature to 45 °C. The optimized conditions[7] were then further applied to ecgonidine methylate (**3**) and styrenes **4a** and **4b** (Scheme 1).[8] A summary of the results is given in Column 2 of Table 1. The 4-arylpiperidine **5**, which is a valuable starting material for the synthesis of

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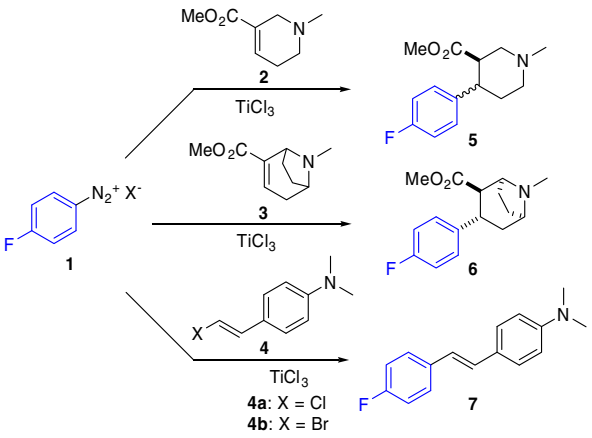

Scheme 1. Fluoroarylation of arecoline **2**, ecgonidine methylate **3** and styrenes **4a** and **4b**.

Table 1
Chemical and radiochemical fluoroarylation of arecoline **2**, ecgonidine methylate **3** and styrenes **4a** and **4b**

Substrate	Product, yield[a] (%)	Product, radiochemical yield (%)
Arecoline **2**	**5**, 54[b]	[^{18}**F**]-**5**, ⩽13[d,b]
Ecgonidine methylate **3**	**6**, 51[c]	[^{18}**F**]-**6**, ⩽16[d]
Chlorostyrene **4a**	**7**, 28	—
Bromostyrene **4b**	**7**, 32	[^{18}**F**]-**7**, 60–70[e]

[a] Reactions according to general procedure. Isolated yields.
[b] Diastereoselectivity: trans:cis = 58:42 (non-radioactive), trans:cis = 50:50 (radioactive).
[c] Diastereoselectivity >80% (43% of 2β,3α-isomer, 8% for remaining three isomers).
[d] Reaction time:10 min.
[e] Reaction time: 5 min.

the anti-depressive drug paroxetine,[9] as well as the (2β, 3α)-aryltropane **6**, which has been found to have high affinity (21 nM) for the dopamine transporter (DAT),[10] were accessible in synthetically useful yields, the latter even with remarkable diastereoselectivity. Hydrogen abstraction from arecoline and ecgonidine methylate, leading to the formation of fluorobenzene, was determined to be the main competing process.[11] We therefore found it surprising that the experiments with both styrenes **4a** and **4b**, which do not bear easily abstractable hydrogen atoms, gave significantly lower yields. Styrenes **4a** and **4b** were chosen since stilbene **7** is an important lead structure for Alzheimer plaque imaging.[12]

In contrast to the preliminary experiments described above, syntheses of no-carrier-added radiopharmaceuticals are usually performed on a much smaller scale (usually μM for the labelling precursor and pM for fluorine-18). The yields obtained for the 'cold' syntheses therefore do not necessarily allow a prediction for yields obtained for radioactive syntheses. Based on the literature-known preparation of 4-[^{18}F]fluorobenzenediazonium salts[4,13] and the procedure developed for the non-radioactive synthesis, we then investigated the [^{18}F]fluoroarylation under radiochemical conditions. The results obtained with the optimized protocol are summarized in Column 3 of Table 1.[14] Although a variety of variations regarding reaction time, temperature and excess of substrates were investigated, suppression of hydrogen abstraction from arecoline **2** and ecgonidine methylate **3** could not be achieved. Consequently, [^{18}F]fluorobenzene was formed in up to 60% yield (see Supplementary data).

In contrast to the fluoroarylation of arecoline **2** and ecgonidine methylate **3**, where significantly lower yields were obtained for radiosyntheses compared to 'cold' syntheses, the small reaction scale and the increase in substrate equivalents turned out to be beneficial for the formation of stilbene **7**. Radiochemical yields of up to 70% were observed after reaction times of only 5 min.[15] The opposed behaviour of arecoline **2** and ecgonidine methylate **3** compared to bromostyrene **4b** in the radiochemical experiments is most probably due to undesired hydrogen abstraction by the aryl radical. In the non-radioactive optimization experiments with arecoline, only a minor increase in yield (from 50% to around 60%) was found when the amount of arecoline was doubled from 2.5 to 5 equiv, since the side reaction also benefits from higher substrate concentrations. Experiments with bromostyrene **4b** gave a comparatively larger relative increase in yield from 21% to 32% when conducted with four instead of two equivalents. In conclusion, substrates which undergo no specific side-reactions (e.g., hydrogen abstraction from allylic positions, radical addition to an alternate functional groups) are much more likely to benefit from the manifold excess in radiochemical syntheses. In the case of stilbene **7**, the dramatic increase in equivalents made a synthetically low-yielding process become an efficient method in radiochemistry.

In combination with the preparation of the intermediate 4-[^{18}F]fluorobenzenediazonium salt, the Alzheimer plaque imaging reagent **7** is now accessible in 80 min total reaction time with overall radiochemical yields of 30–45% (decay corrected) starting from [^{18}F]fluoride, which is the superior to the previously reported procedures.[16]

In summary, the first successful application of aryl radicals for the synthesis of radiopharmaceuticals is reported and exemplified for the production of ^{18}F-labelled stilbenes, one class of Alzheimer imaging agents. Exploiting the characteristics of earlier aryl radical reactions under comparable conditions, this methodology should be insensitive towards many functional groups (e.g., amino groups, hydroxyl groups, carboxylic acids, nitriles and ketones),[5,6] and opens a new route to radiopharmaceuticals not available with commonly used approaches. Furthermore, based on the experiences with ^{18}F-substituted, deactivated aromatic systems it can be assumed that radiopharmaceuticals synthesized by this methodology will show excellent stability towards defluorination in vivo.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.128.

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11. The degree of hydrogen abstraction by the aryl radical cannot easily be determined in experiments with fluorobenzenediazonium salts due to the volatility of fluorobenzene. An attempt with 4-methoxybenzenediazonium tetrafluoroborate and arecoline under standard conditions (see Ref. 8) gave 46% of the desired adduct along with 35% of anisole.
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14. *General procedure for [^{18}F]fluoroarylation (Table 1, column 3)*: Substrates **2**, **3** and **4b** (2–50 mg) were dissolved in aqueous titanium(III) chloride (500 μL) and the 4-[^{18}F]fluorobenzenediazonium salt **1** was added in 100 μL HCl/$NaNO_2$ (90 μL 1 M HCl, 10 μL 1 M $NaNO_2$). The resulting mixture was reacted at room temperature, 40 °C or 60 °C, respectively, and cooled to room temperature. Reaction times were 1 min, 2 min, 5 min, and 10 min. The radiochemical yields were determined by RP-HPLC of the crude mixture (column: Merck Chromolith Performance RP-18e 100 × 4.6 mm) using gradient elution at a flow rate of 3 mL/min and UV detection at 214 nm. Solvent A: 0.05% of TFA in water; solvent B: 0.04% of TFA in CH_3CN. The following gradient was used for **5** and **6**: 0 min 5% B, 8 min 40%. For **7** as the gradient was used 0 min 10% B, 8 min 50% B (for further details see Supplementary data).
15. Highest radiochemical yields were obtained using a relatively high precursor amount of 50 mg. However, good radiochemical yields ⩾50% can also be achieved using smaller precursor amounts. A radiochemical yield of 54% was obtained within 5 min using 10 mg of bromostyrene **4b**.
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