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Accessibility
A Transmetalation Reaction Enables the Synthesis of $[^{18}\text{F}]{\text{5-Fluorouracil}}$ from $[^{18}\text{F}]{\text{Fluoride}}$ for Human PET Imaging

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Abstract: Translation of new $^{18}\text{F}$-fluorination reactions to produce radio tracers for human positron emission tomography (PET) imaging is rare because the chemistry must have useful scope and the process for $^{18}\text{F}$-labeled tracer production must be robust and simple to execute. The application of transition metal mediators has enabled impactful $^{18}\text{F}$-fluorination methods, but to date none of these reactions have been applied to produce a human-injectable PET tracer. In this article we present chemistry and process innovations that culminate in the first production from $[^{18}\text{F}]{\text{fluoride}}$ of human doses of $[^{18}\text{F}]{\text{5-fluorouracil}}$ ($[^{18}\text{F}]{\text{5-FU}}$), a PET tracer for clinical research in oncology, by nickel-mediated oxidative fluorination with $[^{18}\text{F}]{\text{fluoride}}$ (Scheme 1).2d The synthesis of the $[^{18}\text{F}]{\text{5-FU}}$ nickel precursor was enabled by the first transmetalation reaction from arylboronic acid derivatives that yields isolated nickel $\sigma$-aryl complexes. The transmetalation reaction was developed because other methods for nickel $\sigma$-aryl complexes were inadequate. All previously reported syntheses of $[^{18}\text{F}]{\text{5-FU}}$ for human use have employed $[^{18}\text{F}]{\text{F}_2}$ gas,6 which is challenging to produce and handle and is less preferable as a starting material compared to $[^{18}\text{F}]{\text{fluoride}}$.7 Nickel $\sigma$-aryl complexes are employed as precatalysts,8 substrates for mechanistic investigation,9 and precursors for late-stage $^{18}\text{F}$-fluorination.10 Nickel $\sigma$-aryl complexes react with $[^{18}\text{F}]{\text{fluoride}}$ and oxidant in less than 1 min at 23 °C in the presence of water to afford $[^{18}\text{F}]{\text{aryl fluorides}}$.2d

Introduction

Transition-metal-mediated fluorination reactions have increased in scope and application, particularly for the synthesis of $^{18}\text{F}$-labeled molecules for positron emission tomography (PET).1−3 However, no such reaction has yet been translated to enable human PET imaging. Here we report the cGMP production of human doses of $[^{18}\text{F}]{\text{5-fluorouracil}}$ ($[^{18}\text{F}]{\text{5-FU}}$), a PET tracer for cancer imaging in humans. The first preparation of nickel $\sigma$-aryl complexes by transmetalation from arylboronic acids or esters was developed and enabled the synthesis of the $[^{18}\text{F}]{\text{5-fluorouracil}}$ precursor. Routine production of >10 mCi doses of $[^{18}\text{F}]{\text{5-fluorouracil}}$ was accomplished with a new instrument for azeotrope-free $[^{18}\text{F}]{\text{fluoride}}$ concentration in a process that leverages the tolerance of water in nickel-mediated $^{18}\text{F}$-fluorination.

Scheme 1. Strategy for the Synthesis of $[^{18}\text{F}]{\text{5-Fluorouracil}}$
their preparation, which we sought to address with this investigation. Nickel σ-aryl complexes are commonly prepared by oxidative addition of Ni(0) to aryl halides\textsuperscript{10} or by transmetalation from aryllithium, Grignard, and arylzinc reagents.\textsuperscript{12,13} However, the range of accessible nickel σ-aryl complexes is limited due to the strong reducing activity of Ni(0) reagents and the basicity and nucleophilicity of organometallic Li, Mg, and Zn precursors. There are no general methods for nickel σ-aryl preparation from more functional-group-tolerant p-block organometallics such as arylboron, arylltin, or arylsilicon reagents.\textsuperscript{14−16} The preparation of other first-row transition metal σ-aryl complexes from such reagents is rare.\textsuperscript{17} Development of a versatile nickel(II) transmetalation reagent, complex \(\text{LnNi}^{II}(\text{Aryl})X\), which is relevant because the desired \(\text{18F-}\)transmetalation from aryllithium, Grignard, and arylzinc precursors, with almost equivalent Ni−O bond lengths (2.05 and 2.07 Å).

Transmetalation occurs when \(\text{I}\) is treated with aryloboronic acid (or ester) in pyridine at 70 °C for 1 h, to generate the desired complexes (Scheme 4). The preparation of complexes 3a−3i represents the first example of preparative nickel(II) σ-aryl synthesis starting from boronic acids or esters. In addition to the previously inaccessible \(\text{[18F]}\text{5-fluorouracil}\) precursor 3a, diverse nickel(II) σ-aryl and hetearoyl complexes 3b−3i were synthesized. While the previous synthesis of pyridylsulfonamido nickel(II) σ-aryl complexes by oxidative addition with nickel(0) bicsyclooctadiene required a glovebox,\textsuperscript{24} synthesis by transmetalation with 1 does not and is conveniently set up at the bench. Purification of the nickel(II) σ-aryl complexes is accomplished without exclusion of water or oxygen. The transmetalation reaction likely proceeds by dissociation of 1 in pyridine solution, so that the oxygen atom of the nickel hydroxide will be coordinatively unsaturated and, therefore, be able to bond to boron for transmetalation.

Fluorination of the nickel(II) σ-aryl complexes 3a−3e occurs rapidly with \(\text{[18F]}\text{fluoride}\) and iodine(III) oxidant\textsuperscript{25} at 23 °C (Scheme 5). Incorporation of \(\text{18F}^+\) at the 3-position of a thiophene ring system was observed in the synthesis of \(\text{[18F]}\text{4c}\). Electron-rich O/S-heteroarenes are difficult to fluorinate on the same ring as the heteroatom with conventional nucleophilic radiofluorination chemistry.\textsuperscript{26} Furthermore, oxidative \(\text{[18F]}\)-fluorination occurs in the presence of a tertiary amine to afford \(\text{[18F]}\text{4d}\), which is notable because of the reactivity of amines.
Scheme 3. Synthesis of Nickel Hydroxide Cubane 1, a Reagent for Preparative Transmetalation

1.4 = 3).24 Nearly all of the remaining 18F eluted near the baseline of reverse-phase HPLC runs and at the baseline of silica TLC analysis runs, consistent with the presence of unreacted 18F fluoride that remains after the rapid fluoride resolubilization. Formulated 18F 5-FU was isolated with a yield range of 13.5−18.8 mCi (over three runs), starting from 4.0 μCi of 18F fluoride, with a synthesis time of about 1.5 h. A specific activity of 34.3 ± 18.0 Ci/μmol was observed for isolated 18F 5-FU.23 The percent yield of 0.92% ± 0.18% is low due to the RCC of 18F fluoride to 18F 4a (2.9% ± 0.5%, n = 3).24 Nearly all of the remaining 18F eluted near the beginning of reverse-phase HPLC runs and at the baseline of silica TLC analysis runs, consistent with the presence of unreacted 18F fluoride that remains after the rapid fluorination reaction ceases. The origin of low RCC may involve side reactions of the water- and base-sensitive biscationic iodine(III) oxidant or of high-valent nickel intermediates. Application of PPTS to buffer the 18F fluoride solution24 did not substantially improve the RCC (2.96%). Development of robust alternative oxidants or high-valent nickel σ-aryl fluorination precursors toward oxidation with iodine(III) oxidants.22 Formation of 18F 4d can be rationalized on the basis of oxidative fluorination being faster than amine oxidation and that product 18F 4d is spared from oxidation because the starting material 3d is present in slight excess compared to oxidant. Complexes 3g, 3h, and 3i, all of which contain unbound Lewis basic pyridyl substituents, did not undergo radiofluorination to the desired products. In contrast, bisalkoxypyrimidine complex 3a underwent fluorination to form 18F 4a in 15% radiochemical conversion (RCC). This result served as a starting point for our synthesis of 18F 5-FU from 18F fluoride.

Our ultimate goal was to prepare human doses of 18F 5-FU from 18F fluoride to enable PET imaging in oncology. Therefore, an isolated yield of at least 10 mCi was desired.7 Purity to match USP guidelines and production in a cGMP environment were also required. Oxidative fluorination of 3a with 18F fluoride affords 18F 4a, which is protected with hydrophobic tert-butyl groups that facilitate purification by conventional reverse-phase chromatographic methods. All previous preparations of human doses of 18F 5-FU started from 18F F2 gas and uracil, and a challenging separation of 18F 5-FU from uracil and other polar byproducts was required.8 Purified 18F 4a undergoes rapid and clean conversion to 18F 5-FU upon mixing with HCl(aq) in ethanol at room temperature. Neutralization of HCl with NaHCO3 forms a buffered saline solution for in vivo application.

Preliminary efforts to produce 18F 5-FU on a large scale by 18F fluorination of 3a with an established automation platform9 resulted in the isolation of 2.4 mCi of 18F 5-FU (0.2% yield, see the Supporting Information). The yield was prohibitively low for human dose production and was diminished by inefficient separation of 18F fluoride from the 2.4 mL 18O water in which it was produced in a cyclotron (26% yield of dry 18F fluoride). To increase the yield, a more efficient 18F fluoride concentration process was developed that afforded 81% yield of 18F fluoride (Scheme 6, top). This process is performed with an instrument (see the Supporting Information for full details) that leverages a miniaturized ion-exchange cartridge and microfluidic lines in order to elute 18F fluoride with a total of 4 μL of water. The 18F fluoride was eluted into 1 mL of dry MeCN to afford a 0.4% aqueous MeCN solution that has sufficiently low water content for oxidative 18F fluorination, without the need for evaporation steps. Because azeotropic drying and fluoride resolubilization were not necessary, time was saved and radiochemical yield improved.

The streamlined 18F fluoride concentration was incorporated into a cGMP process for the synthesis of 18F 5-FU (Scheme 6, bottom). Formulated 18F 5-FU was isolated with a yield range of 13.5−18.8 mCi (over three runs), starting from 1.4−1.8 Ci of 18F fluoride, with a synthesis time of about 1.5 h. A specific activity of 34.3 ± 18.0 Ci/μmol was observed for isolated 18F 5-FU.23 The percent yield of 0.92% ± 0.18% is low due to the RCC of 18F fluoride to 18F 4a (2.9% ± 0.5%, n = 3).24 Nearly all of the remaining 18F eluted near the beginning of reverse-phase HPLC runs and at the baseline of silica TLC analysis runs, consistent with the presence of unreacted 18F fluoride that remains after the rapid fluorination reaction ceases. The origin of low RCC may involve side reactions of the water- and base-sensitive biscationic iodine(III) oxidant or of high-valent nickel intermediates. Application of PPTS to buffer the 18F fluoride solution24 did not substantially improve the RCC (2.96%). Development of robust alternative oxidants or high-valent nickel σ-aryl fluorination precursors
may lead to a more efficient fluorination reaction. Nevertheless, at this stage the yield of $^{18}$F-5-FU is sufficient for human PET imaging because only 5–10 mCi is needed for a human dose. $^{18}$F-5-FU is obtained as a sterile, colorless saline solution, with >99% radiochemical purity, <10 μg of impurities not arising from USP formulation ingredients, and <0.1 ppm of Ni. The doses of $^{18}$F-5-FU pass quality control protocols for radiopharmaceuticals for human use and are validated for human in vivo application. No other preparation from $^{18}$F-fluoride of $^{18}$F-5-FU for human use has been reported.

**CONCLUSIONS**

The first preparative synthesis of nickel(II) σ-aryl complexes by transmetalation from arylboronic acids and esters was developed and enabled the synthesis of previously inaccessible complex 3a. Oxidative fluorination of 3a allowed for the first synthesis of $^{18}$F-5-fluorouracil from $^{18}$F-fluoride that affords doses suitable for in vivo use in humans. The nickel-mediated synthesis of $^{18}$F-5-fluorouracil represents the first clinical translation of transition-metal-mediated fluorination to enable PET imaging in humans. We aim to advance oncology clinical research by routinely supplying human doses of $^{18}$F-5-fluorouracil.

**EXPERIMENTAL SECTION**

**Synthesis of Nickel Hydroxide Cubane** 1. To a 1 L round-bottomed flask were added nickel(II) acetate tetrahydrate (2.80 g, 11.3 mmol, 1.00 equiv) and a Teflon-coated stirbar. The flask was fitted with a septum, and the headspace was filled with nitrogen. Anhydrous pyridine (114 mL) was added, and a blue solution was observed after mixing. To this solution was added 2-nitro-N-(2-(pyridin-2-yl)-phenyl)benzenesulfonamide $^2$ (4.00 g, 11.3 mmol, 1.00 equiv, as a solution in 166 mL of anhydrous pyridine) by cannula over 3 min, and a green-blue solution was observed. To this solution was added potassium tert-butoxide (2.53 g, 22.5 mmol, 2.00 equiv, as a solution in 80 mL of anhydrous pyridine) by cannula over 5 min. A yellow-green solution with a colorless precipitate was observed, which was stirred at 23 °C for 45 min, before being concentrated in vacuo (by rotary evaporation at 60 °C until all liquid pyridine was removed and then under high vacuum at 23 °C) to give a mixture of green and orange solids. These solid residues were ground with a spatula under anhydrous THF (130 mL) in order to dissolve the green solid. The mixture was filtered through Celite on a glass frit, which was then rinsed with anhydrous THF (2 × 20 mL). The THF filtrates were combined to give a dark green solution, which was treated dropwise with H2O (5.0 mL) over 30 min, with magnetic stirring, which caused a light green solid to precipitate. The solid was collected by filtration on a glass frit, rinsed with THF (2 × 20 mL), and dried in vacuo (0.2 Torr, 50 °C, 40 min; then 0.2 Torr, 150 °C, 2 h) to afford 2.66 g of the title compound (as a solvate with 4 water molecules) as a green solid (50% yield). NMR spectroscopy: $^1$H NMR (600 MHz, pyridine-$d_5$, 23 °C, δ): 46.1, 45.2, 44.8, 44.5, 43.0, 41.8, 40.9, 40.7, 39.6, 39.4, 39.2, 37.4, 36.1, 33.6, 33.1, 32.2, 30.4, 29.4, 24.4, 22.0–19.0, 20.3, 19.9, 19.6, 19.4, 19.2. DOI: 10.1021/acs.organomet.6b00059 Organometallics 2016, 35, 1008–1014
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Scheme 6. cGMP Synthesis of \([^{18}F\)]5-Fluorouracil (>10 mCi) for Use in Human PET Imaging$^c$

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\text{CNMR analysis was not performed.}
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Based on decay-corrected measurement of trapped activity on a microcartridge, relative to initial \([^{18}F\)]fluoride in \([^{18}O\)]water. $^b$Three elutions were applied, with 0.5 μmol of K$_3$PO$_4$ and 3.0 μmol of 18-crown-6 (18c6) in 6.2 μL of MeCN/H$_2$O (4/1, v/v) per elution. $^c$Based on decay-corrected measurement of eluted activity relative to trapped activity. $^d$Yield (not decay corrected) based on \([^{18}F\)]fluoride (range: 7.4–14 mCi) in 2.4 mL of water at the start of synthesis. Starting from 1.7 Ci of \([^{18}F\)]fluoride, the yield (not decay corrected) was 79%. $^e$SPE: solid phase extraction; see Supporting Information for full purification details. $^f$Isolated yield (not decay corrected) is based on activity of \([^{18}F\)]fluoride (range: 1.4–1.8 Ci) in \([^{18}O\)]water at the start of synthesis.

General Procedure for Preparation of Complexes 3a–3i by Transmetalation. Complex 1 (142 mg, 75.0 μmol, 0.250 equiv) and arylboron reagent (1.0 equiv) were dissolved in dry pyridine (12 mL) under N$_2$. The mixture was heated with stirring at 70 °C for 1 h. After cooling to 23 °C, hexanes (120 mL) was added, and the precipitated product was collected by filtration on Celite, dissolved in dichloromethane/pyridine (95:5, v/v), and then passed through the Celite. The filtrate was concentrated in vacuo to afford a residue, which was purified by chromatography on SiO$_2$/K$_2$CO$_3$ (9:1 w/w), eluting with MeCN/H$_2$O (4:1, v/v) per elution. The eluted \([^{18}F\)]fluoride was released with three elutions of 0.5 μmol of K$_3$PO$_4$ and 3.0 μmol of 18-crown-6 in 6.2 μL of MeCN/H$_2$O (4/1, v/v) per elution. The eluted \([^{18}F\)]fluoride was diluted in a vial containing 1.0 mL of dry MeCN and 10.0 mg of 18-crown-6, and the resulting solution was rapidly added to a solid mixture of complex 3a (10.0 mg) and PhI(4-OMe-pyridine)$_2$(OTf)$_2$ (10.0 mg). After 1 min at 23 °C, the reaction solution was diluted with 4.0 mL of water and purified by semipreparative HPLC. The collected fractions were passed through two C18 silica cartridges, which were washed with water and then eluted with ethanol into a vial with concentrated HCl(aq). For some complexes, the solvents used in the workup procedure were varied (see the Supporting Information for full details).

General Procedure for Preparation of \([^{18}F\)]Aryl Fluorides \([^{18}F\]F)4a–\([^{18}F\]F)4e. In a nitrogen-filled glovebox, to an oven-dried 1 dram (4 mL) glass vial were added nickel(II) aryl complex 3 and PhI(4-OMe-pyridine)$_2$(OTf)$_2$ in a 1:1 mass ratio, and the two solids were mixed gently with a metal spatula to give a homogeneous admixture. To an oven-dried 1 dram glass vial was added 2.0 mg of this admixture, and the vial was sealed with a screw cap with a Teflon-lined septum insert under nitrogen and removed from the glovebox. An \([^{18}F\)]fluoride solution with 18-crown-6 and potassium phosphate tribasic was prepared as follows. To an oven-dried 1 dram (4 mL) glass vial was added dry 18-crown-6 (20.0–44.0 mg) under nitrogen, and this vial was sealed with a Teflon-lined cap. The vial was opened under air, dry MeCN (1.0 mL per 10.0 mg of 18-crown-6) was added quickly, and the vial was sealed and mixed until all 18-crown-6 had dissolved. The vial was opened, aqueous potassium phosphate (0.561 M K$_3$PO$_4$ in water, 2.0 μL per 10.0 mg of 18-crown-6) was added quickly, and the vial was sealed, shaken, and then vortexed for 10 s. The vial was opened, aqueous \([^{18}F\)]fluoride from the cyclotron (3.0 μL per 10.0 mg of 18-crown-6) was added quickly, and the vial was sealed, shaken, and then vortexed for 10 s. A portion of the resulting solution (0.50 mL) was added as rapidly as possible, with a 1 mL plastic syringe with an 18 G disposable metal needle, to the vial containing nickel(II) aryl complex and oxidant through the septum. After 1 min at 23 °C, the radiochemical conversion was then measured by radioTLC, and HPLC analysis was performed to confirm the formation of the title compound.
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00059.

Detailed experimental procedures and spectroscopic data for all new compounds (PDF)
Crystallographic data for 1 (CIF)
Crystallographic data for 2 (CIF)
Crystallographic data for 3a (CIF)

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**Notes**
The authors declare no competing financial interest.

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