Supporting Information

A New Class of S_N2 Reactions Catalyzed by Protic Solvents: Facile Fluorination for Isotopic Labeling of Diagnostic Molecules

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Synthesis of 2-[^{18}F]Fluoro-2-deoxyglucose ([^{18}F]FDG). [^{18}F]Fluoride (370 MBq/ 0.1 mL) was trapped on QMA (Waters, USA), and it was eluted with 12 mg of Cs_2CO_3, 22 mg of Krytofix$_{222}$, 300 μL CH_3CN and 300 μL H_2O solution into the reactor. After addition of 20 mg of mannose triflate in 0.1 μL CH_3CN and 500 μL of *t*-BuOH, [^{18}F]fluorination was carried out at 100 °C for 15 min. The [^{18}F]fluorination yield was 96.4±1.8% by radioTLC analysis. After evaporation of the solvent, the intermediate tretraacetate was hydrolyzed with 2 N NaOH 1 mL at room temperature for 5 min. The product was neutralized and purified by chromatography with IC-H (Alltech, USA), C18 (Waters, USA) and Alumina N (Waters, USA) cartridges. The decay corrected radiochemical yield was 85.4±7.8, and synthesis time was 30.5±5.8 min. The radiochemical purity was 98.1±1.4%. (n = 10)

Synthesis of 3-Deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT). We used the GE TracerLab FX module for [^{18}F]FLT synthesis. 37 GBq/1 mL of [^{18}F]fluoride was trapped on PS-HCO_3 cartridge (Machery-Nagel, Germany) on the chemistry module. After elution of [^{18}F]fluoride into the reaction vial with 0.3 mL H_2O, 0.3 mL CH_3CN and 10 μL of $TBAHCO_3$, the activity was dried with 1 mL of CH_3CN with heating at 100 °C under vacuum and N_2 supply. After drying, 20 mg of (5'-*O*-DMTr-2'-deoxy-3'-*O*-nosyl-β-D-threo-pentofuranosyl)-3-*N*-BOC-thymine in 0.8 mL *t*-BuOH and 0.2 mL of CH_3CN was added to reaction vial. [^{18}F]Fluorination was performed at 120 °C for 10 min, and the solvent was evaporated

under N_2 supply and vacuum at 90 °C. HCl (1 N, 1 mL) was added for hydrolysis, which was performed at 85 °C for 5 min. After neutralization with 2 N NaOH 0.5 mL and 1 mL citrate buffer, the reaction mixture was purified by HPLC with EtOH:H_2O=10:90 at 5 mL/min. The decay-corrected radiochemical yield was 65.5±5.4%, and radiochemical purity was 98.1±1.2%. Total synthesis time was 70.5±10.5 min. (n = 10)

Synthesis of *N*-2-[^{18}F]Fluoropropyl-2β-carbomethoxypropyl-3β-(4-iodophenyl)nortropane ([^{18}F]FP-CIT). We used the GE TracerLab FX module for [^{18}F]FP-CIT synthesis. [^{18}F]Fluoride (37 GBq/1 mL) was moved to the reaction without any separation step between [^{18}O]H_2O and [^{18}F]fluoride. After addition of 1 mL CH_3CN, 0.1 mL H_2O and 8 μL of TBAOH (40% solution), the mixture was completely dried under vacuum and heating at 100 °C. The precursor (4 mg) of *N*-[3'-(mesyloxy)propyl]-2β-carbomethoxy-3β-(4'-iodophenyl)nortropane in 0.1 mL CH_3CN and 0.9 mL anhydrous *t*-BuOH was added to the reactor, and [^{18}F]fluorination proceeded at 100 °C for 20 min. The reaction mixture was diluted with 2 mL of MeOH, and the mixture was injected onto an HPLC column for purification. The purified radiolabeled product was diluted 100 mL of H_2O and [^{18}F]FP-CIT was trapped on C_{18} cartridge. After washing of cartridge with 10 mL H_2O, [^{18}F]FP-CIT was eluted with 1 mL EtOH and 4 mL of H_2O. HPLC condition was MeOH:H_2O:NEt_3=750:250:2 solution at 4 mL/min. The decay-corrected radiochemical yield was 35.8±5.2%, and radiochemical purity was 98.5±1.2%. Total synthesis time was 80.8±10.5 min (n = 14).

Synthesis of 1-[^{18}F]Fluoro-3-(2-nitroimidazol-1-yl)propan-2-ol ([^{18}F]FMISO). We used the GE TracerLab MX module for [^{18}F]FMISO synthesis. A disposable cassette was modified as previously reported[S1]; this cassette has 4 reagent supply vials, designated as blue, red, yellow, and green. We added 7 mL of CH_3CN to blue vial, added 10 mg of 3-(2-nitroimidazol-1-yl)-2-*O*-tetrahydropyranyl-1-*O*-toluenesulfonylpropanediol as precursor in 0.2 mL CH_3CN and 1.8 mL of *t*-amyl alcohol, added 0.2 mL of CH_3CN and 2.8 mL of 1 N HCl, and added 2 mL 2 N NaOH and 1.8 mL of citrate buffer. [^{18}F]Fluoride (37 GBq/1 mL) was trapped on PS-HCO_3 cartridge (Machery-Nagel, Germany) on the chemistry module. After elution of [^{18}F]fluoride into the reaction vial with 0.3 mL H_2O, 0.3 mL CH_3CN and 10 μL of TBAHCO_3, the activity was dried with CH_3CN from the blue vial with heating at 100 °C under vacuum and N_2 supply. After drying, precursor from the red vial was added to the reaction vial. [^{18}F]Fluorination was performed at 120 °C for 15 min, and the solvent was then evaporated under N_2 supply and vacuum at 90 °C. HCl solution from green vial was added for hydrolysis, which was

performed at 85 °C for 5 min. After neutralization with buffer solution from the yellow vial, the reaction mixture was purified by HPLC. HPLC conditions were EtOH:H_2O=5:95 solution at 5 mL/min. The decay-corrected radiochemical yield was 69.6±1.8%, and radiochemical purity was 98.1±1.3%. Total synthesis time was 70.0±12.5 min. (n = 10)

The Pictures of Formations of Gel-like Solid during the Reaction. In same concentrations, the higher yield obtained (cases (a) and (b)), the more gel-like solid formed. In case of (c), as the leaving group is iodide instead of sulfonate, there is no hydrogen bond with *t*-butanol and iodide, consequently less forming gel-like solid.

(a) 1 min 30 min 2.5 h

(b) 1 min 2 h

(c) 1 min 4 h 24 h

(a) entry 8, Table 1

(b) entry 1, Table 2

(c) entry 2, Table 2

References in SI

S1. S. J. Oh, D. Y. Chi, C. Mosdzianowski, J. Y. Kim, H. S. Kil, S. H. Kang, J. S. Ryu, D. H. Moon, *Nucl. Med. Biol.* **2005**, *32*, 899.