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DMSO increases radioiodination yield of radiopharmaceuticals

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Abstract

A high-yield radioiodination method for various types of molecules is described. The approach employs DMSO as precursor solvent, a reaction ratio of 2–5 precursor molecules per iodine atom, 5–10 μg oxidant, and a 10–25 μl reaction volume. The solution is vortexed at room temperature for 1–5 min and progress of the reaction is assessed by HPLC. Radioiodinated products are obtained in ≥95% yield and meet the requirements for radiotracer imaging, biodistribution studies, and molecular and cellular biology research.
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Keywords: DMSO; Radioiodination; No carrier added; High yield

1. Introduction

Radioactive isotopes of iodine possess excellent characteristics for non-invasive imaging (^{123}I, ^{124}I), radiotracer studies (^{125}I), tumor therapy (^{125}I, ^{131}I), and molecular biology research. For many types of molecules, radioiodination presents problems of yield, purification, and stability of the radiolabeled product (Prusoff, 1959; Mannan et al., 1991; Tjuvajev et al., 1993; Van den Abbeele et al., 1996; Kumar et al., 2005). In a standard procedure, radioiodide is oxidized and added to the molecule to be labeled. The iodine cation then reacts with the active position (e.g., phenol, hydroxyl, tributyltin, benzamino or vinyl moiety) on the molecule.

During our studies in which radioiodination of water-insoluble precursors in aqueous medium often produces low yields, we observed that dissolving these compounds in DMSO improves the efficiency of radioiodination. While the original purpose of the addition of DMSO was the solubilization of water-insoluble compounds, we have since realized that the presence of DMSO dramatically increases the radioiodination yields of various water-soluble as well as water-insoluble organic and non-organic molecules.

2. Materials and methods

2.1. General methods

Reagents were obtained from Sigma-Aldrich Chemical Company. HPLC separations were performed on a reversed-phase Zorbax SB C_{18} column, 9.4 mm × 250 mm (Agilent Technology), at a flow rate of 3 mL/min, with UV absorption (Waters 486 detector) and γ-ray detection (gamma-ram, IN/US Systems) used to analyze the eluates. Na^{125}I was purchased from GE Healthcare Life Sciences (17.4 Ci/mg [643.8 GBq/mg], 453 mCi/mL [16.76 GBq/mL]) in 0.1 N sodium hydroxide, Na^{123}I from MDS Nordion as a no-carrier-added powder, and Na^{131}I from PerkinElmer Life and Analytical Sciences (16.5 Ci/mg [610.5 GBq/mg], 10 mCi/mL [370 MBq/mL]) in 0.1 N sodium hydroxide.

2.2. Synthesis of radiolabeled (^{123}I/^{125}I) 5-iodo-2′-deoxyuridine (^{123}IUdR/^{125}IUdR)

A stock solution of tributylstannyl-2′-deoxyuridine (SnUdR, 20 μg/μL DMSO) was prepared. Phosphate-buffered saline (PBS, 10 μL, 0.01 M, pH 7.4), SnUdR (1 μL, 1 μg/μL DMSO, methanol, or water), and Na^{125}I (0.5–3 μL) were placed in a reaction vial coated with 1,3,4,6-tetrachloro-3α,6α-diphenylglycouril (Iodogen, 10 μg). When dichloromethane was used as precursor solvent, SnUdR (1 μg/20 μL solvent) also adhered to the

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vial, and the rest of the conditions were the same. The mixture was vortex mixed at ambient temperature for 1 min. Progress of the reaction was checked by C_{18} HPLC with isocratic elution (3 mL/min) using 75% A (phosphate buffer, 0.05 M, pH 2.5) and 25% B (methanol) for 16 min.

For ^{123}IUdR, dry Na^{123}I (10 mCi) was dissolved in HCl (10 μL, 0.1 M) and sodium thiosulfate (1 μL, 1 μg/μL water) was added. The mixture was shaken for 1 min and NaOH (9 μL, 0.1 M) was then introduced, and the solution was vortex mixed for 10 s. Radioiodination then proceeded as above.

2.3. Synthesis of radiolabeled (^{123}I/^{125}I/^{131}I) ammonium 2-(2′-phosphoryloxyphenyl)-6-iodo-4-(3H)-quinazolinone ($^{123}IQ_{2-P}$/$^{125}IQ_{2-P}$/$^{131}IQ_{2-P}$)

A mixture of $SnQ_{2-P(I)}$ and SnQ_{2-P} (0.5 mg) was synthesized (Ho et al., 2002). ESI-HRMS $[M+H]^+$ calcd for $SnQ_{2-P(I)}$, 589.1296, found, 589.1296; calcd for SnQ_{2-P}, 609.1539, found, 609.1539; ^{31}P NMR for $SnQ_{2-P(I)}$, −16.922 ppm, and for SnQ_{2-P}, −2.958 ppm. The mixture was dissolved in DMSO (100 μL), kept overnight until $SnQ_{2-P(I)}$ was converted to SnQ_{2-P} (at which point ^{31}P NMR for solution −2.958 ppm), and then diluted to a stock solution of SnQ_{2-P} (20 μg/μL DMSO.

Phosphate-buffered saline (10 μL, 0.01 M, pH 7.4) and SnQ_{2-P} (1 μL, 1 μg/μL DMSO, methanol, or water) were placed in a reaction vial coated with Iodogen (10 μg), and Na^{123}I/Na^{125}I/Na^{131}I (2.0 μL) was added. The mixture was vortex mixed at ambient temperature for 3 min and analyzed by C_{18} HPLC using phosphate buffer (0.05 M, pH 2.5) as A and methanol as B, going from 10% A to 100% B in 7 min and remaining at 100% B for an additional 9 min (3 mL/min).

2.4. Synthesis of iodinated (^{125}I/^{127}I) rhodamine 123 (^{125}I-Rhod/^{127}I-Rhod)

2.4.1. Synthesis of mono- and di-iodorhodamine 123

To a reaction vial containing rhodamine 123 (4.5 mg, 11.85 μmol) in ammonium acetate (0.5 mL, 0.2 M), peracetic acid (0.2 mL of 2%, 52.6 μmol) and NaI (2 mg/0.1 mL water, 13.3 μmol) were added. After vortex mixing for 2 h at room temperature, the reaction mixture was evaluated by HPLC, and iodorhodamine 123 (I-Rhod) and di-iodorhodamine 123 (I_2-Rhod) were identified by mass spectroscopy. ESI-HRMS calcd for $C_{21}H_{15}N_2O_3I$ $[M+H]^+$, 471.0212, found, 471.0206; calcd for $C_{21}H_{15}N_2O_3I_2$ $[M+H]^+$, 596.9176, found, 596.9172.

2.4.2. Synthesis of radiolabeled (^{125}I) rhodamine 123 (^{125}I-Rhod)

A stock solution of Rhod (3 μg/μL DMSO, methanol, or water) was prepared. Copper chloride solution (2 μL, 50 μg/μL water, pH 4.0), Rhod (0.5 μL DMSO, methanol, or water, 3 μg/μL), and water (20 μL) were placed in a reaction vial. *N*-chloro-*p*-toluenesulfonamide sodium salt (chloramine-T [ChT], 1 μL, 10 μg/μL) and Na^{125}I (0.5–2 mCi) were added. The mixture was vortex mixed for 5 min and then analyzed by C_{18} HPLC using phosphate buffer (0.05 M, pH 2.5) as A and methanol as B, going from 10% A to 100% B in 7 min, and remaining at 100% B for an additional 9 min (3 mL/min).

2.5. Synthesis of radiolabeled (^{123}I/^{125}I/^{131}I) 2-iodo-8-methyl-8H-quino[4,3,2-kl]acridine (^{123}I-Acr/^{125}I-Acr/^{131}I-Acr)

8,13-Dimethyl-2-(tributylstannyl)-8*H*-quinolino[2,3,4-*mn*]acridin-13-ium iodide (SnAcr) was kindly provided by C.A. Laughton, University of Nottingham, UK. A stock solution of SnAcr (20 μg/μL DMSO) was prepared. Phosphate-buffered saline (8 μL, 0.1 M, pH 5.0) and SnAcr (1 μL, 2 μg/μL DMSO, methanol, or water) were placed in a reaction vial and Na^{123}I/Na^{125}I/Na^{131}I (2.0 μL) and ChT (2 μL, 5 μg/μL water) were added. After vortex mixing at ambient temperature for 15 min, the reaction mixture was analyzed by C_{18} HPLC using phosphate buffer (0.05 M, pH 2.5) as A and methanol as B, going from 10% A to 100% B in 7 min, and remaining at 100% B for an additional 9 min (3 mL/min).

2.6. Synthesis of radiolabeled (^{125}I) Bolton–Hunter reagent (^{125}I-BH)

Crystalline *N*-succinimidyl 3-(4-hydroxyphenyl)propionate (Bolton–Hunter [BH] reagent) was dissolved in DMSO or methanol (1 μg/μL). To a reaction vial coated with Iodogen (5 μg), BH reagent in DMSO or methanol (1 μL) and PBS (10 μL, 0.01 M, pH 7.4) were added, followed by Na^{125}I (1 μL, 1 mCi/2.5 μL). When dichloromethane was used as precursor solvent, BH reagent (10 μL, 0.1 μg/μL solvent) also adhered to the vial, and the rest of the conditions were the same. The mixture was vortex mixed at ambient temperature for 1 min and was analyzed by C_{18} HPLC using phosphate buffer (0.05 M, pH 2.5) as A and methanol as B, going from 10% A to 100% B in 7 min, and remaining at 100% B for an additional 9 min (3 mL/min).

2.7. Radioiodination (^{125}I) of immunoglobulin G (^{125}I-IgG)

Immunoglobulin G (20 μg/2 μL DMSO or 20 μg/4 μL water) was placed in a vial coated with Iodogen (20 μg), and sufficient PBS (0.01 M, pH 7.4) to make the reaction volume 24 μL and Na^{125}I (1 μL, 1 mCi/2.5 μL) were added. The mixture was vortex mixed at ambient temperature for 1 min, then transferred to another vial lacking Iodogen. The product was identified by HPLC (Bio-Sil column, 300 mm × 7.8 mm) with isocratic elution using phosphate buffer (0.05 M, pH 6.8) at 1 mL/min.

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