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Introduction

In the previous papers,1,2) we reported that 2-deoxy-2-[18F]fluoroacetamido-D-glucopyranose (N-fluoroacetyl-D-glucosamine) (I), a potential diagnostic imaging agent, was synthesized by a rapid, one-pot synthetic method, starting from [18F]fluoride and ethyl bromoacetate, and its distribution of animal body was measured for cancer diagnosis. The synthetic method was accomplished by a combination of halogen exchange, alkaline hydrolysis and condensation.

As a part of the synthetic study of hexopyranoses labelled with positron emitting radionuclides, an improved synthetic method of I will be reported here.

Results and Discussion

Our interest in preparing additional amino sugars labelled with fluorine-18 led us to reinvestigate the one-pot synthesis of I. The procedure reported previously consisted of halogen exchange, alkaline hydrolysis, and condensation. The synthetic pathway of I from ethyl bromoacetate is shown in Fig. 1. The radiochemical yield of I based on [18F]fluoride was 9.1%.1) It seemed that one reason for the low yield of I was incomplete hydrolysis of ethyl [18F]fluoroacetate due to a shortage of the amount of alkali used as well as of reaction time. Dependence of the hydrolysis of the ester on reaction time was then reevaluated in detail. For the conversion of the ester into the free acid with 1 N aq. potassium hydroxide, the optimal reaction time was 5 min. The analytical high performance liquid chromatographic (HPLC) chromatograms are shown in Fig. 2. This improved hydrolysis is then applied to prepare compound I.
Fluoride was produced by the $^{18}$O(p, n)$^{18}$F nuclear reaction from a circulating 20%-enriched $^{18}$O water target using the Tohoku University Cyclotron. The $^{18}$F nuclide thereby formed was converted to potassium [18F]fluoride with potassium carbonate. After addition of 4,7,13,16,21,24-hexaoxa-1,10-diaza[bicyclo[8.8.8]hexacosan (Kryptofix 222), the resulting mixture was submitted to the improved one-pot synthesis to afford the desired sugar (I) in a 17% radiochemical yield. The yield was about two times that reported previously. The total synthesis time and radiochemical purity were ca. 80 min and >98%, respectively. Compound I has been submitted to animal testings (biodistribution studies, positron emission tomography, and autoradiography) and the results will be reported elsewhere.

**Experimental**

Kryptofix 222 and plates of thin-layer chromatography (TLC) were purchased from E. Merck AG. Ethyl bromoacetate was from Wako Chemical Ltd. and distilled under a reduced pressure. Other reagents were obtained commercially (Wako) and used without further purification. The purity of each compound was always checked by TLC. HPLC analyses were carried out either with Waters Assoc. model 6000 equipped with a refractive index detector or with a Waters Assoc. model 4500 equipped with a radioactivity monitor. The packed columns [Nova-pak (8 × 100 mm), Waters Assoc. USA and YMC-Pack PA-23 (10.0 × 250 mm), Yamamura Chem. Lab. Co., Jpn] were used in HPLC.

[18F] Fluoride was produced from the proton bombardment of 20% enriched [18O] water. To the aqueous solution of [18F] fluoride, a mixture of aqueous potassium carbonate (33 μmol/0.2 ml) and Kryptofix 222 (72 μmol, 27 mg) was added. The resulting solution was dried at 90°C in a stream of dry nitrogen gas. To the residue, a solution of ethyl bromoacetate (0.2 mmol, 33.4 mg) in acetonitrile (1 ml) was added. The resulting mixture was heated at 82°C for 10 min with stirring and cooled. After addition of 1 N aqueous potassium hydroxide (0.4 ml), the reaction mixture was heated for additional 5 min. To the resulting mixture, a mixture of hydrochloride of 2-amino-2-deoxy-D-glucopyranose (II) (0.2 mmol, 43.2 mg) and dicyclohexylcarbodiimide (0.5 mmol, 103 mg) in pyridine (0.5 ml) was added. The mixture was heated at 82°C for 20 min with stirring, diluted with water (2 ml) to decompose an excess of the carbodiimide, and filtered. The filtrate was washed with ethyl ether (10-ml x 2) using a Mixxor (liquid-liquid extraction system; Lidx Co. Ltd., Israel), and evaporated to dryness under a reduced pressure. The residue was dissolved in water (0.5 ml) and the solution was chromatographed through an ion retardation resin (AG11-A8, 2 ml) column using water as an elution solvent. The eluate was then mixed with an approximately equal volume of acetonitrile, passed through a
Millex-HA filter unit (Millipore), and eluted with aqueous acetonitrile (1:1, v/v). The effluent was concentrated to 1/10 of its original volume and then subjected to preparative HPLC (Fig. 3). A radioactivity peak corresponding to I was then collected and the identity of the peak was confirmed by analytical HPLC. The total synthesis time, the radiochemical yield, and purity of I were ca. 80 min, 17%, and >98%, respectively.

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References


\[ \text{BrCH}_2\text{COOEt} \rightarrow { }^{18}\text{FCH}_2\text{COOEt} \rightarrow { }^{18}\text{FCH}_2\text{COOH} \]

Fig. 1. Synthetic pathway of 2-deoxy-2-[18F]fluoracetamido-D-glucopyranose (I) from ethyl bromoacetate.
Fig. 2. Time dependence of the hydrolysis of ethyl $^{18}$Ffluoroacetate. Hydrolysates were analyzed with HPLC.

Fig. 3. Preparative HPLC chromatogram of reaction mixture. The main peak corresponds to compound I.