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A Concise One-pot Synthesis of [^{18}F]Fluoromisonidazole from (2R)-(−)-Glycidyl Tosylate

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SUMMARY

A rapid, one-pot synthesis of [^{18}F]fluoromisonidazole (1*H*-1-(3-[^{18}F]fluoro-2-hydroxypropyl)-2-nitroimidazole) (1) starting from [^{18}F]fluoride and (2R)-(−)-glycidyl tosylate (2) is described. The total time required for the synthesis, the radiochemical yield, and purity of the titled compound are *ca.* 80 min, 20%, and >98%, respectively.

Key Words: [^{18}F]Fluoromisonidazole, 1*H*-1-(3-[^{18}F]fluoro-2-hydroxypropyl)-2-nitroimidazole, one-pot synthesis, (2R)-(−)-glycidyl tosylate, [^{18}F]fluoride.

INTRODUCTION

Misonidazole and its congeners are metabolically trapped in cells that are alive but at low oxygen tension, and are known to be a marker of ischemic cells (1). [^{18}F]Fluoromisonidazole (1*H*-1-(3-[^{18}F]fluoro-2-hydroxypropyl)-2-nitroimidazole) (1) has been developed and studied for in vivo imaging of hypoxic tissue of tumor that is important as a radiotherapy-resistant component, and of ischemic myocardium using positron emission tomography(PET) (2, 3).

In previous papers (4, 5), we reported that the reaction of [^{18}F]fluoride with ethyl tosyloxyacetate in presence of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan (Kryptofix 222) afforded ethyl [^{18}F]fluoroacetate. As part of the investigation of the synthesis of positron emitting compounds for PET study, this paper describes the rapid one-pot synthesis of (1) from (2R)-(−)-glycidyl tosylate (2).

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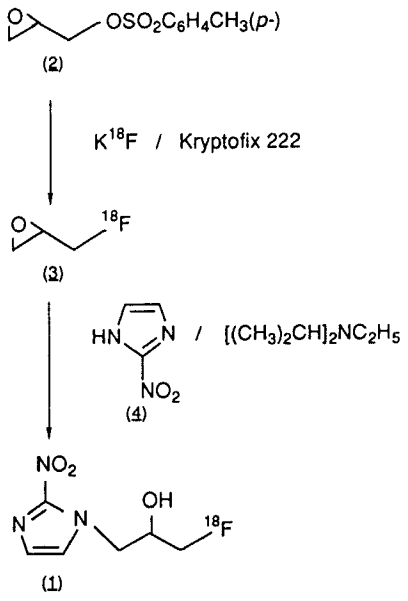

Fig. 1. Synthetic Pathway of [^{18}F]Fluoromisonidazole (1) from (2R)-(−)-Glycidyl Tosylate (2)

RESULTS AND DISCUSSION

The title compound (1) has been reported by Grierson *et al.* (6), by Hwang *et al.*, (7) and by Lim and Berridge (8), respectively. Recently, application of microwave heating to its synthesis has been published (9). These methods presented have their individual advantages and disadvantages. We therefore investigated the method to establish a new one-pot synthesis of (1) from tosylate (2) using a common V-vial. The synthetic pathway is shown in Fig. 1. Briefly, [^{18}F]fluoride is first incorporated into epi[^{18}F]fluorohydrin (3) which is subsequently converted into (1) by coupling to 2-nitroimidazole (4).

[^{18}F]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 (10). A 5-ml V-vial equipped with a Teflon-faced rubber septum and a magnetic spin vane was charged with the aqueous solution of [^{18}F]fluoride thereby prepared and potassium carbonate. After addition of Kryptofix 222, the resulting mixture was evaporated to dryness. The residue and (2) were then heated with stirring to give (3). Yields were optimum at 90 °C for 20 min reaction. Epifluorohydrin (3) was then coupled with (4) in presence of *N,N*-diisopropylethylamine (9), passed through two Sep-Pak Plus Silica cartridges and a Sep-Pak C_{18} cartridge, and subjected to preparative high performance liquid chromatography (HPLC) to afford the title compound (1) in a 20% radiochemical yield. The total synthesis time and radiochemical purity are *ca.* 80 min and >98%, respectively. The HPLC chromatogram of the reaction mixture and retension times of (1) in HPLC systems are shown in Fig. 2 and Table 1, respectively.

Additionally, this method for the preparation of the title compound (1) is suitable for automated synthesis because the simple apparatus and easy operation have been used. All reagents used in this paper were commercially available. Medical uses are being investigated and the results will be reported elsewhere.

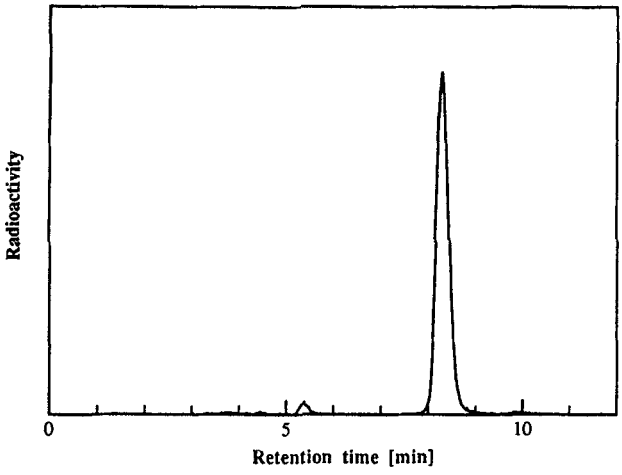

Fig. 2. Radio-preparative HPLC Chromatogram of Reaction Mixture. The large peak is the title compound (1), and chromatographic conditions are shown as Run 2 in Table 1.

EXPERIMENTAL

(2R)-(−)-Glycidyl tosylate (2), 2-nitroimidazole (4), and *N,N*-diisopropylethylamine were purchased from Aldrich Chemical Company, Inc., USA. Kryptofix 222 was from E. Merck AG, Ger. and used without further purification. The other reagents were obtained commercially from Wako Chem. Ltd. Japan. HPLC analyses were carried out either with a Waters Assoc. USA model 6000 equipped with a UV(254 nm) detector and a refractive index detector or with a Waters Assoc. model 4500 equipped with a UV detector and a radioactivity monitor. The packed columns (YMC-Pack A-303 and A-324, Yamamura Chem. Lab. Co., Japan) were used in HPLC.

Table 1. Retention Times of [^{18}F]Fluoromisonidazole (1) in HPLC Systems.

Run	Column (Size, mm)	Flow Rate (ml/min)	Retention Time (min)
1	YMC-Pack A-303 (4.6 × 250)	1.0	8.0
2	YMC-Pack A-324 (10.0 × 300)	5.0	8.3

Mobile phase(Ratio): H_2O/C_2H_5OH(92/8, v/v)

[^{18}F]Fluoromisonidazole (1).

[^{18}F]Fluoride was produced from the proton bombardment of 20% enriched [^{18}O]-water (10). A 5-ml V-vial equipped with a Teflon-faced rubber septum and a magnetic spin vane was charged with the aqueous solution of [^{18}F]fluoride and a mixture of aqueous potassium carbonate (33 μmol/0.2 ml) and Kryptofix 222 (27 mg, 72

μmol). The resulting solution was dried at 90 °C in a stream of dry nitrogen gas. To the residue, a solution of (2) (15 mg, 66 μmol) in a mixture of dimethyl sulfoxide (0.2 ml) and acetonitrile (0.3 ml) was added. The resulting mixture was heated at 90 °C for 20 min with stirring and then coolded. After addition of a mixture of (4) (15 mg, 130 μmol) and *N,N*-diisopropylethylamine (0.15 ml), the mixture was then heated at 115 °C for 15 min with stirring, cooled and diluted with dichloromethane (0.5 ml). The suspension was passed through two Sep-Pak Plus Silica cartridges (Waters Chromatography Div. Milipore Co. USA) connected in series and then eluted with dichloromethane. The eluting solution was evaporated to dryness under reduced pressure, and the residue was dissolved in a mixture of ethanol and water (10/90, v/v)(1 ml). The resulting mixture was then passed through a Sep-Pak C_{18} cartridge (Waters) and eluted with the same solvent. The eluting solution was concentrated to 1/10 of its original volume and then subjected to preparative HPLC. The chromatographic conditions are shown as Run 2 in Table 1.

A radioacitivity peak corresponding to (1) was then collected and the identity of the peak was confirmed by analytical HPLC (Run 1 shown in Table 1). Total synthesis time, the radiochemical yield, and purity are *ca.* 80 min, 20%, and >98% (as judged by HPLC), respectively.

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