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Synthesis of No-Carrier-Added [^{18}F]Fluoroacetate

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SUMMARY

To synthesize no-carrier-added potassium [^{18}F]fluoroacetate, *O*-mesyl glycolate ethyl ester and *O*-tosyl glycolate ethyl ester were synthesized as precursors. These precursors were radiolabeled by reacting with dried tetrabutylammonium [^{18}F]fluoride in the presence of tetrabutylammonium bicarbonate. *O*-Mesyl glycolate ethyl ester showed higer ^{18}F incorporation (77.6% at 100 °C) than *O*-tosyl glycolate ethyl ester (63.2% at 100 °C). Resulting [^{18}F]fluoroacetate ethyl ester was hydrolyzed quantitatively by heating in 1 M potassium hydroxide solution. The [^{18}F]fluoroacetate was adsorbed to strong anion exchange resin and washed with excess water. Following elution with 1 M sodium bicarbonate solution and passing through Sep-Pak neutral alumina column, the [^{18}F]fluoroacetate was obtained with 24.5% recovery (non-decay-corrected). Total labeling time from drying ^{18}F to final product was 70 to 90 min.

Key Words: Fluoroacetate, ^{18}F, oxygen metabolism, positron emitter, methanesulfonyl ethyl glycolate, toluenesulfonyl ethyl glycolate

INTRODUCTION

Fluoroacetate has been used as a rodenticide for the control of rat and rabbit populations. Once taken into the body, fluoroacetate behaves like acetate, being converted to fluoroacetyl-CoA. The fluoroacetyl-CoA enters citric acid cycle and is metabolized to fluorocitrate. The fluorocitrate strongly binds to aconitase and blocks TCA cycle, which is the proved mechanism of toxicity of fluoroacetate (1, 2). So, the [^{18}F]fluoroacetate has been suggested as a possible myocardial or cerebral oxidative metabolism imaging agent for positron emission tomography in stead of [^{11}C]acetate (3).

Production of [^{18}F]fluoroacetate has been reported using ethyl bromoacetate as a precursor (4, 5). In the paper, they used carrier-added [^{18}F]fluoride for labeling, because ^{20}Ne(d,α)^{18}F reaction was used for production of ^{18}F. No-carrier-added [^{18}F]fluoroacetate has been synthesized using ethyl iodoacetate as precursor (6). Another no-carrier-added [^{18}F]ethyl

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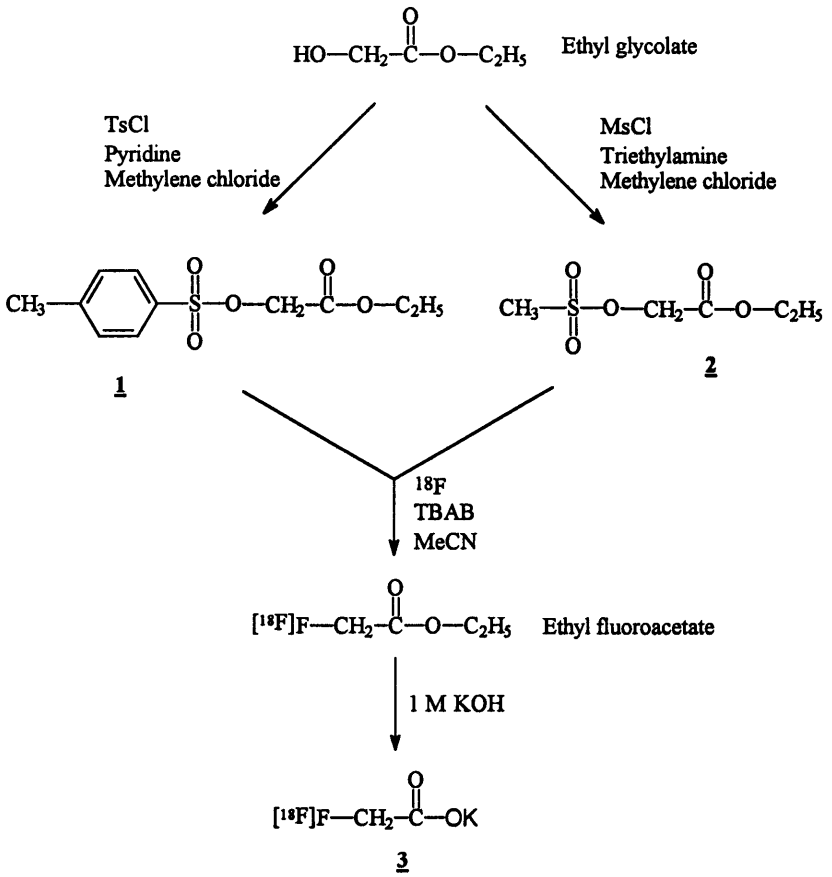
fluoroacetate has been synthesized for the synthesis of [^{18}F]fluoroethanol (7). For the synthesis, they synthesized *O*-tosyl ethyl glycolate as a precursor.

In our experiment, we synthesized *O*-tosyl ethyl glycolate and *O*-mesyl ethyl glycolate as precursors. They were labeled by nucleophilic substitution reaction of [^{18}F]fluoride in the presence of tetrabutyl ammonium bicarbonate, and hydrolyzed by aqueous KOH solution to produce potassium [^{18}F]fluoroacetate (Scheme 1). The final product was purified by ion exchange column and Sep-Pak cartridges.



Scheme 1. Synthesis of *O*-tosyl ethyl glycolate, *O*-mesyl ethyl glycolate, and potassium [^{18}F]fluoroacetate.

EXPERIMENTAL

Ion exchange resin AG1-X8 was purchased from Bio-Rad Laboratories. Sep-Pak alumina N and Sep-Pak silica gel cartridges were purchased from Waters Division of Millipore Corporation. Millex-GS filter was purchased from Millipore Products Division. For TLC,

aluminium backed silica gel 60 F_{254} was purchased from E. Merck Company. All the other reagents and solvents, if not specified, were purchased from Aldrich Chemical Company.

Prepartion of α-(*p*-toluenesulfonyl) ethyl glycolate (*O*-tosyl ethyl glycolate) (1)

1 was synthesized by a modification of published method (7). Briefly, ethyl glycolate (1.0 g, 10 mmoles) and p-toluenesulfonyl chloride (2.1 g, 11 mmoles) were dissolved in 10 ml of methylene chloride in a round bottom flask. Anhydrous pyridine (2 ml) was added dropwise with stirring at room temprature and kept stirring for 15 hr. The reaction mixture was extracted with ice-cold 1 N HCl (20 ml) and washed with water (20 ml) twice. The organic phase was dried over anhydrous sodium sulfate. The solution was diluted by 3 volume of n-hexane and passed through Sep-Pak silica gel cartridge. Recrystalization in methylene chloride:n-hexane (1:4) solution gave white crystal (m.p. = 47-49 °C) with 60% yield (1.8 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3 H), 2.82 (s, 3 H), 4.34 (q, 2 H), 5.50 (s, 2), 7.26-8.20 (m, 4).

Preparation of α-(methanesulfonyl) ethyl glycolate (*O*-mesyl ethyl glycolate) (2)

Ethyl glycolate (1.0 g, 10 mmoles) and methanesulfonyl chloride (1.3 g, 11 mmoles) were dissolved in 25 ml of methylene chloride in round bottom flask. The solution was cooled to 0 ° C and triethylamine (2 ml) was added dropwise with stirring. After stirring for 1 hour, the reaction mixture was extracted with ice-cold 1 N HCl (20 ml) and washed with water (20 ml) twice. The organic phase was dried over anhydrous sodium sulfate. The solution was diluted by 3 volume of *n*-hexane and passed through Sep-Pak silica gel cartridge. Drying in vacuum desiccator gave white oil with 68% yield (1.2 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3 H), 3.21 (s, 3 H), 4.27 (q, 2 H). 4.76 (s, 2).

Preparation of [^{18}F]fluoroacetate (3) from 1 or 2

^{18}F was produced by bombardment with 13 MeV proton to ^{18}O-enriched (>95%) water using TR13 cyclotron (EBCO Technologies). The produced [^{18}F]fluoride was captured by AG1-X8 microcolumn and eluted by 1 ml of tetrabutylammonium bicarbonate (TBAB) solution in MeCN. The eluted [^{18}F]fluoride was dried by purging nitrogen gas at 80 °C. After drying the azeotrophic mixture, 2 ml of MeCN was added and dried again. To the dried tetrabutylammonium [^{18}F]fluoride, 1 ml of 1 or 2 (10 mg/ml in MeCN) was added and heated for 20 min at 80 °C to 100 °C. After evaporation of MeCN with nitrogen purging at 80 °C, the product was hydrolyzed by 3 ml of 1 M KOH solution at 60 °C for 10 min.

Purification of the products

The reaction mixture was passed through an ion exchange column which contains 1 g of quatenary ammonium resin AG1-X8 to adsorb anions such as 3 and [^{18}F]fluoride (Fig. 1(a)). After washing with 10 ml of distilled water, Sep-Pak alumina N cartridge and 0.22 μm syringe filter were connected to outlet of the ion exchange column. To elute the attached anions, 2 ml of saturated sodium bicarbonate solution and 3 ml of distilled water were passed through the ion exchange-cartridge-filter composite successively. [^{18}F]Fluoride was adsorbed to Sep-Pak alumina N cartridge and only 3 was eluted (Fig. 1(b)). Labeling efficiency and purity of the product was determined by silica gel TLC (1 x 6 cm) using 95% MeCN as a solvent.

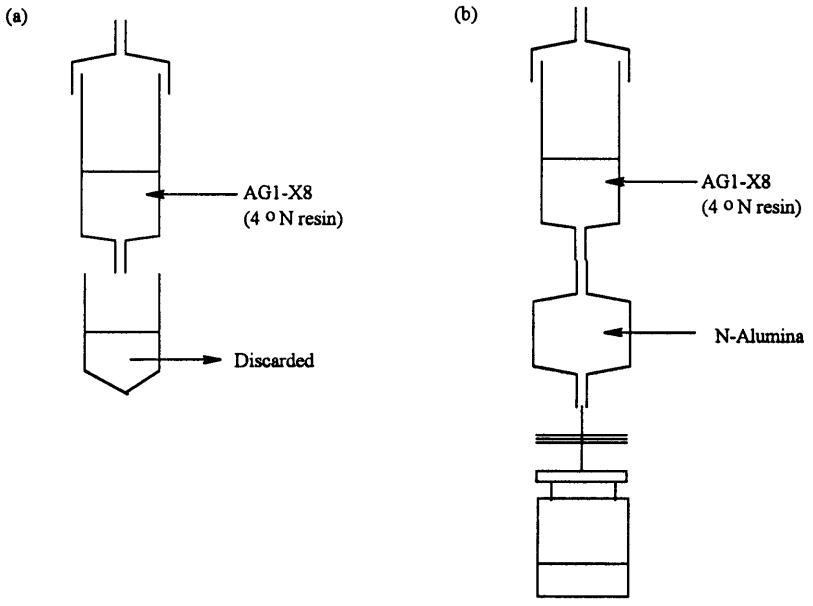


Fig. 1. Purification of [^{18}F]fluoroacetate.

RESULTS AND DISCUSSION

For the labeling with ^{18}F by nucleophilic substitution reaction, tosyl, mesyl, and trifl groups are most commonly used as leaving groups. Although trifl group is most active among the three groups, it is unstable and difficult to handle. Tosyl and mesyl derivatives 1 and 2 were synthesized by well-known reaction pathway with 60% and 68% yield, respectively. Tosylation was performed using pyridine as a catalyzer, however mesylation was performed using triethylamine as a catalyzer to avoid formation of ethyl chloroacetate.

Labeling procedure was monitored by TLC. [^{18}F]Fluoride remained at the origin, and [^{18}F]ethyl fluoroacetate moved to solvent-front (Fig. 2(a)). Hydrolysis was done quantitatively by heating at 60 °C for 10 min with occasional mixing in 1 M KOH. TLC of the hydrolysate showed Rf value of 3 about 0.2 (Fig. 2(b)).

Mesyl group was found to be a better leaving group than tosyl group for nucleophilic substitution reaction by activated fluoride (Table 1). In addition, the reaction favored higher temperature in the range of 80 °C to 100 °C. The highest incorporation was 87.1%.

Table 1. Incorporation percentage of ^{18}F to activated glycolates.

precursor	80 °C	90 °C	100 °C
Ts-ethyl glycolate	27.6 ± 3.5 (n = 3)	35.1 ± 5.4 (n = 3)	63.2 ± 9.7 (n = 4)
Ms-ethyl glycolate	46.0 ± 8.3 (n = 3)	51.1 ± 6.3 (n = 4)	77.6 ± 6.4 (n = 4)

Data represent percentage ± S.D.

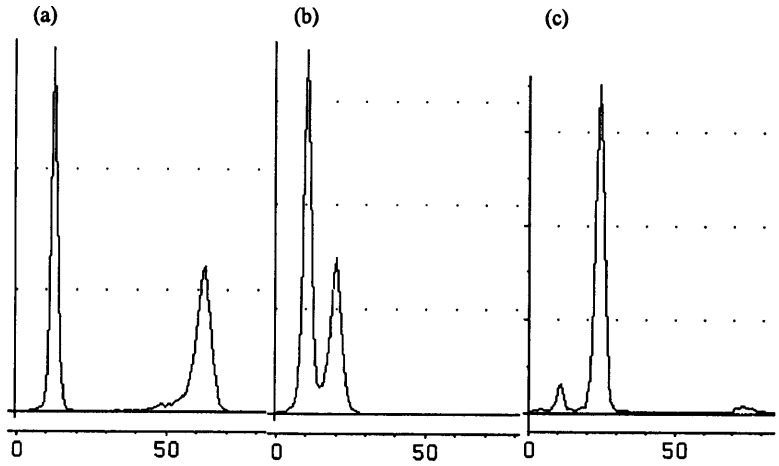


Fig.2. Thin-layer chromatogram of ^{18}F-labled compounds; (a) after fluorination, (b) after hydrolysis, and (c) after purification.

The final product was purified by combination of ion exchange column and Sep-Pak alumina N cartridge. In one example, when the reaction mixture was passed through the quatenary ammonium ion exchange column, 87% of radioactivity was trapped. After elution with saturated sodium bicarbonate solution, 91.2% of the bound radioactivity was eluted from the ion exchanger, 44.6% of radioactivity was trapped by neutral alumina cartridge, and 46.6% of radioactivity was recovered to product vial. Final product showed a little [^{18}F]fluoride activity (<5%) by TLC (Fig. 2(c)).

The total synthesis time was about 70 to 90 min. Additionally, the whole procedure for the labeling was so simple that this method can be easily adapted for automation.

In conclusion, we synthesized no-carrier-added potassium [^{18}F]fluoroacetate in high yield with new precursor and improved simple procedure.

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