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# Preparation of two triflate precursors for *O*-(2-[$^{18}$F] fluoroethyl)-*L*-tyrosine used in positron emission tomography (PET)

LIU ChunYan[1,2] & JIANG ShenDe[1†]

[1] School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China;
[2] Department of Pharmacy, North China Coal Medical College, Tangshan 063000, China

**Two novel triflate precursors for radiolabelling of *L*-tyrosine in positron emission tomography (PET) for tumor imaging, *O*-(2-trifluoromethanesulfonyloxyethyl)-*N*-(*tert*-butoxycarbonyl)-*L*-tyrosine methyl ester 9a and *O*-(2-trifluoromethanesulfonyloxyethyl)-*N*-(*tert*-butoxycarbonyl)-*L*-tyrosine *tert*-butyl ester 9b, are synthesized. The triflate agent, 9a or 9b, is prepared by esterification of methanol or transesterification of *tert*-butyl acetate with *L*-tyrosine, protection of the amine group with di-*tert*-butyl dicarbonate, alkylation with chlorohydrin, and triflation with trifluoromethanesulfonic anhydride in four steps with overall yields of 30% and 15%, respectively.**

positron emission tomography, triflate, L-tyrosine, [18F]FET precursor, PET imaging

## 1 Introduction

Positron emission tomography (PET) is a powerful and non-invasive imaging technique for the quantitative measurement of positron emitters that has been wide applied in medical research and clinical diagnosis[1,2]. Fluorine-18 is considered as the ideal positron-emitting radioisotope for PET imaging due to its low positron energy (0.64 MeV) and its 110 min half life[3]. 2-Deoxy-2-[$^{18}$F]fluoro-*D*-glucose ([$^{18}$F] FDG) is currently the most widely used radiotracer for routine PET cancer imaging[4,5]. However, [$^{18}$F] FDG is not specific for tumor imaging because of its high uptake in normal brain tissues, and also its simultaneous uptake in tumor cells and normal cells. Infection, inflammation, and granulomatous disease and many other physiological or pathological conditions have been shown with increased uptake of [$^{18}$F] FDG[6]. Therefore, other alternative radiotracers for PET have also been developed for better tumor imaging[7].

Radiolabelled amino acids have clinical potential for tumor imaging, as glycolysis, amino acid transport and protein metabolism are more active in tumor cells than in normal cells[8,9]. Among the fluorinated amino acids, *O*-(2-[$^{18}$F]fluoroethyl)-*L*-tyrosine ([$^{18}$F]FET) **4** has emerged as a promising PET tracer for the detection and location of tumors, particularly for brain tumors[10−12].

Early synthesis of [$^{18}$F]FET was carried out by a two-step sequence consisting of $^{18}$F-fluorination of 1,2-bis-toluenesulfonyloxyethane **1** and subsequent $^{18}$F-fluoroethylation of unprotected L-tyrosine (Scheme 1)[10]. The problem of this method is that the $^{18}$F was introduced in the early steps of the radiosynthesis, which resulted in reduced radiochemical yield. And also because of the purification of compound **2** as an $^{18}$F-labelled intermediate, this method is not particularly suitable for automated synthesis. Recently, Hamacher et al. [13,14] used tosylate **5a** and Wang et al. [15] used tosylate **5b** as precursors for [$^{18}$F]FET synthesis. In both cases, [$^{18}$F]FET **4** was synthesized by one-step nucleo-

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†Corresponding author (email: sjiang@tju.edu.cn)
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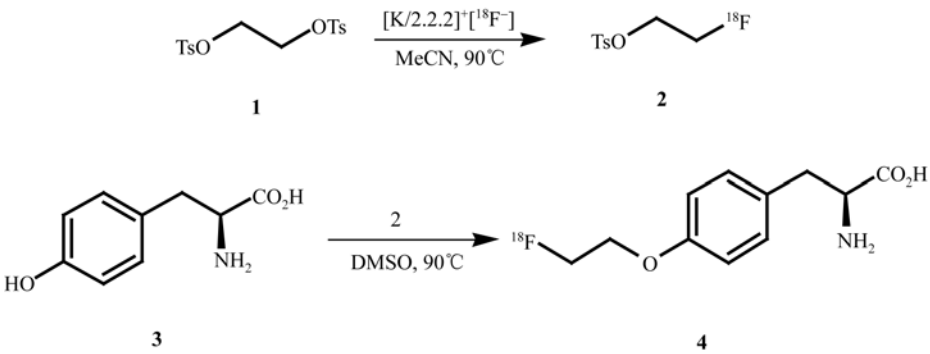



**Scheme 1** Synthesis of [$^{18}$F]FET by two-step reactions.

philic $^{I8}$F-fluorination of these protected *L*-tyrosine precursors. This one-pot synthesis method is convenient and can easily be used on commercial PET tracer synthesizers for automated synthesis (Scheme 2).

We anticipated that a triflate (trifluoromethanesulfonate) version of precursors for [$^{18}$F]FET would provide a better leaving group than the tosylate version of the currently available precursors for the nucleophilic [$^{18}$F]fluorination reaction. Therefore, we set out to synthesize *O*-(2-trifluoromethanesulfonyloxyethyl)-*N*-(*tert*-butoxycarbonyl)-*L*-tyrosine methyl ester **9a** and the other *tert*-butyl ester **9b** as precursors for [$^{18}$F]FET.

## 2 Experimental

General procedures. Melting points were taken on a Reichert Thermovar hot-stage apparatus and uncorrected. $^1$H NMR spectra were recorded on a Bruker AV-400 at 400 MHz. Microanalyses were performed by the analytical services at Nankai University (Tianjin). Flash chromatography was performed on silica gel (300—400 mesh). TLC was run on pre-coated aluminium plates (Merck Kieselgel 60 $F_{254}$) and visualized with UV light and basic aqueous potassium permanganate.

*L*-tyrosine methyl ester (6a): To a suspension of *L*-tyrosine (10 g, 55.53 mmol) in methanol (100 mL) at −15℃ was added thionyl chloride (12 mL, 16.62 mmol) in a dropwise manner. The reaction mixture was allowed to be warmed to room temperature, heated at reflux for 12 h and evaporated. The residue was treated with saturated aqueous sodium hydrogen carbonate to pH 8 and then extracted with ethyl acetate (3 × 200 mL). The organic extracts were dried with sodium sulfate and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate and petroleum ether to give methyl ester **6a** as colorless crystals (9.71 g, 93%). m.p. 138—139℃. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 6.94 (d, 2 H, Ar-H, $J$ = 8.4 Hz), 6.63 (d, 2 H, Ar-H, $J$ = 8.5 Hz), 5.18 (s, 1 H, OH), 3.65 (s, 3 H, $OCH_3$), 3.54 (m, 2 H, $NH_2$), 3.52 (dd, 1 H, $J$ = 7.8 Hz and 5.1 Hz), 2.95 (dd, 1 H, $J$ = 13.7 Hz and 5.1 Hz), 2.72 (dd, 1 H, $J$ = 13.7 Hz and 7.8 Hz).

*N*-(*tert*-butoxycarbonyl)-*L*-tyrosine methyl ester (7a): Di-*tert*-butyl dicarbonate (1.44 g, 6.1 mmol) was added to a solution of methyl ester **6a** (1.07 g, 5.12 mmol) and triethylamine (1.12 g, 11.71 mmol) in dichloromethane (30 mL) at 0℃. The reaction mixture was stirred for 12 h at room temperature and evaporated. The residue was partitioned between dichloromethane (3 × 100 mL) and water (100 mL). The organic extracts were dried with sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate and petroleum ether to give compound **7a** as colorless crystals (1.05 g, 88%). mp 101—102℃. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 6.96 (d, 2 H, Ar-H, $J$ = 8.3 Hz), 6.73 (d, 2 H, Ar-H, $J$ = 8.2 Hz), 5.74 (s, 1 H, OH), 5.01 (d, 1 H, NH, $J$


**Scheme 2** Synthesis of [$^{18}$F]FET by one-step reaction.

= 8.2 Hz), 4.54 (dd, 1 H, CH, $J$ = 13.7 Hz and 5.9 Hz), 3.71 (s, 3 H, $OCH_3$), 3.08—2.96 (m, 2 H, $CH_2$), 1.42 (s, 9 H, $C(CH_3)_3$).

*O*-(2-hydroxyethyl)-*N*-(*tert*-butoxycarbonyl)-*L*-tyrosine methyl ester (8a): A mixture of **7a** (1 g, 3.56 mmol), $K_2CO_3$ (1.17 g, 8.5 mmol), *n*-$Bu_4NI$ (0.13 g, 0.34 mmol), 18-C-6 (0.18 g, 0.68 mmol) and chloroethanol in DMF (25 mL) was heated in an oil bath at 125℃ for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (3 × 25 mL) and water (50 mL). The organic extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure. The residues were purified by flash chromatography on silica gel with petroleum ether and ethyl acetate (3∶2) as eluent. Recrystallization from petroleum ether and ethyl acetate yielded compound **8a** colorless crystals (0.47 g, 41%). m.p. 95—96℃ (from petroleum ether and ethyl acetate)[16]. IR (KBr) $\nu_{max}$: 3446, 3299, 2975, 2936, 1740, 1676, 1610, 1510, 1454, 1367, 1346, 1168 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 7.04 (d, 2 H, Ar-H, $J$ = 8.5 Hz), 6.84 (d, 2 H, Ar-H, $J$ = 8.7 Hz), 4.96 (d, 1 H, NH, $J$ = 7.8 Hz), 4.54 (dd, 1 H, CH, $J$ = 13.7 Hz and 5.9 Hz), 4.06 (m, 2 H), 3.95 (dd, 2 H, $J$ = 9.7 Hz and 5.4 Hz), 3.71 (s, 3 H, $OCH_3$), 3.02 (m, 2 H, $CH_2$), 2.04 (m, 1 H, OH), 1.46 (s, 9 H, $C(CH_3)_3$); MS-EI (*m*/*z*): 362 ($M^+$ + Na); Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13; Found: C, 60.37; H, 7.39; N, 3.92.

*O*-(2-trifluoromethanesulfonyloxyethyl)-*N*-(*tert*-butoxy carbonyl)-*L*-tyrosine methyl ester (9a): Trifluoromethanesulfonic anhydride (0.57 mL, 8.55 mmol) was added to a mixture of **8a** (1 g, 3.42 mmol), pyridine (1.17 g, 8.55 mmol) and DMAP (0.13 g, 0.34 mmol) in dichloromethane (25 mL) at –15℃. The reaction mixture was stirred at the same temperature for 1 h, and water (30 mL) was then added. The resulting mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3∶1) to give compound **9a** as a colorless oil (1.27 g, 92%). IR (KBr) $\nu_{max}$: 3383, 2986, 2939, 1735, 1694, 1607, 1511, 1463, 1452, 1241, 1126 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 6.98 (d, 2 H, $J$ = 8.0 Hz, Ar-H), 6.76 (d, 2 H, $J$ = 8.5 Hz, Ar-H), 4.96 (d, 1 H, $J$ = 7.4 Hz, NH), 4.43 (m, 2 H, $CH_2CH_2$), 4.10 (m, 1 H, CH), 3.96 (m, 1 H, $CH_2CH_2$), 3.85 (m, 1 H, $CH_2CH_2$), 3.63 (s, 3 H, $OCH_3$), 2.93 (m, 2 H, $CH_2$), 1.34 (s, 9 H, $C(CH_3)_3$); MS-EI (*m*/*z*): 494 ($M^+$+Na); Anal. Calcd for $C_{18}H_{24}F_3NO_8S$: C, 45.86; H, 5.13; N, 2.97; Found: C, 46.17; H, 5.25; N, 2.86.

*L*-tyrosine *tert*-butyl ester (6b): Perchloric acid (1.8 mL, 30 mmol) was added to a suspension of *L*-tyrosine (3.63 g, 20 mmol) in *tert*-butyl acetate (50 mL) at 0℃. The reaction mixture was stirred at room temperature for 24 h to which saturated aqueous sodium hydrogen carbonate (50 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate and petroleum ether to give *tert*-butyl ester **6b** as colorless crystals (2.22 g, 45%). m.p. 143—145℃.

*N*-(*tert*-Butoxycarbonyl)-*L*-tyrosine *tert*-butyl ester (7b): Following the same procedure as **7a**, compound **7b** was obtained as colorless crystals, yield 86%, mp 111—112℃ (from petroleum ether and ethyl acetate), $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$6.91 (d, 2 H, Ar-H, $J$ = 8.4 Hz), 6.75 (s, 1 H, OH), 6.66 (d, 2 H, Ar-H, $J$ = 8.5 Hz), 4.98 (d, 1 H, NH, $J$ = 8.3 Hz), 4.32 (dd, 1 H, CH, $J$ = 14.3 Hz and 6.1 Hz), 2.96—2.84 (m, 2 H, $CH_2$), 1.34 (s, 9 H, $C(CH_3)_3$), 1.33 (s, 9 H, $C(CH_3)_3$).

*O*-(2-hydroxyethyl)-*N*-(*tert*-butoxycarbonyl)-*L*-tyrosine *tert*-butyl ester (8b): Following the same procedure as **8a**, compound **8b** was obtained as colorless crystals, yield 42%, mp 92—93℃ (from petroleum ether and ethyl acetate), IR (KBr) $\nu_{max}$: 3598, 3356, 3006, 2981, 1736, 1704, 1609, 1511, 1454, 1368, 1246, 1139 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 7.05 (d, 2 H, Ar-H, $J$ = 8.5 Hz), 6.81 (d, 2 H, Ar-H, $J$ = 8.7 Hz), 4.96 (d, 1 H, NH, $J$ = 7.7 Hz), 4.37 (dd, 1 H, CH, $J$ = 13.1 Hz and 6.0 Hz,), 4.02 (m, 2 H), 3.91 (dd, 2 H, $J$ = 9.5 Hz and 5.2 Hz), 2.97 (m, 2 H, $CH_2$), 2.21 (t, 1 H, OH), 1.39 (s, 9 H, $C(CH_3)_3$), 1.38 (s, 9 H, $C(CH_3)_3$); MS-EI (*m*/*z*): 404 ($M^+$+Na); Anal. Calcd for $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19; N, 3.67; Found: C, 63.18; H, 8.34; N, 3.69.

*O*-(2-trifluoromethanesulfonyloxyethyl)-*N*-(*tert*-butoxyc arbonyl)-*L*-tyrosine *tert*-butyl ester (9b): Following the same procedure as **9a**, compound **9b** was obtained as

a colorless oil, yield 91%, IR (KBr) $\nu_{max}$: 3396, 2983, 2935, 1732, 1691, 1613, 1512, 1467, 1453, 1243, 1130 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 6.93 (d, 2 H, Ar-H, $J$ = 8.2 Hz), 6.62 (d, 2 H, Ar-H, $J$ = 8.9 Hz), 4.93(d, 1 H, NH, $J$ = 7.5 Hz), 4.39 (m, 2 H, $CH_2CH_2$), 4.0 (m, 1 H, CH), 3.91 (m, 1 H, $CH_2CH_2$), 3.83 (m, 1 H, $CH_2CH_2$), 2.97 (m, 2 H, $CH_2$), 1.39 (s, 9 H, $C(CH_3)_3$), 1.38 (s, 9 H, $C(CH_3)_3$); MS-EI ($m/z$): 536 ($M^+$ + Na); Anal. Calcd for $C_{21}H_{30}F_3NO_8S$: C, 49.12; H, 5.89; N, 2.73; Found: C, 49.33; H, 6.15; N, 2.52.

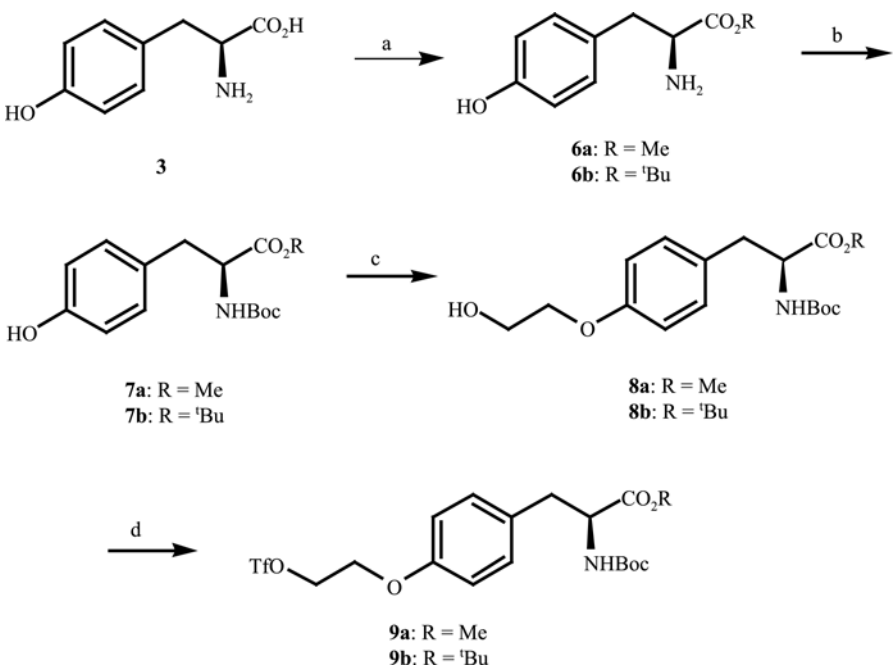
## 3 Results and discussion

Both compounds **9a** and **9b** were synthesized from L-tyrosine **3** as outlined in Scheme 3. For compound **9a**, *L*-tyrosine was treated with methanol in the presence of hydrogen chloride as catalyst that was generated *in situ* by the addition of thionyl chloride[17]. The amine group in methyl ester **6a** was protected by treatment of **6a** with di-tert-butyl dicarbonate and triethylamine in dichloromethane[18]. The fully protected **7a** was refluxed with chloroethanol in the presence of potassium carbonate and potassium iodide in cyclohexanone[19]. Under this condition, the reaction was sluggish, and after prolonged refluxing large proportion of starting material still remained. We sought to improve this reaction by using a combination of tetra-*n*-butylammonium iodide (*n*-$Bu_4NI$), potassium carbonate and 18-crown-6 in dimethylformamide at 125℃ to achieve the complete disappearance of starting material with an isolated yield of 41% for **8a** after flash chromatography. We suspected that the reason for the lower yield was partly due to decomposition of product **8a** during flash chromatography on silica gel. Treatment of alcohol **8a** with trifluoromethanesulfonic anhydride in dichloromethane in the presence of pyridine and DAMP at 0℃ gave desired triflate **9a** in 92% yield.

For compound **9b**, tert-butyl ester **6b** was prepared by transesterification of *tert*-butyl acetate with L-tyrosine [20,21]. Following a sequence of reactions similar to that of compound **9a**, triflate **9b** was obtained from *tert*-butyl ester **6b** in an overall yield of 33%.

## 4 Conclusions

In conclusion, we have synthesized precursors **9a** and **9b** from *L*-tyrosine in four steps with overall yields of 30% and 15%, respectively. Further radiolabelling of compounds **9a** and **9b** for [$^{18}$F]FET and subsequent clinical studies are currently under way, which will be reported in due course.




**Scheme 3** Synthesis of two triflate precursors for *O*-(2-[$^{18}$F] fluoroethyl)-*L*-tyrosine **9a** or **9b** (a); for **6a**: methanol, $SOCl_2$, 93%; for **6b**: perchloric acid, *tert*-butyl acetate, 45%; (b) $Boc_2O$, $Et_3N$, $CH_2Cl_2$, 0℃, 88% for **7a** and 86% for **7b**; (c) chloroethanol, $K_2CO_3$, *n*-$Bu_4NI$, 18-C-6, DMF, reflux, 41% for **8a** and 42% for **8b**; (d) $Tf_2O$, pyridine, DMAP, $CH_2Cl_2$, 92% for **9a** and 91% for **9b**.

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