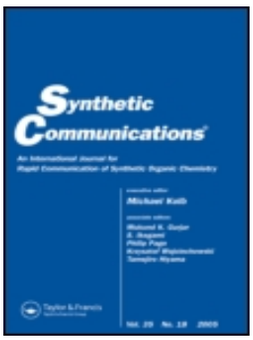

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SYNTHESIS OF TEG-SUBSTITUTED 4-(*N*-METHYL-*N*-*BOC*-AMINO)STYRYLPYRIDINE AS KEY PRECURSOR FOR MONODENTATE AND MULTIDENTATE IMAGING AGENTS FOR Aβ PLAQUES

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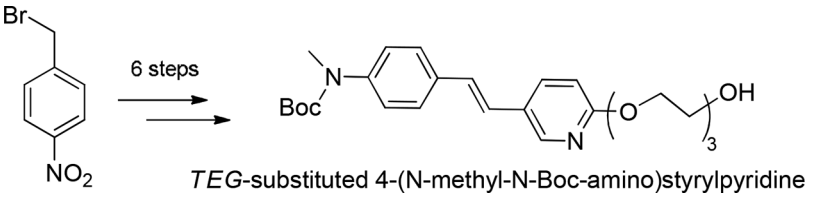
GRAPHICAL ABSTRACT



Abstract *Triethylene glycol (TEG)-substituted 4-(*N*-methyl*-N-Boc-*amino)styrylpyridine, which can serve as key precursor for many monodentate and multidentate imaging agents for Aβ plaques in the human brain, has been readily synthesized with cheap starting materials. Our new method could be employed for mass production of monodentate imaging agent AV-45 and other multidentate imaging agents.*

Keywords AV-105; AV-45; PET imaging agent

INTRODUCTION

Imaging Aβ plaques in the brain is a potentially useful tool for studying the pathophysiology of neurodegenerative diseases (e.g., cerebral amyloid angiopathy and Alzheimer disease) associated with the formation of β-amyloid.[1] As shown in Fig. 1, [^{18}F] **1** (AV-45) is a useful monodentate positron emission tomography (PET) agent for targeting Aβ plaques in the human brain.[2] The phase III clinical trial for **1** was completed[2e] in 2011 and this Aβ-plaque-targeting imaging agent got approval from US Food and Drug Administration in 2012.

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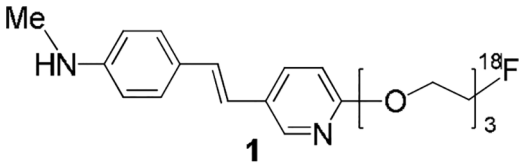


Figure 1. Monodentate ^{18}F Aβ-plaque-imaging agent AV-45.

In 2011, researchers[3] reported a new series of multidentate^{18}F styrylpyridine derivatives for selectively targeting Aβ plaques in the blood vessels of the human brain (Fig. 2). Their research[3] suggested that [^{18}F] **2a** may be a useful PET imaging agent in the brain.

As shown in Scheme 1, TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) is the key precursor for the synthesis of monodentate PET imaging agent **1**[4a] and other multidentate PET imaging agents (**2a, 2b, 2c, 3, 4**).[3]

RESULTS AND DISCUSSION

Although TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) is very important, only one protocol[3] has been reported concerning its synthesis. The reported method involved the air- and moisture-sensitive Heck reaction and microwave reaction in which a special microwave synthesizer (Biotage microwave reaction vial) and harsh reaction conditions (high temperature and high pressure) were required. Herein, we report a new method for the synthesis of TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino) styrylpyridine (**5**) without microwave irradiation or air- and moisture-sensitive metal catalytic reactions (Scheme 2).

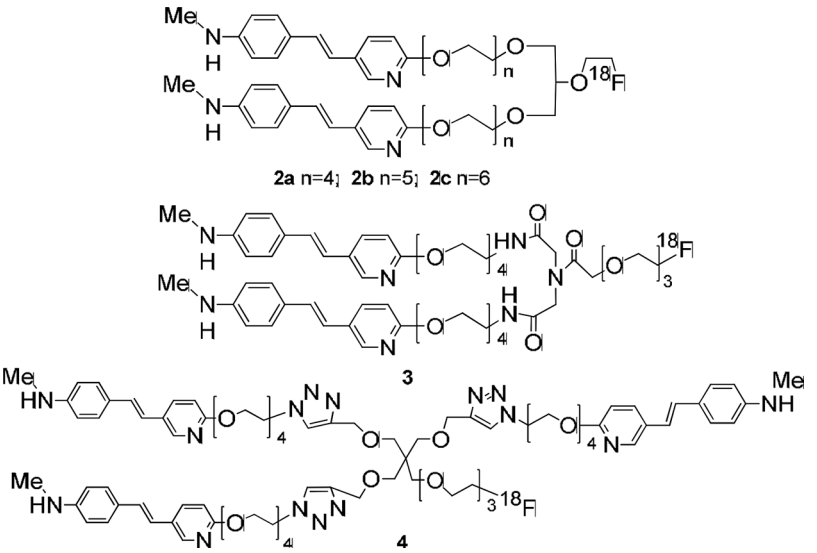
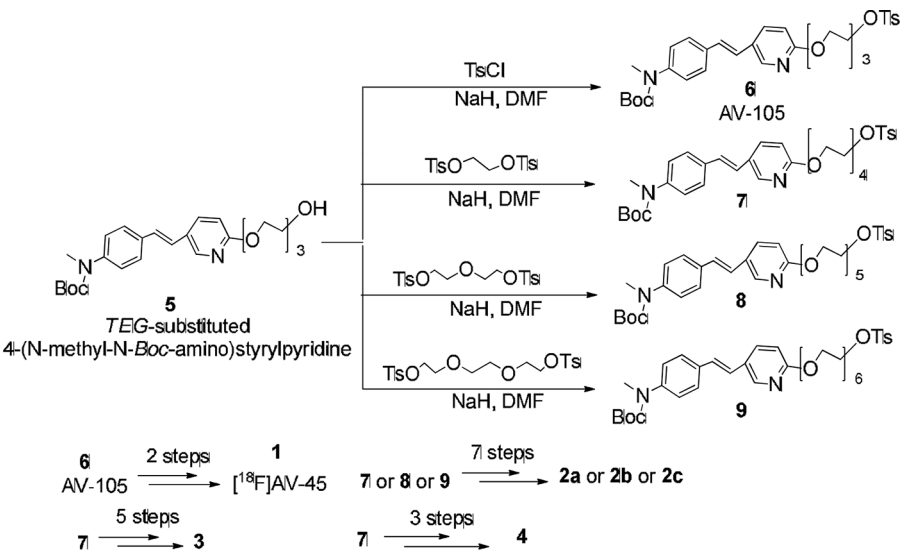
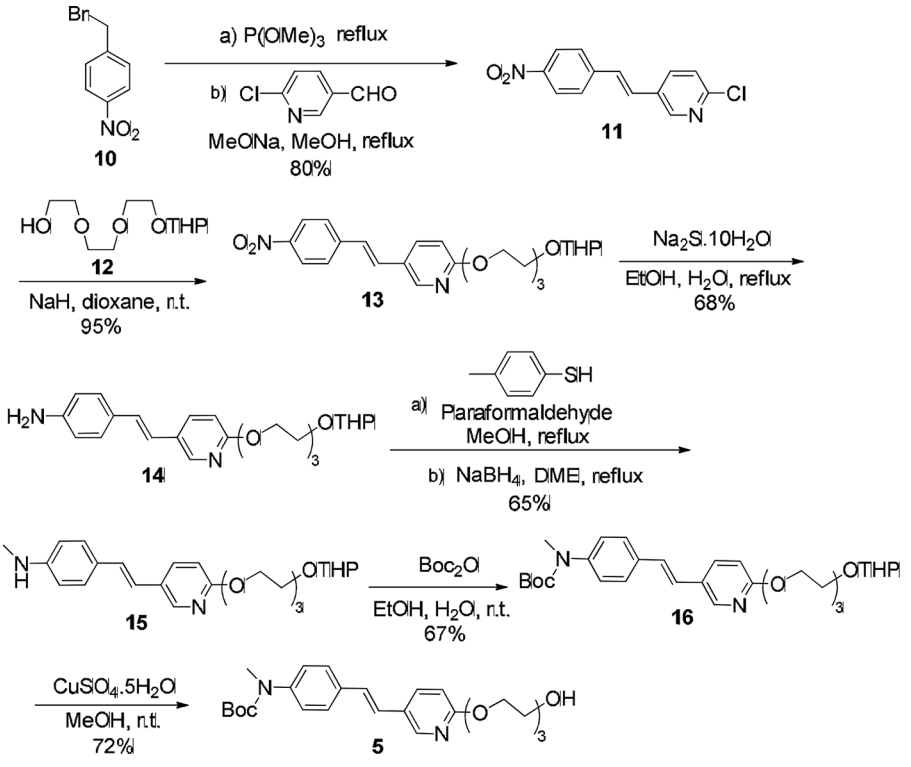


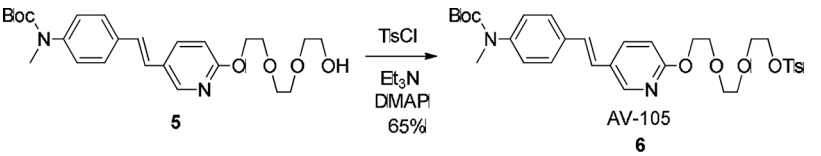
Figure 2. Multidentate ^{18}F Aβ-plaque-imaging agents.



Scheme 1. Synthesis of monodentate and multidentate PET imaging agents from TEG-substituted4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**).



Scheme 2. Synthesis of TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**).



Scheme 3. Synthesis of AV 105 from TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**).

First, (bromomethyl)-4-nitrobenzene (**10**) was transformed into **11** smoothly by the Wittig–Horner reaction.[2f,5,6] Second, substitution of **11** with mono-tetrahydro-2H-pyran (THP)-protected triethylene glycol (**12**) in the presence of NaH afforded **13** in 95% yield. Subsequently, reduction of **13** by $Na_2S \cdot 10H_2O$[7] in $EtOH/H_2O$ (v/v = 2:1) solution afforded **14** in 68% yield. It is worth noting that reduction of **13** should be carried out under basic conditions to avoid deprotection of the THP group. $Na_2S \cdot 10H_2O$ was therefore selected as reductant. Next, **14** was allowed to react with paraformaldehyde and 4-methylbenzenethiol in refluxing MeOH. After removal of MeOH, the residue reacted with $NaBH_4$[2f,8] in dichloroethane (DME) at 100 °C to afford **15** in 65% yield. Protection of **15** with Boc_2O afforded **16** in 67% yield. Finally, the TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) was obtained in 72% yield after selective deprotection of the THP group. $CuSO_4 \cdot 5H_2O$[9] was employed in this step because it can promote depyranylation of alcohol efficiently while keeping the *Boc* group intact.

As described previously, all starting materials and reagents employed in our new method were cheap and readily available. All reactions were simple and easy to handle: (a) No special reactor or harsh reaction conditions (e.g., high temperature and high pressure) were required. (b) No microwave irradiation or air- or moisture-sensitive metal catalytic reactions were involved. Our new method can be employed for mass production of TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**).

With **5** in hand, we further tried to synthesize the key precursor **6** (AV 105)[3] for the monodentate imaging agent **1** (AV-45). As shown in Scheme 3, **6** was obtained in 65% yield by the reaction of **5** with TsCl in the presence of Et_3N and dimethylaminopyridine (DMAP).

CONCLUSION

In summary, TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**), which can serve as key precursor for many monodentate and multidentate imaging agents for Aβ plaques in the human brain, has been synthesized with cheap starting materials via simple reactions. The key precursor **6** (AV-105) for **1** (AV-45) has also been prepared in good yield from **5**. Our new method could be employed for mass production of monodentate imaging agent AV-45 and other multidentate imaging agents. This work is under research in our laboratory and further results will be reported in due course.

EXPERIMENTAL

All commercially available reagents were used without further purification. Column chromatography was performed on silica gel (200–300 mesh). ^1H NMR

and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz on a Bruker NMR spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), and multiplet (m).

Compound 13

NaH (312 mg, 7.81 mmol) was added to a solution of mono-THP-protected triethylene glycol (**12**) (1.83 g, 7.81 mmol) in 16 mL dioxane at rt. The mixture was stirred for 3 h. To the mixture (*E*)-2-chloro-5-(4-nitrostyryl)pyridine (**11**) (750 mg, 2.92 mmol) was added. After stirring at rt for 12 h, the mixture was poured into water and extracted by EtOAc. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, PE/AcOEt = 1:1) to afford **13** (1.21 g, yield: 95%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 8.26 (1H, *s*), 8.22 (2H, *d*, $J = 8.8$ Hz), 7.87 (1H, *dd*, $J = 8.8$ Hz, $J = 2.4$ Hz), 7.62 (2H, *d*, $J = 8.8$ Hz), 7.19 (1H, *d*, $J = 16.4$ Hz), 7.04 (1H, *d*, $J = 16.4$ Hz), 6.89–6.88 (1H, *m*), 4.63 (1H, *t*, $J = 3.6$ Hz), 4.57–4.53 (2H, *m*), 3.89–3.84 (4H, m), 3.73–3.67 (7H, *m*), 3.63–3.58 (1H, *m*), 1.86–1.78 (1H, *m*), 1.75–1.69 (1H, *m*), 1.61–1.52 (4H, *m*). ^{13}C NMR ($CDCl_3$): δ 163.9, 146.8, 143.7, 135.6, 129.5, 126.8, 125.7, 125.4, 124.2, 111.8, 99.0, 70.8, 70.7, 70.6, 70.6, 69.7, 66.7, 65.6, 62.3, 30.6, 25.5, 19.6. HRMS (FAB) calcd. for $C_{24}H_{30}N_2O_7$ (MH+): 458.2053; found: 458.2055.

Compound 14

Compound **13** (1.0 g, 2.2 mmol) and $Na_2S \cdot 10H_2O$ (1.72 g, 22 mmol) were dissolved in a mixture of EtOH and H_2O (15 mL, $V_{EtOH}/V_{H2O} = 2{:}1$). The mixture was heated to reflux for 2 h. After cooling to rt, the mixture was diluted with H_2O and extracted by EtOAc. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, PE/EtOAc = 1:1) to afford **14** (0.63 g, yield: 68%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 8.06 (1H, *d*, $J = 2$ Hz), 7.67 (1H, *dd*, $J = 8.4$ Hz, $J = 2.0$ Hz), 7.22 (2H, *d*, $J = 8.0$ Hz), 6.77 (2H, *q*, $J = 16.0$ Hz), 6.69 (1H, *d*, $J = 8.8$ Hz), 6.58 (2H, *d*, $J = 8.4$ Hz), 4.56 (1H, *t*, $J = 3.6$ Hz), 4.40 (2H, *t*, $J = 4.8$ Hz), 3.81–3.77 (4H, m), 3.74 (2H, *s*), 3.63–3.60 (6H, *m*), 3.56–3.51 (1H, *m*), 3.43–3.39 (1H, *m*), 1.78–1.71 (1H, *m*), 1.66–1.61 (1H, *m*), 1.55–1.41 (4H, *m*). ^{13}C NMR ($CDCl_3$): δ 162.7, 146.4, 145.1, 135.2, 128.2, 127.7, 127.7, 127.4, 121.0, 115.2, 111.4, 99.0, 70.8, 70.7, 70.7, 69.9, 66.7, 65.3, 62.3, 30.7, 25.5, 19.6. HRMS (FAB) calcd. for $C_{24}H_{32}N_2O_5$ (MH+): 428.2311; found: 428.2310.

Compound 15

Compound **14** (500 mg, 0.25 mmol) and paraformaldehyde (120 mg, 0.30 mmol) in 10 mL MeOH was heated to reflux for 30 min. 4-Methylbenzenethiol (160 mg, 0.25 mmol) in 5 mL MeOH was added to the mixture. After 2 h, the mixture was cooled to rt and MeOH was removed under vacuum. The residue was dissolved in 5 mL DME. $NaBH_4$ (100 mg, 0.76 mmol) was added to the solution and the mixture

was heated to 100 °C for 1 h. After cooling to rt, the mixture was poured into water. The mixture was extracted by EtOAc and the combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, PE/EtOAc = 1:1) to afford compound **15** (371 mg, yield: 65%) as yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.13 (1H, *d, J* = 2.4 Hz), 7.75 (1H, *dd, J* = 2.4 Hz, *J* = 8.8 Hz), 7.35 (2H, *d, J* = 8.8 Hz), 6.92–6.65 (5H, *m*), 4.63 (1H, *t, J* = 3.6 Hz), 4.47 (2H, *t, J* = 4.8 Hz), 3.88–3.83 (4H, *m*), 3.71–3.67 (7H, *m*), 3.63–3.58 (1H, *m*), 3.50–3.46 (1H, *m*), 2.87 (3H, *s*), 1.85–1.78 (1H, *m*), 1.74–1.68 (1H, *m*), 1.62–1.52 (4H, *m*).^{13}C NMR ($CDCl_3$): δ 162.6, 149.2, 145.1, 135.1, 128.4, 127.7, 126.4, 120.3, 112.5, 111.4, 100.1, 99.1, 70.8, 70.8, 70.7, 69.9, 66.8, 65.3, 62.3, 58.3, 30.7, 25.6, 19.6. HRMS (FAB) calcd. for $C_{25}H_{34}N_2O_5$ (MH+): 442.2468; found: 442.2469.

Compound 16

Compound **15** (600 mg, 1.5 mmol) and $(Boc)_2O$ (410 mg, 2.2 mmol) were dissolved in a mixture of EtOH and H_2O (10 mL V_{EtOH},/V_{H2O} = 2:1). The mixture was stirred at rt for 12 h. The mixture was diluted with water and extracted by EtOAc. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, PE/EtOAc = 1:1) to afford compound **16** (500 mg, yield: 67%) as yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.16 (1H, *d, J* = 2.0 Hz), 7.77 (1H, *dd, J* = 2.0 Hz, *J* = 8.4 Hz), 7.43 (2H, *d, J* = 8.8 Hz), 7.21 (2H, *d, J* = 8.0 Hz), 6.99–6.90 (2H, *m*), 6.78 (1H, *d, J* = 8.8 Hz), 4.62 (1H, *t, J* = 3.6 Hz), 4.48 (2H, *t, J* = 4.8 Hz), 3.87–3.83 (4H, *m*), 3.70–3.66 (6H, *m*), 3.62–3.57 (1H, *m*), 3.49–3.45 (1H, *m*), 3.25 (3H, *s*), 1.89–1.78 (1H, *m*), 1.73–1.67 (1H, *m*), 1.62–1.53, (2H, *m*), 1.51–1.47 (2H, *m*), 1.45 (9H, *s*). ^{13}C NMR ($CDCl_3$): δ 163.2, 154.8, 145.8, 143.3, 135.4, 134.3, 127.4, 126.8, 126.6, 125.6, 124.6, 111.6, 99.1, 80.6, 70.9, 70.8, 70.7, 69.9, 66.8, 65.5, 62.3, 37.3, 30.7, 28.5, 25.6, 19.6. HRMS (FAB) calcd. for $C_{30}H_{42}N_2O_7$ (MH+): 542.2992; found: 542.2993.

TEG-Substituted 4-(*N*-Methyl-*N*-*Boc*-amino)styrylpyridine (5)

A mixture of compound **16** (1.5 g, 2.9 mmol) and $CuSO_4 \cdot 5H_2O$ (9.0 g, 36 mmol) in 20 mL MeOH was stirred at rt for 12 h. The mixture was diluted with water and extracted by EtOAc. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, EtOAc) to afford TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine **(5)** (1.2 g, yield: 72%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.15 (1H, *d, J* = 2.0 Hz), 7.76 (1H, *dd, J* = 2.4 Hz, *J* = 8.4 Hz), 7.41 (2H, *d, J* = 8.4 Hz), 7.20 (2H, *d, J* = 8.4 Hz), 6.98–6.89 (2H, *m*), 6.77 (1H, *d, J* = 8.8 Hz), 4.48 (2H, *t, J* = 4.8 Hz), 3.84 (2H, *t, J* = 4.8 Hz), 3.71–3.68 (6H, *m*), 3.60–3.58 (2H, *m*), 3.24 (3H, *s*), 2.71 (1H, *t, J* = 6.0 Hz), 1.44 (9H, *s*). ^{13}C NMR ($CDCl_3$): δ 163.1, 154.8, 145.7, 143.3, 135.5, 134.2, 127.4, 126.9, 126.6, 125.6, 124.6, 111.6, 80.6, 72.6, 70.8, 70.5, 69.8, 65.3, 61.9, 37.3, 28.5. HRMS (FAB) calcd. for $C_{25}H_{34}N_2O_6$(MH+): 458.2417; found: 458.2415. The data are identical with those reported in the literature.[3]

FUNDING

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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