Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Facile synthesis of TEG-substituted 4-(N-methyl-N-Boc-amino)styrylpyridine and PET imaging agent [F]florbetapir ([F]AV-45)

Tuo Yao & Zhi Li

To cite this article: Tuo Yao & Zhi Li (2018) Facile synthesis of TEG-substituted 4-(N-methyl-N-Boc-amino)styrylpyridine and PET imaging agent [F]florbetapir ([F]AV-45), Synthetic Communications, 48:4, 422-427, DOI: 10.1080/00397911.2017.1404107

To link to this article: https://doi.org/10.1080/00397911.2017.1404107

View supplementary material

Published online: 18 Jan 2018.

Submit your article to this journal

Article views: 13

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=lsyc20

SYNTHETIC COMMUNICATIONS®
2018, VOL. 48, NO. 4, 422–427
https://doi.org/10.1080/00397911.2017.1404107

Taylor & Francis
Taylor & Francis Group

Check for updates

Facile synthesis of TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino) styrylpyridine and PET imaging agent [F]florbetapir ([F]AV-45)

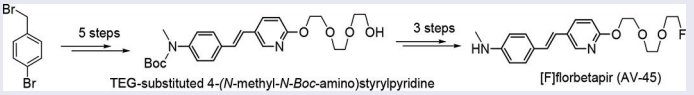
Tuo Yao and Zhi Li

Department of Chemistry, School of Science, Beijing Jiaotong University, Beijing, China

ABSTRACT

Triethylene glycol-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 human brain has been readily synthesized with cost-effective starting materials. The important non-radioactive monodentate positron emission tomography agent [F]florbetapir ([F]AV-45) has also been prepared by our new method.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 11 August 2017

KEYWORDS
[F]AV-45; [F]florbetapir; Aβ plaques; PET imaging agent

Introduction

[^{18}F]AV-45 (Fig. 1, **1**) is a useful monodentate positron emission tomography (PET) agent for targeting Aβ plaques.[1] The phase III clinical trial for [^{18}F]AV-45 was completed[1e] and this PET imaging agent got approval from U.S. FDA in 2012. Recently, Kung et al.[2] reported a new series of multidentate ^{18}F styrylpyridine derivatives for selectively targeting Aβ plaques in the blood vessels of human brain (Fig. 1, **2a, 2b, 2c, 3, 4**). All compounds mentioned above could serve as useful tools for studying the pathophysiology of neurodegenerative diseases associated with the formation of β-amyloid.[1,2]

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

The first synthesis of the key precursor TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino) styrylpyridine (**5**) was reported by Kung et al.[2] Their method involved air/moisture sensitive Heck reaction and microwave reaction in which special microwave synthesizer (Biotage microwave reaction vial) and harsh reaction conditions (high temperature and high pressure) were required.

In 2015, we reported a new method[4] for the synthesis of the TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**). No special reactor or harsh reaction conditions were required in this method. No microwave or air/moisture sensitive metal catalytic reactions were involved too. However, the synthesis route is still not short (six

CONTACT Zhi Li zhili@bjtu.edu.cn Department of Chemistry, School of Science, Beijing Jiaotong University, 3# Shang Yuan Cun Road, Haidian District, Beijing, 100044, China.
Supplemental data (full experimental detail, ^{1}H and ^{13}C NMR spectra) can be accessed on the publisher's website.
© 2018 Taylor & Francis

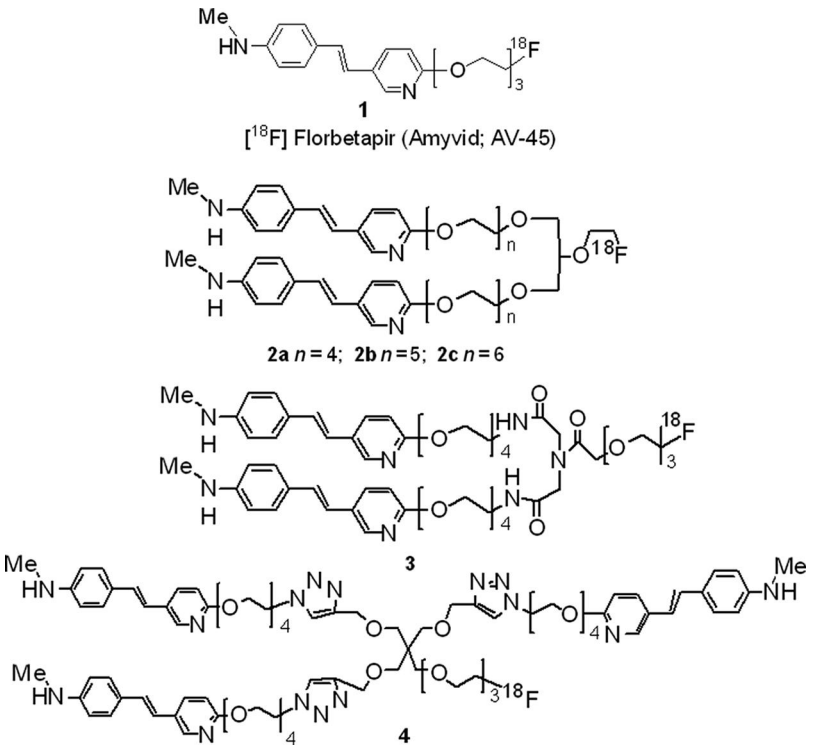
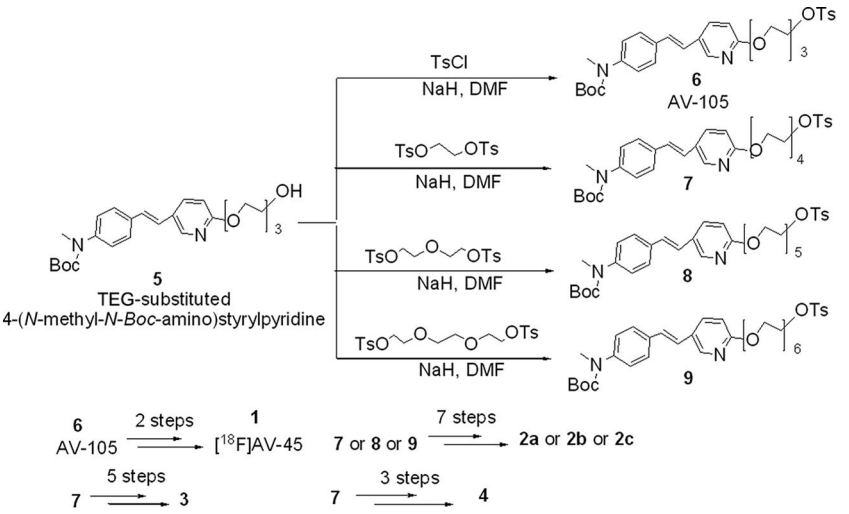


Figure 1. Monodentate and multidentate ^{18}F Aβ-plaque imaging agents.

steps with eight stages). Toxic and smelly reagent 4-methylbenzenethiol was required. The 4-methylbenzenethiol is irritating to eyes, skin and respiratory system. This reagent is harmful by inhalation and in contact with skin.



Scheme 1. Synthesis of monodentate and multidentate PET imaging agents from TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**).

Results and discussion

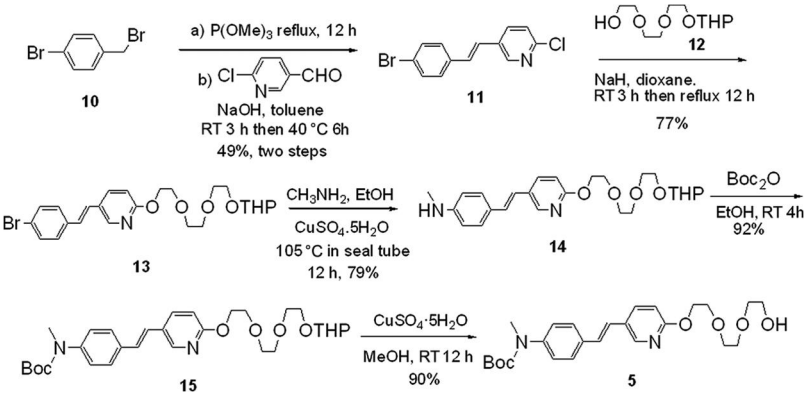
Herein, we report a new method for the synthesis of TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino) styrylpyridine (**5**) and the non-radioactive monodentate PET imaging agent [F] florbetapir ([F]AV-45).

As shown in Scheme 2, 1-bromo-4-(bromomethyl)benzene (**10**) was transformed into **11** smoothly by the Wittig–Horner reaction.[5] Substitution of **11** with the *mono*-tetrahydro-*2H*-pyran (THP)-protected TEG (**12**) in the presence of NaH afforded **13** in 77% yield. Subsequently, substitution of **13** with CH_3NH_2 in the presence of $CuSO_4 \cdot 5H_2O$ afforded **14** in 79% yield. Next, protection of **14** with Boc_2O afforded **15** in 92% yield. Finally, the TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) was obtained in 90% yield after selective deprotection of the THP-group. $CuSO_4 \cdot 5H_2O$[4,6] was employed in this step because it can promote depyranylation of alcohol efficiently while keeping the *Boc*-group intact.

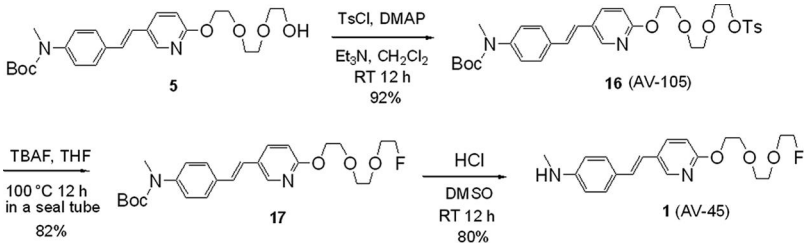
As described above, the method reported herein (five steps with six stages) is more concise than the method[4] (six steps with eight stages) we developed before. The overall yield of the new method is 25%, which is higher than our previously published method[4] (the overall yield is 16%). In our new method, toxic and smelly reagent (e.g., 4-methylbenzenethiol) was excluded. All starting materials and reagents employed were cost-effective and readily available. No special reactor or harsh reaction conditions were required. No microwave or air/moisture sensitive metal catalytic reactions were involved too. Our new method can be applied for synthesis of TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) in multi-gram scale.

With the key precursor TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) in hand, we tried to synthesize the non-radioactive monodentate PET imaging agent [F] florbetapir ([F]AV-45) **1** according to the published procedures.[2,3a,3b,4]

As shown in Scheme 3, **16** (AV-105) was obtained in 92% yield by the reaction of **5** with TsCl in the presence of Et_3N and DMAP.[2,4] Subsequently, the reaction of **16** with TBAF in THF at 100 °C in a seal tube afforded **17** in 82% yield. Finally, the non-radioactive [F] florbetapir ([F]AV-45) **1** was obtained in 80% yield by the deprotection of the *Boc*-group.[3a]



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



Scheme 3. Synthesis of AV-45 **1** from **5**.

Experimental

Synthesis and characterization data for key compounds

(E)-N-methyl-4-(2-(6-(2-(2-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)ethoxy)ethoxy) pyridin-3-yl)vinyl)benzenamine (14)

Compound **13** (0.10 g, 0.2 mmol) and $CuSO_4 \cdot 5H_2O$ (0.05 g, 0.2 mmol) were added to a solution of methylamine in ethanol (33 wt%, 10 mL) in a seal tube. The mixture was heated to 105 °C overnight. After cooling to RT, the mixture was poured into 20 mL NaOH solution 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 **14** (70 mg, yield: 79%). IR (neat): 3164, 2364, 2336, 2178, 1771, 1673, 1609, 1527, 1491 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.15 (d, $J = 2.0$ Hz, 1H), 7.77 (dd, $J = 2.4$ Hz, $J = 8.8$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 2H), 6.92 (d, $J = 16.4$ Hz, 1H), 6.82 (d, $J = 16.4$ Hz, 1H), 6.78 (d, $J = 8.8$ Hz, 1H), 6.61 (d, $J = 8.4$ Hz, 2H), 4.66–4.64 (m, 1H), 4.51–4.49 (m, 2H), 3.91–3.86 (m, 4H), 3.74–3.69 (m, 7H), 3.66–3.60 (m, 1H), 3.54–3.49 (m, 1H), 2.88 (s, 3H), 1.88–1.80 (m, 1H), 1.76–1.70 (m, 3H), 1.64–1.56 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 162.5, 149.0, 144.9, 135.0, 128.2, 127.5, 126.5, 120.4, 112.4, 111.2, 98.9, 70.7, 70.6, 70.6, 69.8, 66.6, 65.2, 62.2, 30.5, 25.4, 19.5. HRMS (FAB) calcd for $C_{25}H_{34}N_2O_5$ (MH+): 442.2468; found: 442.2465. The data are identical with those reported in literature.[4]

TEG-substituted 4-(N-methyl-N-Boc-amino)styrylpyridine (5)

A mixture of compound **15** (0.89 g, 1.64 mmol) and $CuSO_4 \cdot 5H_2O$ (0.5 g, 2 mmol) in 15 mL MeOH was stirred at RT for 12 h. The mixture was diluted with NaOH solution 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)** (684 mg, yield: 90%) as a white solid. IR (neat): 3158, 2358, 2178, 1684, 1404, 1152 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.15 (*d*, $J = 2.0$ Hz, 1H), 7.76 (dd, $J = 2.4$ Hz, $J = 8.4$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 6.98–6.89 (m, 2H), 6.77 (d, $J = 8.8$ Hz, 1H), 4.48 (t, $J = 4.8$ Hz, 2H), 3.84 (t, $J = 4.8$ Hz, 2H), 3.71–3.68 (m, 6H), 3.60–3.58 (m, 2H), 3.24 (*s*, 3H), 2.71 (t, $J = 6.0$ Hz, 1H), 1.44 (*s*, 9H). ^{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: 458.2416. The data are identical with those reported in literature.[2,4]

(E)-4-(2-(6-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methylbenzenamine (1) non-radioactive ([F]AV-45)

A mixture of compound **17** (35 mg, 0.074 mmol) and 5 mL HCl in 5 mL DMSO was stirred at RT overnight. To the mixture 20 mL 4% NaOH solution was added. The mixture was extract 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 compound **1** (22 mg, yield: 80%). IR (neat): 3168, 2364, 2336, 2178, 1614, 1250, 1108 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.13 (d, $J = 2.0$ Hz, 1H), 7.76 (dd, $J = 2.4$ Hz, $J = 8.8$ Hz, 1H), 7.34 (d, $J = 8.8$ Hz, 2H), 6.92–6.75 (m, 3H), 6.59 (d, $J = 8.4$ Hz, 2H), 4.63–4.61 (m, 1H), 4.51–4.47 (m, 3H), 3.88–3.85 (m, 2H), 3.80–3.78 (m, 1H), 3.75–3.70 (m, 5H), 2.86 (s, 3H), 1.25 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 162.5, 149.0, 144.9, 135.0, 128.2, 127.6, 126.4, 120.3, 112.4, 111.2, 84.0, 82.3, 70.8, 70.7, 70.5, 70.3, 69.8, 65.1, 30.6, 29.7. HRMS (FAB) calcd for $C_{20}H_{25}FN_2O_3$ (MH+): 360.1849; found: 360.1854. The data are identical with those reported in literature.[1f]

Conclusion

In summary, TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) which can serve as key precursor for many monodentate and multidentate PET imaging agents has been synthesized with cost-effective starting materials through simple reactions. Our new method is more concise (five steps with six stages) than the reported methods. The overall yield of the new method is 25%, which is higher than our previously published method[4] (the overall yield is 16%). Toxic and smelly reagent (e.g., 4-methylbenzenethiol) was excluded as well. Our new method can be applied for synthesis of TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) in multi-gram scale. The non-radioactive monodentate PET imaging agent ([F]AV-45) **1** has also been prepared in good yield from **5**. Our new method could be employed for mass production of AV-45 and other multidentate imaging agents.

Funding

This work is supported by Fundamental Research Funds for the Central Universities (2016JBM069) and National Science Foundation of China (NSFC 21302011).

References

[1] (a) Wong, D.; Rosenberg, P.; Zhou, Y.; Kumar, A.; Raymont, V.; Ravert, H.; Dannals, R.; Nandi, A.; Brasic, J.; Ye, W.; *J. Nucl. Med.* **2010**, *51*, 913–920; (b) Kung, H.; Choi, S.; Qu, W.; Zhang, W.; Skovronsky, D. *J. Med. Chem.* **2009**, *53*, 933–941; (c) Choi, S.; Golding, G.; Zhuang, Z.; Zhang, W.; Lim, N.; Hefti, F.; Benedum, T.; Kilbourn, M.; Skovronsky, D.; Kung, H. *J. Nucl. Med.* **2009**, *50*, 1887–1894; (d) Zhang, W.; Kung, M.; Oya, S.; Hou, C.; Kung, H. *Nucl. Med. Biol.* **2007**, *34*, 89–97; (e) Clark, C. M.; Schneider, J. A.; Bedell, B. J.; Beach, T. G.; Bilker, W. B.; Mintun, M. A.; Pontecorvo, M. J.; Hefti, F.; Carpenter, A. P.; Flitter, M. L.; *J. Am. Med. Assoc.* **2011**, *305*, 275–283; (f) Kung, M.-P.; Kung, H. F. WO Patent 2007/126733 A2, **2007**.

[2] Zha, Z.; Choi, S. R.; Ploessl, K.; Lieberman, B. P.; Qu, W.; Hefti, F.; Mintun, M.; Skovronsky, D.; Kung, H. F. *J. Med. Chem.* **2011**, *54*, 8085–8098.

[3] For synthesis of AV-45 from TEG-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (5), please see: (a) Hayashi, K.; Tachibana, A.; Tazawa, S.; Mizukawa, Y.; Osaki, K.; Morimoto, Y.; Zochi, R.; Kurahashi, M.; Aki, H.; Takahashi, K. *J. Labelled Compd. Radiopharm.* **2013**, *56*,

295–300. For other methods for synthesis of AV-45, please see: 1f and (b) Benedum, T.; Golding, G.; Lim, N.; Zhang, W. US Patent 2010/172836 A1, **2010**; (c) Lee, S. J.; Oh, S. J.; Moon, D. H.; Ryu, J. S.; Kim, J. S.; Lee, J. J. EP Patent 2810926 A1, **2014**; (d) Piramal, I. S. A; Berndt, M.; Friebe, M.; Samson, F.; Braun, R.; Garke, G.; Patt, M.; Schiddan, A.; Smuda, C. JP Patent 2016/47831 A1, **2016**.

[4] Li, Z.; Liu, B.; Duan, W.; Zhu, L. *Syn. Commun.* **2015**, *45*, 2740–2747.

[5] For some reviews, see: (a) Maercker, A. *Org. React.* 1965, *14*, 270–490 (b) Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, UK, 1971; pp 81–90; (c) Hoffmann, R. W. *Angew. Chem. Int. Ed.* 2001, *40*, 1411–1416.

[6] Abu, T. K.; Lokman, H. C.; Subrata, G. *Tetrahedron Lett.* **2004**, *45*, 7891–7894.