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Improved Syntheses of Precursors for PET Radioligands [^{18}F]XTRA and [^{18}F]AZAN

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Abstract

Improved syntheses of 7-methyl-2-*exo*-[3′-(2-bromopyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptanes (**3**) and 7-methyl-2-*exo*-[3′-(6-bromopyridin-2-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptanes (**4**), precursors for PET radioligands [^{18}F]XTRA (**1**) and [^{18}F]AZAN (**2**), involving a key Stille coupling step followed by deprotection of Boc group and *N*-methylation are described. The new synthetic procedures provided the title compounds in more than 40% overall yields.

Keywords

nAChR; PET radioligand; Stille coupling; *N*-methylation

The neuronal nicotinic acetylcholine receptors (nAChRs) are a family of ligand gated ion channels in the central nervous system (CNS), and regulate a variety of neuronal activities. It is well documented that nAChRs play important role in tobacco dependence and various disorders including Alzheimer's disease, Parkinson's disease, schizophrenia, anxiety, depression, Tourette's syndrome, attention-deficit hyperactivity disorder and pain.[1–5] nAChRs include many subtypes. Development of specific α4β2-nAChRs antagonist is of current interest, which could lead to useful diagnosis and therapeutics for many disorders.[6–9] Recently, we discovered that XTRA (**1**) and AZAN (**2**) exhibited exceptionally high affinity and selectivity at α4β2-nAChRs.[10,11] Pharmacological studies showed that they are α4β2-nAChRs antagonists with low side effects in mice. Their corresponding radioligands [^{18}F]XTRA ([^{18}F]**1**) and [^{18}F]AZAN ([^{18}F]**2**),[10,11] were found to be excellent positron emission tomography (PET) radioligands in baboon. Their optimal imaging properties make them attractive candidates for further PET studies in human subjects. [^{18}F]XTRA ([^{18}F]**1**) and [^{18}F]AZAN ([^{18}F]**2**) were prepared from their corresponding bromo analogues, **3** and **4** and [^{18}F] fluoride ion (Figure 1).

As part of our ongoing research program, large quantities of compounds **3** and **4** were required. Compounds **3** and **4** were previously prepared in 14.5% and 19% overall yields using multi-step procedures[10] (Scheme 1). The previous syntheses suffered from some drawbacks. The critical one is the low reaction yields resulted from the Heck coupling of

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compound **6** with aromatic amine containing bromide **5** and **9**, and the following Sandmeyer diazotiation of compound **7** and **10**. Furthermore, difficulties in the removal of byproducts and tedious purification procedure during the Heck coupling leaded to product quality issues for the manufacturing processes of the products.

Experienced with the difficulties above, we therefore decided to attempt to develop a more practical and scaleable route to compound **3** and **4**. Encouraged by our recent improvement on synthesis of Boc-protected compound **12**12 we decided to explore Stille coupling reaction as the key step for our new strategy since the Stille reaction has proved to be particularly efficient for the synthesis of biaryl systems13‾15. Herein we wish to report that compound **3** and **4** can be easily and efficiently prepared by Stille cross-coupling of pyridyl stannes with iodopyridine followed by Boc deprotection and *N*-methylation. (Scheme 2).

Compounds **13** and **15** were obtained in excellent yields from 2-bromopyridine and 2,6-dibromopyridine respectively.l16›17. The Stille cross-coupling of **12** with stannes **13**16 in DMF in the presence of $Pd(Ph_3P)_4$ and Ag_2O leaded to **14**. The Stille coupling of **12** with stannes **15**17 was effected reproducibly by using $Pd(Ph_3P)_4$ as catalyst and toluene as solvent. Compound **14** and **16** were obtained in 73% and 77% yields respectively after column chromatography18. TFA deprotection of **14** and **16** gave **8** and **11** in 86% and 90% yields19. Compound **3** and **4** were synthesized by reductive methylation of amines **8** and **11** with formaldehyde in the presence of sodium phosphite10›20. Alternatively, compound **3** and **4** can be obtained by simultaneous deprotection of Boc group and *N*-methylation with HCOOH/HCHO under refluxing21. In both procedures, the overall yields are strikingly improved. The final products can be potentially scaled up to obtain multigram quantities since all reactions are very clean and reproducible.

In summary, we have developed an efficient 3-step (and or 2 step) strategy for synthesis of compound **3** and **4** starting from iodo derivaties and stannanes. A main improvement from the original route was the adopting Stille coupling reaction as key step to be performed in good yields and facilitate the isolation of intermediates. Combined with other improvements to optimize conditions for individual reaction step, this approach should enable us to obtain multigram quantities for further studies of our PET radioligands [^{18}F]XTRA and [^{18}F]AZAN.

Acknowledgments

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18. A mixture of 7-*tert*-Butoxycarbonyl-2-*exo*-(3′-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptanes (**12**) (900 mg, 2.5 mmol), tetrakis(triphenylphosphine)palladium(0)(129 mg, 0.11 mmol) and silver (I)oxide (510 mg, 2.25 mmol) in 10 ml of dimethylformamide was stirred at 95 °C. After 5 min, 2-bromo-3-trimethyltinpyridine **13** (freshly prepared, 870 mg, 2.7 mmol, 1.2 equiv) dissolved in 5 mL of dimethylformamide was added, and the mixture was heated in a sealed reaction vessel and stirred at 95 °C for 0.5 h. The reaction mixture was allowed to attain room temperature, the precipitate was filtered off and the filtrate was finally evaporated. The residue was subject to silica gel chromatography to give product **14** as yellow oil (708 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) d 8.53 (bs, 1H), 8.49 (bs, 1H), 8.40 (dd, *J*=4.4 Hz, 2.0 Hz, 1H), 7.81 (m, 1H), 7.63 (dd, *J*=7.2 Hz, 2.0 Hz 1H), 7.37 (m, 1H), 4.39 (bs, 1H), 4.25 (s, 1H), 2.96 (m, 1H), 2.01-2.06 (m, 1H), 1.87-1.93 (m, 3H), 1.53-1.63 (m, 2 H), 1.45 (s, 9H). HRMS calcd for $C_{21}H_{25}BrN_3O_2$ $[M+H]^+$: 430.1125, found 430.1114. Compound **16** was prepared in similar manner as yellow oil (77%) by using $Pd(Ph_3P)_4$ as catalyst and refluxing in toluene. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 9.00 (s, 1H), 8.58 (s, 1H), 8.22 (s, 1H), 7.71 (d, 7.6 Hz, 1H), 7.63 (t, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 4.42 (bs, 1H), 4.29 (s, 1H), 2.99 (m, 1H), 1.88-2.07 (m, 4H), 1.54-1.68 (m, 2H), 1.43 (s, 9H). HRMS calcd for $C_{21}H_{25}BrN_3O_2$ $[M+H]^+$: 430.1125, found 430.1121.

19. To a solution of **14** (675 mg, 1.58 mmol) in CH_2Cl_2 (12 mL) was added TFA (5 mL). The mixture was stirred at room temperature for 2 h until TLC (Hexane/EtOAc 1:2) showed the starting material disappeared. The reaction mixture was poured into NH_4OH:water (50 mL, 1:1). The water layer was extracted with $CHCl_3$ (3 × 40 mL). The organic layers were dried with Na_2SO_4, filtered and concentrated to give a residue which was purified by silica gel chromatography ($CHCl_3$/MeOH 3:1) to give the product **8** as oil (452 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) d 8.61 (d, *J*=2.4 Hz, 1H), 8.55 (d, *J*=1.6 Hz, 1H), 8.39 (dd, *J*=2.0 Hz, 4.8 Hz, 1H), 7.95 (m, 1H), 7.82 (dd, *J*=2.0 Hz, 7.2 Hz, 1H), 7.36 (dd, *J*=4.8 Hz, 7.6 Hz, 1H), 4.20 (br s, 1H), 4.10 (br s, 1H), 3.14 (m, 1H), 2.08-2.17 (m, 5H), 1.65-1.82 (m, 2H). HRMS calculated for $C_{16}H_{17}BrN_3$, [M+H] *m/z*=330.0607, found, 330.0596. Compound **11** was prepared similarly in 90% yield as oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 8.96 (br s, 1H), 8.62 (br s, 1H), 8.30 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 3.84 (m, 1H), 3.67 (m, 1H), 2.92 (m, 1H), 1.74-1.97 (m, 3H), 1.53-1.79 (m, 4H).

20. The secondary amine (**8**, or **11**) (462 mg, 1.4 mmol) was dissolved in 1 M sodium phosphite solution (25 mL). Aqueous formaldehyde (37%) (2.2 mL) was added, and the reaction mixture was heated with stirring at 60 °C in an oil bath until the reaction was complete (about 3 h). The reaction flask was cooled, and 5% K_2CO_3 (25 mL) was added. The mixture was extracted with $CHCl_3$ (4 × 40 mL). The $CHCl_3$ extracts were dried over sodium sulfate, filtered, and evaporated to give a residue that was purified by silica gel chromatography ($CHCl_3$/MeOH 10:1), giving tertiary amines **3** and **4** in 76% and 85% yields, respectively.

21. The compound **14** (200 mg, 0.46 mmol) was dissolved in formic acid (0.5 mL) and aqueous formaldehyde (37%) (1.0 mL), heated at reflux until the completion of the reaction (about 4 h), and cooled to room temperature. The reaction mixture was poured into 5% K_2CO_3 solution (30 mL). The aqueous mixture was extracted with $CHCl_3$ (4 × 20 mL), the combined extracts were washed with water (20 mL), dried over Na_2SO_4, and the solvent was removed. The residue was

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chromatographed on silica gel ($CHCl_3$/MeOH 10:1) to give the product **3** as colorless oil (103 mg, 65%). Compound **4** was prepared similarly as colorless oil (70%). The spectral features of compound **3** and **4** were consistent with previously published values.

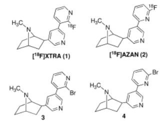
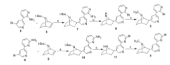


Figure 1.
Chemical structures of nAChR PET radioligands and their precursors.



Scheme 1.
Previous syntheses of compound **3** and **4.** Reagents and conditions: (a) $Pd(PPh_3)_4$, piperidine/HCOOH; (b) HBr, CuBr, $NaNO_2$; (c) NaH_2PO_3, 37% HCHO.

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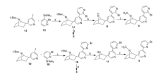

Scheme 2.

New syntheses of compound **3** and **4**. Reagents and conditions: “(a) For compound **14**, $Pd(PPh_3)_4$, Ag_2O, DMF; for compound **16**, $Pd(PPh_3)_4$, toluene; (b) CF_3COOH (TFA); (c) NaH_2PO_3, 37% HCHO; (d) HCOOH, 37% HCHO.