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A novel one-pot palladium-mediated synthesis of *N*-[(2-hydroxyphenyl)methyl]-*N*-(4-phenoxy-3-pyridinyl) acetamide, the precursor to [^{11}C]PBR28, a PET biomarker for the peripheral benzodiazepine receptor

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ABSTRACT

Due to an urgent need to image the peripheral benzodiazepine receptor (PBR) in living human subjects using positron emission tomography imaging, we had cause to prepare *N*-[(2-hydroxyphenyl)methyl]-*N*-(4-phenoxy-3-pyridinyl) acetamide (desmethyl-PBR28 (**1**)), the precursor to [^{11}C]PBR28. Herein, we report a new synthesis of the precursor in which palladium-mediated reduction of the nitro pyridine to the corresponding amino pyridine, and subsequent reductive amination, can be achieved with decaborane in a convenient one-pot procedure. This procedure is operationally simpler than the current alternatives and provides high quality precursor suitable for use in clinical applications.

The use of positron emission tomography (PET) imaging to non-invasively diagnose disease, monitor patient response to therapy, and elucidate biochemical mechanisms, all in living human subjects, is becoming increasingly popular in the global clinical setting.[1] In addition to widespread clinical application, the use of PET imaging within the pharmaceutical arena is also expanding, where it is quickly becoming invaluable in drug discovery programs and to monitor the impact of experimental drugs in clinical trials.[2]

Presently, there is significant interest in imaging the peripheral benzodiazepine receptor (PBR), also known as the translocator protein 18 kDa,[3] and a number of PET biomarkers for the PBR have been reported in recent years.[4–8] The PBR is different from the brain receptors that bind γ-amino butyric acid (GABA) and synthetic benzodiazepines and is found on the outer membrane of mitochondria in a number of cells, as well as plasma membranes in erythrocytes. Imaging PBR using PET is of interest to nuclear medicine physicians because PBR has been implicated in cancer as well as a range of neurodegenerative diseases and nervous system disorders. Moreover, an increase in PBR levels, which could be quantified by increased uptake of a PBR biomarker, is considered to be indicative of inflammation. A number of PET biomarkers that allow for imaging and evaluation of PBR are known and the most common to date is [^{11}C]PK11195.[4] However, this biomarker is reported to have a number of limitations including low brain penetration and high non-specific binding. Therefore, a number of research groups have concentrated in developing new PET ligands for PBR and a number of new PET ligands, including DPA 713,[5] [^{11}C]DAA1106,[6] [^{18}F]FEDAA1106,[7] and [^{11}C]PBR28,[8] have been recently reported. In choosing a PET ligand to make available to clinical investigators at the University of Michigan, we selected *N*-(2-[^{11}C]methoxybenzyl)-*N*-(4-phenoxy-3-pyridinyl) acetamide ([^{11}C]PBR28, **2**), developed by Pike and colleagues, because of its high affinity for PBR (IC_{50} = 0.658 nm), favorable pharmacokinetics, and appropriate dosimetry.[9]

The radiosynthesis of [^{11}C]PBR28 is carried out in our laboratory using well-established radiochemical reactions with carbon-11[10] and has been extensively described by both Pike[8a] and Zheng[8c] last year. Briefly, [^{11}C]CO_2 is delivered from a General Electric (GE) PETTrace cyclotron and converted to [^{11}C]CH_4 using a nickel-mediated reduction in the presence of H_2(g) at 350 °C. [^{11}C]CH_4 is then converted to [^{11}C]CH_3I by reaction with iodine at 720 °C, and the reactivity of [^{11}C]CH_3I is enhanced by passing over a column of AgOTf at 200 °C to provide [^{11}C]CH_3OTf. The *N*-[(2-hydroxyphenyl)methyl]-*N*-(4-phenoxy-3-pyridinyl) acetamide (PBR28 precursor, **1**) is then methylated with [^{11}C]CH_3OTf to provide [^{11}C]PBR28 which is subsequently purified by semi-preparative HPLC. In our laboratory, the whole process is automated by a GE Tracerlab $FX_{C\text{-}Pro}$ synthesis module (Scheme 1). In order to provide [^{11}C]PBR28 to physicians, we needed a supply of high quality precursor **1**, suitable for use in clinical research.

A number of different syntheses for the preparation of desmethyl-PBR28 (**1**) have been reported. They all follow the general schematic illustrated in Figure 1 in which nitro pyridine **5** is first

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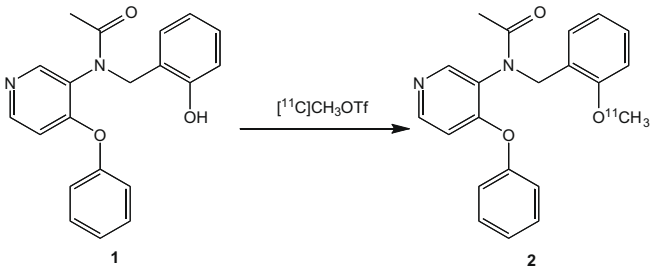


Scheme 1. Radiosynthesis of [^{11}C]PBR28.

reduced to the corresponding amine **6**. Amine **6** is initially coupled with *o*-salicylaldehyde via reductive amination, and subsequent acetylation provides PBR28 precursor **1**. In the synthesis reported by Zheng and co-workers in 2009,[8c] the reduction of the nitro group was achieved by refluxing with concd HCl in methanol in the presence of $SnCl_2$, and then a separate sodium borohydride-mediated reductive amination to provide **1**. This approach is effective and, indeed, we have previously used this strategy to prepare PBR28 precursor in our laboratory. However, as stannous chloride is highly toxic,[11] there is general reluctance to use such tin compounds during the synthesis of precursors that will be used in the syntheses of clinical radiopharmaceutical doses. An alternative and more attractive approach was the two-pot procedure reported by Pike's group in which the reduction was achieved by treating with concd HCl in the presence of iron powder, and subsequent reductive amination, also using sodium borohydride and Dean–Stark conditions.[8a]

However, as we considered strategies for the preparation of the gram quantities of PBR28 precursor necessary to meet our routine clinical demand, we were excited to read Yoon's report of a one-pot palladium/decaborane-mediated reduction of nitroaromatics followed by subsequent reductive amination[12] and were curious as to whether it could be adapted for our needs. The use of Pd/C makes the work-up faster, easier, and sustainable with a low expected Pd contamination.[13] Whilst decaborane is also toxic,[14] in our experience it is easier to remove during work-up than stannous chloride, and such a synthesis of the PBR28 precursor would be operationally simpler than those previously reported.

Our novel synthetic approach to the PBR28 precursor is illustrated in Scheme 2. Initially, commercially available 3-nitropyridin-4-ol **3** was treated with PCl_5 and $POCl_3$ to provide 4-chloro-3-nitropyridine **4** (73% yield) according to Pike's procedure.[8a] With **4** in hand, Wang's procedure[8c] was employed to couple it with phenol, in the presence of potassium carbonate, to provide **5** in 77% yield without the need for chromatographic purification. *Note*: 4-chloro-3-nitropyridine (**4**) is also commercially available, but the commercial material was found to be ~80% pure by ^{1}H NMR analysis. Consequently, following coupling with phenol, **5** had to be purified by flash chromatography and limited recovery from the column

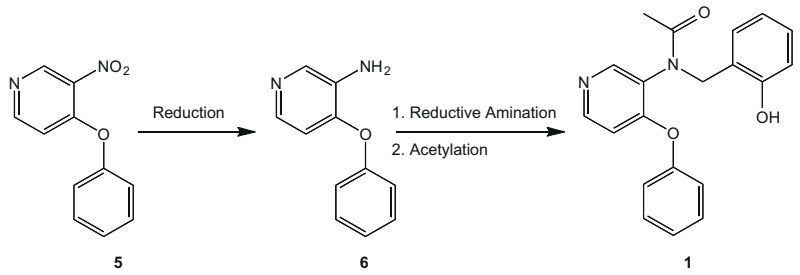
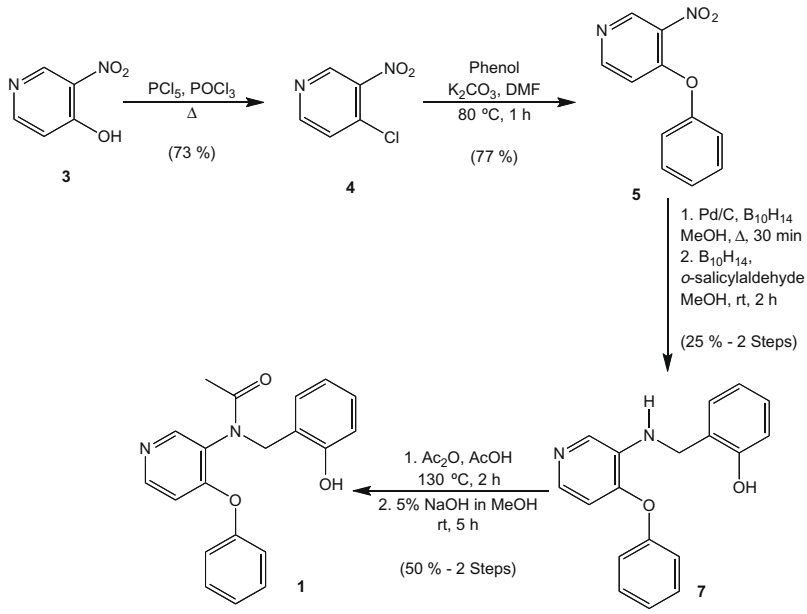


Figure 1. General strategy for preparation of PBR28 precursor.



Scheme 2. Synthesis of *N*-[(2-hydroxyphenyl)methyl]-*N*-(4-phenoxy-3-pyridinyl) acetamide (**1**).

resulted in lower yields (50%) of **5** from this coupling reaction. Therefore, it is preferential to prepare **4** in house (>90% purity) to avoid purification, by flash chromatography, of intermediate **5**.

With nitropyridine **5** in hand, it was subjected to Yoon's procedure,[12] on gram scale, by dissolving in methanol (50 mL) and treating with palladium on carbon (0.05 equiv) and decaborane (0.3 equiv).[15] Refluxing for 30 min was sufficient to reduce the nitro group to the corresponding amine and after this time the reaction was cooled to room temperature. Salicylaldehyde (1.2 equiv) and additional decaborane (0.3 equiv) were added and the reaction was stirred for a further 2 h at rt. After this time, the reaction was concentrated in vacuo and methanol (20 mL) was added to the concentrate to triturate **7** as a white powder (25% yield, >95% purity by ^{1}H NMR). The somewhat low yield was attributed to loss of material during purification by trituration, but the loss was deemed acceptable given the simplicity of the purification. However, due to the toxicity of decaborane,[14] we wished to confirm that, whilst convenient, trituration was indeed also suitable for removal of residual decaborane from product **7**. The proton NMR spectrum of decaborane is complex due to the caged structure and both proton–proton and proton–boron coupling interactions.[16] Nevertheless, the NMR spectrum for intermediate **7** revealed no signals attributable to decaborane, confirming residual levels at least below the NMR limit of detection.

Finally, it was necessary to acetylate **7** to provide desmethyl-PBR28 **1**. Initially, we followed Zheng's room temperature procedure[8c] (AcCl (2.2 equiv), DMAP (2.5 equiv), DCM, rt) but this reaction turned out to be poor in our hands and we only acetylated the phenol function. Therefore, we employed Pike's acetylation procedure[8a] (refluxing mixture of acetic acid and acetic anhydride) to provide the O- and N-diacetylated species. Subsequent treatment with 5% sodium hydroxide in methanol at rt was sufficient to deprotect the phenol, whilst leaving the amide intact, and provided [^{11}C]PBR28 precursor **1** (50% from **7**, >95% purity by ^{1}H NMR).[17]

In conclusion, a simplified synthesis of *N*-[(2-hydroxyphenyl)methyl]-*N*-(4-phenoxy-3-pyridinyl) acetamide (**1**), the precursor for [^{11}C]PBR28, has been developed, employing a one-pot reduction–reductive amination procedure. This synthetic strategy is operationally simpler than other reported two-pot procedures as it eliminates the need to use toxic tin(II) chloride, refluxing hydrochloric acid, and Dean–Stark reductive amination conditions. Clinical research with [^{11}C]PBR28 is currently underway and will be reported in due course.

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15. Typical experimental procedure using the decaborane-Pd/C system: Under argon, Pd/C 10% (307.5 mg, 0.29 mmol, 0.06 equiv) was added to a solution of **5** (1.04 g, 4.83 mmol) in MeOH (50 mL). Then, a solution of $B_{10}H_{14}$ (177 mg, 1.45 mmol, 0.3 equiv) in MeOH (5 mL) was added. The heterogeneous solution was refluxed for 30 min and then cooled back to rt. A solution of salicylaldehyde (682 mg, 5.58 mmol, 1.2 equiv) in MeOH (5 mL) followed by an additional solution of $B_{10}H_{14}$ (180 mg, 1.47 mmol, 0.3 equiv) in MeOH (5 mL) were added to the reaction mixture. The resulting green solution was then stirred at rt for 2 h. After this time, the reaction mixture was filtrated off over a Celite pad, washed with MeOH (200 mL), and concentrated in vacuo. The yellow crude solid was triturated with MeOH (20 mL) to give compound **7** as a white solid (358 mg, 25%, >95% purity by ^{1}H NMR). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.63 (s, 1H), 7.85 (s, 1H), 7.70 (d, J = 5.1 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.26–7.03 (m, 5H), 6.84–6.71 (m, 2H), 6.53 (d, J = 5.1 Hz, 1H), 5.95 (t, J = 6.1 Hz, 1H), 4.34 (d, J = 6.1 Hz, 2H). HRMS calcd for $C_{18}H_{17}N_2O_2$ (M+H$^+$), 293.1290; found, 293.1287.
16. Decaborane: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.17–4.69 (m, 10H), −0.11 to 1.46 (m, 4H).
17. Acylation procedure: under argon, a solution of compound **7** (355 mg, 1.21 mmol), DMAP (56 mg, 0.46 mmol, 0.4 equiv), and Ac_2O (265 mg, 2.60 mmol, 2.1 equiv) in acetic acid (3 mL) was heated at 130 °C for 2 h. After cooling back to rt, the reaction mixture was diluted in water (50 mL) and extracted with ethyl acetate (150 mL). The collected organic layers were washed with aq satd $NaHCO_3$ (25 mL), brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude colorless oil was then re-dissolved in a solution of NaOH in MeOH (5% w/v, 6 mL) and stirred at rt for 5 h. After removing the volatiles in vacuo, the residue was diluted in an aq solution of HCl (pH 5, 50 mL) and extracted with ethyl acetate (150 mL). The combined organic layers were washed with aq satd $NaHCO_3$ (25 mL), brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude white solid was purified by flash chromatography (hexane/ethyl acetate 1/2.5) to give desmethyl-PBR28 (**1**) as a white solid (203 mg, 50%, >95% purity by ^{1}H NMR). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.28 (s, 1H), 8.41 (d, J = 3.4 Hz, 1H), 8.31 (s, 1H), 7.39 (t, J = 7.9 Hz, 2H), 7.28–7.23 (m, 2H), 6.94 (d, J = 8.1 Hz, 1H), 6.77 (d, J = 8.1 Hz, 2H), 6.72 (t, J = 7.9 Hz, 1H), 6.67–6.62 (m, 2H), 4.82 (s, 2H), 2.02 (s, 3H). HRMS calcd for $C_{20}H_{18}N_2NaO_3$ (M+Na$^+$), 357.1215; found, 357.1200.