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Tetrahedron Letters 45 (2004) 3607–3610
Tetrahedron Letters

Synthesis of a new precursor to the nicotinic receptor tracer 5-IA-85380 precursor using trimethylsilyl iodide as deblocking agent

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Received 19 January 2004; revised 4 March 2004; accepted 10 March 2004

Abstract—We describe the synthesis of a new precursor of 5-IA-85380, specific radiotracer for $\alpha_4\beta_2$ nicotinic acetylcholine receptors. (*S*)-5-Trimethylstannyl-3-(2-azetidinylmethoxy)pyridine (**4**) was prepared in six steps and 62% overall yield starting from (*S*)-2-azetidinecarboxylic acid. The key step of this synthesis is selective release of the amine function without removing the stannyl moiety using trimethylsilyl iodine.

Nicotinic acetylcholine receptors are of great interest because they play an important role in tobacco dependence[1] and because drugs active at these receptors may have therapeutic utility in various neuropsychiatric disorders such as Alzheimer's disease.[2] The iodinated analog of A-85380,[3] (*S*)-5-[^{123}I]iodo-3-(2-azetidinylmethoxy)-pyridine ([^{123}I]5-IA, **3**), is a ligand used for single photon emission computerized tomography (SPECT) imaging of human and nonhuman nicotinic acetylcholine receptors in vivo.[4] [^{123}I]5-IA presents a specificity for the $\alpha_4\beta_2$ subtype nicotinic acetylcholine receptors (the predominant high-affinity subtype in brain) and expresses a high binding affinity in rat and human brain with K_D of 10 and 12 pM, respectively.[4c]

[^{123}I]5-IA **3** is a tracer of interest but unfortunately the methods described in the literature to afford it require two steps, one step to label an N-protected precursor (**1a** or **1b**) and another to release the amino group (Scheme 1).[5]

The first step of labeling affords **2** in good yields around 80%, but the following cleavage of the carbamate sometimes presents an issue of reproducibility. This issue, as well as a loss of radioactivity due to the manipulation time for the deprotection, led us to consider a faster and more efficient method to afford **3**. The purpose of the present study was to synthesize, starting from (*S*)-2-azetidinecarboxylic acid (**5**), a new precursor **4** in good overall yield, and which would present the advantage to lead directly to [^{123}I]5-IA (**3**) in one step, rather than requiring deprotection after the labeling step (Scheme 2). The key step of this synthesis appeared to be the release of the azetidine amine function without loss of the stannyl substituent.

The synthesis of **4** required the construction of two primary fragments, namely (*S*)-1-(benzyloxycarbonyl)-2-azetidinemethanol-*p*-tosylate (**8**) and 3-bromo-5-hydroxypyridine (**11**) (Scheme 3). The (*S*)-azetidine moiety was introduced using commercially available (*S*)-2-azetidinecarboxylic acid (**5**), which can also be built starting from L-aspartic acid.[6] The first step of this synthesis involved the protection of the amino group of **5**. A benzyloxycarbonyl (Cbz) group, in a first attempt, appeared to be a choice of interest regarding its abilities to be removed not only in acid conditions[7] but also by catalytic hydrogenolysis.[8]

Acid **6** was obtained in quasi-quantitative yield using the same conditions as Corey et al.[9] starting from (*S*)-proline, namely simultaneous addition of benzyl chloroformate and sodium hydroxide to the amino acid in water. This method appeared to be more efficient compared to those using an organic base like triethylamine,

Keywords: Radiotracer; SPECT; Imaging; Acetylcholine receptors; Organostannane; Trimethylsilyl iodide.
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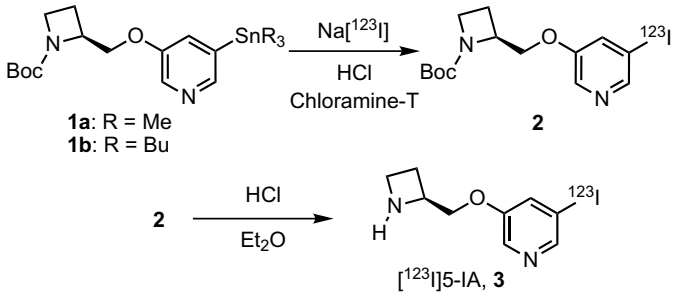
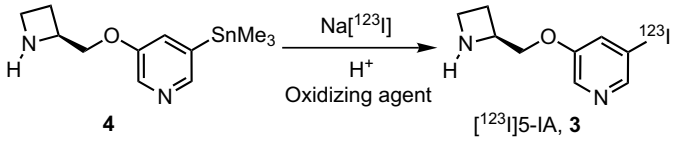
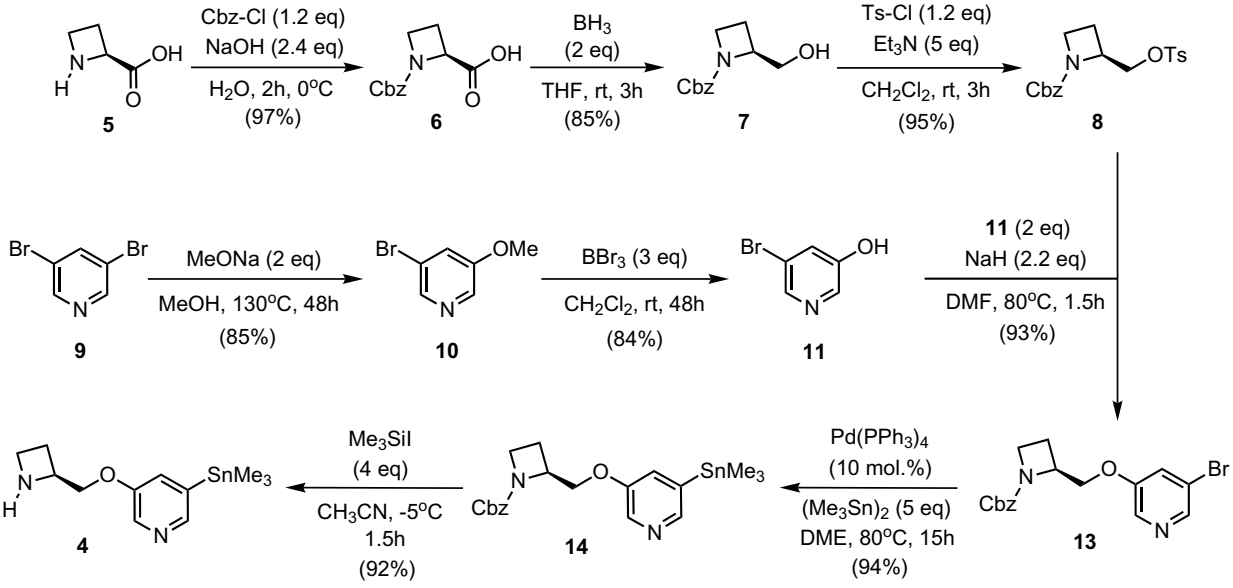
doi:10.1016/j.tetlet.2004.03.061



Scheme 1.



Scheme 2.



Scheme 3.

pyridine, or DMAP in a mixture of dioxane/water. Reduction of acid **6** using BH_3 allowed us to isolate alcohol **7** in 85% yield without epimerization of the chiral carbon in comparison to the specific rotation described in the literature.[10] The first fragment of this synthesis (**8**) was then obtained by tosylation of **7** (95%).

As for the preparation of bromopyridinol **11**, although the literature[11] described its preparation starting from 3-amino-5-bromopyridine by a Sandmeyer reaction, we found that **11** could be obtained more efficiently in two steps starting from 3,5-dibromopyridine (**9**). Heating **9** in MeOH in a sealed tube at 130 °C for 2 days in presence of freshly prepared MeONa led to 3-bromo-5-methoxypyridine (**10**) in 85% yield. Treatment of **10** with excess of BBr_3 allowed cleavage of the methoxy group to afford **11** in good yield (84%). In this last step, we noticed that good recovery of pyridinol **11** could only be obtained with a particular workup.[12]

After formation of the sodium salt of **11** using NaH in DMF, coupling with **8** was performed by heating the mixture at 80 °C for 1.5 h to produce compound **13**[13] in 93% yield. We chose this way of synthesis, which involved one more step instead of a conventional Mitsunobu reaction starting from the alcohol **7**, in view of the result obtained by Musachio for the preparation of an analog of **13** protected by a *tert*-butoxycarbonyl (Boc) group (43% yield).[5a]

A first approach to compound **4** started from **13**, by acid cleavage of the Cbz group before stannylation of the amine thus obtained using Me_6Sn_2 and a palladium

catalyst. Unfortunately, even after some experimentation, the stannylation led to only traces of **4** with recovery or degradation of the starting material. Such a result is not surprising, since the formation of a complex between the free secondary amine and the palladium catalyst can be easily considered, leading therefore to an inhibition of the catalyst.

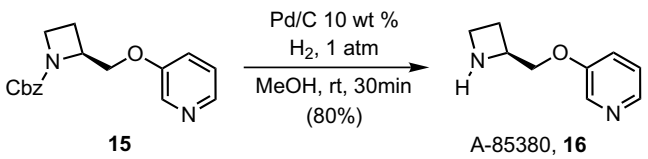
Introduction of the stannyl moiety was realized starting from **13**, using Me_6Sn_2 and $Pd(PPh_3)_4$ as catalyst, to afford compound **14**[14] in 94% yield after one night in DME at 80 °C. The use of THF, dioxane, or toluene as solvent significantly decreased the yield of **14**.

Starting from **14** we tried many ways to selectively deprotect the Cbz group without affecting the trimethyltin moiety, which is crucial for the formation of [^{123}I]5-IA (**3**) (Scheme 2). The first method examined selective hydrogenolysis of **14** using low charges of Pd/C (1–2 wt %) under atmospheric pressure of hydrogen. Surprisingly, no reaction occurred, even with 10, 50 wt %, and greater than stoichiometric amounts of catalyst and up to 5 atm of H_2(g). Neither the Me_3Sn nor the Cbz group was affected. Therefore, it was particularly surprising to observe facile deprotection of compound **15** under catalytic hydrogenolysis (Scheme 4). Indeed, A-85380[3] (**16**) was obtained in 80% yield after 30 min under 1 atm H_2(g).

This result showed that the presence of the stannyl moiety of **14** influences the hydrogenolysis reaction, although it is unclear why. A catalyst inhibition due to the trimethyltin group seems difficult to consider as well as an interaction between both protecting and stannyl groups.

Selective deprotection of the Boc group of **1a** and **1b** (Scheme 1) using acid conditions has been applied unsuccessfully in our group. Although, Li et al.[15] successfully realized the selective deprotection of an acetal moiety without removal of an aryltributyltin group using aqueous HCl, the same conditions or the use of trifluoroacetic acid on **1a** and **1b**, in our case, resulted in loss of both carbamate and tin moieties without significant selectivity. Consequently, acid treatments were not tried on **14**, for which cleavage of the Cbz group means the use of stronger acid conditions, such as HBr in organic or aqueous conditions.[7]

To avoid the loss of the trimethyltin moiety, we decided to employ the commercially available trimethylsilyl iodide (TMSI), a versatile synthetic reagent[16] mostly known for its ability to cleave carbamate, ester, and ether functions. The properties of TMSI make it an attractive reagent since the reactions are carried out under neutral conditions and generally at room temperature.[17]



Scheme 4.

We found that treatment of **14** with 4 M equiv of TMSI in acetonitrile led to the free amine **4** in 92% yield without affecting the stannyl substituent (Scheme 3).[18] Addition of methanol at the end of the reaction decomposed excess TMSI and the silyl ester formed during the reaction. Such a good result can be explained by the difference between TMSI deblocking and acid deblocking procedures, since with TMSI the reactions are carried out under neutral and therefore safe conditions toward the stannyl moiety. Given this outcome with the Cbz protection, we can expect, that compound **4** might be successfully prepared using TMSI on compound **1a**, since removal of Boc group by TMSI has also been reported.[16]

In summary, we realized the synthesis of a new precursor **4** of [^{123}I]5-IA, obtained in 62% overall yield in six steps starting from (*S*)-2-azetidinecarboxylic acid (**5**). The last step of this synthesis, which involves the cleavage of the benzyloxycarbonyl group, was successfully realized using trimethylsilyl iodide, without influence on the stannyl substituent. This new precursor, accessible in good overall yield, also presents the advantage to lead directly to [^{123}I]5-IA in one step of labeling. These radiolabeling studies are currently under investigation, and gave so far encouraging results. This method of obtaining mixed amino-tin compounds using TMSI as deblocking agent may present an advantage for the preparation of other radiotracer precursors.

Acknowledgements

The authors thank Louis Amici for analytical chemistry assistance. This work was supported in part by NIDA/NCI Transdiciplinary Tobacco Use Research Center (P50 DA84733; TTURC) and Veterans Affairs Research Enhancement Award Program (REAP) Center on 'Neural Mechanisms and Treatment Response in Depression'.

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12. Typical procedure for the preparation of 3-bromo-5-hydroxypyridine (**11**): 3-bromo-5-methoxypyridine (**10**) (9.67 g, 51.4 mmol) was dissolved in 100 mL of CH_2Cl_2 and at 0 °C was added BBr_3 (155 mL, 1 M in CH_2Cl_2, 3 equiv). The solution was stirred at room temperature for 2 days, then MeOH (70 mL) was slowly added and the solvent was evaporated. MeOH (100 mL) was added and the mixture was refluxed for 2 h and the solvent was evaporated. Water was added and the pH adjusted to 7–8 with Na_2CO_3 before extracting the mixture three times with EtOAc. The extracts were combined, dried, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel with an eluent of EtOAc/hexane (3:7) to provide a white solid (7.51 g, 84%): mp 162–164 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.11–8.06 (m, 2H), 7.43–7.41 (m, 1H), 5.03 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 156.8 (C), 142.3 (CH), 137.7 (CH), 127.3 (CH), 122.1 (C).
13. Data for (*S*)-5-bromo-3-(1-benzyloxycarbonyl-2-azetidinylmethoxy)pyridine (**13**): colorless oil; $[\alpha]_D^{20}$ −57.8 (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31–8.18 (m, 2H), 7.42–7.21 (m, 6H), 5.15–4.99 (m, 2H), 4.63–4.52 (m, 1H), 4.45–4.22 (m, 1H), 4.13–3.91 (m, 3H), 2.46–2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1 (C), 155.2 (C), 143.2 (CH), 136.5 (CH), 136.4 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 124.0 (CH), 120.3 (C), 68.6 (CH_2), 66.6 (CH_2), 60.1 (CH), 47.3 (CH_2), 19.2 (CH_2). Anal. Calcd for $C_{17}H_{17}BrN_2O_3$: C, 54.13; H, 4.54; N, 7.43. Found: C, 53.87; H, 4.56; N, 7.31.
14. Data for (*S*)-5-trimethylstannyl-3-(1-benzyloxycarbonyl-2-azetidinylmethoxy)pyridine (**14**): colorless oil; $[\alpha]_D^{20}$ −54.8 (*c* 1.36, $CHCl_3$); ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 8.25 (s, 2H), 7.43–7.29 (m, 6H), 5.16–5.07 (m, 2H), 4.68–4.63 (m, 1H), 4.47–4.30 (m, 1H), 4.20–4.16 (m, 1H), 4.05–3.97 (m, 2H), 2.47–2.37 (m, 2H), 0.39 (s, 9H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 156.9 (C), 155.7 (C), 148.7 (CH), 138.4 (C), 138.1 (CH), 137.7 (C), 129.2 (CH), 128.7 (CH), 128.5 (CH), 69.2 (CH_2), 67.1 (CH_2), 61.2 (CH), 48.2 (CH_2), 20.1 (CH_2),−8.9 (CH_3). HRMS (EI) calcd for $C_{20}H_{26}N_2O_3Sn$: 458.0972, found 458.0960.
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18. Typical procedure for the preparation of (*S*)-5-trimethylstannyl-3-(2-azetidinylmethoxy)pyridine (**4**). Me_3SiI (4 equiv, 3 × 0.077 mL, 3 × 1.33 equiv) were added in three times every 30 min to a solution of **14** (188 mg, 0.407 mmol) in CH_3CN (9 mL) at −5 °C. After 1.5 h MeOH (6 equiv) was added and then the solution stirred during 10 more minutes after which the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography on silica gel with an eluent MeOH/EtOAc (2:8) to provide a pale yellow solid (123 mg, 92%): mp 52–54 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.22 (s, 1H), 8.14 (s, 1H), 7.61 (s, 1H), 4.91–4.79 (m, 1H), 4.43–4.38 (m, 2H), 4.13–3.97 (m, 2H), 2.65–2.58 (m, 2H), 0.32 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 156.4 (C), 149.0 (CH), 140.7 (C), 138.4 (CH), 131.2 (CH), 69.0 (CH_2), 60.9 (CH), 45.3 (CH_2), 22.5 (CH_2), −9.1 (CH_3). HRMS (EI) calcd for $C_{12}H_{20}N_2OSn$: 329.0657, found 329.0674.