Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Large-Scale Synthesis of Boc-L-azatyrosine

Hervé Germain [a], Craig S. Harris [a], Fabrice Renaud [a] & Nicolas Warin [a]
[a] AstraZeneca, Centre de Recherches, Z. I. la Pompelle, Reims, France
Published online: 08 Jan 2009.

To cite this article: Hervé Germain, Craig S. Harris, Fabrice Renaud & Nicolas Warin (2009) Efficient Large-Scale Synthesis of Boc-L-azatyrosine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:3, 523-530, DOI: 10.1080/00397910802406695

To link to this article: http://dx.doi.org/10.1080/00397910802406695

Synthetic Communications®, 39: 523–530, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802406695

Taylor & Francis
Taylor & Francis Group

Efficient Large-Scale Synthesis of Boc-L-azatyrosine

Hervé Germain, Craig S. Harris, Fabrice Renaud, and Nicolas Warin
AstraZeneca, Centre de Recherches, Z. I. la Pompelle, Reims, France

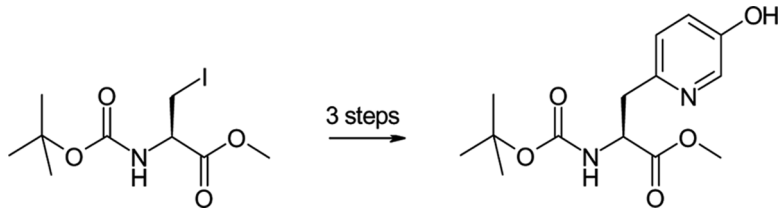
Abstract: A rapid and convenient process for the synthesis of Boc-L-azatyrosine is described from commercially available Boc-β-iodo-Ala-OMe.

Keywords: Hydroxy-deboronation, large scale, Negishi cross-coupling

L-Azatyrosine is an important naturally occurring amino acid first isolated from *Streptomyces chibaensis*[1] and a known antibiotic; it has also shown activity as an anticancer agent.[2] Recently, we became interested in the synthesis of L-azatyrosine as a structural template in one of our anticancer programs. Despite its relatively simple structure, there are few efficient chemical syntheses[3–6] to provide large quantities of optically pure L-azatyrosine, and it is very expensive to buy. We initially considered two approaches by Myers et al., who reported a stereoselective synthesis from 2-methyl-5-hydroxypyridine involving five chemical steps with an overall yield of 17%,[3] and Sooper et al., who reported a racemic total synthesis involving a key enzymatic resolution step to afford, after five chemical steps, optically pure L-azatyrosine in an overall yield of 12%.[4] While both syntheses had their merits, they both involved at least five chemical steps with poor overall yields and chromatography after each step.

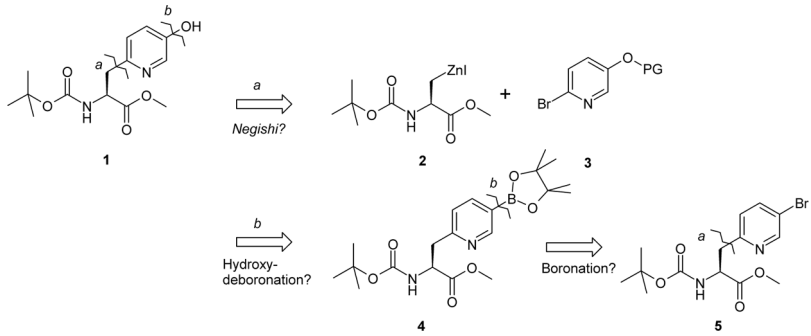
Received August 5, 2008.
Address correspondence to Craig S. Harris, AstraZeneca, Centre de Recherches, Z. I. la Pompelle, BP1050, 51689 Reims Cedex 2, France. E-mail: craig.harris2@astrazeneca.com

Herein, we report a very efficient and reliable formal synthesis of Boc-L-azatyrosine (**1**) in just three steps from commercially available Boc-β-iodo-Ala-OMe.



RESULTS AND DISCUSSION

While there are various asymmetric α-amino acid synthetic approaches available,[7] even nowadays none offers the certainty of near-total chiral transfer or generation of absolute stereochemical configuration at the α-carbon.[7] The Negishi style alkyl-aryl cross-coupling reaction with various halopyridine precursors using the homochiral organozinc reagent derived from L-serine was recently reported with total retention of absolute configuration by Jackson et al.[8,9] Therefore, we based our synthesis on this direct Negishi cross-coupling using the organozincate (**2**).[9] We envisaged two possible disconnections based on this approach: a two-step process based on a successful direct cross-coupling using *O*-protected variants of 2-bromo-5-hydroxypyridine (**3**) as the precursors followed by deprotection to liberate the phenol, and a three-step process relying on the boronation and subsequent hydroxy-deboronation of known bromide (**5**) (Scheme 1).[9]



Scheme 1. Proposed retrosynthetic analysis. Our strategy concentrated on transforming known intermediate **5** to **1** via hydroxy-deboronation.

Our first attempts used *O*-protected variants of 2-bromo-5-hydroxypyridine (**3**) as the precursors, but we never detected any coupled product during the reaction; instead, only reduction of the Ar-Br bond was observed. A successful cross-coupling has already been reported with *O*-protected 2-iodo-5-hydroxypyridine.[6] However, this required preparation of the iodo pyridine precursor and two full equivalents of the organozinc reagent, generated from the expensive Boc-β-iodo-Ala-OMe, which would have been very costly on a large scale. The synthesis of the corresponding 5-bromo analog (**5**) was reported in a yield of 60%.[9] This and subsequent boronate ester (**4**) were very versatile intermediates, offering useful diversification points for the synthesis of other potentially interesting compounds for our program. Therefore, we decided to focus on the synthesis of **5**, with the hope of transforming the bromide to the hydroxy function by passing via a mild oxidative hydroxy-deboronation procedure such as that recently reported for boronic acids and esters at C-3 of pyridines by Voisin et al. (Scheme 1).[10]

Our synthesis of Boc-L-azatyrosine (**1**) started from commercially available Boc-β-iodo-Ala-OMe, which was can also be conveniently prepared from L-serine in three steps.[11]

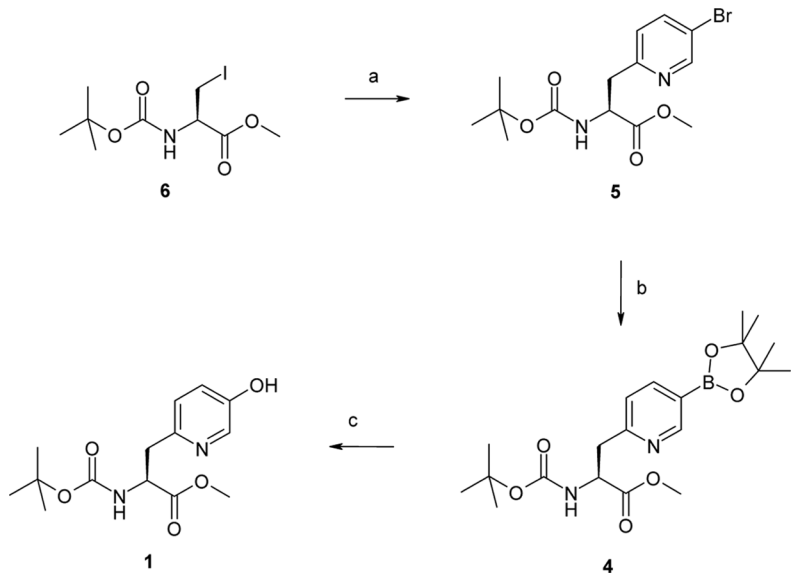
As mentioned previously, the 5-bromo pyridine amino acid ester (**5**) has already been prepared by palladium-catalyzed cross-coupling of serine organozinc reagents with 2,5-dibromopyridine.[9] We were able to routinely reproduce the yields reported,[9] thus affording **5** in yields varying between 50 and 70%.

The transformation of **5** to boronate **4** was achieved under standard boronation conditions using a slight excess of bis(pinacolato)diboron in the presence of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ to afford a quantitative yield of the corresponding boronate (**4**), which, after a simple workup, was used without further purification in the next step.

Oxidation of the resulting boronate (**4**) to phenol (**1**) was achieved using aqueous hydrogen peroxide at 0 °C.[10] The authors note that the use of hydrogen peroxide was essential to avoid the formation of the corresponding pyridine *N*-oxide consistently observed even using just a slight excess of *m*CPBA (Scheme 2).

To check the molecular structure, crystals of L-azatyrosine were prepared after deprotection of (**1**) in refluxing 2M HCl/EtOH (Fig. 1). To our knowledge, this is the first x-ray of L-azatyrosine reported in the literature.

In conclusion, we have developed a very efficient and reproducible large-scale synthesis of chiral Boc-L-azatyrosine methyl ester, using just three chemical steps and two chromatographic purifications, in an overall yield of 43% from Boc-β-iodo-Ala-OMe.



Scheme 2. Reagents and conditions: (a) (i) Zn(s), 1,2-dibromoethane, 90 °C, then TMS-Cl, rt, 1 h followed by **6**, 35 °C, 2 h; (ii) 2,5-dibromopyridine, $Pd(Ph_3P)_2Cl_2$, 68 °C, 2 h, 54%; (b) bis(pinacolato) diboron, $Pd(dppf)Cl_2 . CH_2Cl_2$, KOAc, dioxane, 85 °C, 16 h, quantitative; (c) H_2O_2, DCM, 0 °C to rt, 16 h, 80%.

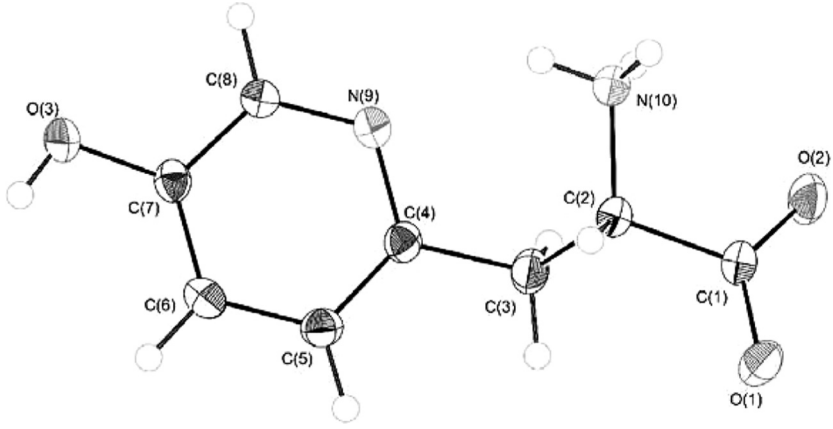


Figure 1. Molecular structure of L-azatyrosine with atomic numbering.

EXPERIMENTAL

General Methods

^{1}H NMR spectra were recorded on a Bruker Biospin Avance 500 spectrometer. Chemical shifts are reported as δ values downfield from internal TMS in appropriate organic solutions. The purity and the structures of the products were confirmed by liquid chromatography-mass spectrometry (LCMS) on a Waters 2690 photodiode array detector system using the following conditions: column, Symmetry C-18; solvent A, water 0.1% formic acid; solvent B, CH_3CN; flow rate, 2.5 ml/min; run time, 4.5 min; gradient, from 0 to 100% solvent B; and mass detector, micro mass ZMD.

Synthetic Chemistry

Methyl (2S)-3-(5-Bromopyridin-2-yl)-2-[(2-methylpropan-2-yl)oxycarbonylamino]-propanoate (**5**)

Zinc dust (148.2 g, 2.28 M) was added to a 4-L, three necked, round-bottomed flask, purged with nitrogen and heated with a heat gun for 10 min under vacuum. The slurry was cooled to room temperature, and a solution of 1,2-dibromoethane (9.78 ml, 114 mmol) in *N*,*N*-dimethyl formamide (DMF) (500 ml) was added dropwise over a period of 10 min. The resulting suspension was heated at 90 °C for 30 min and cooled to room temperature. Chlorotrimethylsilane (2.9 ml, 22.8 mmol) was added, and the suspension was stirred for a further 30 min at room temperature. A solution of Boc-β-iodo-Ala-OMe (125 g, 379.9 mmol) in DMF (800 ml) was added dropwise over a period of 10 min and the resulting suspension was heated at 35 °C for 2 h. After the time, thin-layer chromatography (TLC, silica gel, petroleum ether/AcOEt 75/25 with a ninhydrin stain) showed complete consumption of the starting material. The reaction mixture was cooled to room temperature and 2,5-dibromopyridine (117.1 g, 494 mmol) was added followed by $(Ph_3P)_2PdCl_2$ (13.3 g, 19 mmol). The resulting suspension was heated at 68 °C for 2 h, cooled to room temperature, and filtered to remove the excess of zinc. The filtrate was partitioned between a mixture of water (2 L) and ether (1 L). The phases were separated, and the aqueous phase was re-extracted with ether (2×500 ml); the organic phases were combined, dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. The yellow oil was purified by flash chromatography (pet. ether/AcOEt 75/25) to afford methyl (2S)-3-(5-bromopyridin-2-yl)-2-[(2-methylpropan-2-yl)oxycarbonylamino]-propanoate (**5**) (73.7 g, 54%) as a pale yellow solid. $[\alpha]_D^{17} = -13.3°$, $c = 0.9$

in acetone; LCMS (retention time = 3.47 min. purity 100%), ESI^+ m/z 305 $(M\text{-}tBu)^+$, 359, 361 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 3.19–3.35 (m, 2H), 3.70 (s, 3H), 4.64–4.74 (m, 1H), 5.67 (d, 1H, $J = 7.6$ Hz), 7.05 (d, 1H, $J = 8.3$ Hz), 7.73 (dd, 1H, $J = 8.3$ Hz, $J' = 2.1$ Hz), 8.57 (d, 1H, $J = 2.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 28.2, 38.2, 52.2, 55.1, 79.0, 118.6, 126.1, 132.4, 139.3, 150.0, 155.7, 156.7, 172,7, 176.5.

Methyl (2S)-2-[(2-Methylpropan-2-yl)oxycarbonylamino]-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]propanoate (**4**)

Methyl (2S)-3-(5-bromopyridin-2-yl)-2-[(2-methylpropan-2-yl)oxycarbonylamino]-propanoate (**5**, 7.5 g, 20.9 mmol), bis(pinacolatodiboron) (6.90 g, 27.2 mmol), potassium acetate (6.15 g, 62.6 mmol), and Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (1.01 g, 1.26 mmol) was suspended in 1,4-dioxane (60 ml) and heated at 85 °C for 16 h. The mixture was diluted with CH_2Cl_2 (50 ml), water (20 ml) was added, and the product was extracted with CH_2Cl_2 (150 ml). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to afford methyl (2S)-2-[(2-methylpropan-2-yl)oxycarbonylamino]-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]propanoate (**4**) (8.45 g, 100%) as a pale yellow gum. LCMS (retention time = 3.61 min, purity 95%), ESI^+ m/z 407.3 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.34 (s, 12H), 1.42 (s, 9H), 3.23–3.38 (m, 2H), 3.68 (s, 3H), 4.64–4.70 (m, 1H), 5.90 (d, 1H, $J = 7.3$ Hz), 7.14 (d, 1H, $J = 8.7$ Hz), 7.98 (dd, 1H, $J = 7.7$ Hz, $J' = 1.3$ Hz), 8.84 (s, 1H).

Methyl (2S)-3-(5-Hydroxypyridin-2-yl)-2-[(2-methylpropan-2-yl)oxycarbonylamino] propanoate or Boc-L-azatyrosine (**1**)

Methyl (2S)-2-[(2-methylpropan-2-yl)oxycarbonylamino]-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]propanoate (**4**, 8.45 g, 20.9 mmol) was dissolved in CH_2Cl_2 (40 ml), and H_2O_2 (30%, 5.4 ml, 47.0 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After this time, an aqueous solution of sodium thiosulfate (50 ml) was added to the mixture at 0 °C. The mixture was extracted with CH_2Cl_2 (2×50 ml); the combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography, eluting with CH_2Cl_2/MeOH (98:2/95:5) to give (**1**) (4.9 g, 80%) as a white solid. $[\alpha]^{17}{}_D = -11.4°$, $c = 1.0$ in EtOH); LCMS (retention time = 2.09 min,

purity 100%), MS ESI$^+$ m/z 297.2 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 3.17–3.28 (m, 2H), 3.71 (s, 3H), 4.62–4.69 (m, 1H), 5.74 (d, 1H, $J = 5.5$ Hz), 7.07 (d, 1H, $J = 7.7$ Hz), 7.19 (d, 1H, $J = 7.7$ Hz), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2, 38.1, 52.1, 54.2, 78.6, 122.8, 124.4, 137.5, 147.7, 152.5, 155.7, 173.1.

A sample of (**1**) was hydrolyzed in refluxing EtOH in the presence of 2N HCl and purified by preparative LCMS using a Water Xterra reverse-phase column (5 microns silica, 30 mm in diameter, 250 mm long) and decreasingly polar mixtures of water (containing 0.2% ammonium carbonate) and acetonitrile as eluent. The fractions were evaporated to dryness to afford the desired compound as a white amorphous solid. Crystals were grown from the recuperated solid from hot water. $[\alpha]^{17}_D = +59.8°$, $c = 1.0$ in HCl); LCMS (retention time = 0.45 min, purity 100%), MS ESI$^+$ m/z 181.09 $(M\text{-}H)^+$; ^{1}H NMR (DMSO-d_6 + TFA) δ 3.29–3.43 (m, 2H), 4.58–4.43 (m, 1H), 7.64 (d, 1H, $J = 7.7$ Hz), 7.75 (d, 1H, $J = 7.7$ Hz), 8.34 (s, 1H), 8.49 (ls, 2H); ^{13}C NMR (DMSO-d_6 + TFA) δ 34.6, 52.7, 128.1, 130.0, 132.1, 143.5, 156.6, 170.2.

ACKNOWLEDGMENTS

The authors thank Dr. Geoff Bird, Dr. Bénédicte Delouvrié, and senior analysts Dr. Delphine Dorison-Duval, Christian Delvare, and Dr. Anne Ertan for their assistance.

REFERENCES

1. Inouye, S.; Shomura, T.; Tsuruoka, T.; Ogawa, Y.; Watanabe, H.; Yoshida, J.; Niida, T. L-β-(5-Hydroxy-2-pyridyl)alanine and L-β-(3-hydroxyureido) alanine from streptomyces. *Chem. Pharm. Bull.* **1975**, *23*, 2669–2677.
2. Izawa, M.; Takayama, S.; Shindo-Okada, N.; Doi, S.; Kimura, M.; Katsuki, M.; Nishimura, S. Inhibition of chemical carcinogenesis in vivo by azatyrosine. *Cancer Res.* **1992**, *52*, 1628–1630.
3. Myers, A. G.; Gleason, J. L. A practical synthesis of L-azatyrosine. *J. Org. Chem.* **1996**, *61*, 813–815.
4. Cooper, M. S.; Seton, A. W.; Stevens, M. F. G.; Westwell, A. D. A concise synthesis of either enantiomer of azatyrosine. *Bioorg. Med. Chem. Lett.* **1996**, *21*, 2613–2616.
5. Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. Enantioselective synthesis of (2-pyridyl)alanines via catalytic hydrogenation and application to the synthesis of L-azatyrosine. *Org. Lett.* **2001**, *20*, 3157–3159.
6. Ye, B.; Otaka, B.; Burke Jr., T. R. Preparation of Nα-Boc 4-O-diethylphospho-L-azatyrosine, a reagent potentially useful for the synthesis of signal transduction related peptides. *Synlett* **1996**, 459–460.

7. For a recent review covering all the recent advances in the area of catalytic α amino acid synthesis, see Nàjera, C.; Sansano, J. M. Catalytic asymmetric synthesis of α-amino acids. *Chem. Rev.* **2007**, *117*, 4584–4671.
8. Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. Preparation of enantiomerically pure protected 4-oxo α-amino acids and 3-aryl α-amino acids from serine. *J. Org. Chem.* **1992**, *57*, 3397–3404.
9. Tabanella, S.; Valancogne, I.; Jackson, R. F. W. Preparation of enantiomerically pure pyridyl amino acids from serine. *Org. Biomol. Chem.* **2003**, *1*, 4254–4261.
10. Voisin, A. S.; Bouillon, A.; Lancelot, J. C.; Rault, S. Efficient synthesis of halohydroxypyridines by hydroxydeboronation. *Tetrahedron* **2005**, *61*, 1417–1421.
11. Boc-β-iodo-Ala-OMe can be readily obtained as a stable white solid from Boc-Ser-OMe in just one-step following the procedure described by Trost, B. M.; Rudd, M. T. Chemoselectivity of the ruthenium-catalyzed hydrative diyne cyclization: Total synthesis of (+)-cylindricine C, D, and E. *Org. Lett.* **2003**, *5*, 4599–4602.