Synthesis of all Three Regioisomers of Pyridylalanine

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Abstract: Pyridylalanines **4-6**, differing from one another by the position of attachment on the heterocyclic ring were synthesized in moderate yield starting from serine and 2-, 3- and 4-bromopyridine respectively.

We recently required all three β–pyridylalanine regioisomers **4-6** for use as water soluble isosteric phenylalanine substitutes.[1] Of the various methods described in the literature for the synthesis of unnatural amino acids[2] the technique of Jackson[3] was considered best for our purposes based on the following. First, it is well suited for the synthesis of β-arylalanines having been previously used for the synthesis of **4a**.[4] Second, we prefered a chiron-based approach to ensure that the product possessed the "natural" (*S*) configuration at the α-carbon. Described herein is our synthesis of **4-6** starting from serine and 2-, 3- and 4-bromopyridine. We found (*vide infra*) that, the source of zinc for the zincation reaction, the size of the ester protecting group and the regiochemistry of bromopyridine played major roles in determining the yield and the stereochemcal outcome of the reaction.

To begin the synthesis, Boc-serine benzyl ester (**1a**) and methyl ester (**1b**) were converted to the corresponding tosylate (**2a**) and mesylate (**2b**) respectively (cf. scheme). Reaction of these intermediates with 1.0-2.0 eq. NaI gave the β-iodoalanines **3a** and **3b**. With the iodides in hand we set out to examine the more difficult part of the sequence namely, the one-pot, zincation of **3a,b** and palladium catalyzed coupling with 2-, 3- and 4-bromopyridine.

We examined the zincation/coupling reaction of **3a** with 4-bromopyridine first. The zincation reaction was the more capricious of the two steps and played a large part in determining the overall yield. Zn•Cu proved especially troublesome. When 1.0-2.0eq. of Zn•Cu[5] was used (cf. entry 1 table) the zincate was reluctant to form and the small amount of **6a** formed in the coupling step (10 mol% $PdCl_2$, 1.0-2.0 eq. 4-bromopyridine) was accompanied by a large amount of didehydroalanine (40% isolated yield). Zinc (2.0 eq.) which had been activated using Knochel's method[6] (TMSCl, $BrCH_2CH_2Br$) gave better results. When reacted with **3a** the zincate was formed more rapidly than before, however, the coupling of this intermediate to 4-bromopyridine (1.5-2.0 eq.) was inefficient in producing **6a** (entry 2).[7] Fortunately, we found that the yield for the coupling reaction could be improved by using the corresponding methyl ester (**3b**) instead of the benzyl ester.[8] Thus **6b** was produced in 50% yield using this method. Both **4b**[9] and **5b**[10] were produced in acceptable yields as well (cf entry 3). We speculate that the increase in yield observed for the methyl ester might be due to stronger coordination by the ester carbonyl oxygen to zinc in the zincate and thus activating this intermediate towards reaction with Pd. A steric effect was ruled out by the fact that the corresponding t-butyl ester produced **5** with a yield comparable to the methyl ester (results not shown).

As an alternative procedure we found that Rieke™ zinc worked well in the reaction as indicated by the yields for **4b-6b** in the table (entry 4).[11]

The advantages to using Rieke™ zinc are that only ~1.0-1.5 eq. of zinc is required and it is commercially available[12] which avoids having to carry out the activation step. Of the three methods presented for zincation this proved to be the most reproducible in sequential runs. However, a larger amount of zinc (≥1.5 eq.) was required from older previously used bottles to completely metallate the iodide.

Table. Yield of Palladium Catalyzed Coupling of **3a,b** with Bromopyridine, as a Function of Zinc Activation Method and Ester Group

			yield(%)[a,b]		
entry	R	"Zn"	**4**	**5**	**6**
1	Bn (**a**)	Zn•Cu			0-15
2	Bn (**a**)	Knochel			0-25
3	Me (**b**)	Knochel	56	30	50
4	Me (**b**)	Rieke™	32	40	56

[a]Isolated yields of Pd catalyzed coupling reaction.

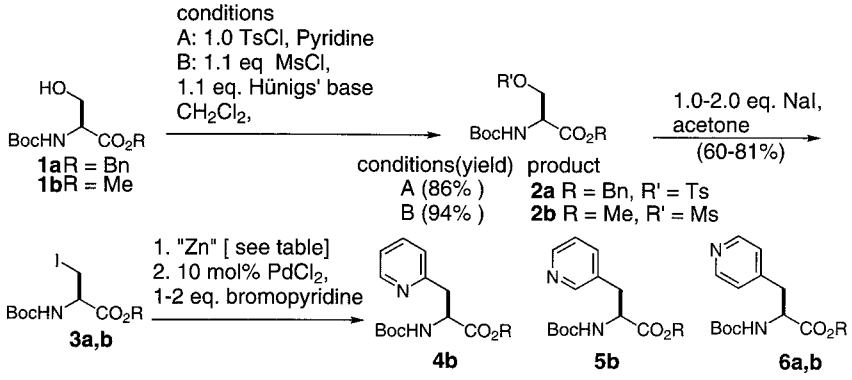
[b]Formed by reaction of **3a,b** with 2-, 3- or 4-bromopyridine respectively.

In order to determine if the enantiomeric purity of the amino acid chiral center had been preserved during the reaction sequence we converted **4b, 5b** and **6b** to their corresponding Moshers amides. The free amino esters were generated by reaction with TFA followed by reaction with both enantiomers of Moshers acid. Both **4b** and **5b**, were found to be enantiomerically pure (by ^1H NMR). We were surprised to find that **6b** was a 70:30 mixture of enantiomers indicating that epimerization of the stereocenter had taken place. Mechanistically this is intriguing. We speculate that the racemization is occurring after **6b**[13] has formed. If the epimerization had occurred before this event than the other products (ie. **4b**, **5b**) would have been obtained as scalemic mixtures also.

In summary, we have found that we can rapidly synthesize all three regioisomers of β–pyridylalanine (**4-6**) using Jackson's coupling procedure. The overall yield is dependent on the source of zinc used in the zincation reaction, the identity of the ester group and the regiochemistry about the pyridyl ring. The enantiomeric integrity of the final product was dependent on pyridine regiochemistry as well. Therefore, this procedure is recommeded for synthesis of 2- and 3-pyridylalanine but not 4-pyridylalanine.

References and Notes

1. Previous syntheses: a) Bozell, J. J.; Bogt, C. E.; Gozum, J.; *J. Org. Chem.* **1991**, *56*, 2584. b) Hoes, C.; Raap, J.; Bloemhoff, W.; Kerling, K. E. J.; *Rec. Trav. Chim.* **1980**, 99. c) Hsieh, K.; Jorgensen, E. C.; Lee, T. C. *J. Med. Chem.* **1979**, *22*, 1199.
2. For a recent review on the synthesis of α-amino acids see: Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.



Scheme. Synthesis of Pyridylalanines **4-6**.

3. Jackson, R. F. W, James, K., Wythes, M. J., Wood, A. *J. Chem. Soc. Chem. Comm.* **1989**, 644.
4. Jackson, R. F. W., Wythes, M. J., Wood, A. *Tetrahedron Lett.* **1989**, *30*, 5941.
5. Tamura, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559.
6. AchyuthaRao, S.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 4591.
7. Procedure: Zn dust (0.49 g, 7.49 mmol) was placed in a 100 mL round bottom flask and heated under vacum with a heat gun and allowed to cool to room temp. 3 times. Dibromoethane (0.06 g, dissolved in 1.0 mL of THF was added and the resulting slurry heated and cooled 2 times. While still warm TMSCl (0.03 mL) was added. **3b** (1.49, 4.53mmol) dissolved in 4.0 mL of THF was added dropwise and the resulting suspension stirred 1.5 h at which point all of the iodide had been consumed (by TLC). In a separatory funnel 4-bromopyridine hydrochloride (1.46 g, 7.53 mmol) was dissolved in 50 mL benzene and washed with 50 mL satd $NaHCO_3$, separated, dried over Na_2SO_4, and concentrated ~5 mL under vacuum. $(PPh_3)_2PdCl_2$ (0.25 g) was added to the bromopyridine solution. The zincate was allowed to settle than transferred away from unreacted zinc via syringe to give a dark brown/red solution. The reaction mixture was warmed to 35 °C and stirred for 2 h during which time the color of the solution became light yellow. EtOAc (150 mL) was added and the reaction was quenched with 50 mL of 0.1 N HCl then transferred to a separatory funnel. The mixture was neutralized with satd $NaHCO_3$. The organic layer was separated, washed with pH 7.0 buffer and dried with Na_2SO_4. After filtration the solvent was removed by rotary-evaporation to give the crude product as an oil. The product was purified by flash column chromatography (SiO_2, 4:6 acetone/ hexanes) to give **6b** as an oil. [α]D +18.99 (*c* 1.05, $CHCl_3$). ^{1}H NMR (300 MHz) δ 1.37 (s, 9), 3.05 (dd, 2, *J* = 6.6, 13.7), 3.70 (s, 3), 4.60 (m, 1), 5.09 (m, 1), 7.08 (d, 2, *J* = 5.9), 8.49 (d, 2, *J* = 5.8). ^{13}C NMR (75 MHz) δ 28.09, 37.74, 52.34, 53.54, 80.14, 124.62, 145.88, 149.16, 154.82, 171.52. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.12; H, 7.10; N, 9.79.
8. Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.
9. Analytical data for **4b**: [α]D: +21.5 (*c* 1.0, $CHCl_3$).^{1}H NMR (300 MHz): δ 1.33 (s, 9), 3.20 (m, 2), 3.59 (s, 3), 4.60 (m, 1), 5.97 (m, 1), 7.05 (dd, 1, *J* = 4.2, 7.7), 7.51 (td, 1, *J* =1.8, 7.7), 8.4 (m, 1). ^{13}C NMR (75 MHz): δ 28.24, 39.23, 52.15, 52.96, 79.59, 121.75, 123,64, 136.48, 149.14, 155.44, 157.12, 172.37. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.97; H, 7.16; N, 9.72.
10. Analytical data for **5b**: mp = 87 °C. [α]D: +53.9 (*c* 1.2, $CHCl_3$). 1H NMR (300 MHz): δ 1.38 (s, 9), 3.00 (dd, 1, *J* = 6.2, 13.9), 3.13 (dd, 1, *J* = 6.2, 13.9), 3.70 (s, 3), 4.57 (m, 1), 5.09 (m, 1), 7.20 (m, 1), 7.45 (m, 1), 8.35 (m, 1), 8.45 (m, 1). ^{13}C NMR (75 MHz): δ 28.23, 35.65, 52.43, 54.08, 80.17, 123.40, 131.83, 136.88, 148.35, 150.42, 154.95, 171.75. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.72,; H, 7.07; N, 9.58.
11. Procedure: Rieke^{TM} zinc (4.0 mL, 10g/100 mL THF) was measured into a Schlenk flask by cannula. To this was added dropwise, **3b** (1.49 g, 4.53 mmol) dissolved in 4.0 mL of THF. The resulting suspension was stirred 30 min then transferred to a solution of $PdCl_2$ (0.25 g) and 4-bromopyridine (1.32 g, 6.79 mmol) prepared according to the above procedure. The reaction was stirred for 5 hrs at 60 °C and worked-up in the usual manner.
12. Rieke Metals, Inc., Lincoln Nebraska.
13. The putative zinc complex **A** might have a stronger field or inductive effect than the 2- or 3-pyridyl regioisomers due to resonance structure **B** and thus activate the α-postion towards deprotonation.