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Preparation of N-Boc-(2,6-Bis-(ethoxycarbonyl)pyridin-4-yl)-L-alanines as Tridentate Ligands

Boris Schmidt,* Dennis K. Ehlert

Institut für Organische Chemie der Universität Hannover, Schneiderberg 1b, D-30167 Hannover, Germany

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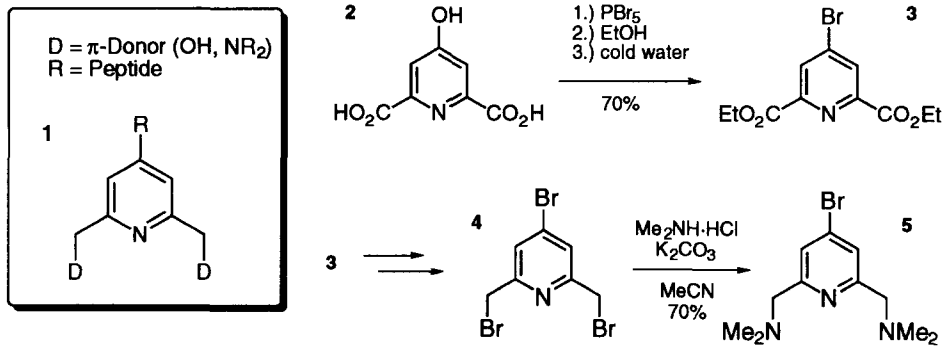
Abstract: The pyridylalanine **7a** was synthesised in good yield from serine and 4-bromopyridine **3**. The pyridylpropionates **12, 13** were synthesised in good yields by either Heckolefination or palladium catalysed cross coupling.

Keywords: pyridine; tridentate ligand; Heck olefination; lanthanide, zinc mediated addition

The complexation of transition metals by amino acids is a well documented way[1,2] to control shape and activity of peptides and proteins. On our way to synthetic kinase inhibitors, kinase markers and designed haloperoxidases[3,4] with the general substructure **1**, we are interested in 4-substituted 2,6-pyridine dicarboxylates such as **7a,b** and **13**. The general motif of a pyridine with two donor systems adjacent to the pyridyl nitrogen is common for tridentate ligands. Alteration of the donor (D) and pH allows selective coordination to a range of cations such as Zn(II), V(V), Cu(I) and Tc(VII). The incorporation of these complexes into peptides may give access to peptide mimetics or enzyme inhibitors with new or improved activity. The alterations in polarity, geometry and additional vacant ligation sites hold potential to control peptide secondary structure. Other applications may be found in identification and purification of synthetic peptides by *Immobilised Metal Affinity Chromatography* (IMAC).[5]

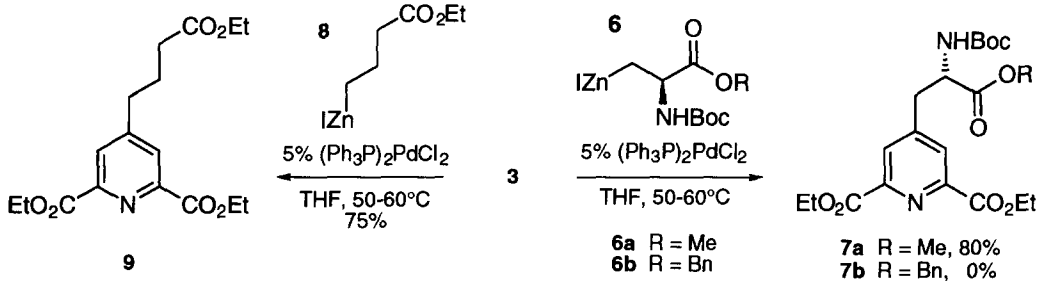


Scheme 1

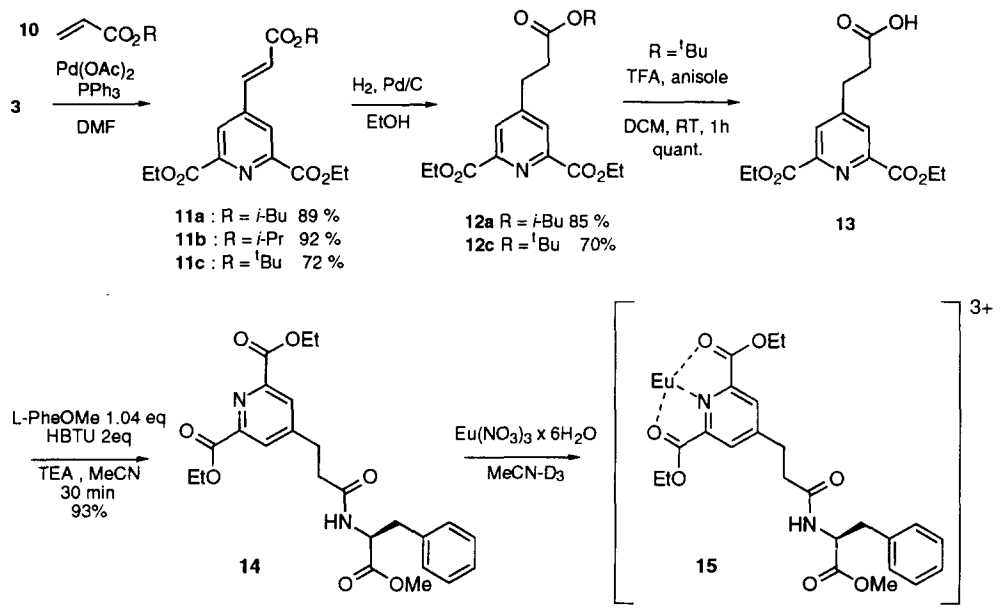
PII: S0040-4039(98)00711-4

Here we report the synthesis of new chelating pyridines, which are designed for use in *Solid Phase Peptide Synthesis* (SPPS). Takalo[6,7] reported the metal binding ligands **3** and **4**, which offer facile elaboration to amino acids via their bromo substituents. Pure **3** is obtained in multigram quantities by precipitation from cold water and repeated recrystallisation. This simple modification improves the yield from 60 to 80% and avoids large scale chromatography. The reduction of **3** by $NaBH_4$[6] and treatment with PBr_3 gives **4**. Substitution of bromide with dimethylamine in MeCN affords the tridentate ligand **5**[8] in appropriate yield. Our synthetic strategy envisioned a palladium mediated coupling process between bromopyridines and metallated amino acids. For this building block we turned to Jackson's [9,10] zinc reagents **6a** and **6b**, which are synthesised from Boc protected serine esters by tosylation and substitution with NaI, which is followed by treatment with activated zinc.

Scheme 2

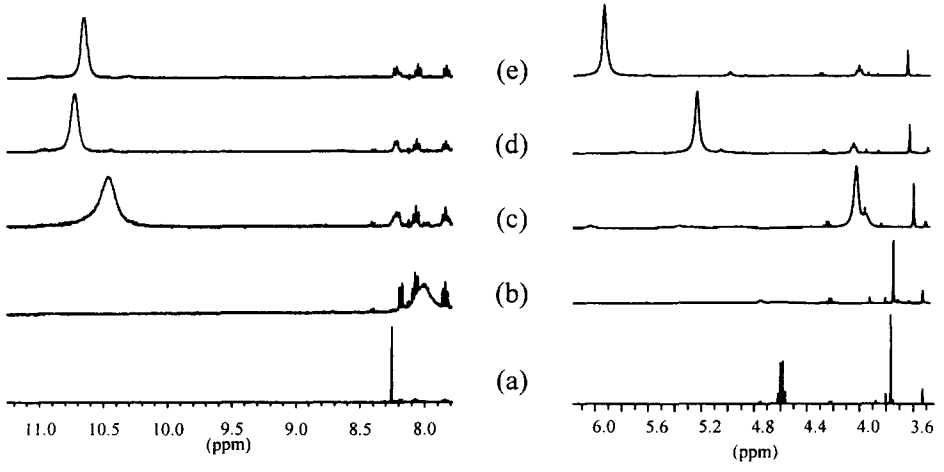


Knochel's zinc activation[11] ($BrCH_2CH_2Br$, TMSCl) turned out to be the method of choice, if zinc dust is replaced for zinc turnings to ease needle filtration. In our hands all other methods of zinc activation such as ultrasound, CuCN, $HgCl_2$, DMA or Rieke™ zinc met with failure. Slow reaction rates and excess of zinc have to be avoided to suppress palladium(0) precipitation and the decomposition of iodo alanine. Best results were obtained, if the zinc amount was reduced to a third of reported reaction conditions. Trapping experiments with D_2O indicate the formation of the zinc species to be the crucial step. The replacements of THF by DMF, DMA, toluene or benzene or combinations thereof were unsuccessful. At optimised conditions the zinc reagent **6a** forms within 2 h, is then transferred via needle filtration to a solution containing **3** and $(Ph_3P)_2PdCl_2$ in THF, heated to 60°C for 24 h to furnish **7a**[12] in 80% yield. Our observation that the zinc reagent of iodo alanine methyl ester forms more rapidly than the analogue benzyl derivative corresponds to recent results by Walker.[13] The extended reaction time required for complete conversion favours the elimination reaction to didehydro alanines. Walker et al.[13] assigned the difference in the reaction rates of **6a/b** to chelation control. Therefore the more versatile **7b**, which offers mild and selective deprotection of the benzyl ester, requires further investigation. The methyl ester **7a** couples readily and in good yield, yet selective deprotection of the methyl group met with failure. A simplified analogue **9** derives from zinc reagent **8** and **3** in good yield. The corresponding acid is limited to N-terminal capping of peptides, but offers a convenient synthesis by Heck olefination of acrylates[14] **10a-c**. The reactions of the bromopyridine **3** with inexpensive acrylates gave the triesters **11a-c** in good to excellent yields under simple, non inert reaction conditions.



Scheme 3

Hydrogenation gives the orthogonally protected triester **12**,[15] which is deprotected by TFA[16] to render the crystalline acid **13**[17] in quantitative yield. **13** couples readily to L-phenylalanine methyl ester to give the pseudo dipeptide **14**,[19] which results in complex **15** when treated with europium(III).



Scheme 4 All samples in MeCN-D_3, 400 MHz (a) **14**, (b) + 0.12 eq $Eu(NO_3)_3$, (c) + 1.2 eq $Eu(NO_3)_3$, (d) + 1.6 eq $Eu(NO_3)_3$, (e) + 2.3 eq $Eu(NO_3)_3$.

The complexation site was established by titration with 0.1 to 2.3 eq of Eu(III) and monitored by ^{1}H NMR (scheme 4). Whereas the signals for the phenylalanine part remain unchanged (see MeO signal at 3.7 ppm), the signals for the aromatic proton and ethyl groups shift towards a maximum. As the shift of the NMR signals differs in trend and magnitude from those reported by Piguet and Bünzli[18] for a simpler ligand, a structure can not be assigned yet.

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(8) 4-Bromo-2,6-bis-(N,N-dimethylaminomethylene)-pyridine (**5**), ^{1}H NMR (200 MHz; $CDCl_3$) 2.3 (12H, s), 3.6 (4H, s), 7.52 (2H, s). ^{13}C NMR (50 MHz; $CDCl_3$) 33.9, 44.8, 125.9, 128.3, 136.7. IR 2924, 2856, 2780, 1564, 1456, M^+ 228/230 (23%, M^+ -NMe_2).
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(12) **7a**: A dry 10 mL RBF was charged with zinc (217 mg, 3.31 mmol), dibromoethane (16 mL, 0.23 eq) and warmed to 60°C for 3 min under inert atmosphere. THF (3 mL) and TMSCl (5 mL, 0.05 eq) were added at 30°C. The mixture was reheated to 60°C for the addition of iodoserine (326.8 mg, 0.993 mmol). A second flask was charged with **3** (250 mg, 0.828 mmol) and $(Ph_3P)_2PdCl_2$ (30.7 mg, 5.3 mol %) under argon. The zinc reagent was transferred to the 2nd flask via syringe and the mixture was warmed to 50°C for 24 h. THF was evaporated and the resulting oil was purified by repeated LC (SiO_2, EE/PE 2:1). IR 3432, 2984, 1736, 1716, 1248, 1160. ^{1}H NMR (400 MHz, $CDCl_3$) 1.44 (s, 9H), 1.48 (t, 7 Hz, 6H), 3.20 (dd, 6 Hz, 13 Hz, 1H), 3.38 (dd, 5.5 Hz, 13 Hz, 1H), 3.79 (s, 3H), 4.50 (q, 7 Hz, 4H), 4.69 (bd, 7 Hz, 1H), 5.18 (bd, 7 Hz, 1H), 8.11 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) 14.2, 28.3, 31.2, 53.2, 60.4, 66.4, 81.0, 129.1, 130.3, 143.6, 164.3, 170.5, 171.3.
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(14) Spencer, A. *J. Organomet. Chem.* **1983**, *258*, 101.
(15) 4-(2-*tert*-Butoxycarbonyl-ethyl)-pyridine-2,4-dicarboxylic acid diethyl ester (**12**) IR 2984, 2936, 1720, 1368, 1336, 1248. ^{1}H NMR (400 MHz; $CDCl_3$) 1.45 (s, 9H), 1.50 (t, 7 Hz, 6H), 2.69 (t, 7.5 Hz, 2H), 3.11 (t, 7.5, 2H), 4.55 (q, 7 Hz, 4H), 8.18 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) 14.2, 28.1, 30.2, 35.5, 62.3, 81.2, 127.8, 148.7, 152.8, 164.7, 171.0, M^+ 352.
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(17) 4-(2-Carboxyethyl)-pyridine-2,4-dicarboxylic acid diethyl ester (**13**) ^{1}H NMR (400 MHz; DMF-d_7) 1.38 (t, 7 Hz, 6H), 2.83 (t, 7.3 Hz, 2H), 3.14 (t, 7.3 Hz, 2H), 4.43 (q, 7Hz, 4H), 8.26 (s, 2H) 12.6 (bs, 1H). ^{13}C NMR (100 MHz, DMF-d_7) 15.8 (C-9), 31.8 (C-3), 35.6 (C-2), 63.6 (C-8), 129.9 (C-5), 151.1 (C-6), 156.2 (C-4), 167.1 (C-7), 175.8 (C-1). IR (KBr) 1732, 1700, 1376, 1212. M^++1=296 (0.5 %), 223 (-CO_2Et, 100%).
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(19) 4-[2-(1-Methoxycarbonyl-2-phenyl-ethylcarbamoyl)-ethyl]-pyridine-2,6-dicarboxylic acid diethyl ester (**14**) ^{1}H-NMR (400MHz, $CDCl_3$) 1.48 (7, 7.2 Hz, 6H), 2.65 (dt, 3.5 Hz, 7.2 Hz, 2H), 3.15 (m, 4H, $PyCH_2$+ Bz), 3.75 (s, 3H, OMe), 4.5 (q, 7.2 Hz, 4H, OEt), 4.9 (ddd, 1H, α-H), 6.1 (bd, 7.52 Hz, 1H, N-H), 7.3 (m, 5H, Ph), 8.2 (s, 2H, Py).