Synthesis of (±)-Homohistidine

Michael C. Pirrung* and Tao Pei

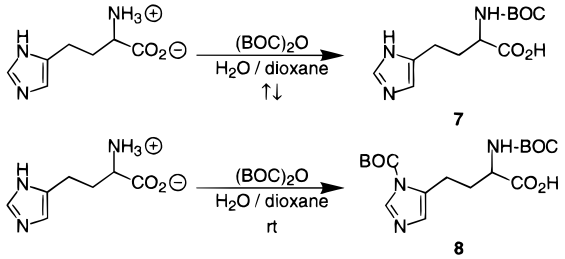
Department of Chemistry, Levine Science Research Center, Box 90317, Duke University, Durham, North Carolina 27708-0317

Received October 19, 1999

For a program studying the inhibition of histidine kinases,[1] we required quantities of several histidine analogues in forms suitable for solid-phase synthesis. Methods for the generation of the histidine homologue homohistidine have been earlier reported.[2] The most recent synthesis of homohistidine was achieved in nine steps with an overall yield of 40%, starting from Z-glutamic acid. Here is described a preparation of homohistidine from the readily available urocanic acid, and conversion to its BOC derivatives (Scheme 1).

Urocanic acid was esterified and hydrogenated. While in earlier work[3] the N−H of the imidazole was left unprotected for the following reduction step, the solubility properties of **2** are sufficiently poor as to limit the synthesis scale. As reported by Browne,[4] tritylation significantly improves its solubility in ethereal solvents, permitting DIBAL-H reduction in quantity to the aldehyde. Strecker reaction gives an aminonitrile whose hydrolysis also causes removal of the trityl group, producing homohistidine (**6**) in 73% overall yield.

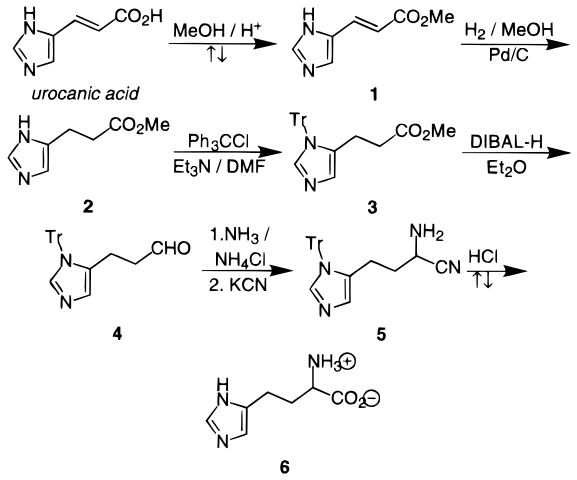
The protection of histidines with activated BOC derivatives can a priori protect either or both nitrogens. The α-amino group is expected to be more nucleophilic/reactive, but it did not prove possible to derivatize selectively this site with stoichiometric BOC protection reagents. It has been reported that treatment of histidine with excess BOC-N_3 gives the bis-BOC derivative, which can be further treated in refluxing methanol to form the α-amino BOC derivative.[5] Treatment of homohistidine with an excess of BOC_2O derivatizes both nitrogens, producing the bis-BOC-homohistidine (**8**) in 17% yield. We attribute this low yield to the reactivity of the BOC-imidazolide toward aqueous reaction conditions, as some α-BOC derivative was also isolated. That suggested a method to obtain selectively the mono-BOC derivative by use of an excess of BOC_2O, followed by an extended reaction time in water to hydrolyze the imidazolide. This produces the target α-BOC-homohistidine (**7**) in 56% yield.



Experimental Section

Methyl Urocanate (1). Urocanic acid (14.08 g, 101.9 mmol) and anhydrous Na_2SO_4 (2.0 g) were added to 150 mL of anhydrous methanol. Concentrated sulfuric acid (8 mL) was added to the reaction, which was heated at reflux for 30 h. The solid Na_2SO_4 was filtered off, and the solvent was removed in vacuo. The remaining white solid was dissolved in a small amount of water and neutralized with saturated $NaHCO_3/H_2O$ until no gas was evolved. The cloudy aqueous solution was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. A white solid remained (15.36 g, 99%). mp 92−94 °C; MS: $MH^+ = 153$. ^{1}H NMR ($CDCl_3$): δ 7.69 (s, 1H), 7.59 (d, J = 15.6 Hz, 1H), 7.27 (s, 1H), 6.45 (d, J = 15.6 Hz, 1H), 5.24 (b, 1H), 3.76 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 165.6, 136.6, 129.2, 128.3, 121.7, 119.8, 51.9. All data were consistent with literature.[6]

Scheme 1



Methyl 3-(Imidazol-4-yl)propionate (2). Urocanic acid methyl ester (**1**) (14.73 g, 96.9 mmol) was dissolved in 125 mL of methanol and 1.5 g of palladium on activated carbon (10%) was added. The reaction was stirred under H_2 at room-temperature overnight, whereupon TLC showed the reaction was complete. The solid was filtered off, and the methanol was removed in vacuo. A white solid remained (14.32 g, 96%). mp 95−97 °C; ^{1}H NMR showed adequate purity for the next step. MS: $MH^+ = 155$. ^{1}H NMR ($CDCl_3$): δ 8.56 (b, 1H), 7.53 (d, J = 1.2 Hz, 1H), 6.78 (d, J = 1.2 Hz, 1H), 3.65 (s, 3H), 2.91 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 173.8, 135.2, 134.5, 117.7, 51.8, 33.9, 21.9. This is a known compound.[7]

Methyl 3-(1-Tritylimidazol-4-yl)propionate (3). A literature procedure was used.[4] To a solution of **2** (4.62 g, 30.0 mmol) and triethylamine (8.40 mL, 60.0 mmol) in 30 mL of anhydrous DMF was added triphenylchloromethane (9.39 g, 33.0 mmol) in 25 mL of anhydrous DMF. The mixture turned cloudy after addition and generated heat. The reaction mixture was stirred overnight at room temperature as it became cloudy and yellowish and was poured onto 300 g of ice. A white solid precipitated, which was collected on a filter and washed with water and small amount of ether. A white powder was obtained (10.88 g, 92%). mp 142−143 °C; MS: $MH^+ = 397$. ^{1}H NMR ($CDCl_3$): δ 7.32 (m, 10H), 7.12 (m, 6H), 6.54 (s, 1H), 3.62 (s, 3H), 2.87 (t, J = 7.8 Hz, 2H), 2.65 (t, J = 7.87 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 173.4, 142.4, 139.9, 138.3, 129.7, 127.9, 117.9, 51.5, 33.9, 24.0. All data were consistent with literature.

(1) Pirrung, M. C. *Chem. Biol.* **1999**, *6*, R167.

(2) Altman, J.; Wilchek, M. *Synth. Comm.* **1989**, *19*, 2069−2076. Bloemhoff, W.; Kerling, K. E. T. *J. R. Neth. Chem. Soc.* **1975**, 183.

(3) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiqara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. *J. Med. Chem.* **1981**, *24*, 1139−1148.

(4) Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E.; Bhatnagar, A. *J. Med. Chem.* **1991**, *34*, 725−736.

(5) Flouret, G.; Morgan, R.; Gendrich, R.; Wilber, J.; Siebel, M. *J. Med. Chem.* **1973**, *16*, 113.

(6) Viguerie, N. L.; Sergueeva, N.; Damiot, M.; Mawlawi, H.; Riviere, M.; Lattes, A. *Heterocycles* **1994**, *37*, 1561.

(7) Schunack, W.; *Arch. Pharm.* **1974**, *307*, 517.

10.1021/jo991630q CCC: $19.00
Published on Web 03/16/2000

3-(1-Tritylimidazol-4-yl)propionaldehyde (4). A modification of a known procedure was used.[4] To a solution of **4** (3.97 g, 10.0 mmol) in 50 mL of anhydrous dichloromethane was added DIBAL-H (1.5 M in toluene) (13.5 mL, 20.3 mmol) at −78 °C. The reaction was kept stirring at this temperature for 45 min before it was quenched by adding 5 mL of methanol and 35 mL of water. After the reaction mixture rose to room temperature, the organic layer was separated and dried over Na_2SO_4. After removal of solvent in vacuo, a slight yellowish white solid was obtained (3.90 g, 100%). mp 84−86 °C; MS: $MH^+ = 367$. ^{1}H NMR ($CDCl_3$): δ 9.81 (t, $J = 1.5$ Hz, 1H), 7.32 (m, 9H), 7.23 (s, 1H), 7.12 (m, 6H), 6.56 (s, 1H), 2.87 (m, 2H), 2.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 202.1, 142.3, 139.6, 138.5, 129.6, 127.9, 118.0, 43.3, 21.3. IR (film) 3060, 3030, 1722 cm^{-1}. All data were consistent with literature.

4-(1-Tritylimidazol-4-yl)-2-aminobutyronitrile (5). To a solution of **4** (2.38 g, 6.5 mmol) in methanol was added NH_4Cl (1.25 g, 23.3 mmol) in 20 mL of ammonia/H_2O. The reaction mixture was stirred at room temperature for 40 min, and KCN (0.76 g, 11.7 mmol) was added. The reaction was kept stirring at room temperature for 18 h followed by removal of the solvent in vacuo. The solid was redissolved in ethyl acetate and water. The organic layer was dried over Na_2SO_4 and evaporated to a slight yellowish residue. The product was recrystallized from CH_2Cl_2/hexane to provide a white solid after filtration (2.15 g, 84%). mp 111−113 °C; MS: $MH^+ = 393.22$. HRMS calcd for $C_{26}H_{24}N_4$: $M = 392.2001$, found $M = 392.2080$. ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 1H), 7.27 (m, 9H), 7.11 (m, 6H), 6.58 (s, 1H), 3.71 (t, $J = 7.2$ Hz, 1H), 2.75 (m, 2H), 2.38 (b, 2H), 2.10 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 142.2, 139.0, 138.4, 129.6, 127.9, 118.5, 118.3, 42.7, 34.9, 24.2. IR (film) 3384, 3153, 3089, 3062, 2251 cm^{-1}.

Homohistidine (6). A modification of a literature procedure was used.[8] To 20 mL of concentrated HCl was added **5** (1.2 g, 3.05 mmol), and the reaction mixture was refluxed overnight. The solution was twice extracted with ether. The aqueous layer was evaporated in vacuo, and a white solid was obtained (0.55 g, 100%). Further purification was accomplished on Dowex cation-exchange resin, eluting with 1 N ammonia. mp 222−224 °C; MS: $MH^+ = 170.13$. ^{1}H NMR (D_2O) δ 7.63 (s, 1H), 6.85 (s, 1H), 3.62 (t, $J = 6.0$ Hz, 1H), 2.61 (t, $J = 8.1$ Hz, 2H), 2.06 (m, 2H). IR (film) 3372, 3048, 1732 cm^{-1}. All data were consistent with literature.[2]

(8) Harada, K.; Okawara, T. *J. Org. Chem.* **1973**, *38*, 707.

Bis-BOC-homohistidine (7). Homohistidine (**6**) (0.29 g, 1.7 mmol) was dissolved in a minimum amount of water. Saturated $NaHCO_3/H_2O$ was added to pH 9. A solution of $(BOC)_2O$ (1.30 g, 5.8 mmol) in dichloromethane was added followed by tetrabutylammonium bromide. The reaction was stirred overnight and acidified to pH 3 with 1 N HCl/H_2O. The resulting solution was extracted with chloroform, and the organic layer was dried over Na_2SO_4. After removal of solvent, the product was purified by flash column chromatography (0.11 g, 17%), R_f (0.3, $CHCl_3$:MeOH = 5:1). MS: $MH^+ = 370.18$. HRMS calcd for $C_{17}H_{28}N_3O_6$: $MH^+ = 370.1978$, found $MH^+ = 370.1978$. ^{1}H NMR ($CDCl_3$) δ 11.94 (b, 1H), 8.11 (s, 1H), 7.14 (s, 1H), 5.40 (d, $J = 7.5$ Hz, 1H), 4.31 (m, 1H), 2.66 (m, 2H), 2.11 (m, 2H), 1.58 (s, 9H), 1,41 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 174.3, 155.2, 146.3, 141.0, 136.2, 113.6, 86.2, 79.6, 52.9, 32.8, 28.4, 27.9, 23.1. IR (film) 3303, 3065, 1772, 1711, 1692, 1649 cm^{-1}.

BOC-homohistidine (8). Homohistidine (**6**) (1.80 g, 10.6 mmol) was dissolved in a minimum amount of water and adjusted to pH 9 with saturated $NaHCO_3/H_2O$. $(BOC)_2O$ (4.62 g, 21.2 mmol) in dioxane was added, and the reaction was refluxed overnight. After cooling to room temperature, most of the solvent was removed and the residue was acidified to pH 3 with 1 N HCl/H_2O. The cloudy mixture was extracted with chloroform. The aqueous layer was evaporated in vacuo, and the solid was redissolved in methanol. Chloroform was added to induce precipitation. After filtration of the solid, the solute was evaporated in vacuo. A slight yellowish sticky oil was obtained (1.60 g, 56%). MS: $MH^+ = 270$. HRMS calcd for $C_{12}H_{20}N_3O_4$: $MH^+ = 270.1454$, found $MH^+ = 270.1454$.^{1}H NMR ($CDCl_3$) δ 8.44 (s, 1H), 7.10 (s, 1H), 3.85 (m, 1H), 2.70 (t, $J = 7.35$ Hz, 2H), 2.07 (m, 1H), 1.88 (m, 1H), 1.27 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.5, 155.4, 133.7, 133.3, 115.8, 78.0, 52.7, 29.9, 28.2, 21.6. IR (KBr) 3397, 3134, 1754, 1691 cm^{-1}.

Acknowledgment. Financial support provided by NIH AI-42151. The assistance of L. LaBean in administrative support of this work is greatly appreciated.

Supporting Information Available: NMR spectra for **5**, **7**, and **8**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

JO991630Q