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Synthesis of *N*-Methylpyrrole and *N*-Methylimidazole Amino Acids Suitable for Solid-Phase Synthesis

David Jaramillo,[†] Qi Liu,[‡] Janice Aldrich-Wright,[†] and Yitzhak Tor*[,‡]

College of Science, Technology & Environment, University of Western Sydney, Penrith South DC NSW 2560, Australia, and Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093-0358

ytor@ucsd.edu

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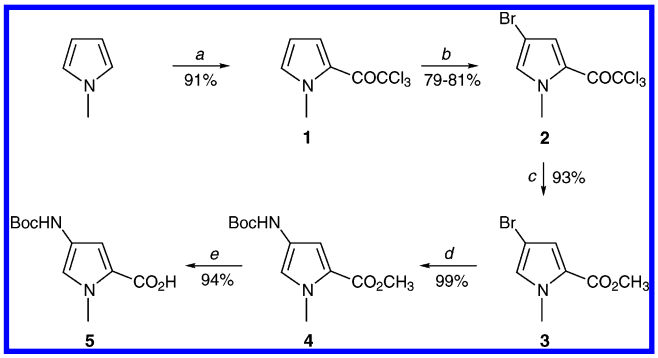
Abstract: New and higher yielding synthetic routes to *N*-protected *N*-methylpyrrole and *N*-methylimidazole amino acids are introduced to circumvent difficulties associated with established schemes. Key steps in each synthesis include copper-mediated cross-coupling reaction to directly install a carbamate-protected 4-amine in the *N*-methylpyrrole derivative and effective nitration followed by a one-pot reduction/Boc protection of the amine in the synthesis of the *N*-Me-imidazole amino acid.

Polyamides based on *N*-methylpyrrole and *N*-methylimidazole have emerged as a unique family of sequence-specific DNA binders.[1,2] These synthetic low MW ligands form dimeric complexes within the DNA minor groove with unprecedented affinity and selectivity. The recognition rules, established over the past decade by Dervan and co-workers, allow one to control the sequence specificity of these "designer" molecules according to the linear sequence of the individual building blocks.[3] The strength of this DNA recognition motif and its demonstrated utility[4] have therefore led to the development of efficient solid-phase synthesis of such oligomeric polyamides.[5]

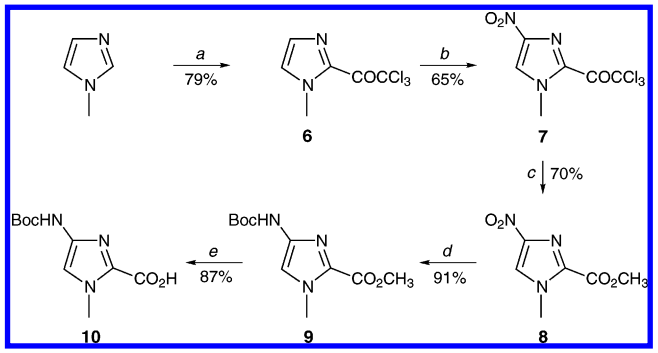
Key to the successful synthesis and application of these DNA binders is the availability of the protected building blocks, 4-[(*tert*-butoxycarbonyl)amino]-1-methylpyrrole-2-carboxylic acid **5** and 4-[(*tert*-butoxycarbonyl)amino]-1-methylimidazole-2-carboxylic acid **10** (Schemes 1 and 2, respectively). Unlike common amino acids, the preparation of these *N*-protected precursors requires rather elaborate synthetic schemes typically starting from the parent heterocycles.[5] While the introduction of the 2-carboxyl moiety is rather straightforward, the implementation of a nitrogen-containing moiety at the 4 position is more challenging. Traditionally, nitration of the parent heterocycles or their corresponding carboxylic acid derivatives has been followed by hydrogenation and protection of the amine to afford the desired building blocks.[5] This arduous sequence has been recognized as the Achilles' heel of these syntheses resulting in relatively low overall yields (16% for **5**[5a] and 18% for **10**[5b]). We have sought to explore alternative schemes to functionalize the 4 position, in particular, routes that rely on metal-mediated amination/amidation reactions. In this paper, we disclose our optimized protocols that afford these useful building blocks in improved yields.

SCHEME 1[a]



[a] Reagents and conditions: (a) CCl_3COCl, CH_2Cl_2, 24 h; (b) NBS, $CHCl_3$, −10 °C, 16 h; (c) NaOMe, MeOH, 1 h; (d) 10% CuI, K_3PO_4, 20% *N*,*N*′-dimethylethylenediamine, *tert*-butyl carbamate, dioxane, 110 °C, 48 h; (e) LiOH, H_2O, THF/MeOH, 60 °C, 9 h.

SCHEME 2[a]



[a] Reagents and conditions: (a) CCl_3COCl, CH_2Cl_2, 9 h; (b) fuming HNO_3, H_2SO_4, Ac_2O, 0 °C to rt, 24 h; (c) NaOMe, MeOH, 3 h; (d) Boc_2O, 10% Pd/C, H_2, MeOH, 28 h; (e) *t*-BuOK, H_2O, THF, rt, 1 h.

Scheme 1 shows the optimized scheme for the synthesis of the pyrrole building block **5**. The copper-catalyzed amidation of methyl 4-bromomethylpyrrole-2-carboxylate **3** began with the synthesis of the trichloroacetyl heterocycle **1** as previously reported.[6] Bromination of **1** with equimolar amounts of *N*-bromosuccinimide (NBS) at low temperature gave **2** in 79−81% yield. Substitution of the trichloroacetyl for the more stable carbomethoxy group

[†] University of Western Sydney.
[‡] University of California.

(1) Dervan, P. B.; Edelson, B. S. *Curr. Opin. Struct. Biol.* **2003**, *13*, 284−299.
(2) Schmitz, K.; Schepers, U. *Angew. Chem., Int. Ed.* **2004**, *43*, 2472−2475.
(3) Marques, M. A.; Doss, R. M.; Urbach, A. R.; Dervan, P. B. *Helv. Chim. Acta* **2002**, *85*, 4485−4517.
(4) For selected examples, see: Mapp, A. M.; Ansari, A. Z.; Ptashne, M.; Dervan, P. B. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 3930−3935. Gottesfeld, J. M.; Belitsky, J. M.; Melander, C.; Dervan, P. B.; Luger, K. *J. Mol. Biol.* **2002**, *321*, 249−263. Arndt, H.-D.; Hauschild, K. E.; Sullivan, D. P.; Lake, K.; Dervan, P. B.; Ansari, A. Z. *J. Am. Chem. Soc.* **2003**, *125*, 13322−13323. Nguyen-Hackley, D. H.; Ramm, E.; Taylor, C. M.; Joung, J. K.; Dervan, P. B.; Pabo, C. O. *Biochemistry* **2004**, *43*, 3880−3890.
(5) (a) Baird, E. E.; Dervan, P. B. *J. Am. Chem. Soc.* **1996**, *118*, 6141−6146. (b) Wurtz, N. R.; Turner, J. M.; Baird, E. E.; Dervan, P. B. *Org. Lett.* **2001**, *3*, 1201−1203.
(6) Nishiwaki, E.; Tanaka, S.; Lee, H.; Shibuya, M. *Heterocycles* **1988**, *27*, 1945−1952.

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with sodium methoxide followed, giving the ester **3** in excellent yield. Reaction of **3** with *tert*-butyl carbamate employing Buchwald's catalyst system, comprised of CuI, *N*,*N*′-dimethylethylenediamine, and K_3PO_4,[7] produced the Boc-protected precursor **4** in 99% yield. Final ester hydrolysis using LiOH[8] afforded the *N*-methylpyrrole acid building block **5** in five steps, from *N*-methylpyrrole, with an improved overall yield of 62−64%.

It is important to note that the synthetic scheme outlined above represents the culmination of numerous attempts to explore and optimize alternative reaction conditions. The major difficulties we have encountered with alternate schemes include (a) loss of selectivity in reactions of **2** with NBS at room temperature, with both the 5-bromo and 4,5-dibromo as the major products, (b) unsatisfactory bromination of related *N*-methylpyrrole esters resulting in low yields (20−30%), and (c) unsuccessful palladium and copper catalyzed cross-coupling reactions[7,9] of **2** with other substrates, including benzophenone imine, 4-methoxybenzylamine, and acetamide. Additionally, the trichloroacetyl group was found to be unstable under the various conditions employed.

Similar efforts for the synthesis of the imidazole amino acid **10** utilizing the same and related cross-coupling reactions failed. A possible reason may be the coordination of imidazole to the catalysts employed. Attempts to displace 4-halogen-substituted *N*-methylimidazoles with nitrogen-containing nucleophiles (such as N_3^-) were not successful. This has led us to explore other modifications of the existing method.[5] Here, the versatility of the trichloroacetyl group was again employed with the synthesis of the nitro derivative **7** through initial trichloroacetylation[6] of *N*-methylimidazole and subsequent nitration using HNO_3/H_2SO_4. The nitro ester **8** was then obtained through base hydrolysis of **7**, and a one-pot catalytic reduction and Boc-protection gave the desired compound **9** in 91% yield for the two steps. Final hydrolysis with *t*-BuOK in THF/H_2O[10] produced the imidazole acid building block **10** in five steps, with an improved overall yield of 28%.

In summary, we have reported on alternative synthetic schemes to two useful heterocyclic amino acids extensively employed in the synthesis of highly selective DNA minor groove binders.

Experimental Section

2-Trichloroacetyl-1-methylpyrrole (1).[6] *N*-Methylpyrrole (10 g, 0.12 mol) in CH_2Cl_2 (40 mL) was added dropwise to trichloroacetyl chloride (22 g, 0.12 mol) in CH_2Cl_2 (40 mL) over a period of 3 h and then stirred overnight. The solvent was removed and the residue purified by flash chromatography (silica gel, 3:7 CH_2Cl_2/hexane, R_f 0.73) yielding **1** (25.3 g, 91%) as a light yellow solid: mp 66−67 °C (lit.[6] 65−66 °C); IR (KBr) 3131, 1647, 1525, 1404, 1335 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 4.4$ Hz), 6.95 (d, 1H, $J = 1.6$ Hz), 6.21 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 4.4$ Hz), 3.95 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8, 133.6, 124.0, 121.7, 108.8, 96.3, 38.5; APCI-MS *m/z* calcd for $C_7H_8Cl_2NO$ $[M + H - Cl]^+$ 191.99, found 191.98; C_7H_9ClNO $[M + H - Cl_2]^+$ 158.03, found 158.01.

4-Bromo-2-trichloroacetyl-1-methylpyrrole (2). To compound **1** (5.0 g, 22 mmol) in $CHCl_3$ (65 mL) at −10 °C was added NBS (4.13 g, 23 mmol) and the reaction stirred for 2 h. The solution was warmed to room temperature and stirred for a further 16 h. The solution was concentrated and the residue purified by flash chromatography (silica gel, 1:9 CH_2Cl_2/hexane, R_f 0.23) yielding **2** (5.32 g, 79%) as a white solid:[11] mp 105−107 °C; IR (KBr) 3131, 1677, 1464, 1358, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, $J = 1.6$ Hz), 6.92 (d, 1H, $J = 1.6$ Hz), 3.89 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.3, 132.8, 124.5, 122.1, 108.8, 96.1, 38.7; APCI-MS *m/z* calcd for C_7H_9BrNO $[M + H - Cl_3]^+$ 201.98, found 201.98.

Methyl 4-Bromomethylpyrrole-2-carboxylate (3). To compound **2** (2.0 g, 6.6 mmol) in dry MeOH (75 mL) was added sodium methoxide (0.43 g, 7.9 mmol) and the mixture stirred for 1 h. The reaction was cooled and quenched with HCl (1 M, 1.3 mL). The solvent was evaporated, H_2O added, and the mixture extracted with CH_2Cl_2. The organics were dried (Na_2SO_4), solvent removed, and the residue purified by flash chromatography (silica gel, 1:1 hexane/CH_2Cl_2, R_f 0.35), yielding **3** (1.34 g, 93%) as a white solid: mp 65−66 °C; IR (KBr) 3123, 1693, 1442, 1388, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, 1H, $J = 2.0$ Hz), 6.74 (d, 1H, $J = 2.0$ Hz), 3.87 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.8, 128.7, 122.8, 119.2, 95.0, 51.2, 36.9; GC−MS *m/z* calcd for $C_7H_9BrNO_2$ $[M + H]^+$ 217.97, found 218.2.

Methyl 4-[(*tert*-Butoxycarbonyl)amino]-1-methylpyrrole-2-carboxylate (4). CuI (0.020 g, 0.1 mmol, 10 mol %), K_3PO_4 (0.43 g, 2 mmol), and *N*,*N*′-dimethylethylenediamine (0.022 mL, 0.2 mmol, 20 mol %) in dry dioxane (5 mL) were stirred under argon for 5 min. Compound **3** (0.22 g, 1 mmol) and *tert*-butyl carbamate (0.47 g, 4 mmol) were added, and the mixture was heated at 110 °C for 48 h. The solvent was removed and the residue purified by flash chromatography (silica gel, gradient 1:19 MeOH/CH_2Cl_2, R_f 0.56) to yield **4** (0.26 g 99%) as a light brown solid: mp 115−116 °C (lit.[12] 109 °C); IR (KBr) 3344, 2963, 1716, 1685, 1594 cm^{-1}; ^1H NMR [400 MHz, $(CD_3)_2SO$] δ 9.11 (s, 1H), 7.09 (s, 1H), 6.61 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H) 1.43 (s, 9H); ^{13}C NMR [100.6 MHz, $(CD_3)_2SO$] δ 160.7,152.7, 123.1, 119.2, 118.6, 107.3, 78.5, 50.8, 36.0, 28.1; ESI-MS *m/z* calcd for $C_{12}H_{18}N_2O_4$ $[M + Na]^+$ 277.13, found 276.96.

4-[(*tert*-Butoxycarbonyl)amino]-1-methylpyrrole-2-carboxylic Acid (5). To compound **4** (0.05 g, 0.20 mmol) in THF/MeOH (3:1, 4 mL) was added LiOH (1 M, 0.79 mL, 0.79 mmol) and the mixture stirred at 60 °C for 9 h. H_2O and EtOAc were added, and the aqueous layer was acidified with HCl (1 M, 0.79 mL). The aqueous layer was extracted with EtOAc, dried (Na_2SO_4), and concentrated, yielding **5** (0.044 g, 94%) as a white solid (1:9 MeOH/CH_2Cl_2, R_f 0.22): mp 160−161 °C (lit.[13] 151−151.5 °C); IR (KBr) 3395, 3131, 2930, 1693, 1590, 1450, 1393, 1250, 1163 cm^{-1}; ^1H NMR [400 MHz, $(CD_3)_2SO$] δ 12.10 (s, 1H), 9.05 (s, 1H), 7.04 (s, 1H), 6.56 (s, 1H), 3.76 (s, 3H), 1.42 (s, 9H); ^{13}C NMR [100.6 MHz, $(CD_3)_2SO$] δ 161.9; 152.7; 122.8, 119.6, 118.8, 107.4, 78.4, 36.1, 28.2; ESI-MS *m/z* calcd for $C_{11}H_{16}N_2O_4$ $[M + Na]^+$ 263.11, found 262.94.

2-Trichloroacety-1-methylimidazole (6). *N*-Methylimidazole (10 g, 0.12 mol) in CH_2Cl_2 (80 mL) was added dropwise to trichloroacetyl chloride (22 g, 0.12 mol) in CH_2Cl_2 (80 mL) over a period of 2.5 h. The mixture was then stirred for 6 h and cooled to 0 °C, and Et_3N (17 mL, 0.12 mol) was added dropwise over 1 h. The solvent was evaporated and the residue purified by flash chromatography (silica gel, 1:4 hexane/CH_2Cl_2, R_f 0.17) to yield **6** (21.8 g, 79%) as a light yellow solid: mp 83−84 °C (lit.[6] 79−80 °C); IR (KBr) 3123, 1647, 1518, 1404, 1305 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.13 (s, 1H), 4.01 (s, 3H); ^{13}C

(7) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem.* Soc. **2002**, *124*, 7421−7428.
(8) Boger, D. L.; Fink, B. E.; Hedrick, M. P. *J. Am. Chem.* Soc. **2000**, *122*, 6382−6394.
(9) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796.
(10) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918−920.
(11) Slightly higher yield (81%) is obtained when the reaction is executed on a smaller (ca. 0.5 g) scale.
(12) Bailly, C.; Pommery, N.; Houssin, R.; Henichart, J. P. *J. Pharm. Sci.* **1989**, *78*, 910−917.
(13) Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1981**, *46*, 3492−3497.

NMR (100.6 MHz, $CDCl_3$) δ 172.0, 135.9, 130.4, 128.5, 94.7, 37.1; ESI-MS *m/z* calcd for $C_6H_6Cl_3N_2O$ $[M + H]^+$ 226.95, found 226.96.

4-Nitro-2-trichloroacety-1-methylimidazole (7). To acetic anhydride (38 mL) at 0 °C was added dropwise fuming HNO_3 (3 mL, 0.07 mol), followed by H_2SO_4 (0.14 mL). Compound **6** (5 g, 0.02 mol) was added slowly, and the solution was warmed to room temperature and stirred overnight. $CHCl_3$ was added and the solution washed with $NaHCO_{3(aq)}$ and brine. The organics were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (silica gel, 1:1 EtOAc/ hexane, R_f 0.43) yielding **7** (3.89 g, 65%) as a light yellow solid: mp 139−140 °C (lit.[6] mp 140−141 °C); IR (KBr) 3146, 2355, 1708, 1541, 1343 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 4.15 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8, 133.6, 125.9, 94.4, 93.5, 38.3; ESI-MS *m/z* calcd for $C_6H_5Cl_3N_3O_3$ $[M + H]^+$ 271.93, found 271.92.

Methyl 1-Methyl-4-nitroimidazole-2-carboxylate (8). To compound **7** (3.47 g, 0.01 mol) in dry MeOH (130 mL) was added sodium methoxide (0.83 g, 0.02 mol) and the solution stirred for 3 h. The reaction was cooled and quenched by the addition of HCl (1 M, 13 mL). The solvent was evaporated, H_2O added, and the mixture extracted with CH_2Cl_2. The organics were dried (Na_2SO_4), and the residue was purified by flash chromatography (silica gel, 3:7 hexane/EtOAc, R_f 0.48) to yield **8** (1.65 g, 70%) as a white solid: mp 157−158 °C; IR (KBr) 3435, 3138, 2956, 1731, 1556, 1487, 1305, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 4.09 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.5, 146.0, 134.6, 124.4, 52.9, 37.0; APCI-MS *m/z* calcd for $C_6H_8N_3O_4$ $[M + H]^+$ 186.04, found 185.96.

Methyl 4-[(*tert*-Butoxycarbonyl)amino]-1-methylimidazole-2-carboxylate (9). To compound **8** (1.24 g, 0.01 mol) in dry MeOH (120 mL) was added *tert*-butyl dicarbonate (5.86 g, 0.03 mol) followed by 10% Pd/C (0.12 g), and the mixture was stirred under a hydrogen atmosphere for 3 h. $H_{2(g)}$ was removed and the mixture stirred for 28 h. The catalyst was filtered (Celite) and the solvent evaporated. The residue was washed with $NaHCO_{3(aq)}$ and extracted with CH_2Cl_2. The organics were dried (Na_2SO_4), and the residue was purified by flash chromatography (silica gel, 1:19 MeOH/CH_2Cl_2, R_f 0.45), yielding **9** (1.56 g, 91%) as a white solid: mp 130−132 °C; IR (KBr) 3291, 2979, 1716, 1579 cm^{-1}; ^1H NMR [400 MHz, $(CD_3)_2SO$] δ 9.68 (s, 1H), 7.31 (s, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 1.43 (s, 9H); ^{13}C NMR [100.6 MHz, $(CD_3)_2SO$] δ 158.8, 152.7, 138.1, 130.7, 113.8, 79.0, 51.6, 35.3, 28.0; APCI-MS *m/z* calcd for $C_{11}H_{18}N_3O_4$ $[M + H]^+$ 256.12, found 255.80.

4-[(*tert*-Butoxycarbonyl)amino]-1-methylimidazole-2-carboxylic Acid (10). To potassium *tert*-butoxide (0.35 g, 3.13 mmol) in dry THF (6 mL) at 0 °C was added H_2O (14 mL, 0.78 mmol) and the solution stirred for 5 min. Compound **9** (0.1 g, 0.39 mmol) was added and the mixture stirred at room temperature for 1 h. It was then diluted with cold H_2O and EtOAc, the layers were separated, and the aqueous layer was acidified by addition of HCl (1 M, 3.1 mL). The aqueous layer was extracted with EtOAc, dried (Na_2SO_4), and concentrated, yielding **10** (0.08 g, 87%) as a white solid (1:9 MeOH/CH_2Cl_2, R_f 0.25): mp 200−201 °C (lit.[14] mp 201−202 °C); IR (KBr) 3389, 3230, 2979, 1716, 1624, 1571, 1358, 1160 cm^{-1}; ^1H NMR [400 MHz, $(CD_3)_2SO$] δ 9.63 (s, 1H), 7.25 (s, 1H), 3.86 (s, 3H), 1.42 (s, 9H); ^{13}C NMR [100.6 MHz, $(CD_3)_2SO$] δ 160.0, 152.8, 137.7, 131.7, 113.5, 78.9, 35.4, 28.1; ESI-MS *m/z* calcd for $C_{10}H_{15}N_3O_4$ $[M + Na]^+$ 264.11, found 263.93.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Grehn, L.; Ding, L.; Ragnarsson, U. *Acta Chem. Scand.* **1990**, *44*, 67−74.