

Parham-type cyclacylation with Weinreb amides. Application to the synthesis of fused indolizinone systems

Javier Ruiz, Nuria Sotomayor, and Esther Lete*

Departamento de Química Orgánica II, Facultad de Ciencias, Universidad del País Vasco, Apdo. 644. 48080 Bilbao (Spain).

gopleexe@lg.ehu.es

Supporting Information

Preparation of 1-benzyl-*N*-methoxy-*N*-methylpyrrole-2-carboxamides.

Typical procedure for 2d.

2-Iodo-4,5-dimethoxybenzyl alcohol. A solution of I₂ (250 mg, 1 mmol) in dry CHCl₃ (30 mL) was added over a suspension of CF₃COOAg (220 mg, 1 mmol) and 3,4-dimethoxybenzyl alcohol (168 mg, 1 mmol) in CHCl₃ (5 mL). The reaction mixture was stirred at rt during 30 min, the resulting AgI precipitate was filtered, and the resulting solution was washed with saturated Na₂S₂O₃. Evaporation of the solvent afforded 2-iodo-4,5-dimethoxybenzyl alcohol as an oil, which was crystallized from Et₂O (188 mg, 64%): mp (Et₂O) 83-85 °C; IR (KBr) 3270 cm⁻¹; ¹H NMR (CDCl₃) 2.40 (s, 1H), 3.84 (s, 6H), 4.56 (s, 2H), 6.97 (s, 1H), 7.18 (s, 1H); ¹³C NMR (CDCl₃) 55.8, 56.1, 68.9, 85.2, 111.4, 121.3, 135.1, 148.7, 149.3; MS (EI) *m/z* (rel intensity) 294 (M⁺, 100), 277 (10), 139 (57), 124 (23), 96 (18), 95 (13), 77 (13), 65 (11). Anal. Calcd for C₉H₁₁IO₃: C, 36.76; H, 3.77. Found: C, 36.97; H, 3.54.

2-Iodo-4,5-dimethoxybenzyl bromide (1d). PBr₃ (0.19 mL, 2 mmol) was added over a solution of 2-iodo-4,5-dimethoxybenzyl alcohol (294 mg, 1 mmol) in dry CH₂Cl₂ (10 mL), and the reaction mixture was stirred at rt for 16 h. Solvent was evaporated, and the resulting oil was treated with saturated NaHCO₃. The resulting aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*, yielding 2-iodo-4,5-dimethoxybenzyl bromide as an oil, which was crystallized from Et₂O (339 mg, 95%): mp (Et₂O) 74-75 °C; IR (KBr) 3270 cm⁻¹; ¹H NMR (CDCl₃) 3.86 (s, 3H), 3.87 (s, 3H), 4.58 (s, 2H), 6.96 (s, 1H), 7.22 (s, 1H); ¹³C NMR (CDCl₃) 39.4, 56.0, 56.2, 88.5, 112.7, 121.8, 132.5, 149.6; MS (EI) *m/z* (rel intensity) 312 (35), 277 (100), 150 (9), 107 (6), 77 (5). Anal. Calcd for C₉H₁₀BrIO₂: C, 30.28; H, 2.82. Found: C, 30.42; H, 2.56.

***N*-Methoxy-*N*-methylpyrrole-2-carboxamide.** SOCl₂ (7.83 mL, 107.3 mmol) was added over a suspension of pyrrole-2-carboxylic acid (4.77 g, 42.9 mmol) in dry toluene (60 mL), and the mixture was refluxed for 3 h. Solvent was evaporated, and the resulting oil was solved in dry CH₂Cl₂ (60 mL). The solution was cooled down to 0 °C, *N*-methoxy-*N*-methylamine (5.02 g, 51.5 mmol) and EtN₃ (14.3 mL, 103.0 mmol) were added sequentially, and the reaction mixture was stirred at rt for 14 h. H₂O (60 mL) was added and the resulting aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Flash column chromatography (silicagel, 50% hexane/AcOEt) afforded *N*-Methoxy-*N*-methylpyrrole-2-carboxamide as a colorless oil (6.32 g, 96%), whose spectroscopic data were identical to those reported in the literature¹: IR (CHCl₃) 3276, 1598 cm⁻¹; ¹H NMR (CDCl₃) 3.35 (s, 3H), 3.79 (s, 3H), 6.27-6.31 (m, 1H), 6.90-6.93 (m, 1H), 6.95-6.98 (m, 1H), 9.48 (broad s, 1H); ¹³C NMR (CDCl₃) 32.7, 60.7, 109.8, 114.6, 122.1, 123.1, 161.2; MS (EI) *m/z* (rel intensity) 154 (M⁺, 22), 95 (8), 94 (100), 85 (5), 83 (7), 66 (15).

1-(2-Iodo-4,5-dimethoxybenzyl)-*N*-methyl-*N*-methoxypyrrol-2-carboxamide (2d). *N*-Methoxy-*N*-methylpyrrole-2-carboxamide (154 mg, 1mmol) was added over a suspension of powdered KOH (224 mg, 4 mmol) in DMSO (5 mL). The mixture was stirred at rt for 2 h, bromide **1d** (714 mg, 2 mmol) was added, and the reaction mixture was stirred for 3 h. H₂O (10 mL) was added and the resulting aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **2d** as a colorless oil, that was crystallized from pentane (409 g, 95%): IR (CHCl₃) 1623 cm⁻¹; ¹H NMR (CDCl₃) 3.30 (s, 3H), 3.65 (s, 3H), 3.67 (s, 3H), 3.84 (s, 3H); 5.46 (s, 2H), 6.19 (dd, *J* = 4.0, 2.8 Hz, 1H), 6.28 (s, 1H), 6.82 (dd, *J* = 2.8, 1.8 Hz, 1H), 6.97 (dd, *J* = 4.0, 1.8 Hz, 1H), 7.22 (s, 1H); ¹³C NMR (CDCl₃) 33.7, 55.6, 56.1, 56.6, 60.9, 85.6, 108.1, 111.1, 116.6, 121.3, 123.2, 127.4, 133.6, 148.6, 149.5, 162.2. MS (EI) *m/z* (rel intensity) 430 (M⁺, 6), 370 (22), 243 (100), 83 (29). Anal. Calcd for C₁₆H₁₉IN₂O₄: C, 44.67; N, 4.45; H, 6.51. Found: C, 45.12; N, 4.44; H, 5.96.

¹ Banwell, M.; Smith, J. *Synth. Commun.* **2001**, *31*, 2011.

Parham Cyclization of *N*-(*o*-iodobenzyl)pyrrole-2-carboxamides 2a-g. Synthesis of 5*H*-pyrrolo[1,2-*b*]isoquinolin-10-ones 3a-g. General Procedure. To a solution of iodinated *N*-(*o*-iodobenzyl)pyrrole-2-carboxamide **2a-g** (1 mmol) in dry THF (15 mL), *t*-BuLi (2.2 mmol) was added at -78 °C, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by the addition of sat. NH₄Cl (10 mL). Et₂O (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Flash column chromatography afforded pyrroloisoquinolones **3a-g**.

5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (3a). According to the General Procedure pyrrole-2-carboxamide **2a** (288 mg, 0.78 mmol) was treated with *t*-BuLi (1.07 mL of a 1.6 M solution in pentane, 1.72 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **3a** as a colorless oil (125 mg, 87%): IR (neat) 1642 cm⁻¹; ¹H NMR (CDCl₃) 5.38 (s, 2H), 6.44 (dd, *J* = 4.0, 2.4 Hz, 1H), 7.08-7.09 (m, 1H), 7.20 (dd, *J* = 4.0, 1.5 Hz, 1H), 7.33 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.47 (td, *J* = 7.3, 0.9 Hz, 1H), 7.56 (td, *J* = 7.3, 1.4 Hz, 1H), 8.30 (dd, *J* = 7.6, 1.4 Hz, 1H); ¹³C NMR (CDCl₃) 46.9, 111.6, 113.6, 125.6, 127.1, 127.8, 129.6, 130.5, 132.4, 135.6, 174.7; MS (EI) *m/z* (rel intensity) 183 (*M*⁺, 100), 182 (58), 155 (11), 154 (51), 128 (12), 127 (30), 89 (16), 77 (20), 63 (20), 51 (13). Anal. Calcd for C₁₂H₉NO: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.88; H, 4.82; N, 7.54.

7,8-Dimethyl-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (3b). According to the General Procedure pyrrole-2-carboxamide **2b** (84 mg, 0.21 mmol) was treated with *t*-BuLi (0.42 mL of a 1.6 M solution in pentane, 0.67 mmol). After work up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **3b** as a colorless oil (35 mg, 80%): IR (neat) 1638 cm⁻¹; ¹H NMR (CDCl₃) 2.35 (s, 6H), 5.33 (s, 2H), 6.43 (dd, *J* = 4.0, 2.8 Hz, 1H), 7.06 (dd, *J* = 2.8, 1.6 Hz, 1H), 7.10 (s, 1H), 7.18 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.06 (s, 1H); ¹³C NMR (CDCl₃) 19.5, 20.1, 46.6, 111.4, 113.2, 125.3, 126.6, 127.6, 128.3, 129.7, 133.2, 136.6, 142.2, 175.1; MS (EI) *m/z* (rel intensity) (*M*⁺, 100), 210 (28), 197 (12), 196 (80), 168 (13), 167 (15).

7-Methoxy-5*H*-pyrrolo[1,2-*b*]isoquinolin-10-one (3c). According to the General Procedure pyrrole-2-carboxamide **2c** (387 mg, 0.97 mmol) was treated with *t*-BuLi (1.33 mL of a 1.6 M solution in pentane, 2.1 mmol). After work up, flash column

chromatography (silicagel, 50% hexane/AcOEt) afforded **3c** as a colorless oil (142 mg, 69%): IR (neat) 1638 cm^{-1} ; ^1H NMR (CDCl_3) 3.88 (s, 3H), 5.34 (s, 2H), 6.41 (dd, $J = 4.0, 2.4$ Hz, 1H), 6.78 (dd, $J = 2.4, 1.2$ Hz, 1H), 6.98 (dd, $J = 8.7, 2.4$ Hz, 1H), 7.04 (dd, $J = 2.4, 1.6$ Hz, 1H), 7.16 (dd, $J = 4.0, 1.2$ Hz, 1H), 8.25 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3) 47.0, 55.5, 110.1, 111.4, 113.1, 114.0, 123.9, 125.2, 129.4, 129.6, 137.9, 162.8, 174.3; MS (EI) m/z (rel intensity) 213 (M^+ , 100), 212 ($\text{M}^+ - 1$, 30), 182 (24), 170 (41), 169 (14), 142 (13), 141 (13), 115 (10), 87 (14), 85 (66), 83 (94).

7,8-Dimethoxy-5H-pyrrolo[1,2-*b*]isoquinolin-10-one (3d). According to the General Procedure pyrrole-2-carboxamide **2d** (449 mg, 1.04 mmol) was treated with *t*-BuLi (1.3 mL of a 1.6 M solution in pentane, 2.08 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **3d** as a colorless oil (218 mg, 86%): IR (neat) 1650 cm^{-1} ; ^1H NMR (CDCl_3) 3.90 (s, 3H), 3.92 (s, 3H), 5.17 (s, 2H), 6.35 (dd, $J = 4.0, 2.4$ Hz, 1H), 6.64 (s, 1H), 6.95-6.97 (m, 1H), 7.08 (dd, $J = 4.0, 1.5$ Hz, 1H), 7.63 (s, 1H); ^{13}C NMR (CDCl_3) 46.4, 56.0, 56.0, 107.1, 107.9, 111.1, 112.7, 123.7, 125.2, 129.2, 129.7, 148.7, 152.8, 174.1; MS (EI) m/z (rel intensity) 243 (M^+ , 100), 242 (22), 228 (21), 212 (28), 200 (13), 199 (13). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.24; H, 5.41; N, 5.84.

6,7-Dimethoxy-5H-pyrrolo[1,2-*b*]isoquinolin-10-one (3e). According to the General Procedure pyrrole-2-carboxamide **2e** (242 mg, 0.56 mmol) was treated with *t*-BuLi (0.77 mL of a 1.6 M solution in pentane, 1.24 mmol). After work up, flash column chromatography (silicagel, 20% hexane/AcOEt) afforded **3e** as a white powder, that was crystallized from Et_2O (85 mg, 62%): mp(Et_2O) 177-179 $^\circ\text{C}$; IR (KBr) 1640 cm^{-1} ; ^1H NMR (CDCl_3) 3.94 (s, 3H), 3.97 (s, 3H), 5.37 (s, 2H), 6.43 (dd, $J = 4.0, 2.4$ Hz, 1H), 7.05 (d, $J = 8.7$ Hz, 1H), 7.10 (dd, $J = 2.4, 1.6$ Hz, 1H), 7.17 (dd, $J = 4.0, 1.6$ Hz, 1H), 8.09 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3) 43.4, 55.9, 60.3, 111.5, 113.1, 123.9, 124.1, 125.7, 129.3, 129.9, 143.8, 155.6, 174.2; MS (EI) m/z (rel intensity) 243 (M^+ , 100), 242 (12), 213 (16), 212 (63), 198 (10), 185 (16), 157 (16).

7,8-Methylenedioxy-5H-pyrrolo[1,2-*b*]isoquinolin-10-one (3f). According to the General Procedure pyrrole-2-carboxamide **2f** (159 mg, 0.38 mmol) was treated with *t*-BuLi (0.52 mL of a 1.6 M solution in pentane, 0.84 mmol). After work up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **3f** as a white powder, that was crystallized from Et_2O (163 mg, 73%): mp(Et_2O) 181-183 $^\circ\text{C}$; IR (KBr) 1640 cm^{-1} ; ^1H NMR (CDCl_3) 5.24 (s, 2H), 6.03 (s, 2H), 6.38 (dd, $J = 4.0, 2.8$ Hz, 1H), 6.69 (s, 1H), 7.02 (broad s, 1H), 7.10 (dd, $J = 4.0, 1.2$ Hz, 1H), 7.64 (s, 1H); ^{13}C NMR (CDCl_3) 46.9,

101.9, 105.0, 105.9, 111.3, 112.9, 125.2, 129.2, 131.7, 147.8, 151.5, 173.8; MS (EI) m/z (rel intensity) 227 (M^+ , 66), 226 (M^+-1 , 26), 169 (17), 141 (14), 87 (14), 85 (72), 83 (100) Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.28; H, 3.86; N, 5.94.

7,8,9-Trimethoxy-5H-pyrrolo[1,2-*b*]isoquinolin-10-one (3g). According to the General Procedure pyrrole-2-carboxamide **2g** (202 mg, 0.43 mmol) was treated with *t*-BuLi (0.59 mL of a 1.6 M solution in hexanes, 0.95 mmol). After work up, flash column chromatography (silicagel, 50% hexane/AcOEt) afforded **3e** as a colorless oil (80 mg, 68%): IR (neat) 1639 cm^{-1} ; ^1H NMR (CDCl_3) 3.91 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 5.30 (s, 2H), 6.38 (dd, $J = 4.0, 2.4\text{ Hz}$, 1H), 6.60 (s, 1H), 6.97 (dd, $J = 2.4, 1.6\text{ Hz}$, 1H), 7.10 (dd, $J = 4.0, 1.6\text{ Hz}$, 1H); ^{13}C NMR (CDCl_3) 47.0, 56.0, 61.2, 61.7, 104.3, 111.1, 112.7, 118.4, 124.0, 130.4, 133.8, 142.6, 155.5, 156.6, 174.0; MS (EI) m/z (rel intensity) 273 (M^+ , 76), 272 (6), 259 (14), 258 (100), 256 (12), 240 (9), 230 (11), 228 (8), 227 (14), 215 (17), 213 (6), 212 (14), 207 (9), 198 (8), 197 (6), 184 (6), 170 (6), 137 (17), 94 (15), 85 (7), 83 (8), 51 (7).

Parham Cyclization of *N*-(2-iodothenyl)pyrrole-2-carboxamide 4b. Synthesis of 5H-thieno[3,2-*f*]indolizin-9-one (5). According to the General Procedure pyrrole-2-carboxamide **4b** (199 mg, 0.53 mmol) was treated with *t*-BuLi (0.73 mL of a 1.6 M solution in pentane, 1.17 mmol). After work up, flash column chromatography (silicagel, 30% hexane/AcOEt) afforded **5** as a white powder that was crystallized from EtOH (71 mg, 71%): mp (EtOH) 160-163 °C [lit.² 168-170 (EtOH/H₂O)]; IR (KBr) 1632 cm^{-1} ; ^1H NMR (CDCl_3) 5.33 (s, 2H), 6.39-6.40 (m, 1H), 7.05-7.11 (m, 3H), 7.67 (d, $J = 5.1\text{ Hz}$, 1H); ^{13}C NMR (CDCl_3) 46.3, 111.5, 112.5, 125.2, 125.8, 129.6, 133.4, 136.1, 141.8, 170.4; MS (EI) m/z (rel intensity) 189 (M^+ , 100), 160 (33), 134 (5), 83(5).

Parham Cyclization of *N*-(2-iodoquinolinylmethyl)pyrrole-2-carboxamide 6b. Synthesis of 11H-pyrrolo[1,2-*b*]acridin-4-one (7). To a solution of pyrrole-2-carboxamide **6** (190 mg, 0.51 mmol) in dry THF (25 mL), *n*-BuLi (0.63 mL of a 1.6 M solution in hexanes, 1.02 mmol) was added at -90 °C, and the resulting mixture was stirred at this temperature for 5 min. The reaction was quenched by the addition of sat. NH_4Cl (10 mL). Et_2O (15 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 ($3 \times 15\text{ mL}$). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography

² Decroix, B.; Morel, J. *J. Heterocycl. Chem.* **1991**, 28, 81.

(silicagel, 50% hexane/AcOEt) afforded **7** (72 mg, 61%): IR (neat) 1650 cm^{-1} ; ^1H NMR (CDCl_3) 5.62 (s, 2H), 6.50 (dd, $J = 4.0, 2.4$ Hz, 1H), 7.15 (broad s, 1H), 7.38 (dd, $J = 4.0, 1.2$, 1H), 7.65 (distorted t, $J = 7.5$ Hz, 1H), 7.79 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.85 (d, $J = 8.3$, 1H), 8.20 (s, 1H), 8.43 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (CDCl_3) 46.7, 112.6, 115.9, 126.3, 126.9, 127.3, 128.3, 129.7, 130.5, 131.3, 131.8, 133.9, 146.4, 148.8, 173.1.