A Modified Friedlander Condensation for the Synthesis of 3-Hydroxyquinoline-2-carboxylates

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In conjunction with efforts on the total synthesis of sandramycin,[1] quinaldopeptin,[2] BE22179,[3] and the luzopeptins,[4] symmetrical cyclic decadepsipeptides possessing a 2-fold axis of symmetry which exhibit high-affinity sequence-selective DNA binding with bis-intercalation of the pendant heterocyclic chromophores,[5,6] we required access to suitably protected derivatives of the 3-hydroxyquinoline-2-carboxylic acids **1a** and **1b** and related agents[6] (Chart 1).

To the best of our knowledge, only one indirect synthesis of **1a** has been disclosed[7] and is of limited practical value and our initial efforts on their preparation proved less straightforward than their structures would suggest. Unlike our successful condensation of pyruvic acid with a substituted 2-aminobenzaldehyde incorporated into a total synthesis of streptonigrone,[8] attempts to directly condense 3-hydroxy- or 3-(benzyloxy)pyruvic acid or their methyl esters with 2-aminobenzaldehyde (**2a**) provided intractable mixtures with little or no evidence of the generation of the desired quinoline (Scheme 1). Similarly, the condensation of ethyl 2,4-dioxopentanoate with **2a** cleanly provided the expected quinoline **3**,[9] but initial efforts to subsequently convert the C3 acetyl group to a phenol were not productive. Conventional Baeyer–Villiger oxidation with *m*-CPBA provided the corresponding *N*-oxide preferentially, and efforts to employ strongly acidic conditions in efforts to protonate and protect the quinoline nitrogen were not successful in altering the course of the reaction.[10] Similarly, reduction of **3** to provide **4** followed by acid-catalyzed benzylic hydroperoxide formation and rearrangement also failed to provide the corresponding *O*-acetate or phenol.[11]

An effective solution to the direct preparation of selectively protected derivatives of **1** was found through use of a modified Friedlander condensation[12] employing the readily accessible *O*-methyloxime **6** (Scheme 2). Although such oximes have not been previously employed in a Friedlander condensation, we have found that the enolate derived from oxime **6**, which was prepared in one step from the *O*-methyloxime of ethyl 3-bromopyruvate[13] by treatment with the lithium alkoxide salt of benzyl alcohol, is sufficiently reactive to condense selectively with 2-aminobenzaldehydes without undergoing preferential self-condensation. Thus, treatment of a solution of **2a–d** and **6** in EtOH with KOH (4 equiv) at reflux provided good conversion to the quinoline Friedlander condensation products produced as the carboxylic acids which were converted to the corresponding methyl esters **7** (5 equiv of CH_3I, 0.2 equiv of catalytic Bu_4NI, CH_2Cl_2-saturated aqueous $NaHCO_3$, 25 °C, 24 h) prior to isolation and characterization.

Benzyl ether deprotection (H_2, catalytic 10% Pd–C, CH_3OH, 25 °C, 96% for **7a**) of the methyl esters **7a–d** provides the corresponding methyl 3-hydroxyquinoline-2-carboxylates. The 3-(benzyloxy)quinoline-2-carboxylic acids **8a–d** derived from LiOH hydrolysis of **7a–d** should prove useful in the synthesis of sandramycin, the luzopeptins and related analogs, and the reagent **6** or related oximes effective for the preparation of other related 3-hydroxyquinoline-2-carboxylates.

Experimental Section

Ethyl 3-(Benzyloxy)-2-(methoxyimino)propanoate (6). A solution of benzyl alcohol (1.30 g, 12 mmol) in 40 mL of THF was cooled to 0 °C and treated with *n*-BuLi (6.3 mL, 12 mmol, 1.9 M in hexane). The resulting solution was stirred at 0 °C for 30 min and transferred to a flask containing ethyl 3-bromo-2-(methoxyimino)propanoate (**5**,[13] 2.24 g, 10 mmol) in 40 mL of THF at 0 °C through a cannula. The reaction mixture was allowed to warm to 25 °C and stirred for an additional 20 h. The mixture was poured onto 30 mL of H_2O and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography (SiO_2, EtOAc–hexane 1:15) provided **6** (1.95 g, 78%) as a colorless liquid: R_f 0.5 (SiO_2, 20% EtOAc–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.40–7.30 (m, 5H), 4.55 (s, 2H), 4.42 (s, 2H), 4.34 (q, 2H, J = 7.0 Hz), 4.08 (s, 3H), 1.35 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.3, 149.7, 138.1, 128.8, 128.7, 128.2, 73.5, 63.7, 62.0, 60.2, 14.1; IR (neat) ν_{max} 2982, 1722, 1604, 1498, 1374, 1240, 1150, 1094, 928, 858 740 cm^{-1}; CIHRMS (isobutane) m/z 252.1234 ($C_{13}H_{17}NO_4$ requires 252.1236).

General Procedure for the Synthesis of Substituted Methyl 3-(Benzyloxy)quinoline-2-carboxylates. A solution of the substituted 2-aminobenzaldehyde (**2**, 2 equiv) and **6** (1 equiv) in absolute EtOH (10 mL/1 mmol of **2**) was treated with solid KOH (pellets, 4 equiv), and the resulting mixture was warmed at reflux for 48 h. The reaction mixture was cooled, poured onto H_2O, and acidified to pH = 1 with the addition of aqueous 3 M HCl. The aqueous solution was extracted with EtOAc, and the organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue containing the 3-(benzyloxy)-quinoline-2-carboxylic acids proved difficult to purify. Consequently, the crude acid was converted to its corresponding methyl ester. The crude 3-(benzyloxy)quinoline-2-carboxylic acid was dissolved in CH_2Cl_2 (40 mL/10 mmol) and treated sequentially with saturated aqueous $NaHCO_3$ (20 mL/10 mmol), *n*-Bu_4-NI (1 equiv based on **6**), and CH_3I (5 equiv based on **6**), and the reaction mixture was stirred at 25 °C for 24 h. The organic layer was separated and the aqueous layer was extracted with CH_2-Cl_2. The combined organic layers were dried (Na_2SO_4), filtered,

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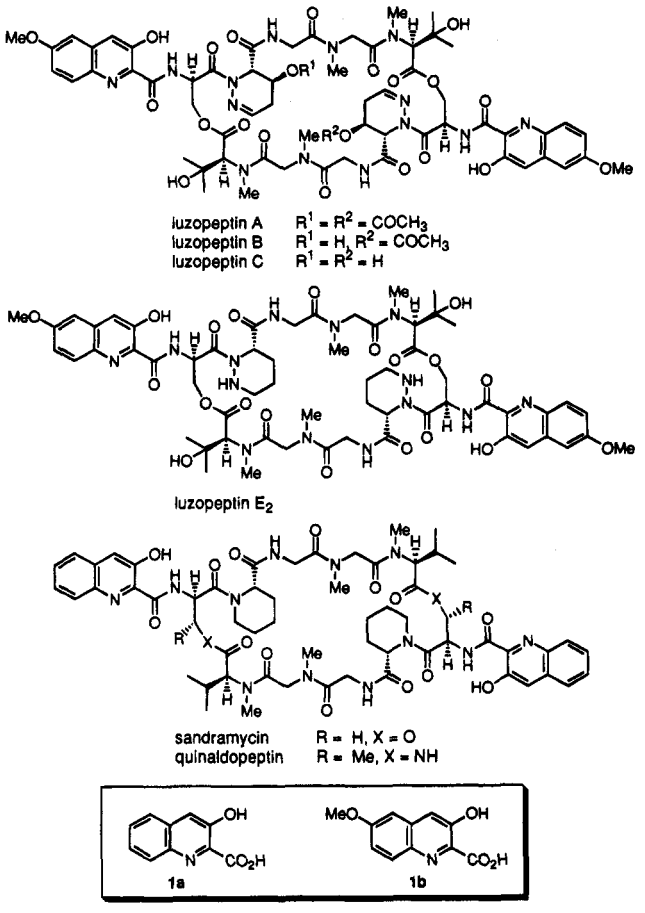
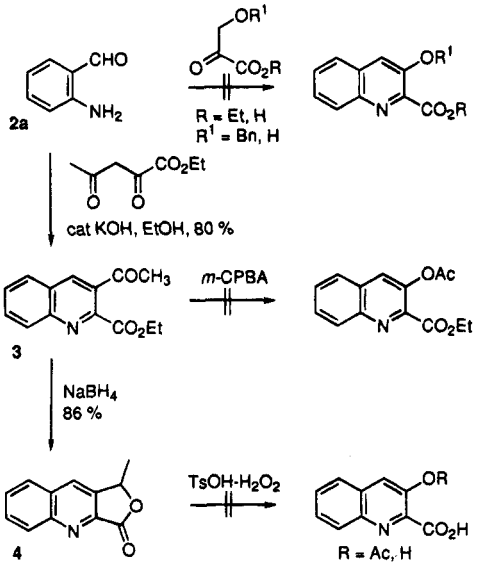
0022-3263/95/1960-7369$09.00/0

Chart 1



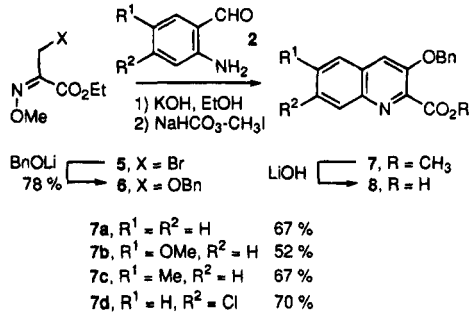
Scheme 1



and concentrated *in vacuo*, and the residue was purified by flash chromatography.

Methyl 3-(Benzyloxy)quinoline-2-carboxylate (7a). The crude residue was purified by flash chromatography (SiO_2, 5 × 16 cm, 10% EtOAc–hexane) to afford **7a** (3.01 g, 67%) as a colorless oil: R_f 0.29 (20% EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, J = 8.3 Hz), 7.68 (d, 1H, J = 7.6 Hz), 7.56 (s, 1H), 7.60–7.45 (m, 4H), 7.39 (t, 2H, J = 7.6 Hz), 7.32 (m, 1H), 5.26 (s, 2H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 150.1, 144.0, 142.2, 135.7, 129.7, 129.6, 128.7, 128.4, 128.1, 127.6, 126.9, 126.4, 115.9, 70.6, 52.9; IR (neat) ν_{max} 3062, 2950, 1738, 1600, 1296, 1214, 1087 cm^{-1}; FABHRMS (NBA–CsI) m/z 426.0089 (M + Cs$^+$, $C_{18}H_{15}NO_3$ requires 426.0106).

Scheme 2



Methyl 3-(Benzyloxy)-6-methoxyquinoline-2-carboxylate (7b). The crude residue was purified by flash chromatography (SiO_2, 4 × 16 cm, 10–20% EtOAc–hexane gradient) to afford **7b** (673 mg, 1.29 g theoretical, 52%) as a white solid which was further recrystallized from EtOAc–hexane: mp 131–133 °C (white plates); R_f 0.17 (20% EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, 1H, J = 9.2 Hz), 7.49 (d, 2H, J = 7.2 Hz), 7.46 (s, 1H), 7.41–7.37 (m, 2H), 7.34–7.29 (m, 1H), 7.22 (dd, 1H, J = 9.2, 2.7 Hz), 6.93 (d, 1H, J = 2.7 Hz), 5.25 (s, 2H), 4.02 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 159.4, 151.1, 140.6, 138.2, 135.9, 131.4, 131.2, 128.7, 128.0, 126.8, 120.6, 115.2, 104.0, 70.5, 55.5, 52.8; IR (neat) ν_{max} 3005, 2967, 1734, 1618, 1600, 1496, 1439, 1373, 1302, 1203, 1093, 1026, 1008, 838, 757 cm^{-1}; FABHRMS (NBA–NaI) m/z 346.1068 (M + Na$^+$, $C_{19}H_{17}NO_4$ requires 346.1055).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.67; H, 5.43; N, 4.53.

Methyl 3-(Benzyloxy)-6-methylquinoline-2-carboxylate (7c). The crude residue was purified by flash chromatography (SiO_2, 4 × 16 cm, 10% EtOAc–hexane) to afford **7c** (899 mg, 67%) as a white solid which was further recrystallized from EtOAc–hexane: mp 133–135 °C (white plates); R_f 0.26 (20% EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, 1H, J = 8.6 Hz), 7.49 (s, 1H), 7.47 (s, 1H), 7.46 (d, 2H, J = 8.7 Hz), 7.42–7.37 (m, 3H), 7.34–7.29 (m, 1H), 5.28 (s, 2H), 4.03 (s, 3H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 150.4, 142.8, 140.8, 138.7, 135.9, 130.0, 129.9, 129.4, 128.7, 128.1, 126.9, 125.3, 115.5, 70.5, 52.9, 21.7; IR (KBr) ν_{max} 3024, 2947, 1740, 1605, 1500, 1418, 1376, 1287, 1203, 1098, 1023, 827, 752 cm^{-1}; FABHRMS (NBA–NaI) m/z 308.1296 (M + H$^+$, $C_{19}H_{17}NO_3$ requires 308.1287).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.27; H, 5.25; N, 4.67.

Methyl 3-(Benzyloxy)-7-chloroquinoline-2-carboxylate (7d). The crude residue was purified by flash chromatography (SiO_2, 4 × 16 cm, 10% EtOAc–hexane) to afford **7d** (671 mg, 70%) as a white solid which was further recrystallized from EtOAc–hexane: mp 118–119 °C (white needles); R_f 0.38 (20% EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, J = 2.1 Hz), 7.64 (d, 1H, J = 8.7 Hz), 7.54 (s, 1H), 7.49 (dd, 1H, J = 8.7, 2.1 Hz), 7.47 (d, 2H, J = 7.5 Hz), 7.42–7.38 (m, 2H), 7.36–7.31 (m, 1H), 5.27 (s, 2H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 150.2, 145.1, 142.4, 135.5, 133.3, 129.4, 128.7, 128.6, 128.2, 128.0, 127.6, 126.9, 115.8, 70.7, 53.0; IR (KBr) ν_{max} 3026, 2933, 1720, 1595, 1437, 1356, 1280, 1204, 1140, 1095, 934, 870, 741 cm^{-1}; FABHRMS (NBA–NaI) m/z 350.0572 (M + Na$^+$, $C_{18}H_{14}ClNO_3$ requires 350.0560).

Anal. Calcd for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 66.07; H, 3.91; N, 4.43.

General Procedure for the Preparation of Substituted 3-(Benzyloxy)quinoline-2-carboxylic Acids. Lithium hydroxide monohydrate (3 equiv) was added to a solution of **7** in THF–CH_3OH–H_2O (3:1:1, 10 mL/1 mmol of **7**) at 25 °C, and the reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was extracted with EtOAc before the aqueous phase acidified with 10% aqueous HCl to pH = 1 and extracted with EtOAc. The latter organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

3-(Benzyloxy)quinoline-2-carboxylic Acid (8a). The crude acid was recrystallized from CH_3OH to give **8a** (630 mg, 1.21 g theoretical, 52%) as white needles: mp 150–151 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, 1H, J = 8.0 Hz), 7.76 (d, 1H, J = 7.6 Hz), 7.73 (s, 1H), 7.68–7.50 (m, 4H), 7.41 (t, 2H, J = 7.5

Hz), 7.35–7.30 (m, 1H), 5.39 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.7, 152.5, 140.6, 137.5, 135.5, 131.5, 129.7, 129.2, 128.8, 128.5, 128.2, 126.8, 126.5, 118.6, 70.9; IR (KBr) ν_{max} 3431, 2913, 1725, 1603, 1330, 1214, 1145, 1101, 1022, 880, 865, 741 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 411.9955 (M + Cs^+, $C_{17}H_{13}NO_3$ requires 411.9950).

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 74.18; H, 4.69; N, 5.02. Found: C, 73.90; H, 4.92; N, 5.17.

3-(Benzyloxy)-6-methoxyquinoline-2-carboxylic Acid (8b). The crude acid was recrystallized from benzene to provide **8b** (210 mg, 280 mg theoretical, 75%) as white needles: mp 145–146 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, 1H, *J* = 9.2 Hz), 7.60 (s, 1H), 7.58 (d, 2H, *J* = 7.2 Hz), 7.41 (dd, 2H, *J* = 7.4, 7.2 Hz), 7.35–7.30 (m, 1H), 7.28 (dd, 1H, *J* = 2.7, 9.2 Hz), 6.97 (d, 1H, *J* = 2.7 Hz), 5.37 (s, 2H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 160.4, 153.1, 136.8, 135.6, 134.5, 133.4, 130.7, 128.8, 128.1, 126.8, 122.0, 117.3, 103.6, 70.8, 55.7; IR (KBr) ν_{max} 3436, 2920, 1773, 1621, 1469, 1364, 1345, 1234, 1077, 1021, 823, 736 cm^{-1}; FABHRMS (NBA) *m/z* 310.1077 (M + H^+, $C_{18}H_{15}NO_4$ requires 310.1079).

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.76; H, 4.76; N, 4.52.

3-(Benzyloxy)-6-methylquinoline-2-carboxylic Acid (8c). The crude acid was recrystallized from benzene to provide **8c** (138 mg, 197 mg theoretical, 70%) as white needles: mp 146–148 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, 1H, *J* = 8.6 Hz), 7.62 (s, 1H), 7.58 (d, 2H, *J* = 7.4 Hz), 7.51 (s, 1H), 7.47 (dd, 2H, *J* = 1.5, 8.6 Hz), 7.40 (dd, 2H, *J* = 7.7, 7.4 Hz), 7.34–7.30 (m, 1H), 5.37 (s, 2H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 152.5, 140.2, 139.2, 136.5, 135.6, 131.6, 130.9, 128.8, 128.7, 128.1, 126.8, 125.4, 117.8, 70.8, 21.9; IR (KBr) ν_{max} 3426, 3065, 1759, 1621, 1592, 1500, 1456, 1345, 1272, 1199, 1076, 1024, 896, 822, 730, 696 cm^{-1}; FABHRMS (NBA) *m/z* 294.1139 (M + H^+, $C_{18}H_{15}NO_3$ requires 294.1130).

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.27; H, 5.02; N, 4.73.

3-(Benzyloxy)-7-chloroquinoline-2-carboxylic Acid (8d). The crude acid was recrystallized from benzene to provide **8d** (241 mg, 297 mg theoretical, 81%) as white needles: mp 146–148 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (broad s, 1H), 8.04 (s, 1H), 7.70 (s, 1H), 7.69 (d, 1H, *J* = 8.3 Hz), 7.60–7.50 (m, 3H), 7.41–7.35 (m, 2H), 7.33–7.29 (m, 1H), 5.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 161.8, 152.4, 140.7, 138.7, 135.2, 134.2, 130.6, 129.7, 128.8, 128.2, 127.9, 127.2, 126.8, 118.4, 70.9; IR (KBr) ν_{max} 3426, 3067, 2872, 1724, 1595, 1428, 1353, 1268, 1197, 1144, 1095, 938, 736 cm^{-1}; FABHRMS (NBA–NaI) *m/z* 314.0570 (M + H^+, $C_{17}H_{12}ClNO_3$ requires 314.0580).

General Procedure for Benzyl Ether Deprotection: Methyl 3-Hydroxyquinoline-2-carboxylate. A solution of **7a** (270 mg, 0.92 mmol) in 9 mL of CH_3OH was treated with 10% Pd-C (27 mg), and the resulting black suspension was stirred at 25 °C under H_2 (1 atm) for 5 h. The catalyst was removed by filtlration through Celite, and the filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2, 2 × 18 cm, 10% Et_2O–hexane eluent) afforded the methyl ester of **1a** (180 mg, 187 mg theoretical, 96%) as a white solid: mp 122–124 °C; R_f 0.3 (SiO_2, 20% EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.41 (s, 1H), 8.13 (d, 1H, *J* = 8.6 Hz), 7.71 (d, 1H, *J* = 8.9 Hz), 7.70 (s, 1H), 7.56 (m, 2H), 4.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 153.8, 142.6, 133.4, 132.1, 130.4, 129.5, 127.7, 126.3, 120.8, 53.6; IR (KBr) ν_{max} 3187, 2946, 1701, 1685 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 335.9637 (M + Cs^+, $C_{11}H_9NO_3$ requires 335.9637).

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Supporting Information Available: ^{1}H NMR spectra of **6**, **7a**, **8d**, and the methyl ester of **1a** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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