Facile Construction and Divergent Transformation of Polycyclic Isoxazoles: Direct Access to Polyketide Architectures

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Supporting Information

General Methods. All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry N₂. EtOH, MeOH, and iPrOH were distilled from Na and stored over 4 Å MS. Commercially available anhydrous, stabilizer-free THF (Kanto No. 41001) and Et₂O (Kanto No. 14547-95) were used without further purification. Diisopropylamine (DIPA), and triethylamine (NEt₃) were distilled from KOH and stored over 4 Å MS. Other reagents were used without further purification. Thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F₂₅₄, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF₂₅₄ (Art 7747). Column chromatography was performed on E. Merck Silica Gel 60 (230–400 Mesh) using a forced flow of 0.5–1.0 bar. Melting point (mp) determinations were performed using a Yanaco MP-S3 instrument and are uncorrected. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were measured on a JEOL JMN Lambda-400 spectrometer. Chemical shifts are expressed in parts per million (PPM) downfield from internal tetramethylsilane (δ = 0) and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Jasco IRA-202 spectrometer and are reported as wavenumbers (cm⁻¹).

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General Procedure for Oxime Chlorination. To a solution of salicylaldehyde (4.23 g, 30.8 mmol) in CHCl_3 (29 mL) was added pyridine (243 mg, 3.07 mmol). The temperature was raised to 40 °C and *N*-chlorosuccinimide (4.53 g, 33.9 mmol) was added to the resulting solution. Stirring was continued at this temperature for 3 h before the reaction mixture was diluted by CH_2Cl_2 (200 mL). The organic layer was washed by water (2 X 100 mL) and brine, dried over Na_2SO_4 , and concentrated under reduced pressure to afford hydroxyiminoyl chloride **1** (5.05 g, 95%, >95% purity) as light yellow powder.

^1H NMR (CDCl_3 , 400 MHz) δ 10.04 (s, 1 H), 8.07 (s, 1 H), 7.82 (dd, 1 H, $J = 8.3, 1.4$), 7.35 (dd, 1 H, $J = 8.3, 7.9$), 6.96–7.04 (m, 2 H)

^{13}C NMR (CDCl_3 , 400 MHz) δ 156.3, 142.9, 132.3, 129.4, 119.9, 117.1, 115.7

IR (thin film) ν 3305, 1608, 1584, 1475, 1413, 1243, 1160, 944, 758

Anal. Calc'd for $\text{C}_7\text{H}_6\text{ClNO}_2$; C, 49.00; H, 3.52; N, 8.17. Found: C, 48.74; H, 3.70; N, 8.08

3

General Procedure for Isoxazole Formation: To a solution of sodium isopropoxide, prepared from 0.045 g of Na in 10 mL of isopropyl alcohol, was added 1,3-cyclohexanedione (**2a**) (0.219 g, 1.96 mmol) and hydroxyiminoyl chloride **1** (0.161 g, 0.937 mmol) successively. After stirring 30 min at rt, the reaction mixture was poured into water, and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide isoxazole **3** as a white solid (0.162 g, 76% yield).

¹H NMR (CDCl₃, 400 MHz) δ 9.46 (br s, 1 H), 8.57 (dd, 1 H, J = 8.0, 1.7), 7.37 (ddd, 1 H, J = 8.3, 7.3, 1.7), 7.05 (dd, 1 H, J = 7.3, 1.5), 7.01 (ddd, 1 H, J = 8.3, 8.0, 1.5), 3.04 (dd, 2 H, J = 6.5, 6.3), 2.61 (dd, 2 H, J = 7.0, 6.6), 2.30–2.23 (m, 2 H)

¹³C NMR (100 MHz, CDCl₃) δ 192.1, 181.6, 159.3, 156.5, 132.3, 131.8, 119.7, 117.3, 114.6, 112.8, 38.8, 23.2, 21.4

IR (KBr) $\bar{\nu}$ 3146, 1684, 1586, 1568, 1497, 1485, 1449, 1429, 1395, 1352, 1297, 1237, 1020, 762, 658, 596

Anal. calc'd for C₁₃H₁₁NO₃: C, 68.11; H 4.84; N, 6.11; found, C, 67.92; H, 4.82; N, 5.94.

m.p. 107.3–110.7 °C

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¹H NMR (CDCl₃, 400 MHz) δ 7.45 (ddd, 1 H, J = 1.8, 6.4, 8.5), 7.41 (dd, 1 H, J = 7.3, 1.8), 7.02 (dd, 1 H, J = 7.3, 6.4), 7.00 (d, 1 H, J = 8.5), 3.79 (s, 3 H), 3.06 (t, 2 H, J = 6.2), 2.51 (dd, 2 H, J = 5.5, 7.0), 2.30–2.25 (m, 2 H)

¹³C NMR (100 MHz, CDCl₃) δ 191.3, 180.6, 157.9, 157.5, 131.6, 130.6, 120.4, 116.8, 115.6, 111.2, 55.7, 38.3, 23.3, 22.2

IR (KBr) $\bar{\nu}$ 2691, 2839, 1684, 1607, 1474, 1435, 1280, 1255, 1017, 756

Anal. calc'd for C₁₄H₁₃NO₃: C, 69.12; H 5.39; N, 5.76; found, C, 69.29; H, 5.53; N, 5.58.

M.P. 95.1–96.0 °C

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¹H NMR (CDCl₃, 400 MHz) δ 7.68 (d, 1 H, J = 7.8), 7.30–7.45 (m, 3 H), 3.10 (t, 2 H, J = 6.4), 2.54 (t, 2 H, J = 6.4), 2.23–2.33 (m, 2 H)

¹³C NMR (CDCl₃, 100 MHz) δ 191.3, 180.9, 159.3, 133.0, 131.3, 131.2, 129.1, 123.3, 115.3, 112.7, 38.1, 23.3, 22.2

IR (thin film) $\bar{\nu}$ 3061, 2982, 2928, 2868, 1689, 1585, 1460, 1348, 1062, 1014, 887, 844, 748, 596

Anal. Calc'd for C₁₃H₁₀BrNO₂: C, 53.45; H, 3.45; N, 4.80. Found: C, 53.63; H, 3.67; N, 4.56

M.P. 99 °C

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¹H NMR (CDCl₃, 400 MHz) δ 7.71 (dd, 1 H, J = 2.5, 1.5), 7.66 (ddd, 1 H, J = 8.0, 1.5, 0.6 Hz), 7.37 (t, 1 H, J = 8.0), 7.33 (ddd, 1 H, J = 8.0, 2.5, 0.6), 3.88 (s, 3 H), 3.07 (t, 2 H, J = 6.6), 2.61 (t, 2 H, J = 6.6), 2.30–2.23 (m, 2 H)

¹³C NMR (CDCl₃, 100 Hz) δ 192.0, 182.2, 159.8, 159.4, 129.4, 128.5, 117.1, 114.1, 113.9, 121.4, 55.3, 38.8, 23.4, 21.9

IR (thin film) ν 3084, 2957, 1688, 1605, 1574, 1472, 1435, 1242, 1047, 1018, 894, 830, 793, 690, 594

Anal. Calc'd for C₁₄H₁₃NO₃: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.08; H, 5.35; N, 5.47.

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General procedure for the reaction of isolated diketone salts in toluene

To a suspension of **7** (438 mg, 1.99 mmol) in toluene (5 mL) was added hydroximinoyl chloride **1** (172 mg, 1.00 mmol) in toluene (5 mL) at ambient temperature. After stirring for 30 min, the reaction mixture was poured into water and the products were extracted with EtOAc (3 x 10 mL). The extracts were washed by H₂O and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/Hexane) to give **11** as a white solid (221 mg, 70%).

¹H NMR (CDCl₃, 400 MHz) δ 9.38 (br s, 1 H), 8.57 (dd, 1 H, J = 7.3, 0.7), 7.38 (t, 1 H, J = 7.3), 7.07–6.99 (m, 2 H), 4.29 (q, 2 H, J = 7.0), 3.38–3.31 (m, 2 H), 2.94–2.85 (m, 1 H), 2.80 (dd, 1 H, J = 17.8, 9.8), 1.32 (t, 3 H, J = 7.0), 1.25 (d, 3 H, J = 6.6)

¹³C NMR (100 MHz, CDCl₃) δ 187.0, 180.4, 159.7, 169.0, 156.6, 132.6, 131.8, 119.8, 117.3, 113.7, 112.2, 62.6, 61.7, 32.5, 29.7, 19.6, 14.2

IR (thin film) ν 3230 (OH), 2974, 1739, 1691, 1590, 1482, 1253, 1024

Anal. calc'd for C₁₇H₁₇NO₅, C 64.75, H, 5.43, N, 4.44; found C 64.53, H 5.45, N 4.25

MP 118–119 °C

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¹H NMR (CDCl₃, 400 MHz) δ 7.19–7.10 (m, 2 H), 7.05 (ddd, 1 H, J = 0.7, 7.0, 7.6), 6.95 (dd, 1 H, J = 0.7, 8.2), 4.33–4.21 (m, 2 H), 3.48 (br s, 2 H), 3.11 (d, 1 H, J = 11.1), 2.61–2.69 (m, 2 H), 2.34 (br dd, 1 H, J = 9.7, 18.6), 1.31 (t, 3 H, J = 7.1), 1.13 (d, 3 H, J = 6.3)

¹³C NMR (100 MHz, CDCl₃) □ 192.8, 170.0, 165.7, 149.5, 129.6, 127.6, 124.7, 120.4, 116.4, 109.0, 61.0, 60.4, 34.4, 30.8, 21.0, 19.5, 14.1

IR (KBr) □ 2963, 1734, 1636, 1582, 1495, 1459, 1396, 1315, 1235, 1196, 1176, 1146, 1089, 1008, 768

Anal. calc'd for C₁₇H₁₈O₄: C, 71.31; H, 6.34; found C 71.14; H, 6.26

M.P. 91.0–94.2 °C

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¹H NMR (CD₃OD, 400 MHz) □ 10.61–10.50 (br s, 1 H), 7.76 (d, 1 H, *J* = 8.0), 7.43 (dd, 1 H, *J* = 7.2, 8.2), 7.11 (d, 1 H, *J* = 8.2), 7.09 (dd, 1 H, *J* = 7.2, 8.0), 6.02–5.83 (br s, 1 H), 4.11 (q, 2 H, *J* = 7.0), 3.00–2.93 (m, 1 H), 2.68 (dd, 1 H, *J* = 6.8, 15.7), 2.16 (dd, 1 H, *J* = 1.9, 15.7), 1.24 (t, 3 H, *J* = 7.0), 0.93 (d, 3 H, *J* = 6.8)

¹³C NMR (100 MHz, CD₃OD) □ 199.7, 168.4, 159.0, 155.4, 152.7, 135.3, 124.7, 124.5, 118.3, 115.3, 97.4, 96.8, 60.6, 48.4, 45.4, 28.5, 14.9

IR (KBr) □ 2963, 1734, 1636, 1582, 1494, 1459, 1396, 1315, 1235, 1196, 1176, 1146, 1089, 1008, 768

Anal. calc'd for C₁₇H₁₇NO₄: C, 68.21; H, 5.72; N, 4.68; found C, 67.97; H, 5.54; N, 4.53

M.P. 167.6–174.1 °C

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¹H NMR (CDCl₃, 400 MHz) □ *7.99 (d, 1 H, *J* = 8.0), 7.81 (d, 1 H, *J* = 2.4), 7.59 (d, 1 H, *J* = 8.8), *7.45 (dd, 1 H, *J* = 8.0, 8.0), *7.37 (s, 1 H), 7.19 (dd, 1 H, *J* = 8.8, 2.4), *7.07 (d, 1 H, *J* = 8.0), 6.80 (s, 1 H), *3.99 (s, 3 H), 3.95 (s, 3 H), 3.14 (t, 2 H, *J* = 6.0), 2.88 (t, 2 H, *J* = 6.0), 2.26–2.19 (m, 2 H) (* denotes minor positional isomer peaks)

¹³C NMR (CDCl₃, 400 MHz) □ 168.2, 158.0, 154.6, 130.7, 129.9, 127.7, 122.0, 119.1, 118.3, 116.0, 106.2, 55.6, 25.8, 24.4, 23.8

IR (thin film) □ 2942, 2834, 1662, 1598, 1520, 1471, 1435, 1328, 1240, 1109, 1032, 883, 843, 794