Catalytic Intramolecular Crossed Aldehyde–Ketone Benzoin Reaction: A Novel Synthesis of Functionalized Preanthraquinones

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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 Ar. EtOH was distilled from Na and stored over 4A MS. Toluene was distilled over CaH₂ and stored over 4A MS. ^tBuOH was distilled prior to use. Thiazolium salts were purified according to a reported protocol.¹ DBU was distilled from BaO. Et₃N was distilled from KOH. 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 spectrophotometer and are reported as wavenumbers (cm⁻¹).

(1) Stetter H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–647.

Table 1, entry 7

General Procedure for Benzoin Reaction. To a suspension of ketoaldehyde **1** (59.4 mg, 0.197 mmol) and thiazolium salt **4** (10.1 mg, 0.0401 mmol) in ^tBuOH (3 mL) at 40 °C was added DBU (21.0 mg, 0.138 mmol) in ^tBuOH (1 mL). Stirring was continued at this temperature for 30 min before the reaction mixture was quenched by addition of saturated aq NH₄Cl solution. The products were extracted with EtOAc (2 x). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 4/6) to afford benzoin product **2** (56.5 mg, 95%).

¹H NMR (CDCl₃, 400 MHz) δ 7.75 (dd, 1 H, *J* = 6.6, 2.4 Hz), 7.47–7.55 (m, 2 H), 5.37 (d, 1 H, *J* = 7.1 Hz), 5.34 (d, 1 H, *J* = 7.1 Hz), 3.53 (s, 3 H), 2.99 (dd, 1 H, *J* = 16.3, 6.4 Hz), 2.62–2.74 (m, 1 H), 2.58 (bs, 1 H), 2.18–2.46 (m, 3 H), 1.64 (td, 1 H, *J* = 14.2, 3.2 Hz);

¹³C NMR (CDCl₃, 400 MHz) δ 195.1, 171.1, 154.0, 153.3, 133.3, 131.5, 122.9, 120.4, 117.8, 113.6, 94.4, 67.1, 56.4, 28.9, 22.3, 17.8;

IR (KBr) δ 3484, 2957, 1702, 1665, 1576, 1264, 1155, 1012, 911, 801, cm⁻¹;

Anal. Calc'd for C₁₆H₁₅NO₅; C, 63.78; H, 5.02; N, 4.65. Found: C, 63.74; H, 5.25; N, 4.43.

m.p. 195 °C (decomp.)

Table 2, entry 2

Benzoin Reaction with Lower Catalyst Loading. To a suspension of ketoaldehyde **5** (152 mg, 0.560 mmol) and thiazolium salt **4** (6.9 mg, 0.027 mmol) in ^tBuOH (5 mL) at 40 °C was added DBU (8.8 mg, 0.058 mmol) in ^tBuOH (0.5 mL). Stirring was continued at this temperature for 30 min before the reaction mixture was diluted by EtOAc. The organic layer was washed by water (2 x) and insoluble materials were collected by filtration to give pure product **6** (89.6 mg, 59%). The supernatant was

concentrated under reduced pressure, and precipitates were collected by filtration to afford **6** (46.6mg, 31%). The remaining solution was concentrated and purified by PTLC (CH₂Cl₂/MeOH=96/4) to afford compound **6** (8.1 mg, 5%). Total yield = 95%

¹H NMR (CDCl₃, CD₃OD, 400 MHz) δ 7.68 (dd, 1 H, *J* = 7.8, 1.0 Hz), 7.56 (t, 1 H, *J* = 7.8 Hz), 7.30 (dd, 1 H, *J* = 7.8, 1.0 Hz), 4.05 (s, 3 H), 2.92 (dd, 1 H, *J* = 16.3, 6.4 Hz), 2.62–2.74 (m, 1 H), 2.16–2.44 (m, 3 H), 1.56–1.68 (m, 1 H);

¹³C NMR (CDCl₃, CD₃OD, 400 MHz) δ 196.0, 170.6, 156.4, 153.2, 133.3, 131.7, 121.6, 116.8, 116.4, 113.8, 66.7, 55.9, 28.6, 22.1, 17.6;

IR (KBr) ν 3263, 2973, 2942, 1696, 1664, 1578, 1487, 1281, 800, 766 cm⁻¹;

Anal. Calc'd for C₁₅H₁₃NO₄; C, 66.41; H, 4.83; N, 5.16. Found: C, 66.30; H, 5.02; N, 5.40.

m.p. 240 °C (sublimation)

Table 2, entry 3

¹H NMR (CDCl₃, CD₃OD, 400 MHz) δ 7.66 (dd, 1 H, *J* = 8.4, 0.8 Hz), 7.56 (t, 1 H, *J* = 8.4 Hz), 7.31 (dd, 1 H, *J* = 8.4, 0.8 Hz), 4.03 (s, 3 H), 3.04 (dd, 1 H, *J* = 18.1, 5.6 Hz), 2.58–2.74 (m, 1 H), 2.16–2.34 (m, 2 H), 1.47 (t, 1 H, *J* = 13.4 Hz), 1.28 (d, 3 H, *J* = 6.8 Hz);

¹³C NMR (CDCl₃, CD₃OD, 400 MHz) δ 195.7, 170.9, 156.2, 152.9, 133.3, 131.6, 121.3, 116.3, 116.1, 113.7, 66.6, 55.5, 37.2, 30.1, 25.6, 20.6;

IR (KBr) ν 3263, 2953, 2868, 1705, 1669, 1576, 1277, 1253, 1062, 1026, 789, 772 cm⁻¹;

Anal. Calc'd for C₁₆H₁₅NO₄; C, 67.36; H, 5.30; N, 4.91. Found: C, 67.06; H, 5.56; N, 4.76.

m.p. 230–238 °C (decomp.)

Table 2, entry 4

¹H NMR (CDCl₃, 400 MHz) δ 7.63 (d, 1 H, *J* = 8.0 Hz), 7.53 (t, 1 H, *J* = 8.0 Hz), 7.28 (d, 1 H, *J* = 8.0 Hz), 5.72 (s, 1 H), 4.32–4.46 (m, 2 H), 4.06 (s, 3 H), 3.15 (dd, 1 H, *J* = 18.2, 5.8 Hz), 2.88–3.02 (m, 1 H), 2.38–2.52 (m, 2 H), 1.42 (t, 3H, *J* = 7.2 Hz), 1.22 (d, 3 H, *J* = 6.8 Hz);

¹³C NMR (CDCl₃, 400 MHz) δ 195.0, 176.4, 169.6, 156.7, 153.4, 132.9, 131.8, 121.8, 117.0, 116.9, 113.1, 69.1, 61.6, 56.4, 48.5, 31.0, 29.6, 18.6, 14.1;

m.p. 180 °C (decomp.)

m.p. 111–112 °C

m.p. 201–205 °C

Preparation of iminoanthraquinone 15. To a 30 mL two-necked round-bottom flask equipped with a reflux condenser was added benzoin product **2** (9.9 mg, 0.033 mmol) and 10% palladium on carbon (7.0 mg). Toluene (3 mL) was added and resulting solution was stirred under a hydrogen atmosphere for 1.5 h. The hydrogen balloon was removed, the reaction mixture was opened to the air, and the reaction temperature was raised to 110 °C and stirred for 5 h. After cooling to ambient temperature, the resulting suspension was passed through celite and eluted with EtOAc. The supernatant was concentrated under reduced pressure, and residue was purified by flash chromatography (Hexane/EtOAc = 25/75) to afford **15** (7.0 mg, 75%).

¹H NMR (CDCl₃, 400 MHz) δ 16.8 (s, 1 H), 11.4 (s, 1 H), 8.11 (dd, 1 H, J = 8.0, 1.4 Hz), 7.62–7.70 (m, 2 H), 7.57 (dd, 1 H, J = 8.6, 1.4 Hz), 7.49 (t, 1 H, J = 7.6 Hz), 7.25 (dd, 1 H, J = 8.4, 1.2 Hz), 5.50 (s, 2 H), 3.60 (s, 3 H);

¹³C NMR (CDCl₃, 400 MHz) δ 182.6, 168.4, 165.2, 157.4, 134.2, 133.6, 133.5, 131.6, 127.2, 122.1, 120.1, 118.4, 117.3, 114.6, 95.4, 57.0;

IR (KBr) δ 3345, 2964, 1663, 1608, 1590, 1295, 1000, 924, 746 cm⁻¹;

Anal. Calc'd for C₁₆H₁₃NO₄; C, 67.84; H, 4.63; N, 4.94. Found: C, 67.54; H, 4.86; N, 4.73.

m.p. 177–180 °C

Preparation of 1,8-dihydroxyanthraquinone (16). To a solution of iminoanthraquinone **15** (5.0 mg, 0.017 mmol) in dioxane (0.5 mL) and methanol (0.5 mL) was added 20% H₂SO₄ aqueous solution (0.5 mL). After stirring 96 h at ambient temperature, the reaction mixture was diluted with water. The products were extracted by EtOAc (2x). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The crude products were purified by flash chromatography (hexane/EtOAc = 8/2) to afford the title compound (3.6 mg, 86%).

¹H NMR (CDCl₃, 400 MHz) δ 12.1 (s, 2 H), 7.85 (d, 2 H, J = 7.6 Hz), 7.70 (t, 2 H, J = 7.6 Hz), 7.31 (d, 2 H, J = 7.6 Hz).

This compound was identical to an authentic sample in all respects.

General Procedure for the Preparation of Keto-Aldehyde Substrates

To a solution of the acetal² (245 mg, 0.682 mmol) in THF (4 mL) was added 1 M HCl aqueous solution (2 mL) at 0 °C. The temperature was raised to room temperature and stirring was continued at this temperature for 11 h. The reaction mixture was poured into NaHCO₃ aqueous solution (0 °C), and the products were extracted by EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. Diethylether was added to a residue and the resulting precipitates were collected by filtration to give pure product **1** (140 mg, 68%). The remaining solution was concentrated and purified by PTLC (Hexane/EtOAc=3/7) to afford **1** (31.3 mg, 15%). Combined yield = 83%.

¹H NMR (CDCl₃, 400 MHz) δ 9.84 (s, 1H), 7.68 (dd, 1 H, J = 8.0, 1.4 Hz), 7.58 (t, 1 H, J = 8.0 Hz), 7.53 (dd, 1 H, J = 8.0, 1.4 Hz), 5.17 (d, 1H, J = 6.8 Hz), 5.05 (d, 1H, J = 6.8 Hz), 3.39 (s, 3 H), 3.14 (t, 2 H, J = 6.4 Hz), 2.52 (dd, 2 H, J = 7.2, 5.6 Hz), 2.25–2.35 (m, 2 H);

¹³C NMR (CDCl₃, 400 MHz) δ 191.4, 190.5, 180.9, 156.3, 154.3, 136.1, 131.4, 122.4, 120.2, 119.4, 116.4, 95.3, 56.2, 38.0, 23.2, 22.2;

IR (KBr) δ 2955, 2900, 1697, 1594, 1467, 1254, 1244, 1152, 1028, 910, 906, 798 cm⁻¹;

Anal. Calc'd for C₁₆H₁₅NO₅; C, 63.78; H, 5.02; N, 4.65. Found: C, 63.60; H, 5.19, N, 4.47.

(2) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Tetrahedron Lett.* **2003**, *44*, 3555–3558

Supporting Figure 1. ORTEP representation of **10** (50% probability level). See additional Supporting Information for the corresponding CIF file.