A Practical Synthesis of Pyrene-4,5-dione

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Pyrene-4,5-dione (3) has been used extensively to prepare and study its corresponding K-region oxide.¹ Arene oxides are the primary oxidative metabolites of polycyclic aromatic hydrocarbons and consequently are of significant biological interest.² In addition, pyrene-4,5-dione (3) participates in a variety of cyclization reactions useful for the construction of other molecules of interest.³ The *o*-quinone **3** is much less readily available than related aromatic guinones because direct oxidation of pyrene generally gives rise to a mixture of products derived from competitive oxidation at other sites, for example, C(1), C(6), and C(8).⁴ Thus, pyrenedione **3** is usually obtained through either oxidation of pyrene with the costly and highly toxic reagent osmium tetroxide^{3a,5} or oxidation of 4,5-dihydropyrene, which is prepared by a problematic dissolving metal reduction.⁶

We have recently been investigating the photochemically promoted cycloaromatization reactions of o-dialkynylarenes and their DNA cleavage properties.⁷ We developed an efficient protocol for synthesizing o-dialkynylarenes from aromatic o-quinones and therefore desired large quantities of pyrenedione 3. Finding the aforementioned methods unsatisfactory, we envisioned that an intramolecular acyloin condensation⁸ of a phenanthrene bay-region diester might provide a route more amenable for the large-scale production of pyrenequinone 3

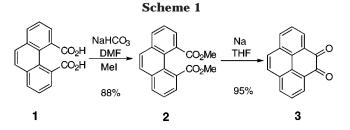
Fortunately, pyrene can be regioselectively oxidized to 4,5-phenanthrenedicarboxylic acid (1, Scheme 1) in nearly quantitative yields using hydrogen peroxide/tungstic

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acid.9 Not surprisingly, the attempted esterification of the sterically congested diacid 1 using the standard protocol of sulfuric acid in refluxing methanol resulted in mixtures of starting material, monoester, and diester. However, the sterically more accessible carboxylate ions of 1 (vis-à-vis the carbonyl carbons) could be generated with sodium bicarbonate and alkylated with iodomethane in DMF¹⁰ to produce the desired dimethyl 4,5-phenanthrenedicarboxylate (2) in good yield (88%). Initial attempts to effect the intramolecular acyloin condensation of diester 2 using standard dissolving metal conditions in NH₃¹¹ produced pyrenedione **3** contaminated with suspected Birch reduction products. However, treatment of diester 2 with excess sodium in refluxing THF provided the desired pyrenequinone 3 after aerobic workup in excellent yield (95%).

In summation, this route provides pyrenedione 3 in multigram quantities from pyrene in three steps (76%) overall yield).

Experimental Section

4,5-Phenanthrenedicarboxylic Acid (1). To a solution of pyrene (30.0 g, 148 mmol) in chlorobenzene (80.0 mL) were added WO4 (1.53 g, 6.14 mmol), Aliquat 336 (2.40 mL, 5.84 mmol), and H₃PO₄ (10%, 1.40 mL). H₂O₂ (50%, 85 mL) was then added via addition funnel at an appropriate rate to maintain gentle reflux. Caution: extremely exothermic! The reaction was heated to 80 °C for an additional 6 h, cooled to 0 °C, and filtered. The mudlike filtrate was dissolved in 1.25 M NaOH (2.0 L), decolorized with activated charcoal, and neutralized with glacial acetic acid to provide a reddish brown precipitate (36.1 g, 91%): mp 248-250 °C; IR (DMSO-d₆) 3460, 3049, 2908, 2743, 1702, 1255, 991 cm⁻¹; ¹H NMR (200 MHz, DMSO- d_6) δ 8.11 (d, J =7.7 Hz, 2 H), 7.98 (d, J = 7.3 Hz, 2 H), 7.91 (s, 2 H), 7.67 (t, J = 7.7 Hz, 2 H); ¹³C NMR (50 MHz, DMSO-*d*₆) δ 170.4, 135.1, 134.2, 131.5, 128.2, 127.7, 126.7; exact mass calcd for $C_{16}H_{10}O_4$ 266.0579, found 266.0572.

Dimethyl 4,5-Phenanthrenedicarboxylate (2). To a slurry of dicarboxylic acid 1 (16.52 g, 62.0 mmol) and NaHCO₃ (27.0 g, 321 mmol) in DMF (330 mL) was added a solution of MeI (50.0 mL, 800 mmol) in DMF (100 mL). After 22 h of stirring at room temperature, the reaction mixture was diluted with ethyl acetate (1 L), washed with water (5 \times 500 mL), dried (Na₂SO₄), and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided a bright yellow solid (16.98 g, 88%): mp 159-161 °C; IR (CDCl₃) 3060, 2954, 1713, 831, 743 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.04 (dd, J = 7.7, 1.4 Hz, 2 H), 7.99 (dd, J= 7.7, 1.4 Hz, 2 H), 7.75 (s, 2 H), 7.62 (t, J = 7.7 Hz, 2 H), 3.80 (s, 6 H); ¹³C NMR (50 MHz, CDCl₃) δ 169.6, 134.2, 132.7, 131.9, 128.8, 127.5, 126.4, 104.8, 52.1; exact mass calcd for C18H14O4 294.0892, found 294.0894. Anal. Calcd for C18H14O4: C, 73.44; H, 4.79. Found: C, 73.41; H, 4.67.

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Pyrene-4,5-dione (3). To a refluxing mixture of Na (3.80 g, 158 mmol) in THF (100 mL) was added diester **2** (12.0 g, 40.8 mmol) in THF (200 mL). The reaction progress was followed by NMR aliquots, and additional Na (2.81 g, 116 mmol) was added in small portions until the reaction was complete (3 h). The dark red solution was then cooled to room temperature, residual Na was carefully removed, the reaction mixture was poured into ethyl acetate (500 mL) and water (200 mL), and the resulting emulsion was left to stand overnight. The aqueous layer was extracted with ethyl acetate (1 L), combined with the organic layer, dried (Na₂SO₄), and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided a bright orange solid (9.0 g, 95%): mp 302–304 °C (lit.^{3a} mp 304.5–306.4 °C);

¹H NMR (200 MHz, CDCl₃) δ 8.52 (dd, J = 7.8, 1.3 Hz, 2 H), 8.20 (dd, J = 7.8, 1.3 Hz, 2 H), 7.87 (s 2 H), 7.77 (t, J = 7.8 Hz, 2 H); ¹³C NMR (50 MHz, DMSO- d_6) δ 180.1, 135.4, 132.1, 131.0, 129.1, 128.4, 128.2, 127.6; MS (EI) *m*/*z* (relative intensity) 232 (40), 221 (24), 218 (11), 204 (94), 189 (16), 176 (55), 150 (11); exact mass calcd for C₁₆H₁₈O₂ 232.0524, found 232.0513.

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