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An Efficient Approach to 3-Bromo-6-chloro-phenanthrene-9,10-dione

John Limanto,* Benjamin T. Dorner, Frederick W. Hartner, and Lushi Tan

Merck & Co., Inc., Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065, U.S.A.

Abstract:

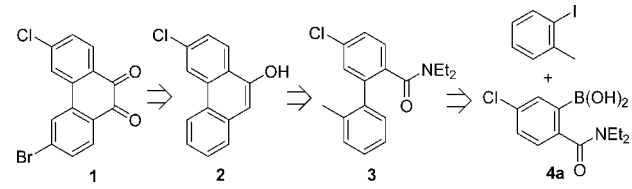
A practical and efficient synthesis of 3-bromo-6-chloro-phenanthrene-9,10-dione was developed and demonstrated on a large scale. The synthetic approach involves six chemical steps and two isolations in 73% overall yield. The key transformations feature an anionic cyclization for generation of the phenanthrene ring, followed by sequential tribromination and hydrolysis for the incorporation of the bromo-diketone functionality.

Introduction

Phenanthrene-9,10-diones (9,10-phenanthrenequinones) are oxidative metabolites of polyaromatic hydrocarbons, possessing interesting physical and chemical properties and potent biological activities. While the highly toxic unsubstituted (parent) compound[1] has been detected in polluted air samples[2] and used as a redox-dependent receptor for the recognition of urea and amide groups,[3] other functionalized derivatives have been utilized to probe polyaromatic-induced carcinogenicity and certain immunological-related diseases.[4] Furthermore, some of these quinoids have been studied as potential anticancer agents[5] and clinically administered as chemotherapeutic agents.[6]

Several methods for the preparation of phenanthrene-9,10-diones have been published and reviewed.[7] The most common procedure involves oxidation of phenanthrenes, which are generally prepared via a photochemical electrocyclic ring closure of stilbene derivatives. While these methods certainly provide access to phenanthrene-9,10-diones, the use of a large excess of toxic and expensive metal oxidants is impractical and undesirable for large-scale productions.

Scheme 1. **Retrosynthetic analysis of phenanthrenedione 1**



We recently required an efficient route to differentially substituted dihalophenanthrenequinone **1**, which is a useful building block for accessing other modularly derivatized phenanthrenequinones or pharmaceutically important phenanthreneimidazoles.[8] Our strategy involves an oxidative bromination of chlorophenanthrol **2**, which would, in turn, be prepared via an anionic cyclization of biaryl amide **3** (Scheme 1). This latter intermediate could then be generated from readily accessible boronic acid **4a** via a Suzuki−Miyaura cross-coupling reaction.

Results and Discussion

Preparation of boronic acid **4a** started with amidation of *p*-chlorobenzoyl chloride with diethylamine under Schotten−Baumann conditions to give the corresponding amide **5** in 99% yield. Without further purification, the crude amide was then subjected to a directed ortho metalation[9] with LDA (1.4 equiv) in dry DME in the presence of B(*i*-OPr)$_3$ (1.6 equiv) at −30 °C to afford the corresponding boronic acid **4a** in >97:1 regioselectivity. The regioselectivity on the borylation was highly dependent on the reaction solvent, with DME being the best (**4a**:**4b** = >97:1) and heptane the worst (**4a**:**4b** = 6:1) (Scheme 2).

Subjection of the crude boronic acid **4a** (1 equiv) to 2-iodotoluene (0.93 equiv) in the presence of 0.5 mol % Pd(OAc)$_2$,1 mol% PPh$_3$, and K$_2$CO$_3$ (2.5 equiv) under biphasic

* Corresponding author. E-mail: john_limanto@merck.com.

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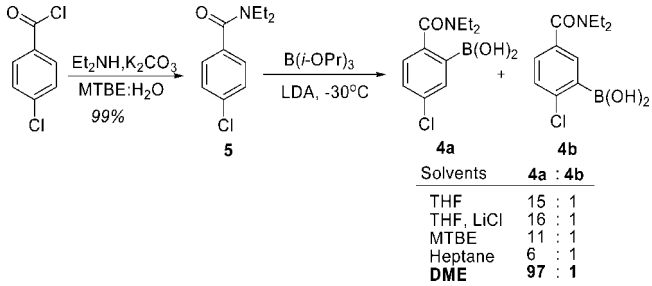
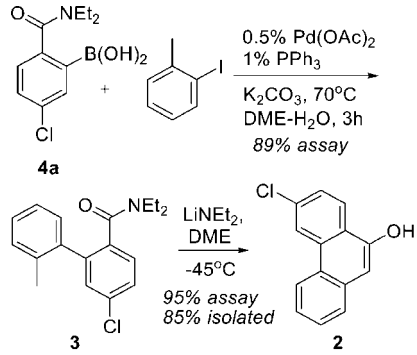
Scheme 2. **Preparation of boronic acid 4a**



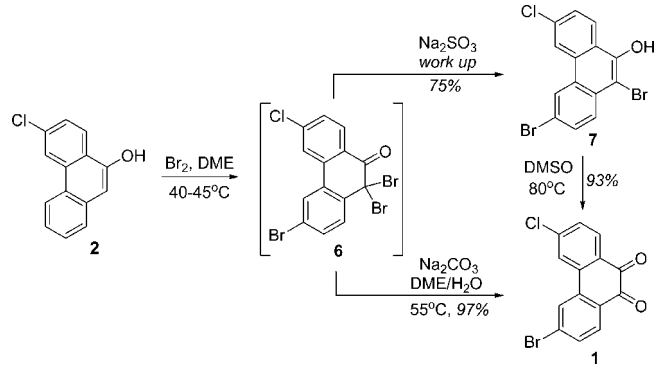
Suzuki−Miyaura cross-coupling conditions[10] afforded the corresponding biaryl amide **3** in 89% overall assay yield from the starting amide **5**.[11] Subsequent anionic cyclization[12] was performed by subjecting **3** to lithium diethylamide (LEA) in DME at −45 °C to cleanly generate chlorophenanthrol **2** in 95% assay yield (Scheme 3). While lithium diisopropylamide (LDA) could also be used to effect this transformation, under identical reaction conditions, a transamidation event ($Et_2N \rightarrow i\text{-}Pr_2N$) was observed to subsequently afford somewhat less effective cyclization (90% vs 95% assay yield). Crystallization of the crude product from toluene/methylcyclohexane afforded pure **2** in 85% isolated yield or in 76% overall yield from amide **5**.

Scheme 3. **Synthesis of phenanthrol 2**



With 6-chloro-9-phenanthrol **2** in hand, subsequent bromination at the 3-position and oxidation at the 10-position of the phenanthrene ring was investigated. While monobromination of 9-phenanthrol at the 10-position has been established,[13] selective monobromination at the 3-position was less well-known. On the other hand, dibromination at both the 3- and 10-position of 9-phenanthrol using Br_2 in CS_2 has previously been reported.[14] In our hands, treatment of **2** with Br_2 (2.5−3.0 equiv) in either AcOH or CH_2Cl_2 at 30 °C for 24−36 h afforded

Scheme 4. **Oxidative bromination approach to phenanthrenedione 1**



the corresponding 6-chloro-3,10-dibromo-9-phenanthrol **7** in 75% yield, after aqueous Na_2SO_3 workup and crystallization from $CHCl_3$. Heating dibromophenanthrol **7** to 80 °C in DMSO[15] for 1 h promoted the oxidation event to afford the desired phenanthrenedione **1** in 93% isolated yield (Scheme 4).

Further investigation of the bromination step revealed that when using 2.5−3 mol equiv of Br_2 in either AcOH, CH_2Cl_2, or DME, the only entity observed by NMR spectroscopy at the end of reaction was the tribromoketone **6**.[16] Upon workup with aqueous Na_2SO_3 or during purification attempts by crystallization from acetone, this tribromo intermediate underwent a reduction to yield the corresponding dibromophenanthrol **7**. These results led us to investigate the possibility of directly hydrolyzing the α,α-dibromoketone functionality in **6** to the corresponding diketone. Gratifyingly, subjection of the crude bromination reaction mixture in DME to a 16 wt % aqueous Na_2CO_3 (3 equiv) or to a 50 wt % aqueous NaOH (2 equiv) at 55 °C for 12 h cleanly afforded the corresponding phenanthrene-9,10-dione **1**. After most of the DME was distilled away, the compound directly crystallized from the reaction mixture to afford pure **1** in 97% isolated yield.

Conclusion

In summary, an efficient and practical approach to differentially substituted dihalophenanthrene-9,10-dione **1** has been identified and demonstrated on few hundred grams scale. Furthermore, the current process and procedures have been sufficiently developed in order to support potential pilot-plant activities or other multikilogram campaigns. The titled compound offers modular derivatization of the halide groups to provide rapid entries to other pharmaceutically and biologically important phenanthrodione or phenanthroimidazole derivatives. The key transformation involves a sequential bromination of chlorophenanthrol **2** with Br_2 in DME, followed by *in situ* hydrolysis of the resulting tribromoketone intermediate **6** with Na_2CO_3 in DME/H_2O to afford the titled compound in 97% isolated yield. The current route, involving six chemical steps

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(16) Reaction monitoring by reverse-phase HPLC (MeCN/H_2O eluent) indicated fast initial bromination in AcOH or CH_2Cl_2 at 20−25 °C, consuming all starting material within 15 min, followed by subsequent slower di- and tribromination events, which took over 24−36 h at 30 °C. A faster reaction time was obtained when performing the tribromination in DME at 45 °C, in which a full conversion was observed within 3−4 h.

and two isolation steps, allows for the preparation of **1** in 73% overall yield, starting from inexpensive *p*-chlorobenzoyl chloride.

Experimental Section

General Methods. All reagents and HPLC-grade or anhydrous solvents are purchased from commercial suppliers and used directly without further purification or treatment. MP-TMT (trimercaptotriazine) resins were obtained from Biotage (previously Argonaut Laboratories) and Ecosorb C-941 from Graver Technologies. All reactions were conducted under N_2 atmosphere. Concentration *in vacuo* refers to removal of the solvent using a rotary evaporator at reduced pressure (10−20 Torr). High performance liquid chromatography (HPLC) analysis was performed using Waters Xbridge C18 (250 mm × 4.6 mm I.D.) column under the following mobile phase: 20% MeCN (A): 80% 0.1% v H_3PO_4/H_2O (B) ramped to 90% A:10% B over 17 min, 1.5 mL/min flow rate, 210 nm, 40 °C column temperature. ^{1}H and ^{13}C NMR spectra were all measured on either a 400 or 500 MHz instrument. Infrared (IR) spectra were reported in wavenumbers and measured on an FT-IR spectrometer. Melting points were uncorrected. Elemental analyses were performed by an external specialist.

***N,N*-Diethyl-*p*-chlorobenzamide 5.** To a solution of Et_2NH (131 mL, 1.25 mol, 1.1 equiv) in MTBE (1.6 L) was added solid Na_2CO_3 (72.3 g, 0.68 mol, 0.6 equiv), followed by H_2O (600 mL) to give a clear biphasic layer, which was then cooled to 15 °C. Neat *p*-chlorobenzoyl chloride (200 g, 1.14 mol, 1.0 equiv) was then added over 30 min, while maintaining the temperature below 25 °C. At the end of addition, the mixture was aged for another 30 min, and the aqueous layer was separated. The organic layer was then washed with brine and concentrated to dryness to give colorless oil (238 g, 99.9 wt %, 98.7% assay yield), which was used directly in the next step without further purification. HPLC t_R: 3.93 min. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.35 (2H, dm, J = 8.4 Hz), 7.30 (2H, dm, J = 8.4 Hz), 3.51 (2H, br m), 3.23 (2H, br m), 1.14 (6H, br m). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 170.2, 135.7, 135.2, 128.6, 128.1, 43.4, 39.5, 14.2, 13.0. IR (NaCl thin film): 3555, 3486, 3048, 2974, 2936, 2876, 1632, 1597, 1463, 1426, 1382, 1364, 1316, 1288, 1220, 1194, 1096, 1016, 875, 838, 758, 562, 503 cm^{-1}. Anal. Calcd for $C_{11}H_{14}ClNO$: C, 62,41; H, 6.67; Cl, 16.75. Found: C, 62.81; H, 6.73; Cl, 16.76.

Aryl Boronic Acid 4a. To a solution of crude amide **5** (245.7 g, 1.16 mol, 1.0 equiv) in 6 mL/g dry DME (1.47 L) was added neat triisopropyl borate (356 g, 1.86 mol, 1.6 equiv), and the resulting solution was cooled to −35 °C. A freshly prepared solution of LDA (1.62 mol, 1.4 equiv) in THF was then added dropwise over 45 min, while maintaining the internal temperature between −35 to −25 °C. [LDA was generated according to a typical procedure by treatment of *N,N*′-diisopropylamine (231 mL, 1.62 mol, 1.4 equiv) in THF (237 mL) with 2.5 M solution of *n*-butyllithium in hexanes (654 mL, 1.64 mol, 1.41 equiv), maintaining the temperature below 0 °C during the addition.] At the end of addition, the reaction mixture was aged for additional 15 min at −25 °C, at which point all starting material has been consumed to give the corresponding boronic acid in >97:1 regioselectivity as analyzed by both HPLC and NMR spectroscopy. The mixture was then slowly quenched with 150 mL of H_2O at −10 to 0 °C to give a yellow suspension, which was used directly in the next step without further purification. HPLC t_R: 2.29 min.

***N,N*′-Diethyl-4-chloro-2-(*o*-tolyl)benzamide (3).** The previously quenched suspension of crude boronic acid **4a** (1.16 mol, 1.0 equiv) in DME/THF/H_2O was diluted with degassed water (1.18 L, total of ∼4.5 vol or 2 M of K_2CO_3) and additional DME (300 mL, total of ∼6 vol). Successively, solid K_2CO_3 (401 g, 2.9 mol, 2.5 equiv), 2-iodotoluene (240 g, 1.08 mol, 0.93 equiv), PPh_3 (3.04 g, 11.6 mmol, 0.01 equiv), and $Pd(OAc)_2$ (1.3 g, 5.80 mmol, 0.005 equiv) were added, and the resulting biphasic suspension was degassed several times at RT. The reaction mixture was then heated to 70 °C and aged for 8 h, at which point a complete consumption of 2-iodotoluene was observed. At this point, the slurry mixture was then concentrated to about one-third of its volume, diluted with 8 mL/g of MTBE (2.4 L), and filtered. The resulting biphasic layer was separated, and the organic layer was washed with 15% aqueous NaCl (250 mL), followed by brine (250 mL) and concentrated to dryness to give **3** as yellow oil (311.5 g assay, 89% yield). The material was then used directly in the next step without further purification. HPLC t_R: 6.67 min. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.40−7.10 (7H, series of m), 3.91−2.60 (4H, br m), 2.23 (3H, br s), 0.91 (3H, br m), 0.69 (3H, br t, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 169.2, 140.3 (br), 137.9 (br), 135.7, 135.3, 134.1, 132.2, 130.3, 128.8, 128.2, 127.9, 127.6, 125.5, 42.5, 38.1, 20.3, 13.8, 11.8.

6-Chloro-phenanthren-9-ol (2). To a precooled solution of the crude amide **3** (311 g, 1.03 mol, 1 equiv) in 7 mL/g DME (2.18 L) at −45 °C was added a freshly prepared 1.44 M solution of $LiNEt_2$ (0.93 L, 1.34 mol, 1.3 equiv) in THF (1.3 equiv of $HNEt_2$ in 1 vol THF, 1.31 equiv of 2.5 M *n*-BuLi in hexanes) over 25 min. The resulting brown solution was aged at −45 °C for 2 h, at which >99.5% conversion of starting material was observed by HPLC. The reaction was then quenched by a slow addition of 6 N HCl (0.69 L, 4.12 mol, 4 equiv), while maintaining the temperature between 0−5 °C (pH of solution was 2−3). The resulting orange solution was then concentrated to about one-third of its volume and then diluted with MTBE (2.18 L, 7 vol wrt SM). The organic layer was separated and was washed with 15 wt % aqueous NaCl (2 × 300 mL) and then brine (300 mL). The crude organic solution was then treated with 1% MP-TMT resin and 1% Ecosorb C-941, aged at RT over 1.5 h and then filtered through a plug of SiO_2 gel (30 wt % wrt SM, 93 g). The filtrate was then assayed to contain 225 g of the desired product (95% yield). The organic layer was then concentrated, and the solvent was switched to $PhCH_3$ at 8 vol (wrt to product assay, 1.8 L), while maintaining the temperature above 70 °C during the solvent switch. At the end of the solvent switch, the slurry was further concentrated to about 6 vol wrt product (1.3 L) and heated to reflux to give a homogeneous brown solution. Crystallization was then initated by cooling the solution to 95−98 °C, and the slurry was further cooled to 70 °C and then treated with methylcyclohexane (8 vol, 1.8 L) over 1 h at this temperature. The needle-thread-like slurry was then cooled to RT over 30 min, aged at RT for 2 h and then at −10 °C for another 2 h. The slurry was then filtered, and the wetcake was washed with a cold 1:4 mixture of toluene/methyl cyclohexane, followed by

drying under a constant flow of N_2 for 1 day at RT. The dry solid contained 200 g of the desired product (100 wt %, 85% yield from **3** or 76% from **5**). Mp: 197−198 °C. HPLC t_R: 6.38 min. ^{1}H NMR (500 MHz, d_6-acetone, ppm): δ 9.35 (1H, s), 8.78 (1H, d, J = 2.1 Hz), 8.68 (1H, d, J = 8.5 Hz), 8.38 (1H, d, J = 8.8 Hz), 7.74 (1H, dd, J = 8.0, 1.2 Hz), 7.65 (1H, dd, J = 8.8, 2.1 Hz), 7.55 (1H, m), 7.49 (1H, m), 7.18 (1H, s). ^{13}C NMR (125 MHz, d_6-acetone, ppm): δ 150.7, 134.0, 132.9, 127.6, 126.7, 126.4, 125.2, 124.8, 124.7, 124.1, 122.8, 122.2, 105.7. IR (KBr pellet): 3307,1677, 1581, 1470, 1392, 1271, 1223, 1080, 918, 895, 821 cm^{-1}. Anal. Calcd for $C_{14}H_9ClO$: C, 73.53; H, 3.97; Cl, 15.50. Found: C, 73.08; H, 3.76; Cl, 15.57.

3-Bromo-6-chloro-phenanthrene-9,10-dione (1). To a solution of **2** (150 g, 656 mmol, 1 equiv) in dry DME (15 vol, 2.25 L) at 10 °C was added Br_2 (118 mL, 2296 mmol, 3.5 equiv) over 30 min, at which a 20 °C exotherm was observed during the addition. The resulting suspension was then heated to 45 °C and aged for 4 h to give a clear, red solution, at which a complete conversion of the starting material to tribromoketone intermediate **6** was obtained. A solution of Na_2SO_3 (24.8 g, 131 mmol, 0.2 equiv) in 100 mL of H_2O was then added, followed by a solution of Na_2CO_3 (209 g, 1968 mmol, 3 equiv) in 900 mL of H_2O over 30 min. The resulting suspension was warmed to 55 °C and aged for 6 h, at which a complete hydrolysis was obtained (additional of H_2O might be necessary to redissolve precipitated Na_2CO_3). The reaction mixture was then concentrated at 35−40 °C (35−40 Torr) to about a third of its volume (~1.2 L, 8 vol) and then solvent switched to give a 9:1 mixture of H_2O/DME. The slurry was filtered at this temperature, and the wetcake was successively washed with 4:1 H_2O/DME (5 vol) and H_2O (10 vol) and then dried under a constant flow of N_2 at 30 °C. Pure **1** was obtained in 97% yield as a yellow solid. Mp: 282−285 °C. HPLC t_R: 8.56 min. ^{1}H NMR (500 MHz, d_6-DMSO, ppm): δ 8.65 (1H, d, J = 1.99 Hz), 8.53 (1H, d, J = 1.99 Hz), 8.02 (1H, d, J = 8.34 Hz), 7.93 (1H, d, J = 8.34 Hz), 7.77 (1H, dd, J = 8.34, 1.99 Hz), 7.62 (1H, dd, J = 8.34, 1.99 Hz). ^{13}C NMR (125 MHz, d_6-DMSO, ppm): δ 177.6, 177.4, 140.5, 135.9, 135.9, 132.7, 130.8, 130.8, 130.7, 130.4, 129.9, 129.7, 127.7, 124.9. IR (NaCl thin film): 1677, 1581, 1470, 1392, 1271, 1223, 1080, 918, 895, 821 cm^{-1}. HRMS (TOF) Calcd for [$C_{14}H_6BrClO_2$+H]: 320.9318. Found: 320.9324. Anal. Calcd for $C_{14}H_6BrClO_2$: C, 52.29; H, 1.88. Found: C, 52.43; H, 1.65.

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