A Practical, Large-Scale Synthesis of Pyrene-2-Carboxylic Acid

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Abstract

Pyrene-2-carboxylic acid is a versatile intermediate for introducing the unusual 2-pyrenyl unit into functional organic molecules. A classical preparation for this molecule has been revised and improved to give a robust and efficient three-step process. The method has been applied on a multigram scale to give pyrene-2-carboxylic acid in >70% overall yield from pyrene.

Key words

condensed aromatic compounds - electrophilic aromatic substitution - ring closure - ring opening - Haller–Bauer cleavage

The pyrene nucleus occupies an important position in photochemistry, molecular electronics and supramolecular chemistry. It possesses useful fluorescence properties[2] which have been exceptionally well studied[3] (indeed, it has been called ‘the fruit fly of photochemists’[4]), and has been widely used in biological probes and chemosensors.[5] It also serves as a key component of many organic electronic systems, where it may appear either as a terminus or a multivalent core unit.[4] Its potential for π-stacking and hydrophobic interactions has been used for non-covalent attachment to carbon nanotubes[6] and graphene,[7] and for binding to nucleic acids.[8]

The scope for exploiting pyrenes in these areas depends strongly on the methodology available for the regioselective synthesis of derivatives. Electrophilic attack on pyrene (**1**) is electronically favoured at positions 1, 3, 6 and 8 (see Figure [1]), so substitution at one or all of these positions is relatively straightforward.[4] [9] [10] Consequently, for example, a range of 1-substituted pyrenes are commercially available for use as fluorescence tagging reagents. However other substitution patterns are less accessible, frequently requiring the application of indirect methods.[11,12] In particular, obtaining pyrenes with functionality at position 2 is much more difficult. This is significant for two reasons. Firstly the position of substitution affects the photophysical properties of the pyrene chromophore.[13,14] Secondly, linkage via position 2 may be required for architectural reasons, especially when higher symmetry is required. This may, for instance, be important for chromophore positioning; rotation of a pyrene unit about a C1 linkage moves the chromophore considerably, while rotation about a C2 linkage has much less effect (see Figure [2]).

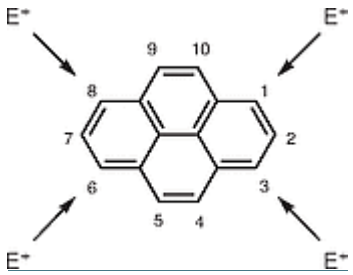


Figure 1 Numbering system for pyrene **1**, highlighting positions of reactivity towards electrophiles

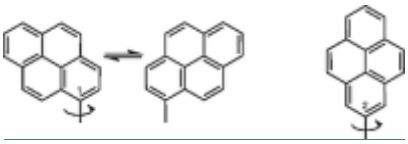
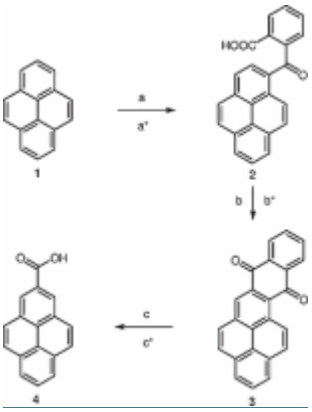


Figure 2 Positioning the pyrene chromophore via C1 and C2 linkages. A 180° rotation about a C1 bond moves the chromophore by several Å. The corresponding rotation about a C2 linkage has no effect, so conformations are more predictable.

Although a variety of methods have been reported for 2-functionalised pyrenes, most involve multistep procedures which do not seem convenient for large-scale use. Examples include (a) the synthesis of cyclophanes followed by valence isomerisation–dehydrogenation, (b) photochemical cyclisation of 2,2'-divinylbiphenyls, (c) thermal annulations of 2,2'-disubstituted dithiobenzylbiphenyls, (d) aromatisation of substituted 4,5,9,10-tetrahydropyrenes, and (e) the transition-metal-catalysed electrocyclisation of 2,6-diethynyl-1,1'-biphenyls.[11] [12] Direct substitution at pyrene C2 is possible with very hindered species, but most examples (e.g. the *tert*-butyl cation[15]) do not lead to versatile intermediates. A notable exception is the recent Ir(I)-catalysed borylation of pyrene with bispinacolatodiborane, which is directed to positions 2 and 7 (presumably) by the hindered nature of the reacting complex.[16] [17] Given the range of transformations possible for arylboranes this procedure seems likely to be widely useful.[13] [14] [18] However, as described[17] it employs a glove box, and requires careful control to achieve just monosubstitution.

We recently required a large-scale supply of pyrene-2-carboxylic acid (**4**; Scheme [1]) as a starting point for receptor synthesis. Notwithstanding its promise as a fluorescence tagging reagent and intermediate for other 2-substituted pyrenes, this compound has received few mentions in the literature.[8a] [19] However, there was a three-step procedure from pyrene dating from 1937 which seemed potentially viable.[9,20] We now report an updated and improved version of this method, which is capable of providing **4** in >70% overall yield and on multigram scales (≥5 g using standard laboratory equipment). Despite the advent of newer methodology (see above) we believe this is the most convenient and effective method for this compound, and is competitive as an entry to a range of C2-functionalised pyrene derivatives.



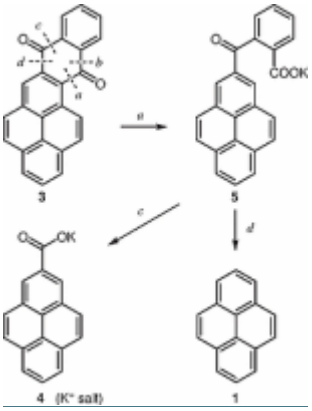
Scheme 1 Route to pyrene-2-carboxylic acid (**4**) reported in ref 9, showing original reagents, conditions and yields (a–c) and the revised versions developed in the present work (a*–c*). *Original (1937) conditions*:[9] (a) phthalic anhydride (1 equiv), $AlCl_3$ (1.1 equiv), benzene (3.7 mL/g), 40–50 °C, 1 h, yield not given; (b) benzoyl chloride (3 equiv), 1-chloronaphthalene (3.7 mL/g), reflux, 1 h, 53%; (c) molten KOH (24 equiv), 195–215 °C, 30 min, then H_2O (50 mL/g), 47–54%. *From the present work*: (a*) phthalic anhydride (1 equiv), $AlCl_3$ (2.5 equiv), CH_2Cl_2 (30 mL/g), reflux, 3 h, 98%; (b*) PCl_5 (1.5 equiv), $AlCl_3$ (1.5 equiv), chlorobenzene (19 mL/g), reflux, 2.5 h, ca. quantitative; (c*) *t*-BuOK (20 equiv), H_2O (6 equiv), 1,2-dimethoxyethane (14 mL/g), reflux, 7 h, 75% from **2**.

The route to **4** discussed in this paper is summarised in Scheme [1]. Friedel–Crafts acylation of pyrene (**1**) with phthalic anhydride gives the derivative **2** via attack at pyrene C1 (as expected). This is followed by an intramolecular Friedel–Crafts reaction which is directed towards C2, presumably by steric effects. The resulting hexacyclic diketone **3** is then treated with strong base, resulting in hydrolytic cleavage to pyrene-2-carboxylic acid (**4**). In the original (1937) version due to Vollmann and co-workers,[9] acid **4** was reported to be produced in an overall yield of 23%. Not only is this quite low, but some of the conditions were unusual and inconvenient from a present-day viewpoint [for example the use of chloronaphthalene as solvent or molten KOH as a reaction medium; see Scheme [1], conditions (a–c)]. We therefore decided to reinvestigate this sequence and develop a version more suited to the modern laboratory.

The conditions described by Vollmann et al. for the Friedel–Crafts addition of phthalic anhydride to pyrene involved $AlCl_3$ as promoter in refluxing benzene.[9] These conditions did not give satisfactory results in our hands, but the problem was readily solved by switching to dichloromethane as solvent. The revised procedure[21] gave highly pure **2** as a bright yellow solid in 98% isolated yield. The identity of **2** was readily confirmed by the ^1H NMR spectrum (see Supporting Information), in which all aromatic protons were inequivalent (excluding 2-substitution) and all showed at least one vicinal coupling (excluding 4-substitution). For the conversion of **2** to diketone **3**, we again found Vollmann's 1937 methodology inconvenient and difficult to reproduce. Treatment of **2** with benzoyl chloride in 1-chloronaphthalene did not yield the reported[9] precipitate of **3**, and further handling of the mixture was impeded by the high boiling point of the solvent (256 °C). Instead, we employed PCl_5 and $AlCl_3$ in chlorobenzene, as reported by Du et al. for a similar cyclisation.[22] After evaporation of solvent and treatment of the residue with water, diketone **3** was isolated by filtration as a dark red solid, apparently pure by ^1H NMR, and suitable for direct use in the next step.[23] Further purification could be achieved by chromatography, but this procedure is less suitable for large-scale use due to poor

solubility of **3** in the eluent (CH_2Cl_2–MeOH, 10:1). The structures of **2** and **3**, previously established through classical arguments, were confirmed by modern spectroscopic methods (see Supporting Information).

The final step of the Vollmann procedure involves heating **3** with molten KOH at ca. 200 °C, effecting Haller–Bauer cleavage[24] [25] [26] [27] as shown in Scheme [2]. Of the four Ar–CO bonds in **3** (*a*–*d*, see Scheme [2]), it is necessary to break *a* and *c* to yield the product **4**. This outcome may be predicted on the basis that (i) of the four options, pyrene C1 is best able to support a negative charge, favouring cleavage of *a* as the first step, and (ii) an *ortho*-carboxylate accelerates bond-breaking, favouring *c* over *d* in the second step.[27] Nonetheless, the method of Vollmann did not give especially good selectivity, affording **4** in 47–54% yield along with a considerable amount of pyrene side-product.[9] Moreover, the conditions applied would be difficult to achieve with standard laboratory equipment. Recent work on the Haller–Bauer cleavage has employed the milder conditions of potassium *tert*-butoxide–water in polar aprotic solvents,[26] [27] so we decided to test this methodology in the present case. We were pleased to find that treatment of **3** with H_2O–*tert*-BuOK (molar ratio 3:10) in 1,2-dimethoxyethane at ca. 85 °C for seven hours gave a cleaner conversion to **4**.[28] Purification was achieved by (i) trituration of the acidified crude product with water to remove benzoic and phthalic acid by-products, and (ii) short column chromatography (30 mL silica gel per gram of starting material) to remove pyrene and unreacted **3**. On a preparative scale (10 g of crude diketone **3**) the method gave **4** in 75% yield from **2**. Pyrene (**1**) was isolated in just 13% yield and 10% unreacted **3** could be recovered.[28] Trace contaminants could be removed by recrystallisation from nitrobenzene,[9] [20] but the material derived from the column should be pure enough for most purposes (see Figures S5 and S6, Supporting Information).



Scheme 2 Base-induced Haller–Bauer cleavage of 1,2-phthaloylpyrene (**3**). In the first step cleavage of *a* is promoted by the ability of pyrene C1 to support a negative charge, while in the second step the CO_2^- group in **5** accelerates cleavage of *c* with respect to *d*.

In conclusion, a classical but somewhat impractical synthesis of pyrene-2-carboxylic acid (**4**) has been updated and improved such that it can be applied conveniently and efficiently in a modern laboratory. The method has been tested on a multigram scale by several workers, yielding the product **4** in >70% overall yield from pyrene. By providing easy access to **4**, this work should facilitate the use of 2-pyrenyl units in the design of sensors, receptors and other functional organic molecules.

Acknowledgment

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Supporting Information

for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/ 10.1055/s-00000083.

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- **21 Preparation of 1-(*o*-Carboxybenzoyl)pyrene (2)**: $AlCl_3$ (15.4 g, 116 mmol) was added to a suspension of pyrene (9.4 g, 46 mmol) and phthalic anhydride (6.9 g, 46 mmol) in anhyd CH_2Cl_2 (280 mL) under N_2 atmosphere. The mixture was heated under reflux for 3 h. The solvent was then evaporated and the residue was cooled to 0 °C and suspended in H_2O (500 mL). The pH of the solution was adjusted to 0–1 by adding concd aq HCl (20 mL), and the solid was isolated by filtration, washed with ice water (2 × 150 mL) and dried by addition–evaporation of toluene. The solid was suspended in glacial AcOH (500 mL) and heated at 130 °C for 5 min, after which the insoluble material was removed by hot filtration and washing with hot glacial AcOH (3 × 50 mL). The filtrate was poured into ice water (1 L) and the resulting solid was isolated by filtration, washed with ice water (2 × 100 mL) and dried by addition–evaporation of toluene to give **2** (15.96 g, 45.6 mmol, 98%) as a bright yellow powder; mp 224–225 °C (Lit.[9] mp 225–226 °C); R_f = 0.35 (CH_2Cl_2–MeOH, 10:1). FTIR (ATR): 3039, 2910, 2786, 2617, 2546, 2492, 1714, 1591, 1578, 1234, 941, 838, 708 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 13.01 (br s, 1 H, COOH), 9.18 (d, ^3J = 9.2 Hz, 1 H, H-10), 8.41 (d, ^3J = 9.2 Hz, 1 H, H-9), 8.40 (br d, J = 7.6 Hz, 2 H, H-6, H-8), 8.32 (d, ^3J = 9.1 Hz, 1 H, H-5), 8.21 (d, ^3J = 8.1 Hz, 1 H, H-3), 8.18 (d, ^3J = 9.1 Hz, 1 H, H-4), 8.15 (t, ^3J = 7.6 Hz, 1 H, H-7), 7.99 (br d, J = 7.6 Hz, 1 H, H-6'), 7.83 (d, ^3J = 8.1 Hz, 1 H, H-2), 7.77 (ddd, J = 7.6, 7.2, 1.2 Hz, 1 H, H-4'), 7.71 (ddd, J = 7.6, 7.2, 1.2 Hz, 1 H, H-5'), 7.63 (br d, J = 7.2 Hz, 1 H, H-3'). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 198.7 (CO), 167.5 (COOH), 142.9 (C-2'), 133.5 (C-3a), 132.1 (C-4'), 131.1 (C-1), 130.8 (C-1'), 130.6 (C-5a), 130.3 (C-5'), 130.0 (C-8a), 129.9 (C-5), 129.8 (C-10a), 129.7 (C-6'), 129.5 (C-9), 128.9 (C-2), 128.5 (C-3'), 127.2 (C-4), 126.8 (C-7), 126.7 (C-6), 126.3 (C-8), 125.1 (C-10), 124.1 (C-3a[1]), 123.9 (C-3), 123.3 (C-5a[1]). HRMS (ESI^-): *m/z* $[M - H]^-$ calcd for $C_{24}H_{13}O_3$: 349.0870; found: 349.0881.

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- **23 Preparation of 1,2-Phthaloylpyrene (3)**: 1-(*o*-Carboxy-benzoyl)pyrene (**2**; 16.0 g, 45.7 mmol) was suspended in chlorobenzene (300 mL) under N_2 atmosphere, and PCl_5 (14.44 g, 69.3 mmol) and $AlCl_3$ (9.58 g, 71.9 mmol) were added. The resulting dark green mixture was heated under reflux for 2.5 h. The solvent was removed by evaporation and the residue was cooled to 0 °C and suspended in H_2O (450 mL). The dark red precipitate was collected by filtration, washed with H_2O (4 × 100 mL), toluene was added and evaporated (3 × 200 mL), and the resulting solid was further dried in vacuo (overnight) to give **3** (15.5 g, ca. quantitative). This material appeared pure by ^1H NMR and was used directly in the next step. Trace amounts of a highly coloured contaminant were removed by flash chromatography (CH_2Cl_2–hexane, 1:1 → CH_2Cl_2–MeOH, 10:1) to give a sample for characterisation; mp 255–256 °C (Lit.[9] 254 °C); R_f = 0.51 (EtOAc–hexane, 1:4). FTIR (ATR): 3119, 3024, 2804, 1716, 1661, 1615, 1443, 1392, 620 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.87 (d, ^3J = 9.8 Hz, 1 H, H-10), 8.90 (s, 1 H, H-3), 8.34 (dd, J = 7.6, 0.9 Hz, 1 H, H-3'), 8.28 (dd, J = 7.6, 0.9 Hz, 1 H, H-6'), 8.24 (d, ^3J = 9.8 Hz, 1 H, H-9),

8.21 (d, ^3J = 7.5 Hz, 1 H, H-8), 8.18 (d, ^3J = 7.5 Hz, 1 H, H-6), 8.13 (d, ^3J = 8.9 Hz, 1 H, H-5), 8.09 (d, ^3J = 8.9 Hz, 1 H, H-4), 8.02 (t, ^3J = 7.5 Hz, 1 H, H-7), 7.80 (dt, J = 7.5, 1.2 Hz, 1 H, H-4'), 7.75 (dt, J = 7.5, 1.2 Hz, 1 H, H-5'). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.9 [C-1(*C*O)C-2'], 184.3 [C-2(*C*O)C-1'], 136.2 (C-2'), 135.0 (C-3a), 134.4 (C-4'), 133.5 (C-5'), 133.1 (C-1'), 132.0 (C-2), 131.9 (C-9), 131.8 (C-5a), 131.7 (C-10a), 131.2 (C-5), 131.0 (C-8a), 128.3 (C-4), 127.8 (C-7), 127.7 (C-3a^1), 127.6 (C-3'), 127.5 (C-6), 127.1 (C-8), 126.8 (C-6'), 126.5 (C-10), 124.3 (C-1), 124.2 (C-3), 123.8 (C-5a^1). HRMS (EI$^+$): *m/z* $[M]^+$ calcd for $C_{24}H_{12}O_2$: 332.0837; found: 332.0842.

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- **28 Preparation of Pyrene-2-carboxylic Acid (4)**: Crude **3** (10 g) was suspended in 1,2-dimethoxyethane (140 mL). H_2O (3 equiv per carbonyl group, 3.3 mL, 180.6 mmol) was added, then potassium *tert*-butoxide (10 equiv per carbonyl group, 67.6 g, 602 mmol) was added portionwise with vigorous stirring to ensure that a fine suspension was maintained throughout the addition. The mixture was vigorously stirred under reflux for 7 h and the solvent was evaporated. The residue was cooled to 0 °C, suspended in H_2O (1 L), and acidified to pH 1–2 with concd aq HCl. The resulting solid was removed by filtration, suspended in H_2O (2 L), stirred overnight, collected by filtration, washed with H_2O (2 × 250 mL) and dried in vacuo. The material was ground into a fine powder then slowly added to CH_2Cl_2–MeOH (1:1, 250 mL), forming a suspension. Silica (30 g) was then added and the mixture was concentrated to dryness. The resulting fine powder was carefully loaded (band height = 1.8 cm) on a short column (diameter = 6.5 cm, ca. 300 mL, silica gel, height = 5 cm) packed with CH_2Cl_2–hexane (1:1). Pyrene (**1**; 0.79 g, 3.9 mmol, 13% from **2**) and starting diketone **3** (0.96 g, 2.9 mmol, 10% from **2**) eluted with CH_2Cl_2–hexane (1:1, 500 mL) and CH_2Cl_2 (1.5 L), respectively. The polarity of the eluent was increased to 10% MeOH in CH_2Cl_2 (150 mL per 2.5% increment) and finally to CH_2Cl_2–MeOH–30% aq NH_3 (90:9:1, 2 L) to elute the product. Elution of diketone **3** (bright yellow/orange fluorescence) and product **4** (dark purple fluorescence) could be monitored by irradiating the column with a 365 nm UV lamp. Pyrene-2-carboxylic acid (**4**; 5.46 g, 22.2 mmol, 75% from **2**) was obtained as a light grey solid; mp 326 °C (Lit.[9] 326 °C); R_f = 0.33 (CH_2Cl_2–MeOH, 10:1). FTIR (ATR): 2596, 1685, 1305, 1247, 896, 840, 820, 704 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.31 (br s, 1 H, COOH), 8.86 (s, 2 H, H-1, H-3), 8.33 (d, ^3J = 7.6 Hz, 2 H, H-6, H-8), 8.31 (d, ^3J = 9.2 Hz, 2 H, H-4, H-10), 8.24 (d, ^3J = 9.2 Hz, 2 H, H-5, H-9), 8.13 (t, ^3J = 7.6 Hz, 1 H, H-7). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8 (COOH), 131.2 (C-5a, C-8a), 130.5 (C-3a, C-10a), 128.1 (C-2), 128.0 (C-5, C-9), 127.7 (C-4, C-10), 127.3 (C-7), 125.8 (C-3a^1), 125.5 (C-1, C-3, C-6, C-8), 123.3 (C-5a^1). HRMS (ESI$^-$): *m/z* $[M - H]^-$ calcd for $C_{17}H_9O_2$: 245.0608; found: 245.0615.