Synthesis of 1- and 3-Nitrobenzo[*a*]pyrene

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Keywords: Aromatic substitution / Carboxylic acids / Dechlorination / Nitrogen heterocycles / Thermolysis

The synthesis of the important carcinogens 1-nitrobenzo[*a*]pyrene and 3-nitrobenzo[*a*]pyrene was achieved in four steps starting from the parent compound. A hexyl ester functionality was introduced as a removable blocking group, controlling the regioselectivity of the synthesis.

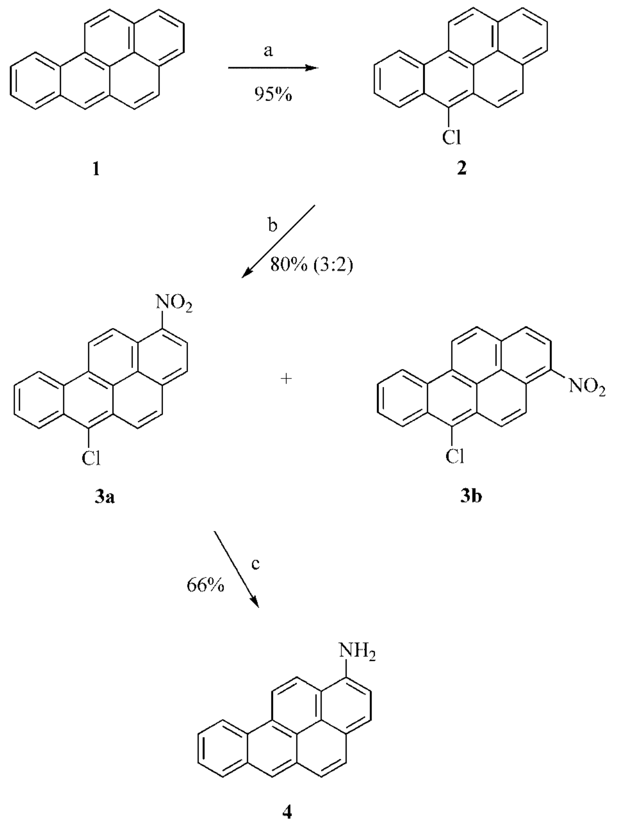
Introduction

Among polycyclic aromatic hydrocarbons, benzo[*a*]pyrene (**1**) − abbreviated as B[*a*]P − is well known as a potent carcinogen.[1−2] It has become evident that its widespread occurrence is often accompanied by that of its nitro derivatives:[3] whereas 6-nitro-B[*a*]P seems to be relatively harmless, the 1-nitro derivative **8a** and the 3-nitro isomer **8b** are reputed to be even more mutagenic than the parent compound **1**. Availability of pure samples of **8a** and **8b** is therefore important for applications in environmental analytical chemistry such as, for instance, as reference substances.

The direct nitration of **1** gives mixtures of isomers, with 6-nitro-B[*a*]P as by far the main component and a quota of **8a** and **8b** of less than 5%. Because of the low solubilities of the nitro-B[*a*]Ps, **8a** and **8b** have been separated by HPLC only in extremely small amounts.[4−5] A multistep synthesis of these compounds according to Fu et al.[6] also needed a HPLC separation step and developing alternative syntheses[7−11] would not circumvent this problem. We therefore decided to attempt a new approach: the reversible introduction into the 6-position of a blocking group that should simultaneously modify the solubility and the dipole moment. In a second step, the nitro groups should be introduced into the 1- and/or the 3-position. After separation of the two anticipated regioisomers, the blocking group should finally be removed.

Results and Discussion

For our first attempt (Scheme 1) we chose a chloro substituent[12] as blocking group, on the basis of several simple considerations: firstly, the chloro substituent is easily introduced and should be easily removed. Even more importantly, according to AM1 calculations the chloro substituent should significantly change the difference in the dipole moments of the regioisomers, thus increasing the chances of separating the isomers by crystallization; in the case of the 1-nitro isomer **8a** (with 6.3 Debye as calculated dipole mo-



Scheme 1. a: CuCl$_2$, CCl$_4$, reflux, 8 h; b: HNO$_3$, Ac$_2$O, 0 °C, 4 h; c: 5% Pd(OAc)$_2$, sodium formate, propylene carbonate, 2 h sonication at 70−80 °C, 2 days at 100−110 °C

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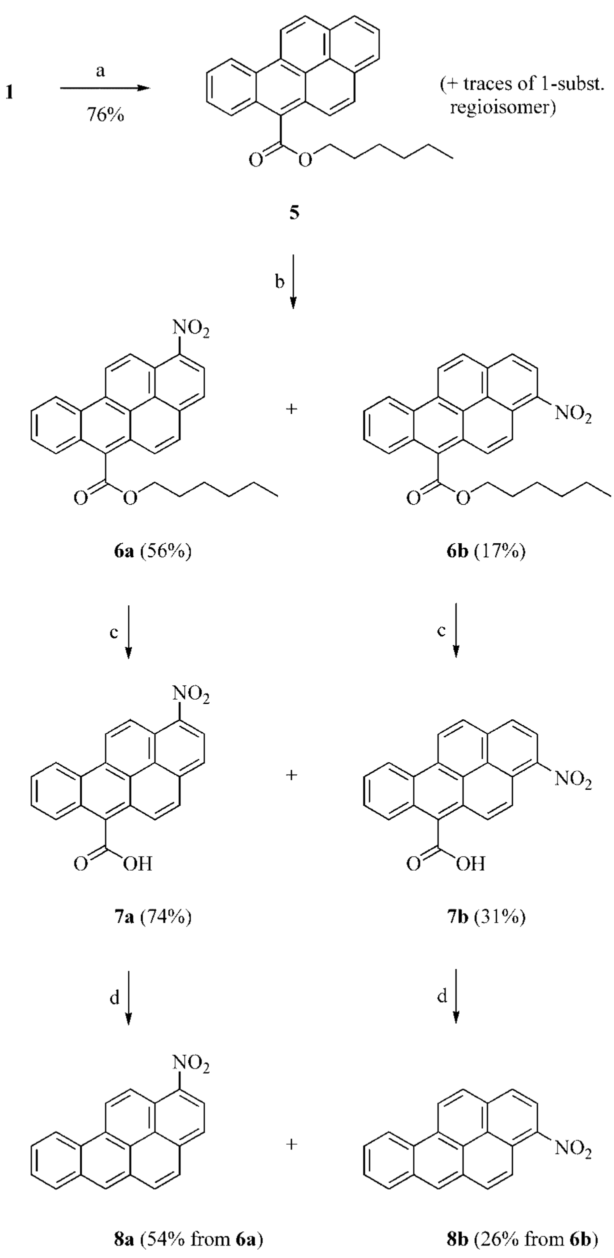
ment) the chloro substituent in the 6-position diminishes the dipole moment by about 1.2 Debye, whereas for the 3-nitro isomer **8b** (initially with 6.5 Debye) a slight increase in the dipole moment of about 0.2 Debye is calculated.

Chlorination of **1** with copper(II) chloride indeed succeeded in excellent yield,[13] and the subsequent nitration gave rise to a 3:2 mixture of 6-chloro-1-nitro- (**3a**) and 6-chloro-3-nitro- B[*a*]P (**3b**). The difference in the polarities of the two isomers was indeed sufficient for separated spots to be obtained on TLC (silica, acetone/*n*-hexane, 1/4, R_f = 0.44 and 0.53). Unfortunately, though, low solubility prevented separation of larger quantities by flash chromatography. By multiple crystallizations from acetone we succeeded in isolating a pure sample of the somewhat less soluble major isomer **3a**. The chloro substituent proved to be completely inert under conventional conditions for hydrodechlorination (copper powder, benzoic acid, nitrobenzene, reflux).[14−15] With catalytically active palladium clusters[16] instead, in the presence of sodium formate as reducing agent, the chloro substituent was successfully removed, but the nitro group was also reduced to give the corresponding aniline **4**. Reoxidation to the nitro compound with dimethyldioxirane[17−18] failed, due to the sensitivity of the electron-rich aromatic.

Overall, the use of a chloro substituent as blocking group was causing more troubles than anticipated, so we decided to try an ester functionality as an alternative (Scheme 2). Introduction of a hexyl ester into the 6-position succeeded with high selectivity through a one-pot procedure initially described for the functionalization of anthracene.[19−22] Treatment of **1** with oxalyl bromide, with loss of one equivalent of carbon monoxide, was supported by sonication to give the intermediary carboxylic acid bromide, which was directly transformed with sodium hexoxide to give **5** in good yield, containing only trace amounts of the 1-isomer. Nitration gave a 2:1 mixture of the 1-nitro- and the 3-nitro derivatives **6a** and **6b**. The solubilities of the esters **6** in conventional solvents were indeed higher than those of the chloro-substituted compounds **3**, but still not sufficient for preparative column chromatography. Toluene was the solvent of choice for a fractionating crystallization, firstly to isolate the less soluble 3-nitro-compound **6b** in a 17% yield and then the 1-isomer in a remarkable 56% yield. Under standard basic reaction conditions for ester hydrolysis (KOH/EtOH), as well as under acidic conditions (trifluoroacetic acid/toluene), the esters **6** proved to be completely inert. Harsher or more sophisticated conditions developed for the hydrolysis of sterically hindered esters,[23] such as KOH in 2-methoxyethanol at 170 °C or BCl_3 in dichloromethane or KCN in DMSO, were also unsuitable. Since the MS spectra of the esters **6** nicely showed fragmentation by McLafferty rearrangement, we tried ester pyrolysis supported on silica gel: the fragmentation starts at about 260 °C. To avoid carbonization the temperature should remain below 300 °C. On washing of the silica gel with ethyl acetate, unchanged starting material was recovered, already accompanied by small amounts of the final products **8a** or **8b**. The pure acids **7a** and **7b** were obtained by treatment of the impregnated silica gel with boiling methanol in a Soxhlet extractor. As the final step in the synthesis of **8a** or **8b**, complete decarboxylation was achieved by treatment with copper powder in boiling quinoline.



Scheme 2. a: 1. Oxalyl bromide, 120 °C, 4 h, 2. sodium hexoxide in *n*-hexanol, 20 °C, 1 h; b: HNO_3, Ac_2O, 0 °C, 4 h; c: silica gel 260−280 °C, 6−8 h; d: Cu powder, quinoline, reflux, 10−12 h

The B[*a*]P derivatives were characterized and identified by IR, MS and NMR spectra; by use of 2D NMR techniques such as HMBC, HMQC and COSY it was possible to assign all ^1H NMR and generally also ^{13}C NMR signals, as listed in the Exp. Sect..

Conclusion

The overall yields starting from the parent compound **1** were 30% for 1-nitro-B[*a*]P (**8a**) and 4% for 3-nitro-B[*a*]P

(**8b**). The presented procedure is suitable for the synthesis of 30−50 mg of each final product in one run.

Experimental Section

General Remarks: M.p. (uncorrected): Reichert Thermovar. IR: Perkin−Elmer 841. NMR: Bruker DRX 500, Bruker DRX 400. ^{1}H NMR spectra (500 MHz or 400 MHz) were recorded in $CDCl_3$ or CD_3OD (**7a**, **7b**) with TMS as the internal standard. ^{13}C NMR spectra (125.8 MHz or 100.6 MHz) were measured by use of $CDCl_3$, $[D_6]$DMSO or CD_3OD (**7a**, **7b**) as the solvent and the internal standard. MS: MAT 700 ITD (70 eV) and Varian MAT 311 A. For analytical TLC, precoated plastic sheets "POLYGRAM SIL G/UV254" from Macherey−Nagel were used. The ^{1}H NMR, mass and UV spectra of 1- and 3-nitro-B[*a*]P **8a** and **8b** were previously reported by Fukuhara (^{1}H NMR: 400 MHz in $[D_6]$DMSO), by Johansen (^{1}H NMR: 400 MHz in $CDCl_3$, the sample was a mixture of **8a** and **8b**) and by Fu (^{1}H NMR: 500 MHz in $[D_6]$acetone).[4−6]

Warning! *Because of the mutagenicity of B[a]P (**1**) and its derivatives one must carefully avoid any contact of these substances with the skin and must prevent accidental inhalation of powder or contaminated dust by use of appropriate protective measures.*

All new compounds were pure according to their ^{1}H NMR spectra; because of their potential mutagenicity elemental analyses were dispensed with.

6-Chlorobenzo[*a*]pyrene (2): A suspension of benzo[*a*]pyrene (**1**, 500 mg, 1.98 mmol) and dry $CuCl_2$ (613 mg, 4.55 mmol) in dry CCl_4 (30 mL) was heated at reflux under nitrogen for 8 h. The hot solution was decanted from the copper salt, dry $CuCl_2$ (266 mg, 1.98 mmol) was added, and the mixture was again heated at reflux under nitrogen for 8 h. The hot suspension was filtered and the solvent was evaporated to dryness to give **2** (542 mg, 95%) as a yellow solid; R_f = 0.39 (silica, *n*-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82−7.88 (m, 2 H, 8-H, 9-H), 7.96 (t, *J* = 7.5 Hz, 1 H, 2-H), 7.98 (d, *J* = 9.4 Hz, 1 H, 4-H), 8.08 ("d", *J* = 7.5 Hz, 1 H, 3-H), 8.20 ("d", *J* = 7.5 Hz, 1 H, 1-H), 8.25 (d, *J* = 9.2 Hz, 1 H, 12-H), 8.47 (d, *J* = 9.4 Hz, 1 H, 5-H), 8.79−8.81 (m, 1 H, 7-H), 8.94 (d, *J* = 9.2 Hz, 1 H, 11-H), 8.99−9.08 (m, H, 10-H) ppm.

6-Chloro-1-nitrobenzo[*a*]pyrene (3a) and 6-Chloro-3-nitrobenzo[*a*]pyrene (3b): Compound **2** (542 mg, 1.88 mmol) was dissolved in acetic acid anhydride (250 mL) under gentle warming. At a carefully controlled 0 °C, a solution of concentrated nitric acid (0.62 mL, 13 mmol) in acetic acid anhydride (15 mL) was added with stirring over 30 min. After 4 h additional stirring at 0 °C, the orange precipitate was collected and dried in vacuo, to afford a mixture of **3a** and **3b** (500 mg, 80%) in a ratio of 3:2. The crude product was heated at reflux for 2 h in acetone (1000 mL) and after 2 h at room temperature the supernatant was decanted from the precipitate. This procedure was repeated six times and finally yielded the pure 1-nitro isomer **3a** (150 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96−8.00 (m, 2 H, 8-H, 9-H), 8.09 ("d", *J* = 9.6 Hz, 1 H), 8.14 (d, *J* = 8.4 Hz, 1 H), 8.73 (d, *J* = 8.3 Hz, 1 H), 8.77 (d, *J* = 9.5 Hz, 1 H), 8.89−8.91 (m, 1 H, 7-H), 9.13−9.15 (m, 1 H, 10-H), 9.18 (d, *J* = 9.4 Hz, 1 H, 12-H), 9.29 (d, *J* = 9.4 Hz, 1 H, 11-H) ppm.

1-Aminobenzo[*a*]pyrene (4): A mixture of **3a** (142 mg, 429 mmol), palladium acetate (4.7 mg, 21 mmol) and sodium formate (583 mg, 8.58 mmol) in propylene carbonate (20 mL) was heated under nitrogen at 70−80 °C for 2 h in a sonicator and for 2 days whilst stirring at 100−110 °C. The solvent was removed in vacuo and the residue was filtered through silica gel (5 g) with diethyl ether (200 mL) to give **4** (75 mg, 66%) as a yellow solid; m.p. 130−135 °C. R_f = 0.84 (silica, diethyl ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 7.9 Hz, 1 H, 1-H), 7.73−7.77 (m, 4 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 8.22−8.24 (m, 2 H), 8.38 (s, 1 H, 6-H), 8.98−9.00 (m, 2 H, H-11, 10-H) ppm.

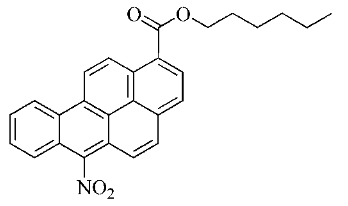
***n*-Hexyl Benzo[*a*]pyrene-6-carboxylate (5):** A suspension of B[*a*]P (**1**, 635 mg, 2.50 mmol) and oxalyl bromide (550 µL, 2.50 mmol) was heated under argon to 120 °C. The overall reaction time was 4 h, with several interruptions to redisperse newly formed precipitate by treatment of the reaction flask in a sonic bath. Unchanged oxalyl bromide was removed under reduced pressure (membrane pump and a trap with water). A *n*-hexoxide solution, freshly prepared from sodium (138 mg, 6.0 mmol) and dry *n*-hexanol (4 mL), was added to the solid residue. After the mixture had been stirred for 1 h, water (50 mL) was added and the reaction mixture was extracted three times with MTBE (40 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, and the solvent was distilled off to give a remaining volume of 10 mL. Methanol was added to this hot suspension until a clear solution resulted, from which the product crystallized at room temperature to give pale yellow crystals of **5** (720 mg, 1.9 mmol, 76%) with m.p. 78−79 °C. TLC (silica, toluene/petroleum ether, 1:10). R_f = 0.61. IR (KBr): $\tilde{\nu}$ = 3039 cm^{-1} (w), 2925 (w), 2866 (w), 1717 (vs), 1461 (m), 1243 (m), 837 (m), 754 (s), 695 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.1 Hz, 3 H, 6′-H), 1.32−1.43 (m, 4 H, 5′-H, 4′-H), 1.46−1.57 (m, 2 H, H-3′), 1.89−1.96 (m, 2 H, H-2′), 4.68 (t, *J* = 6.8 Hz, 2 H, H-1′), 7.79−7.86 (m, 2 H, 8-H, 9-H), 7.98 (d, *J* = 9.3 Hz, 1 H, 4-H), 8.00 (t, *J* = 7.7 Hz, 1 H, 2-H), 8.01 (d, *J* = 9.3 Hz, 1 H, 5-H), 8.11 (d, *J* = 7.3 Hz, 1 H, 3-H), 8.25 (d, *J* = 7.3 Hz, 1 H, 1-H), 8.27 (d, *J* = 7.5 Hz, 1 H, 7-H), 8.35 (d, *J* = 9.0 Hz, 1 H, 12-H), 9.04 (d, *J* = 9.0 Hz, 1 H, 11-H), 9.07 (d, *J* = 9.0 Hz, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 ppm (q, C-6′), 22.6 (t, C-5′), 25.8 (t, C-3′), 28.8 (t, C-2′), 31.5 (t, C-4′), 66.1 (t, C-1′), 122.0 (d, C-11), 122.9 (s, C-12c), 123.3 (d, C-10), 124.8 (d, C-5), 125.1 (s, C-12b), 125.8 (d, C-3), 125.9 (d, C-7), 126.2 (d, C-9), 126.4 (d, C-1), 126.5 (d, C-2), 126.8 (s, C-6), 127.0 (d, C-8), 127.0 (s, C-5a), 127.7 (s, C-10a), 127.8 (s, C-6a), 128.6 (s, C-10b), 128.7 (d, C-12), 129.4 (d, C-4), 130.7 (s, C-3a), 131.3 (s, C-12a), 170.3 (s, COO) ppm. MS (EI): *m*/*z* (%) = 380 (100) [M$^+$], 296 (28), 297 (26), 251 (33), 125 (6).

Nitration of 5: A solution of fuming HNO_3 (1.1 mL, 23 mmol) in Ac_2O (10 mL) was added slowly at 0 °C to a well stirred suspension of the ester **5** (1.20 g, 3.20 mmol) in Ac_2O (80 mL). After the mixture had been stirred for 1 h, water (50 mL) was added and the suspension was transferred to a separating funnel. Extraction with toluene (350 mL, then 50 mL) gave a combined organic layer that was washed with aqueous Na_2CO_3 solution (30 mL), with water (50 mL) and with brine (50 mL). After the mixture had been dried with $MgSO_4$, the solvents were distilled off and the orange residue was dried in vacuo. The resulting isomer mixture of **6a** and **6b** (1.4 g, 3.2 mmol, 100%) in a ratio of 2:1 was separated by the following crystallization steps. Triple recrystallization from ethyl acetate gave pure **6a** (500 mg). The combined filtrates were evaporated to dryness to give a 1:1 mixture of **6a** and **6b** (900 mg). By triple crystallization from toluene (always using three times as much toluene as needed for solubilization at reflux temperature) pure **6b** (100 mg) was obtained. The combined residues were again recrystallized four times from ethyl acetate, yielding additional **6a** (260 mg). A second portion of **6b** (130 mg) resulted from several further crystallization steps with toluene. Flash chromatography (silica, toluene/petroleum ether) of all the remaining residues provided the by-product **9** (30 mg, 0.07 mmol, 2%). Overall, 760 mg (1.8 mmol, 56%) of **6a** and 230 mg (0.54 mmol, 17%) of **6b** were isolated.

***n*-Hexyl 1-Nitrobenzo[*a*]pyrene-6-carboxylate (6a):** R_f = 0.21 (silica, toluene/petroleum ether, 1:10). IR (KBr): $\tilde{\nu}$ = 2957 cm^{-1} (w), 2927 (w), 2856 (w), 1717 (vs), 1505 (m), 1333 (s), 843 (m), 824 (m), 750 (s), 695 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.1 Hz, 3 H, 6′-H), 1.35−1.41 (m, 4 H, 5′-H, 4′-H), 1.50−1.58 (m, 2 H, 3′-H), 1.91−1.98 (m, 2 H, 2′-H), 4.71 (t, *J* = 6.5 Hz, 2 H, 1′-H), 7.83−8.00 (m, 2 H, 8-H, 9-H), 7.99 (d, *J* = 9.3 Hz, 1 H, 4-H), 8.11 (d, *J* = 8.3 Hz, 1 H, 3-H), 8.18 (d, *J* = 9.3 Hz, 1 H, 5-H), 8.29 ("d", *J* = 8.3 Hz, 1 H, 7-H), 8.69 (d, *J* = 8.3 Hz, 1 H, 2-H), 9.10 ("d", *J* = 9.0 Hz, 1 H, 10-H), 9.12 (d, *J* = 9.7 Hz, 1 H, 12-H), 9.26 (d, *J* = 9.7 Hz, 1 H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (q, C-6′), 22.6 (t, C-5′), 25.8 (t, C-3′), 28.8 (t, C-2′), 31.5 (t, C-4′), 66.5 (t, C-1′), 121.8 (s, C-12c), 123.1 (d, C-12), 123.4 (d, C-10), 123.7 (d, C-2), 124.3 (s, C-12a), 124.3 (d, C-3), 125.4 (s, C-5a), 125.4 (d, C-11), 125.8 (s, C-12b), 126.1 (d, C-7), 127.5 (d, C-9), 127.8 (s, C-10b), 127.8 (d, C-8), 127.9 (s, C-6a), 128.1 (d, C-5), 128.2 (s, C-10a), 128.3 (d, C-4), 130.1 (s, C-6), 135.3 (s, C-3a), 143.6 (s, C-1), 169.5 (s, COO) ppm. MS: (EI): *m*/*z* (%) = 425 (100) [M$^+$], 379 (5), 341 (4), 324 (5), 311 (23), 295 (12), 278 (5), 250 (27), 238 (6), 125 (5).

***n*-Hexyl 3-Nitrobenzo[*a*]pyrene-6-carboxylate (6b):** R_f = 0.21 (silica, toluene/petroleum ether, 1:10). IR (KBr): $\tilde{\nu}$ = 2955 cm^{-1} (m), 2928 (w), 2860 (w), 1720 (vs), 1519 (m), 1326 (vs), 844 (m), 748 (m), 693 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.1 Hz, 3 H, 6′-H), 1.34−1.42 (m, 4 H, 5′-H, 4′-H), 1.52−1.56 (m, 2 H, 3′-H), 1.91−1.98 (m, 2 H, 2′-H), 4.72 (t, *J* = 6.8 Hz, 2 H, 1′-H), 7.86−7.94 (m, 2 H, 8-H, 9-H), 8.20 (d, *J* = 8.5 Hz, 1 H, 1-H), 8.26 (d, *J* = 9.7 Hz, 1 H, 5-H), 8.30 ("d", *J* = 8.0 Hz, 1 H, 7-H), 8.34 (d, *J* = 9.0 Hz, 1 H, 12-H), 8.55 (d, *J* = 8.5 Hz, 1 H, 2-H), 8.77 (d, *J* = 9.5 Hz, 1 H, 4-H), 9.05 ("d", *J* = 8.0 Hz, 1 H, 10-H), 9.15 (d, *J* = 9.0 Hz, 1 H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (q, C-6′), 22.6 (t, C-5′), 25.8 (t, C-3′), 28.8 (t, C-2′), 31.5 (t, C-4′), 66.6 (t, C-1′), 122.3 (s, C-12c), 122.4 (d, C-2), 123.1 (d, C-4), 123.4 (d, C-10), 124.9 (d, C-11), 125.0 (s, C-5a), 125.1 (s, C-3a), 125.2 (s, C-12b), 126.0 (d, C-1), 126.3 (d, C-7), 27.5 (d, C-9), 127.8 (d, C-8), 127.9 (s, C-6a), 128.2 (d, C-12), 128.7 (s, C-10a), 128.8 (s, C-10b), 129.1 (d, C-5), 129.8 (s, C-6), 134.1 (s, C-12a), 150.7 (s, C-3), 169.4 (s, COO) ppm. MS: (EI): *m*/*z* (%) = 425 (100) [M$^+$], 379 (5), 341 (4), 324 (5), 311 (23), 295 (12), 278 (5), 250 (27), 238 (6), 125 (5).

***n*-Hexyl 6-Nitrobenzo[*a*]pyrene-1-carboxylate (9):** R_f = 0.50 (silica, toluene/petroleum ether, 1:10). IR (KBr): $\tilde{\nu}$ = 2963 cm^{-1} (m), 2933 (w), 2860 (w), 1714 (vs), 1520 (s), 1356 (vs), 825 (m), 804 (m), 758 (m), 693 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3 H, 6′-H), 1.38−1.42 (m, 4 H, 5′-H, 4′-H), 1.42−1.61 (m, 2 H, 3′-H), 1.89−1.96 (m, 2 H, 2′-H), 4.53 (t, *J* = 6.6 Hz, 2 H, 1′-H), 7.88−7.93 (m, 2 H, 8-H, 9-H), 7.94 (d, *J* = 9.5 Hz, 1 H, 4-H), 8.05 (d, *J* = 9.5 Hz, 1 H, 5-H), 8.13 (d, *J* = 7.8 Hz, 1 H, 3-H), 8.14 ("d", *J* = 8.0 Hz, 1 H, 7-H), 8.64 (d, *J* = 7.8 Hz, 1 H, 2-H), 9.06 ("d", *J* = 9.6 Hz, 1 H, 10-H), 9.09 (d, *J* = 8.0 Hz, 1 H, 12-H), 9.54 (d, *J* = 9.7 Hz, 1 H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (q, C-6′), 22.7 (t, C-5′), 25.9 (t, C-3′), 28.9 (t, C-2′), 31.6 (t, C-4′), 65.8 (t, C-1′), 120.7 (s, C-12b), 121.8 (s, C-12c), 122.3 (s, C-10b), 122.4 (d, C-3), 122.6 (d, C-5), 123.4 (d, C-10), 123.5 (d, C-12), 124.8 (s, C-10a), 125.9 (d, C-7), 126.4 (s, C-5a), 127.6 (d, C-11), 127.6 (d, C-9), 128.2 (s, C-6a), 128.4 (s, C-12a), 128.7 (d, C-8), 129.8 (d, C-2), 130.5 (s, C-1), 131.1 (d, C-4), 133.5 (s, C-3a), 143.9 (s, C-6), 167.5 (s, COO) ppm. MS: (EI): *m*/*z* (%) = 425 (100) [M$^+$], 379 (5), 341 (4), 324 (5), 311 (23), 295 (12), 278 (5), 250 (27), 238 (6), 125 (5).



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1-Nitrobenzo[*a*]pyrene-6-carboxylic Acid (7a): The ester **6a** (100 mg, 0.24 mmol) was coated onto silica (by evaporation of a CH_2Cl_2 solution with 5 g of silica) and then heated at 280 °C for 4 h at a pressure of less than $1 \cdot 10^{-2}$ mbar. After cooling to room temperature, the silica was extracted with ethyl acetate (200 mL). From this fraction, **6a** (32 mg) was recovered. The silica was then transferred to a Soxhlet extractor and was extracted with methanol for 10 h. Evaporation of the methanol gave the acid **7a** (61 mg, 0.18 mmol, 74%; 90% based on recovered starting material). TLC (silica, ethyl acetate): R_f = 0.00. IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1} (vs), 3430 (w), 2927 (w), 2856 (w), 1581 (vs), 1518 (s), 1495 (m), 1305 (s), 840 (m), 745 (m). ^{1}H NMR (400 MHz, [D_4]MeOH): δ = 7.90−7.94 ppm (m, 1 H, 8-H), 7.96−8.00 (m, 1 H, 9-H), 8.10 (d, *J* = 9.3 Hz, 1 H, 4-H), 8.22 (d, *J* = 8.3 Hz, 1 H, 3-H), 8.51 (d, *J* = 9.3 Hz, 1 H, 5-H), 8.61 ("d", *J* = 8.0 Hz, 1 H, 7-H), 8.73 (d, *J* = 8.3 Hz, 1 H, 2-H), 9.10 (d, *J* = 9.5 Hz, 1 H, 12-H), 9.25 ("d", *J* = 8.5 Hz, 1 H, 10-H), 9.47 (d, *J* = 9.5 Hz, 1 H, 11-H) ppm.

No ^{13}C NMR of **7a** was recorded, due to its extremely low solubility; an EI mass spectrum also failed.

3-Nitrobenzo[*a*]pyrene-6-carboxylic Acid (7b): By starting from the ester **6b** (100 mg, 0.24 mmol) and using the same procedure as described for **7a**, starting material (40 mg) and **7b** (30 mg, 31%; 51% based on recovered starting material) were obtained. R_f = 0.00 (silica, ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3453 cm^{-1} (vs), 2927 (w), 2925 (w), 2861 (w), 1562 (vs), 1519 (s), 1493 (m), 1317 (vs), 836 (m), 791 (w), 746 (m), 698 (w). ^{1}H NMR (400 MHz, [D_4]MeOH): δ = 7.04−7.08 ppm (m, 1 H, 8-H), 7.10−7.14 (m, 1 H, 9-H), 7.52 (d, *J* = 9.0 Hz, 1 H), 7.62 (d, *J* = 9.0 Hz, 1 H), 7.73 (d, *J* = 9.5 Hz, 1 H), 7.75 (d, *J* = 9.0 Hz, 1 H, 12-H), 7.78 ("d", *J* = 8.0 Hz, 1 H, 7-H), 7.83 (d, *J* = 9.5 Hz, 1 H, 2-H), 8.39 ("d", *J* = 8.5 Hz, 1 H, 10-H), 8.55 (d, *J* = 9.0 Hz, 1 H, 11-H) ppm. No ^{13}C NMR of **7b** was recorded, due to its extremely low solubility; an EI mass spectrum also failed.

1-Nitrobenzo[*a*]pyrene (8a): The crude acid **7a**, resulting from silica gel-supported ester pyrolysis, was suspended in freshly distilled quinoline (80 mL). Copper powder (100 mg, 2.7 mmol) was added and the degassed suspension was heated at reflux under argon for 12 h. Toluene (150 mL) was added and the copper was filtered off. The solution was washed four times with half-concentrated hydrochloric acid. Alumina (neutral, 3 g) was added and the toluene was distilled off. The residue was poured onto a small column of neutral alumina and a 1:1 mixture of toluene and pentane was applied as eluent. Yield: 41 mg (0.14 mmol, 54%) of pure **8a**. R_f = 0.21 (silica, toluene/pentane). IR (KBr): $\tilde{\nu}$ = 2932 cm^{-1} (w), 1520 (s), 1505 (m), 1334 (s), 844 (w), 823 (w), 809 (m), 749 (m), 705 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93−7.97 (m, 1 H, 8-H), 8.00−8.03 (m, 1 H, 9-H), 7.96 (d, *J* = 9.0 Hz, 1 H, 4-H), 8.08 (d, *J* = 8.3 Hz, 1 H, 3-H), 8.19 (d, *J* = 9.0 Hz, 1 H, 5-H), 8.33 ("d", *J* = 8.3 Hz, 1 H, 7-H), 8.67 (s, 1 H, 6-H), 8.72 (d, *J* = 8.3 Hz, 1 H, 2-H), 9.08 ("d", *J* = 8.3 Hz, 1 H, 10-H), 9.19 (d, *J* = 9.5 Hz, 1 H, 12-H), 9.29

(d, J = 9.5 Hz, 1 H, 11-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 121.6 (d, C-12), 122.0 (s, C-12c), 123.5 (d, C-10), 123.6 (s, C-12a), 123.9 (d, C-2), 124.2 (d, C-3), 124.9 (s, C-12b), 126.1 (s, C-10b), 126.5 (d, C-11), 127.1 (d, C-4), 127.4 (d, C-8), 127.8 (d, C-9), 128.2 (s, C-10a), 128.5 (d, C-6), 128.6 (s, C-5a), 129.2 (d, C-7), 131.2 (s, C-6a), 131.8 (d, C-5), 136.1 (s, C-3a), 142.6 (s, C-1) ppm. MS (EI): *m/z* (%) = 297 (100) [M$^+$], 267 (28), 266 (1), 251 (69), 250 (55), 239 (21), 224 (4), 125 (45).

3-Nitrobenzo[*a*]pyrene (8b): The ester **6b** (170 mg, 0.35 mmol) was treated by the procedure described for **8a**. Yield: 27 mg (0.09 mmol, 26%) of **8b**. R_f = 0.21 (silica, toluene/pentane). IR (KBr): $\tilde{\nu}$ = 2926 cm^{-1} (w), 1519 (s), 1505 (m), 1340 (s), 884 (m), 842 (w), 840 (m), 791 (m), 746 (w), 687 (m). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.85−7.88 (m, 1 H, 8-H), 7.91−7.95 (m, 1 H, 9-H), 8.24 (d, J = 8.8 Hz, 1 H, 1-H), 8.28 (d, J = 10.0 Hz, 1 H, 5-H), 8.36 ("d", J = 8.0 Hz, 1 H, 7-H), 8.37 (d, J = 9.0 Hz, 1 H, 12-H), 8.60 (d, J = 8.8 Hz, 1 H, 2-H), 8.69 (s, 1 H, 6-H), 8.75 (d, 1 H, 4-H), 9.08 ("d", J = 8.0 Hz, 1 H, 10-H), 9.23 (d, J = 9.0 Hz, 1 H, 11-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 121.1 (d, C-4), 122.4 (s, C-12c), 122.4 (d, C-2), 123.8 (d, C-10), 124.6 (s, C-12b), 124.9 (s, C-3a), 125.9 (d, C-1), 126.0 (d, C-11), 127.5 (s, C-10b), 127.5 (d, C-8), 127.5 (d, C-12), 127.7 (s, C-5a), 127.9 (d, C-9), 128.0 (d, C-6), 128.2 (s, C-10a), 129.0 (d, C-7), 129.5 (s, C-6a), 131.4 (d, C-5), 133.0 (s, C-12a), 147.0 (s, C-3) ppm. MS (EI): *m/z* (%) = 297 (100) [M$^+$], 267 (28), 266 (1), 251 (69), 250 (55), 239 (21), 224 (4), 125 (45).

Acknowledgments

Financial support by the Fonds der Chemischen Industrie is gratefully acknowledged. We thank R. Nießner, D. Knopp and U. Pöschl from the Institute of Hydrochemistry of the TU Munich for helpful discussions and support.

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Received April 4, 2003