# Efficient Synthesis of 4,5,9,10-Tetrahydropyrene: A Useful Synthetic Intermediate for the Synthesis of 2,7-Disubstituted Pyrenes

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## Introduction

Although the chemistry of pyrene, **1**, is well-known,[1,2] there is considerable interest in the synthesis of new derivatives for investigation of the carcinogenesis of polycylic aromatic hydrocarbons (PAHs),[3] as solvents in coal liquification,[4] and as fluorogens.[5] Direct electrophilic aromatic substitution on the pyrene ring occurs almost exclusively at the electron rich 1-position,[6] leading to 1-, 1,3-, 1,6-, 1,8-, 1,3,6-, and 1,3,6,8-substituted products. Only *tert*-butylation is directed to the 2- (and 7-) position(s).[7] Pyrenes substituted in the 2- (and 7-) position(s) have been sought as intermediates for the synthesis of higher PAHs[8,910,11] and as monomers for the synthesis of electroluminescent polymers.[12] Synthesis of 2,7-substituted pyrenes requires indirect routes such as the base-promoted decomposition of diphthaloylpyrenes,[13] oxidative ring fusion of substituted *m*-cyclophanes,[14] photochemical ring closure of 2,2′-divinylbiphenyls,[12] and substitution of 4,5,9,10-tetrahydropyrene, **2**, followed by aromatization.[9,10,11,15] Previous syntheses of **2** have been limited in scale or hampered by side reactions. Methods for preparation of **2** include oxidation of *m*-cyclophanes,[16] ring closure of biphenyl-2,2′-bis(acetic acid),[17] photochemical ring closure of 2,2′-divinylbiphenyl,[18] and electrochemical[19] and photochemical[8] reduction of pyrene. Reported procedures[4,20,21] for the catalytic hydrogenation of pyrene to **2** lead to mixtures of products that are difficult to separate.[22,23] A commonly practiced alternative to hydrogenation is the cumbersome procedure of metal−ammonia reduction[24] of pyrene to afford the unstable 1,9-dihydropyrene, acid isomerization to the more stable 4,5-dihydropyrene,[25,26] and subsequent reduction by catalytic hydrogenation[9,20,28] or metal−ammonia reduction to afford **2**.[27,28] Here we report an efficient procedure for the direct hydrogenation of pyrene to prepare **2** on a multigram scale. Electrophilic aromatic substitution of **2** takes place selectively at the 2- and 7-positions to give disubstituted analogues. The only previously reported dicarboxyl-functionalized 2,7-pyrenes were made by an eight-step synthesis via cleavage of diphthaloylpyrenes[13] and by a long route via oxidative coupling of substituted *m*-cyclophanes.[29] We report a simple conversion of **2** to 2,7-diacetyl-4,5,9,10-tetrahydropyrene, **4**, followed by oxidation, methylation, and aromatization to give dimethyl 2,7-pyrenedicarboxylate, **8**, on a preparative scale. The synthesis of significant quantities of **2**, **4**, and **8** could

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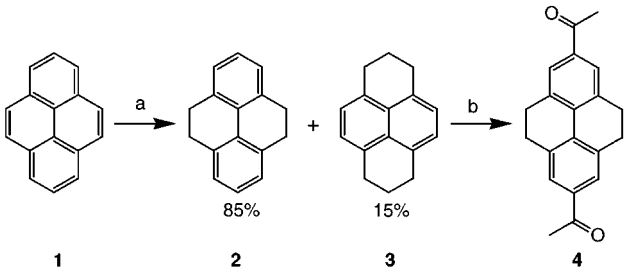
**Scheme 1**[a]




(a) $H_2$ (45 psi.), 10% Pd/C, EtOAc, 3 d (b) AcCl, $AlCl_3$, $CH_2Cl_2$, 3 h

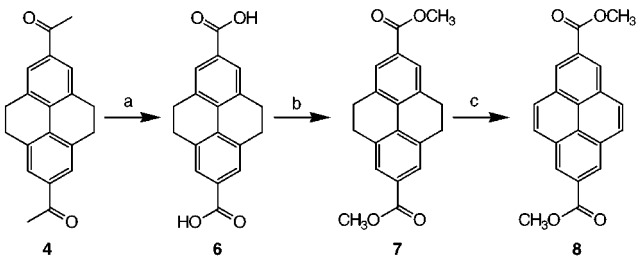
facilitate the synthesis of new larger fused aromatics for cancer research and provide new difunctional monomers.

## Results and Discussion

Catalytic hydrogenation of commercially available pyrene (Aldrich) with 10% Pd on carbon in dry EtOAc[20] gave no reaction, similar to the results reported elswhere.[28] However, the hydrogenation proceeded smoothly if the pyrene was first desulfurized by treatment with Raney nickel in EtOAc. This simple desulfurization procedure proved easier than the careful recrystallization and column chromatography reported by others.[26,28] A commonly cited procedure for hydrogenation (10% Pd/C, EtOAc, 50 psi for 65 h) is reported to yield a 45/45/10 mixture of tetrahydropyrene (**2**), dihydropyrene, and pyrene (**1**).[20] By optimizing the conditions of this procedure (10% Pd/C, desulfurized pyrene, *wet* EtOAc, 40 psi for 64−72 h), we obtained a 85/15 mixture of tetrahydropyene (**2**) and overreduced product hexahydropyene (**3**). The use of Raney nickel as an aqueous slurry for the desulfurization of pyrene introduces water (ca. 0.5%) to the reaction mixture. We found that drying the pyrene/EtOAc solution over $MgSO_4$ increases the extent of overreduction (i.e., formation of **3**). This is the most selective hydrogenation of pyrene to tetrahydropyrene to our knowledge and avoids the difficulties involved in separating the product from unreacted starting material and underreduced products (i.e., dihydropyrene). Rather than separate **2** from the overreduced byproduct **3** by charge-transfer chromatography,[22] we chose to convert the crude mixture to the diacetyl compounds **4** and **5**, Scheme 1.

Functionalization of **2** in the 2- and 7-positions was performed by diacylating according to a published procedure.[9] Trituration of the crude product once with 10% (v/v) $Et_2O$ in benzene provided pure **4** in good yield. It was through purification and identification of the byproduct of this procedure, **5** (from the soluble fraction of the crude mixture), that we were able to identify the byproduct of the hydrogenation mixture as 1,2,3,6,7,8-hexahydropyrene, **3**. This simple purification, coupled with the efficient direct hydrogenation of pyrene, is a significant advancement in the synthetic availability of 2,7-disubstituted pyrenes. Oxidation of **4** to the diacid was performed using iodine in pyridine[30] or by NaOBr.[31] Methylation ($CH_3I$, $Li_2CO_3$, DMF)[32] gave the dimethyl ester **7** in moderate yield (not optimized), Scheme 2. This method has proved particularly useful to us for the

**Scheme 2**[a]




(a) $Br_2$, NaOH, dioxane/water (b) $Li_2CO_3$, MeI, DMF (c) $Br_2$, $CS_2$

methylation of aromatic diacids which are insoluble in acidic methanol at reflux.[33] Aromatization of **7** (DDQ in benzene)[9] afforded quantitative conversion to **8**, but separation from the reduced DDQ proved difficult and led to low isolated yields. However, treatment of **7** with bromine in $CS_2$[10] gave **8** in high yield with a simple procedure for workup and purification.

The method described above provides an improved synthesis of 4,5,9,10-tetrahydropyrene, **2**, for use as an intermediate in the synthesis of various 2,7-disubstituted pyrenes. Electrophilic aromatic substitution (illustrated here by Friedel−Crafts acylation, followed by oxidation of the methyl ketone to the corresponding carboxylic acid) and subsequent aromatization provides 2,7-disubstituted pyrenes. The synthesis of dimethyl 2,7-pyrenedicarboxylate shown here has been scaled-up to prepare tens of grams of product in 5 steps (33% overall yield, not optimized) with minimal purification throughout.

## Experimental Section

**4,5,9,10-Tetrahydropyrene, 2.** Raney nickel (ca. 10 g as a thick water slurry) was added to a solution of pyrene (21.0 g, 104 mmol) in EtOAc (250 mL), and the mixture was stirred vigorously for 2 d. The mixture was vacuum filtered (caution was exercised not to let the Raney nickel become dry). The filtrate was hydrogenated at 40−45 psi in the presence of palladium on carbon (5.0 g of 10% Pd/C) for 64−72 h. The mixture was filtered through a fine fritted glass filter, and the solvent was removed under reduced pressure to give crude product (quantitative) containing 4,5,9,10-tetrahydropyrene, **2**, and ca. 15% of 4,5,9,10-hexahydropyrene, **3**. The crude product was used without further purification. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.89 (s, 8H, benzylic), 7.1 (m, 6H, Ar H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 28.3, 125.9, 127.0, 130.6, 135.4. IR ($CHCl_3$): 3065, 3048, 2941, 2833, 1605, 1451, 914, 730 cm$^{-1}$. *1,2,3,6,7,8-Hexahydropyrene* (present in the mixture): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.03 (t, 4H, $J$ = 6.1 Hz, $H_{2,7}$), 3.05 (t, 8H, $J$ = 6.1 Hz, $H_{1,3,6,8}$), 7.10 (s, 4H, Ar H).

**2,7-Diacetyl-4,5,9,10-tetrahydropyrene, 4, and 4,10-Diacetyl-1,2,3,6,7,8-hexahydropyrene, 5.** A solution of crude 4,5,9,10-tetrahydropyrene (40.0 g, 0.194 mol) containing ca. 15% **3** in freshly distilled $CH_2Cl_2$ (1 L) was added dropwise under $N_2$ to a mixture of $AlCl_3$ (64.6 g, 0.485 mol) and acetyl chloride (345 mL, 4.85 mol) at 0 °C. The mixture was stirred at 0 °C for an additional 30 min and at room temperature 2 h. The dark brown solution was poured onto ice (ca. 1.5 L) and stirred overnight. The layers were separated, and the aqueous phase was washed with $CH_2Cl_2$ (1 × 300 mL). The combined organic layers were washed with 5% NaOH (2 × 300 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was triturated with ca. 100 mL of 10% $Et_2O$ in benzene to give 2,7-diacetyl-4,5,9,10-tetrahydropyrene, **4**, as an off-white solid (30 g, 53% from pyrene). Mp: 226−228 °C (lit.[9] mp 225−

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227 °C). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.60 (s, 6H, methyl), 2.95 (s, 8H, benzylic), 7.68 (s, 4H, Ar H). IR (KBr) 2881, 1683 cm$^{-1}$.

The solvent was removed from the filtrate of the trituration, and the residue was recrystallized from $CH_2Cl_2$ and then toluene to give 4,10-diacetyl-1,2,3,6,7,8-hexahydropyrene, **5**, as a colorless crystalline solid (333 mg, 20% yield based on 1,2,3,6,7,8-hexahydropyrene present in the crude mixture). Mp: 181.0−183.5 °C (lit.[2] mp 182 °C). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39 (s, 2H, Ar H), 3.21 (t, 4H, $J$ = 6.2 Hz, benzylic-$H_{1,3\text{ or }6,8}$), 3.09 (t, 4H, $J$ = 6.2 Hz, benzylic $H_{1,3\text{ or }6,8}$), 2.62 (s, 6H, methyl), 2.05 (quintet, 2H, $J$ = 6.2 Hz, methylene $H_{2\text{ or }7}$), 1.94 (quintet, 2H, $J$ = 6.2 Hz, methylene $H_{2\text{ or }7}$). IR (KBr): 2987, 2861, 1690, 1591, 1256, 1131, 887 cm$^{-1}$.

**4,5,9,10-Tetrahydropyene-2,7-dicarboxylic acid, 6. (a) $I_2$/Pyridine Route.** A mixture of 2,7-diacetyl-4,5,9,10-tetrahydropyrene, **4** (20 g, 68 mmol), and $I_2$ (37.9 g, 0.150 mol) in 300 mL of freshly distilled pyridine was heated at reflux under $N_2$ for 45 min. More $I_2$ (17.2 g, 68 mmol) was added, and the mixture was heated at reflux for an additional 1 h and then stirred for 21 h at room temperature. The volume was reduced to ca. 50 mL under reduced pressure. Saturated NaOH (50 mL) and 20% ethanol/water (700 mL) were added, and the solution was heated at reflux for 2 h. The dark brown solution was cooled to room temperature and vacuum filtered. The filtrate was acidified with concentrated HCl, and the brown precipitate was collected by vacuum filtration to give 4,5,9,10-tetrahydropyrene-2,7-dicarboxylic acid (19.4 g, 97%). Mp: >300 °C dec. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.71 (s, 4H, Ar H), 2.90 (s, 8H, $CH_2$). IR (KBr): 3374, 1683, 1604, 1308 cm$^{-1}$.

**(b) NaOBr Route.** A solution of $Br_2$ (43 mL, 0.84 mol) and NaOH (93.8 g, 2.34 mol) in $H_2O$ (635 mL) was added over 30 min to a solution of **4** (26.01 g, 89.59 mmol) in 1,4-dioxane (1.2 L) at room temperature and the mixture was stirred for 4 h at 60 °C. A solution of 5% $Na_2S_2O_4$ (100 mL) was added, the mixture was vacuum filtered, and the filtrate was acidified with concentrated HCl. The resulting white precipitate was collected by vacuum filtration and dried in a vacuum oven to give **6** (28.24 g, 100%) as a white solid.

**Dimethyl 4,5,9,10-Tetrahydropyene-2,7-dicarboxylate, 7.** A mixture of 4,5,9,10-tetrahydropyrene-2,7-dicarboxylic acid, **6** (20.86 g, 70.95 mmol), $Li_2CO_3$ (31.46 g, 425.7 mmol), and methyl iodide (88 mL, 1.4 mol) in *N*,*N*-dimethylformamide (1 L) was stirred at room temperature for 24 h. The mixture was added to 1 M HCl (1.2 L), and the yellow precipitate was collected by vacuum filtration and dried under reduced pressure to give dimethyl 4,5,9,10-tetrahydropyrene-2,7-dicarboxylate, **7** (14.03 g, 61%), as a pale yellow solid. Mp: 209−212 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.93 (s, 4H, $CH_2$), 3.91 (s, 6H, methyl), 7.76 (s, 4H, Ar H). IR (KBr): 2956, 1720, 1429, 1290, 1206, 768 cm$^{-1}$.

**Dimethyl 2,7-Pyrenedicarboxylate, 8. (a) ($Br_2$/$CS_2$ Route).** A solution of $Br_2$ (6.28 mL) in $CS_2$ (1.25 L) was added dropwise to a solution of dimethyl 4,5,9,10-tetrahydropyene-2,7-dicarboxylate, **7** (16.4 g, 50.9 mmol), in $CS_2$ (1.25 L) at 0 °C over 1 h. The solution was stirred overnight at room temperature. A solution of 5% $Na_2S_2O_3$ (250 mL) followed by $H_2O$ (250 mL) was added with vigorous stirring, the layers were separated, and the organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure to give dimethyl 2,7-pyrenedicarboxylate, **8**, as a yellow solid (15.86 g, 98%). Mp: 287−289 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.08 (s, 6H, methyl), 8.16 (s, 4H, Ar $H_{4,5,9,10}$), 8.85 (s, 4H, Ar $H_{1,3,6,8}$). IR (KBr): 2953, 1723, 1302, 1235 cm$^{-1}$. Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.47; H, 4.43. Found: C, 75.63; H, 4.44.

**(b) DDQ Route.** A solution of dimethyl 4,5,9,10-tetrahydropyrene-2,7-dicarboxylate, **7** (6.09 g, 20.7 mmol), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (17.0 g, 74.9 mmol) in benzene (250 mL) was heated to reflux for 3 d. The mixture was filtered through a fine fritted glass filter, and the solid was triturated with 5% NaOH (500 mL) and refiltered. The filtrate was extracted with $CH_2Cl_2$ (1 × 300 mL, 1 × 100 mL), and the combined extracts were washed with 5% NaOH (300 mL) and $H_2O$ (300 mL). After drying of the sample over $MgSO_4$, the solvent was removed under reduced pressure to give dimethyl 2,7-pyrenedicarboxylate, **8** (1.41 g, 26%), as a pale yellow solid.

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