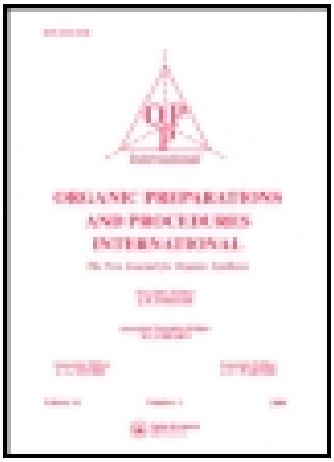

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

A FACILE SYNTHESIS OF 9-HYDROXYBENZO[a]PYRENE

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Published online: 09 Feb 2009.

To cite this article: Shoujun Chen, Chunhua Wang & Peter P. Fu (1997) A FACILE SYNTHESIS OF 9-HYDROXYBENZO[a]PYRENE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 29:1, 131-134, DOI: 10.1080/00304949709355177

To link to this article: http://dx.doi.org/10.1080/00304949709355177

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8. An Aldrich "coffee pot" Kugelrohr, cat. Z10,046-3, was used. The receiving bulb was cooled in an ice bath.

9. The product at this point exhibited satisfactory ^{1}H NMR and GC-MS spectra, and had a mp. 100-102°.

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A FACILE SYNTHESIS OF 9-HYDROXYBENZO[a]PYRENE

Submitted by (03/05/96) Shoujun Chen*†, Chunhua Wang and Peter P. Fu

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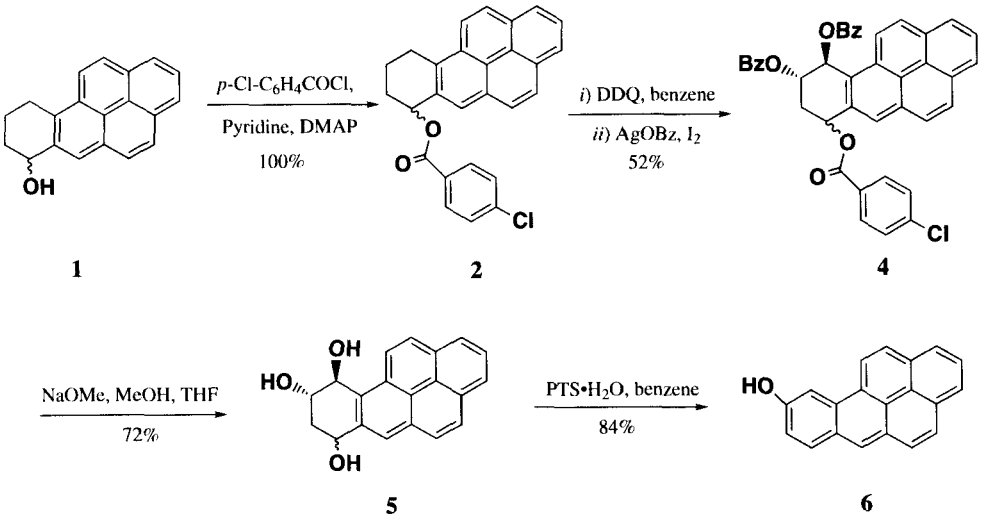
One important way to elucidate the mechanisms of metabolic activation of polyaromatic hydrocarbons is to study the DNA adducts formed thereof.[1] Synthetic DNA adducts are also molecular biomarkers for measuring human exposures to chemical carcinogens.[2] It is well documented that the *bay-region* diol epoxides of BAP** are the principal active forms of this carcinogen[3] and the key step in its tumor initiation is thought to be the covalent binding of these epoxides to DNA.[4] Although the corresponding K-region epoxides were shown not to be responsible for the binding to DNA found in cellular systems,[5] evidence indicated that 9-hydroxy-BAP-4,5-oxide might also be an active metabolite of BAP which could bind to nucleic acids *in vivo*.[6-8] In order to assess the human health risk posed by BAP, it is necessary and timely to synthesize the DNA adduct of 9-hydroxy-BAP-4,5-oxide as a biomarker. The key intermediate is 9-hydroxy BAP (**6**) which was synthesized by Harvey,[6] Yagi[9] and Sims[10] from 9,10-dihydrobenzo(a)pyren-7(8H)-one. However, these syntheses require either several steps under harsh conditions[9,10] or the use of expensive and hazardous osmium tetroxide.[6]

We now report here a facile synthetic route to 9-hydroxy-BAP from a relatively more economical starting material, 7-hydroxy-7,8,9,10-tetrahydro-BAP (**1**) which was converted to 7-*p*-chlorobenzoyloxy-7,8,9,10-tetrahydro-BAP (**2**) quantitatively by treatment with *p*-chlorobenzoyl chloride, pyridine and catalytic amount of DMAP in chloroform at room temperature. 7-*p*-Chlorobenzoyloxy-7,8-dihydro-BAP (**3**) can be obtained selectively when **2** is treated with DDQ in hot benzene. The process can be easily monitored by TLC on silica gel.



It should be pointed out that, in our hands, both 7,8,9,10-tetrahydro-BAP and the 7-acetoxy derivative of **2** lack this selectivity. Treatment of either compounds with DDQ leads to the formation of BAP without control. The arene **3** thus obtained can be employed in the Prevost reaction without isolation to give **4** in a "one pot" procedure. After debenzoylation[11] and dehydration[12,13] in the usual manner, 9-hydroxy-BAP (**6**) can be obtained with a total yield of 31% (from **1**).The structure of **6** was confirmed by the comparison of its UV/VIS and proton NMR spectra with those of an authentic sample prepared through other methods.[6,14] The experimental result obtained here is consistent with those predicted by molecular orbital theoretical calculation.[15]

EXPERIMENTAL SECTION

Melting points were measured on an Electrothermal melting point apparatus and are not corrected. UV/VIS spectra were obtained on a Beckman DU-65 spectrophotometer; ^{1}H-NMR spectra were taken with a Varian Gemini-300 instruments. Silver benzoate and 7,8,9,10-tetrahydro-7-hydroxy BAP (**1**) were purchased from Aldrich Chem. Co. The former was recrystallized from water before use.

7-(*p*-Chlorobenzoyloxy)-7,8,9,10-tetrahydro-BAP (2) was prepared from **1** and *p*-chlorobenzoyl chloride in chloroform in quantitative yield, mp 154-156°;

Anal. Calcd. for $C_{27}H_{19}ClO_2$: C, 78.92; H, 4.67. Found: C, 78.57; H, 4.67

^{1}H NMR($CDCl_3$): δ 2.12-2.24 (m, 2 H_9), 3.30-3.44 (m, 2 H_8), 3.61-3.72 (dt, 2 H_{10}), 6.66-6.72 (t, 1 H_7), 7.3-8.3 (m, 12 H_{aryl}).

7-(*p*-Chlorobenzoyloxy)-9,10-dibenzoyloxy-7,8,9,10-tetrahydrobenzo-[a]pyrene (4).- DDQ (0.12 g, 0.53 mmol) was added to a hot solution of **2** (0.22g, 0.54 mmol) in benzene (20 mL) under N_2, and the mixture was stirred at 70°. The progress of the reaction was monitored by TLC. After consumption of the starting material (*ca* 40 min), the hot solution was filtered quickly through a column of silica gel and Celite, and washed thoroughly with benzene. The filtrate was concentrated to *ca* 20 mL

under reduced pressure without heating. In another flask, a mixture of silver benzoate (0.28g, 1.2 mmol) and iodine (0.14 g, 0.55 mmol) in benzene (20 mL) was heated to reflux for 30 min. To this yellow suspension was added the above benzene solution of **3** and the reaction mixture was heated to reflux for 1hr. After being cooled, the reaction mixture was filtered through a layer of celite. The filtrate was concentrated, chromatographed on silica gel and eluted with a mixture of hexane and ethyl acetate (10:1, v/v) to give 0.18g (52% based on **2**) of **4** as a light yellow solid, mp 201-203°;

Anal. Calcd. for $C_{41}H_{27}ClO_4$: C, 79.53; H, 4.40. Found: C, 79.34; H, 4.52

^{1}H NMR ($CDCl_3$): δ 0.8-0.9 (m, 1 H_{8a}), 1.2-1.3 (m, 1 H_{8b}), 6.0 (d, 1 H_{10}, J = 2.4 Hz), 6.9-7.0 (m, 1 H_9), 7.2-8.4 (m, 25 H, H_{aryl}+H_7).

7,8,9-Trihydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene (5).- To a stirred solution of **4** (0.18 g, 0.28 mmol) in THF (5 mL) and methanol (95 mL) was added sodium methoxide (86 mg, 1.6 mmol) and the resultant solution was heated to reflux for 0.5 hr, and then cooled to room temperature; 15 mL of cold water was added to the reaction solution which was stirred at rt for 1 hr and extracted with EtOAc (3 x 15 mL). The EtOAc extracts was washed with water (2 x 10 mL). Removal of EtOAc under reduced pressure followed by chromatography on Florisil^R afforded 0.06 g (72%) of **5** as a white solid, mp 215-216° (dec);

Anal. Calcd. for $C_{20}H_{16}O_3$: C, 78.92; H, 5.31. Found: C, 78.61; H, 5.49

^{1}H NMR (CD_3OD): δ 2.2-2.3 (m, 1 H_{8a}), 2.55-2.65 (m, 1 H_{8b}), 4.35-4.45 (m, 1 H_9), 5.23 (t, 1 H_7, J = 4.7 Hz), 5.58 (d, 1 H_{10}, J = 3.8 Hz), 8.0-8.3 (m, 9H, 8 H_{aryl} +OH), 8.61(s, 1H, OH), 8.64 (s, 1H, OH).

9-Hydroxybenzo[a]pyrene (6).- A solution of **5** (54 mg, 0.18 mmol) and PTS·H_2O (34 mg, 0.18 mmol) in dry benzene (20 mL) was heated to reflux under an atmosphere of argon for 1 hr, and it was then allowed to cool to rt, washed with water (2 x 10 mL), dilute sodium bicarbonate solution (1 x 10 mL) and water (10 mL). Evaporation of the benzene solution followed by chromatography on silica gel afforded 0.04 g (84%) of **6** as a crystalline solid, mp 194-196°, lit.[10] mp 196°; UV/VIS spectra were identical with those reported.[10,16] ^{1}H NMR (THF-d_8): δ 7.44 (d, 1 H_8, J = 8Hz), 7.80-8.26 (m, 7 H), 8.39 (s, 1 H_{10}), 8.51 (s, 1 H_6), 9.01 (d, 1 H_{11}, J = 9Hz), 9.11 (br, 1 H, OH).

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** The abbreviations used are: BAP, Benzo[a]pyrene; DDQ, 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; DMAP, 4-Dimethylaminopyridine; EtOAc, Ethyl acetate; PTS·H_2O, *p*-Toluenesulfonic acid hydrate.

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14. Compound **6** was converted to 9-acetoxy-BAP in 92% yield by stirring with Ac_2O and pyridine at rt for 12 hrs. 9-Acetoxy-BAP has been previously used as a precursor for the preparation of 9-hydroxy-BAP.[6]

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