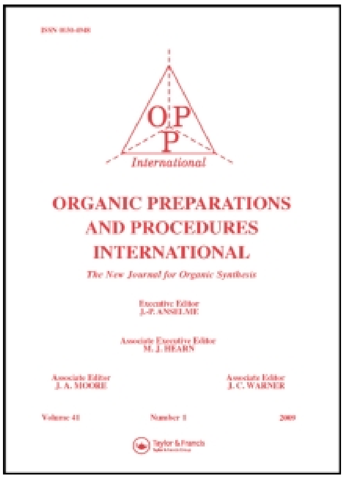

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NEW AND RENEWED SYNTHESES OF 10-PHENYLANTHRONE AND 10-HYDROXY-10-PHENYLANTHRONE

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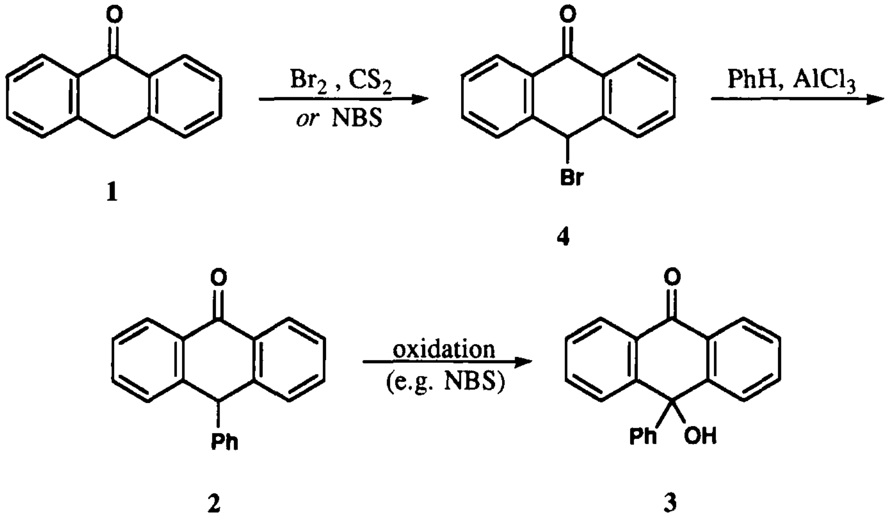
The emergence of organic chemistry as a recognized discipline in the latter half of the nineteenth century was intimately linked to developments in anthrone (**1**) chemistry.[1] This paper describes improved syntheses of 10-phenylanthrone (**2**) and 10-hydroxy-10-phenylanthrone (**3**), both prepared by Baeyer in 1880.[2]

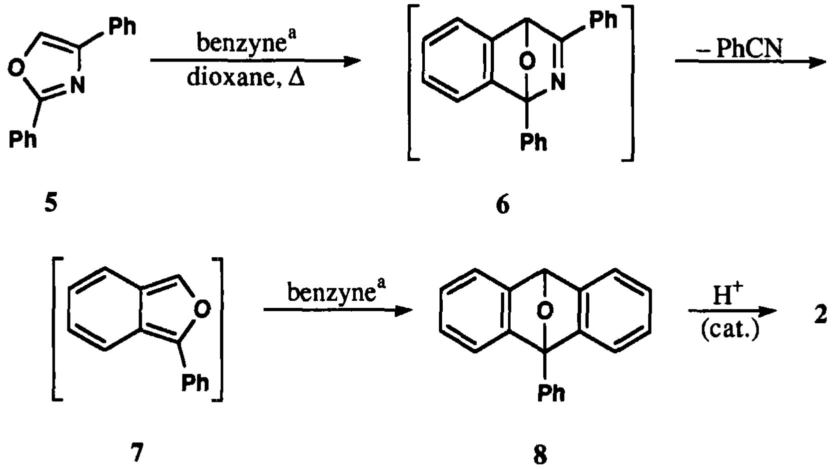
In previously published work involving 10-phenylanthrone,[3] we initially chose to follow a more convenient method[4] which begins with the direct bromination of anthrone (Br_2/CS_2) (**Scheme 1**). The present work reports that the use of NBS (N-bromosuccinimide) in either carbon tetrachloride or benzene results in the formation of 10-bromoanthrone (**4**) in higher yield (91%) and greater purity than the Br_2/CS_2 method. 10-Phenylanthrone prepared from this crude material is suitable for synthetic elaboration without further purification.[5] 10-Hydroxy-10-phenylanthrone (**3**) was first



Scheme 1

prepared by the oxidation of 10-phenylanthrone (**2**).[2,6] While attempting to prepare 10-bromo-10-phenylanthrone,[7] we discovered that NBS also serves to effect this oxidation (in 36% yield). Presumably the initially formed bromide is hydrolyzed during workup.[8]

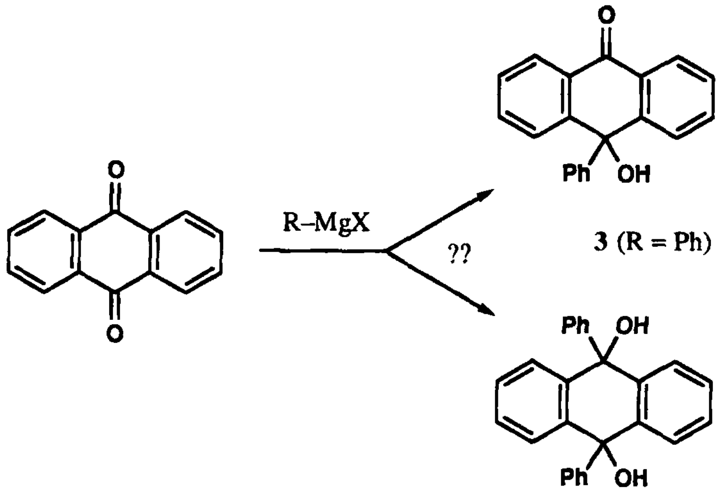
We have also developed an alternate synthetic strategy (**Scheme 2**) based on cycloaddition reactions[9,10] Benzyne, generated *in situ* by the simultaneous addition of anthranilic acid and isoamyl nitrite to refluxing dioxane (101°), serves as a dienophile twice in this one-pot reaction sequence. In the first Diels-Alder reaction, benzyne and 2,4-diphenyloxazole (**5**) react to give an unstable adduct (**6**) which in turn extrudes benzonitrile in a *retro* Diels-Alder reaction. 1-Phenylisobenzofuran (**7**) reacts with a second equivalent of benzyne to give a bridged anthracene (**8**) in 37% yield. Subsequent acid-catalyzed rearrangement of **8** leads to the *quantitative* formation of 10-phenylanthrone (**2**) (26% overall yield from benzamide, the precursor of **5**).



a) From anthranilic and isoamyl nitrite

Scheme 2

The most direct route to 10-hydroxy-10-phenylanthrone is the addition of a phenyl carbanion to anthraquinone (**Scheme 3**). This general route has been known for some time, although there has been a certain degree of controversy about the nature of the products. Cohen and coworkers[11] found that unhindered Grignard reagents (methyl, ethyl, *n*-propyl), when used in excess, gave two isomeric *cis*-9,10-dialkyl-9,10-dihydroxy-9,10-dihydroanthracenes as the major products; residual anthraquinone was always present as well as smaller quantities of the monoadducts. With an excess of more hindered Grignard reagent (isopropyl, *tert*-butyl, neopentyl), yields were typically lower but the diadducts isolated were 3,10-dialkyl-10-hydroxyanthrones (the products of 1,6 addition reactions, *not* the expected 9,10-diaddition products). We have reinvestigated the reaction of phenylmagnesium bromide with anthraquinone[12] in an attempt to optimize the yield of the monoaddition product **3**.



Scheme 3

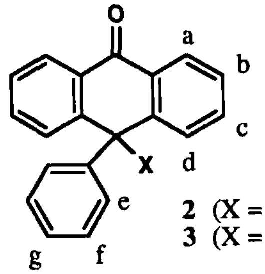
The use of molar ratios ranging from 1:1 to 1:10 (excess Grignard) was investigated. A ratio of 1:2 appears best, leading to a 29% yield of **3**. The stoichiometric 1:1 ratio gave lower yields; the 1:10 ratio lead primarily to diadduct, with no monoadduct isolated. In all cases, residual anthraquinone was isolated. No monoadduct could be isolated in the reactions (in ether) of phenyllithium with anthraquinone.

In summary, NBS is recommended over direct bromination for the preparation of 10-bromoanthrone (**4**). It is also a clean alternative for the oxidation of 10-phenylanthrone (**2**) to 10-hydroxy-10-phenylanthrone (**3**), but the one-step Grignard method (**Scheme 3**), despite its limitations, is preferred in this case. Compound **2** is best prepared by the isobenzofuran route (**Scheme 3**), although the syringe pump required in this method may not be available in all laboratories. The conceptually direct route (**Scheme 1**) for the synthesis of **2** is a reasonable alternative.

EXPERIMENTAL SECTION

Unless stated otherwise, all reactions were run under a nitrogen atmosphere. Anhydrous ether (EM®) from freshly opened cans was used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Melting points were determined with an Electrothermal capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 710B Infrared Spectrophotometer. ^{1}H NMR spectra were determined on Varian T60 (60 MHz), Varian EM 390 (90 MHz), GE QE-300 (300 MHz), Bruker AM500 (300 MHz), or Bruker AM500 (500 MHz) spectrometers. ^{13}C NMR spectra were obtained on GE QE-300 (75 MHz) or Bruker AM500 (125 MHz) spectrometers. GC/MS data were collected on a Finnigan MAT 8230. Elemental analyses were performed by Chemical Analytical Services (UC Berkeley) and Syntex Research.

10-Bromoanthrone (4).- Anthrone (**1**) (1.9 g, 10.0 mmol) and N-bromosuccinimide (NBS) (1.96 g, 11.0 mmol) were dissolved in benzene (150 mL). The stirred solution was irradiated with a 60W lamp for 3 h, then washed successively with saturated sodium bicarbonate (2 x 100 mL), water (2 x 100 mL), then saturated sodium chloride (2 x 100 mL). After drying (MgSO$_4$), the solution was concentrated to give a brownish yellow solid (2.48 g, 91%), mp 139-145° (dec.), lit.[13] mp 148°, suitable for further reaction. An analytical sample, mp. 122° (dec.), was obtained by recrystallization from chloroform-hexane. IR (nujol) 1655, 1595 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.64 (s, 1 H), 7.52 (t, J_{ortho} = 7.5 Hz, 2 H$_b$), 7.64 (t, J_{ortho} = 7.5 Hz, 2 H$_c$), 7.72 (d, J_{cd} =7.5 Hz, 2 H$_d$), 8.27 (d, J_{ab} =7.5 Hz, 2 H$_a$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 43.75 (d), 127.87 (d), 129.22 (d), 130.11 (d), 131.12 (s), 133.57 (d), 141.00 (s), 182.96 (s); MS (EI) *m/z*: 271 ((M-H), 20), 193 (100); MS (CI) *m/z*: 307 ((M+N$_2$H$_7$), 24), 290 ((M+NH$_4$), 44), 273 ((M+H), 15).



2 (X = H)
3 (X = OH)

10-Hydroxy-10-phenylanthrone (3) by NBS Oxidation.- Phenylanthrone (2) (1.35 g, 5 mmol) and NBS (0.979 g, 5.5 mmol) were dissolved in benzene (100 mL). The stirred solution was irradiated with a 60W lamp overnight, then washed successively with saturated sodium thiosulfate (2 x 100 mL, to remove excess NBS), saturated sodium carbonate (2 x 100 mL, to remove succinimide), water (2 x 100 mL), and saturated sodium chloride (2 x 100 mL). After drying (MgSO$_4$), the solution was concentrated using a rotary evaporator (without any heating) until it reached one-fifth of its original volume. The slightly brownish precipitate which separated from the deep brown mother liquor had a crude mp 212-214°. Recrystallization from chloroform-hexane gave white crystals (36%), mp 218°, lit.[8] mp 213-214°; IR (KBr): 1650, 1600 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.14 (tt, J_{fg} = 7.5 Hz, J_{eg} = 1.0 Hz, 1 H$_g$), 7.22 (t, J_{ortho} = 7.5 Hz, 2 H$_f$), 7.35 (dd, J_{ef} = 8.0 Hz, J_{eg} = 1.0 Hz, 2 H$_e$), 7.42 (dt, J_{ortho} = 7.5 Hz, J_{bd} = 1.0 Hz, 2 H$_b$), 7.56 (dt, J_{ortho} = 7.5 Hz, J_{ac} = 1.5 Hz, 2 H$_c$), 7.62 (dd, J_{cd} = 8.0 Hz, J_{bd} = 1.0 Hz, 2 H$_d$), 8.25 (dd, J_{ab} = 8.0 Hz, J_{ac} = 1.5 Hz, 2 H$_a$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 73.10 (s), 125.43 (d), 126.86 (d), 126.93 (d), 128.24 (d), 128.38 (d), 129.80 (s), 134.12 (d), 145.93 (s), 147.73 (s), 183.74 (s); MS (EI) *m/z*: 286 (M$^+$, 68), 268 (20), 209 (100); MS (CI) *m/z*: 304 ((M+NH$_4$), 16), 287((M+H), 16), 269 (100).

10-Hydroxy-10-phenylanthrone (3) by Grignard Addition.- All attempts were conducted in ether at room temperature. Phenylmagnesium bromide, [prepared by the addition of a solution of bromobenzene (7.85 g, 50 mmol) in ether (150 mL) to magnesium metal (1.23 g, 50 mmol)] was added at 0° by cannula to a stirred suspension of anthraquinone (10.4 g, 50 mmol) in ether (350 mL). Despite the initial exothermicity of the reaction, it never reached completion. After 1-2 days stirring, the reaction mixture was extracted with saturated ammonium chloride (2 x 250 mL); a thick emulsion necessitated a back extraction of the ether layer with water (2 x 200 mL). Careful partial evaporation of the organic layer lead to the precipitation of most of the residual anthraquinone. Removal of the remaining ether followed by recrystallization from chloroform-hexane gave several crops of white crystals (29%), mp. 213.3-214.5°, lit.[8] mp 213-214°. The product was identical to that prepared by the NBS method.

2,4-Diphenyloxazole (5).- The century-old methodology of Blumlein[14] and Lewy[15] is still unsurpassed. Benzamide (12.11 g, 0.1 mol) and α-bromoacetophenone (9.95 g, 0.05 mol) were added to a 125-mL Erlenmeyer flask. The mixture was stirred and heated at 130-140° for 3-4 hrs. The reaction mixture was cooled, then partitioned between ethyl ethereal (100 mL) and water (40 mL). The aqueous layer was extracted with ethyl ether (2 x 50 mL). The combined ether layers were dried ($MgSO_4$), then concentrated. The crude product (16.5 g) was dissolved in ether (100 mL). Residual benzamide (2.27 g, insoluble in ether) was removed by filtration. The ethereal solution was concentrated to a volume of 20 mL, to yield the light yellow crystals (3.99 g) which were washed with cold ethanol. Purification by column chromatography (aluminum oxide, 10% ether in hexane) yielded another 3.80 g of **5**. The total yield was 7.80 g (70%). Analytical samples were recrystallized from hexane or ethanol, mp 103.5-104°, lit.[16] mp 103°. IR (nujol): 2950, 1580, 1140, 1080, 780, 760, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25-7.50 (m, 6 H), 7.75-7.85 (m, 2 H), 7.91 (s, 1 H), 8.05-8.15 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 125.73 (d), 126.61 (d), 127.60 (s), 128.20 (d), 128.84 (two overlapping resonances, both doublets), 130.48 (d), 131.23 (s), 133.54 (d), 142.09 (s), 162.01 (s); MS (EI) *m/z*: 221 (M^+, 100), 193 (82), 89 (97).

9,10-Epoxy-9,10-dihydro-10-phenylanthracene (8).- The procedure of Reddy and Bhatt[6] was followed. A three-necked flask fitted with a reflux condenser was charged with 2,4-diphenyloxazole (**5**) (2.21 g, 10 mmol) and dioxane (20 mL). The solution was brought to reflux, then solutions of anthranilic acid (4.11 g, 30 mmol) in dioxane (20 mL) and isoamyl nitrite (3.35 g, 30 mmol) in dioxane (20 mL) were added *simultaneously via* syringe pump over a period of 1 hr; heating was continued for 1 hr after the addition was completed. The mixture was cooled, then ether (50 mL) was added, followed by 3 M sodium hydroxide (ca. 50 mL). The layers were separated and the aqueous phase was washed twice with small volumes of ether. The combined organic layers were dried ($MgSO_4$) then concentrated to give a dark oily residue consisted mainly of compound **8** and benzonitrile (by NMR). Recrystallization from ethanol-water gave colorless crystals, 1.01 g (37%), mp 152-153°; IR (nujol): 2960, 1450, 1380, 1240, 1180, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.18 (s, 1 H), 6.95-7.10 (m, 4 H), 7.25-7.60 (m, 7 H), 7.84 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.37 (d), 92 (s), 120.33 (two overlapping resonances-both doublets), 125.76 (d), 125.92 (d), 126.41 (d), 128.18 (d), 128.72 (d), 135.03 (s), 149.13 (s), one quaternary carbon not observed.

Anal. Calcd for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.76; H, 4.91

10-Phenylanthrone (2).- One small crystal of toluenesulfonic acid was added to a solution of **8** (20 mg, 0.07 mmol) in methylene chloride (0.5 mL); the solution turned red, then green. After about 0.5 hr at room temperature, the solvent was removed with a gentle stream of nitrogen. The product was obtained in 100% yield as a single spot by TLC (silica gel, 10% ether in hexane; there was one additional small spot on the baseline due to residual catalyst, toluenesulfonic acid), mp 80° (dec.), lit.[3] 139-140°). Except for its lower mp (also due to TsOH), this compound was identical to that prepared by the method of Branz and Carr:[3] ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.42 (s, 1 H), 7.11 (d, J_{cd} =8.0 Hz, 2 H_d), 7.20 (t, J_{fg} = 7.5 Hz, 1 H_g), 7.24 -7.30 (m, 2 H_e and 2 H_f), 7.42 (t, J_{ortho} = 7.5 Hz, 2 H_c), 7.49 (dt, J_{ortho} = 7.5 Hz, J_{bd} = 1 Hz, 2 H_b), 8.39 (dd, 2H, J_{ab} =7.5 Hz, J_{ac} = 1 Hz, 2 H_a); ^{13}C NMR (125 MHz, $CDCl_3$): δ 48.44 (d), 126.92 (d), 127.16 (d), 127.29 (d), 128.86 (d), 129.03 (d), 129.66 (d), 131.14 (s), 133.16 (d), 144.14 (s), 144.40 (s), 184.38 (s).

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