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Synthesis of phenanthrenes from formylbenzoquinone

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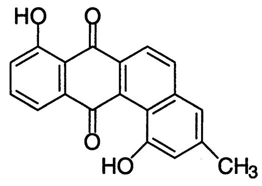
Abstract—Phenanthrenes are synthesized by condensation of formylbenzoquinone with a substituted toluene followed by *O*-methylation and cyclization using the phosphazine base P_4-*t*Bu. © 2002 Elsevier Science Ltd. All rights reserved.

Functionalized phenanthrenes are useful intermediates for natural product synthesis.[1] Natural products such as tetrangulol (**1**),[2] denbinobin (**2**),[3] and bungone B (**3**)[4] contain an oxidized phenanthrene subunit.

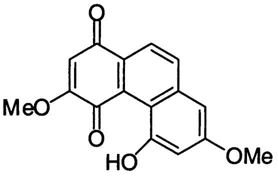
Many phenanthrenes are prepared by photochemical cyclizations of stilbenes. Both Mallory and Giles have demonstrated that certain stilbenes undergo photocyclization in the presence of oxidizing agents to afford phenanthrene dimethyl ethers.[5] Snieckus and co-workers have synthesized phenanthrenes via an innovative approach involving directed *ortho* metalation followed by a palladium-catalyzed cyclization.[6] Catellani has synthesized phenanthrenes via a palladium-mediated bis-addition to aryl acetylenes.[7] Ramana has synthesized phenanthrenes by a tandem intermolecular acylation/intramolecular acylation strategy.[8] DeKoning and co-workers developed a clever intramolecular cyclization using base and light.[9] Kraus and Melekhov recently synthesized phenanthrenes via a Lewis acid-mediated cyclization reaction.[10]

In the reaction sequence that we have developed, formylbenzoquinone reacts with a substituted toluene near ambient temperature. The resulting hydroquinone is *O*-methylated and then converted into the phenanthrene using the hindered phosphazine base P_4-*t*Bu. This sequence is illustrated below. Deprotonation, cyclization and dehydration occur in a one-pot reaction to generate the phenanthrene structure.

This methodology affords a straightforward and novel synthesis of highly substituted phenanthrenes. Initially, we prepared formylbenzoquinone from the hydro-



1



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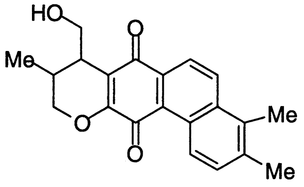

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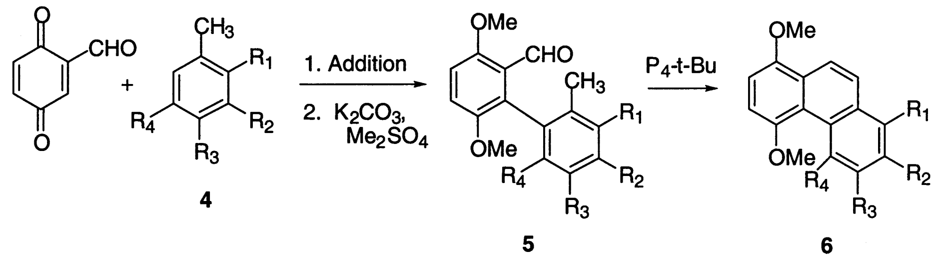

$P_4\text{-tBu} = \text{tBuN=P}\left[\text{-N=P(NMe}_2)_3\right]_3$

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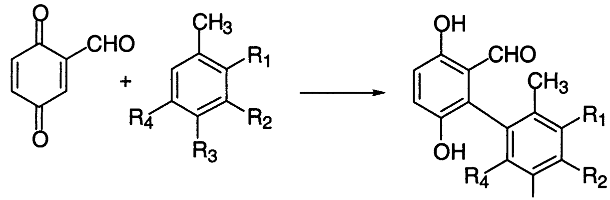
quinone using silver oxide in benzene at ambient temperature.[11] The reaction product was filtered through Celite and immediately reacted with the substituted toluene **4** and stannic chloride at 0°C to room temperature.[12] The yields of purified product were modest despite variations in temperature, Lewis acid and reaction time.

We then tried the oxidation of 2,5-dihydroxybenzaldehyde using DDQ according to the method of Bruce.[13] This method afforded a quinone that was much more pure than that produced by the silver oxide method. Formylbenzoquinone generated from the reaction with DDQ reacted with the substituted toluenes **4** and trifluoroacetic acid to provide adducts in improved yields. The best yields were obtained using no Lewis acid and simply extending the reaction time. The yields of the products are shown below in Table 1.

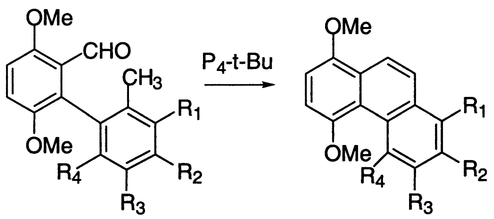
With a good preparation of the adducts **5**, we next focused on the cyclization. Magnus and co-workers had previously reported the synthesis of phenanthrenols from biphenyl esters using lithium diisopropylamide.[14] DeKoning had reported a related cyclization using potassium *tert*-butoxide and light. With adduct **5**, the use of both reagents returned recovered starting material. We had previously employed the hindered phosphazine base P_4-*t*Bu in a novel synthesis of benzofurans.[15] The reaction of adduct **5** with P_4-*t*Bu generated the phenanthrene cleanly in good yield at 100°C.[16] The results of cyclizations using P_4-*t*Bu are collated in Table 2. This reaction has been successfully conducted on scales ranging from 1 to 10 mmol.

Table 1. Reactions using formylbenzoquinone prepared from DDQ



R_1	R_2	R_3	R_4	% Yield
H	CH_3	H	H	75 (29% with Ag_2O)
CH_3	CH_3	H	H	58 (23% with Ag_2O)
H	CH_3	H	CH_3	67 (21% with Ag_2O)
H	OCH_3	H	OCH_3	60
H	OCH_3	H	CH_3	51 (24% with Ag_2O)

Table 2. Cyclizations using P_4-*t*Bu



R_1	R_2	R_3	R_4	% Yield
H	CH_3	H	H	59
CH_3	CH_3	H	H	81
H	H	CH_3	H	73
H	CH_3	H	OCH_3	62
H	OCH_3	H	OCH_3	90
H	OCH_3	H	CH_3	60

The procedure described above represents a mild and efficient method for the regiochemical construction of highly substituted phenanthrenes.[17] The phosphazine cyclization is compatible with a variety of substituents. This methodology will be applied to the total synthesis of denbinobin and bungone B.

Acknowledgements

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16. One example of this transformation using silver oxide to generate formylbenzoquinone and P_4-*t*Bu to make the phenanthrene has been reported as part of a synthesis of tetrangulol: Kraus, G. A.; Zhang, N.; Melekhov, A.; Jensen, J. *Synlett* **2001**, 521.
17. Representative example:
    DDQ method: The quinine was prepared by combining equimolar amounts of 2,5-dihydroxybenzaldehyde and DDQ in a 100 mL flask in about 50 mL of dry benzene. This was allowed to react at rt for 16 h. The benzene was evaporated and the crude product was re-dissolved in Et_2O. This was allowed to react with **4** for 24 h. The crude product was poured onto ice and extracted three times with ethyl acetate. The organic layer was washed once with brine and dried. The product was purified by sgc (50:1 H:EA). The hydroquinone was then dissolved in acetone and Me_2SO_4 and K_2CO_3 were added. This reaction was boiled for 24 h and allowed to cool. The mixture was filtered and the acetone was removed. The solid was then dissolved in ether and washed with 1N NaOH solution once and extracted with ether twice. The combined ether layers were washed with brine twice and dried over $MgSO_4$. The crude product was then purified by sgc (10:1 H:EA).
    The hydroquinone dimethyl ether was placed in an argon-flushed sealable tube with benzene and 1.05 equiv. of P_4-*t*Bu (purchased from Fluka) and heated in an oil bath to 100°C for 24 h. The solvent was evaporated and the crude product was purified by sgc (100:1 H:EA).