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A Novel Method for the Synthesis of Phenanthrenes and Benzo[*a*]carbazoles

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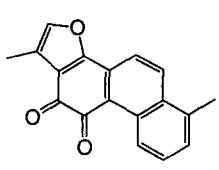
Abstract: The synthesis of several phenanthrenes and carbazoles utilising a novel reaction mediated by potassium *t*-butoxide and light through a quartz filter is described.

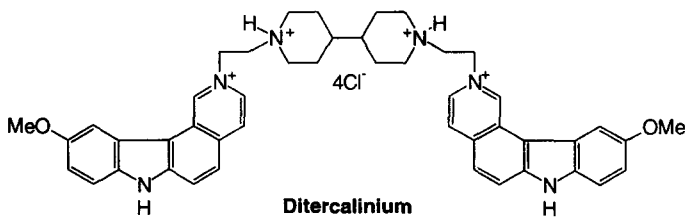
Keywords: Polycyclic aromatic compounds; Polycyclic heterocyclic compounds; Suzuki reactions

Methods for the efficient and regioselective synthesis of phenanthrenes[1] and benzo- or pyrido-fused carbazoles[2] are of interest to synthetic chemists because these systems occur as subunits of biologically active products. For example, the phenanthrene nucleus is found in some of the compounds isolated from *Dan Shen*, a drug used in Chinese folk medicine and for the clinical treatment of a variety of ailments, including viral hepatitis, hypertension and heart and menstrual problems.[3] It has also been shown to possess antipyretic, antimicrobial, anti-inflammatory and antineoplastic properties. The broad spectrum of activity of *Dan Shen* is due to a number of diterpenoid quinones,[4] one of these being the phenanthrenequinone tanshinone I.[5]

While benzo-fused carbazoles occur infrequently as natural products, these compounds are interesting as they have the potential for development as antitumour agents.[6] An interesting example of a biologically active pyrido[4,3-*c*]carbazole is the clinically active drug ditercalinium.[2b] Many pyrido[*b*]carbazoles also show antitumour properties, for example "elliptinium" (2-methyl-9-hydroxyellipticinum acetate), which is often used for the treatment of thyroid, breast and kidney cancer.[2b]

Tanshinone I





Ditercalinium

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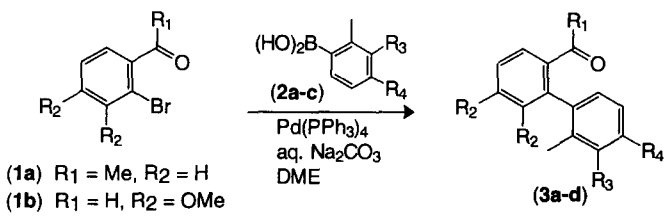
We have recently described the regiospecific synthesis of a number of aryl and alkyl naphthalenes from *o*-allyl acylbenzenes in the presence of potassium *t*-butoxide and irradiation from a 400W high pressure mercury lamp through a quartz filter.[7] In this paper we describe an extension of this reaction which results in the synthesis of phenanthrenes and carbazoles.

Suzuki coupling of acylbenzenes (**1a, 1b**) containing a bromine *ortho* to a carbonyl group[8] with a variety of toluene-derived boronic acids (**2a-c**) in the presence of palladium(0)[9,10] afforded the desired phenanthrene precursors (**3a-d**)[11] in generally high yields as shown in **Table 1**.



Reaction of each of these biphenyls (**3a-d**) with potassium *t*-butoxide in dimethylformamide at 70-80°C with simultaneous irradiation from a high pressure mercury lamp gave the desired substituted phenanthrenes (**4a-d**) in yields of 37-70%[12] (**Table 1**). Although the reaction also proceeded without irradiation, the yields were invariably poorer (*e.g.*, 48% *vs* 62% in the case of **4b**). It appears that oxygen substituents on the aromatic rings facilitate phenanthrene formation, as the yield of **4a** is substantially lower than in the other three examples.

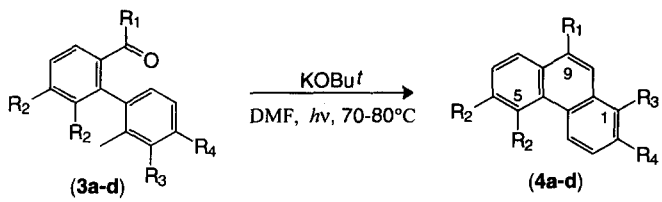


Table 1

ArBr (**1**)	Boronic acid (**2**)	Biphenyl (**3**); Yield (%)	Phenanthrene (**4**); Yield (%)
1a	**2a** (R_3=R_4=H)	**3a** (R_1=Me; R_2=R_3=R_4=H); 98	**4a** (R_1=Me; R_2=R_3=R_4=H); 37
1b	**2a** (R_3=R_4=H)	**3b** (R_1=R_3=R_4=H, R_2=OMe); 96	**4b** (R_1=R_3=R_4=H, R_2=OMe); 62
1b	**2b** (R_3=Me, R_4=H)	**3c** (R_1=R_4=H, R_2=OMe, R_3=Me); 99	**4c** (R_1=R_4=H, R_2=OMe, R_3=Me); 70
1b	**2c** (R_3=H, R_4=OMe)	**3d** (R_1=R_3=H, R_2=R_4=OMe,); 71	**4d** (R_1=R_3=H, R_2=R_4=OMe); 61

The above procedure provides a novel method for the synthesis of substituted phenanthrenes. By using this methodology we are now able to synthesise phenanthrenes containing oxygen substituents in positions 2, 5 and 6 as well as introduce alkyl groups in positions 1 and 9 of the phenanthrene nucleus. Our route is related to that documented by Snieckus and co-workers, who cyclised biphenyl-2-carboxylates with LDA to produce phenanthrols.[13] Irradiation was not investigated by these workers.

We have extended this methodology to the synthesis of carbazoles. 2-Bromoindole-3-carbaldehyde (**5a**)[14] or the *N*-methyl analogue (**5b**) also underwent Suzuki coupling with boronic acids in the presence of palladium(0) to afford substrates (**6a-c**).[11] Indole (**6a**) was treated with potassium (bistrimethylsilyl)amide (KHMDS) and then methyl iodide to afford the *N*-methyl precursor (**6d**) in 76% yield. Treatment of the 2-arylindoles (**6b-d**) with potassium *t*-butoxide as described previously[12] afforded the desired carbazoles (**7b-d**) in good yields as shown in **Table 2**.

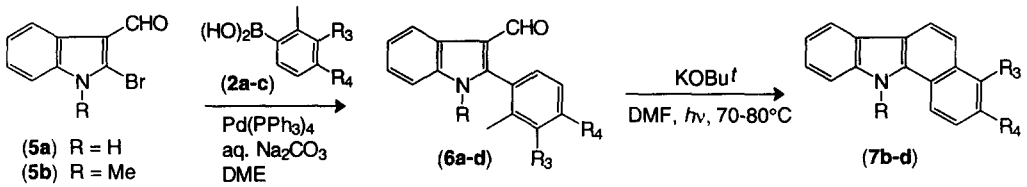


Table 2

Indole (**5**)	Boronic acid (**2**)	Biaryl (**6**); Yield (%)	Carbazole (**7**); Yield (%)
5a	**2a** (R_3=R_4=H)	**6a** (R=R_3=R_4=H); 99	———
5b	**2b** (R_3=Me, R_4=H)	**6b** (R=R_3=Me; R_4=H); 93	**7b** (R=R_3=Me; R_4=H); 78
5b	**2c** (R_3=H, R_4=OMe)	**6c** (R=Me; R_3=H, R_4=OMe); 94	**7c** (R=Me; R_3=H, R_4=OMe); 52
		6d (R=Me; R_3=R_4=H); see text	**7d** (R=Me; R_3=R_4=H); 77

Clearly, the scope of these reactions resulting in the formation of both the phenanthrenes and carbazoles needs to be broadened. Work in progress in the phenanthrene area includes the synthesis of tanshinone I utilising the developed methodology. Work towards the synthesis of more highly oxygenated carbazoles is also in progress. The utilisation of this methodology for the synthesis of the non-linear pyrido[*a*]carbazoles related to ellipticine and the synthesis of carbolines by employing suitably substituted boronic acid pyridine salts instead of the toluene-substituted boronic acids (**2a-c**) is also under way.

Acknowledgements

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10. Typical experimental procedure: The aromatic bromide (200-500 mg) in 1,2-dimethoxyethane (5-10 cm^3) was deoxygenated by bubbling nitrogen gas through the mixture. This solution was added to tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (0.1 mole equivalents) and stirred for 10 mins under a nitrogen atmosphere. A deoxygenated solution of the boronic acid (1.5 mole equivalents) in ethanol (2-5 cm^3) was added to the mixture and stirring was continued for a further 10 mins. An aqueous sodium carbonate solution (2M, 8.5 mole equivalents, 2-5 cm^3) was then added and stirring was maintained for 5 mins at room temperature. The reaction mixture was then heated under reflux for 24-48h. Water was added to the completed reaction and the organic material extracted with dichloromethane (2 x 40 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, 5-30% ethyl acetate/hexane) to afford the desired products in yields of 71-99%.
11. All new compounds were characterised spectroscopically and by elemental analysis or high resolution mass spectrometry.
12. Typical experimental procedure: A solution of the carbonyl-containing compound (150-300 mg) in dry dimethylformamide (20-40 cm^3) was heated to 70-80°C. Potassium *t*-butoxide (4 mole equivalents) was added and heating was maintained for 10-20 minutes with concomitant irradiation from a 400W high pressure mercury lamp through a quartz filter. Water (20-40 cm^3) was added, and the mixture was acidified with dilute aqueous HCl. The solution was extracted with several portions of diethyl ether, after which the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, 5-30% ethyl acetate/hexane) to afford the desired products in yields of 37-78%.
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