

Directed *ortho* Metalation - Cross Coupling Connections. Remote Lateral Metalation - Cyclization of 2-Imino-2'-Methyl Biaryls to 9-Aminophenanthrenes. A Synthesis of the Alkaloid Piperolactam C⁺

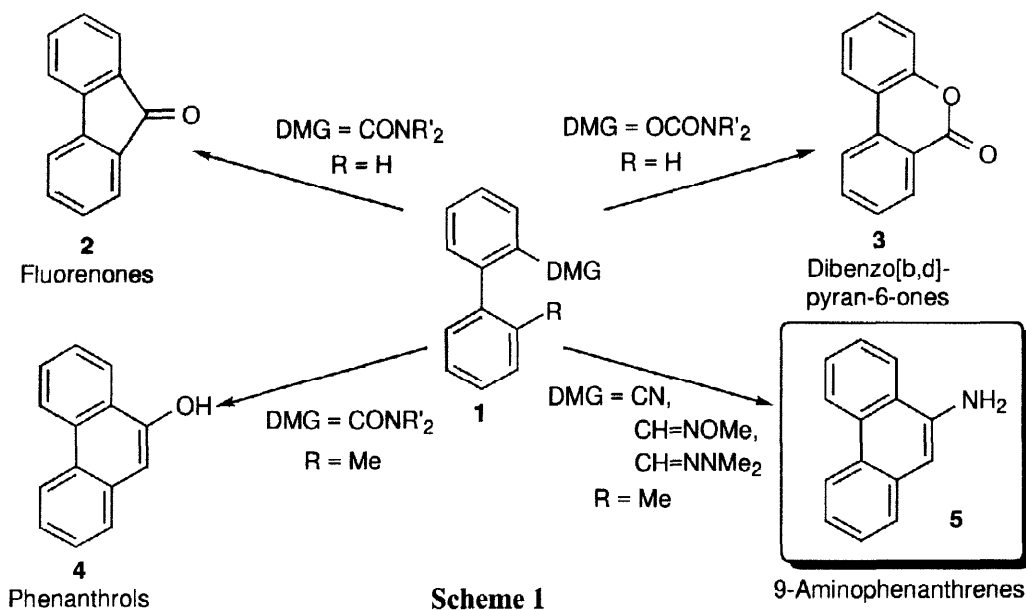
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Abstract: 2-Imino-2'-methyl biaryls, conveniently available by Suzuki cross coupling protocol, undergo lithium diethyl amide-mediated metalation - cyclization to give 9-aminophenanthrenes (Table 1). The application of this new general methodology to the first synthesis of the alkaloid piperolactam C (9) is described. © 1998 Elsevier Science Ltd. All rights reserved.

In efforts aimed to link Directed *ortho*-metalation (DoM)¹ and cross coupling tactics for the development of new synthetically useful methodologies, we recently described general and regioselective routes to fluorenones (2),² dibenzo[b,d]pyranones (3)³ and 9-phenanthrols (4)⁴ and demonstrated their application in natural product synthesis (Scheme 1). In continuation of these goals, we report a general route to 9-aminophenanthrenes (5) via a remote lateral metalation-cyclization sequence of 2-imino-2'-methyl biaryls 1 (DMG = CN, CH=NOMe, CH=NNMe₂; R = Me). We thereby provide a new synthetic method for 9-aminophenanthrenes which proceeds under mild anionic conditions thus superceding classical methods requiring harsh conditions that are of limited scope.⁵ In addition, we demonstrate application by a successful synthesis of Piperolactam C (9, Scheme 2), a benzyloisoquinoline alkaloid isolated from various *Piper* species which is of some pharmacological and biosynthetic interest.⁶



⁺ To Carl Johnson, on occasion of his birthyear - a fine vintage, for his many original and enkindling contributions to organic synthesis.

Table 1. Synthesis of 9-Aminophenanthrene Derivatives **5**

Reaction scheme: Starting material **6** (phenanthrene derivative with substituents R¹, R², G, and CH₃) reacts with Et₂NLi in 50 mM THF for 2-5 hr to yield Product **7** (9-aminophenanthrene derivative with substituents R¹ and R²).

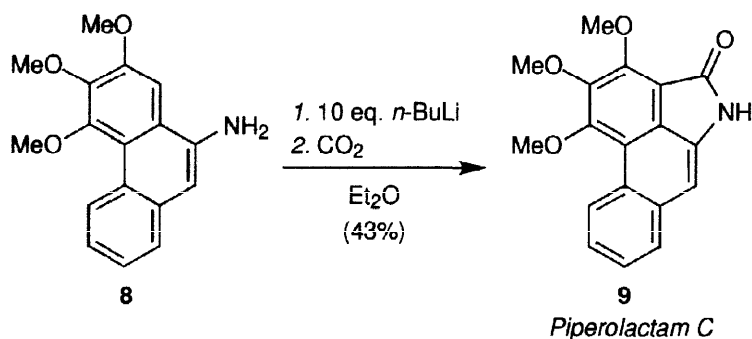
Entry	Starting Material (6)	G	Product (7)	Yld, % ^a
1		CN		88
		CH=NNMe ₂		50
		CH=NOMe		58
2		CN		42
		CH=NNMe ₂		67
		CH=NOMe		58
3		CN		81
		CH=NNMe ₂		72
		CH=NOMe		64
4		CN		66
		CH=NNMe ₂		12
		CH=NOMe		73
5		CN		40
		CH=NNMe ₂		61
6		CN		89
		CH=NNMe ₂		43
		CH=NOMe		63
7		CN		52
		CH=NNMe ₂		41
		CH=NOMe		74
8		CH=NNMe ₂		46
		CH=NOMe		45

^a Yield of isolated (chromatographed and/or recrystallized) product.

Exploratory studies led to optimization of the prototype conversions $6^7 \rightarrow 7$ (Table 1).⁸ Although the nitrile gave the best result, the methoxyimine and the hydrazone also afforded acceptable yields of product 7 (entry 1). The intermediacy of the nitrile in the cyclization reactions of methoxyimine and hydrazone is indicated.⁹

The generality of the lateral metalation - cyclization route (Table 1) deserves brief comment. Thus, the synthesis of alkyl (entries 2 and 3) and alkoxy (entries 4 and 5) 9-aminophenanthrenes in which the regioselectivity is predetermined by the cross coupling bond⁷ is feasible by this method. Benzo fused analogs (entries 6-8) are likewise obtained from readily available biaryl precursors. Although acceptable yields are observed for all three G groups with one exception (entry 4), there is substantial variability as a function of substrate.

To achieve the synthesis of piperolactam C (9), insertion of a carbonyl dication equivalent into the aminophenanthrene 8 (Table 1, entry 5 and Scheme 2) was required. After a number of unfruitful attempts,¹⁰ direct metalation¹¹ with excess *n*-BuLi followed by carbonation afforded piperolactam C in 43% yield (based on recovered 8) whose spectroscopic properties were identical with those of the natural product.^{6c}



Scheme 2

In summary, a new method for the synthesis of 9-aminophenanthrene derivatives based on remote lateral metalation - cyclization has been developed and applied to the first synthesis of the alkaloid piperolactam C (9). The regioselectivity and mild conditions as well as the presence of the 9-aminophenanthrene moiety in aporphine-related alkaloids⁶ are aspects of this methodology which suggest further synthetic application.¹²

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- (7) Compounds of general structure **6** were prepared by Suzuki cross coupling of readily available *ortho*-bromo-benzaldehydes or -benzonitriles with *ortho*-tolyl boronic acids, which, in turn, were obtained *via* lithium/halogen exchange of the corresponding bromotoluenes. The methoximes and *N,N*-dimethylhydrazones were prepared in high yields from the corresponding aldehydes by standard procedures. Benesch, L. M.Sc. Thesis, University of Waterloo, 1995.
- (8) *Typical Experimental Procedure:* To a stirred solution of LiDEA (1.2 equiv, prepared by treatment of Et_2NH (0.14 mL, 1.35 mmol) in dry THF (10 mL) at 0 °C under a dry nitrogen atmosphere with *n*-BuLi (0.90 mL, 1.35 mmol, 1.50 M solution in hexanes) for 10 min) was added dropwise a solution of 2'-methyl-biphenyl-2-carbonitrile (222 mg, 1.15 mmol) in dry THF (10 mL) over 5 min *via* cannula. The bright yellow solution was allowed to warm to rt over 5 h, quenched with water (2 mL), and the whole was evaporated to dryness *in vacuo*. Chromatography (silica gel, hexane-ethyl acetate 2:1 eluent) afforded 9-aminophenanthrene, as a light brown solid (197 mg, 88 %); mp 134-135 °C, lit mp^{5a} 133-135 °C.
- (9) Treatment of the methoximine (**Table 1**, entry 5) with 2.5 equiv of LiDEA, gave the corresponding nitrile as the only isolable product in 73% yield. It was converted into 9-aminophenanthrene in 60% yield (21% recovered starting material) using 1.2 equiv of LiDEA. The LDA-mediated conversion of an aromatic *N,N*-dimethylhydrazone into the corresponding nitrile is precedented, see Mao, Y.-L.; Boekelheide, V. *J. Org. Chem.* **1980**, *45*, 2746.
- (10) *N*-*t*-Boc 9-aminophenanthrene underwent predominant DoM reaction at C-10; attempts to effect cyclization of the *N,N*-diethyl amide of the biaryl of entry 5 (**Table 1**) failed; and electrophilic reactions of **8**, e.g. with $(\text{COCl})_2$ afforded the C-10 acid as the sole isolable product. Benesch, L.; Bury, P.; Houldsworth, S.J.; Guillaneux, D.; Snieckus, V. unpublished results.
- (11) The amino group is a weak *ortho* metalation director (Gschwend, H.W.; Rodriguez, H.R., *Org. React.* **1979**, *26*, 1) but has been used in remote (Narasimhan, N.S.; Chandrachood, P.S. *Synthesis* **1979**, 589; Narasimhan N.S.; Alurkar, R.H. *Indian J. Chem.* **1969**, *7*, 1280) and *peri*-metalation as the diethylamine (Jastrzebski, J.T.B.H.; Van Koten, G.; Goubitz, K.; Arlen, C.; Pfeffer, M. *J. Organometal. Chem.* **1983**, *246*, C75; Jastrzebski, J.T.B.H.; Knapp, C.T.; Van Koten, G. *J. Organometal. Chem.* **1983**, *255*, 287.). In the case of **8**, the synergism of OMe and NH_2 directors appears not to be effective.
- (12) All new compounds show analytical and spectral data consistent with the given structures.