Pergamon

Tetrahedron Letters 39 (1998) 961–964

TETRAHEDRON LETTERS

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+

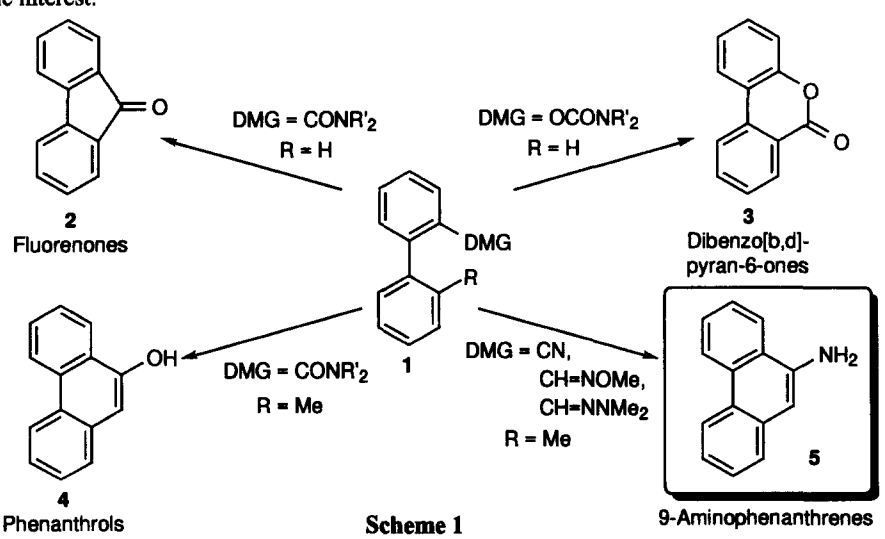
Lisbeth Benesch, Paul Bury, Denis Guillaneux, Stephen Houldsworth, X. Wang and Victor Snieckus*

Guelph-Waterloo Centre for Graduate Work in Chemistry, Department of Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada. E-mail: snieckus@buli.uwaterloo.ca

Received 10 October 1997; revised 5 November 1997; accepted 10 November 1997

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.

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 regiospecific 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, $CH=NNMe_2$; R = Me). We thereby provide a new synthetic method for 9-aminophenanthrenes which proceeds under mild anionic conditions thus superceeding 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 benzylisoquinoline alkaloid isolated from various *Piper* species which is of some pharmacological and biosynthetic interest.[6]

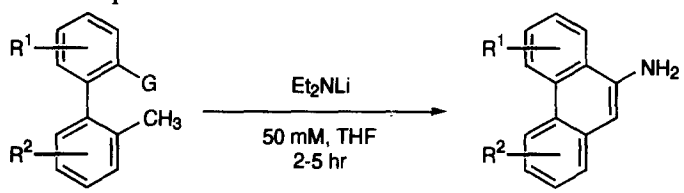


Scheme 1

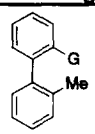
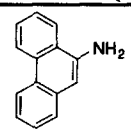
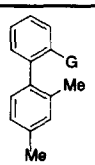
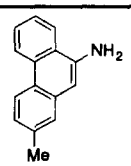
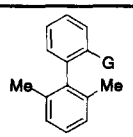
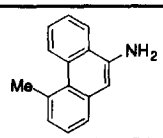
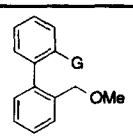
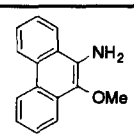
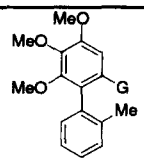
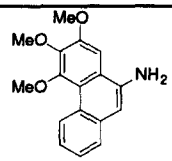
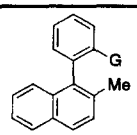
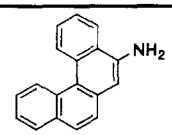
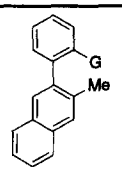
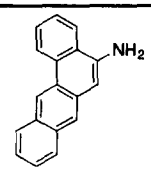
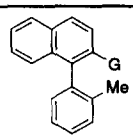
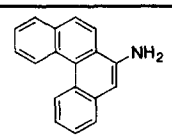
+ To Carl Johnson, on occasion of his birthyear - a fine vintage, for his many original and enkindling contributions to organic synthesis.

0040-4039/98/$19.00
PII: S0040-4039(97)10670-0

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



6 **7**

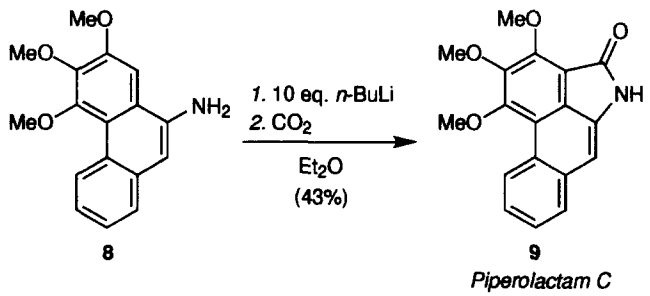
Entry	Starting Material (6)	G	Product (7)	yld, %[a]
1		CN CH=NNMe2 CH=NOMe		88 50 58
2		CN CH=NNMe2 CH=NOMe		42 67 58
3		CN CH=NNMe2 CH=NOMe		81 72 64
4		CN CH=NNMe2 CH=NOMe		66 12 73
5		CN CH=NNMe2		40 61
6		CN CH=NNMe2 CH=NOMe		89 43 63
7		CN CH=NNMe2 CH=NOMe		52 41 74
8		CH=NNMe2 CH=NOMe		46 45

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

Exploratory studies led to optimization of the prototype conversions **6**[7] → **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 regiospecificity is predetermined by the cross coupling bond[7] 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 metalation[11] 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]



8 **9**

Piperolactam C

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 regiospecificity and mild conditions as well as the presence of the 9-aminophenanthrene moiety in aporphine-related alkaloids[6] are aspects of this methodology which suggest further synthetic application.[12]

Acknowledgements:

We gratefully acknowledge NSERC Canada for support under the Research Grant and Industrial Research Chair programs and l'Association Française pour la Recherche Thérapeutique for a fellowship to D.G. We thank Prof. G.I. Dmitrienko for initial mechanistic insight.

References and Notes:

(1) a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879; b) Snieckus, V. *Chemical Synthesis: Gnosis to Prognosis*, Chatgilialoglu, C.; Snieckus, V., Eds.; Kluwer Academic Publishers: The Netherlands, **1996**, Vol. 320, 625.

(2) Fu, J.-M.; Zhao, B.-P.; Sharp, M.J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683.

(3) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424.

(4) Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 4879.

(5) *Inter alia,* bromination-$NaNH_2$ displacment: (a) Altiparmakian, R.H.; Braithwaite, R.S.W. *J. Chem. Soc., C* **1967**, 1818; (b) Bergstrom, F.W.; Horning, C.H. *J. Org. Chem.* **1946**, *11*, 334; (c) Mirsadeghi, S.; Prasad, G.K.B.; Whittaker, N.; Thakker, D.R. *J. Org. Chem.* **1989**, *54*, 3091. By Curtius rearrangement of the acyl azide: (d) Goldberg, M.A.; Ordas, E.P.; Carsch, G. *J. Am. Chem. Soc.* **1947**, *69*, 260; (e) Newman, M.S.; Blum, J. *J. Am. Chem. Soc.* **1964**, *86*, 1835; (f) Mosby, W.L. *J. Org. Chem.* **1959**, *24*, 421; (g) Newman, M.S.; Kosak, A.I. *J. Org. Chem.* **1949**, *14*, 375. By nitration-reduction: Bavin, P.M.G.; Dewar, M.J.S. *J. Chem. Soc.* **1956**, 164. By addition-elimination of NH_3 or BrN_3: (i) Yasuda, M.; Harada, T.; Ansho, Y.; Shima, K. *Bull. Chem. Soc. Jpn* . **1993**, *66*, 1451. (j) Denis, J.N.; Krief, A. *Tetrahedron* **1979**, *35*, 2901. By Friedel-Crafts reaction of 2-phenyl phenylacetonitrile: (k) Bradsher, C.K.; Little, E.D.; Beavers, D.J. *J. Am. Chem. Soc.* **1956**, *78*, 2153.

(6) (a) Desai, S.J.; Prabhu, B.R.; Mulchandani, N.B. *Phytochemistry* **1988**, *27*, 1511. (b) Olsen, C.E.; Tyaggi, O.D.; Boll, P.M.; Hussaini, F.A.; Parmar, V.S.; Sharma, N.K.; Taneja, P.; Jain, S.C. *Phytochemistry* **1993**, *33*, 518. (c) Desai, S.J.; Chaturvedi, R.N.; Badheka, L.P.; Mulchandani, N.B. *Indian J. Chem.* **1989**, *28B*, 775. For approaches towards this and related classes of alkaloids, see: (d) Estevez, J.C.; Villaverde, M.C.; Estevez, R.J.; Castedo, L. *Tetrahedron Lett.* **1992**, *33*, 5145. (e) Castedo, L.; Guitian, E.; Saa, J.M.; Suau, R. *Heterocycles*, **1982**, *19*, 279. (f) Castedo, L.; Guitian, E.; Saa, J.M.; Suau, R. *Tetrahedron Lett.* **1982**, *23*, 457. (g) Estevez, J.C.; Estevez, R.J.; Guitian, E.; Villaverde, M.C.; Castedo, L. *Tetrahedron Lett.*, **1989**, *30*, 5785.

(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 $(COCl)_2$ 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.