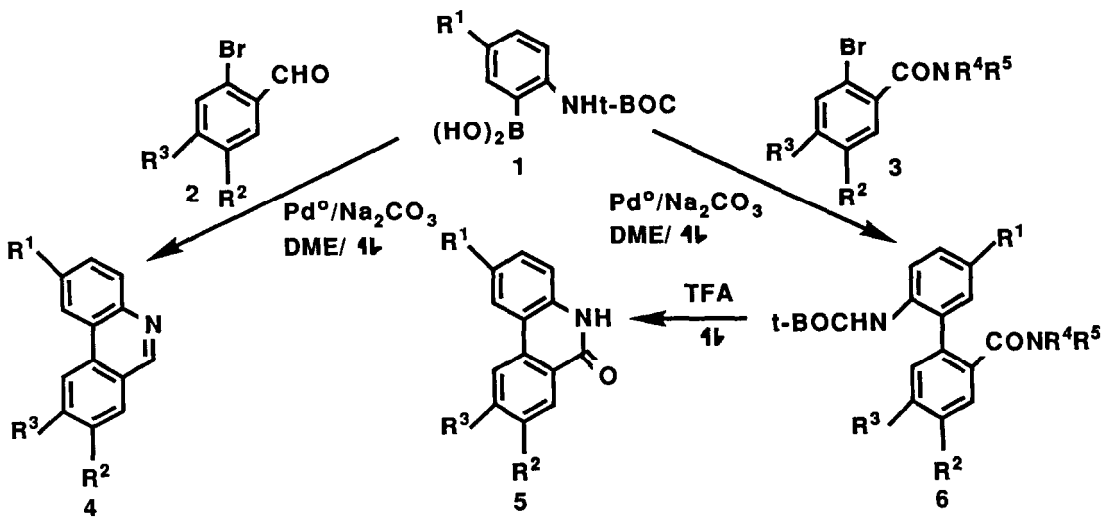
Tetrahedron Letters,Vol.29,No.43,pp 5463-5466,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE DIRECTED METALATION CONNECTION TO ARYL-ARYL CROSS COUPLING. REGIOSPECIFIC SYNTHESIS OF PHENANTHRIDINES, PHENANTHRIDINONES AND THE BIPHENYL ALKALOID ISMINE

M.A. Siddiqui and V. Snieckus*
Guelph-Waterloo Centre for Graduate Work in Chemistry
University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Summary: Concise general routes to phenanthridines **4** and phenanthridinones **5** based on directed ortho metalation and cross coupling tactics are described; a short synthesis of the *Amaryllidaceae* alkaloid ismine (**8b**) is reported.

The phenanthridine heterocycles derive significance from their presence as subunits in several classes of alkaloids,[1] their pharmacological[2] properties, and recently, their detection in environmental sources.[3] Major synthetic approaches[4] to phenanthridines and phenanthridinones include a) Bischler-Napieralski[4b] and directed metalation-based[4c] cyclization of 2-substituted biphenyls, b) cyclization of 2,2′-substituted biphenyls,[4d] c) Pschorr reaction,[4e] d) photocyclization of benzanilides[4f] and N-arylbenzamides,[4g] e) benzyne-mediated condensation of o-halo benzylanilines,[4h] f) Beckmann and Schmidt rearrangement of fluorenones,[4a] and g) Pd(II)-promoted ring closure of N-arylbenzamides.[4i] As a further demonstration of the favorable marriage between the directed ortho

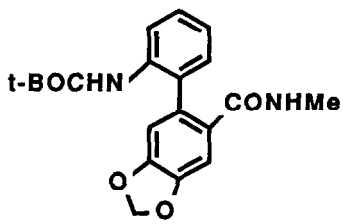


Scheme

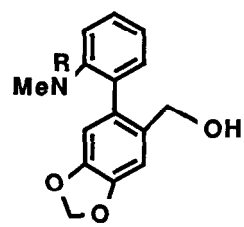
metalation[5] and the Pd(0)-catalyzed cross coupling[6] strategies, we report a new general route to phenanthridine (**4**) and phenanthridinone (**5**) derivatives from the reaction of o-N-t-BOC arylboronic acids (**1**) with o-bromobenzaldehydes (**2**) and -benzamides (**3**) respectively (**Scheme**). In addition, we provide an application of this methodology in a simple synthesis of the *Amaryllidaceae* alkaloid ismine (**8b**).[7] The new method has advantage in regiospecificity, efficiency, and brevity over established phenanthridine construction processes.[4,8]

Treatment of the arylboronic acid **1**, R^1 = OMe with o-bromobenzaldehyde **2**, $R^1 = R^2 = H$[9] under the previously developed conditions[6a] led directly to 2-methoxyphenanthridine (**Table**, entry 2) in modest yield. After aryl-aryl bond formation, the thermal loss of the N-t-BOC group is presumably triggered by initial carbinol amine formation. Additional entries (**Table**) of this one pot phenanthridine synthesis is indicative of the scope of substitution patterns which may be achieved. In two cases (entries 1 and 5), cross coupling products were isolated and cyclized into the corresponding phenanthridines by treatment with TFA (reflux/10 h). Entry 6 represents a one-pot preparation of the benzophenanthridine alkaloid skeleton.[1a,10] Under identical conditions, cross coupling of **1**, R^1 = H with the N,N-dimethyl-2-bromobenzamide[9] afforded the corresponding 2,2'-substituted biphenyl which, upon treatment with TFA (reflux/4 h) provided the phenanthridinone (entry 7). A further representative example (entry 8) shows that this sequence is tolerant of similar substitution as that observed in the phenanthridine series.

The synthesis of ismine (**8b**) was initiated by coupling **1**, R^1 = H with N-methyl 2-bromo-4,5-methylenedioxybenzamide[11] to give biphenyl **7** (75%) which, upon sequential N-methylation (NaH/MeI/THF, > 95%) and chemoselective reduction ($LiEt_3BH$/THF/0°C → RT, 72%)[12] furnished the N-protected benzyl alcohol **8a**. Standard TFA deprotection under several conditions[13] led only to cyclic product **9** in high yield. However, adaptation of the excellent Ohfune two-step procedure (1. TBDMSOTf/CH_2Cl_2/2,6-lutidine/RT/30 min; 2. TBAF/3 equiv H_2O/THF/reflux/30 min)[14] afforded ismine (**8b**) in 85% overall yield.[15]

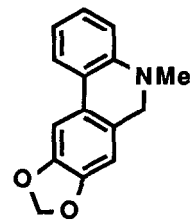


7



8

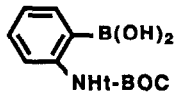
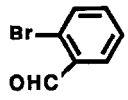
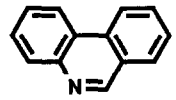
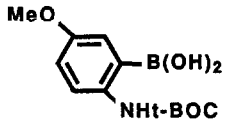
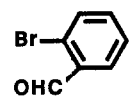
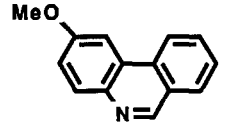
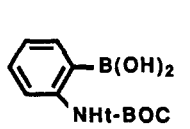
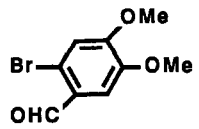
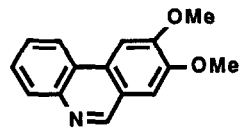
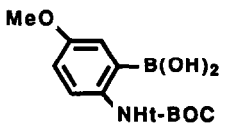
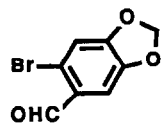
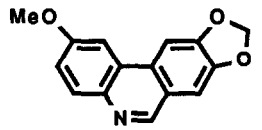
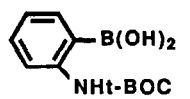
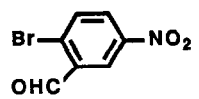
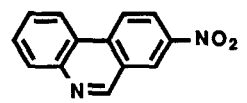
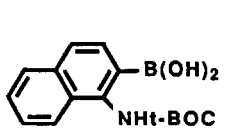
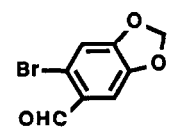
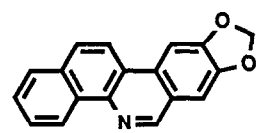
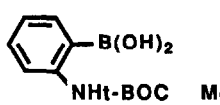
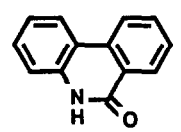
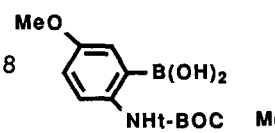
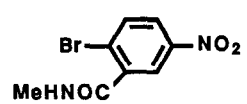
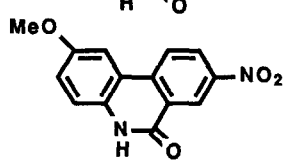
a: R = t-BOC
b: R = H



9

In summary, a new general cross coupling method for the synthesis of phenanthridines and phenanthridinones has been develoved. Being based on the versatile directed metalation tactic,[6] it promises broad scope for the rapid access of phenanthridines with a variety of substitution patterns. Methodological extension and application to alkaloid synthesis is in progress.[16,17]

Table. Synthesis of Phenanthridines and Phenanthridinones

Entry	$ArB(OH)_2$	ArBr	Phenanthridine/ Phenanthridinone	Yield, %[a]	mp °C
1				77	107-108[b] (EtOH)
2				45	89-90[c] (Subl)
3				54	163-164[d] (Subl)
4				69	211-215[e] (Subl)
5				89	186-187[f] (MeOH)
6				47	236-238[g] ($CHCl_3$)
7				63	282-285[h] (MeOH)
8				67	340-344 (decomp) (TFA)

[a]Represents yields of products purified by column chromatography; [b] Lit.[8] 104-105°C ; [c] Lit. mp 87-88°C (Kessar, S. V.; Pal, D.; Singh, M.Tetrahedron. **1973** , 29 , 177); [d] Lit. mp 164-165°C (Prabhakar, S; Lobo, A. M.; Tavares, M. R. J. Chem. Soc., Chem. Commun. **1978** , 884); [e] Lit. 213-214°C (Onaka, T.; Kanada, Y.; Natsume, M. Tetrahedron Lett. **1974**, 1179); [f]Lit. 180°C (Arcus, C. L.; Coombs, M. M. J. Chem. Soc. **1954** , 4319); [g] Lit.[10] 240-242°C; [h]Lit. 285°C (Moriconi, E. J.; Spano, F. A. J. Am. Chem. Soc. **1964** , 86 , 38).

References and Footnotes

1. a) Simanek, V., **The Alkaloids** (N.Y.), **1985**, 26, 185; b) Ghosal, S.; Singh, S.K. Srivastava, R.S., Phytochemistry, **1986**, 25, 1975.

2. Preininger, V., **The Alkaloids** (N.Y.), **1975**, 15, 241; Cordell, G.A.; Farnsworth, N.R., Heterocycles, **1976**, 4, 393.

3. a) Adams, J.; Giam, C.-S., Environ. Sci. Technol., **1984**, 18, 391; b) Seixas, G.M.; Andon, B.M.; Hollingshead, P.G.; Thilly, W.G., Mutat. Res., **1982**, 102, 201.

4. a) Keene, B.R.; Tissington, P. Advan. Heterocyclic Chem., **1971**, 13, 315; b) Matrelashvili, G.S.; Belevskii, S.F.; Fedotova, O.Y.; Kolesnikov, G.S. Khim. Geterotsikl. Soedin., **1969**, 1044; Chem. Abstr., **1970**, 72, 111265w; c) Narasimhan, N.S.; Chandrachood, P.S.; Shete, N.R. Tetrahedron, **1981**, 37, 825; d) Dokunikhin, N.S.; Migachev, G.I.; Andrievskii, A.M. Zh. Org. Khim., **1978**, 14, 891; Chem. Abstr., **1978**, 89, 24118h; e) Hey, D.H.; Jones, G.H.; Perkins, M.J. J. Chem. Soc. Perkin Trans I, **1972**, 113; f) Mallory, F.B. and Mallory, C., Org. React., **1984**, 30, 1; see also Leardini, R.; Tundo, A.; Zanardi, G. Synthesis, **1985**, 107; g) Ninomiya, I. Heterocycles, **1980**, 14, 1567; h) Kessar, S. Accts. Chem. Research, **1978**, 11, 283; i) Ames, D.E.; Opalko, A. Tetrahedron, **1984**, 40, 1919.

5. Snieckus, V. Bull. Soc. Chim. France II, **1988**, 67.

6. a) Sharp, M.J.; Cheng, W.; Snieckus, V. Tetrahedron Lett., **1987**, 28, 5093; b) Cheng, W.; Snieckus, V. ibid. **1987**, 28, 5097; c) Fu, J.-m.; Sharp, M.J.; Snieckus, ibid. accompanying paper in this issue.

7. a) Prabhakar, S.; Lobo, A.M.; Marques, M.M.; Tavares, M.R. J. Chem. Research (S), **1985**, 394; b) Highet, R.J. J. Org. Chem., **1961**, 26, 4767.

8. Recently, in an innovative study leading to unusual heterocyclic systems, the cross coupling between o-formyl benzeneboronic acid and 2-bromoaniline to give phenanthridine has been reported: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.-H. Chem. Scripta, **1986**, 26, 311.

9. With the exception of o-bromobenzaldehyde (Aldrich Chem. Co.), all other bromo coupling partners were prepared by standard literature procedures.

10. For recent synthetic work, see Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L.; Roussi, G. J. Org. Chem., **1985**, 50, 4933.

11. Prepared from the corresponding bromo acid: Brown, E.; Robin, J.P.; Dhal, R. Tetrahedron, **1982**, 38, 2569.

12. Brown, H.C.; Kim, S.C.; Krishnamurthy, S. J. Org. Chem., **1980**, 45, 1.

13. Greene, T.W. **Protective Groups in Organic Synthesis**, Wiley, New York, **1981**, p 232.

14. Sakaitani, M.; Ohfune, Y. Tetrahedron Lett., **1985**, 26, 5543. Our attention to this method was drawn by the recent report of Grieco, P.A.; Hon, Y.S.; Perez-Medrano, A. J. Am. Chem. Soc., **1988**, 110, 1630.

15. mp 85-91°C, lit [7a] mp (PhH-hex) 99.5-101°C; picrate mp 161-162°C, lit [7b] mp 158-159°C; NMR ($CDCl_3$) δ 1.57 (s, 1H, D_2O exchangeable, 2.75 (s, 3H, NCH_3), 3.20 (s, 1H, D_2O exchangeable), 4.25 (dd, 2H, J = 12.0 Hz), 6.00 (s, 2H), 6.69-7.02 (m, 4H, ArH), 7.26-7.36 (m, 2H, ArH); MS, m/e 257; exact mass calculated for $C_{15}H_{15}NO_3$ 257.1053, found 257.1053.

16. All new compounds show analytical and spectral (IR, 1H NMR, MS) data in full agreement with the assigned structures.

17. We are grateful to NSERC Canada and Merck Frosst Canada for their support of our synthetic programs.

(Received in USA 14 July 1988)