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CONCISE SYNTHESES OF THE AMARYLLIDACEAE ALKALOIDS UNGERIMINE AND HIPPADINE VIA THE SUZUKI ARYL-ARYL CROSS COUPLING REACTION

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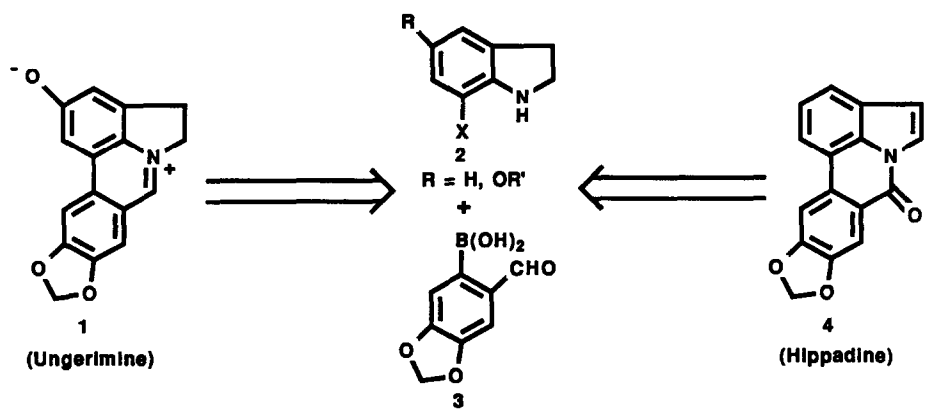
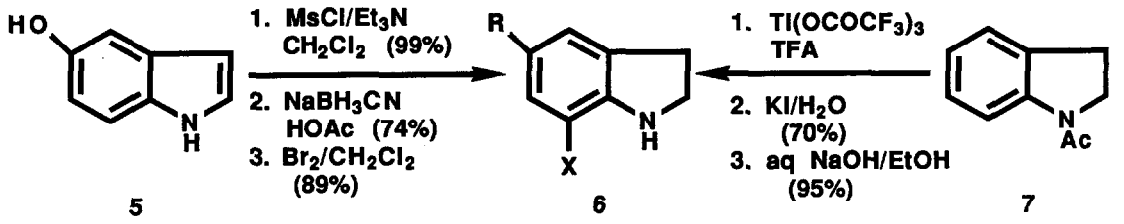
Summary: Short syntheses of the betaine alkaloid ungerimine (1) and the lactam alkaloid hippadine (4) based on aryl boronic acid - aryl halide cross coupling methodology are described.

Ungerimine (1)[1] and hippadine (4)[2] constitute two members of the pyrrolophenanthridine alkaloids which enjoy wide distribution in various *Crinum* species (Amaryllidaceae).[3] The recent finding of significant biological activities[4] has regenerated considerable synthetic interest[5] in this class of alkaloids, although to date few general approaches have been reported.[5a] As part of work aimed to develop synthetically useful connections between the directed *ortho* metalation[6] and the Suzuki cross coupling[7] strategies, we described a new general route to phenanthridines.[8] Herein we delineate short syntheses of ungerimine and hippadine based on the one-pot cross coupling - cyclization[8] of halo indolines **2** with o-formyl aryl boronic acids **3** (**Scheme 1**). This regimen embodies factors of ready accessibility of starting materials, brevity, and convenience which may have fruitful and widely encompassing consequences for the construction of pyrrolophenanthridine alkaloids and analogues.[9]



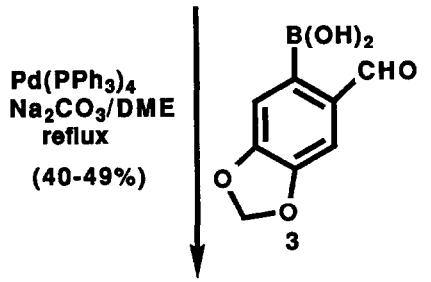
Scheme 1



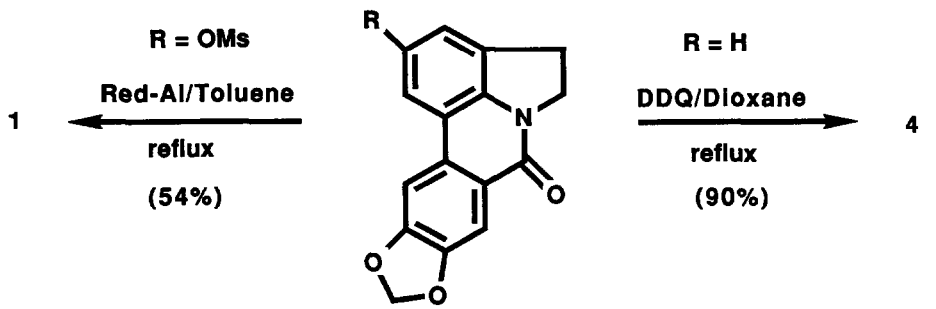
5 6 7

a: R = OMs, X = Br

b: R = H, X = I



3



1 8 4

a: R = OMs

b: R = H

Scheme 2

The synthesis of ungerimine was initiated by standard mesylation and $NaCNBH_3$ reduction[10] of commercially available 5-hydroxyindole (**5**) to give the intermediate indoline which was subjected to electrophilic bromination[11] to afford the bromoindoline **6a** in good yield. Cross coupling with the *ortho*-formyl boronic acid **3**[12] under modified Suzuki conditions [$Pd(Ph_3)_4$/aq Na_2CO_3/DME/reflux/24h][8] resulted in concomitant cyclization and aerial oxidation of the intermediate carbinol amine to give the lactam **8a** in modest yield. Reduction with excess (5 equiv) of Red-Al[13] followed by column chromatography afforded ungerimine **1** (**Scheme 2**).[14] Although ungerimine has been previously obtained from lycorine,[15] this work constitutes the first total synthesis of this alkaloid.

The synthesis of hippadine (**4**) was effected in a similarly convergent fashion. Thus thallium-mediated iodination[16] of 1-acetylindoline[17] followed by basic hydrolysis furnished the intermediate **6b**. Cross coupling using the modified Suzuki conditions mentioned above afforded the analogous lactam **8b**. DDQ oxidation[2a] led to hippadine **4** in excellent yield (**Scheme 2**).

In summary, the synthesis of ungerimine and hippadine have been achieved in 17% and 24% overall yields respectively by a short, convenient, and potentially general route which competes favorably with previous syntheses (2-18%)[5a-c] of this group of Amaryllidaceae alkaloids.[18,19]

References and Footnotes

1. Ghosal, S.; Kumar, Y.; Singh, S.K.; Kumar, A. *J. Chem. Research (S)* **1986**, 112; b) Ghosal, S.; Singh, S.K.; Srivastava, R.S. *Phytochemistry* **1986**, 25, 1975; c) Ali, A.A.; Sayed, H.M.; Abdallah, O.M.; Steglich, W. *Ibid.* **1986**, 25, 2399; d) Evidente, A.; Arrigoni, O.; Liso R.; Calabrese, G.; Randazzo, G. *Ibid.* **1986**, 25, 2739.

2. a) Ghosal, S.; Rao, P.H.; Jaiswal, D.K.; Kumar, Y.; Frahm, A.W. *Phytochemistry* **1981**, 20, 2003; b) Ghosal, S.; Saini, K.S.; Frahm, A.W. *Ibid.* **1983**, 22, 2305.

3. Grundon, M.F. *Natural Product Reports* **1989**, 6, 79.

4. Antileukemic activity (ungerimine): Cheng, R.K.Y.; Yan, S.J.; Cheng, C.C. *J. Med. Chem.* **1978**, 21, 199. Reversible inhibition of fertility (hippadine): Chattopadhyay, S.C.; Chattopadhyay, V.; Mathur, P.P.; Saini, K.S.; Ghosal, S. *Planta Med.* **1983**, 49, 252; ref 1d and refs cited therein.

5. a) Black, D.C.; Keller, P.A.; Kumar, N. *Tetrahedron Lett.* **1989**, 30, 5807 and refs cited therein; b) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Ibid.* **1987**, 28, 5895; c) Prabhakar, S.; Lobo, A.M.; Marques, M.M. *J. Chem. Research (S)* **1987**, 167; d) Joshi, B.S.; Desai, H.K.; Pelletier, S.W. *J. Natural Products* **1986**, 49, 445; e) Onaka, T.; Kanda, Y.; Natsume, M. *Tetrahedron Lett.* **1974**, 1179; f) Hara, H.; Hoshino, O.; Umezawa, B. *Ibid.* **1972**, 5031; ref 2b.

6. Snieckus, V. *Chem. Rev.* **1990**, in press; Snieckus, V. *Bull. Soc. Chim. France II.* **1988**, 67.

7. Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, 61, 3008; Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405 and refs cited therein.

8. Siddiqui, M.A.; Snieckus, V. *Tetrahedron Lett.* **1988**, 29, 5463 and refs cited therein.

9. For other recent applications of cross coupling reactions to alkaloid synthesis, see a) Miller, R.B.; Dugar, S. *Tetrahedron Lett.* **1989**, 30, 297; b) Pena, M.R.; Stille, J.K. *J. Am. Chem. Soc.* **1989**, 111, 5417.

10. Gribble, G.W.; Hoffman, J.H. *Synthesis* **1977**, 859.

11. Gall, W.G.; Astill, B.D.; Boekelheide, V. *J. Org. Chem.* **1955**, 20, 1538.

12. Gronowitz, S.; Hörnfeldt, A.B.; Yang, Y.H. *Chim. Scripta* **1986**, 26, 311.

13. Pilichowski, J.F.; Lehn, J.M.; Sauvage, J.P.; Gramain, J.C. *Tetrahedron* **1985**, 41, 1959.

14. Shown to be identical with the natural product by comparison of physical and spectral (IR, NMR, MS) properties with those reported in the literature: ungerimine (refs 1a,b); hippadine (ref 2a).

15. Fales, H.M.; Warnhoff, E.W.; Wildman, W.C. *J. Am. Chem. Soc.* **1955**, 77, 5885.

16. Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, 35, 3146.

17. Bennett, G.M.; Hafez, M.M. *J. Chem. Soc.* 1941, 287.

18. All new compounds show analytical and spectral (IR, NMR, MS) data consistent with the indicated structures.

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