

A New Approach to Pyrrolophenanthridone Alkaloids *via* Intramolecular Radical Cyclization

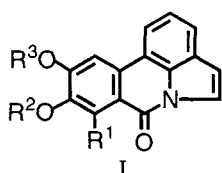
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(Received October 2, 1997; CL-970759)

A new approach to the synthesis of pyrrolophenanthridone class of alkaloids is described. The method is based on intramolecular radical cyclization of easily accessible 1-aryl-7-bromoindoles with Bu_3SnH and AIBN.

Hippadine (**1a**), pratosinine (**1b**), pratorimine (**1c**), and pratorinine (**1d**) are representative members of the pyrrolophenanthridone alkaloids isolated from various *Crinum* species (Amarillidaceae).¹ Since of their discovery, several of these alkaloids have been shown to possess significant biological activity. It has been demonstrated, for example, that hippadine (**1a**) reversibly inhibits fertility in male rats² and kalbretorine (**1e**) exhibits antitumor activity.³



- a: $\text{R}^1=\text{H}$, $\text{R}^2\text{R}^3=-(\text{CH}_2)-$
 b: $\text{R}^1=\text{H}$, $\text{R}^2=\text{R}^3=\text{CH}_3$
 c: $\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=\text{CH}_3$
 d: $\text{R}^1=\text{R}^3=\text{H}$, $\text{R}^2=\text{CH}_3$
 e: $\text{R}^1=\text{OH}$, $\text{R}^2\text{R}^3=-(\text{CH}_2)-$

Pyrrolophenanthridones have previously prepared *via* a variety of synthetic strategies⁴ involving formation of an aryl aryl bond through an inter or intramolecular coupling reaction starting from indoline derivatives. Examples of this include DDQ-dehydrogenation of dihydropyrrolophenanthridones prepared *via* oxazoline-mediated process,^{4a} intramolecular aryne cycloaddition,^{4b} palladium catalyzed coupling,^{4c,e} and modified Suzuki coupling.^{4g}

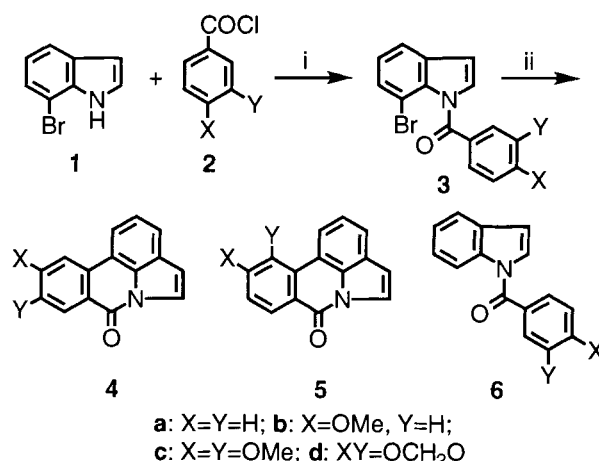
On the other hand, free radical cyclizations now constitute a major tactic in the synthesis of mono-, bi-, and polycyclic ring systems.⁵ Indeed, several examples of synthesis of 1,2-fused indoles by radical cyclization have been demonstrated.⁶⁻⁹ To the best of our knowledge, however, attempts to prepare 1,7-fused indoles by intramolecular radical strategy have not heretofore been reported. Intramolecular radical cyclization of 1-aryl-7-bromoindoles seems to provide a promising route to pyrrolophenanthridones. In fact this strategy offered a new concise synthetic route to pyrrolophenanthridones including hippadine (**1a**) and pratosinine (**1b**). In this connection intramolecular radical cyclization of 1-(2-bromobenzoyl)-3-methylindole is also described.

1-Aroyl-7-bromoindoles (**3**) were prepared by the reaction of 7-bromoindole (**1**)¹⁰ with the corresponding aroyl chlorides (**2**) as shown in Scheme 1. Thus aroylation of the indole **1** using NaH in THF furnished the corresponding aroylindoles (**3**) in good yield, respectively.

Treatment of **3** (1.0 mmol) with Bu_3SnH (1.5 mmol) in the presence of azobisisobutyronitrile (AIBN) (0.25 mmol) in boiling benzene (150 ml) for 10 h resulted in radical cyclization with oxidation to give regioisomeric pyrrolophenanthridones (**4**) and (**5**) along with reduction product (**6**).¹¹ The result stands in a

striking contrast to the palladium catalyzed cyclization in which 1-piperonylindole gave a mixture of two regioisomeric 1,2-fused indoles.^{4c}

The results are shown in Scheme 1 and Table 1.



Reagents and conditions: i, NaH, rt, THF, 15 h
 ii, Bu_3SnH , AIBN, reflux, C_6H_6 .

Scheme 1.

Table 1. N-Aroylation of **1** and radical cyclization of aroylindoles **3**^a

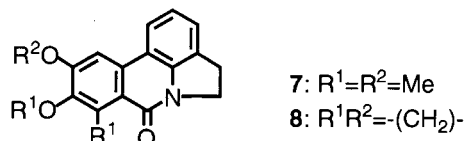
Aroylation of 1 ^b		Radical cyclization of 3 ^c			
		Pyrrolophenanthridones			
Aroylindoles 3		4		5	
	Mp/°C Yield/%	Mp/°C	Yield/%	Mp/°C	Yield/%
3a	68-69 84	4a	145-147 48		
3b	99 75	4b	187-188 52		
3c	177 82	4c	238-239 42	5c	201-202 26
4d	107-108 78	4d	218-219 29	5d	226-227 20

^aIsolated yield are shown. ^bIn all aroylations, the corresponding 1,3-diaroylindoles were formed in small amounts. ^cReduction products **6a**, **6b**, **6c** and **6d** were also isolated in 21, 8, 2, and 20% yields, respectively.

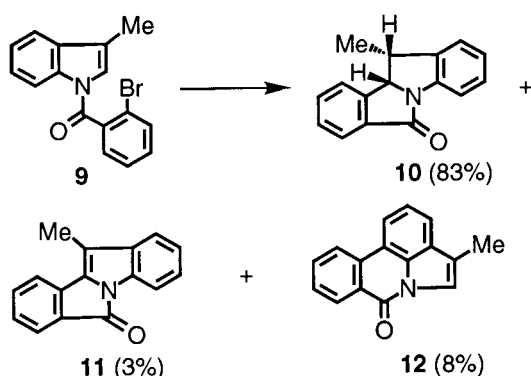
On the basis of their spectral data **4c** and **4d** were assigned to pratosinine (**1b**) and hippadine (**1a**), respectively.¹² Since **1a** has previously been converted into pratorinine (**1d**),¹³ this work also constitutes a formal synthesis of **1d**.

In addition, **4c** and **4d** were quantitatively converted into oxoassoarine (**7**) (mp 269 °C, lit.^{4a} mp 268-269 °C) and

anhydrolycocyin-7-one (**8**) (mp 233 °C, lit.¹³ mp 228-230 °C), respectively, by formic acid-catalytic transfer hydrogenation.¹⁴



In connection with the above work, we became interested in the radical cyclization of 1-(2-bromobenzoyl) substituted indole. Thus, the similar radical cyclization of 1-(2-bromobenzoyl)-3-methylindole (**9**)¹⁵ with Bu_3SnH and AIBN in refluxing benzene for 3 h was investigated. Interestingly, 1,7-fused pyrrolophenanthridone (**12**) was obtained,¹⁶ besides 1,2-fused cis-10b,11-dihydro-6H-11-methylisoidolo[2,1-a]indol-6-one (**10**) and its dehydrogenated derivative (**11**) (Scheme 2).



Scheme 2.

In conclusion, intramolecular radical cyclization of 1-aryl-7-bromindoles offered a versatile route to pyrrolophenanthridones: The synthesis of hippadine (**1a**) and pratosinine (**1b**) has been achieved in 23 and 34% overall yields respectively by a short, convenient and potentially general route which competes favorably with previous syntheses⁴ of this group of Amaryllidaceae alkaloids.

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- 11 All the new compounds gave satisfactory analytical and spectroscopic data.
- 12 **4c**: pale yellow needles (CH_3CN), mp 238-239 °C (lit.^{4a} mp 234-235 °C); 1H NMR ($CDCl_3$) δ 4.03, 4.10 (each 3H, s), 6.87 (1H, d, $J=3.6$ Hz, H-4), 7.43 (1H, t, $J=7.6$ Hz, H-2), 7.58 (1H, s, H-11), 7.60-7.91 (2H, m, H-1, H-3), 7.94 (1H, s, H-8), 8.02 (1H, s, H-5); ^{13}C NMR ($CDCl_3$) δ 56.20, 56.24, 103.69, 110.09, 110.61, 116.60, 117.98, 120.79, 122.32, 123.49, 123.86, 128.47, 129.44, 131.11, 149.65, 153.67, 158.30. **4d**: colorless needles (EtOH), mp 218-219 °C (lit.^{4a} mp 217-218 °C); 1H NMR ($CDCl_3$) δ 6.15 (2H, s), 6.88 (1H, d, $J=3.6$ Hz, H-4), 7.44 (1H, t, $J=7.6$ Hz, H-2), 7.62 (1H, s, H-11), 7.70-7.90 (2H, m, H-1, H-3), 7.96 (1H, s, H-8), 8.03 (1H, d, $J=3.6$ Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 101.62, 1002.27, 107.94, 110.73 (2), 116.63, 118.31, 122.55, 123.47 (2), 123.92, 128.35, 131.56, 148.46, 152.52, 158.06.
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- 15 The compound **9** (mp 111 °C) was obtained in 94% yield by the reaction of 3-methylindole with 2-bromobenzoyl chloride in the presence of NaH in dry THF.
- 16 **12**: Yellow needles (hexane), mp 184-185 °C; 1H NMR ($CDCl_3$) δ 2.41 (3H, d, $J=1.3$ Hz), 7.21-7.70 (3H, m), 7.76 (1H, d, $J=1.3$ Hz), 7.80-8.71 (3H, m); ^{13}C NMR ($CDCl_3$) δ 10.16, 116.51, 118.50, 120.32, 121.04, 121.43, 122.59, 123.70, 127.34, 128.01, 129.41, 129.66, 1331.78, 132.77, 134.29, 158.22; MS m/z 233 (M^+). Dehydrogenation of **10** (mp 124 °C) with 5% Pd-C in decalin (reflux, 20 h) gave **11** (mp 174-175 °C) in 65% yield.