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Intramolecular Palladium-Catalyzed Cyclization of Methyl 1-(2-Bromobenzyl)indole-2-carboxylates: Synthesis of Pratosine and Hippadine

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Abstract: Palladium-catalyzed cyclization of methyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2-carboxylate in the presence of potassium acetate in hot 1,4-dioxane gave a 7*H*-pyrrolo[3,2,1-*de*]phenanthridine derivative, which was converted to pratosine in four steps. In a similar manner, hippadine was also prepared.

Keywords: Alkaloids; Coupling reaction; Decarbonylation; Indoles; Palladium and compounds

Pratosine (**1a**),[1] hippadine (**1b**),[2] and kalbretorine (**1c**)[3] are 7*H*-pyrrolo[3,2,1-*de*]phenanthridine alkaloids, isolated from various species of *Amaryllidaceae*. This family has significant biological activities; for example, hippadine (**1b**)[4] inhibits fertility in male rats and kalbretorine (**1c**)[3] has antitumor activity. 7*H*-Pyrrolo[3,2,1-*de*]phenanthridine alkaloids were synthesized by allene intramolecular cycloaddition,[5] intramolecular cycloaddition of α-pyrone,[6] aryl-aryl cross-coupling reaction of 7-unsubstituted,[7a] 7-halogeno,[7b,c] 7-cuprated,[7d] and 7-stanylated indolines,[7e] and aryl-aryl cross-coupling reaction of 7-bromoindole derivatives.[8] Attempts to synthesize 7*H*-pyrrolo[3,2,1-*de*]phenanthridine from radical cyclization of 1-benzyl-7-bromoindole resulted in low yields.[9] In this paper we report a simple and useful synthesis of pratosine (**1a**) and hippadine (**1b**) by palladium-catalyzed intramolecular cyclization of methyl 1-(2-bromobenzyl)indole-2-carboxylate derivatives (**2**).

Treatment of dimethyl 1-(2-bromo-4,5-dimethoxybenzyl)indole-2,3-dicarboxylate (**2a**) in hot dioxane in the presence of $Pd(PPh_3)_4$ and potassium acetate gave dimethyl 9,10-dimethoxy-7*H*-pyrrolo[3,2,1-*de*]-phenanthridine-4,5-dicarboxylate (**3a**) in 76% yield. In a similar manner, methyl 7*H*-pyrrolo[3,2,1-*de*]-phenanthridine-5-carboxylates (**3b**) and (**3c**) were easily obtained from **2b** and **2c** in 96% and 91% yields, respectively.

$LiAlH_4$ reduction of methyl ester (**3b**) (95%) followed by the Dess-Martin oxidation (84%) gave the corresponding aldehyde, which was converted to pratosine (**1a**) by MnO_2 oxidation (76%), then decarbonylation using $RhCl(PPh_3)_3$ in hot xylene in the presence of dppp ($Ph_2P(CH_2)_3PPh_2$) in 84% yield. In a similar manner, hippadine (**1b**) was also obtained from **3c** by $LiAlH_4$ reduction (94%), Dess-Martin oxidation and MnO_2 oxidation (71%), and decarbonylation(79%).

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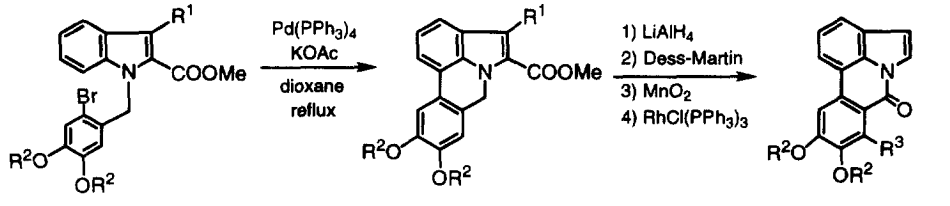

a; R^1 = COOMe, R^2 = Me
b; R^1 = H, R^2 = Me
c; R^1 = H, R^2 = -CH_2-

a; R^2 = Me, R^3 = H
b; R^2 = -CH_2-, R^3 = H
c; R^2 = -CH_2-, R^3 = OH

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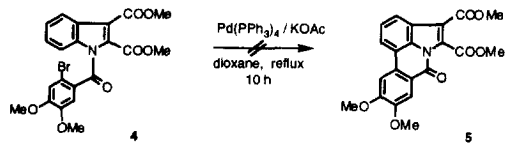
10. Methyl 1-(2-bromobenzyl)indole-2-carboxylates (**2a-c**) were prepared from 2-bromobenzyl bromides and methyl indole-2-dicarboxylates in hot acetonitrile in the presence of potassium carbonate in 78%, 83%, and 85% yields, respectively.
11. Attempts to obtain the 7*H*-pyrrolo[3,2,1-*de*]phenanthridone (**5**) from dimethyl 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**4**) resulted in failure and the starting material was recovered.



12. Pratosine (**1a**): mp 234-235°C (Et_2O-MeOH) (lit.,[1] 232-233°C); IR (Nujol) cm^{-1}: 1670; ^{1}H-NMR ($CDCl_3$) δ: 4.07 (3H, s, OMe), 4.12 (3H, s, OMe), 6.90 (1H, d, *J* = 4 Hz, H-4), 7.48 (1H, t, *J* = 7.5 Hz, H-2), 7.64 (1H, s, H-8), 7.75 (1H, dd , *J* = 7.5, 0.5 Hz, H-3), 7.96 (1H, dd , *J* = 7.5, 0.5 Hz, H-1), 7.99 (1H, s, H-11), 8.05 (1H, d, *J* = 4 Hz, H-5). HRMS *m/z* (M^+) calcd for $C_{17}H_{13}NO_3$: 279.0895. Found: 279.0891.
Hippadine (**1b**): mp 215-216°C (*n*-hexane-acetone) (lit.,[2] 209-210°C, lit.,[13] 217-218°C); IR (Nujol) cm^{-1}: 1673; ^{1}H-NMR ($CDCl_3$) δ: 6.17 (2H, s, CH_2), 6.90 (1H, d, *J* = 4 Hz, H-4), 7.48 (1H, t, *J* = 8 Hz, H-2), 7.66 (1H, s, H-8), 7.76 (1H, dd, *J* = 8, 0.5 Hz, H-3), 7.92 (1H, dd, *J* = 8, 0.5 Hz, H-1), 7.99 (1H, s, H-11), 8.04 (1H, d, *J* = 4 Hz, H-5). HRMS *m/z* (M^+) calcd for $C_{16}H_9NO_3$: 263.0582. Found: 263.0579.