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CONCISE SYNTHESIS OF PYRROLOPHENANTHRIDINE ALKALOIDS USING A Pd-CATALYZED BIARYL COUPLING REACTION WITH REGIOSELECTIVE C-H ACTIVATION

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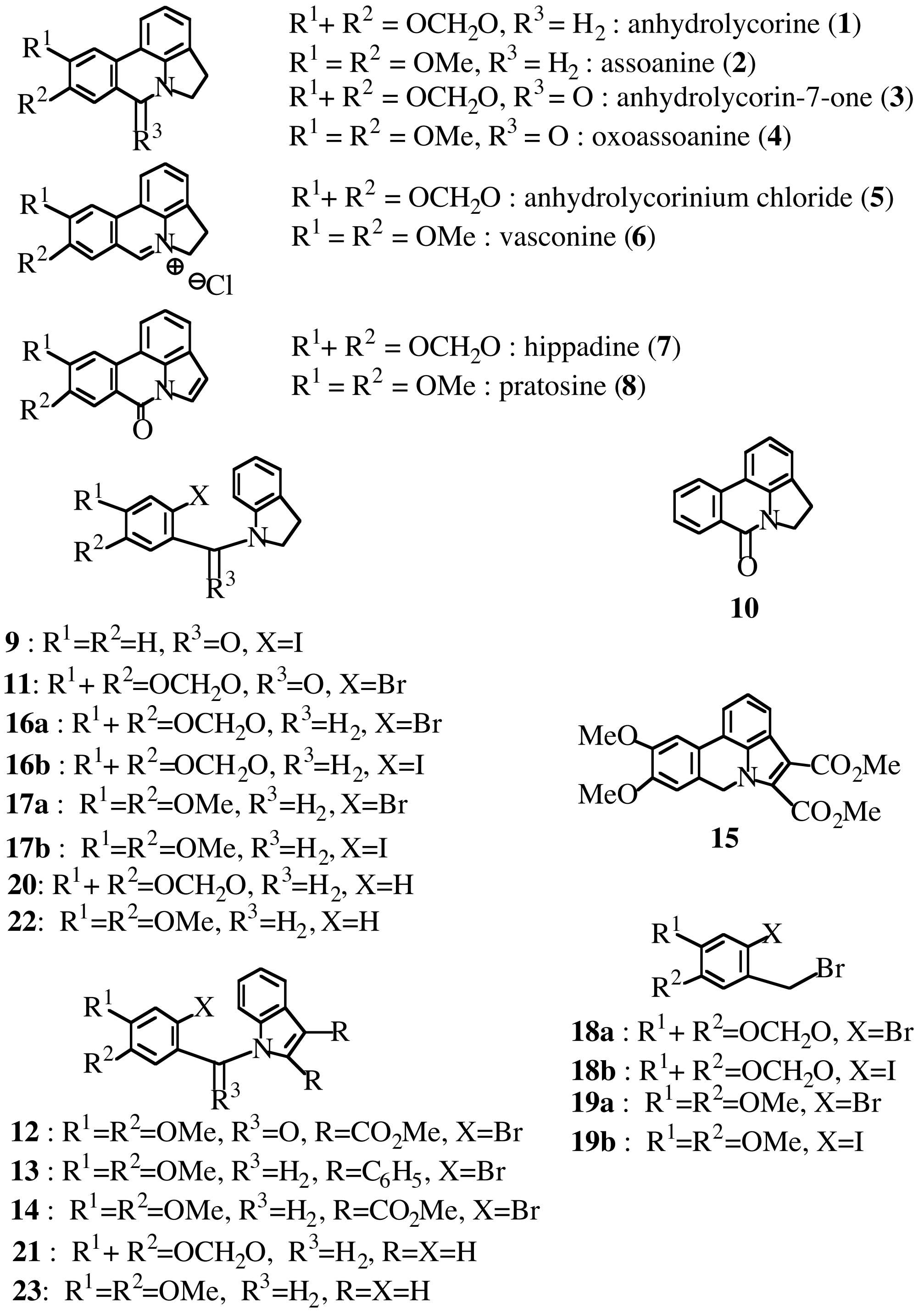
Abstract – The concise synthesis of the pyrrolophenanthridine alkaloids such as anhydrolycorine, assoanine, anhydrolycorin-7-one, and oxoassoanine, was achieved using the Pd-catalyzed biaryl coupling reaction of 1-(2-halobenzyl)-2,3-dihydroindole by applying the regioselective C-H activation method with intramolecular coordination of the benzylamino group to Pd.

The significant biological activities[1] and unique polycyclic structures of pyrrolophenanthridine alkaloids (*e.g.*, **1** ~ **8**) has led to recent interest in developing new synthetic methods for these alkaloids.[2, 3] Some of these attempts involve an intramolecular aryl-aryl coupling reaction with Pd reagent as the key step, including the dehydrogenation between an arene and an arene with $Pd(OAc)_2$ in acetic acid,[4] a Heck-type reaction between a monobromoarene and an arene with a Pd reagent,[3, 4a, 5] and the intramolecular coupling reaction of a bis-haloarene with a Pd reagent.[6] We reported the synthesis of several benzo[*c*]phenanthridine alkaloids using Pd-catalyzed biaryl coupling reactions of 2-halo-*N*-naphthylbenzamides.[7] In a preliminary study on the synthesis of pyrrolophenanthridine alkaloids, the biaryl coupling reaction of 1-(2-iodobenzoyl)-2,3-dihydroindole (**9**) with $Pd(OAc)_2$ in the presence of K_2CO_3 in DMA was examined. However, the desired dihydropyrrolophenanthridone (**10**) was obtained only in 8% yield.[8] Cai *et al.* reported that the reaction of 1-(2-bromobenzoyl)-2,3-dihydroindole (**11**) using $Pd(OAc)_2$ and K_2CO_3 in DMA in the absent of phosphine ligand afforded **1** in 55% yield,[5a, 9] whereas Miki *et al.* recorded that 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**12**) with $Pd(PPh_3)_4$ gave no coupling product.[3] Moreover, the Heck-type reaction of 1-(2-bromobenzyl)-2,3-diphenylindole (**13**) gave no coupling product,[4a] whereas the reaction of dimethyl 1-(2-bromobenzyl)indole-2,3-dicarboxylate (**14**) with $Pd(PPh_3)_4$ gave the coupling product (**15**).[3] Recently, we developed a method of synthesizing a new skeletal compound, naphthobenzazepine, by regioselective C-H activation using the intramolecular coordination of a benzylamine to Pd.[11, 12] We applied this strategy to the synthesis of pyrrolophenanthridine alkaloids, as shown in Scheme 2. We envisioned that the intramolecular biaryl coupling reaction of 1-(2-halobenzyl)dihydroindole (**A**) using Pd reagent would afford dihydropyrrolophenanthridine (**B**) directly, *via* an oxidative addition to Pd(0) and coordination of



$R^1 + R^2 = OCH_2O$, $R^3 = H_2$: anhydrolycorine (**1**)
$R^1 = R^2 = OMe$, $R^3 = H_2$: assoanine (**2**)
$R^1 + R^2 = OCH_2O$, $R^3 = O$: anhydrolycorin-7-one (**3**)
$R^1 = R^2 = OMe$, $R^3 = O$: oxoassoanine (**4**)

$R^1 + R^2 = OCH_2O$: anhydrolycorinium chloride (**5**)
$R^1 = R^2 = OMe$: vasconine (**6**)

$R^1 + R^2 = OCH_2O$: hippadine (**7**)
$R^1 = R^2 = OMe$: pratosine (**8**)

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9 : $R^1 = R^2 = H$, $R^3 = O$, X=I
11: $R^1 + R^2 = OCH_2O$, $R^3 = O$, X=Br
16a : $R^1 + R^2 = OCH_2O$, $R^3 = H_2$, X=Br
16b : $R^1 + R^2 = OCH_2O$, $R^3 = H_2$, X=I
17a : $R^1 = R^2 = OMe$, $R^3 = H_2$, X=Br
17b : $R^1 = R^2 = OMe$, $R^3 = H_2$, X=I
20: $R^1 + R^2 = OCH_2O$, $R^3 = H_2$, X=H
22: $R^1 = R^2 = OMe$, $R^3 = H_2$, X=H

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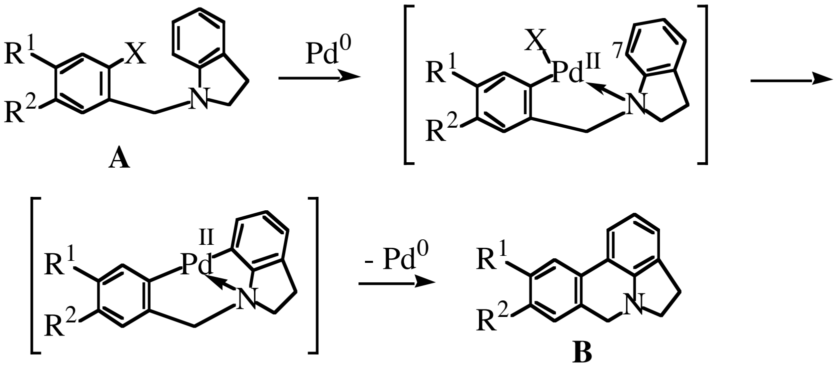
18a : $R^1 + R^2 = OCH_2O$, X=Br
18b : $R^1 + R^2 = OCH_2O$, X=I
19a : $R^1 = R^2 = OMe$, X=Br
19b : $R^1 = R^2 = OMe$, X=I

12 : $R^1 = R^2 = OMe$, $R^3 = O$, $R = CO_2Me$, X=Br
13 : $R^1 = R^2 = OMe$, $R^3 = H_2$, $R = C_6H_5$, X=Br
14 : $R^1 = R^2 = OMe$, $R^3 = H_2$, $R = CO_2Me$, X=Br
21 : $R^1 + R^2 = OCH_2O$, $R^3 = H_2$, R=X=H
23: $R^1 = R^2 = OMe$, $R^3 = H_2$, R=X=H

Scheme 1. Pyrrolophenanthridine alkaloids and related compounds



Scheme 2. Strategy and proposed mechanism for synthesis of pyrrolophenanthridine (**B**) from 1-(2-halobenzyl)dihydroindole (**A**)

Table 1. Results of biaryl coupling reactions of 1-(2-halo-4,5-methylenedioxybenzyl)-2,3-dihydroindole (**16**). a)

substrate		Pd $(OAc)_2$ (mol%)	ligand (L/Pd) b)	temp.	time	yield (%)			
						1	**3**	**20**	**21**
16a	1	10	P(*o*-tol)$_3$ (2)	125°C	1.5 h	37	15	23	16
	2	10	Cy$_3$P (2)	125°C	1 h	50	6	17	8
	3c)	20	P(*o*-tol)$_3$ (2)	125°C	3 h	trace	45	19	8
16b	4	5	Cy$_3$P (2)	125°C	1.5 h	48	12	21	12
	5d)	5	-	115°C	3.5 h	50	11	17	12

a) The reaction was carried out in a degassed DMF and under Ar atmosphere. 200 mol% of K_2CO_3 was added. b) Molar ratio between ligand and Pd. c) The reaction was carried out in an air atomosphere. d) 100 mol% of n-Bu_4NCl and 300 mol % of K_2CO_3 were added.

Table 2. Results of biaryl coupling reactions of 1-(2-halo-4,5-dimethoxybenzyl)-2,3-dihydroindole (**17**). a)

substrate		Pd $(OAc)_2$ (mol%)	ligand (L/Pd) b)	temp.	time	yield (%)			
						2	**4**	**22**	**23**
17a	1	10	P(*o*-tol)$_3$ (2)	140°C	2 h	28	13	28	18
	2	10	Cy$_3$P (2)	125°C	1 h	45	13	26	3
	3c)	20	P(*o*-tol)$_3$ (2)	125°C	3 h	trace	34	11	10
17b	4	5	Cy$_3$P (2)	125°C	1 h	24	10	33	4
	5d)	5	-	125°C	4 h	43	6	22	11

a) The reaction was carried out in a degassed DMF and under Ar atmosphere. 200 mol% of K_2CO_3 was added. b) Molar ratio between ligand and Pd. c) The reaction was carried out in an air atomosphere. d) 100 mol% of n-Bu_4NCl and 300 mol % of K_2CO_3 were added.

the amine to Pd(II), followed by the regioselective electrophilic substitution of Pd(II) at the C_7 position of the dihydroindole moiety (forming a four-membered palladacycle)[13] and the reductive elimination of

Pd(0).

The starting materials (**16**[14] and **17**[14]) for the synthesis of anhydrolycorine (**1**) and assoanine (**2**) were prepared from dihydroindole and the 2-halobenzyl bromides (**18a**,[15a] **18b**,[15b] **19**,[15c] and **19b**[15d]) in the presence of *i*-Pr_2NEt in dry CH_3CN at 70°C, in 64~91% yield. The intramolecular coupling reaction of 1-(2-bromobenzyl)-2,3-dihydroindole (**16a**[14] and **17a**[14]) and 1-(2-iodobenzyl)-2,3-dihydroindole (**16b**[14] and **17b**[14]) using Pd were examined; the results are summarized in Tables 1 and 2. The reaction of **16a** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in a degassed DMF under an Ar atmosphere gave **1**[16a, 17] and anhydrolycorin-7-one (**3**) [16a, 17] in 37% and 15% yield, respectively, along with **20**[14] and **21**[14] (run 1, Table 1), and the reaction under an air atmosphere gave **3** in 45% yield (run 3, Table 1).[16a, 18] The reaction of **17a** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in a degassed DMF under an Ar atmosphere gave **2**[16d, 17] and oxoassoanine (**4**) [16c, 17] along with **22**[14] and **23**[14] (run 1, Table 2), and the reaction under an air atmosphere gave **4** in 34% yield (run 3, Table 2).[18]. The reaction of **16a** and **17a** using PCy_3 as a ligand gave the coupling products in better yield (runs 2, Tables 1 and 2). [16c]

Subsequently, the biaryl coupling reaction of **16b**[14] and **17b**[14], which are more reactive than bromo compounds, was examined, in order to improve the yield, but the yields were not improved. (runs 4, Tables 1 and 2) In these cases, Jeffery's conditions[18] gave the coupling products in higher yields. (runs 5, Tables 1 and 2)

In conclusion, the concise synthesis of pyrrolophenanthridine alkaloids was accomplished by applying a strategy utilizing regioselective C-H activation by the intramolecular coordination of the benzylamino group to Pd. [11]

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8 The biaryl coupling reaction of 1-benzoyl-7-iodo-2,3-dihydroindole with Pd(OAc)$_2$, *n*-Bu$_3$P, diphenylphosphinopropane, and Ag$_2$CO$_3$ in DMF under reflux for 30 min[7d] gave **10** in 79% yield. However, the reaction of **9** under the same conditions gave a mixture of **9** and an unidentified compound.

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14 **16a** : mp 66-67°C; ^{1}H-NMR (200 MHz, CDCl$_3$) δ=3.01 (2H, t, *J*=8.3), 3.41 (2H, t, *J*=8.0), 4.21 (2H, s). **16b** : mp 74.5-75.5°C; ^{1}H-NMR (200 MHz, CDCl$_3$) δ=3.02 (2H, t, *J*=8.1), 3.40 (2H, t, *J*=8.1), 4.15

(2H, s). **17a** : mp 68-69°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ=3.01 (2H, t, *J*=8.3), 3.38 (2H, t, *J*=8.32), 4.23 (2H, s). **17b** : mp 93-94°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ=3.01 (2H, t, *J*=8.2), 3.40 (2H, t, *J*=8.2), 4.20 (2H, s). **20** : oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ=2.96 (2H, t, *J*=8.2), 3.29 (2H, t, *J*=8.2), 4.16 (2H, s). **21** : mp 82-83°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ=5.22 (2H, s), 6.53 (1H, d, *J*=3.4), 7.12 (1H, d, *J*=3.4). **22** : mp 77-78°C ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ=2.97 (2H, t, *J*=8.0), 3.33 (2H, t, *J*=8.0), 4.21 (2H, s). **23** : mp 61.5-62.5°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ=5.25 (2H, s), 6.53 (1H, d, *J*=3.6), 7.11 (1H, d, *J*=3.6).

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17 **Anhydrolycorin** (**1**) **:** mp 110-112.5°C (lit.,[16a] 108-111°C). **Anhydrolycorin-7-one** (**3**) **:** mp 236-237°C (lit.,[16b] 232-234°C). **Assoanine** (**2**) **:** mp 165.5-168°C (lit.,[16d] 175-176°C). **Oxoassoanine** (**4**) **:** mp 272.5-274.5°C (lit.,[16d] 271-272°C). It is known that the compounds (**1** and **3**) were easily oxidized in an air to produce **2**[16a] and **4**[16c], repectively. The ^{1}H-NMR spectral data of the synthetic samples were identical with the reported data of the authentic samples.[16b, 16d]

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