

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

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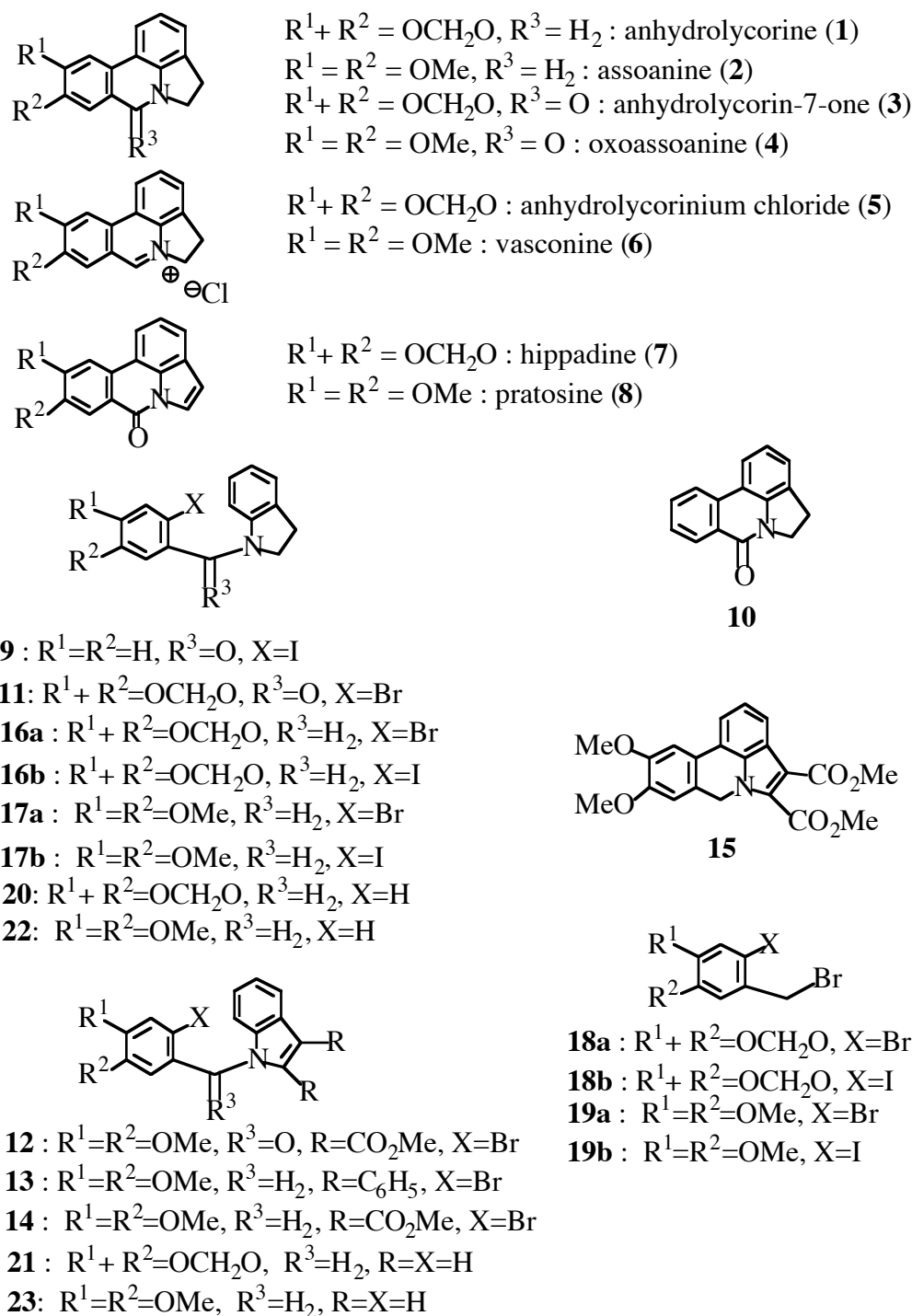
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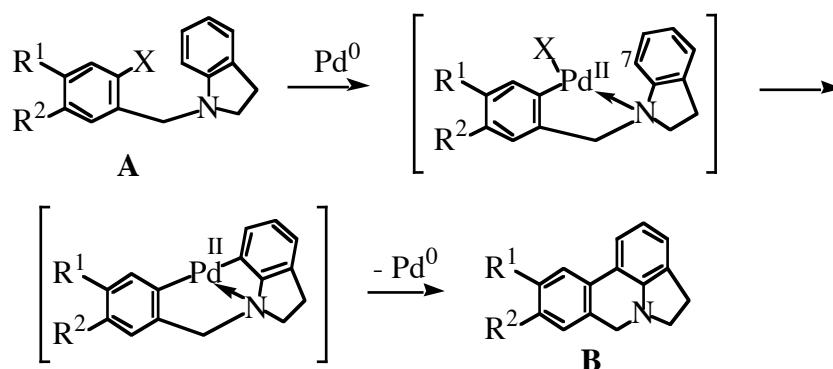
Abstract – The concise synthesis of the pyrrolophenanthridine alkaloids such as anhydrolycorine, assoanine, anhydrolycorin-7-one, and oxoassoanine, was achieved using the Pd-catalyzed biaryl coupling reaction of 1-(2-halobenzyl)-2,3-dihydroindole by applying the regioselective C-H activation method with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

The significant biological activities¹ 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 K₂CO₃ 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 K₂CO₃ 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(PPh₃)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(PPh₃)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



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(<i>o</i> -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
	3 ^{c)}	20	P(<i>o</i> -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
	5 ^{d)}	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 K₂CO₃ was added. b) Molar ratio between ligand and Pd. c) The reaction was carried out in an air atmosphere. d) 100 mol% of n-Bu₄NCl and 300 mol % of K₂CO₃ 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(<i>o</i> -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
	3 ^{c)}	20	P(<i>o</i> -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
	5 ^{d)}	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 K₂CO₃ was added. b) Molar ratio between ligand and Pd. c) The reaction was carried out in an air atmosphere. d) 100 mol% of n-Bu₄NCl and 300 mol % of K₂CO₃ were added.

the amine to Pd(II), followed by the regioselective electrophilic substitution of Pd(II) at the C₇ 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*-Pr₂NEt in dry CH₃CN 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 K₂CO₃ 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 K₂CO₃ 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 PCy₃ 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 conditions¹⁸ 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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 - 14 **16a** : mp 66-67°C; ¹H-NMR (200 MHz, CDCl₃) 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; ¹H-NMR (200 MHz, CDCl₃) δ =3.02 (2H, t, *J*=8.1), 3.40 (2H, t, *J*=8.1), 4.15

- (2H, s). **17a** : mp 68-69°C; ¹H-NMR (200 MHz, CDCl₃) δ =3.01 (2H, t, *J*=8.3), 3.38 (2H, t, *J*=8.32), 4.23 (2H, s). **17b** : mp 93-94°C; ¹H-NMR (200 MHz, CDCl₃) δ =3.01 (2H, t, *J*=8.2), 3.40 (2H, t, *J*=8.2), 4.20 (2H, s). **20** : oil; ¹H-NMR (200 MHz, CDCl₃) δ =2.96 (2H, t, *J*=8.2), 3.29 (2H, t, *J*=8.2), 4.16 (2H, s). **21** : mp 82-83°C; ¹H-NMR (200 MHz, CDCl₃) δ =5.22 (2H, s), 6.53 (1H, d, *J*=3.4), 7.12 (1H, d, *J*=3.4). **22** : mp 77-78°C ; ¹H-NMR (200 MHz, CDCl₃) 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; ¹H-NMR (200 MHz, CDCl₃) 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}, respectively. The ¹H-NMR spectral data of the synthetic samples were identical with the reported data of the authentic samples.^{16b, 16d}
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