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REGIOSELECTIVITY IN THE BIARYL COUPLING REACTIONS OF 1-[(1,3-BENZODIOXOL-5-YL)METHYL]-7-IODO-2,3-DIHYDROINDOLE USING PALLADIUM REAGENT

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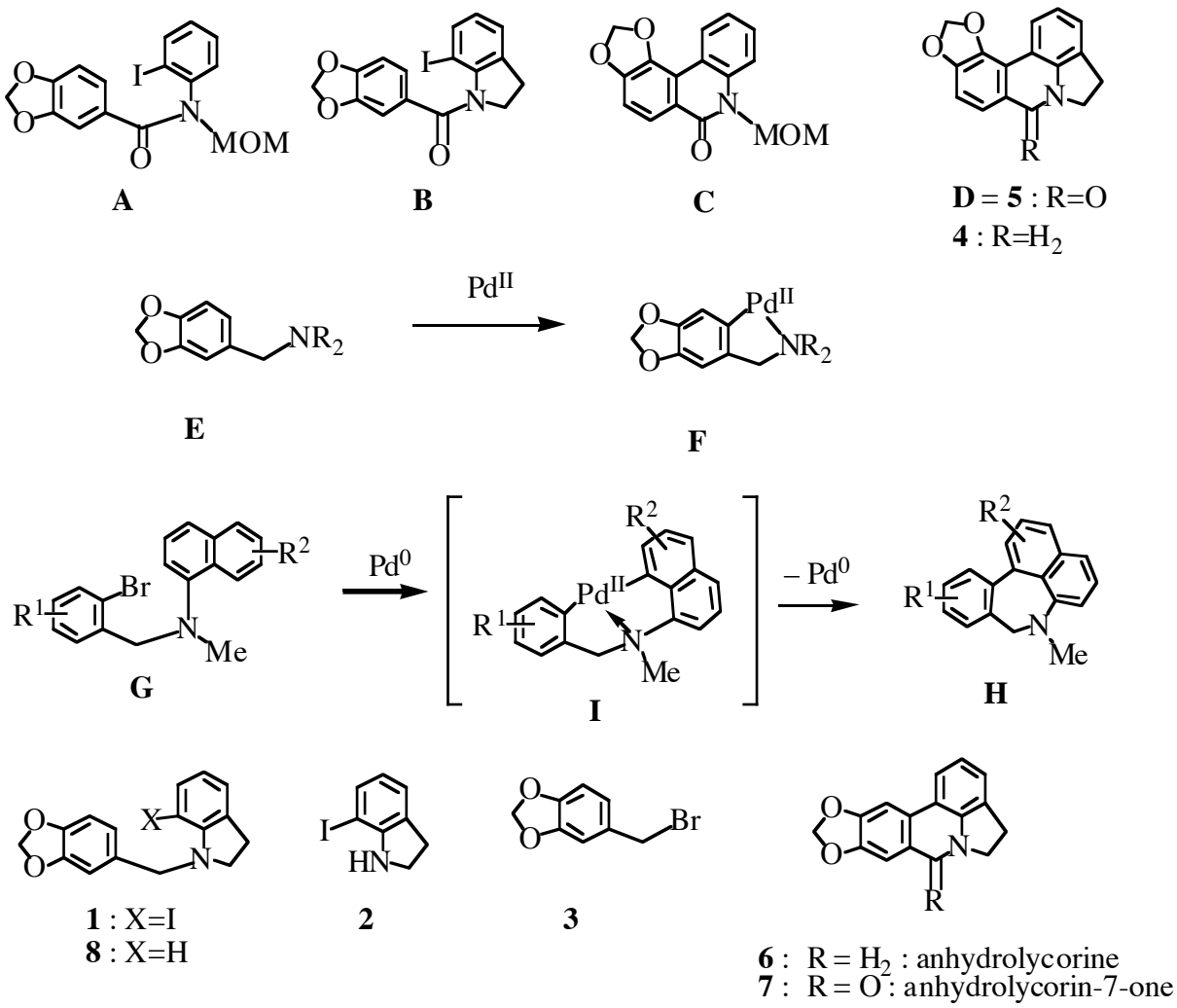
Abstract – The biaryl coupling reaction of 1-[(1,3-benzodioxol-5-yl)methyl]-7-iodo-2,3-dihydroindole (**1**) using $Pd(OAc)_2$ gave selectively 4,5-dihydro-7*H*-[1,3]dioxolo[4,5-*k*]pyrrolo[3,2,1-*de*]phenanthridine (**4**), which was formed by connection to a more hindered carbon, in 3.4~4.2:1 ratios.

Palladium-assisted biaryl coupling reactions have been used to synthesize many polycyclic aromatic compounds.[1] Recently, we reported that an intramolecular biaryl coupling reaction of 2-halo-*N*-arylbenzamides using palladium reagents was a convenient and versatile method to synthesize condensed aromatic lactams, some of which can be transformed into polycyclic aromatic alkaloids.[2] Moreover, we successfully synthesized pyrrolophenanthridine and quinazoline alkaloids *via* an intramolecular palladium-assisted aryl-aryl coupling reaction.[3]

In studies of the synthesis of trisphaeridine and pyrrolophenanthridine alkaloids, we found a palladium-assisted biaryl coupling reaction of amides possessing a methylenedioxy group on the benzoyl part and an iodo group as the leaving group on the aniline part, such that **A** and **B**, produced *ortho*-products such as **C** and **D** as major products, in 4~6:1 ratios.[2d,4] These results indicate that the biaryl coupling of amides (**A** and **B**) occurred selectively at the more hindered position and that the methylenedioxy group would affect the regioselectivity at the cyclization position. By contrast, the cyclopalladation of benzylamine (**E**) gave the palladacycle (**F**), the *para*-product.[5] Moreover, we reported that the coupling reaction of *N*-benzylnaphthylamine (**G**) produced a seven-membered compound (**H**) *via* a coordinated intermediate (**I**) of benzylamine to Pd^{II}.[6] Therefore, we were interested in investigating whether similar selectivity



Scheme 1. Pyrrolophenanthridine alkaloids and related compounds

Table 1. Results of biaryl coupling reaction of 1-[(1,3-benzodioxol-5-yl)methyl]-7-iodo-2,3-dihydroindole (**1**)[a)]

run		ligand (L/Pd) [b)]	temp.	time	yeild (%)				
					4	**6**	**5+7 (5:7)**[c)]	**8**	**(4+5) :(6+7)**
1	A	P(*o*-tol)$_3$ (2)	125°C	2.5 h	55	14	3 (3.5:1)	17	3.9:1
2	B	P(*o*-tol)$_3$ (2)	125°C	2 h	trace	trace	75 (4.0:1)	12	4.0:1
3	A	n-Bu$_3$P (2)	125°C	1 h	40	9	4 (3.2:1)	17	4.2:1
4[d)]	A	-	115°C	3 h	52	15	4 (2.5:1)	5	3.4:1

a) The reaction was carried out using Pd(OAc)$_2$(5 mol%), K_2CO_3 (200 mol%) in degassed DMF under the conditions indicated (A: Ar, B: air). b) The molar ratio of the ligand and Pd. c) The ratio was determined by ^{1}H-NMR spectral(200 MHz) and HPLC (Chemcosorb 5Si-U, λ =254 nm, flow rate = 0.5 ml/min, IPA:hexane = 1:6, t_R = 15.5 and 17.7 min.) analysis. d)100 mol% of n-Bu$_4$NCl and 300 mol% of K_2CO_3 were added.

occurred in the palladium-assisted coupling reaction of 1-[(1,3-benzodioxol-5-yl)methyl-7-iodo-2,3-dihydroindole (**1**), possessing a methylenedioxy group, in which coordination of benzylamine to palladium was expected.

The amine (**1**) was prepared by benzylation of 7-iododihydroindole (**2**)[7] with 5-bromomethyl-1,3-benzodioxole (**3**)[8] in 83% yield. The results of the coupling reaction of **1** using a palladium reagent are summarized in Table 1. The reaction of **1** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 under an argon atmosphere afforded the *ortho*- (**4** and **5**) and *para*- (**6** and **7**) coupled products in a ratio of 3.9:1 with a total yield of 72%, along with a 17% yield of the deiodo amine (**8**) (run 1 in Table 1). The reaction of **1** under air gave a mixture of the oxidized *ortho*- (**5**) and *para*-(**7**) coupled products, in a 4.0:1 ratio (run 2 in Table 1).[3b] The reaction of **1** under butylphosphine produced the *ortho*-coupled products selectively in 4.2:1 ratio (run 3 in Table 1). Interestingly, the reaction under Jeffery's conditions in the absence of phosphine ligand[9] gave the *ortho*-products selectively in 3.4:1 ratio, which was compatible to those in the presence of phosphine ligand (run 4 in Table 1). Minor compounds (**6** and **7**) were identified with authentic samples of pyrrolophenenthridine alkaloids (anhydrolycorin[3b] and anhydrolycorin-7-one,[3b] respectively) by comparison with the ^{1}H-NMR spectra and retention times on HPLC.

In the Pd-assisted biaryl coupling reaction of benzylamine (**1**), the methylenedioxy group on the benzyl part would influence the coupling position. The coupling reactions of benzamides and benzylamines, which possess other oxygen substituents, are now under investigation.

EXPERIMENTAL

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO FT/IR 350 spectrophotometer and ^{1}H-NMR spectra in deuteriochloroform on Varian VXR-200 (200 MHz) or -500 (500 MHz) spectrometers, unless otherwise stated. NMR spectral data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0), and the coupling constants are given in Hertz. Column chromatography was carried out on a Merck silica gel (230-400 mesh) and Wako activated alumina (300 mesh). All the extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered; the filtrate was concentrated to dryness under reduced pressure. $Pd(OAc)_2$ was treated with boiling benzene, and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

1-[(1,3-Benzodioxol-5-yl)methyl]-7-iodo-2,3-dihydroindole (1) :

To a solution of 7-iododihydroindole (735 mg, 3.00 mmol) in dry MeCN (8 mL) were added 5-bromomethyl-1,3-benzodioxole (**3**)[8] (710 mg, 3.30 mmol), Et_4NI (77 mg, 0.30 mmol), and *i*-Pr_2NEt (2.1 mL, 12.0 mmol), and the reaction mixture was stirred for 1 h at rt. The mixture was diluted with AcOEt, and

the organic layer was washed with aqueous 5% NaOH solution and brine. The residue was dissolved in $CHCl_3$ and was subjected to column chromatography through silica gel. Elution with hexane-AcOEt (15:1) gave **1** (945 mg, 83%) as a pale yellow oil.^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.94 (2H, t, *J*=8.5 Hz), 3.38 (2H, t, *J*=8.5 Hz), 4.57 (2H, s, Ar-CH_2-N), 5.95 (2H, s, OCH_2O), 6.47 (1H, dd, *J*=7.0, 8.0 Hz), 6.77 (1H, d, *J*=7.5 Hz), 6.81 (1H, dd, *J*=7.5, 1.5 Hz), 6.95 (1H, d, *J*=1.5 Hz), 7.06 (1H, dd, *J*=7.0, 1.5 Hz), 7.53 (1H, dd, *J*=8.0, 1.5 Hz). *Anal*. Calcd for $C_{16}H_{14}NO_2I$: C, 50.68; H, 3.72; N,3.69. Found: C, 50.65; H, 4.11; N, 3.45.

General Procedure for the Coupling Reaction of 1-[(1,3-Benzodioxol-5-yl)methyl]-7-iodo-2,3-dihydroindole (1) (runs 1~3 in Table 1)

1-[(1,3-Benzodioxol-5-yl)methyl]-7-iodo-2,3-dihydroindole (**1**) (0.3 mmol) was reacted with $Pd(OAc)_2$ (5 mol%), a phosphine ligand (10 mol%), and K_2CO_3 (200 mol%) in dry DMF (8 mL) at 125˚C for the times indicated in Table 1. Then, the reaction mixture was diluted with ether, and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in $CHCl_3$ and was subjected to column chromatography on alumina. Elution with hexane-AcOEt (50:1) gave **8**, and successive elution with the same solvent gave **4** and **6**. Elution with AcOEt afforded a mixture of **5** and **7**. The mixture was recrystallized from $CHCl_3$–MeOH to give **5**. The ratio of **5** to **7** was determined by ^{1}H-NMR (200MHz) and HPLC (Chemcosorb 5Si-U) by comparison with authentic samples.[3b]

The Coupling Reaction of 1-[(1,3-benzodioxol-5-yl)methyl]-7-iodo-2,3-dihydroindole (1) under Jeffery's Conditions (run 4 in Table 1)[9]

1-[(1,3-Benzodioxol-5-yl)methyl]-7-iodo-2,3-dihydroindole (**1**) (0.3 mmol) was reacted with $Pd(OAc)_2$ (5 mol%), n-Bu_4NCl (100 mol%), and K_2CO_3 (300 mol%) in dry DMF (8 mL) at 115˚C for 3 h. Then, the reaction mixture was diluted with ether, and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in $CHCl_3$ and was subjected to column chromatography on alumina. The products were separated using the procedure mentioned above.

4,5-Dihydro-7*H*-[1,3]dioxolo[4,5-*k*]pyrrolo[3,2,1-*de*]phenanthridine (4) : pale yellow prisms (EtOH), mp 110-114˚C. IR (KBr) cm^{-1}: 1245, 1045. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.03 (2H, t, *J*=8.0 Hz), 3.35 (2H, t, *J*=8.0 Hz), 4.07 (2H, s), 6.06 (2H, s), 6.64 (1H, d, *J*=8.0 Hz), 6.67 (1H, d, *J*=8.0 Hz), 6.78 (1H, dd, *J*=7.5, 7.5 Hz), 7.05 (1H, dd, *J*=7.5, 1.0 Hz), 7.70 (1H, dd, *J*=7.5, 1.0 Hz). *Anal*. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N,5.57. Found: C, 76.51; H, 5.36; N, 5.57.

4,5-Dihydro-7*H*-[1,3]dioxolo[4,5-*k*]pyrrolo[3,2,1-*de*]phenanthridin-7-one (5) : colorless needles ($CHCl_3$-MeOH), mp 243.5-246˚C. IR (KBr) cm^{-1}: 1655. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.43 (2H, t, *J*=8.0 Hz), 4.73 (2H, t, *J*=8.0 Hz), 6.23 (2H, s), 7.09 (1H, d, *J*=8.5 Hz), 7.20 (1H, dd, *J*=8.0, 7.0 Hz), 7.33 (1H, dd, *J*=7.0, 1.0 Hz), 8.16 (1H, dd, *J*=8.0, 1.0 Hz), 8.18 (1H, d, *J*=8.5 Hz). *Anal*. Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N,5.28. Found: C, 72.48; H, 4.43; N, 5.37.

1-[(1,3-Benzodioxol-5-yl)methyl]-2,3-dihydroindole (**8**), anhydrolycorin (**6**), and anhydrolycorin-7-one (**7**) were identified by comparison with the ^{1}H-NMR (200 MHz) spectra and HPLC retention times of authentic samples.[3b]

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