PALLADIUM-CATALYZED COUPLING REACTION OF CHLOROPYRAZINES WITH INDOLE

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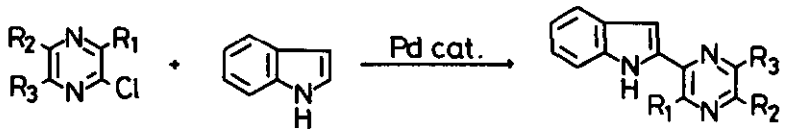
Abstract —— The palladium-catalyzed cross-coupling reaction of 2-chloropyrazines with indole was shown to proceed in moderate to good yields, giving 2-(pyrazin-2-yl)indoles. The structure determination of the products was made on the basis of the X-Ray diffraction and ^{13}C-NMR spectroscopic analyses.

The palladium-catalyzed coupling reactions of indoles have been extensively investigated in recent years[1]. Among these reactions, allylation[2] prompted us to pay attention to the synthesis of the Cypridina luciferin[3]. Recently, we reported the simple procedures for the introduction of the cyano[4], alkenyl and alkynyl[5], and methyl[6] groups into the pyrazine ring by the aid of the palladium catalysts. Our attempt was to couple chloropyrazines with indole to prepare 3-(pyrazin-2-yl)-indoles, which constitute the carbon skeleton of the Cypridina luciferin, isolated from Cypridina hilgendorfii[3].

When a mixture of 2-chloro-3,6-diisobutylpyrazine (1d), indole, potassium acetate and tetrakis(triphenylphosphine)palladium in N,N-dimethylformamide (DMF) was refluxed for 6 h, the coupling product (2d) was obtained in 25% yield. By replacing the solvent by N,N-dimethylacetamide (DMA) and by elongating the reaction time to 12 h, the yield became to 49%. Thus, some other 2-chloro-3,6-dialkylpyrazines (1a-c) were submitted to the reaction under the same conditions and the results are shown in Table 1. On the other hand, the reaction of 2-chloro-diphenylpyrazines with indole was achieved successfully, by replacing the catalyst

with a combination of bis(triphenylphosphine)palladium dichloride and copper(I) iodide, and the base with potassium carbonate, as shown in Table 1.

Table 1. Reaction of 2-Chloropyrazines with Indole



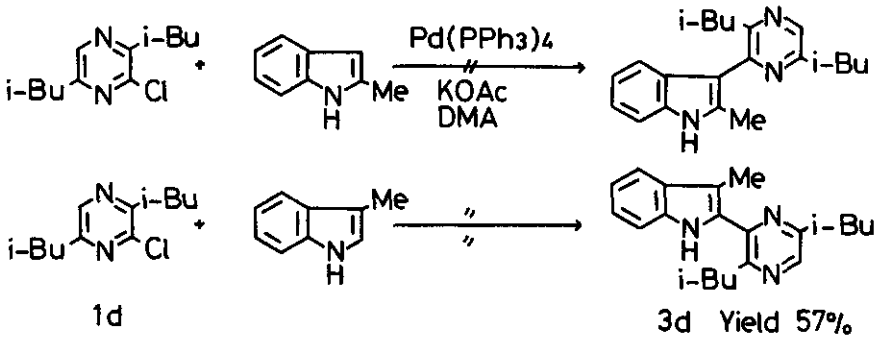
1a-g 2a-g

	Substrate			Catalyst	Base	Product	Yield (%)
	R_1	R_2	R_3				
1a[9]	CH_3	H	CH_3	A	KOAc	2a	54
1b[10]	C_2H_5	H	C_2H_5	A	KOAc	2b	52
1c[11]	i-C_3H_7	H	i-C_3H_7	A	KOAc	2c	45
1d[12]	i-C_4H_9	H	i-C_4H_9	A	KOAc	2d	49
1e[13]	C_6H_5	H	C_6H_5	B	K_2CO_3	2e	70
1f[14]	C_6H_5	C_6H_5	H	B	K_2CO_3	2f	79
1g[15]	H	C_6H_5	C_6H_5	B	K_2CO_3	2g	68

Catalyst A: $Pd(PPh_3)_4$

B: $Pd(PPh_3)_2Cl_2$-CuI

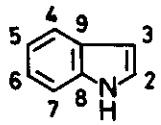
Scheme 1. Reaction of 2- and 3-Methylindoles with 2-Chloro-3,6-diisobutylpyrazine (1d)



Although the compound (1d) reacted successfully with 3-methylindole under the same conditions as the reaction of 1d with indole, to give a coupling product (3d) in 57% yield, the reaction with 2-methylindole failed. These results might suggest that the coupling occurred at the C-2 of indole. In the ^{13}C-NMR spectrum of 2a,

prepared by the coupling reaction of 1a with indole, the signal of the C-2 of the indole part appeared in the same region as the one of 2-phenylindole[7,8]. These results suggested also the occurrence of the reaction at the C-2 of indole.

Table 2. ^{13}C-Chemical Shifts ($CDCl_3$/TMS, ppm) of Indole Derivatives and 2a



Position	Indole[7]	2-Phenylindole[8]	3-Phenylindole[8]	2a
2	125.2	137.4	121.3	134.0
3	102.6	98.5	117.5	104.8
4	121.3	119.7	119.2	121.5
5	122.3	121.2	121.8	123.7
6	120.3	119.1	119.8	120.0
7	111.8	110.9	111.1	111.0
8	136.1	136.8		136.0
9	128.8	128.2	125.1	129.2

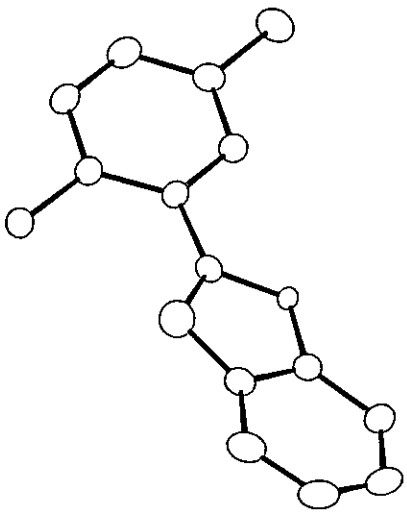
The definitive structure determination of 2a was performed by the X-Ray diffraction analysis. The crystal data of 2a were as follows: $C_{14}H_{13}N_3$, orthorhombic with the space group P_{bnb}, a = 12.862 (1) Å, b = 19.692 (6) Å, c = 9.184 (1) Å, u = 2326.02 $Å^3$, z = 8, D_x = 1.275 g/cm^3. A total of 1566 independent reflections ($2^\circ < 2\theta < 135^\circ$) was collected with the Rigaku AFC-5 automatic diffractometer, using graphite-monochromated MoK_α radiation. The final R value was 0.078. The molecular framework was illustrated in Scheme 2.

Consequently, the coupling reaction of 2-chloropyrazines occurred at the C-2 of indole, contrary to our expectations. Extension of our new observations and detailed studies are now in progress.

EXPERIMENTAL

All melting and boiling points are uncorrected. The following instruments were used for obtaining the spectral data: ^{1}H-NMR: Varian EM-360; ^{13}C-NMR: JEOL FX-100; UV spectra: Hitachi Model 557; MS: Hitachi M-80 spectrometer.

Scheme 2. A Perspective View of 2a



General Procedure for the Reaction of 2-Chloro-3,6-dialkylpyrazines with Indole --- After a mixture of a substrate (2 mmol), indole (280 mg, 2.4 mmol), KOAc (294 mg, 3 mmol), and tetrakis(triphenylphosphine)palladium (116 mg, 0.1 mmol) in DMA (5 ml) was refluxed for 12 h under an argon stream, the solvent was removed by distillation in vacuo. The residue was triturated with water (10 ml) and extracted with CH_2Cl_2 to give a brown solid or oil, which was purified by column chromatography on silica gel (Wakogel C-200, 10 g) eluting with hexane containing an increasing amount of AcOEt.

General Procedure for the Reaction of 2-Chloro-diphenylpyrazines with Indole --- A mixture of a 2-chloro-diphenylpyrazine (266 mg, 1 mmol), indole (176 mg, 1.5 mmol), bis(triphenylphosphine)palladium dichloride (7 mg, 0.01 mmol), and CuI (10 mg, 0.05 mmol) in DMA (5 ml) was refluxed for 12 h under an argon atmosphere. The same work-up as before gave a brown solid, which was chromatographed on silica gel (Wakogel C-200, 10 g) with hexane containing an increasing amount of benzene. 2-(3,6-Dimethylpyrazin-2-yl)indole (2a): pale yellow needles (from hexane); mp 133-136°C; MS: m/e 223 (M^+); UV: λ_{max}^{EtOH} 239.5 (log ε = 4.29), 305 (4.14), 348 (4.41) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.57 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 7.10-7.73 (m, 4H, indole H), 7.73-8.00 (m, 1H, indole H), 8.38 (s, 1H, pyrazine H), 10.05 (broad s, 1H, NH) ppm; ^{13}C-NMR ($CDCl_3$/TMS): δ 21.0 (CH_3), 23.9 (CH_3), 104.8 (indole C-3),

111.0 (indole C-7), 120.0 (indole C-6), 121.5 (indole C-4), 123.7 (indole C-5), 129.2 (indole C-9), 134.0 (indole C-2), 136.0 (indole C-8), 140.6 (pyrazine C), 143.2 (pyrazine C), 148.3 (pyrazine C), 149.6 (pyrazine C) ppm; Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.13; H, 5.87; N, 18.82. Found: C, 75.07; H, 5.92; N, 18.61.

2-(3,6-Diethylpyrazin-2-yl)indole (2b): pale yellow needles (from MeOH); mp 89-90°C; MS: m/e 251 (M^+); UV: λ_{max}^{EtOH} 236.5 (log ε = 4.22), 241 (4.21, shoulder), 311-313 (4.10), 346.5 (4.31) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.48 (t, J = 7 Hz, 3H, $CH_2\underline{CH}_3$), 1.55 (t, J = 7 Hz, 3H, $CH_2\underline{CH}_3$), 3.00 (q, J = 7 Hz, 2H, $\underline{CH}_2CH_3$), 3.37 (q, J = 7 Hz, 2H, $\underline{CH}_2CH_3$), 7.15-7.83 (m, 4H, indole H), 7.83-8.08 (m, 1H, indole H), 8.55 (s, 1H, pyrazine H), 10.08 (broad s, 1H, NH) ppm; Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.67; H, 6.78; N, 16.61.

2-(3,6-Diisopropylpyrazin-2-yl)indole (2c): colorless prisms (from hexane or MeOH-H_2O); mp 98-100°C; MS: m/e 279 (M^+); UV: λ_{max}^{EtOH} 234.5 (log ε = 4.25), 242 (4.20), 252 (3.86, shoulder), 306 (4.11, shoulder), 345 (4.29) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.36 (d, J = 7 Hz, 6H, $CH(\underline{CH}_3)_2$), 1.40 (d, J = 7 Hz, 6H, $CH(\underline{CH}_3)_2$), 3.11 (m, J = 7 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.85 (m, J = 7 Hz, 1H, $C\underline{H}(CH_3)_2$), 6.83-7.78 (m, 5H, indole H), 8.28 (s, 1H, pyrazine H), 9.65 (broad s, 1H, NH) ppm; Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.14; H, 7.61; N, 14.89.

2-(3,6-Diisobutylpyrazin-2-yl)indole (2d): colorless prisms (from MeOH-H_2O); mp 82-83°C; MS: m/e 307 (M^+); UV: λ_{max}^{EtOH} 236.5 (log ε = 4.32), 282 (4.31, shoulder), 311 (4.23), 348 (4.42) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.00 (d, J = 7 Hz, 6H, $CH_2CH(\underline{CH}_3)_2$), 1.03 (d, J = 7 Hz, 6H, $CH_2CH(\underline{CH}_3)_2$), 2.33 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.68 (d, J = 7 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$), 3.08 (d, J = 7 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$), 7.00-7.87 (m, 5H, indole H), 8.27 (s, 1H, pyrazine H), 9.87 (broad s, 1H, NH) ppm; Anal. Calcd. for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20; N, 13.67. Found: C, 78.30; H, 8.23; N, 13.88.

2-(3,6-Diphenylpyrazin-2-yl)indole (2e): colorless prisms (from EtOH); mp 150-153°C; MS: m/e 347 (M^+); UV: λ_{max}^{EtOH} 261-263 (log ε = 4.39), 312 (4.29), 353-355 (4.04) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 6.63 (d, J = 4 Hz, 1H, indole H), 7.00-7.93 (m, 13H, benzene and indole H), 8.07-8.33 (m, 2H, benzene H), 9.17 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.70; H, 4.88; N, 12.12.

2-(3,5-Diphenylpyrazin-2-yl)indole (2f): colorless prisms (from MeOH); mp 119-123°C; MS: m/e 347 (M^+); UV: λ_{max}^{EtOH} 242.5-245 (log ε = 4.14), 267 (4.06, shoulder), 279 (4.00, shoulder), 309-312 (3.98), 353 (3.87) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 6.60 (d, J = 4 Hz, 1H, indole H), 7.00-7.83 (m, 13H, benzene and indole H), 8.13-8.43 (m,

2H, benzene H), 9.03 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 83.00; H, 4.89; N, 12.20.

2-(5,6-Diphenylpyrazin-2-yl)indole (2g): pale yellow prisms (from MeOH); mp 149-150°C; MS: m/e 347 (M^+); UV: λ_{max}^{EtOH} 267-271 (log ε = 4.23), 307-311 (4.25), 349 (4.18) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 6.82 (d, J = 4 Hz, 1H, indole H), 7.20-7.87 (m, 13H, benzene and indole H), 7.90 (d, J = 4 Hz, 1H, indole H), 8.30-8.60 (m, 1H, indole H), 8.97 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.77; H, 4.87; N, 12.10.

2-(3,6-Diisobutylpyrazin-2-yl)-3-methylindole (3d): yellowish viscous oil; bp 170-175°C/0.05 torr; MS: m/e 321 (M^+); UV: λ_{max}^{EtOH} 275 (log ε = 3.97, shoulder), 295 (3.99), 338.5 (3.72) nm; ^{1}H-NMR ($CDCl_3$/TMS): δ 0.72 (d, J = 6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.92 (d, J = 6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.58-2.17 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.24 (s, 3H, CH_3), 2.65 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.78 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 6.87-7.33 (m, 3H, indole H), 7.37-7.70 (m, 1H, indole H), 8.30 (s, 1H, pyrazine H), 8.63-8.83 (broad s, 1H, NH) ppm; Anal. Calcd. for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.18; H, 8.41; N, 12.98.

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