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Photo-Arylation. VII.[1] Photoreaction of 2-Halopyridine with Indole[2]

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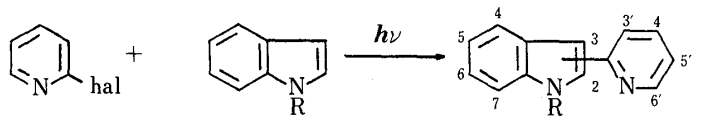
Photolysis of 2-halopyridine with indole afforded the (2-pyridyl)indoles as a regioisomeric mixture. On the basis of the isomer distributions, an electron transfer mechanism is suggested for the present reaction. The regioselectivity was found to be fairly dependent on the solvent polarity.

Keywords——(2-pyridyl)indole; photo-arylation; photolysis; 2-halopyridine; indole; electron transfer; solvent effect; isomer distribution

We have reported on the regioselective syntheses of (2- and 4-pyridyl)heterocycles by the photoreaction of 2- and 4-iodopyridines with electron-rich heterocycles.[1,3] In our continuing studies on the scope of this reaction, we intend to extend our work to the photoreactions of halopyridines with indoles. Various studies on the photo-substitution of indoles have been reported from synthetic, mechanistic, and biological viewpoints.[4-7] Photo-excited indole reacts with methyl chloroacetate[4] and acrylonitrile[5] to give a mixture of 3-, 4-, and 6-substituted indoles as major products, while the bromo compounds, 5-bromo-1,3-dimethyluracil[6] and bromomaleimides,[7] attack indole exclusively at the 2-position.[6,7] We now report our findings that the photoreaction of 2-halopyridines (halogen; I, Br, Cl) with indole proceeds non-regioselectively to afford a mixture of all of the possible isomers of (2-pyridyl)indole. The product distribution varies with the solvent polarity.

Photolysis of 2-iodopyridine (**1a**) (1 mmol) and indole (**2a**) (1 mmol) was carried out in



1a : hal=I
1b : hal=Br
1c : hal=Cl

2a : R=H
2b : R=CH_3

3a$_x$: R=H
3b$_x$: R=CH_3

Chart 1

TABLE I. Photoreaction of Halopyridine (**1**) with Indole (**2a**) in Acetonitrile[a]

1	3a$_x$; 3a$_1$	3a$_2$	3a$_3$	3a$_4$	3a$_5$	3a$_6$	3a$_7$	Total yield (%)[b]	Conversion of 1 (%)
			Isomer distribution (%)						
a	5	11	37	17	<1	21	9	49	40
b	6	12	31	18	<1	24	9	32	28
c	6	15	32	15	<1	21	11	25	36

a) The yields and isomer distributions were determined by GLC. *b*) Based on **1** consumed.

acetonitrile (10 ml) with a low-pressure mercury lamp (12 h) to afford isomeric *x*-(2-pyridyl)indoles (**3a**$_x$; $x=1$—7), together with recovery of **1a** (Chart 1); the results are summarized in Table I.

The structures of **3a**$_1$,[8] **3a**$_2$,[9] and **3a**$_3$[8] were confirmed by comparison of their ultraviolet (UV) spectra, mass spectra (MS), and melting points with those of authentic samples prepared by the reported methods. The structures of **3a**$_4$, **3a**$_5$, **3a**$_6$, and **3a**$_7$ were determined on the basis

TABLE II. Physical Data for (2-Pyridyl)indoles (**3a**) and 1-Methyl-(2-pyridyl)indoles (**3b**)

3_x	mp (°C)	Crystn. solvent (Crystal form)	Formula	Analysis (%) Calcd (Found) C	H	N	MS *m/z* (%)
3a$_1$	98—100 (Picrate)	EtOH					194 (100 M^+)
	(lit. 101.5—103.5)[8]	(Needles)					193 (41.5)
3a$_2$	156—157	Benzene					194 (100 M^+)
	(lit. 155)[9]	(Needles)					193 (22.9)
3a$_3$	153—154	Benzene					194 (100 M^+)
	(lit. 150—154)[8]	(Needles)					193 (59.5)
3a$_4$	194—195	EtOH	$C_{13}H_{10}N_2$	80.38	5.19	14.42	194 (100 M^+)
		(Prisms)		(80.48	5.15	14.43)	193 (63.8)
3a$_5$	Colorless oil		$C_{13}H_{10}N_2$	194.0843 (194.0825)[a]			194 (100 M^+)
							193 (61.4)
3a$_6$	134.5—135.5	Benzene	$C_{13}H_{10}N_2$	78.58	5.28	14.10	194 (100 M^+)
		(Needles)	$\cdot 1/4H_2O$	(78.44	5.02	14.18)	193 (26.1)
3a$_7$	65—66	Hexane	$C_{13}H_{10}N_2$	80.38	5.19	14.42	194 (100 M^+)
		(Prisms)		(80.57	5.32	14.17)	193 (43.4)
3b$_2$	90—91	Hexane					208 (95.9 M^+)
	(lit. 90—91)[10]	(Prismatic needles)					207 (100)
3b$_3$	240—241	Acetone	$C_{20}H_{15}N_5O_7$	54.92	3.46	16.01	208 (100 M^+)
	(Picrate)	(Needles)		(55.11	3.39	15.91)	207 (34.3)
3b$_4$	169—171	EtOH	$C_{20}H_{15}N_5O_7$	54.92	3.46	16.01	208 (100 M^+)
	(Picrate)	(Needles)		(55.13	3.28	16.10)	207 (59.6)
3b$_5$	Colorless oil		$C_{14}H_{12}N_2$	208.1000 (208.0981)[a]			208 (100 M^+)
							207 (38.5)
3b$_6$	216—218	Acetone	$C_{20}H_{15}N_5O_7$	54.92	3.46	16.01	208 (100 M^+)
	(Picrate)	(Needles)		(54.91	3.36	15.92)	207 (49.3)
3b$_7$	179—181	EtOH	$C_{20}H_{15}N_5O_7$	54.92	3.46	16.01	208 (46.6 M^+)
	(Picrate)	(Needles)		(54.67	3.45	16.01)	207 (100)

a) High-resolution MS, taken with a JEOL JMS-D 300 mass spectrometer.

TABLE III. ^{1}H-NMR Chemical Shifts, δ (ppm), for **3a**$_x$ and **3b**$_x$

Compd.	2-H	3-H	4-H	5-H	6-H	7-H	3′-H	4′-H	5′-H	6′-H	NCH_3
3a$_4$[a]	7.43	7.03	—	7.58	7.23	7.53	7.95	7.88	7.31	8.73	
3a$_5$[b]	7.25	6.64	8.28	—	7.89	7.48	7.79	7.74	7.19	8.69	
3a$_6$[a]	7.43	6.52	7.66	7.82	—	8.29	7.96	7.85	7.28	8.65	
3a$_7$[b]	7.37	6.60	7.77 or 7.74	7.21	7.74 or 7.77	—	8.04	7.79	7.21	8.72	
3b$_3$[b]	7.70	—	8.29	7.25	7.29	7.36	7.69	7.68	7.07	8.63	3.48
3b$_4$[a]	7.30	7.01	—	7.61	7.28	7.47	7.92	7.86	7.30	8.72	3.87
3b$_5$[b]	7.09	6.57	8.27	—	7.92	7.41	7.79	7.73	7.17	8.69	3.83
3b$_6$[a]	7.32	6.47	7.64	7.85	—	8.26	8.01	7.86	7.28	8.66	3.93
3b$_7$[a]	7.18	6.51	7.63	7.09	7.08	—	7.61	7.91	7.40	8.69	3.40

a) Acetone-d_6 solution. *b*) $CDCl_3$ solution.

TABLE IV. Spin–Spin Coupling Constants (J=Hz) of Protons on $\mathbf{3a}_x$ and $\mathbf{3b}_x$[11]

Compd.	2–3	4–5	4–6	4–7	5–6	5–7	6–7	3–7	3′–4′	3′–5′	3′–6′	4′–5′	4′–6′	5′–6′
$\mathbf{3a}_4$	3.3	—	—	—	7.6	0.8	7.8	0.8	8.0	0.9	1.0	7.5	1.9	4.8
$\mathbf{3a}_5$	2.9	—	1.8	0.7	—	—	8.4	1.1	8.2	1.1	1.0	7.4	1.9	5.0
$\mathbf{3a}_6$	2.9	8.3	—	0.7	—	1.5	—	1.1	8.2	1.1	1.0	7.5	1.9	4.9
$\mathbf{3a}_7$	2.9	7.7	—	—	7.7	—	—	—	8.3	1.0	1.0	7.6	1.9	4.9
$\mathbf{3b}_3$	—	8.2	1.0	0.7	7.3	1.0	8.2	—	8.2	1.2	1.5	7.5	1.6	5.0
$\mathbf{3b}_4$	3.2	—	—	—	7.4	0.9	8.1	0.9	8.1	0.9	1.1	7.5	1.8	4.9
$\mathbf{3b}_5$	3.0	—	1.8	0.5	—	—	8.4	0.9	7.9	0.9	1.0	7.7	1.9	4.9
$\mathbf{3b}_6$	3.1	8.2	—	0.6	—	1.6	—	0.7	8.1	0.9	1.0	7.4	1.8	4.8
$\mathbf{3b}_7$	3.3	7.3	1.9	—	7.5	—	—	—	7.7	1.2	1.0	7.6	1.8	5.0

—, not determined.

TABLE V. Photoreaction of 2-Iodopyridine (**1a**) with Indole (**2a**) in Various Solvents[a]

Solvent	($\mathbf{3a}_x$), Isomer distribution (%)						Total yield (%)[b]	Consumed **1a** (%)
	$\mathbf{3a}_1$	$\mathbf{3a}_2$	$\mathbf{3a}_3$	$\mathbf{3a}_4$	$\mathbf{3a}_6$	$\mathbf{3a}_7$		
Hexane	4	37	19	3	8	29	25	10
Cyclohexane	2	40	20	3	4	31	38	13
Ether	1	20	50	5	9	15	40	10
Ethyl acetate	2	16	45	9	15	13	88	12
tert-BuOH	1	16	47	10	16	10	50	16
CH_3CN	5	11	37	17	21	9	49	40
CH_3OH	4	12	38	16	22	8	51	43

a) The yields and isomer ratios were determined by GLC. *b*) Based on **1** consumed.

of their MS, elemental analyses (Table II), and proton nuclear magnetic resonance (^{1}H-NMR) spectra (Tables III and IV).

The observed isomer distribution seems to reflect the values of the calculated frontier electron densities of the indole-1-radical as reported by Naruto and Yonemitsu,[12] suggesting that the present reaction might proceed *via* the electron transfer mechanism.

The photoreaction of 2-bromo- (**1b**) and 2-chloropyridines (**1c**) with indole, carried out under the same conditions as described above, gave $\mathbf{3a}_x$ in similar isomer ratios, though the yields were lower than that of **1a** (Table I).

In the expectation of a regioselective coupling reaction, the photoreaction of **1a** (0.1 mmol) with **2a** (0.1 mmol) was carried out in acetonitrile (10 ml) or in hexane (10 ml), using a high-pressure mercury lamp with a Pyrex filter; under these conditions, **1a** could be excited preferentially.[13] However, no significant change in the isomer distribution was observed in either solvent. We then carried out the photolysis of **1a** (1 mmol) and **2a** (1 mmol) under similar conditions but in various solvents (10 ml) and the results are summarized in Table V.[14] The regioselectivities are seen to be clearly dependent on the solvent polarity, and moreover the extent of reaction increased as the solvent polarity increased; the latter observation is again suggestive of the electron transfer mechanism.

The reaction in methanol (very polar solvent) gave a mixture of regioisomers in a similar ratio to that observed in the reaction in acetonitrile. In both moderately polar solvents (ether, ethyl acetate, *tert*-BuOH) and non-polar solvents (hexane and cyclohexane), the substitution on the benzene ring of indole was fairly depressed at the 4- and 6-positions. A fair amount of 3-substituted indole ($\mathbf{3a}_3$) was produced in the former solvents, while 2-substituted indole ($\mathbf{3a}_2$) and 7-substituted indole ($\mathbf{3a}_7$) were produced in the latter solvents as the major products.

The formation of $\mathbf{3a}_7$ in an appreciable ratio in non-polar solvent might be attributable to the participation of hydrogen bonding between NH of **2a** and the nitrogen atom of **1a**. The infrared (IR) spectrum showed a new absorption at 3280 cm^{-1} due to hydrogen bonding on the addition of **1a** to a solution of **2a** in tetrachloromethane.[15] In fact, the photolysis of 1-methylindole (**2b**) in cyclohexane afforded the 2- and 3-isomers ($\mathbf{3b}_2$, $\mathbf{3b}_3$) in yields of 45% and 39%, respectively, as the major products, while the 7-isomer ($\mathbf{3b}_7$) was obtained in low yield (11%) (based on the total yield of the isomeric 1-methyl-*x*-(2-pyridyl)indoles ($\mathbf{3b}_x$, $x=2$—7). The mechanism for the selective formation of the 3-isomer ($\mathbf{3a}_3$) in less polar solvents is not clear. However, in view of the report on the photoreaction of indole with acrylonitrile,[5] it may be assumed that the formation of $\mathbf{3a}_3$ as a major product in less polar solvents was derived from the intermediate exciplex, reflecting its conformation.

Neither a triplet sensitizer (acetone, acetophenone) nor a triplet quencher (piperylene, diacetyl) had any significant effect on the photo-coupling reaction. Stern-Volmer plots for quenching of indole fluorescence[16] by **1b** and **1c** were linear, and the rate constants (k_q) were estimated to be *ca.* 1.3×10^{10} M^{-1} s^{-1} (methanol at room temperature) from the slopes and the reported life time of indole fluorescence ($\tau=4.3$ ns)[17]; the above value is close to the diffusion limit (1.5×10^{10} M^{-1} s^{-1}).[5] According to the Rehm-Weller treatment,[18] the free energy change ($\Delta G=-12.3$ kcal mol^{-1}) calculated by using Eq. 1 predicts that the electron transfer process from **2a** to **1b** is exothermic. These results suggest that the present reaction may proceed *via* singlet excited states, followed by an electron transfer mechanism (Chart 2).

$$\Delta G\ (\text{kcal mol}^{-1}) = 23.06(E^{ox} - E^{red}) - E^{s} \qquad (1)$$

E^{ox}: oxidation potential of **2a** (0.94 V *vs.* SCE)[19]
E^{red}: reduction potential of **1b** (−2.30 V *vs.* SCE)[20]
E^{s}: excited singlet energy of **2a** (87 kcal mol^{-1}, estimated from the fluorescence maximum of **2a**)

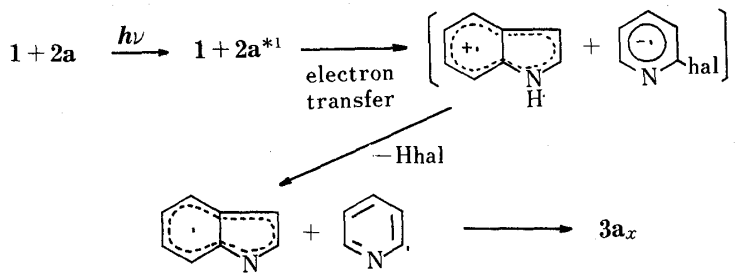


Chart 2

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were measured with a JEOL JNM-GX 270 spectrometer (270 MHz) and chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard. MS were determined on a Shimadzu LKB-9000 GC-mass spectrometer. IR spectra were recorded on a Hitachi 270-30. UV and fluorescence spectra were taken on a Shimadzu UV-240 and Hitachi 650-60, respectively. Gas liquid chromatography (GLC) was carried out with a gas chromatograph (Shimadzu GC-6A) equipped with a hydrogen flame-ionization detector using a glass column (1.5 m, 3 mm) with 3% OV-17 on Shimalite-W, with nitrogen as a carrier gas (30 ml/min). Column chromatography was performed with a prepacked column (Lobar, Lichroprep Si-60, Merck) and thin layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) TLC plates. UV irradiation was carried out with either a 60 W low-pressure mercury lamp (Eiko-sha) or a 500 W high-pressure mercury lamp (Eiko-sha) with a Pyrex filter at room temperature under atmospheric pressure of argon. A merry-go-round apparatus (Eiko-sha) was used for analytical-scale photoreactions. Preparative-scale photoreactions were performed with a low-pressure mercury lamp with the use of a Pyrex vessel at room temperature under an argon atmosphere.

Preparative-Scale Photoreaction of 2-Iodopyridine (1a) with Indole (2a)[21]——A solution of **1a** (10 mmol) and **2a** (5 mmol) in CH_3CN (400 ml) was irradiated with a 60 W low-pressure mercury lamp for 12 h. After evaporation of the

solvent, the reaction mixture was dissolved in ether (40 ml) and extracted with 10% hydrochloric acid (30 ml, 5 times). The aqueous layer was neutralized with potassium carbonate, followed by extraction with dichloromethane (CH_2Cl_2) (30 ml, 5 times). The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum, and the residual oil was subjected to column chromatography using benzene, and then benzene–ethyl acetate (5 : 1) to afford **3a**$_7$, **3a**$_1$, **3a**$_2$, **3a**$_4$, **3a**$_5$, **3a**$_6$, and **3a**$_3$, successively. The physical data are listed in Tables II—IV.

Preparative-Scale Photoreaction of 1a with 1-Methylindole (2b)[21]——The photolysis of **1a** and **2b** was carried out and worked up in the manner described above. The resulting oil thus obtained was separated into three fractions (f1, f2, f3) by column chromatography using CH_2Cl_2 as an eluent. The first fraction (f1) afforded 1-methyl-2-(2-pyridyl)indole (**3b**$_2$) (27 mg, 2.6%) on passage through a Lobar column with hexane–ether (1 : 1). The second fraction (f2) was submitted to column chromatography with hexane–ether (4 : 1) to give 1-methyl-6-(2-pyridyl)indole (**3b**$_6$) (35 mg, 3.4%) and a mixture of 1-methyl-4-(2-pyridyl)indole (**3b**$_4$) (11 mg, 1.1%), 1-methyl-7-(2-pyridyl)indole (**3b**$_7$) (20 mg, 1.9%), and 1-methyl-5-(2-pyridyl)indole (**3b**$_5$) (1 mg, 0.1%), which was separated by preparative TLC on a TLC plate pre-treated with acetic acid, using CH_2Cl_2 as a developing solvent. The third fraction (f3) afforded pure **3b**$_3$ (89 mg, 8.6%) on TLC with CH_2Cl_2–acetone (20 : 1). The physical data are summarized in Tables II—IV.

General Procedure for Analytical-Scale Photoreaction of 1 with 2——A solution of **1** (1 mmol) and **2** (1 mmol) in a solvent (10 ml) was irradiated with a low-pressure mercury lamp for 12 h. The reaction mixture was subjected to GLC analyses.

Photolysis of 1a and Indole (2a) in the Presence of an Additive——A solution of **1a** (0.1 mmol) and **2a** (0.1 mmol), containing an additive (*trans*-piperylene, 0.12 mmol; diacetyl, 0.12 mmol; acetone, 0.27 mmol; acetophenone, 0.1 mmol) in hexane (10 ml) was irradiated with a high-pressure mercury lamp for 12 h. Similarly, the effect of the quencher on the photoreaction was examined with a low-pressure mercury lamp. Comparison (GLC) of these results with those obtained with no additive present showed no significant difference.

Fluorescence Quenching of 2a by 1b and 1c——Methanol solutions of **2a** (1.8×10^{-3} M) containing various amounts of **1b** and **1c** (10^{-3}—10^{-2} M) were prepared. Excitation was induced at 298 nm (under the conditions used, the incident light was selectively absorbed by **2a**), and the fluorescence emissions of **2a** at 329 nm were measured at room temperature.

References and Notes

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13) It is recognized that photo-excited indole reacts with methyl chloroacetate[3] and acrylonitrile[4] less regioselectively to give a mixture of 3-, 4-, and 6-substituted indoles as major products, while the brominated enones bromomaleimides[5] and 5-bromo-1,3-dimethyluracil[6] attack indole in the ground state exclusively at the 2-position.[6,7b]
14) Similar solvent effects on the isomer distribution were observed for the photoreaction of **1b** with **2a**, but the dependency of the product distribution on the solvent polarity was less significant.[2]
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