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PHOTO AND THERMALLY INDUCED REACTION OF 3- AND 4-FLUOROPYRIDINES WITH THE INDOLE 1-ANION

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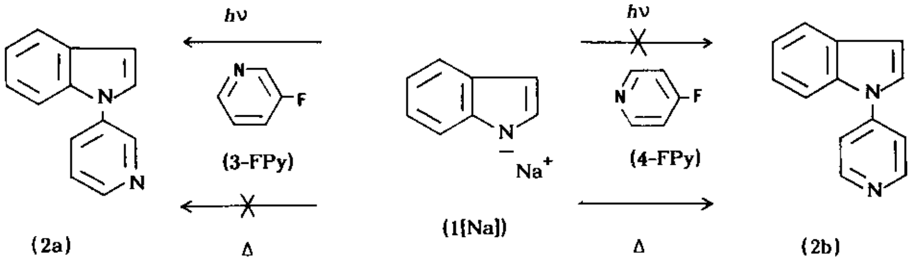
Abstract—Photoreaction of 3-fluoropyridine with the indole 1-anion gave 1-(3-pyridyl)indole exclusively, albeit in low yield. 4-Fluoropyridine and the anion reacted in the dark to afford 1-(4-pyridyl)indole in good yield, however uv light retarded its formation.

The photosubstitution reactions of indole have been studied intensively. These reactions can be roughly classified into two groups on the basis of their regioselectivity: a) non-regioselective substitution with such entities as chloroacetate[1] or halopyridines (I, Br Cl),[2] and b) regioselective reactions with 5-bromo-1,3-dimethyluracil[3] or bromomaleimides[4] at C-2 of the indole ring. In a preceding paper,[5] we reported that the photoreaction of 2-fluoropyridine (2-FPy) with the indole 1-anion (**1**[-]) gave 1-(2-pyridyl)indole in satisfactory yield. In our continuing study on the scope of this reaction, we now report on the photoreaction of 3- and 4-fluoropyridines (3-FPy and 4-FPy, respectively) with **1**[-]. Photolysis of **1**[-] and 3-FPy afforded 1-(3-pyridyl)indole (**2a**) regioselectively, but in low yield, while **1**[-] and 4-FPy afforded 1-(4-pyridyl)indole (**2b**) in good yield in the dark; however the reaction was remarkably retarded by ultraviolet (uv) light. Thus, the behaviors of 3- and 4-FPy are quite different from that of 2-FPy. On the other hand, 3- and 4-FPys reacted photochemically with neutral indole at its 1- and 3-positions to give mixtures of 1- and 3-(n-pyridyl)indoles (n = 3, 4), though in low yields. This could be regarded as belonging to another class of photosubstitution of indole.

Photolysis of a solution of 3-FPy and the sodium salt of indole (**1**[Na]) in dimethylformamide (DMF) for 5 h afforded (**2a**) in 1.5% yield as a single isomer, together with 81% recovery of indole (**1**) (Scheme 1). Similar photolysis of 4-FPy and **1**[Na] gave **2b** in 7.5 % yield as the sole product together with recovered **1** (70%), while, in the dark at room temperature, the solution produced **2b** in 45 % yield with 48 % recovery of **1**. A 25.5 % yield of **2b** at 7°C (recovered **1**, 70%) implied that **2b** was not derived photochemically but thermally, and that uv-irradiation inhibited the thermal reaction. This finding suggests that thermally induced coupling reaction of 4-FPy and **1**[-] provides a facile method for the synthesis of 1-(4-pyridyl)indole derivatives. In fact, at 90°C for 30 min 4-FPy afforded **2b** in high yield (83 %) together with a small amount of recovered **1** (5 %). The results, including those reported for 2-FPy,[5] are summarized in Table 1.

Thus, each FPy results in the regioselective substitution with the indole 1-anion photochemically or thermally, depending on the positions of the fluorine atom.



Scheme 1

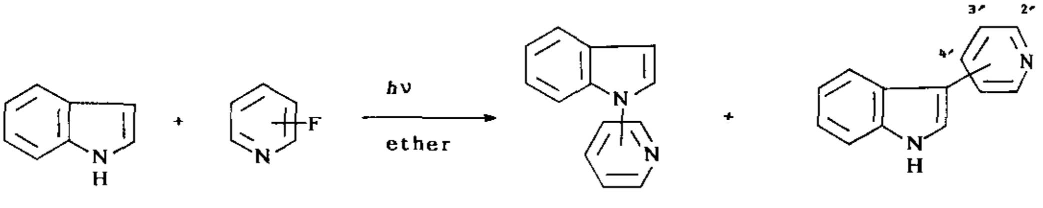
Table 1. Reaction of 2-, 3- and 4-Fluoropyridine with the Indole 1-Anion

n-FPy (n)	Conditions [°C]	Reaction Time (h)	Yield of **2** (%)[a,b]	Consumed **1** (%)[a]
3	uv [22]	5	1.5(8)[6]	19
3	dark [22]	5	0 (0)	5
4	uv [22]	5	7.5(25)[6]	30
4	dark [22]	5	45 (86.5)	52
4	uv [7]	5	6 (18)	33
4	dark [7]	5	25.5(85)	30
4	dark [90]	0.5	83 (87)	95
2	uv [22]	5	50 (85)	59
2	dark [22]	5	5 (59)	8.5

a) Determined by glc. b) ( ); based on **1** consumed.

A simple consideration based on the electron densities, energies or coefficients, obtained by a molecular orbital calculation (MOPAC/MNDO)[7] seemed inefficient for the explanation of the changes in the reactivities of the FPys, because no significant difference was observed among the values. Beer and Clark reported on the calculation of the localization energies for the nucleophilic substitution of fluoropyridines by methoxide ion, in which the energy difference between a reactant and the Wheland intermediate is 96.3 kJ mol^{-1} greater for 3-FPy than that for 4-FPy, while that of 2-FPy is only 6.3 kJ mol^{-1} greater.[8] These are in good agreement with the fact that 4-FPy and 2-FPy, though the latter being less efficiently (Table 1), are susceptible to the thermal nucleophilic substitution with **1**[-], while 3-FPy needs great activation energy through photoexcitation to reach at the intermediate. A mixture of **1**[-] and 3-FPy did not show a new charge transfer absorption spectrum, but taking into account the same regioselectivity with 2-FPy,[5] it would be supposed that the reaction of 3-FPy may proceed by an analogous mechanism to that of 2-FPy; that is an electron transfer mechanism. However it remains unelucidated why the photoreaction of **1**[-] with 4-FPy retarded; it seems unlike that dimethylamine, generated through the photodecomposition of DMF, consumed 4-FPy effectively during the reaction, since no 4-N,N-dimethylaminopyridine was detected on glc.

In contrast to the reaction described above, the photolysis of 3-FPy with neutral indole in ether[5] (10 h) proceeded slowly but afforded the mixtures of 1- and 3-(3-pyridyl)indoles (**2a,3a**) in the ratio of 4 : 3 as only detectable products (Scheme 2, Table 2). Similarly, 4-FPy furnished 1- and 3-(4-pyridyl)indoles (**2b**, **3b**) in the ratio of 1 : 3. Thus, the ratio of 3-isomer vs. 1-isomer increased in the order 2-FPy[5] < 3-FPy < 4-FPy. The present reaction involving a regioselective substitution of indole at the 1- and 3-positions can be regarded as a novel photosubstitution of indole.



(1) **(n-FPy)** **(2)** **(3)**

Scheme 2

Table 2. Reaction of 2-, 3-, and 4-Fluoropyridine with Indole

n-FPy (n)	Yield of **2**	**3** (%)[a,b]	Consumed **1** (%)[a]
3	3.2	2.4	37
4	2	6.3	40
2	19.5	3.9	52

a) Determined by glc. b) Based on **1** consumed.

EXPERIMENTAL

Proton nuclear magnetic resonance (^{1}H-nmr) spectra were measured with a JNM-GX 270 (270 MHz) spectrometer in acetone-d_6, and chemical shifts were given on the δ (ppm) scales with tetramethylsilane as an internal standard. Abbreviations are used as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (ms) were determined on a JEOL QH-100 mass spectrometer. Uv spectra were taken on a Shimadzu UV-240 at room temperature. Gas-liquid chromatography (glc) was performed on a Shimadzu GC-7A gas chromatograph equipped with a hydrogen flame-ionization detector using nitrogen as a carrier gas (30 ml/min). Glass columns (1.5 m, 3 mm i.d.) of 3% OV-17 on Shimalite W (80-100 mesh) were used. Thin layer chromatography (tlc) was carried out on Kieselgel 60 F_{254} (Merck) tlc plates. Uv-irradiation was carried out with a 60 W low-pressure mercury lamp (Eiko-sha). External irradiation was conducted for analytical scale photoreaction in a quartz tube under argon atmosphere using a merry-go-round apparatus at room temperature.

Materials —— 3-Fluoropyridine (3-FPy) (Aldrich Chemical Company Inc.) and indole (Wako Pure Chemical Industries Ltd., Japan) are commercially available. 4-FPy was prepared according to the reported procedure.[9]

Photolysis of a FPy and the Sodium Salt of Indole (**1**[Na]); General Procedure——A solution of a FPy (0.17 mmol) and **1**[Na] (0.1 mmol), prepared from **1** and the equimolar amount of sodium hydride, *in situ*, in DMF (10 ml) was irradiated externally for 5 h. The reaction mixture was submitted to glc with naphthalene as an internal standard. The products (**2a**,[10] **2b**,[10] **3b**[11]) were identified by comparison of their spectroscopic (ms, ^{1}H-nmr) and chromatographic behaviors with the authentic samples prepared by the reported procedures.

Photolysis of a FPy and Indole (**1**); General Procedure——A solution of a FPy (0.11 mmol) and **1** (0.1 mmol) in ether (10 ml) was irradiated externally under argon for 10 h. The reaction mixture was neutralized with 30 % aqueous K_2CO_3, and dried over anhydrous Na_2SO_4 followed by glc analysis with an internal standard of naphthalene.

Preparative-Scale Photoreaction of 3-FPy with **1**——A solution of 3-FPy (3.3 mmol) and **1** (3.0 mmol) in ether (300 ml) was irradiated internally in a Pyrex vessel for 14 h. The reaction mixture was worked-up in the same manner as described above and the residual oil was submitted to column chromatography on silica gel (Kieselgel 60, Merck) eluted with benzene, then with CH_2Cl_2, and finally with CH_2Cl_2-ether (1:1). The benzene eluate afforded **1** (1.85 mmol) in 62% yield and the CH_2Cl_2 and the CH_2Cl_2-ether eluates were further submitted to tlc developed with benzene-ethyl acetate (5:1) and benzene-acetone (5:2), respectively, to give 1-(3-pyridyl)indole (**2a**)(0.016 mmol, 0.5 %) and 3-(3-pyridyl)indole (**3a**) (0.019 mmol, 0.6%). **3a**: mp 154-155°C (colorless prisms from benzene). Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.42. Found: C, 80.60; H, 5.14; N, 14.26. ^{1}H-Nmr: 7.10-7.25 (2H, m, 5-H, 6-H), 7.42 (1H, ddd, J = 8.1, 4.8, 0.7, 5'-H), 7.52 (1H, dd, J = 7.3, 1.5, 7-H), 7.74 (1H, d like, s on D_2O added, 2-H), 7.91 (1H, dd, J = 7.0, 1.5, 4-H), 8.07 (1H, dt, J = 8.1, 1.8, 4'-H), 8.45 (1H, dd, J = 4.8, 1.5, 6'-H), 8.94 (1H, d, J = 1.8, 2'-H). Ms m/z (relative intensity): 194(M^+, 100), 193(34), 167(16), 166(22), 139(16).

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6) No other product derived from **1** and FPy was detected on glc: The low yields of the products may be attributable to photo-lability of **1**[-]; irradiation of a solution of **1**[-] in DMF in the absence of FPy (5 h) gave tremendously many peaks on glc and 52 % of **1** was consumed.

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