A FACILE SYNTHESIS OF *N*-(2- AND 4-PYRIDYL)INDOLES

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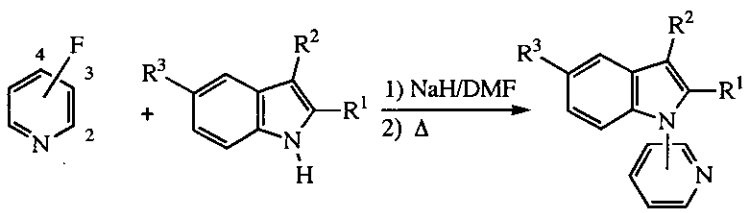
Abstract ——— The reactions of the sodium salts of indoles with 2- and 4-fluoropyridines afforded the corresponding *N*-pyridylindoles in good yields, whereas the reaction with 3-fluoropyridine gave no coupling product.

The synthesis of *N*-pyridylindoles are of interest from a chemotherapeutic point of view; for example, 2-imidazolinyl-*N*-pyridylindoles have recently been reported to possess antidiabetic activities.[1] However the methods introducing a pyridyl moiety directly to the indole ring at the nitrogen atom are few.[2,3] Previously we have reported that photoreaction of 2- and 3-fluoropyridines (2- and 3-FPy's) with the indole 1-anion (**1a**$^-$) yielded the corresponding *N*-pyridylindoles (**2a**, **3a**) in fair yields as the sole regio isomers,[4~6] while 4-fluoropyridine (4-FPy) was insensitive to the uv light, but reacted in the dark to give *N*-(4-pyridyl)indole (**4a**) in fair yield.[6] With a view to develop a new method for the preparation of *N*-(pyridyl)indoles, our attention was focused on the thermal reaction of FPy's and the sodium salts of indoles (1-Na) (Scheme 1). In the present paper, we describe our findings that *N*-(2- and 4-pyridyl)indoles (**2**, **4**) were synthesized in fair yields under rather mild conditions, whereas the 3-isomers (**3**) were obtained in sparing yields under the analogous conditions.



n-FPy;
n = 2, 3, 4

1a~f

2a~f
3a
4a~f

a ; R^1, R^2, R^3 = H: **b** ; R^1 = H, R^2 = CH_3, R^3 = H: **c** ; R^1, R^2 = $(CH_2)_4$, R^3 = H:
d ; R^1, R^2= $(CH)_4$, R^3 = H: **e** ; R^1, R^2 = H, R^3 = OCH_3: **f** ; R^1, R^2 = H, R^3 = CN

Scheme 1

Treatment of a solutions of 2-FPy (1.7 mmol) with the sodium salts of indole derivatives (**1x**-Na: **x** = **a**, indole; **b**, skatole; **c**, tetrahydrocarbazole; **d**, carbazole; **e**, 5-methoxyindole; **f**, 5-cyanoindole) (1 mmol) in dimethylformamide (DMF) at 95-100°C (for **1a**, **b**, **e**, and **f**) or at 125-130°C (for **1c** and **d**) afforded the corresponding *N*-(2-pyridyl)indoles (**2a**~**d**,[5] **e**, **f**) in good yields (Scheme 1, Table I). The scaled up reaction with **1a**-Na (ten-fold) yielded **2a** in the similar yield (92%).

Table I. The reaction of 2-fluoropyridine (2-FPy) with the sodium salts of indole derivatives (**1**-Na) in dimethylformamide (DMF).

Indole (**1**)	2-XPy/ X	Reaction time (h)	Reaction temp. (°C)	Yield of **2** (%)
a	F	1	95-100	91[a]
a	Cl	1	95-100	14[b]
a	Br	1	95-100	15[b]
b	F	3	95-100	81[a]
c	F	4	125-130	76[a]
d	F	1	125-130	85[a]
e	F	2	95-100	100[a]
f	F	2	95-100	88[a]

a) Isolated yield. *b*) Determined by glc.

The reaction with 3-FPy and **1a**-Na at 95-100°C for 4 h gave *N*-(3-pyridyl)indole (**3a**)[6] only in the sparing yield (12%) together with unreacted **1a** (77%). By contrast, treatment of 4-FPy with **1a**-Na (7 h) and its derivatives (**1b**-Na~**d**-Na) (40 h) under the similar conditions described above but at room temperature gave the corresponding *N*-(4-pyridyl)indoles (**4a**[6]~**d**) in fair yields (78, 56, 60 and 40%) (Table II): In the case of **1d**-Na, 33% unreacted **1d** was recovered.

When 2-chloro- or 2-bromopyridine (2-ClPy, 2-BrPy) was used in place of 2-FPy, the reactions were retarded

Table II. The reaction of 4-fluoropyridine (4-FPy) with the sodium salts of various indoles (**1**) in DMF

4-XPy/X	Substrate (**1**)	Reaction time (h)	Yield of **4** (%)
F	**a**	7	78[a]
Cl	**a**	7	-- [b,c]
F	**b**	40	56[a]
F	**c**	40	60[a]
F	**d**	40	40[a,d]

a) Isolated yield. *b*) Determined by glc. *c*) Not detected.

d) Accompanied by 33% unreacted **1d**.

significantly to give **2a** only in 14 (unreacted **1a**, 84%) and 15% (unreacted **1a**, 83%) yields (glc), respectively. Further, no detectable **4a** was obtained from 4-ClPy under the conditions employed for 4-FPy (Table II). These observations demonstrate the synthetic potential of fluoropyridines[2] for the regiospecific preparation of *N*-(pyridyl)indoles.

Because of a simple procedure and appreciable yields, the present reaction provides a prominent synthesis of *N*-pyridylindoles especially *N*-(4-pyridyl)indole derivatives.[7]

EXPERIMENTAL

^{1}H-Nmr spectra were measured with a JEOL JNM-EX400 (400 MHz) spectrometer, and chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard. Mass spectra (ms) were determined on a Shimadzu GCMS 9100-MK spectrometer. Gas-liquid chromatography (glc) was performed with a capillary column (CPB1-M50-025, Shimadzu) on a Shimadzu GC-7A gas-chromatogaraph equipped with a hydrogen flame-ionization detector using helium as a carrier gas. Short-column chromatography was conducted on Kieselgel Si-60 (Merck).

Materials-----2-Fluoropyridine (FPy), 3-FPy (Aldrich Chemical Company Inc.), and indole derivatives (**1a~d**, Wako Pure Chemical Industries Ltd., Japan; **1e**, Tokyo Chemical Industry Co., Ltd; **1f**, Aldrich Chemical Company Inc.) are commercially available. 4-FPy was prepared according to the reported procedure.[8]

General Procedure for the Preparation of 2 and 4 -----A solution of 2- or 4-FPy (165 mg, 1.7 mmol) and **1**-Na (1 mmol), prepared from **1** and the equimolar amount of sodium hydride, in situ, in DMF (6 ml) was heated or kept at room temperature under argon. The reaction mixture was acidified with concentrated hydrochloric acid and the solvent was evaporated under reduced pressure. The residue was dissolved in 20% hydrochloric acid. The solution was washed with hexane and neutralized with potassium carbonate (solid), followed by extraction with ether. The extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residual oil afforded a *N*-(pyridyl)indole on passage through a short silica gel column with hexane-acetone (4: 1) as an eluent. The products (**2a~d**, and **4a**) were identified by chromatographic and spectroscopic comparison with authentic samples prepared previously.[5,6]

5-Methoxy-*N*-(2-pyridyl)indole (2e): Colorless oil: Ms *m/z* (%) 224 (M^+, 100), 209 (75); ^{1}H-nmr ($CDCl_3$): δ 3.81 (3H, s, OCH_3), 6.58 (1H, d, *J* = 3.4 Hz, H-3), 6.91 (1H, dd, *J* = 8.3, 2.0 Hz, H-3'), 7.00 (1H, ddd, *J* = 7.3, 4.9, 2.0 Hz, H-5'),7.07 (1H, *d*, *J* = 2.4 Hz, H-4), 7.29 (1H, d, *J* =8.3 Hz, H-6), 7.61 (1H, d, *J* = 3.4 Hz, H-2), 7.62 (1H, ddd, *J* = 8.3, 7.3, 2.0 Hz, H-4'), 8.16 (1H, d, *J* = 8.3 Hz, H-7), 8.46 (1H, br dd, *J* = 4.9, 2.0 Hz, H-6'). mp of picrate 115-116°C (from ethanol). *Anal*. Calcd for $C_{20}H_{15}N_5O_8$ (picrate): C, 52.98; H, 3.34; N, 15.45. Found: C, 52.93; H, 3.14; N, 15.29.

5-Cyano-*N*-(2-pyridyl)indole (2f): Colorless oil: Ms *m/z* (%) 219 (M^+, 100), 218 (61); ^{1}H-nmr ($CDCl_3$): δ 6.70 (1H, d, *J* =3.4 Hz, H-3), 7.21 (1H, dd, *J* = 7.3, 4.9 Hz, H-5'), 7.39 (1H, d, *J* = 8.3 Hz, H-3'), 7.45 (1H, *d*, *J* = 8.8 Hz, H-6), 7.72 (1H, d, *J* = 3.4 Hz, H-2), 7.82 (1H, ddd, *J* = 8.3, 7.3, 2.0 Hz, H-4'), 7.92 (1H, s, H-4), 8.29 (1H, d, *J* = 8.8 Hz, H-7), 8.55 (1H, dd, *J* = 4.9, 2.0 Hz, H-6'). mp 108-109°C (from hexane). *Anal*. Calcd for $C_{14}H_9N_3$: C, 76.69; H, 4.14; N, 19.17. Found: C, 76.82; H, 4.11; N, 19.11.

3-Methyl-*N*-(4-pyridyl)indole (4b): Colorless oil: Ms *m/z* (%) 208 (M^+, 71), 207 (100); ^{1}H-nmr ($CDCl_3$): δ 2.38 (3H, d, *J* =1.1 Hz, CH_3), 7.21 (1H, q, *J* =1.1 Hz, H-2), 7.24 (1H, td, *J* = 7.0, 1.1 Hz, H-

5), 7.30 (1H, ddd, J = 7.7, 7.0, 1.5 Hz, H-6), 7.46 (2H, *d*, J = 5.9 Hz, H-3' and H-5'), 7.63 (1H, dd, J = 7.0, 1.5 Hz, H-4), 7.72 (1H, dd, J = 7.7, 1.1 Hz, H-7), 8.68 (2H, br, H-2' and H-6'). mp of picrate 270-273°C (from aq. ethanol). *Anal.* Calcd for $C_{20}H_{15}N_5O_8$ (picrate): C, 54.92; H, 3.46; N, 16.01. Found: C, 54.83; H, 3.34; N, 15.92.

***N*-(4-Pyridyl)-1,2,3,4-tetrahydrocarbazole (4c)**: Ms *m/z* (%) 248 (M^+, 92), 247 (34), 220 (69), 219 (100); ^{1}H-nmr ($CDCl_3$): δ 1.80-2.00 (4H, m, 2-H_2 and 3-H_2), 2.61-2.85 (4H, m, 1-H_2 and 4-H_2), 7.11-7.22 (2H, m, H-6 and H-7), 7.35 (2H, d like, J = 5.9 Hz, H-3' and H-5'), 7.35-7.42 (1H, m, H-5), 7.47-7.57 (1H, m, H-8), 8.72 (2H, d like, J = 5.9 Hz, H-2' and H-6'). mp 99-100°C (from hexane). *Anal.* Calcd for $C_{20}H_{15}N_5O_8$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.19; H, 6.57; N, 11.19.

***N*-(4-Pyridyl)carbazole (4d)**: Ms *m/z* (%) 244 (M^+, 100), 243 (33); ^{1}H-nmr ($CDCl_3$): δ 7.33 (2H, ddd, J = 7.7, 7.3, 1.1 Hz, H-3 and H-6), 7.44 (2H, td, J = 7.7, 1.5 Hz, H-2 and H-7), 7.56 (2H, ddd, J = 7.7, 1.5, 0.7 Hz, H-4 and H-5),7.58 (2H, d like, J = 6.2 Hz, H-3' and H-5'), 8.13 (2H, ddd, J = 7.7, 1.1, 0.7 Hz, H-1 and H-8), 8.84 (2H, d like, J = 6.2 Hz, H-2' and H-6'). mp 133-134°C (from hexane). *Anal.* Calcd for $C_{20}H_{15}N_5O_8$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.72; H, 4.91; N, 11.35.

REFERENCES AND NOTES

1) C. B. Chapleo and G. P. Fagan, *Annu. Drug Data Rep.*, 1993, **15**, 59 (*Chem. Abstr.*, 1992, **117**, 90283f).

2) J. C. Powers reported (*J. Org. Chem.*, 1965, **30**, 2534) the synthesis of **2a** by the reaction of **1**-Na and 2-ClPy under rather drastic conditions (7 h at 170°C in a sealed tube) without citation of the yield.

3) M. A. Khan and J. B. Polya, *J. Chem. Soc. (C)*, **1970**, 85.

4) K. Seki, K. Ohkura, M. Terashima, and Y. Kanaoka, *Heterocycles*, 1987, **26**, 3101.

5) K. Seki, K. Ohkura, K. Matsuda, M. Terashima, and Y. Kanaoka, *Chem. Pharm. Bull.*, 1988, **36**, 4693.

6) K. Ohkura, K. Seki, M. Terashima, and Y. Kanaoka, *Heterocycles*, 1990, **31**, 1833.

7) *N*-(2- and 3-pyridyl)indoles have been prepared in appreciable yields by the methods involving a photoreaction[4,5] or an Ullmann-type condensation,[3] whereas substantial synthesis of the 4-isomers has not yet been reported.

8) P. B. Desai, *J. Chem. Soc., Perkin Trans.* 1, **1973**, 1865.

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