Annulation of Pyridine to Indole by A Tandem Aza-Wittig/Electrocyclization Strategy: Synthesis of Pyrido[2,3-*b*]indoles

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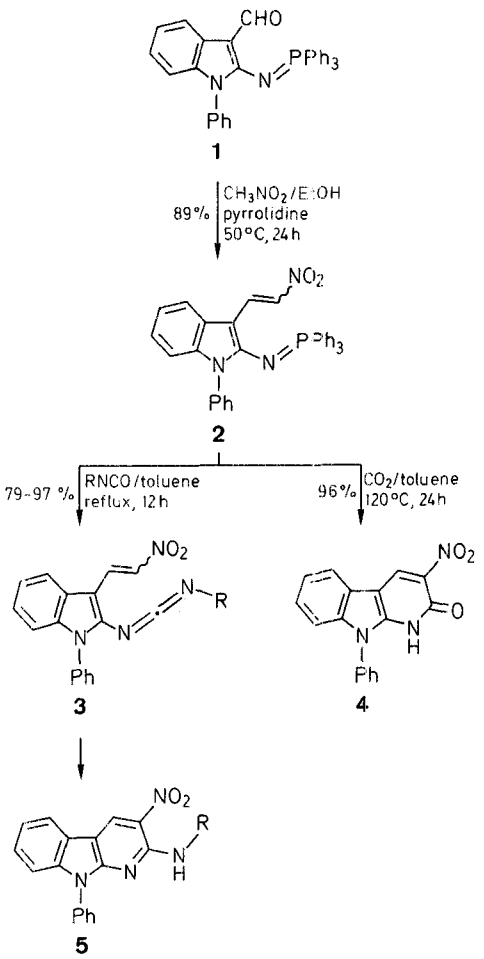
Iminophosphorane **2**, prepared from **1** and nitromethane, reacts with isocyanates to give directly 2-alkyl(aryl)amino-3-nitro-9-phenyl-9*H*-pyrido[2,3-*b*]indoles **5**.

Recently, pyrido[2,3-*b*]indoles (α-carbolines) have received much attention because they are pharmacologically active compounds, they display strong cytostatic and antitumor activity,[1-3] and have therefore attracted interest concerning their synthesis. So far, only two methods for the synthesis of α-carbolines have been developed, both of them keep the pyridine and benzene parts of the molecule separate until the latter stage of the synthesis and to form the pyrrole ring in the last step. The first method involves N–C bond formation of the pyrrole ring by a nitrene insertion reaction, e.g. thermal decomposition of 3-(*o*-azidophenyl)pyridine[4] or phosphorus trivalent promoted deoxygenation of 3-(*o*-nitrosophenyl)pyridine;[5] in both cases a mixture of α- and γ-carbolines is obtained. The second method is based on the γ-C–C bond formation of the pyrrole ring from diazonium salts derived from *N*-(3-amino-2-pyridyl)anilines either with copper powder[6] or polyphosphoric acid.[7,8]

In connection with our studies on heteropolycyclic compounds with potential biological activity, we have devised a new approach to the β- and γ-carbolines systems,[9] and report here a novel synthesis of α-carbolines, involving formation of a simple bond β to the nitrogen atom of the pyridine ring. Our approach is centered on the aza-Wittig reaction of the iminophosphorane derived from 3-substituted 2-azido indole with isocyanates to give an 2-aza-1,3,5-hexatriene moiety containing cumulated double bonds at one end, which subsequently undergo electrocyclic ring-closure to yield the cyclic valence tautomer pyridine ring.



5	R
a	Et
b	Ph
c	4-ClC_6H_4
d	4-$CH_3C_6H_4$
e	4-$MeOC_6H_4$

Iminophosphorane **1**, readily available from 2-azido-3-formyl-1-phenylindole and triphenylphosphine,[9] reacts with nitromethane in the presence of pyrrolidine to give the crystalline iminophosphorane **2** in 89% yield. The reaction of iminophosphorane **2** with several isocyanates in dry toluene at reflux temperature for 12 h leads directly to the corresponding 2-alkyl(aryl)amino-3-nitro-9-phenyl-9*H*-pyrido[2,3-*b*]indoles **5** in excellent yields (79–97%) (Table). Iminophosphorane **2** also reacts with carbon dioxide in dry toluene at 120°C in a sealed tube glass to give **4** in 96% yield. Presumably, the conversion **2** into **5** involves initial aza-Wittig reaction between the iminophosphorane and the isocyanate to give a carbodiimide **3** as highly reactive intermediate, which easily undergoes electrocyclic ring closure followed by 1,3-proton shift to give the otherwise not readily available α-carboline derivative **5**.

Mass spectra of compounds **5** show the expected molecular ion peak, the IR spectra show absorption band in the region $\nu = 3368-3268\ cm^{-1}$ due to the amino group. The ^1H-NMR spectra also support the correct structure of **5**; for **5a** the methylene signal appears as a complex multiplet.

The above method demonstrates that the tandem aza-Wittig/electrocyclization strategy affords a new and general high yield entry to a variety of α-carbolines with variable substituents at the pyridine ring. Due to the easy access of the starting materials, the good yields in the iminophosphoranes preparation as well as in the cyclization step, and due to the simplicity of the experimental one pot procedure; this synthetic approach compares favorably with other methods.

IR spectra were recorded on a Nicolet FT 5DX spectrophotometer. ^1H-NMR spectra were recorded on a Bruker AC 200 spectrometer at 200 MHz using TMS as internal standard. Mass spectra were measured on a Hewlett-Packard 5993 C instrument.

3-[(*E*/*Z*)-2-Nitroethenyl]-1-phenyl-2-(triphenylphosphoranylidenamino)-indole (2):

A solution of 3-formyl-1-phenyl-2-(triphenylphosphoranylideneamino)indole[9] (**1**; 1.5 g, 3 mmol) in EtOH (10 mL) is added to a well stirred solution of nitromethane (0.61 g, 10 mmol), and pyrrolidine (0.71 g, 10 mmol) in EtOH (10 mL). The mixture is stirred at 50°C for 24 h. After cooling, the separated solid is collected by filtration and recrystallized from EtOH to give **2**; yield: 1.44 g (89%), red prisms; mp 210°C.

$C_{34}H_{26}N_3O_2P$	calc.	C 75.68	H 4.86	N 7.79
(539.6)	found	75.55	4.93	7.91

IR (Nujol): $\nu = 1600, 1515, 1253, 1187, 997\ cm^{-1}$.

^1H-NMR ($CDCl_3$): $\delta = 7.14$ (m, 1H); 7.30–7.70 (m, 24H); 8.27 (d, 1H, $J = 12.5$ Hz).

^{13}C-NMR ($CDCl_3$): $\delta = 97.7, 109.5, 119.4, 122.1, 124.4, 125.4, 128.1, 128.9, 129.3, 129.4, 132.4, 132.7, 135.7, 137.1, 137.6, 156.8, 157.0$.

MS (70 eV): $m/z = 539$ (M^+, 23); 493 (5); 483 (10); 379 (13); 304 (30); 261 (15); 246 (10); 204 (8); 185 (15); 184 (25); 183 (100); 152 (15); 108 (46); 77 (20).

2-Alkyl(aryl)amino-3-nitro-9-phenyl-9*H*-pyrido[2,3-*b*]indoles 5; General Procedure:

A solution of the appropriate isocyanate (10 mmol) in dry toluene (3 mL) is added dropwise under N_2 to a well stirred solution of iminophosphorane **2** (0.5 g, 10 mmol) in the same solvent (10 mL). The mixture is stirred at reflux temperature for 12 h. After cooling, the solvent is removed under reduced pressure and the residual material is slurried with Et_2O (20 mL), and the solid is separated by filtration and recrystallized from CH_2Cl_2/hexane (1:1) to give **5** (Table).

3-Nitro-9-phenyl-2-oxo-2,9-dihydro-1*H*-pyrido[2,3-*b*]indole (4):

Iminophosphorane **2** (0.5 g, 10 mmol), dry toluene (10 mL), and excess of solid CO_2 are heated in a sealed tube at 120°C for 24 h. After cooling, the solvent is removed under reduced pressure and the crude product is slurried with Et_2O (20 mL), filtered, and recrystallized from EtOH to give **4**; yield: 0.29 g (96%); yellow prisms; mp 232°C.

$C_{17}H_{11}N_3O_3$	calc.	C 66.88	H 3.63	N 13.76
(305.3)	found	67.04	3.58	13.66

Table. Compounds **5** Prepared

Product	Yield[a] (%)	mp (°C)[b] (appearance)	Molecular Formula[c]	IR (nujol) ν (cm^{-1})	^1H-NMR[d] δ, J (Hz)	MS (70 eV) m/z (%)
5a	80	172 (dec) (orange prisms)	$C_{19}H_{16}N_4O_2$ (332.4)	3368, 1640, 1604, 1598, 1505, 1312, 1229, 922, 775, 747, 702	1.24 (t, 3H, $J = 7$); 3.51 (m, 2H); 7.2–7.3 (m, 1H); 7.30–7.40 (m, 1H); 7.40–7.50 (m, 1H); 7.50–7.70 (m, 4H); 7.83 (dd, 1H, $J = 6.5, 1.6$); 8.57 (t, 1H, $J = 5$); 8.95 (s, 1H)	332 (M^+, 100); 315 (43); 298 (20); 285 (21); 271 (26); 259 (23); 258 (20); 244 (30); 243 (37); 166 (14); 122 (14); 77 (30)
5b	80	212 (dec) (red prisms)	$C_{23}H_{16}N_4O_2$ (380.4)	3286, 1636, 1597, 1574, 1517, 1498, 1280, 1238, 1214, 1270, 773, 760, 699	6.95–7.15 (m, 1H); 7.20–7.65 (m, 12H); 7.93 (dd, 1H, $J = 7$); 9.06 (s, 1H); 10.53 (br s, 1H)	380 (M^+, 100); 345 (15); 335 (10); 334 (41); 333 (38); 257 (12); 247 (11); 229 (15); 190 (16); 166 (24); 77 (40)
5c	93	259–261 (red prisms)	$C_{23}H_{15}ClN_4O_2$ (414.9)	3290, 1634, 1614, 1573, 1520, 1462, 1282, 1240, 1215, 825, 773, 756, 730, 693	7.28 (d, 2H, $J = 9$); 7.40–7.50 (m, 1H); 7.65–7.82 (m, 6H); 7.78 (d, 2H, $J = 9$); 8.32 (d, 2H, $J = 9$); 9.45 (s, 1H); 10.51 (br s, 1H)	416 ($M+2$, 35); 414 (M^+, 100); 369 (14); 367 (27); 334 (11); 332 (29); 247 (16); 229 (22); 207 (15); 166 (33); 139 (10); 127 (12); 111 (15); 77 (60)
5d	79	220–221 (red prisms)	$C_{24}H_{18}N_4O_2$ (394.4)	3290, 1636, 1603, 1570, 1518, 1461, 1280, 1233, 1214, 1180, 1151, 825, 774, 698	2.31 (s, 3H); 7.03 (d, 2H, $J = 8$); 7.30–7.70 (m, 10H); 7.93 (dd, 1H, $J = 7$); 9.12 (s, 1H); 10.72 (br s, 1H)	394 (M^+, 100); 377 (5); 359 (20); 349 (18); 348 (29); 347 (25); 333 (13); 174 (33); 166 (33); 77 (58)
5e	97	198 (dec) (red prisms)	$C_{24}H_{18}N_4O_3$ (410.4)	3295, 1638, 1607, 1575, 1519, 1462, 1239, 1212, 1176, 1164, 1031, 824, 773, 730, 692	3.81 (s, 3H); 6.77 (d, 2H, $J = 9$); 7.40–7.70 (m, 10H); 7.92 (d, 1H, $J = 7$); 9.10 (s, 1H); 10.64 (br s, 1H)	410 (M^+, 100); 395 (18); 375 (11); 348 (10); 320 (25); 244 (10); 243 (15); 205 (13); 174 (13); 166 (17); 160 (21); 77 (28)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.25, H ±0.23, N ±0.26.
[d] Solvent: for **5a**, **5d** and **5e**, $CDCl_3$; for **5b** and **5c**, DMSO-d_6.

IR (Nujol): ν = 1638, 1567, 1462, 1324, 1300, 1229, 1150, 1032, 755, 693 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 7.22 (dd, 1 H, J = 8.2, 1.05 Hz); 7.36 (dd, 1 H, J = 7.3, 1.05 Hz); 7.44 (dd, 1 H, J = 7.3, 1.4 Hz); 7.50–7.87 (m, 5 H); 8.28 (dd, 1 H, J = 6.8, 1.4 Hz); 9.34 (s, 1 H); 12.7 (br s, 1 H).

^{13}C-NMR (DMSO-d_6): δ = 109.0, 110.4, 120.8, 121.0, 122.1, 126.7, 126.9, 127.7, 128.6, 129.6, 129.8, 134.8, 140.5, 151.6, 157.0.

MS (70 eV): m/z = 305 (M^+, 100); 288 (5); 259 (10); 247 (25); 244 (10); 231 (20); 204 (20); 127 (15); 115 (20); 77 (35).

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(1) Wieczorek, J., Peczynska-Czoch, W., Mordarski, M., Kaczmarek, L., Nantka-Namirski, P. *Arch. Immunol. Ther. Exp.* **1986**, *34*, 315.
(2) Fiszer-Maliszewska, L., Mordarski, M. *Arch. Immunol. Ther. Exp.* **1987**, *35*, 221.
(3) Peczynska-Czoch, W. *Arch. Immunol. Ther. Exp.* **1987**, *35*, 139.
(4) Smith, P.A.S., Boyer, J.H. *J. Am. Chem. Soc.* **1951**, *73*, 2626.
(5) Bunyan, P.J., Cadogan, J.I.G. *J. Chem. Soc.* **1963**, 42.
(6) Abramovitch, R.A. Hey, D.H., Mulley, R.D. *J. Chem. Soc.* **1954**, 4263.
(7) Rivalle, C., Ducroq, C. Lhoste, J.M., Wendling, F. Bisagni, E., Chermann, J.C. *Tetrahedron* **1981**, *37*, 2097.
(8) Nantka-Namirski, P., Kalinowski, J. *Acta Pol. Pharm.* **1974**, *31*, 137.
(9) Molina, P., Fresneda, P.M. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1819.