RING TRANSFORMATION OF FUSED PYRIDAZINES. VI.[1] CONSTRUCTION OF 3-(2-PYRIDYL)INDOLE SKELETON BY MEANS OF N-N BOND CLEAVAGE REACTION OF FUSED PYRIDAZINES WITH YNAMINES

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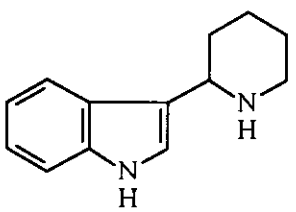
Abstract- We established a new N-N bond cleavage reaction of pyridazino[4,5-*b*]indoles with ynamines to form 3-(2-pyridyl)indoles. The latter are easily converted to 3-(2-piperidyl)indoles, which are key intermediates for the synthesis of indole alkaloids.

The 3-(2-piperidyl)indole skeleton (**I**) is common to a large number of indole alkaloids,[2,3] and current synthetic approaches to indole alkaloids involve fabrication of the basic piperidylindole system followed by elaboration of the individual alkaloid structures.



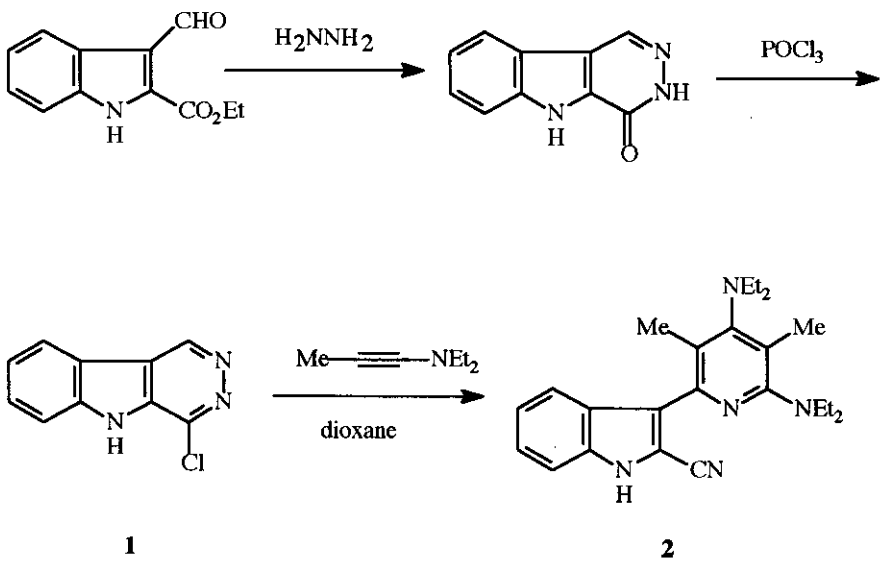
I

Many methods of constructing the 3-(2-piperidyl)indole system have been reported. van Tamelen and Knapp[4] developed a synthesis of simple piperidylindoles that involves the nucleophilic attack of indole on the immonium salt.

In addition, 3-(2-pyridyl)indoles can be converted into 3-(2-piperidyl)indoles by quaternization of the pyridine ring followed by reduction of the pyridinium salt.[5,6] Consequently, various methods have been developed for synthesis of the 3-(2-pyridyl)indole system. One example is the application of palladium-cata-

lyzed cross-coupling reaction of indolezinc halide with halopyridine.[7] Thus, many of the above methods involve nucleophilic attack of indole to yield the desired piperidyl- or pyridylindole. However a convenient method for introducing substituents at the alpha- or beta-position of the indole ring is still required.

We have reported[8] that halogen-substituted condensed pyridazines undergo N-N bond cleavage of the pyridazine ring by ynamines to give pyridylheteroarenecarbonitriles. This reaction affords heteroarenecarbonitrile compounds having a pyridine moiety at the alpha-position to the cyano group. We therefore decided to apply this reaction to construct the 3-(2 pyridyl)indole structure (Scheme 1).

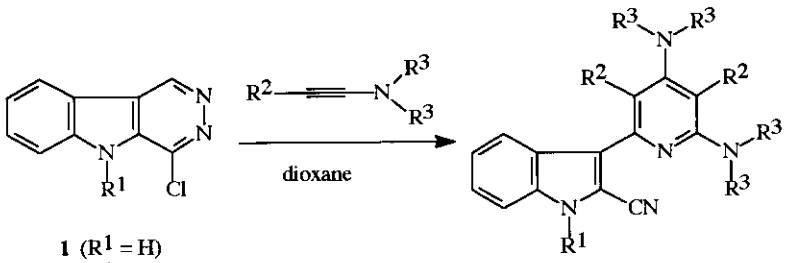


1 **2**

Scheme 1

Here we describe the synthesis of 3-(2-pyridyl)indoles by the reaction of pyridazinoindoles with ynamines. The starting compounds, 4-substituted pyridazino[4,5-*b*]indoles, were easily prepared as shown in Scheme 1. 4-Chloro-5*H*-pyridazino[4,5-*b*]indole (**1**) reacted with a two fold excess of *N,N*-diethyl-1-propynylamine to give 3-[2-[4,6-bis(diethylamino)-3,5-dimethylpyridinyl]indole]-2-carbonitrile (**2**) in 57.0 % yield. However, the product was difficult to purify because presence of the free NH of the indole ring, so we examined the reactivities of N-protected pyridazino[4,5-*b*]indoles with ynamines (Scheme 2).

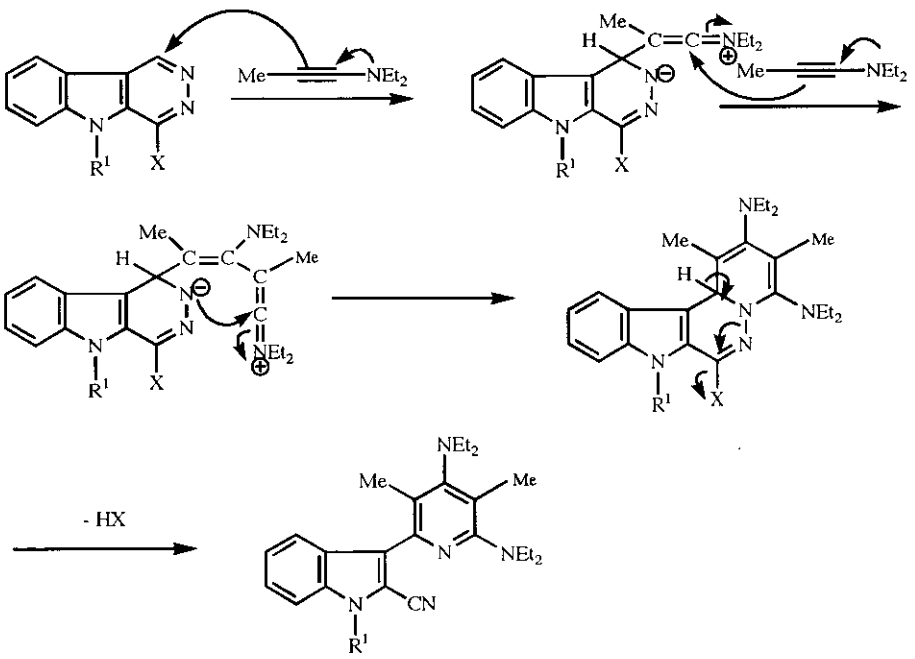
4-Chloro-5-methylpyridazino[4,5-*b*]indole (**3**) reacted with ynamines to give the corresponding 3-(2-pyridyl)indole-2-carbonitriles (**5 -7**) in moderate yields. Purification was relatively easy, and final purification was carried out as the picrates. In the case of entry 5, the yield of the 3-(2-pyridyl)indole-2-carbonitrile (**8**) is low, presumably because of the high LUMO energy of 5-benzyl-4-chloropyridazino[4,5-*b*]indole (**4**).



1 (R^1 = H)
3 (R^1 = Me)
4 (R^1 = CH_2Ph)

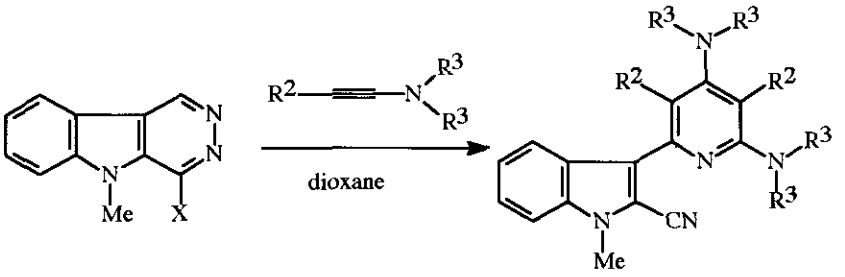
entry	R^1	R^2	NR^3_2	product	Yield (%)
1	H	Me	NEt_2	**2**	57.0
2	Me	Me	NEt_2	**5**	60.0
3	Me	H		**6**	63.3
4	Me	Me		**7**	58.0
5	CH_2Ph	Me	NEt_2	**8**	28.8

Scheme 2



Scheme 3

If the mechanism of this reaction is as shown in Scheme 3, the yield should increase with increasing ease of elimination of the substituent. Therefore we examined the reactivities of 4-bromo-5-methylpyridazino[4,5-*b*]indole (**9**) and 5-methyl-4-tosylpyridazino[4,5-*b*]indole (**10**) with ynamines (Scheme 4). The results were as expected. Compound (**9**) with *N,N*-diethyl-1-propynylamine gave the corresponding 3-(2-pyridyl)indole-2-carbonitrile (**5**) in good yield (84.0 %), while **10** gave **5** in 64.6% yield. On the other hand, 4-cyano-5-methylpyridazino[4,5-*b*]indole (**11**) reacted with 1-acetylmorpholine to give **6** in low yield.



Starting material	X	R^2	NR^3_2	product	Yield (%)
9	Br	Me	NEt_2	**5**	84.0
9	Br	H		**6**	87.2
9	Br	Me		**7**	72.5
10	Ts	Me	NEt_2	**5**	64.6
10	Ts	H		**6**	68.0
11	CN	H		**6**	23.9

Scheme 4

Conversion of 3-(2-pyridyl)indole into 3-(2-piperidyl)indole is a well established procedure involving quaternization of the pyridine ring followed by reduction over platinum dioxide. The use of an appropriate ynamine in this N-N bond cleavage reaction makes it possible to prepare 3-(2-piperidyl)indole having no substituent on the piperidine ring.

In conclusion, our methods convenient for the constructing 3-(2-pyridyl)indoles, which are important precursors of 3-(2-piperidyl)indoles. Further, a cyano group can be introduced at the 2-position of the indole

ring. Further studies are in progress.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were taken with a JASCO A-102 diffraction grating IR spectrophotometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer and at 270 MHz on a JEOL instrument, and ^{13}C-NMR spectra were obtained with a JEOL JNM-FX90Q FTNMR spectrometer. Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as an internal standard. MS spectra were recorded with a JEOL JMS D-100 mass spectrometer. Column chromatography was carried out on silica gel (Merck Co. Ltd., 200 mesh).

4-Chloro-*5H*-pyridazino[4,5-*b*]indole (1)

Akagi's method[9] was modified. Pyridazino[4,5-*b*]indol-4-one (4.2 g, 22.7 mmol) was treated with $POCl_3$ (42 mL, 450 mmol) and the mixture was refluxed for 3 h. After removal of the excess $POCl_3$ under reduced pressure, the residue was taken up in ether. The yellow solid was collected by filtration, and suspended in water, then neutralized with 25 % NH_4OH. The precipitate was collected by filtration and washed with ether to give 4-chloro-*5H*-pyridazino[4,5-*b*]indole (**1**) (3.33 g, 72.0 %).

Reaction of 1 with *N,N*-diethyl-1-propynylamine

To a solution of **1** (200 mg, 0.98 mmol) in 4 mL of dioxane was added *N,N*-diethyl-1-propynylamine (228 mg, 2.1 mmol) and the mixture was heated at 80°C for 20 min. The reaction mixture was then cooled, water was added, and the whole was extracted with chloroform twice. The combined organic layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$) to give 3-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]indole-2-carbonitrile (**2**) (218 mg, 57.0 %) as a pale yellow oil. MS m/z: 389 (M^+). ^{1}H-NMR ($CDCl_3$): 7.39 - 7.37 (2H, m), 7.23 - 7.18 (2H, m), 3.23 (8H, q, J = 7.2 Hz), 2.25 (3H, s), 2.18 (3H, s), 1.10 (6H, t, J = 7.2 Hz). IR (neat): 2223 cm^{-1}.

4-Chloro-5-methylpyridazino[4,5-*b*]indole (3)

98 % Hydrazine hydrate (18 g, 350 mmol) was dissolved in 80 mL of ethyl cellosolve and to this solution was added ethyl 3-formyl-1-methylindole-2-carboxylate (8.0 g, 34.6 mmol) in 720 mL of ethyl cellosolve during 2 h under reflux. Then the reaction mixture was refluxed for 10 h. After cooling, it was concentrated and the precipitate was filtered, washed with ether and recrystallized from ethanol to give 5-methylpyridazino[4,5-*b*]indol-4-one (4.4 g, 63.2 %). mp 271 °C. Chlorination of 5-methylpyridazino[4,5-*b*]indol-4-one (8.0 g, 40 mmol) by the procedure mentioned above gave **4** (7.6 g, 87.3 %). mp 177 - 180 °C. ^{1}H-NMR (DMSO): 9.91 (1H, s), 8.37 (1H, d, J = 7.9 Hz), 7.89 - 7.44 (3H, m), 4.24 (3H, s). IR (KBr): 1546,

1362, 1270, 1096, 761 cm^{-1}. *Anal.* Calcd for $C_{11}H_8N_3Cl$: C, 60.70; H, 3.70; N, 19.31. Found: C, 60.68; H, 3.55; N, 19.30.

4-Bromo-5-methylpyridazino[4,5-*b*]indole (**9**) was prepared similarly with $POBr_3$. mp 278 - 275°C. ^{1}H-NMR (DMSO): 9.84 (1H, s), 8.39 - 8.26 (1H, d, J = 7.4 Hz), 7.79 - 7.22 (3H, m), 4.22 (3H, s). IR (KBr): 1543, 1357, 1260, 1083, 759 cm^{-1}. *Anal.* Calcd for $C_{11}H_8N_3Br$: C, 50.41; H, 3.08; N, 16.03. Found: C, 51.26; H, 2.81; N, 16.50.

5-Methyl-4-tosylpyridazino[4,5-*b*]indole (10)

A mixture of **9** (500 mg, 2.3 mmol) and sodium *p*-toluenesulfinate (492 mg, 2.76 mmol) was dissolved in 10 mL of DMF. The reaction mixture was refluxed for 2 h, the cooled and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to afford a residue, which was purified by silica gel column chromatography ($CHCl_3$) to give **10** (589 mg, 79.6 %).

Reaction of 3, 4, 9, 10, 11 with ynamines

A solution of **3** (200 mg, 0.92 mmol) in dioxane (4 mL) was treated with *N,N*-diethyl-1-propynylamine (214 mg, 1.93 mmol), and the mixture was refluxed for 2 h. It was then cooled, and extracted with ethyl acetate twice. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2) to give 3-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-3-methylindole-2-carbonitrile (**5**) (193 mg, 52.0 %). mp 103 °C (from ethyl acetate - hexane). MS m/z: 403 (M^+). ^{1}H-NMR ($CDCl_3$): 7.66 (1H, d, J = 7.9 Hz), 7.40 - 7.17 (3H, m), 3.94 (3H, s), 3.24 (8H, q, J = 7.0 Hz), 2.22 (3H, s), 2.14 (3H, s), 1.10 (12H, t, J = 7.1 Hz). ^{13}C-NMR ($CDCl_3$): 161.17, 158.39, 145.72, 137.84, 128.70, 125.72, 125.66, 123.22, 122.88, 121.06, 114.11, 110.02, 109.94, 46.10, 44.66, 31.52, 16.56, 15.95, 14.47, 13.11. IR (neat): 2214 cm^{-1}. *Anal.* Calcd for $C_{25}H_{33}N_5$: C, 74.22; H, 8.59; N, 17.15. Found: C, 74.40; H, 8.24; N, 17.35.

The reaction of **3** with morpholinoacetylene afforded 3-[4,6-bis(morpholino)pyridin-2-yl]-3-methylindole-2-carbonitrile (**6**) (155.3 %) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): 7.47 - 7.24 (4H, m), 6.83 (1H, s), 5.97 (1H, s), 3.95 (3H, s), 3.89 - 3.86 (8H, m), 3.63 (4H, t, J = 4.7 Hz), 3.35 (4H, t, J = 4.7 Hz). IR (neat): 2210 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.24; N, 17.36. Found: C, 67.97; H, 6.11; N, 17.95.

The reaction of **3** with 1-(morpholino)-1-propyne afforded 3-[4,6-bis(morpholino)-3,5-dimethylpyridin-2-yl]-3-methylindole-2-carbonitrile (**7**) (36.0 %) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): 7.71 (1H, d, J=8.2 Hz), 7.55 - 7.37 (3H, m), 3.96 (3H, s), 3.84 (8H, t, J = 4.6 Hz), 3.26 (4H, t, J = 4.6 Hz), 3.19 (4H, t, J = 4.6 Hz), 2.32 (3H, s), 2.25 (3H, s). *Anal.* Calcd for $C_{25}H_{29}N_5O_2$: C, 69.58; H, 6.77; N, 16.23. Found: C, 69.11; H, 6.33; N, 15.80.

The reaction of 5-benzyl-4-chloropyridazino[4,5-*b*]indole (**4**) with *N,N*-diethyl-1-propynylamine afforded 3-[4,6-bis(diethylamino)-3,5-dimethylpyridin-2-yl]-3-benzylindole-2-carbonitrile (**8**) (28.8 %). mp 95°C

(from ethyl acetate - hexane). MS m/z: 480 (M^+). ^{1}H-NMR ($CDCl_3$): 7.70 (1H, d, J = 7.9 Hz), 7.35 - 7.17 (8H, m), 5.52 (2H, s), 3.23 (8H, q, J = 7.0 Hz), 2.23 (3H, s), 2.16 (3H, s), 1.10 (12H, t, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$): 161.16, 158.38, 145.60, 137.14, 136.28, 128.93, 127.97, 126.12, 125.83, 123.31, 123.05, 121.26, 121.11, 114.17, 110.63, 109.74, 49.03, 46.10, 44.66, 16.62, 15.95, 14.44, 13.11. IR (neat): 2214 cm^{-1}. *Anal.* Calcd for $C_{31}H_{37}N_5$: C, 77.62; H, 7.77; N, 14.60. Found: C, 78.03; H, 7.29; N, 14.59.

The reaction of 4-bromo-5-methylpyridazino[4,5-*b*]indole (**9**) with *N,N*-diethyl-1-propynylamine gave **5** in 84.0% yield.

The reaction of **9** with 1-acetylmorpholine gave **6** in 87.2 % yield.

The reaction of **9** with 1-(morpholino)-1-propyne gave **7** in 72.5 % yield.

The reaction of 5-methyl-4-tosylpyridazino[4,5-*b*]indole (**10**) with *N,N*-diethyl-1-propynylamine gave **5** in 64.6% yield.

The reaction of **10** with 1-acetylmorpholine gave **6** in 68.0 % yield.

The reaction of 4-cyano-5-methylpyridazino[4,5-*b*]indole (**11**) with 1-acetylmorpholine gave **6** in 23.9% yield.

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