Ring Closure of 4-Azido-3-phenyl-pyridazines to Pyridazino[4,3-*b*]indoles[1]

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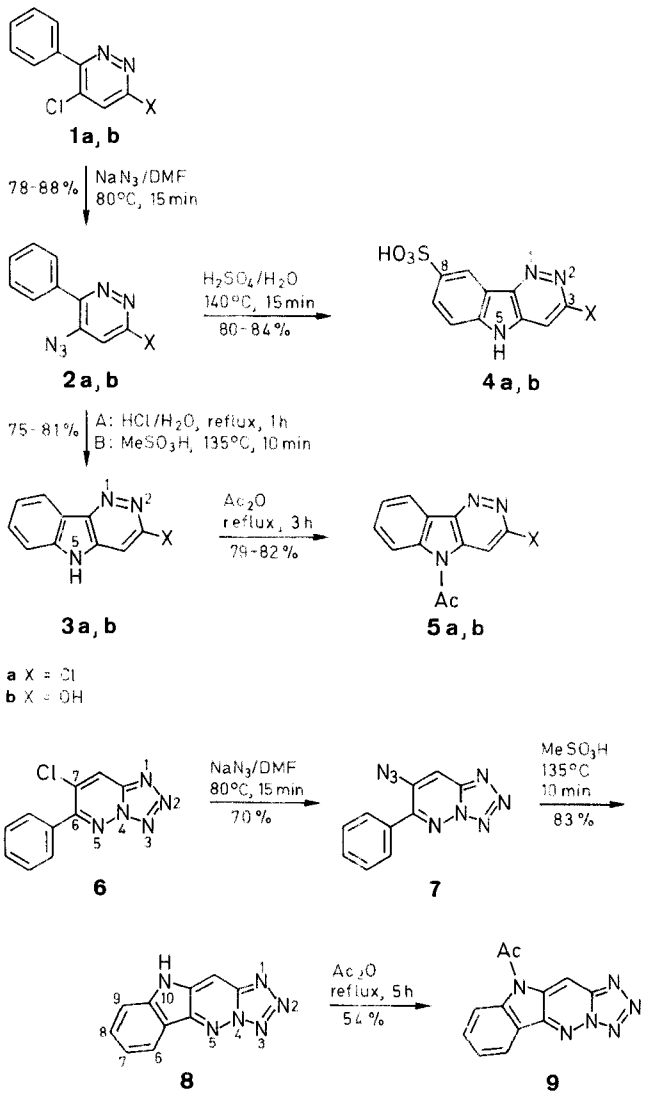
The cyclization of 4-azido-3-phenylpyridazines and 7-azido-6-phenyltetrazolo[1,5-*b*]pyridazine by heating with strong acids like methanesulfonic acid affords 5*H*-pyridazino[4,3-*b*]indoles or 10*H*-tetrazolo[1′,5′:1,6]pyridazino[4,3-*b*]indoles, respectively, whereas the conventional photochemical or thermolytic methods fail.

The cyclization of *ortho*-phenylazidoarenes or -heteroarenes to indolderivatives is a known reaction,[2] which in most cases is carried out thermically or photochemically. We have demonstrated the cyclization of some azidoquinolines, azidobenzopyrans,[3] and azidopyrimidines[4] using this methodology to yield the corresponding indolo derivatives. Mechanistic studies[2,5] have shown that a singlet nitrene is involved in these reactions. Extending this type of ring-closure reaction to 4-azido-3-phenyl-azidopyridazines **2** and to 7-azido-6-phenyltetrazolo [1,5-*b*]pyridazine (**7**) (obtained from the corresponding chloro derivatives **1** and **6**), we observed obvious differences in the behavior of these compounds under different conditions. The thermolysis in various solvents, such as dimethylformamide, butanol, high-boiling benzene derivatives, etc., showed that pyridazines of the types **2** and **7** are rather stable compunds, which undergo partial decomposition slowly upon heating for extended periods, but no indole derivatives can be isolated from the decomposition products. Attempts to carry out the thermolysis without solvents at 120–130°C led to complete decomposition. Similar observations were made when photolytical degradation was attempted in different solvents.

However, when the azidopyridazines **2** were heated in conc. sulfuric acid at 120°C, slow nitrogen evolution was observed. Isolation of the reaction product showed, that the desired indole cyclization had occured in about 80% yield, but the phenyl ring had also been sulfonated in position *para* to the indole *N*-atom. The only alternative possibility, a sulfonic acid group in *ortho*-position, could be ruled out by the ^{1}H-NMR spectra, which show *ortho* and *meta* coupling, for two protons, whereas the third proton shows only *meta* coupling.

To avoid the introduction of a sulfonic acid group, other acids were investigated as potential catalysts. Cyclization of azido compound **2a** in boiling 6N hydrochloric acid afforded 3-chloro-5*H*-pyridazino[3,4-*b*]indole (**3a**) but with the hydroxy



analog **2b** no reaction to **3b** occured. The best results were obtained using methanesulfonic acid at 120°C, which was not dependant upon pyridazine substitution. In this way, the azido compounds **2** and **7** could be cyclized to the 5*H*-pyridazino[3,4-*b*]indoles **3** and 10*H*-tetrazolo[1′,5′:1,6]pyridazino[4,3-*b*]indole **(8)**, respectively, without substitution or attack on the fused tetrazole ring. However, with larger quantities some care must be taken to control the exothermic reaction and nitrogen evolution. The most suitable way is to use acetic acid as a solvent for the reaction. Further reactions such as *N*-acetylation of **3** or **8** gave **5** and **9** in good yield.

There are a few examples in the literature, which describe the ring closure of azides to indoles catalyzed by proton acids[6,7] or Lewis acids.[8] Mechanistic studies report the occurrence of nitrenium ions after the release of nitrogen.[7,9] Our attempts to achieve the cyclization step from the azidopyridazine derivatives **2** or **7** to fused indoles by use of catalysts (e.g., sodium perrhenate), which should facilitate the elimination of nitrogen as reported in Lit.[10] were not successful.

Melting points are uncorrected and were obtained on a Gallenkamp melting point apparatus, Mod. MFB-595 (open capillary tubes). Microanalyses were performed on a C,H,N-Automat Carlo Erba 1106. Mass spectra were recorded on a Finnigan 4021 (EI: 70 eV, CI: m/z(%) 120 eV, methane). IR spectra were recorded on a Perkin-Elmer 298 instrument. ^{1}H-NMR-spectra were recorded on a Varian EM 360 instrument, ^{13}C-NMR spectra on a Varian XL 200 instrument.

4-Azido-6-chloro-3-phenylpyridazine (2a):
Sodium azide (3.9 g, 0.06 mol) is added to a solution of 4,6-dichloro-3-phenylpyridazine[11] (**1a**; 4.5 g, 0.02 mol) in DMF (20 mL). The suspension is stirred for 2 h at room temperature. Then, the mixture is diluted with H_2O (100 mL) and the precipitated product is isolated by suction; yield: 4.2 g (88%); yellow needles, mp 115–117°C ($MeOH/H_2O$).

$C_{10}H_6ClN_5$	calc.	C 51.85	H 2.61	N 30.23	Cl 15.30
(231.6)	found	51.81	2.87	30.18	15.60

IR (KBr): ν = 2300 (w); 2180 (w); 2130 (s); 1585 (w); 1560 (m); 1540 cm^{-1} (m).

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.3–7.55 (m, 3 H_{arom}); 7.6–7.8 (m, 2 H_{arom}); 7.9 (s, H-4).

4-Azido-6-hydroxy-3-phenylpyridazine (2b):
From 4-chloro-6-oxo-3-phenyl-1,6-dihydropyridazine[12] (**1b**; 25 g, 12 mol) using the procedure described for **2a**, 3 h at 90°C; yield: 20.1 g (78%); yellow prisms, mp 160°C (dec) (EtOH).

$C_{10}H_7N_5O$	calc.	C 56.34	H 3.31	N 32.85
(213.2)	found	56.47	3.29	32.66

IR (KBr): ν = 3210 (w); 3140 (w); 3050–2800 (b); 2250 (w); 2115 (s); 1710 (s); 1645 (s); 1595 (m); 1500 cm^{-1} (w).

^{1}H-NMR (DMSO-d_6/TMS): δ = 6.8 (s, H-4); 7.1–7.5 (m, 5 H_{arom}).

3-Chloro-5*H*-pyridazino[4,3-*b*]indole (3a):
Method A: A solution of 4-azido-6-chloro-3-phenylpyridazine (**2a**; 2.31 g, 0.01 mol) in 6 N aqueous HCl (30 mL) is refluxed for 1 h. After cooling, the mixture is poured into ice water (100 mL). The precipitated product is isolated by suction and recrystallized from DMF; yield: 1.58 g (77%); colorless needles, mp 265–285°C (slow dec) (DMF).

Method B: A solution of 4-azido-6-chloro-3-phenylpyridazine (**2a**; 2.31 g, 0.01 mol) in $MeSO_3H$ (20 mL) is heated slowly to 130°C, N_2 being evolved. After 10 min at 130–135°C, the mixture is cooled and poured into ice water (100 mL). The precipitated product is isolated by suction and recrystallized from DMF; yield: 1.65 g (81%).

To control this exothermic reaction on a larger scale it is better to use diluted solutions, e.g., azidopyridine (0.1 mol) in $MeSO_3H$ (20 mL) + AcOH (200 mL).

$C_{10}H_6ClN_3$	calc.	C 58.98	H 2.97	N 20.63	Cl 17.41
(203.6)	found	58.92	2.93	20.72	17.61

MS (EI): m/z = 203 (M^+, 100%); 168 (14); 140 (50); 113 (12).

IR (KBr): ν = 3060 (m, b); 3020 (w); 2940 (w); 2920 (w); 1640 (m); 1615 (s); 1590 (m); 1540 (sh); 1500 cm^{-1} (s).

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.3–8.4 (m, 4 H_{arom}); 7.8 (s, H-4).

3-Hydroxy-5*H*-pyridazino[4,3-*b*]indole (3b):
A mixture of 4-azido-6-hydroxy-3-phenylpyridazine (**2b**; 2.13 g, 0.01 mol) and $MeSO_3H$ (15 mL) is treated as described for **3a** (Method B); yield: 1.39 g, (75%); yellow prisms, mp 307–343 (slow dec) (DMF).

$C_{10}H_7N_3O$	calc.	C 64.86	H 3.81	N 22.69
(185.2)	found	64.56	3.83	22.64

IR (KBr): ν = 3250 (w, b); 3120 (b); 2979 (b); 2840 (b); 1660 (sh); 1625 (sh); 1560 cm^{-1} (s).

^{1}H-NMR (DMSO-d_6/TMS): δ = 6.3 (s, H-4); 7.1–7.9 (m, 4 H_{arom}); 11.0, 13.0 (s, 2 acidic H).

3-Chloro-5*H*-pyridazino[4,3-*b*]indole-8-sulfonic Acid (4a):
A solution of 4-azido-6-chloro-3-phenylpyridazine (**2a**; 2.31 g, 0.01 mol) in conc. H_2SO_4 (20 mL) is heated slowly to 140°C. The mixture is kept at this temperature for 15 min, N_2 being evolved. After cooling, the mixture is poured into ice water (200 mL). On cooling the resultant yellow solution to 0–4°C for 12 h, the product crystallizes as yellow prisms; yield: 2.38 g (84%); mp 325–358°C (slow dec) (H_2O).

$C_{10}H_6ClN_3O_3S$	calc.	C 42.34	H 2.13	N 14.81	S 11.31
(283.6)	found	42.95	2.53	14.42	11.22

IR (KBr): ν = 3050 (b); 2800 (b); 1660 (m); 1615 (s); 1580 (m); 1535 (sh); 1475 cm^{-1} (s).

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.6 (d, J = 8 Hz, H-6); 7.9 (s, H-4); 8.0 (dd, J = 8, 1.5 Hz, H-7); 8.6 (d, J = 1.5 Hz, H-9); 12.2 (s, NH).

3-Hydroxy-5*H*-pyridazino[4,3-*b*]indole-8-sulfonic Acid (4b):
A solution of 4-azido-6-hydroxy-3-phenylpyridazine (**2b**; 2.13 g, 0.01 mol) in conc. H_2SO_4 (25 mL) is treated as described for **4a**; yield: 2.12 g (80%); yellow prisms, mp 343–368°C (slow dec) (H_2O).

$C_{10}H_7N_3O_4S$	calc.	C 45.29	H 2.66	N 15.85
(265.2)	found	45.90	3.04	15.48

IR (KBr): ν = 3060 (m); 2780 (b); 1660 (s); 1625 (s); 1605 (m); 1590 (m); 1565 cm^{-1} (m).

^{1}H-NMR (DMSO-d_6/TMS): δ = 6.8 (s, H-4); 7.5 (d, J = 8 Hz, H-6); 7.8 (dd, J = 8, 1.5 Hz, H-7); 8.2 (d, J = 1.5 Hz, H-9); 11.9 (s, NH).

5-Acetyl-3-chloro-5*H*-pyridazino[4,3-*b*]indole (5a):
A mixture of compound **3a** (2.04 g, 0.01 mol) in Ac_2O (40 mL) is refluxed. The starting material has dissolved completely after 2–3 h. Heating is continued for 3 h and the mixture then cooled, whereupon the product crystallizes as colorless needles. The product is isolated by suction and washed with EtOH; yield: 2.0 g (82%); colorless needles, mp 240–242°C (AcOH).

$C_{12}H_8ClN_3O$	calc.	C 58.67	H 3.28	N 17.10	Cl 14.43
(245.7)	found	58.72	3.34	17.12	14.33

MS: m/z = 245 (M^+, 44%); 203 (100); 185 (3); 168 (22); 140 (18); 102 (4).

IR (KBr): ν = 3110 (w); 1710 (s); 1620 (m); 1580 cm^{-1} (m).

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.4 (s, CH_3); 7.2–8.3 (m, 5 H_{arom}).

5-Acetyl-3-hydroxy-5*H*-pyridazino[4,3-*b*]indole (5b):
Compound **3b** (1.85 g, 0.01 mol) is heated in boiling Ac_2O (40 mL). The starting material has dissolved completely after 30 min. Heating is continued for 2 h and the solvent then removed under reduced pressure. The solid residue is digested with EtOH (50 mL) and isolated by suction; yield: 1.79 g (79%); colorless needles, mp 286–296°C (slow dec) (DMF).

$C_{12}H_9N_3O_2$	calc.	C 63.43	H 3.99	N 18.49
(227.2)	found	63.41	4.01	18.59

IR (KBr): ν = 3280 (w); 3140 (m); 2990 (b); 1710 (s); 1650 (s, b); 1630 (sh); 1605 (w); 1565 cm^{-1} (sh).

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.45 (s, CH_3); 7.1–8.2 (m, 5 H_{arom}).

7-Azido-6-phenyltetrazolo[1,5-*b*]pyridazine (7):
From 7-chloro-6-phenyltetrazolo[1,5-*b*]pyridazine[1] (**6**; 23.17 g, 0.1 mol) using the procedure described for **2a**, 15 min at 80°C (attention: the reaction is exothermic, the reaction temperature should not exceed 80°C); yield: 16.65 g (70%); colorless needles, mp 188–190°C (dec) (DMF/H_2O).

$C_{10}H_6N_8$	calc.	C 50.42	H 2.54	N 47.04
(238.2)	found	50.31	2.56	46.99

IR (KBr): ν = 3040 (w); 2140 (s); 2110 (s); 1620 (m); 1600 (m); 1535 (m); 1475 cm^{-1} (s).

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.4–7.8 (m, 5 H_{arom}); 8.7 (s, H-8).

10*H*-Tetrazolo[1′,5′:1,6]pyridazino[4,3-*b*]indole (8):
A solution of the azide **7** (2.38 g, 0.01 mol) in $MeSO_3H$ (15 mL) is treated and worked up as described for **3a** (Method B); yield: 1.75 g (83%); mp 301 °C (dec) (DMF/H_2O).

$C_{10}H_6N_6$	calc.	C 57.14	H 2.88	N 39.99
(210.2)	found	56.87	2.96	39.97

MS (EI): m/z = 210 (M^+, 15%); 168 (5); 154 (77); 140 (3); 127 (100); 100 (20).

IR (KBr): ν = 3120 (w, b); 3090 (w, b); 1645 (m); 1620 (s); 1570 (sh); 1520 (s); 1500 cm^{-1} (s).

10-Acetyl-10*H*-tetrazolo[1′,5′:1,6]pyridazino[4,3-*b*]indole (9):
A mixture of compound **8** (2.10 g, 0.01 mol) in Ac_2O (25 mL) is refluxed. The starting material has dissolved completely after 30 min. Heating is continued for 5 h, the mixture then cooled, and whereon the precipitated product isolated by suction; yield: 1.36 g (54%): colorless needles, mp 270–271 °C (slow dec) (AcOH).

$C_{12}H_8N_6O$	calc.	C 57.14	H 3.20	N 33.32
(252.2)	found	56.89	3.16	32.99

IR (KBr): ν = 3140 (m); 2990 (w); 1695 (s); 1620 (m); 1610 (s); 1550 (s); 1510 cm^{-1} (s).

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