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The Cycloaddition of 1,2,4,5-Tetrazines with Indoles. The Formation of 5*H*-Pyridazino[4,5-*b*]indoles

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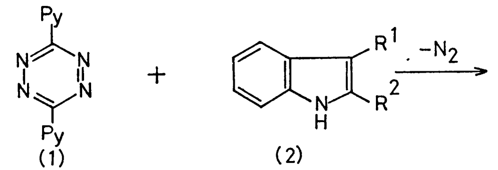
Synopsis. The cycloaddition of 3,6-disubstituted 1,2,4,5-tetrazines (**1**) with indoles (**2**) gave 1,4-disubstituted 5*H*-pyridazino[4,5-*b*]indoles (**4**).

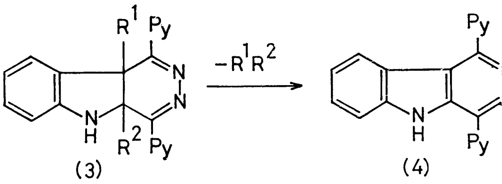
It is well known[1] that indoles add at the C_2 or C_3 position to certain olefins and acetylenes substituted by electron-withdrawing substituents. On the other hand, the cycloaddition at the C_2 and C_3 positions of indoles with some dipolarophiles has been reported. The cycloaddition of indoles with acetylenedicarboxylate[2] has been studied in detail, and the ring-expansion of the adducts has been observed to give benzoazepines. The 1 : 2 adducts were obtained by the reaction with *p*-benzoquinone and 1,4-naphtoquinone.[3] 1,3-Dipolar cycloaddition to indoles has been reported in the cases of azides[4] and nitrilimines.[5]

Previously, we have described the reaction of 1,2,4,5-tetrazines with 2-phenyl-1-azirine.[6] In this paper we wish to report the cycloaddition of 1,2,4,5-tetrazines with indoles. Heating a toluene solution of 3,6-di-(2-pyridyl)-1,2,4,5-tetrazine (**1a**) and indole (**2a**) gave a crystalline product (35% yield). The elemental analysis and the mass spectral measurement supported the molecular formula of $C_{20}H_{13}N_5$. The IR spectrum showed an NH absorption at 3220 cm^{-1}, but the NMR spectrum did not show the methine protons anticipated for compound (**3a**). From these data it was concluded that the product was not the expected compound, **3a**, but the further-dehydrogenated compound, 1,4-di(2-pyridyl)-5*H*-pyridazino[4,5-*b*]indole (**4a**). The same product, **4a**, was also obtained in a low yield by the treatment of **1a** with 3-methylindole (**2b**). When **1a** was treated with 2-methylindole (**2c**), two products were obtained. One product was identical with **4a**, while the other was (**3d**), an intermediate to **4a**. From these results it has become apparent that the primary cycloadducts, **3a**—**d**, immediately aromatize on the extrusion of R^1R^2 (H_2, CH_4) to form **4a**—**b**. Similar results have been reported recently by Seitz *et al.*[7] for the reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with thiophene, *N*-methylimidazole, 2,5-dimethylfuran, or *N*-methylpyrrole.



(1)
a : Py=2-pyridyl
b : Py=4-pyridyl

(2)
a : R^1=H R^2=H
b : R^1=CH$_3$ R^2=H
c : R^1=H R^2=CH$_3$



(3)
a : Py=2-pyridyl
R^1=H R^2=H
b : Py=4-pyridyl
R^1=H R^2=H
c : Py=2-pyridyl
R^1=CH$_3$ R^2=H
d : Py=2-pyridyl
R^1=H R^2=CH$_3$

(4)
a : Py=2-pyridyl
b : Py=4-pyridyl

Experimental

The IR, UV, and NMR spectra were measured with a JASCO Model IRA-2 spectrometer, a Shimadzu Model MPS-501 spectrometer, and a Hitachi Model R-20 spectrometer respectively. A Shimadzu Model UM-3B apparatus was used for the elemental analysis.

*Reaction of **1a** with **2a**.* A toluene solution (20 ml) of **1a** (1.44 g, 6.1 mmol) and **2a** (0.68 g, 5.8 mmol) was refluxed for 3 h. After cooling, the precipitates were filtered off and then washed with methanol to remove a by-product, 3,5-di(2-pyridyl)-1,2-dihydro-1,2,4,5-tetrazine, to give 1,4-di-(2-pyridyl)-5*H*-pyridazino[4,5-*b*]indole **4a** (0.65 g, 35% yield). Recrystallization from benzene afforded pale yellow prisms; mp 202—204 °C. Found: C, 74.11; H, 3.76%. Calcd for $C_{20}H_{13}N_5$: C, 74.29; H, 4.05%. IR (KBr, cm^{-1}): 3220, 1615, 1587, 1579, 1538. UV (MeOH, nm (log ε)): 270 (sh, 4.45), 286 (4.52), 358 (3.85). NMR ($CDCl_3$, δ): 11.95 (s, 1H, NH), 7.10—9.15 (m, 12H, aromatic H). MS *m/e* (%): 323 (M$^+$, 90), 322 (100), 294 (7.8), 293 (11), 266 (5.4), 245 (30), 219 (4.6), 192 (3.5), 161 (11).

*Reaction of **1b** with **2a**.* 1,4-Di(4-pyridyl)-5*H*-pyridazino[4,5-*b*]indole **4b** (0.88 g, 24% yield) was obtained by refluxing a xylene solution (30 ml) of **1b** (2.4 g, 10 mmol) and **2a** (2.7 g, 23 mmol) for 7h. Recrystallization from pyridine afforded pale yellow prisms; mp>300 °C. Found: C, 74.22; H, 4.40%. Calcd for $C_{20}H_{13}N_5$: C, 74.29; H, 4.05%. IR (KBr, cm^{-1}): 3360, 3030, 2930, 2880, 2780, 1600, 1585, 1566, 1549. UV (MeOH, nm (log ε)): 224 (4.54), 272 (4.45), 352 (3.58).

*Reaction of **1a** with **2b**.* A toluene solution (40 ml) of **1a** (0.94 g, 4.0 mmol) and **2b** (0.84 g, 6.4 mmol) was refluxed for 68 h. After cooling, the precipitates were filtered, washed with methanol, and recrystallized from methanol to give a pale yellow product (0.18 g, 15% yield). Its mp and IR spectrum were identical with those of **4a**.

*Reaction of **1a** with **2c**.* A toluene solution (30 ml) of **1a** (0.71 g, 3.0 mmol) and **2c** (0.57 g, 3.6 mmol) was refluxed for 22 h. After cooling, the precipitates were filtered, washed with methanol, and recrystallized from methanol to give **4a** (0.13 g, 13% yield). The filtrate was concentrated *in vacuo* to give a small amount of precipitates, which were then recrystallized from methanol to afford red needles;

mp 177—183 °C. Found: C, 74.33; H, 4.80%. Calcd for $C_{21}H_{17}N_5$: C, 74.31; H, 5.05%. MS *m/e* (%): 339 (M^+, 9.3), 325 (25), 324 (100), 261 (11), 78 (12).

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