

1,3-DIPOLAR CYCLOADDITION OF 2-DIAZOPROPANE TO AZOLOAZINES,
DERIVATIVES OF 10π -ELECTRON SYSTEMS. THE SYNTHESIS OF PYRAZOLO-
/4,3-d/AZOLOPYRIDAZINES AND PYRAZOLO/3,4-d/AZOLOPYRIDAZINES¹

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Abstract - 1,3-Dipolar cycloaddition of 2-diazopropane occurs across C_7-C_8 partially localized double bond of azolopyridazines 1, derivatives of 10π -electron systems, to produce derivatives of novel heterocyclic systems pyrazoloazolopyridazines 4 and 5.

The cycloadditions of diazoalkanes to heteroaromatic systems are rare. So far, only cycloadditions to pyridine², pyridazinones³⁻⁵ and the cycloaddition of diazoacetates to nitrobenzofuroxans⁶ have been reported. Recently, we observed an unexpected 1,3-dipolar cycloaddition of 2-diazopropane to the imidazo/1,2-b/pyridazines (1a) to give the corresponding imidazo/1,2-b/pyrazolo/4,3-d/pyridazines (4a) in high yields⁷.

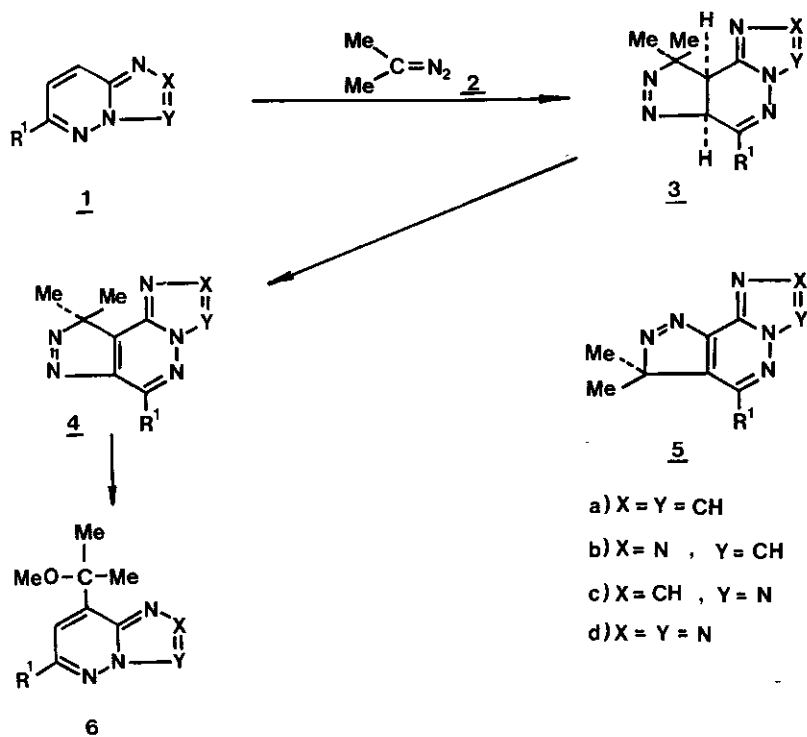
As an extension of these studies we wish to report the cycloaddition of 2-diazopropane to other 10π -electron heterocyclic systems with a bridgehead nitrogen atom in which the corresponding pyrazolo/4,3-d/azolopyridazines are formed. In this connection, 6-chloro-s-triazolo/4,3-b/pyridazine (1b, $R^1=Cl$), 6-chloro-s-triazolo/1,5-b/pyridazine (1c, $R^1=Cl$) and 6-chloro-tetrazolo/1,5-b/pyridazine (1d, $R^1=Cl$) were selected as starting compounds.

To a solution of azolopyridazine derivative 1 (0,001 mole) in ethanol (10 ml), a solution of 2-diazopropane⁸, prepared from 1.5 g of acetone hydrazone in diethyl ether, was added. The addition of the same amount of 2-diazopropane was repeated in 12 hours intervals, until tlc showed that all the starting material was consumed. Evaporation of the reaction mixture in vacuo gave the corresponding pyrazoloazolopyridazines 4.⁹ The derivatives of the following novel heterocyclic systems were prepared according to this procedure:

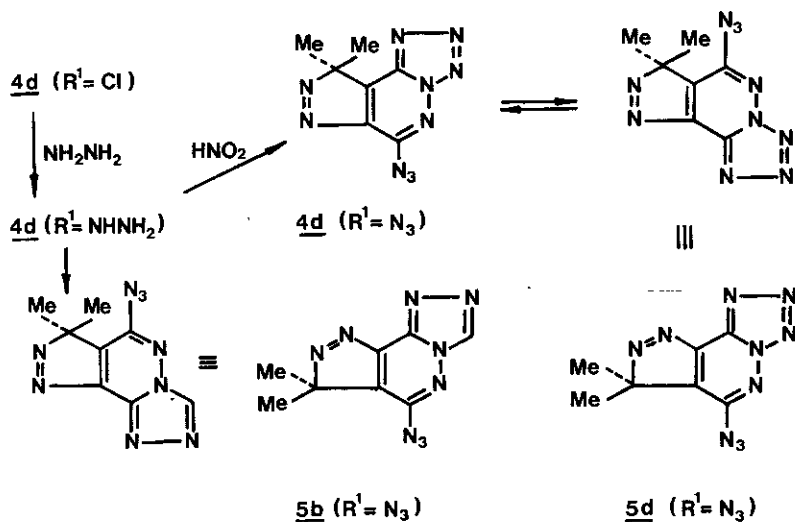
6-Chloro-9,9-dimethyl-9H-pyrazolo/4,3-d/-s-triazolo/4,3-b/pyridazine (4b, $R^1=Cl$) from 1b ($R^1=Cl$)¹⁰, in 60% yield, mp 185-190°C (from ethanol), nmr: (DMSO- d_6) δ : 1.70 (6H, s, 9,9-di-Me), 9.82 (1H, s, 3-H),

6-Chloro-9,9-dimethyl-9H-pyrazolo/4,3-d/-s-triazolo/1,5-b/pyridazine (4c, $R^1=Cl$) from 1c ($R^1=Cl$)¹¹, in 60% yield, mp 146-148°C (from ethanol), nmr: (CDCl₃) δ : 1.85 (6H, s, 9,9-di-Me), 8.55 (1H, s, 2-H), and

6-Chloro-9,9-dimethyl-9H-pyrazolo/4,3-d/-tetrazolo/1,5-b/pyridazine (4d, $R^1=Cl$) from 1d ($R^1=Cl$)¹⁰ in 80% yield, mp 193°C (decomp.) (from ethanol), nmr: (DMSO- d_6) δ : 1.75 (6H, s, 9,9-Me).



SCHEME 1



SCHEME 2

The reaction between azolopyridazines 1b-d and 2-diazopropane is assumed to proceed as a regiospecific 1,3-dipolar cycloaddition of 2-diazopropane across C₇-C₈ double bond of the pyridazine part of the molecule followed by elimination of a molecule of hydrogen from the primary cycloadducts 3b-d to give the stable pyrazolo/4,3-d/azolopyridazines 4b-d.

The structure of the compounds 4b-d were confirmed by the photochemical transformations into the corresponding 8-(2'-methoxy-2'-propyl)-azolopyridazines 6b-d (R¹=Cl), according to the following procedure:

The compounds 4b-d (0.001 mole) dissolved in methanol (20 ml) were irradiated at 300 nm in a Rayonet RPR 100 photochemical reactor until the evolution of nitrogen ceased (6-12 h, 30°C). Evaporation of methanol in vacuo gave the products 6b-d, respectively. The following compounds were prepared in this manner:

6-Chloro-8-(2'-methoxy-2'-propyl)-s-triazolo/4,3-b/pyridazine (6b, R¹=Cl) in 70% yield, mp 75-79°C, (subl. 100°C, 3 torr), nmr (CDCl₃) δ: 1.82 (6H,s,CMe₂), 3.36 (3H,s,OMe), 7.19 (1H,s,7-H), 8.96 (1H,s,2-H).

6-Chloro-8-(2'-methoxy-2'-propyl)-s-triazolo/1,5-b/pyridazine (6c, R¹=Cl) in 68% yield, mp 72-75°C (from cyclohexane), nmr (CDCl₃) δ: 1.78 (6H,s,CMe₂), 3.36 (3H,s,OMe), 7.47 (1H,s,7-H), 8.37 (1H,s,2-H), and

6-Chloro-8-(2'-methoxy-2'-propyl)tetrazolo/1,5-b/pyridazine (6d, R¹=Cl) in 58% yield, mp 62-66°C (subl. 130°C, 3 torr), nmr (CDCl₃) δ: 1.80 (6H,s,CMe₂), 3.40 (3H,s,OCH₃), 7.58 (1H,s,7-H).

The chemical shifts for 7-H (δ 7.19-7.58) of compounds 6b-d are consistent with the chemical shifts for 7-H of other 8-alkyl substituted azolopyridazines^{12,13}, thus strongly suggesting the adducts 4, and excluding the alternative structures 5, as precursors (SCHEME 1).

The derivatives of the alternative structures 5b and 5d were prepared by azido-tetrazolo isomerization, observed previously in tetrazolo/1,5-b/pyridazine series¹⁴, of 4d (R¹=Cl) in the following manner: 4d (R¹=Cl) (0.001 mole) was treated with hydrazine hydrate (80%, 250 mg) in ethanol (5 ml, reflux, 1 h) to give 4d (R¹=NHNH₂) in 74% yield, mp 194°C (decomp.) (from ethanol), nmr (DMSO-d₆) δ: 1.70 (6H,s,9,9-di-Me), 3.31 (3H,br s,NHNH₂). The treatment of 4d (R¹=NHNH₂) (0.005 mole) in hydrochloric acid (conc. HCl, 2.5 ml and water, 2.5 ml, 0°C) with a solution of sodium nitrite (5% in water, 0°C) gave 4d (R¹=N₃) in 84% yield, mp 133-135°C (from ethanol), nmr (CDCl₃) δ: 1.87 (6H,s,9,9-di-Me). When the solution of 4d (R¹=N₃) in DMSO-d₆ was heated (110°C) in an NMR tube an azidotetrazolo isomerization was observed to produce a mixture of 4d (R¹=N₃) and the isomeric 6-azido-7,7-dimethyl-7H-pyrazolo/3,4-d/tetrazolo/1,5-d/pyridazine 5d (R¹=N₃)¹⁶ in the ratio of 4:1 [5d (R¹=N₃), nmr (DMSO-d₆) δ: 1.73 (6H,s,9,9-di-Me)].

When 4d (R¹=NHNH₂) (0.001 mole) was allowed to react with a mixture of ethyl orthoformate (2 ml) and acetic anhydride (0.5 ml) (reflux, 2.5 h), followed by evaporation of the volatile components in vacuo, the corresponding 6-azido-7,7-dimethyl-7H-pyrazolo/3,4-d/-s-triazolo/4,3-b/pyridazine (5b, R¹=N₃) in 42% yield, mp 165-169°C [from hexane-ethanol (3:1), nmr (CDCl₃) δ: 1.70 (6H,s,9,9-di-Me), 9.09 (1H,s,3-H)], was obtained (SCHEME 2).

Satisfactory elemental analyses and mass molecular weights were obtained for all new compounds.

The scope and limitations of this surprisingly ease cycloadditions of 2-diazo-propane to heteroaromatic bicyclic 10π -electron systems and thermal and photo-chemical transformations of these novel systems are under further investigations in our laboratory.

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