1,3-DIPOLAR CYCLOADDITION OF 2-DIAZOPROPANE TO PYRIMIDO/1,2-b/PYRIDAZIN-4-ONE DERIVATIVES. THE SYNTHESIS OF PYRAZOLO/4,3-d/PYRIMIDO/1,2-b/-PYRIDAZIN-4(10H)-ONES, DERIVATIVES OF A NOVEL HETEROCYCLIC SYSTEM[1]

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Abstract - Facile regiospecific cycloaddition of 2-diazopropane (2) to the pyrimido/1,2-b/pyridazin-4-ones (1a-d), derivatives of 10π-electron heteroaromatic bicyclic system, give the pyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-ones (4a-d) in 32-52% yields.

1,3-Dipolar cycloaddition of diazoalkanes to pyridine[2], pyridazinones[3-5], and nitrofuroxans[6] are the only examples described so far in the literature. Recently, an unexpected cycloaddition of 2-diazopropane to the imidazo/1,2-b/pyridazines, derivatives of a 10π-electron heteroaromatic system was observed in our laboratory to give the imidazo/1,2-b/pyrazolo/4,3-d/pyridazines in high yields.[7]

This facile cycloaddition prompted us to extend the reaction to pyrimido/1,2-b/pyridazin-4-one derivatives 1, as another type of bicyclic heteroaromatic 10π-electron system with a bridgehead nitrogen atom, to give the corresponding pyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-ones (4), derivatives of a novel heterocyclic system.

To a solution of pyrimido/1,2-b/pyridazin-4-one derivative 1 (0.001 mole) in methanol or ethanol (10 ml) a solution of 2-diazopropane (2)[8], prepared from acetone hydrazone (1.5 g) in diethyl ether[9], was added. The addition of the same amount of 2-diazopropane (2) was repeated in 12 h intervals, until tlc showed that all the starting material was consumed. Evaporation of the reaction mixture in vacuo gave the corresponding pyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-ones 4. According to this procedure the following derivatives of the novel heterocyclic system were prepared:

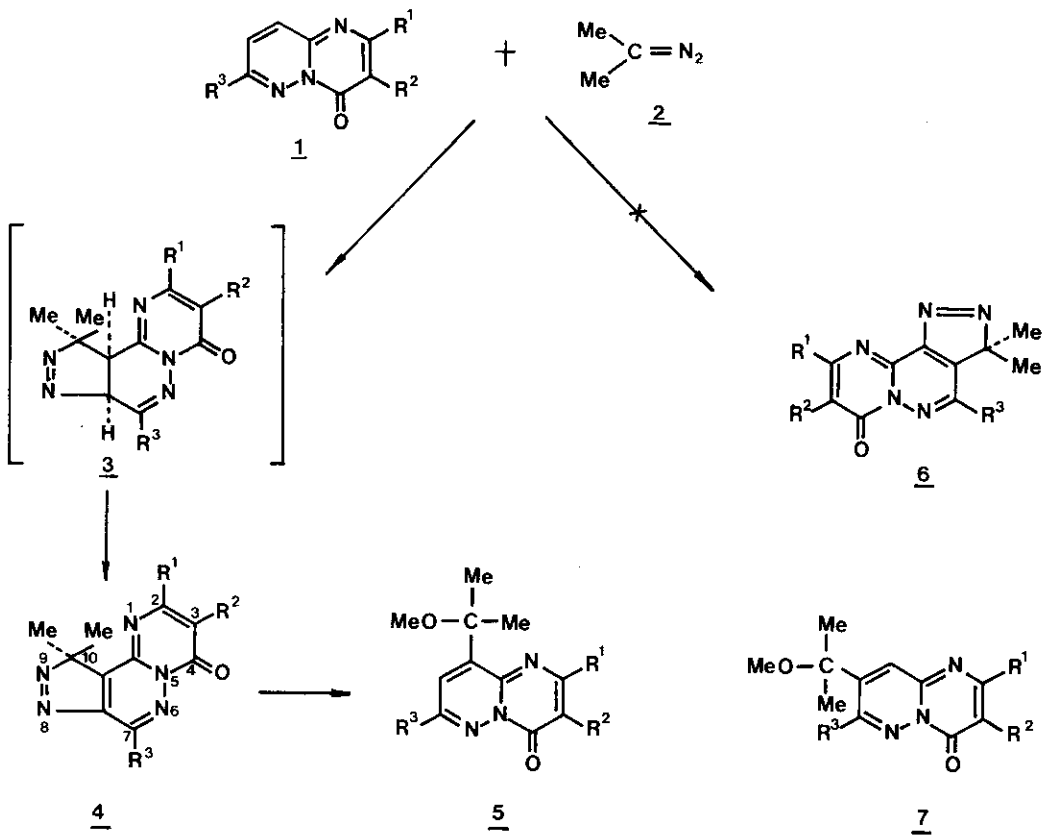
7-Amino-10,10-dimethylpyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-one (4a) from 7-azidopyrimido/1,2-b/pyridazin-4-one (1g)[10] in 49% yield, mp 250°C (decomp) (from methanol), m/e 230 (M^+), nmr (DMSO-d_6) δ: 1.64 (s, 10,10-di-Me), 6.33 (d, H_3), 7.71 (br s, NH_2), 8.03 (d, H_2), J_{H_2,H_3} = 6.1 Hz).[12]

10,10-Dimethyl-2-phenylpyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-one (4b) from 2-phenylpyrimido/1,2-b/pyridazin-4-one (1b)[13] in 32% yield, mp 234-237°C (from ethanol and DMF (10:1), m/e 291 (M^+), nmr ($CDCl_3$/TMS) δ: 1.85 (s, 10,10-di-Me), 7.18

(s, H_3), 7.25-7.50 (m) and 7.9-8.1 (m) (2-Ph), 9.3 (s,H_7).

7-Chloro-10,10-dimethyl-2-phenylpyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-one (4c) from 7-chloro-2-phenylpyrimido/1,2-b/pyridazin-4-one (1c)[14] in 52% yield, mp 254-255°C (from ethanol and DMF (5:1)), m/e 325 (M^+), nmr DMSO-d_6/TMS) δ : 1.79 (s, 10,10-di-Me), 7.00 (s, H_3), 7.25-7.50 (m) and 7.90-8.15 (m) (2-Ph).

3-Bromo-10,10-dimethyl-2-phenylpyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-one (4d) from 3-bromo-2-phenylpyrimido/1,2-b/pyridazin-4-one (1d)[15] in 45% yield, mp 231-233°C (from ethanol), m/e 369 (M^+), nmr ($CDCl_3$/TMS) δ: 1.77 (s, 10,10-di-Me), 7.33-7.60 (m) and 7.65-7.90 (m) (2-Ph), 9.3 (s, H_3).



a) $R^1 = R^2 = H$, $R^3 = NH_2$

b) R^1 = Ph , $R^2 = R^3 = H$

c) R^1 = Ph , $R^2 = H$, $R^3 = Cl$

d) R^1 = Ph , $R^2 = Br$, $R^3 = H$

e) $R^1 = H$, R^2 = COOEt , $R^3 = Cl$

f) $R^1 = R^2 = H$, $R^3 = Cl$

g) $R^1 = R^2 = H$, $R^3 = N_3$

SCHEME

7-Chloro-10,10-dimethyl-3-ethoxycarbonylpyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-one (4e) from 7-chloro-3-ethoxycarbonylpyrimido/pyridazin-4-one (1e)[11] in 42% yield, mp 196°C (from methanol), m/e 321 (M^+), nmr ($CDCl_3$/TMS) δ: 1.39 (t, CH_3CH_2), 1.82 (s, 10,10-di-Me), 4,37 (q, $CH_3\underline{CH_2}$), 8.93 (s, H_2), $J_{CH_3CH_2}$ = 7.6 Hz.

The reaction between pyrimido/1,2-b/pyridazin-4-ones (1) and 2-diazopropane (2) is assumed to proceed as a regiospecific 1,3-dipolar cycloaddition accross C_8-C_9 double bond of the pyridazine nucleus, followed by elimination of a molecule of hydrogen from the primary cycloadducts 3, to give the stable pyrazolo/4,3-d/pyrimido/1,2-b/pyridazin-4(10H)-ones 4, derivatives of a novel heterocyclic system.

The photochemical transformation of the compound 4c into the corresponding 7-chloro-9-(2'-methoxy-2'-propyl)-pyrimido/1,2-b/pyridazin-4-one (5c) was achieved in the following manner. The compound 4c (0.001 mole) dissolved in methanol (20 ml) was irradiated in a quarz tube at 300 nm in a Rayonet RPR 100 photochemical reactor until the evolution of nitrogen caesed (~24 h, 30°C). Evaporation of methanol in vacuo gave the product 5c in 23% yield, mp 130-135°C (from methanol and water (3:2)), m/e 329 (M^+), nmr ($CDCl_3$/TMS) δ: 1.85 (s, CMe_2), 3.40 (s, OMe), 7.05 (s,H_3), 7.40 (s, H_8), 7.3-7.6 (m) and 7.7-8.1 (m) (2-Ph).

The chemical shift for H_8 (δ 7.40) of the compound 5c is consistent with the chemical shifts for H_8 of other pyrimido/1,2-b/pyridazines (δ 7.40-7.73)[11,16], excluding thus the alternative structure 7c. Consequently, this observation strongly supports the adducts 4, and excludes the alternative structures 6, as precursors.

Satisfactory elemental analyses for C,H, and N were obtained for all new compounds.

The scope and limitations of these surprisingly ease cycloadditions of diazoalkanes to bicyclic 10π electron systems, which are in contrast to the generally known unreactivity of the pyridazine part of the molecule,[17] and thermal and photochemical transformations of the novel system are under further investigation.

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1. We thank Dr.K.L.Loening, Nomenclature Director, Chemical Abstracts Service, for his help in connection with the naming, numbering, and orientation of the novel heterocyclic system.

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9. Essentially the same procedure was used as previously described for the preparation of imidazo/1,2-b/pyrazolo/4,3-d/pyridazines.[7]

10. The compound 1g was prepared in the following manner: 7-Chloropyrimido/1,2-b/pyridazin-4-one (1f) was prepared from 3-amino-6-chloropyridazine (1.29 g) and diethyl ethoxymethylenemalonate (2.16 g) in PPA (15 g, 120°C, 2 h) and isolated according to the procedure described in lit.[11] for 1e, to give 1f in 67% yield, mp 163°C (from ethanol), m/e 181 (M^+), nmr ($CDCl_3$/TMS) δ: 6.58 (d,H_3), 7.36 (d, H_8), 7.76 (d, H_9), 8.11 (d, H_2), J_{J_2,H_3}= 6.9 Hz, J_{H_8,H_9}= 9.2 Hz. The treatment of the compound 1f (1.81 g) with sodium azide (0,65 g)[12] in a mixture of ethanol (40 ml) and water (5 ml) (reflux, 1 h), followed by evaporation of solvent in vacuo, gave 1g in 31% yield, mp 124°C (from ethanol), m/e 188 (M^+), nmr (DMSO-d_6/TMS) δ : 6.45 (d, H_3), 7.33 (d, H_8), 7.87 (d, H_9), 8.10 (d, H_2), J_{H_2,H_3}=6.9 Hz, J_{H_8,H_9} = 9.2 Hz.

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14. The compound 1c was prepared from 3-amino-6-chloropyridazine (0.65 g) and ethyl benzoylacetate (1,38 g) in PPA (5 g, 120°C, 5 h) and isolated according to the procedure described for 1f[10], to give 1c in 54% yield, mp 243-245°C (from methanol), m/e 257 (M^+), nmr ($CDCl_3$/TMS) δ : 6.97 (s, H_3), 7.35 (d, H_8), 7.76 (d, H_9), 7.1-7.4 (m) and 7.5-8.0 (m) (2-Ph), J_{H_8,H_9}= 9.0 Hz.

15. The compound 1d was prepared in the following manner: To a solution of 1b[13] (300 mg) in acetic acid (5 ml) a solution of bromine (400 mg) in acetic acid (3 ml) was added dropwise. The solid which separated after heating (100°C,45 min) was suspended in aqueous sodium hydrogen carbonate solution (10%, 10 ml) to give 1d in 76% yield, mp 230°C (from ethanol), m/e 301 ($M^{\bullet}$), nmr ($CDCl_3$/TMS) δ : 7.30-7.80 (m, 2-Ph), 7.48 (dd, H_8), 7.83 (dd, H_9), 8,60 (dd, H_7), J_{H_7,H_8}=4.0 Hz, J_{H_8,H_9}= 8.5 Hz. J_{H_7,H_9}= 1.5 Hz.

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