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[4+2]- and [2+4]-Cycloaddition Processes of 4,5-Dicyanopyridazine with 2,3-Dimethylbuta-1,3-diene

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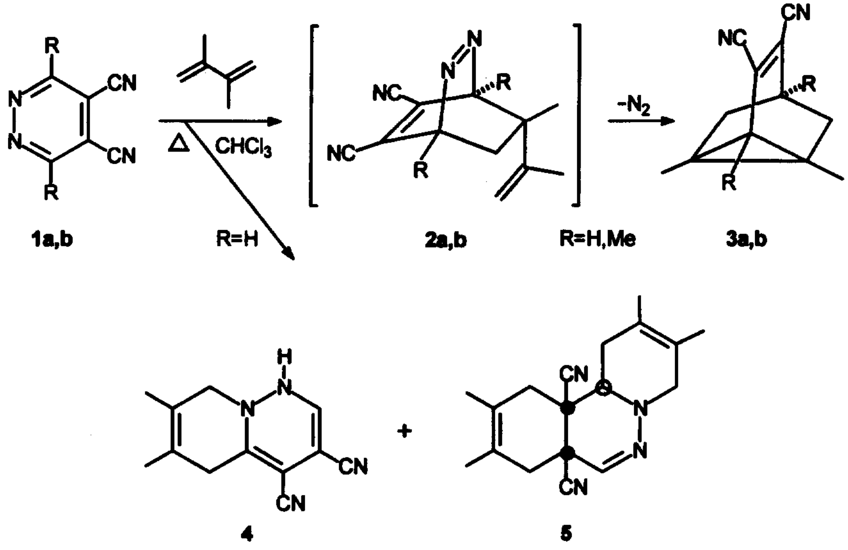
Abstract: The title compounds afforded under relatively mild conditions the polycyclic systems **3a**, **4**, and **5** through alternative concomitant cycloadditions; the reactivity of the dicyanopyridazine system was critically influenced by the presence of methyl groups at the 3 and 6 positions. The skeleton of **3a** and the stereochemistry of **5** were established by X-ray experiments.

It is well known that aromatic pyridazine derivatives can enter as 4π components into concerted cycloadditions.[1] In particular, *N*-oxides, *N*-imides, and *N*-ylides behave as 1,3-dipoles with different dipolarophiles to give polynuclear nitrogen heterocycles;[1,2] on the other hand, since the pioneering work of German[3] and Japanese groups,[4] suitably substituted pyridazines have been exploited over the past two decades as azadienes in inverse electron demand Diels-Alder reactions, especially with electron-rich or strained dienophiles.[5]

Conversely, the possibility of carrying out [2+4] cycloaddition processes on the double bonds of the aromatic pyridazine moiety was, to our knowledge, completely disregarded. Thus, we decided to explore the reactivity of the strongly electron-deficient 4,5-dicyanopyridazine **1a** towards 2,3-dimethylbuta-1,3-diene (DMB): the former derivative, partially resembling the higly dienophilic tetracyanoethylene, was prepared according to Di Stefano and Castle[6] from the corresponding diethyl ester which, in turn, could be easily obtained by one step synthesis from commercially available pyridazine.[7]

RESULTS AND DISCUSSION

When **1a** was heated with an excess of DMB in chloroform at 110°C, compounds **3a**, **4**, and **5** were obtained in 64%, 11%, and 8% yields, respectively. Surprisingly, the preferential reaction pattern involves in the first step an intermolecular [4+2] cycloaddition of the pyridazine azadiene moiety with a double bond of the diene counterpart, that leads to the bicyclic derivative **2a**;[8] the latter can then evolve into the final tricyclic system **3a** by loss of nitrogen and intramolecular Diels-Alder ring closure of a probable 5-vinylcyclohexa-1,3-diene intermediate (Scheme 1).[9]



Scheme 1

This rationale agrees well with the only precedent in pyridazine chemistry, relating to the peculiar behaviour of the tetramethyl ester with cycloocta-1,5-diene.[10] The structure of the cage compound **3a**, reported in Figure 1, was unambiguously determined by a single crystal X-ray analysis.

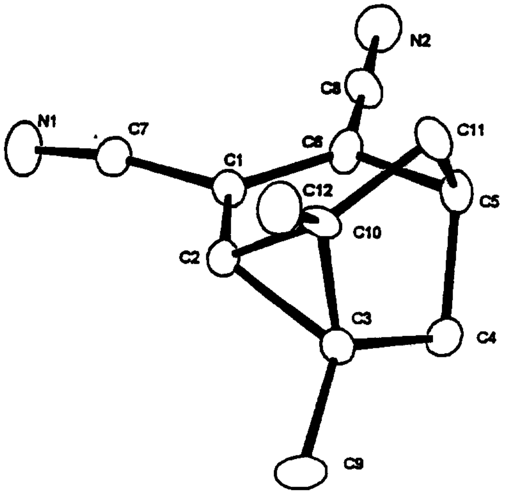
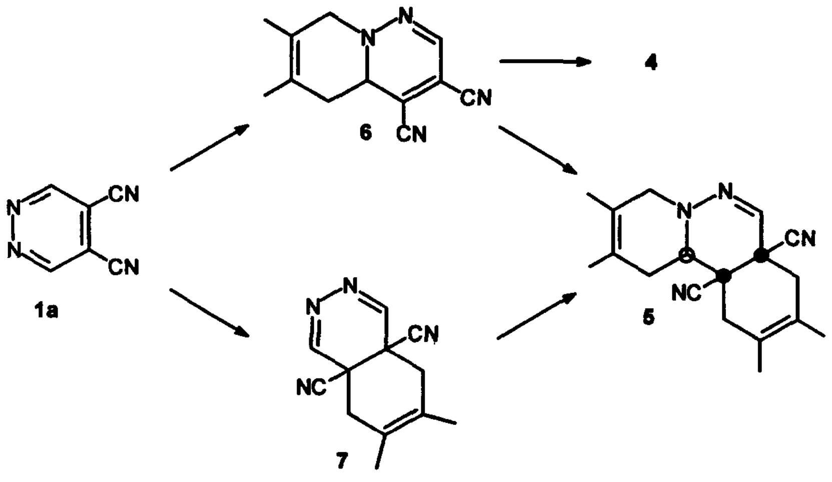


Figure 1. ORTEP drawing of **3a**. Selected bond lengths (Å) and angles (°): C(1)-C(2) 1.455(5), C(1)-C(6) 1.356(4), C(2)-C(3) 1.551(10), C(2)-C(10) 1.534(10), C(3)-C(4) 1.476 (12), C(3)-C(10) 1.484(6), C(4)-C(5) 1.51(2), C(5)-C(6) 1.501(5), C(5)-C(11) 1.57(2), C(10)-C(11) 1.547(11); C(3)-C(2)-C(10) 57.5(2), C(2)-C(10)-C(3) 61.8(6), C(2)-C(3)-C(10) 60.7(6).



Scheme 2

On the other hand, the formation of minor amounts of 4 and 5 can be accounted for by concomitant less favorable [2+4] cycloaddition processes: whereas the former compound represents the tautomerization product of the primary adduct of DMB on the N(2)-C(3) double bond of **1a**, the latter arises by a second attack of the diene on the same adduct 6 or, alternatively, from sequential C-4/C-5 and C-1/N-2 cycloadditions of DMB on the starting 1,2-diazine system and the intermediate tetrahydrophthalazine 7, respectively (Scheme 2). The stereochemistry of 5, characterized by a *trans* configuration of the external rings, was elucidated by an X-ray structure determination (Figure 2).

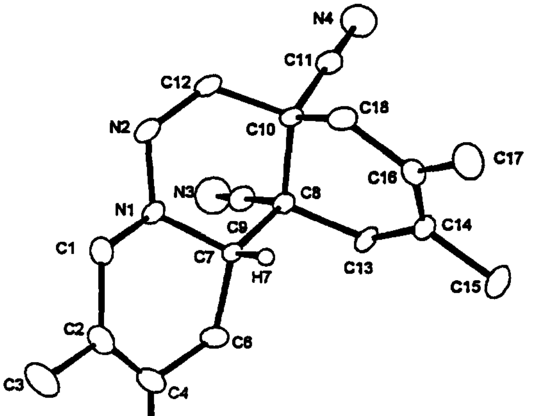


Figure 2. Crystal structure of 5. Selected bond distances (Å) and angles (°): C(1)-C(2) 1.492(6), C(1)-N(1) 1.466(5), N(1)-N(2) 1.365(5), N(1)-C(7) 1.473(4), N(2)-C(12) 1.263(5), C(2)-C(4) 1.329(6), C(4)-C(6) 1.503(7), C(6)-C(7) 1.518(5), C(7)-C(8) 1.529(5), C(8)-C(10) 1.550(5), C(8)-C(13) 1.525(4), C(10)-C(12) 1.514(5), C(10)-C(18) 1.549(5), C(13)-C(14) 1.508(5), C(14)-C(16) 1.320(5), C(16)-C(18) 1.497(5); C(1)-N(1)-C(7) 114.1(3), N(1)-C(7)-C(6) 106.8(3), C(8)-C(10)-C(18) 109.7(3), C(10)-C(8)-C(13) 110.3(3).

A remarkable decrease in reactivity was observed on going from **1a** to the corresponding 3,6-dimethylderivative **1b**, probably due both to steric and electronic effects. Treatment of the latter with DMB as above allowed us to recover nearly quantitatively the unreacted starting material, together with trace amounts of the polycyclic product **3b**; an appreciable conversion of **1b**, leading to the same compound in 26% yield, was achieved only under more drastic conditions.

Some synthetic opportunities emerging from the above results will be carefully evaluated, mainly as regards the possibility of carrying out on **1a** simple and tandem [4+2] cycloaddition processes with unactivated dienophiles and suitable dienes, respectively.

EXPERIMENTAL SECTION

General Procedures. Melting points were taken on a Büchi 510 apparatus and are uncorrected. IR spectra were measured as KBr pellets with a Perkin-Elmer 881 spectrophotometer, while ^{1}H- and ^{13}C- NMR spectra were recorded in $CDCl_3$ solutions with a Varian Gemini-200 instrument operating at 200 MHz and 50 MHz, respectively: chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz). The relative assignement of the ^{13}C resonances was achieved by the use of coupled spectra and long-range heteronuclear correlation experiments. Elemental analyses were obtained by a Perkin-Elmer 240C Analyzer. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230-400 mesh) were used for TLC and flash chromatography, respectively; the yields of the reaction products were determined on the basis of the recovered starting materials.

Reaction of Compound 1a with DMB. A mixture of the dicyanoderivative (0.13 g, 1 mmol) and the diene (0.41 g, 0.56 ml, 5 mmol) in $CHCl_3$ (1 ml) was heated in a sealed tube at 110°C for 48h. Evaporation to dryness under reduced pressure left a residue which was resolved into four components by flash chromatography with 40-70°C petroleum ether/AcOEt (3:1 v/v) as eluent. The fastest moving band gave 3,4-dicyano-1,7-dimethyltricyclo[3.2.1.$0^{2,7}$]oct-3-ene (**3a**) (R_f = 0.60, 0.104 g, 64%) that was recrystallized from Et_2O as colourless needles, m.p. 152-153°C; IR ν 3032 (cyclopropane CH), 2202, 2195 (conjugated CN), 1580 cm^{-1} (C=C); ^{1}H NMR δ 0.95 (d, $J_{6,6}$=$J_{8,8}$=12.2 Hz, 2H, 6-H *endo* and 8-H *endo*), 1.30 (s, 6H, 1-CH_3 and 7-CH_3), 1.59 (s, 1H, 2-H), 1.77 (dd, $J_{6,6}$=$J_{8,8}$=12.2 Hz, $J_{5,6}$=$J_{5,8}$=4.8 Hz, 2H, 6-H *exo* and 8-H *exo*), 2.88 (t, $J_{5,6}$=$J_{5,8}$=4.8 Hz, 1H, 5-H); ^{13}C NMR δ 14.0 (q, 1-CH_3 and 7-CH_3), 31.0 (s, C-1 and C-7), 33.9 (t, 6-CH_2 and 8-CH_2), 34.7 (d, C-2), 35.8 (d, C-5), 114.9 (s, 3-CN/4-CN), 115.2 (s, 4-CN/3-CN), 121.7 (s, C-4), 124.5 (s, C-3). Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 77.97; H, 6.73; N, 15.30.

The second fraction afforded (7a*SR*,11a*RS*,11b*RS*)-7a,11a-dicyano-2,3,9,10-tetramethyl-1,4,7a,8,11,11a-hexahydro-11b*H*-pyrido[2,1-*a*]phthalazine (**5**) (R_f = 0.45, 0.021 g, 8%) as an ivory-coloured solid, m.p. 172-173°C (from Et_2O); IR ν 3040 (imine CH), 2240 (CN), 1593 cm^{-1} (C=C and C=N). ^{1}H NMR δ 1.63 (s, 6H, 2xCH_3), 1.69 (s, 6H, 2xCH_3), 2.02-2.83 (m, 6H, 1-CH_2, 8-CH_2, and 11-CH_2), 3.09 (dd, J=10.5 and 4.2 Hz, 1H, 11b-H), 3.70 (AB system, J_{AB}=16.4 Hz, 2H, 4-CH_2), 6.74 (s, 1H, 7-H); ^{13}C NMR δ 15.8 (q, CH_3), 18.2 (q, CH_3), 18.3 (q, CH_3), 18.6 (q, CH_3), 33.75 (t, 8-CH_2/11-CH_2), 34.0 (t, 11-CH_2/8-CH_2), 37.9 (s, C-7a/C-11a), 39.2 (s, C-11a/C-7a), 40.6 (t, 1-CH_2), 51.9 (d, C-11b), 57.6 (t, 4-CH_2), 118.4 (s, 7a-CN/11a-CN), 118.5 (s, olefinic carbon), 118.8 (s, 11a-CN/7a-CN), 121.9 (s), 122.1 (s), 123.4 (s) (olefinic carbons), 129.7 (d, C-7). Anal. Calcd. for $C_{18}H_{22}N_4$: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.22; H, 7.66; N, 19.12.

After the unreacted starting material (R_f = 0.28, 0.015 g) was recovered from the following band, the slowest moving one yielded 3,4-dicyano-6,7-dimethyl-5,8-dihydro-1*H*-pyrido[1,2-*b*]pyridazine (**4**) (R_f = 0.16, 0.021 g, 11%) that was crystallized from $CHCl_3$ as ivory-coloured needles, m.p. 199-200°C; IR ν 3330, 3300 (NH), 3115 (CH), 2208, 2195 (conjugated CN), 1600 cm^{-1} (C=C); ^1H NMR δ 1.72 (br s, 3H, 6-CH_3/7-CH_3), 1.81 (br s, 3H, 7-CH_3/6-CH_3), 3.78 (br s, 2H, 5-CH_2/8-CH_2), 4.42 (br s, 2H, 8-CH_2/5-CH_2), 4.62 (br s, 1H, NH), 6.67 (s, 1H, 2-H); ^{13}C NMR δ 18.6 (q, 6-CH_3/7-CH_3), 19.7 (7-CH_3/6-CH_3), 49.1 (t, 5-CH_2/8-CH_2), 51.8 (t, 8-CH_2/5-CH_2), 77.2 (s, C-3/C-4), 91.5 (s, C-4/C-3), 113.8 (s, 3-CN/4-CN), 114.2 (s, 4-CN/3-CN), 124.6 (d, C-2), 125.1 (s, C-6/C-7) 131.1 (s, C-7/C-6), 148.3 (s, C-4a). Anal. Calcd. for $C_{12}H_{12}N_4$: C, 67.91; H, 5.70; N. 26.40. Found: C, 67.84; H, 5.69; N, 26.67.

3,4-Dicyano-1,2,5,7-tetramethyltricyclo[3.2.1.0^{2,7}]oct-3-ene (3b). A mixture of compound **1b**[11] (0.158 g, 1 mmol) and DMB (0.41 g, 0.56 ml, 5 mmol) in xylene (1 ml) was heated in a sealed tube at 150°C for 24h. The residue left by evaporation to dryness was treated with CH_2Cl_2 (10 ml) and the insoluble tarry material was filtered off; removal of the solvent from the filtrate gave a crude product that was subjected to flash chromatography with 40-70°C petroleum ether/AcOEt (5:1 v/v) as eluent. After some fast running sticky impurities were discarded, the second band afforded **3b** (R_f = 0.59, 0.028 g, 26%) as a white solid, m.p. 159°C (from 30-50°C petroleum ether); IR ν 2205 (conjugated CN) 1583 cm^{-1} (C=C); ^1H NMR δ 1.01 (d, $J_{6,6}$=$J_{8,8}$=12.4 Hz, 2H, 6-H *endo* and 8-H *endo*), 1.18 (s, 6H, 1-CH_3 and 7-CH_3), 1.38 (s, 3H, 2-CH_3/5-CH_3), 1.40 (s, 3H, 5-CH_3/2-CH_3), 1.61 (d, $J_{6,6}$=$J_{8,8}$=12.4 Hz, 2H, 6-H *exo* and 8-H *exo*); ^{13}C NMR δ 10.5 (q, 1-CH_3 and 7-CH_3), 12.2 (q, 2-CH_3), 20.4 (q, 5-CH_3), 31.5 (s, C-2), 34.2 (s, C-1 and C-7), 39.4 (s, C-5), 43.2 (t, 6-CH_2 and 8-CH_2), 113.8 (s, 3-CN/4-CN), 114.5 (s, 4-CN/3-CN), 128.9 (s, C-4), 129.8 (s, C-3). Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.34; H, 7.69; N, 13.35.

The unreacted **1b** (R_f = 0.14, 0.079 g) was recovered from the following fractions.

X-Ray Structural Analyses of 3a and 5.[12] Compound **3a**: $C_{12}H_{12}N_2$, M=184.2, orthorhombic, space group $P2_1cn$, a = 7.254(2), b = 10.725(2), c = 13.409(2) Å, V = 1043.2(4) Å^3, Z = 4, F(000) = 392, μ = 0.549 mm^{-1}, D_c = 1.773 g cm^{-3}, graphite monochromated (Cu-Kα) radiation (λ = 1.5418 Å). Compound **5**: $C_{18}H_{22}N_4$, M = 294.4, monoclinic, space group $P2_1/c$, a = 8.776(2), b = 10.693(3), c = 35.475(8) Å, β = 90.94(2)°, V = 3329(1) Å^3, Z = 8, F(000) = 1264, μ = 0.559 mm^{-1}, D_c = 1.175 g cm^{-3}, graphite monochromated (Cu-Kα) radiation (λ = 1.5818 Å).

Data sets consisting of 956 and 3560 reflections ($2\theta_{max}$ = 140° and 120°, respectively) were collected on an Enraf-Nonius CAD4 automatic diffractometer. Data were corrected for Lorentz and polarization effects and for absorption using the Walker and Stuart method.[13] The structures were solved by direct methods of SIR88,[14] and refined using the full-matrix least squares on F^2 provided by SHELXL-93.[15] The final R indexes were 0.078 and 0.089, respectively, for 130 and 406 refined parameters and the 803 and 3485 reflections having $I > 2\sigma(I)$. Anisotropic thermal parameters were used for all the non hydrogen atoms. Two crystallographically independent, but structurally identical molecules were found for **5**.

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