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Phthalonitriles by hetero Diels-Alder reactions of 4,5-dicyanopyridazine with enamines: isolation and characterization of unprecedented intermediates

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Abstract

The title conversions were shown to involve as key intermediates new dicyanodiene systems, that can be isolated in high yields under mild conditions; their structures, inferred from analytical and spectral data, were confirmed by an X-ray study. Some improvements for the synthetic methodology connected with this finding are discussed.

1. Introduction

Since the first report of Stork and co-workers [1], enamines have been widely investigated over the past four decades [2], and their large utility in organic synthesis is well documented [3]. Particularly, they can be advantageously employed as highly reactive partners in inverse electron-demand Diels-Alder reactions with electrophilic carbo- and hetero-dienes for the build-up of six-membered rings [4,5].

After recent results from our laboratory clearly showed that 4,5-dicyanopyridazine (DCP) (1) behaves as an excellent azadiene with several 2π electron counterparts [6], more recently we successfully exploited the same substrate for a novel complementary direct approach to variously substituted phthalonitriles with alkynes and enamines, respectively [7]. While the conversion of 1 with the former reagents could be simply accounted for by concerted cycloadditions followed by loss of nitrogen from the primary adducts, spectroscopic monitoring of the reactions of DCP with the latter suggested a more intriguing pattern, prompting us to gain better insight into this topic.

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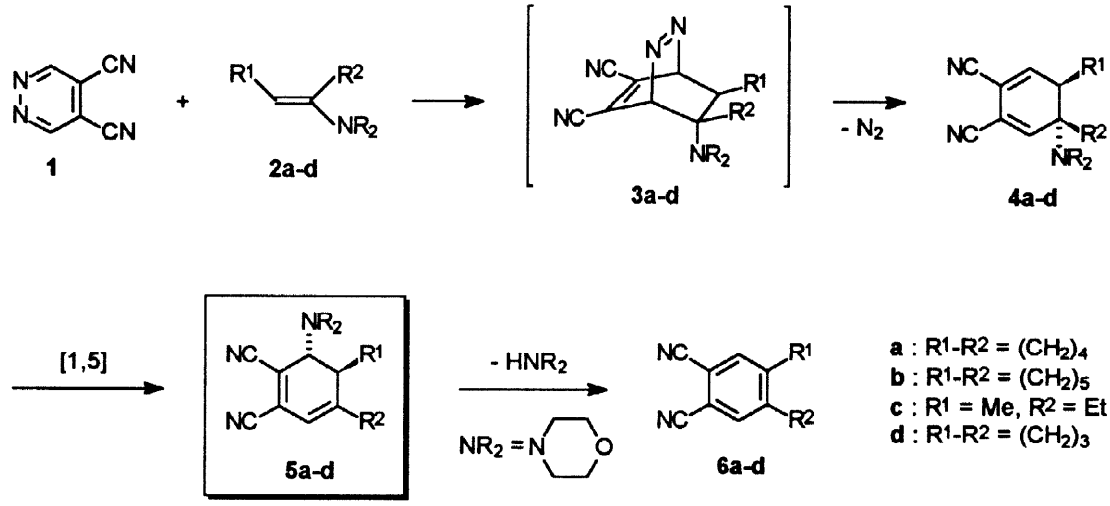
2. Results and discussion

Treatment of **1** with 4-(1-cyclohexen-1-yl)morpholine (**2a**) in chloroform at 70°C for 6 days afforded **6a** in 82% yield [7]; nevertheless, when the same reaction was carried out in dichloromethane at room temperature for 24 hours, a quantitative yield of a yellow-orange solid still containing the morpholino group was obtained.



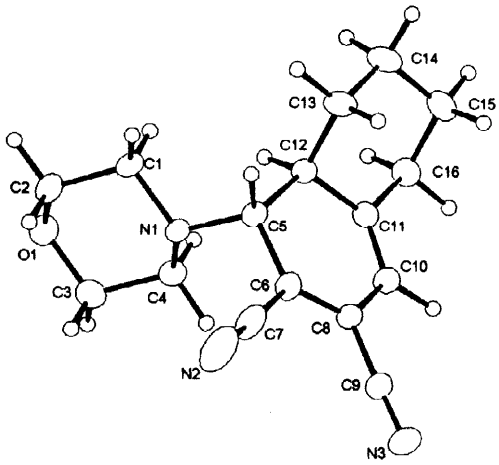
Scheme 1

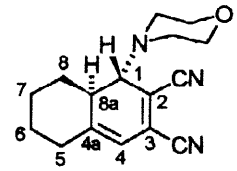
Although at first glance the structure **4a** appeared quite reasonable for this precursor in the light of previous reports on the isolation of similar intermediates for cycloadditions of 1,2,4-triazines [8,9], 1,2,4,5-tetrazines [10], and condensed pyridazines [11] with enamines, spectral evidence led us to identify the above product as the amino-dicyanocyclohexadiene derivative **5a** arising from a [1,5] sigmatropic rearrangement of **4a** (Scheme 1).

According to the different conjugation of the substituents on the diene moiety, two well separated bands are present in the IR spectrum at 2231 and 2216 cm^{-1} for the CN stretching vibrations, but a sole CH signal was detected for the same fragment in the ^{1}H- and ^{13}C-NMR spectra at δ 5.76 and 115.4, respectively. Moreover, whereas the first pattern shows a doublet and a multiplet at δ 3.23 and 2.38 for the vicinal H-1 and H-8a protons, the second one is characterized by a singlet at δ 156.8 attributable to the quaternary C-4a, strongly deshielded by the electron drift. The structure of **5a**, as well as its relative stereochemistry, was confirmed by a single crystal X-ray analysis (Figure 1).

Apart from a slightly greater reactivity, a similar behaviour was also observed with the enamines **2b** and **2c** at room temperature: compounds **5b** and **5c** were isolated in 98% yields, their structures being unambiguously determined on the basis of analytical and spectral data (Experimental). Repeated attempts to detect the species **4a-c** by ^{1}H NMR monitoring of the above reactions in CD_2Cl_2

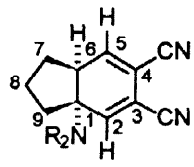
solution failed, certainly due to a rapid conversion into the more stable isomers **5a-c**. By contrast, when DCP was treated with 4-(1-cyclopenten-1-yl)morpholine **2d** under the same conditions, a vigorous reaction afforded nearly exclusively the bicyclic derivative **4d** in a few minutes' time.



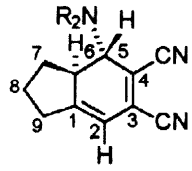


5a

Figure 1. ORTEP drawing of **5a**. Selected bond lengths (Å) and angles (°): C(5)-C(6) 1.510(3), C(5)-C(12) 1.552(3), C(6)-C(7) 1.434(3), C(6)-C(8) 1.349(3), N(2)-C(7) 1.139(4), C(8)-C(9) 1.438(3), N(3)-C(9) 1.138(3), C(8)-C(10) 1.454(3), C(10)-C(11) 1.329(3), C(11)-C(12) 1.495(3); N(1)-C(5)-C(6) 107.1(2), C(6)-C(5)-C(12) 113.5(2), C(8)-C(6)-C(5) 122.6(2), C(6)-C(8)-C(10) 121.7(2), C(11)-C(10)-C(8) 121.2(2), C(10)-C(11)-C(12) 122.2(2), C(11)-C(12)-C(5) 116.6(2).



4d



5d

Although this intermediate was not isolated as a pure product, its structure was deduced from spectral evidence. Particularly, a singlet and a doublet are present in the ^{1}H NMR spectrum at δ 6.58 and 7.0 for H-2 and H-5, whereas the resonances of the tertiary diene carbons were at δ 146.4 and 149.5. Compound **4d** rearranged more slowly into **5d**, which could be obtained as a yellow solid by fast chromatographic workup of a suitable mixture of the two isomers; the peculiar behaviour of **4d** with respect to **4a-c** can be accounted for on the basis of the resulting strained ring-fusion of **5d**. The most diagnostic spectral data of this compound were strictly comparable with those of the dicyano derivatives **5a-c** (Experimental), except for the coupling constant (J = 18.3 Hz) between H-5 and H-6 due to a rigid *trans* configuration with a dihedral angle of about 180°; quite different values (70-90°) were obtained by molecular modeling (Monte Carlo method in MacroModel) for the corresponding angles of the lowest energy conformations of **5a-c**.

While compound **5d** was cleanly converted into the corresponding aromatic derivative **6d** by heating in chloroform at 70°C for 24 hours, removal of morpholine from **5a-c** required several days with formation of by-products mainly due to concomitant oxidation processes; this problem could be circumvented when the above reactions were performed in dichloromethane-acetic acid at 50°C, thus obtaining the desired products **6a-c** in nearly quantitative yields.

3. Conclusion

A new facet has been revealed for the cycloaddition chemistry of the pyridazine system, together with the possibility of optimizing previous results [7] for the conversion of DCP into phthalonitriles with enamine dienophiles. Further synthetic opportunities, connected with the electrophilic diene moiety of the readily available intermediates **4a** and **5a-d**, will be explored.

4. Experimental[1]

Cycloadditions of 1 with the enamines 2a-c at room temperature: preparation of compounds 5a-c. General procedure.

A solution of DCP (0.065 g, 0.5 mmol) and the enamine (0.51 mmol) in CH_2Cl_2 (1.5 ml) was stirred in a screw-capped tube (Pyrex N.13) for 24 h; the reaction mixture was evaporated to dryness under reduced pressure.

A. Treatment of **1** with 4-(1-cyclohexen-1-yl)morpholine (**2a**) (0.085 g, 0.086 ml) afforded (1*RS*, 8a*SR*)-2,3-dicyano-1-(4-morpholino)-1,5,6,7,8,8a-hexahydronaphthalene (**5a**) (0.134 g, quantitative yield) that was crystallized from ether as yellow needles, m.p. 113-114°C; IR ν 3069, 2231, 2216, 1643, 1571 cm^{-1}; ^1H NMR δ 1.29-1.95 (m, 6H), 2.0-2.25 (m, 2H), 2.34-2.42 (m, 1H), 2.54 (m, 4H), 3.23 (d, J = 2.6 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 5.76 (sbr s, 1H); ^{13}C NMR δ 26.3 (t), 31.1 (t), 35.65 (t), 37.5 (t), 40.35 (d), 47.9 (t), 63.5 (d), 66.8 (t), 111.5 (d), 114.4 (s), 115.0 (s), 117.1 (s), 123.0 (s), 156.8 (s). Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 70.96; H, 6.98; N, 15.92.

B. The residue obtained by reaction of **1** with 4-(1-cyclohepten-1-yl)morpholine (**2b**) (0.092 g, 0.093 ml) was taken up in *n*-pentane (2-3 ml) and filtered to give (1*SR*, 11*RS*)-9,10-dicyano-11-(4-morpholino)bicyclo[5.4.0]undeca-7,9-diene (**5b**) as a yellow solid (0.139 g, 98%), m.p. 84-85°C; IR ν 3056, 2233, 2210, 1630, 1554 cm^{-1}; ^1H NMR δ 1.05-1.31 (m, 2H), 1.40-1.95 (m, 6H), 2.30-2.62 (m, 7H), 3.25 (sbr s, 1H), 3.63 (t, J = 4.6 Hz, 4H), 5.81 (t, J = 0.9 Hz, 1H); ^{13}C NMR δ 24.9 (t), 25.6 (t), 29.0 (t), 35.4 (t), 35.5 (t), 37.7 (d), 48.5 (t), 65.3 (d), 66.8 (t), 113.2 (s), 115.0 (s), 115.8 (d), 117.25

[1]Instruments and general techniques are described in reference [7].

(s), 122.9 (s), 156.5 (s). Anal. Calcd. for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 71.82; H, 7.54; N, 15.10.

C. Reaction of **1** with (*E*)-4-(pent-2-en-3-yl)morpholine (**2c**) (0.079 g, 0.085 ml) afforded (5*SR*, 6*RS*)-1,2-dicyano-4-ethyl-5-methyl-6-(4-morpholino)cyclohexa-1,3-diene (**5c**) as a yellow oil (0.126 g, 98%); an analytical sample was obtained by dissolution in *n*-pentane, filtration, evaporation to dryness, and prolonged evacuation at room temperature (10^{-2} mmHg); IR (liquid film) ν 2967, 2230, 2212, 1632, 1554 cm^{-1}; ^1H NMR δ 1.04 (d, J = 7.4 Hz, 3H), 1.13 (t, J = 7.4 Hz, 3H), 2.15-2.60 (m, 7H), 3.23 (sbr s, 1H), 3.64 (t, J = 4.6 Hz, 4H), 5.79 (t, J = 1.8 Hz, 1H); ^{13}C NMR δ 11.3 (q), 18.9 (q), 27.9 (t), 33.4 (d), 48.4 (t), 64.5 (d), 66.8 (t), 112.8 (s), 113.0 (d), 115.1 (s), 117.3 (s), 123.0 (s), 158.15 (s). Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.72; H, 7.23; N, 16.60.

*Reactions of **1** with 4-(1-cyclopenten-1-yl)morpholine (**2d**).*

A. The enamine (0.039 g, 0.041 ml, 0.255 mmol) was added at room temperature to a solution of DCP (0.0325 g, 0.25 mmol) in CD_2Cl_2 (0.75 ml) in a NMR tube; after nitrogen evolution subsided (5-10 min), the starting material was converted nearly quantitatively into (1*SR*, 6*RS*)-3,4-dicyano-1-(4-morpholino)bicyclo[4.3.0]nona-2,4-diene (**4d**); ^1H NMR δ 1.36-1.70 (m, 3H), 1.75-1.94 (m, 1H), 2.08-2.32 (m, 2H), 2.38-2.57 (m, 4H), 2.66-2.82 (m, 1H), 3.59 (t, J = 4.7 Hz, 4H), 6.58 (s, 1H), 7.0 (d, J = 6.1 Hz, 1H); ^{13}C NMR δ 23.2 (t), 35.5 (t), 40.2 (t), 42.6 (d), 47.6 (t), 66.3 (s), 67.7 (t), 105.2 (s), 108.4 (s), 115.7 (s), 116.0 (s), 146.4 (d), 149.5 (d).

B. A solution of **1** (0.065 g, 0.5 mmol) and **2d** (0.078 g, 0.082 ml, 0.51 mmol) in CH_2Cl_2 (1.5 ml) was stirred at room temperature for 24 h; the residue left by evaporation to dryness was rapidly subjected to flash chromatography with petroleum ether/AcOEt (2:1 v/v) as eluent. The first band afforded compound **6d** (R_f = 0.52, 0.010 g, 12%), identical with a specimen previously described [7]; the second one gave (5*SR*, 6*RS*)-3,4-dicyano-5-(4-morpholino)bicyclo[4.3.0]nona-1,3-diene (**5d**) as a yellow solid (R_f = 0.26, 0.090 g, 71%), m.p. 91-92°C (after treatment with ether and filtration); IR ν 3074, 2224, 2205, 1638, 1535 cm^{-1}; ^1H NMR δ 1.30-1.70 (m, 2H), 1.95-2.08 (m, 1H), 2.22-2.50 (m, 2H), 2.55-2.90 (m, 6H), 3.50 (d, J = 18.3 Hz, 1H), 3.75 (t, J = 4.8 Hz, 4H), 5.88 (sbr s, 1H); ^{13}C NMR δ 24.0 (t), 30.6 (t), 33.1 (t), 41.5 (d), 50.05 (t), 67.1 (t), 67.2 (d), 112.8 (d), 115.0 (s), 115.6 (s), 124.8 (s), 125.4 (s), 161.1 (s). Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.81; H, 6.66; N, 16.65.

*Improved syntheses of the phthalonitriles **6a-d** from **1** and **2a-d**. General procedure.*

After a solution of **1** (0.065 g, 0.5 mmol) and the enamine (0.51 mmol) in CH_2Cl_2 (1.5 ml) was stirred at room temperature for 24 h, acetic acid (1.5 ml) was added and the mixture was heated at 50°C for further 24 h. The residue left by evaporation to dryness was taken up in water (5-10 ml),

filtered, and dried. Compounds **6a-d**, identical with the products previously reported [7], were isolated in 99%, 96%, 95%, and 98% yields, respectively.

X-Ray structural analysis of ***5a***.[2]

Compound **5a**: $C_{16}H_{19}N_3O$, M = 269.3, monoclinic, space group $P2_1/a$, a = 8.780(2), b = 15.319(3), c = 11.247(3) Å, β = 90.12 (2)°, V = 1512.7(6) Å^3, Z = 4, $F(000)$ = 576, μ = 0.601 mm^{-1}, D_c = 1.183 g cm^{-3}, graphite monochromated (Cu-Kα) radiation (λ = 1.54178 Å).

2896 Reflections ($2\theta_{max}$ = 140°) were collected on an Enraf-Nonius CAD4 automatic diffractometer. Intensity data were corrected for Lorentz and polarization effects and an absorption correction was applied by using the Walker and Stuart method [12]. The crystal structure was solved by direct methods of SIR 92 [13], and refined using the full-matrix least squares on F^2 provided by SHELXL-93 [14]. 193 Parameters were refined and the final R factor over the 2658 reflections having $I > 2\sigma(I)$, was 0.076. All the non hydrogen atoms were refined anisotropically, while for the hydrogen ones, which were introduced in calculated positions and refined according to their linked atoms, an overall isotropic temperature factor was used and refined to 0.078(2) Å^2.

5. Acknowledgement

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6. References

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[2]Supplementary X-ray material has been deposited at the Cambridge Crystallographic Data Centre.