Tandem Inverse Electron-Demand Diels−Alder Reactions of 4,5-Dicyanopyridazine with Nonconjugated Dienes: An Excellent Direct Entry into Carbo- and Hetero-Cage Systems

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Suitable carbodienes, such as cyclopentadienones,[1] thiophene 1,1-dioxides,[2] and to a greater extent, 2-pyrones,[3] have been employed for the buildup of bridged polycyclic systems: the common synthetic strategy is based on sequential reactions with bis dienophiles involving an intermolecular cycloaddition followed by extrusion of CO, SO_2, and CO_2, respectively, from the primary adducts and a terminal intramolecular Diels−Alder ring closure.

Attempts to extend this profitable route to heteroaromatic azadienes were only partially successful. Particularly, whereas a few 1,2,4-triazines were converted in good yields into 7-azatetracyclo[7.3.0.0.^{2,6}0^{5,10}]dodec-7-enes with cycloocta-1,5-diene (COD) (**2**),[4] a dramatic decrease in reactivity was observed for 1,2-diazine counterparts: several electron-deficient derivatives were completely inert toward the same reagent even under drastic conditions, and only the "highly activated" tetraester **1** was found to react with COD at 150 °C to give compound **3** in 19% yield (Scheme 1).[4]

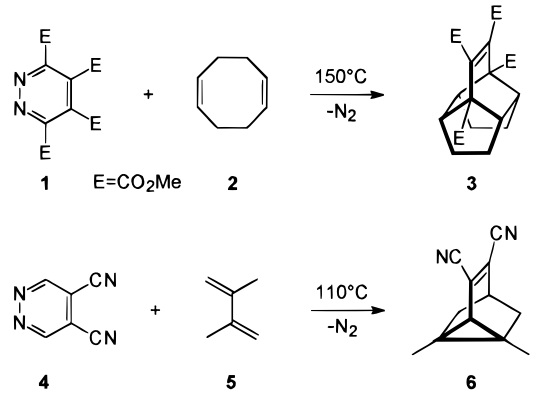
Nevertheless, we have recently shown that treatment of 4,5-dicyanopyridazine (**4**) with 2,3-dimethylbuta-1,3-diene (**5**) under milder conditions afforded the polycyclic system **6** in 64% yield (Scheme 1).[5]

After a preliminary screening clearly evidenced for **4** a remarkable reactivity with unactivated dienophiles,[6] we decided to gain better insight into the possibility of exploiting this heterodiene for a convenient approach to different cage skeletons.

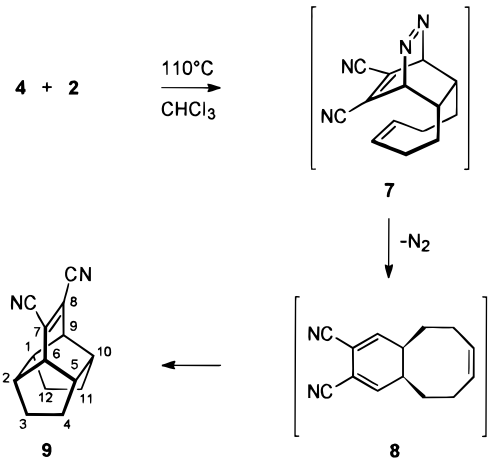
Results and Discussion

When **4** was allowed to react with an excess of COD in chloroform at 110 °C in a sealed tube, compound **9** was isolated in 98% yield as the outcome of cascade pericyclic processes. A first intermolecular IEDDA reaction of a double bond of **2** on the azadiene **4** leads to the tricyclic adduct **7**, which suffers from a retro Diels−Alder loss of N_2; the resulting key intermediate **8** then evolves into **9** by an intramolecular ring closure of the second 2π component on the activated cyclohexadiene moiety (Scheme 2).

Scheme 1



Scheme 2



A quite different reaction course was observed when cyclohexa-1,4-diene (**10**) was used in place of diene **2**, and we isolated 4-cyanopyridazine (**12**) as the main product (40%) together with a small amount (6%) of the dihydronaphthalene **14** (Scheme 3). A hydrogen transfer[7] from **10** to **4**, followed by elimination of HCN from **11**, now prevails over the expected conversion into **13** that, on the other hand, preferentially gives rise to **14** by a partial aromatization process.

Very satisfactory results were obtained both with different open-chain α,ω-carbodienes and bis-allyl derivatives. Whereas **4** reacted with penta-1,4-diene (**15a**) to give the tricyclic dicyano derivative **16** in 71% yield, treatment of the same substrate with an excess of hexa-1,5-diene (**15b**) and hepta-1,6-diene (**15c**) afforded nearly quantitatively the cage systems **17** and **18**, respectively (Scheme 4). Analogously, the variously heterosubstituted skeletons **20a−c** were easily obtained in excellent yields by replacement of the above reagents with compounds **19a−c** (Scheme 5).

(1) (a) Fray, G. I.; Oppenheimer, A. W. *J. Chem. Soc., Chem. Commun.* **1967**, 599. (b) Harano, K.; Yasuda, M.; Kanematsu, K. *J. Org. Chem.* **1982**, *47*, 3736−3743. (c) Eguchi, S.; Ishiura, K.; Noda, T.; Sasaki, T. *J. Org. Chem.* **1987**, *52*, 496−500. (d) Harano, K.; Uchida, K.; Izuma, M.; Aoki, T.; Eto, M.; Hisano, T. *Chem. Pharm. Bull.* **1988**, *36*, 2312−2322.

(2) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856−867.

(3) For comprehensive reviews on this topic, see: (a) Shusherina, N. P. *Russ. Chem. Rev.* **1974**, *43*, 851−861. (b) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111−9171. (c) Kvita, V.; Fischer, W. *Chimia* **1993**, *47*, 3−18. (d) Markò, I. E. In *Organometallic Reagents in Organic Synthesis*; Bateson, J. H., Mitchell, M. B., Eds.; Academic Press: London, 1994; Chapter 2, pp 44−56.

(4) Lantos, I.; Sheldrake, P. W.; Wells, A. S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1887−1890.

(5) Nesi, R.; Giomi, D.; Turchi, S.; Paoli, P. *Tetrahedron* **1994**, *50*, 9189−9194.

(6) Nesi, R.; Giomi, D.; Turchi, S.; Falai, A.. *J. Chem. Soc., Chem. Commun.* **1995**, 2201−2202.

(7) For similar reactions of **10** with electron-deficient alkenes and quinones, see: (a) Jacobson, B. M.; Soteropulos, P.; Bahadori, S. *J. Org. Chem.* **1988**, *53*, 3247−3255. (b) Brückner, R.; Huisgen, R. *Tetrahedron Lett.* **1991**, *32*, 1875−1878. (c) Müller, P.; Joly, D. *Helv. Chim. Acta* **1983**, *66*, 1110−1118. (d) Müller, P.; Joly, D.; Mermoud, F. *Helv. Chim. Acta* **1984**, *67*, 105−112. (e) Brock, M.; Hintze, H.; Heesing, A. *Chem. Ber.* **1986**, *119*, 3727−3736.

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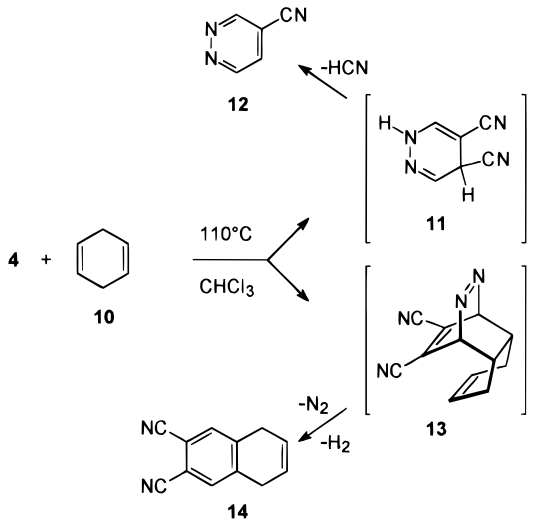
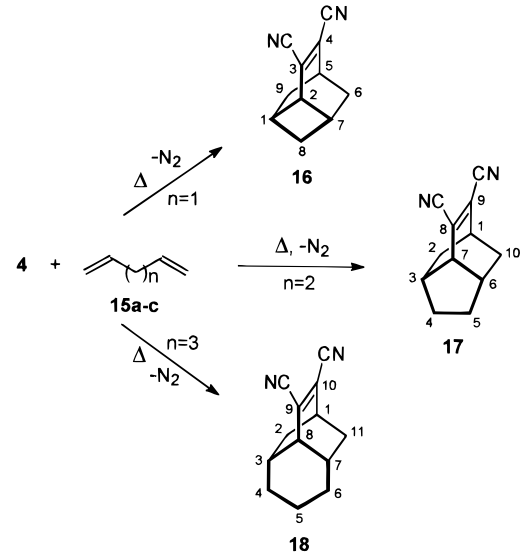
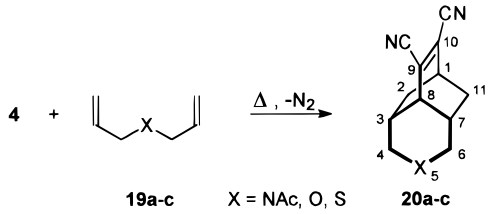
Scheme 3



Scheme 4



Scheme 5



The structures of the new products **9**, **14**, **16**−**18,** and **20a**−**c** were determined from analytical and spectral evidence (Experimental Section). In particular, the different cage frameworks exhibit highly diagnostic ^{13}C NMR patterns:[8] while the spectrum of the tetracyclic system **9** shows only five signals according to a C_{2v} symmetry, those of compounds **16**−**18** are characterized by nine resonances due to a common C_s symmetry. Likewise, **20b** and **20c** give rise to eight and nine signals, respectively, but 13 absorptions are present in the spectrum of **20a**, the above symmetry being destroyed by the amide moiety.

In conclusion, our findings open new perspectives in the pyridazine chemistry, and despite the low reputation enjoyed by symmetrical 1,2-diazines,[9] the azadiene **4** is enabled by peculiar electronic and geometrical features to enter the baggage of organic chemists as an effective tool for one-pot syntheses of vicinal unsaturated dicyano cage compounds.

(8) Isochronism was observed for the CN groups of **18**, **20a**, and **20b**.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were measured for dispersions in KBr, while ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 200 and 50 MHz, respectively. Silica gel plates (Merck F_{254}; 0.2 mm) and silica gel (ICN; 32−63, 60 A) were used for analytical and flash chromatographies, respectively.

Thermal Reactions of 4,5-Dicyanopyridazine (4)[10] with the Dienes 2, 15a−c, and 19a−c: Synthesis of Compounds 9, 16−18, and 20a−c. General Procedure. A mixture of **4** (1 mmol) and the reagent (5 mmol) in $CHCl_3$ (1 mL) was heated in a sealed tube (Pyrex, no. 13) at 110 °C until the starting material disappeared (TLC, ^1H NMR). Unless otherwise indicated, the residue left by evaporation to dryness under reduced pressure was simply washed with a small amount of *n*-pentane, and analytical samples were obtained by crystallization from ether.

A. 7,8-Dicyanotetracyclo[7.3.0.$0^{2,6}$0^{5,10}]dodec-7-ene (**9**)[11] (0.206 g, 98%): colorless needles; mp 225−226 °C; IR 2971, 2951, 2934, 2880, 2215, 1611 cm^{-1}; ^1H NMR δ 1.55−1.89 (m, 8H), 2.01 (br s, 4H), 2.64 (m, 2H); ^{13}C NMR δ 25.5 (t), 40.9 (d), 46.4 (d), 114.7 (s), 128.2 (s). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.67; H, 6.65; N, 13.46.

B. The crude reaction product of **4** with **15a** was subjected to flash chromatography [40−70 °C petroleum ether/ethyl acetate (7:1 v/v) as eluent] to give 3,4-dicyanotricyclo[3.3.1.$0^{2,7}$]-non-3-ene (**16**)[12] (R_f = 0.32, 0.12 g, 71%) as a colorless crystalline solid: mp 150 °C; IR 2963, 2870, 2215, 1597 cm^{-1}; ^1H NMR δ 1.11 (d, J = 8.8 Hz, 1H), 1.24 (m, 2H), 1.96 (dd, J = 13.2 and 4.0 Hz, 2H), 2.35 (m, 3H), 3.35 (br s, 1H), 3.58 (m, 1H); ^{13}C NMR δ 31.7 (t), 33.7 (d), 36.6 (d), 36.8 (t), 40.1 (d), 114.5 (s), 114.9 (s), 126.15 (s), 134.2 (s). Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.37; H, 5.97; N, 16.18.

C. 8,9-Dicyanotricyclo[4.3.1.$0^{3,7}$]dec-8-ene (**17**)[12] (0.18 g, 98%): colorless crystals; mp 107 °C; IR 2956, 2876, 2217, 1599 cm^{-1}; ^1H NMR δ 1.51 (AB system, J_{AB} = 13.2 Hz, 4H), 1.53−1.60 (m, 2H), 1.90−1.97 (m, 2H), 2.06−2.09 (m, 2H), 2.79 (t, J = 4.2 Hz, 1H), 2.87 (quintet, J = 2.7 Hz, 1H); ^{13}C NMR δ 31.1 (t), 33.7 (d), 35.05 (d), 36.4 (t), 46.0 (d), 114.2 (s), 114.8 (s), 128.95 (s), 132.7 (s). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 77.93; H, 6.76; N, 15.40.

D. 9,10-Dicyanotricyclo[5.3.1.$0^{3,8}$]undec-9-ene (**18**)[12] (0.192 g, 97%): colorless needles; mp 154−155 °C; IR 2943, 2856, 2219, 1595 cm^{-1}; ^1H NMR δ 1.35−1.70 (m, 10H), 1.80−1.98 (m, 2H), 2.57 (t, J = 3.0 Hz, 1H), 2.98 (quintet, J = 2.9 Hz, 1H); ^{13}C NMR δ 13.5 (t), 28.2 (t), 29.0 (d), 29.4 (t), 35.1 (d), 43.35 (d), 114.4 (s), 132.1 (s), 133.2 (s). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.60; H, 7.23; N, 14.21.

E. Chromatographic workup (ethyl acetate as eluent) of the crude reaction product of **4** with **19a** [2] afforded 5-acetyl-9,10-dicyano-5-azatricyclo[5.3.1.$0^{3,8}$]undec-9-ene (**20a**)[12] (R_f = 0.22, 0.207 g, 86%) that was crystallized from the same solvent as ivory-colored needles: mp 233−234 °C; IR 2957, 2935, 2861, 2218, 1631 cm^{-1}; ^1H NMR δ 1.24−1.37 (m, 2H), 1.57−1.79 (m, 2H), 1.86−2.01 (m, 2H), 2.12 (s, 3H), 2.56 (br d, J = 13.5 Hz, 1H), 2.79 (t, J = 3.0 Hz, 1H), 2.94 (quintet, J = 2.5 Hz, 1H), 3.16 (br d, J = 13.2 Hz, 1H), 3.72 (br d, J = 13.5 Hz, 1H), 4.64 (br d, J = 13.2 Hz, 1H); ^{13}C NMR δ 21.6 (q), 29.1 (t), 29.4 (t), 29.5 (d), 29.8 (d), 34.75 (d), 41.3 (d), 44.2 (t), 49.4 (t), 113.9 (s), 131.2 (s), 133.0 (s), 170.6 (s). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.83; H, 6.32; N, 17.14.

F. 9,10-Dicyano-5-oxatricyclo[5.3.1.$0^{3,8}$]undec-9-ene (**20b**)[12] (0.196 g, 98%): ivory-colored crystals; mp 110−111 °C; IR 2959,

(9) Ho, T.-L. In *Symmetry: A Basis for Synthesis Design*; J. Wiley & Sons Inc.: New York, 1995; Chapter 9, p 474.

(10) Di Stefano, L.; Castle, R. N. *J. Heterocycl. Chem.* **1968**, *5*, 53−59.

(11) This product was numbered as the corresponding tetraester **3**.[4]

(12) Beilstein's names were adopted for the tricyclic cage systems.

2937, 2857, 2223, 1595 cm^{-1}; ^1H NMR δ 1.58−1.76 (m, 6H), 2.78 (t, J = 2.6 Hz, 1H), 3.01 (quintet, J = 2.4 Hz, 1H), 3.56 (AB system, J_{AB} = 11.5 Hz, 4H); ^{13}C NMR δ 29.4 (t), 29.8 (d), 34.9 (d), 40.2 (d), 69.4 (t), 114.1 (s), 131.1 (s), 133.1 (s). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.84; H, 6.15; N, 14.00.

G. 9,10-Dicyano-5-thiatricyclo[5.3.1.$0^{3,8}$]undec-9-ene (**20c**)[12] (0.21 g, 97%): ivory-colored crystals; mp 161−162 °C; IR 2953, 2925, 2856, 2218, 1597 cm^{-1}; ^1H NMR δ 1.50−1.70 (m, 2H), 1.89−2.10 (m, 4H), 2.55 (t, J = 2.5 Hz, 1H), 2.60 (AB system, J_{AB} = 14.0 Hz, 4H), 3.06 (quintet, J = 2.6 Hz, 1H); ^{13}C NMR δ 28.4 (t), 28.6(d), 31.1 (t), 35.3 (d), 42.3 (d), 114.05 (s), 114.2 (s), 132.6 (s), 133.1 (s). Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.64; H, 5.59; N, 12.95. Found: C, 66.90; H, 5.73; N, 12.66.

Reaction of 4 with Cyclohexa-1,4-diene (10). A mixture of **4** (0.130 g, 1 mmol) and **10** (0.40 g, 0.47 mL, 5 mmol) in $CHCl_3$ (1 mL) was heated in a sealed tube at 110 °C for 48 h. Chromatographic resolution [40−70 °C petroleum ether/ethyl acetate (3:2 v/v) as eluent] of the residue left by evaporation to dryness afforded 2,3-dicyano-5,8-dihydronaphthalene (**14**) (R_f = 0.71, 0.010 g, 6%) as ivory-colored needles: mp 210 °C (from ether); IR 3040, 2891, 2874, 2232, 1598 cm^{-1}; ^1H NMR δ 3.46 (br s, 4H), 5.92 (m, 2H), 7.56 (br s, 2H); ^{13}C NMR δ 29.6 (t), 112.9 (s), 115.6 (s), 123.5 (d), 133.5 (d), 141.0 (s). Anal. Calcd for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.54. Found: C, 79.90; H, 4.42; N, 15.76.

The slower moving band gave 4-cyanopyridazine (**12**) (R_f = 0.27, 0.042 g, 40%) that was sublimed at 50−55 °C (4 Torr) to give colorless crystals: mp 78−79 °C (lit.[13] mp 79−80 °C); IR 3076, 3050, 2246, 1577 cm^{-1}; ^1H NMR δ 7.76 (dd, J = 5.3, 2.2 Hz, 1H), 9.40 (dd, J = 2.2, 1.3 Hz, 1H), 9.47 (dd, J = 5.3, 1.3 Hz, 1H); ^{13}C NMR δ 113.1 (s), 114.1 (s), 127.9 (d), 150.4 (d), 151.2 (d).

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(13) Robba, M. *Ann. Chim.* **1960**, *5*, 351−379.