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Reactions of 4,5-Dicyanopyridazine with Alkynes and Enamines: a New Straightforward Complementary Route to 4-Mono- and 4,5-Disubstituted Phthalonitriles

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Abstract: The preparation of the 1,2-dicyanobenzenes **6a-m** in fairly good to excellent yields by one-pot procedures based on [4+2] cycloaddition processes of the title compound **1** with acetylenic or enamine dienophiles, is reported; some features of this new synthetic strategy are emphasized.

While the 1,2-diazine system has been scarcely employed as heterodiene in intermolecular inverse electron demand Diels-Alder reactions,[1] probably due to discouraging results even with 'activated' derivatives,[2] we have recently shown that 4,5-dicyanopyridazine (**1**), easily available from the corresponding parent compound,[3] exhibits a remarkable reactivity with several 2π electron counterparts.[4] On the other hand, the title phthalonitriles, generally obtained by multistage elaboration of aromatic precursors, represent in many instances the key building blocks of phthalocyanines,[5] whose growing importance in different fields of material science clearly emerged over the past two decades.[6]

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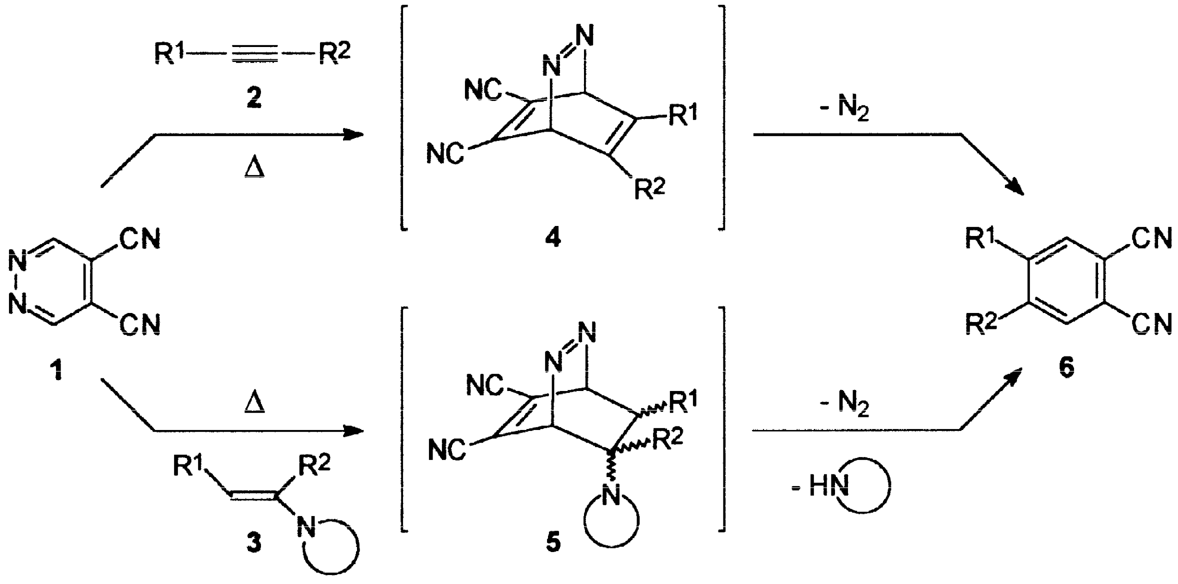
With these factors in mind, and on the basis of some promising preliminary results,[4b] we decided to undertake a systematic investigation on the possibility of exploiting **1** as a valuable synthon for alternative direct approaches to phthalonitriles from suitable dienophiles.

RESULTS AND DISCUSSION

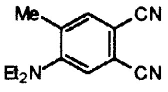
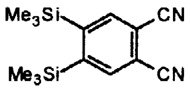
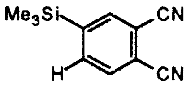
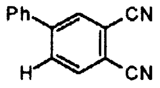
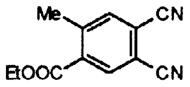
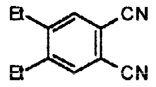
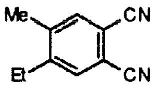
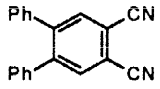
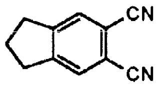
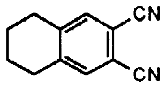
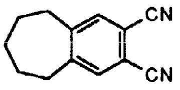
The results obtained from reactions of **1** with the alkynes **2a-h** and enamines **3a-g** are summarized in Table 1: [4+2] cycloadditions are followed by nitrogen extrusion or sequential loss of nitrogen and amine, respectively, to afford the desired dicyano derivatives **6a-m** (Scheme 1).[7]



Scheme 1

Increasingly forcing conditions were required on going from the strongly activated ynamine **2a** (entry 1) to the less reactive acetylenes **2d-h** (entries 4, 6, 8, 9, and 11), through the silylated reagents **2b,c** (entries 2, 3); correspondingly, a substantial change from very good yields to fair ones was observed. Whereas the diphenyl derivative **3d** showed poor dienophilic properties towards **1** (entry 12), replacement of **2d** and **2g** with enamines **3a** and **3c** enabled us to achieve higher yields for compounds **6d** and **6g**, respectively (entries 5 and 10 *vs* 4 and 9); finally, very satisfactory results were obtained for the condensed systems **6i-m** with the cyclic enamines **3e-g** (entries 13-15).

Table 1. Reactions of **1** with Alkynes and Enamines.

entry	reagent	solvent, T(°C), time	product	yield %
1	**2a**: R^1=Me, R^2=NEt_2	CH_2Cl_2, 25°C, 19h	 **6a**	85
2	**2b**: R^1=R^2=$SiMe_3$	$CHCl_3$, 110°C, 48h	 **6b**	98
3	**2c**: R^1=$SiMe_3$, R^2=H	$CHCl_3$, 110°C, 8d	 **6c**	98
4	**2d**: R^1=Ph, R^2=H	xylene, 150°C, 24h	 **6d**	42
5	**3a**: R^1=Ph, R^2=H	$CHCl_3$, 70°C, 24h		72
6	**2e**: R^1=Me, R^2=COOEt	xylene, 150°C, 5d	 **6e**	55
7	**3b**: R^1=COOEt, R^2=Me	$CHCl_3$, 70°C, 24h		29
8	**2f**: R^1=R^2=Et	xylene, 150°C, 10d	 **6f**	55
9	**2g**: R^1=Me, R^2=Et	xylene, 150°C, 18d	 **6g**	51
10	**3c**: R^1=Me, R^2=Et	$CHCl_3$, 70°C, 7d		73
11	**2h**: R^1=R^2=Ph	xylene, 150°C, 21d	 **6h**	72
12	**3d**: R^1=R^2=Ph	$CHCl_3$, 110°C, 48h		11
13	**3e**: R^1-R^2=$(CH_2)_3$	$CHCl_3$, 70°C, 24h	 **6i**	96
14	**3f**: R^1-R^2=$(CH_2)_4$	$CHCl_3$, 70°C, 6d	 **6l**	82
15	**3g**: R^1-R^2=$(CH_2)_5$	$CHCl_3$, 70°C, 7d	 **6m**	71

Compounds **6d** and **6l** were also isolated from the reactions of **1** with styrene and cyclohexene, respectively,[4d] but their preparation from the corresponding enamines is much more efficient.

Among the above findings, it is noteworthy that the new silyl derivative (**6b**) was easily prepared in nearly quantitative yield, and an effective alternative route was provided for **6c**, previously obtained by a six-step sequence from 4-chloro-*o*-xylene.[8]

In summary, the outstanding reactivity of **1** towards the aforementioned reagents opens new perspectives for the synthesis of phthalonitriles; further possibilities of expanding the scope of this attractive strategy will be thoroughly investigated.

EXPERIMENTAL SECTION

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Unless otherwise stated, 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 instrument operating at 200 MHz and 50 MHz, respectively: chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz). Elemental analyses were obtained with 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 chromatographies, respectively; petroleum ether employed for crystallizations and chromatographic workup refers to the fractions of b.p. 30-50°C and 40-70°C, respectively.

General Procedure for the Reactions of 1 with Alkynes and Enamines. Unless otherwise stated, all the cycloadditions were carried out in a screw-capped tube (Pyrex N. 13) on 1 mmol scale with an excess of the reagent (1.1-10 equiv.) in the specified solvent (1 ml); the reaction mixtures, obtained under different conditions (Table 1), were evaporated to dryness under reduced pressure. When the conversion of **1** was incomplete, the yields of the isolated compounds were determined on the basis of the recovered starting material.

1,2-Dicyano-4-diethylamino-5-methylbenzene (6a). The raw product from the reaction of **1** with 1-diethylaminopropyne (**2a**) (0.122 g, 0.156 ml, 1.1 mmol) in CH_2Cl_2 (3 ml) was subjected to flash chromatography with toluene/AcOEt (20:1 v/v) as eluent to give the phthalonitrile **6a** (R_f = 0.42, 0.181 g, 85%) as a light yellow solid, m.p. 68.5-69°C (from *n*-pentane); IR ν 3081, 3037, 2980, 2232, 2223, 1591, 1266, 1063, 901 cm^{-1}; ^{1}H NMR δ 1.05 (t, J = 7.2 Hz, 6H), 2.33 (s, 3H), 3.12 (q, J = 7.2 Hz, 4H), 7.24 (s, 1H), 7.50 (s, 1H); ^{13}C NMR δ 12.2 (q), 19.5 (q), 45.6 (t), 106.8 (s), 113.5 (s), 116.0 (s), 116.2 (s), 124.7 (d), 136.3 (d), 138.5 (s), 154.6 (s). Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.54; H, 7.07; N, 20.02.

1,2-Dicyano-4,5-bis(trimethylsilyl)benzene (6b). Treatment of **1** with bis(trimethylsilyl)acetylene (**2b**) (0.852 g, 5 mmol) afforded compound **6b** (0.267 g, 98%) that was crystallized from *n*-pentane as colourless needles, m.p. 156-157°C; IR ν 3070, 2955, 2229, 1559, 1269, 1253, 842 cm^{-1}; ^{1}H NMR δ 0.41 (s, 18H), 7.99 (s, 2H); ^{13}C NMR δ 1.25 (q), 114.0 (s), 115.85 (s), 138.4 (d), 154.3 (s). Anal. Calcd. for $C_{14}H_{20}N_2Si_2$: C, 61.71; H, 7.40; N, 10.28. Found: C, 61.43; H, 7.40; N, 10.32.

1,2-Dicyano-4-trimethylsilylbenzene (6c). Reaction of **1** with trimethylsilylacetylene (**2c**) (0.972 g, 1.4 ml, 10 mmol) gave compound **6c** (0.196 g, 98%) as colourless needles, m.p. 86°C (from petroleum ether) (lit.[8] m.p. 86°C); IR ν 3050, 3021, 2956, 2898, 2235, 1369, 1244, 880, 832 cm^{-1}; ^{1}H NMR δ 0.33 (s, 9H), 7.76 (dd, *J* = 7.7 and 0.65 Hz, 1H), 7.85 (dd, *J* = 7.7 and 1.1 Hz, 1H), 7.91 (dd, *J* = 1.1 and 0.65 Hz, 1H); ^{13}C NMR δ -1.7 (q), 114.9 (s), 115.4 (s), 115.5 (s), 115.8 (s), 132.2 (d), 137.6 (d), 138.0 (d), 149.0 (s).

3,4-Dicyanobiphenyl (6d).

A. Chromatographic workup [petroleum ether/AcOEt (5:1 v/v)] of the reaction product of **1** with phenylacetylene (**2d**) (1.0 g, 1.12 ml, 10 mmol) afforded compound **6d** (R_f = 0.42, 0.086, 42%) identical with a specimen previously described.[4d]

B. The same compound (R_f = 0.41, 0.147 g, 72%) was isolated by flash chromatography [toluene/AcOEt (20:1 v/v)] of the residue from the reaction of **1** with *N*-styrylmorpholine (**3a**) (0.208 g, 1.1 mmol).

Ethyl 3,4-Dicyano-6-methylbenzoate (6e).

A. Chromatographic resolution [petroleum ether/AcOEt (5:1 v/v)] of the raw product from **1** and ethyl 2-butynoate (**2e**) (1.12 g, 1.16 ml, 10 mmol) yielded **6e** (R_f = 0.43, 0.065 g, 55%) that was crystallized from ether as ivory-coloured crystals m.p. 112°C; IR ν 3112, 3043, 2995, 2236, 1722, 1259, 1131 cm^{-1}; ^{1}H NMR δ 1.42 (t, *J* = 7.2 Hz, 3H), 2.71 (s, 3H), 4.42 (q, *J* = 7.2 Hz, 2H), 7.71 (s, 1H), 8.30 (s, 1H); ^{13}C NMR δ 14.1 (q), 21.8 (q), 62.3 (t), 113.2 (s), 114.7 (s), 114.8 (s), 117.8 (s), 134.5 (s), 135.3 (d), 136.7 (d), 146.3 (s), 164.25 (s). Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.95; H, 4.76; N, 13.27.

The unreacted **1** (R_f = 0.18, 0.058 g) was recovered from the following fractions.

B. Chromatographic workup with the same eluent of the reaction mixture of **1** with ethyl 3-(1-pyrrolidino)crotonate (**3b**) (0.208 g, 1.1 mmol) gave **6e** (0.062 g, 29%), identical with the product obtained as above.

1,2-Dicyano-4,5-diethylbenzene (6f). The residue from the reaction of **1** with 3-hexyne (**2f**) (0.822 g, 1.14 ml, 10 mmol) was mixed with sand and sublimed at 70°C/10^{-2} mmHg to give compound **6f** (0.101 g, 55%) as white crystals, m.p. 103.5-104°C (from ether); IR ν 3077, 3046, 2974, 2885, 2230, 1598, 1490, 1426, 897 cm^{-1}; ^{1}H NMR δ 1.26 (t, *J* = 7.5 Hz, 6H), 2.74 (q, *J* = 7.5 Hz, 4H), 7.58 (s, 2H); ^{13}C NMR δ 14.0 (q), 25.3 (t), 112.9 (s), 115.8 (s), 133.0 (d), 148.4 (s). Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 78.15; H, 6.67; N, 15.48.

1,2-Dicyano-4-ethyl-5-methylbenzene (6g).

A. Operating as above, the reaction product of **1** with 2-pentyne (**2g**) (0.681 g, 0.960 ml, 10 mmol) afforded **6g** (0.087 g, 51%) as ivory-coloured crystals, m.p. 109°C (from ether); IR ν 3038, 2978, 2230, 1600, 1454, 919, 894 cm^{-1}; ^{1}H NMR δ 1.25 (t, *J* = 7.5 Hz, 3H), 2.40 (s, 3H), 2.71 (q, *J* = 7.5 Hz, 2H), 7.55 (s, 1H), 7.57 (s, 1H); ^{13}C NMR δ 13.2 (q), 19.4 (q), 26.0 (t), 112.7 (s), 113.1 (s), 115.7 (s), 115.8 (s), 132.6 (d), 134.6 (d), 142.9 (s), 148.9 (s). Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.34; H, 5.98; N, 16.34.

B. The same phthalonitrile (R_f = 0.49, 0.124 g, 73%) was obtained from the reaction of **1** and (*E*)-4-(pent-2-en-3-yl)morpholine **3c** (0.171 g, 0.184 ml, 1.1 mmol) by flash chromatography with petroleum ether/AcOEt (4:1 v/v) as eluent.

1,2-Dicyano-4,5-diphenylbenzene (6h).

A. The raw product from **1** and diphenylacetylene (**2h**) (0.891 g, 5 mmol) was resolved into two components [petroleum ether/AcOEt (7:1 v/v)]: the first band yielded compound **6h** (R_f = 0.36, 0.109 g, 72%) as white crystals, m.p. 174.5-175°C (from ether) (lit.[9] m.p. 174-175°C); IR ν 3045, 3028, 2231, 1584, 1478, 910 cm^{-1}; ^{1}H NMR δ 7.05-7.15 (m, 4H), 7.22-7.36 (m, 6H), 7.85 (s, 2H); ^{13}C NMR δ 114.4 (s), 115.4 (s), 128.55 (d), 128.6 (d), 129.3 (d), 135.55 (d), 137.6 (s), 145.9 (s).

The unreacted **1** (R_f = 0.10, 0.060g) was recovered from the second fraction.

B. Operating as above, the same product **6h** was obtained in lower yield (0.031 g, 11%) from the reaction of **1** with (*E*)-1-(4-morpholino)-1,2-diphenylethylene (**3d**) (0.292 g, 1.1 mmol).

5,6-Dicyano-2,3-dihydroindene (6i). The crude product from the reaction of **1** with 4-(1-cyclopenten-1-yl)morpholine (**3e**) (0.174 g, 0.182 ml, 1.1 mmol) was treated with water (5 ml), filtered and dried to give **6i** (0.161 g, 96%) that was crystallized from ether as ivory-coloured needles, m.p. 172-173°C ; IR ν 3035, 2965, 2929, 2231, 1596, 1482, 1426, 1247, 904 cm^{-1}; ^{1}H NMR δ 2.17 (quintet, *J* = 7.5 Hz, 2H), 3.02 (t, *J* = 7.5 Hz, 4H), 7.60 (s, 2H); ^{13}C NMR δ 24.75 (t), 32.9 (t), 113.4 (s), 115.9 (s), 129.25 (d), 151.0 (s). Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.65. Found: C, 78.20; H, 4.91; N, 17.0.

2,3-Dicyano-5,6,7,8-tetrahydronaphthalene (6l). The residue obtained from **1** and 4-(1-cyclohexen-1-yl)morpholine (**3f**) (0.188 g, 0.189 ml, 1.1 mmol) was subjected to flash chromatography [petroleum ether/AcOEt (7:2 v/v)] to yield compound **6l** (R_f = 0.55, 0.149 g, 82%), identical with a sample previously reported.[4d]

2,3-Dicyano-6,7,8,9-tetrahydrobenzocycloheptene (6m). Chromatographic workup [petroleum ether/AcOEt (7:1 v/v)] of the crude product from **1** and 4-(1-cyclohepten-1-yl)morpholine (**3g**) (0.210 g, 0.211 ml, 1.1 mmol) afforded the bicyclic derivative **6m** (R_f = 0.39, 0.139 g, 71%) as ivory-coloured crystals m.p. 166-167°C (from ether); IR ν 3038, 2933, 2855, 2230, 1589, 1444, 907 cm^{-1}; ^{1}H NMR δ 1.60-1.75 (m, 4H), 1.80-1.95 (m, 2H), 2.82-2.94 (m, 4H), 7.51 (s, 2H); ^{13}C NMR δ 27.0 (t), 31.9 (t), 36.3 (t), 113.0 (s), 115.7 (s), 133.6 (d), 150.1 (s). Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.72; H, 6.31; N, 14.39.

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7. Whereas the structure of the primary adducts **4**, coming from concerted processes, appear well-defined, the stereochemistry of **5** is portrayed arbitrarily; moreover, a stepwise mechanism involving dipolar intermediates could be taken into consideration for the formation of **6** from **1** and **3**.

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