

Full Paper

Revisiting the Reaction Between Diaminomaleonitrile and Aromatic Aldehydes: a Green Chemistry Approach

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Abstract: The reaction between diaminomaleonitrile (DAMN) and aldehydes and the resulting monoimines are well known. Since the standard reaction conditions involve the use of toxic solvents (typically methanol), we have sought to apply green chemistry principles to this reaction by either using water as the solvent without any catalysts or employing “solvent-free” conditions. The monoimines derived from DAMN are of interest as precursors for obtaining different heterocyclic systems and linear polymers. The methodologies used have significant advantages with regards to cost and environmental considerations.

Keywords: DAMN, monoimines, Green Chemistry, aromatic aldehydes.

Introduction

Tetrameric HCN (diaminomaleonitrile, DAMN) is one of the most versatile reagents in Organic Chemistry. It has been used as a precursor for producing nucleotides and for synthesising a wide variety of heterocyclic compounds [1] including purines [2,3], pyrimidines [4], pyrazines [5] (some which are widely employed in the fluorescent dye industry [6]), imidazoles [7], biphenylenes [8], porphyrazines (which have great potential in optical sensor technology [9]) and diimines that are used

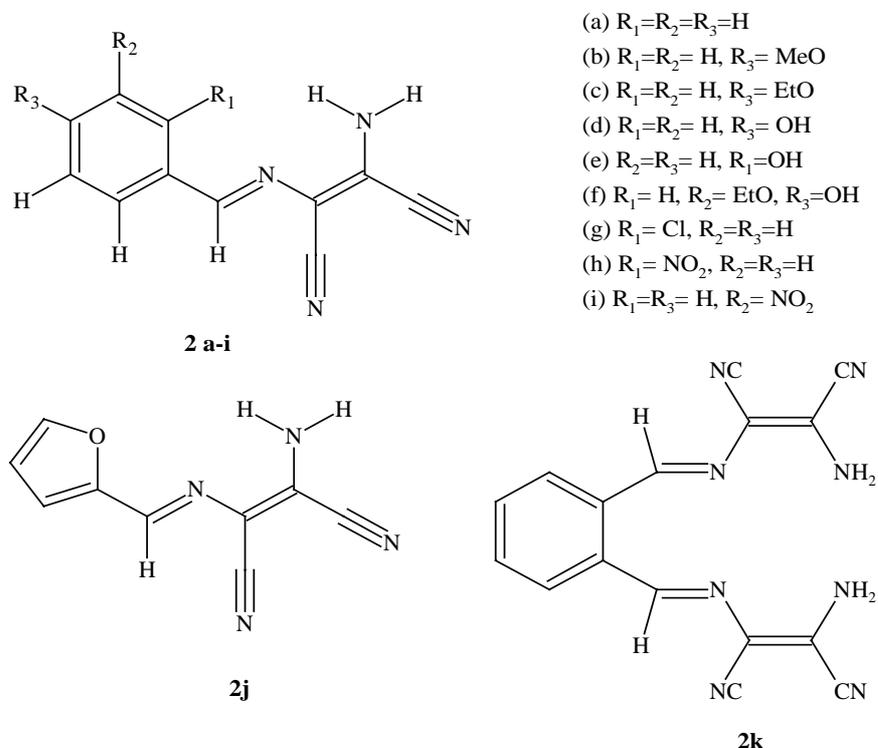
as catalysts [10]. The reaction of DAMN with aromatic aldehydes is widely known to produce monoimines [11]. These compounds are important as synthetic intermediates and they are also used in pharmacology [12]. Their great potential has recently been demonstrated in the synthesis of conjugated linear polymers [13] and in the thermostable optical material industry [14]. Most reaction methods described to date involve the use methanol as a solvent without catalysts, but ethanol and acid catalysis are required if the aldehyde bears a strong electron-withdrawing group [4,5,14].

Based on our investigations of the reaction between 1,2-diamines and formaldehyde generating macrocyclic amins [15] and on reactions reported in the literature for preparing imines and amins [16,17], we carried out the reaction between DAMN and various aromatic aldehydes employing either water as solvent without catalysts or under “solvent-free” conditions, thus obtaining the respective monoimines. The fact that water was used as solvent in this type of reaction makes this a cleaner, more efficient and attractive method for preparing this type of substances. In addition the reactions carried out in water were also shown to be chemoselective. The cyano groups could be identified and differentiated and their ^{13}C -NMR and IR signals were unambiguously assigned.

Results and Discussion

The reactions of DAMN with aromatic aldehydes in water as solvent or under “solvent-free” conditions proceeded as usual to give the respective monoimines **2a-k** in good to excellent yields (Scheme 1).

Scheme 1.



Reaction yields fluctuated between 50-100%, with the lower values, which we attribute to pH effects, corresponding to the reactions with hydroxybenzaldehydes. IR, ^1H -NMR, ^{13}C -NMR spectral

analysis and 2-D experiments allowed us to establish the structures of the momoimines **2a-2k**. Compounds **2a,b,d-j** have been previously described [3,7,11,18,19] and the physical properties determined during this work are in complete agreement with those reported. It is noteworthy that no complete spectroscopic data for compounds **2a** and **2g** were found in the literature, while compounds **2c** and **2k** have not been described previously, although preparation of **2k** under acid catalysis and using DMSO as solvent was claimed in a patent [20].

This article reports on the full assignment of NMR spectra for compounds **2a-2k** deduced from the correlations established in the 2-D (COSY, HSQC, HMBC) experiments, especially for the imine hydrogen (Table 1). Despite the fact that these substances are well known (with the aforementioned exceptions of **2c** and **2k**), to our knowledge this is the first time that these compounds have been obtained using water as solvent.

Table 1. ^{13}C -NMR and ^1H -NMR Chemical Shift Data of **2a-k**.

	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k
NH₂	7.94	7.77	7.76	7.76	7.86	7.72	8,19	8.27	8.27	7.77	7.77
1	113.7	115.1	115.1	115.2	115.0	115.2	114.6	114.9	114.6	114.9	114.8
2	126.9	126.3	126.3	125.9	126.5	125.8	128.4	129.4	128.6	126.7	127.7
3	103.9	103.6	103.6	103.9	103.9	103.9	103.0	103.0	102.0	103.7	103.7.
4	112.9	114.3	114.3	114.4	114.4	114.4	114.0	114.5	114.1	114.1	114.3
ArCHN	156.1	155.2	155.2	155.6	153.4	155.8	150.4	150.9	153.2	143.5	153.6
	8.31	8.21	8.20	8.16	8.59	8.13	8.56	8.61	8.39	8.08	8.85
1'	135.7	128.9	128.7	127.4	121.7	127.8	133.3	130.2	137.7	151.9	134.8
2'	128.5	131.4	131.5	131.7	158.6	112.7	135.1	149.9	123.3	---	134.8
	7.93	7.98	7.97	7.87	---	7.65	---	---	8.87	---	---
3'	128.6	114.7	115.2	116.2	116.9	147.8	130.5	125.6	148.7	118.1	130.0
	7.47	7.02	7.00	6.84	6.92	---	7.55	8.08	---	7.27	8.28
4'	131.3	162.6	161.9	161.4	133.7	151.3	133.7	132.6	125.8	113.5	131.4
	7.48	7.44	---	6.97	7.33	---	7.50	7.71	8.29	6.73	7.56
5'	128.6	114.7	115.2	116.2	119.9	115.9	127.9	134.3	130.6	147.5	131.4
	7.47	7.02	7.00	6.84	6.91	6.85	7.40	7.81	7.75	7.96	7.56
6'	128.5	131.4	131.5	131.7	129.4	125.2	129.5	130.4	135.5	---	130.0
	7.93	7.98	7.97	7.87	8.03	7.35	8.44	8,53	8.44	---	8.28

Spectroscopic analysis of the products thus obtained led us to establish that the respective monoimine was always formed. Diimines could not be obtained in any of the cases, in agreement with the results obtained by Rasshofer and Vogtle when using methanol as solvent [18], despite the fact that

reactions were carried out using a small excess of the corresponding aldehydes. This led us to carry out a series of experiments that allowed us to unequivocally establish that the chemoselectivity of these reactions was not affected by the experimental conditions employed. When the reaction was carried out using the “solvent-free” process, directly mixing the DAMN with the respective aryl aldehyde, the expected monoimines were also always obtained. The chemoselectivity of this reaction appears to have been governed by the structure of the monoimine itself, since all the attempts to prepare diimines carried out using the monoimines and benzaldehyde were unsuccessful, proving that Schiff base formation at one nitrogen deactivates the second one. This chemoselectivity was even more evident when *o*-phthalaldehyde (OPA) reacted with DAMN in water, to give diimine **2k** in a good yield, while no cyclic structures such as the corresponding phthalimidines [21] were obtained.

The signals of both the amino ($\delta \geq 8.20$ ppm) and ArCHN ($\delta \geq 8.30$ ppm) groups in the $^1\text{H-NMR}$ spectra (Table 2) were shifted to low field when the aromatic ring bore electron-withdrawing groups (Cl and NO_2). On the other hand, when an electron-releasing group (OH, OR) was involved, signals were observed at high field ($\delta \leq 7.90$ ppm). An unusual chemical shift value was observed for the ArCHN group of compound **2e**, in which although the ring bears an electron-releasing group (OH), the hydrogen nucleus was found to be deshielded, resonating at low field (δ 8.59 ppm). This difference was attributed to the presence of a hydrogen bond intramolecular interaction [14]. These experimental facts also accounted for the chemoselectivity of the reaction – the conjugation of the lone pair on the amino group with the conjugated system led to the partial charge density on nitrogen becoming delocalised, rendering it a soft nucleophile. Bearing in mind that aldehydes are considered to be hard electrophiles, the reactivity of the second amino group towards the aldehydes was very low, in turn explaining the absence of disubstitution.

Table 2. $^1\text{H-NMR}$ Chemical Shift Data of NH_2 and ArCHN for **2a-k**.

	2a	2b	2d	2e	2f	2g	2h	2i	2j	2k
ArCHN	8.31	8.21	8.16	8.59	8.13	8.56	8.61	8.39	8.08	8.85
NH ₂	7.94	7.77	7.76	7.86	7.72	8.19	8.27	8.27	7.77	7.77

This mesomeric effect results in a differentiation between both cyano groups in the $^1\text{H-NMR}$ and IR spectra. Based on the frequencies and the difference in intensity observed for the two signals close to the frequencies of the cyano groups (Table 3), we unequivocally assigned the two infrared frequencies corresponding to each cyano group.

Table 3 IR frequencies of cyano groups of **2a-k**.

	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k
CN1	2240	2231	2237	2247	2235	2231	2245	2247	2237	2237	2237
CN4	2205	2207	2197	2200	2206	2212	2203	2204	2200	2200	2200

In order to avoid using water as solvent, we then decided to carry out several experiments to establish a “solvent-free” methodology (*Procedure B*) and compare the yields obtained for some benzaldehydes when using water as solvent (*Procedure A*). Table 4 shows the yields obtained using each methodology. The explanation for the yield differences may reside in the hydrophobic activation

undergone by some organic reactions, produced by the tendency of organic compounds to associate in order to reduce interface area [22].

Table 4. Yields (%) obtained using procedures A and B.

Aldehyde	Product	Procedure A	Procedure B
Benzaldehyde	2a	78	49
<i>p</i> -Methoxybenzaldehyde	2b	93	62
3-Ethoxy-4-hydroxybenzaldehyde	2f	53	38
<i>o</i> -Chlorobenzaldehyde	2g	79	14
<i>o</i> -Nitrobenzaldehyde	2h	76	12

Conclusions

In summary, to the best of our knowledge, the use of water in reactions involving DAMN as reagent has been little explored. A literature search revealed only one example, in which an unsuccessful attempt was made to condense DAMN with glyoxal to obtain pyrazines [23]. This is the first example of the formation of Schiff bases via the condensation of DAMN with aromatic aldehydes in water, without the use of catalysts. It would be worthwhile to explore the use of water at the subcritical temperature [24], a method known to be highly advantageous and environmentally friendly. The complete assignment of the ^1H and ^{13}C -NMR spectral data for this important type of compounds is also reported herein for the first time.

Experimental

General

DAMN was obtained from Aldrich and used without further purification. The aromatic aldehydes: benzaldehyde, anisaldehyde, *p*-ethoxybenzaldehyde, *p*-hydroxybenzaldehyde, *o*-salicylaldehyde, 3-ethoxy-4-hydroxybenzaldehyde, *o*-chlorobenzaldehyde, *o*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, furfuraldehyde and *o*-phthalaldehyde were obtained from Merck. The reactions were carried out in distilled water or by mixing the reagents directly from the bottle without a solvent. Infrared spectra (KBr disks) were recorded on a Perkin-Elmer Paragon FT-IR instrument. NMR spectra were recorded in DMSO- d_6 at room temperature on a Bruker AMX 400 Avance operating at 400 (^1H) and 100 MHz (^{13}C), respectively. Melting points were taken with an Electrothermal apparatus and are uncorrected. HR-EIMS and HR-FABMS were taken on a Micromass model Autospec (70 eV) spectrometer.

General procedures for the synthesis of imines **2a-k**

Procedure A (with solvent): Under vigorous stirring DAMN (0.34 mmol) was suspended in water (5 mL) and the respective aldehyde **1a-j** (0.34 mmol; 0.17 mmol for **1k**) was slowly added. Stirring was continued for 2-3 h at room temperature until a precipitate appeared. The solid was filtered off, washed

with water and dried under reduced pressure in an Abderhalden drying apparatus and, when necessary, recrystallised from methanol.

Procedure B (solvent-free): In the case of liquid aryl aldehydes, DAMN (x mmol) was added slowly with constant stirring to the corresponding aldehyde (0.25 mL, *i.e.* for benzaldehyde 0.261 g, 2.46 mmol were used) and the reaction flask was maintained at 60 °C using a water bath. A homogeneous solution was formed after 5 min, and after another 10 min a solid began to precipitate. After 5 min at 60 °C, the solid was filtered and the crude product was washed with water and then with ethanol. The solid thus obtained was dried under reduced pressure in an Abderhalden drying apparatus and, if necessary, recrystallised from a suitable solvent, usually methanol. For solid aldehydes, DAMN (52 mg, 0.50 mmol) was thoroughly mixed with the respective aldehyde (0.50 mmol) and the reaction mixture was stirred and gently heated to 80 °C. After 10 min, the viscous liquids thus obtained were allowed to stand overnight, whereupon the reaction mixtures solidified. The crude products obtained were washed with hot ethanol and recrystallised from methanol. The products, unless otherwise noted, were yellow solids.

(2Z)-2-Amino-3-[[*(1E)*-(phenyl)methylene]-amino]but-2-enedinitrile (**2a**). Yield: 78%; mp 193.6–194.8°C (from methanol, lit. [3,12]: 206–208°C, 191°C); IR: $\nu_{\max}/\text{cm}^{-1}$: 3419, 3302, 3162, 2240, 2205, 700; $^1\text{H-NMR}$: δ 8.31 (s, 1H), 7.94 (broad s, 2H), 7.93 (d, $J = 7.9$ Hz, 2H), 7.48 (m, 1H), 7.47 (m, 2H); $^{13}\text{C-NMR}$: δ 156.1, 135.7, 131.3, 128.6, 128.5, 126.9, 113.7, 112.9, 103.9. The spectral data were consistent with literature values [3].

(2Z)-2-Amino-3-[[*(1E)*-(4-methoxyphenyl)methylene]-amino]but-2-enedinitrile (**2b**). Yield: 93.3%; mp 231.5–231.8°C (from methanol, lit. [18] 227°C); IR: $\nu_{\max}/\text{cm}^{-1}$: 3462, 3419, 3309, 3172, 2231, 2207; $^1\text{H-NMR}$: δ 8.21 (s, 1H), 7.98 (d, $J = 8.8$ Hz, 2H), 7.77 (broad s, 2H), 7.02 (d, $J = 8.8$ Hz, 2H), 3.83 (s, 3H); $^{13}\text{C-NMR}$: δ 162.6, 155.2, 131.4, 128.9, 126.3, 115.1, 114.7, 114.3, 103.6, 55.9.

(2Z)-2-Amino-3-[[*(1E)*-(4-ethoxyphenyl)methylene]-amino]but-2-enedinitrile (**2c**). Yield: 84%; mp 223.2–224.0°C (from methanol); IR: $\nu_{\max}/\text{cm}^{-1}$: 3421, 3307, 3160, 2237, 2197, 1254; $^1\text{H-NMR}$: δ 8.20 (s, 1H), 7.97 (d, $J = 8.0$ Hz, 2H), 7.76 (broad s, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 4.10 (q, $J = 7.0$ Hz, 2H), 1.38 (t, $J = 7.0$ Hz, 3H); $^{13}\text{C-NMR}$: δ 161.9, 155.2, 131.5, 128.7, 126.3, 115.2, 115.1, 114.3, 103.6, 63.9, 15.0; HRFABMS (%) 240.1007 [M^+] (calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}$, 240.1011) (36), 219 (6), 154 (100), 137 (61), 136 (60), 124 (9), 120 (10), 107 (19); Anal. calc. for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}$: C, 65.03; H, 5.04; N, 23.33. Found: C, 65.06; H, 4.99; N, 23.13.

(2Z)-2-Amino-3-[[*(1E)*-(4-hydroxyphenyl)methylene]-amino]but-2-enedinitrile (**2d**). Yield: 55%; mp 213.2–213.9°C (from methanol, lit. [11] 222.5–223.0°C); IR: $\nu_{\max}/\text{cm}^{-1}$: 3554, 3482, 3421, 3304, 3160, 2247, 2200, 1249; $^1\text{H-NMR}$: δ 10.20 (broad s, 1H), 8.16 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 2H), 7.76 (broad s, 2H), 6.84 (d, $J = 8.5$ Hz, 2H); $^{13}\text{C-NMR}$: δ 161.4, 155.6, 131.7, 127.4, 125.9, 116.2, 115.2, 114.4, 103.9.

(2Z)-2-Amino-3-[[*(1E)*-(2-hydroxyphenyl)methylene]-amino]but-2-enedinitrile (**2e**). Yield: 49.2%; mp 242.0–244.0°C (from ethanol, lit. [19] 234.0°C); IR: $\nu_{\max}/\text{cm}^{-1}$: 3554, 3418, 3309, 3195, 2235, 2206; $^1\text{H-NMR}$: δ 10.50 (broad s, 1H), 8.59 (s, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 7.86 (broad s, 2H), 7.33 (t, $J = 7.9$ Hz, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 6.91 (t, $J = 7.9$ Hz, 1H); $^{13}\text{C-NMR}$: δ 158.6, 153.4, 133.7, 129.4, 126.5, 121.7, 119.9, 116.9, 115.0, 114.4, 103.9.

(2Z)-2-Amino-3-[[*(1E)*-(3-ethoxy-4-hydroxyphenyl)methylene]-amino]but-2-enedinitrile (**2f**). Yield: 53%; mp 209.0–210.0°C (from methanol); IR: $\nu_{\max}/\text{cm}^{-1}$: 3461, 3333, 2231, 2212, 1613, 1275; $^1\text{H-NMR}$: δ 9.70 (broad s, OH), 8.13 (s, 1H), 7.72 (broad s, 2H), 7.65 (d, $J = 1.6$ Hz, 1H), 7.35 (dd, $J = 1.6, 8.2$ Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 1H), 4.10 (q, $J = 9.0$ Hz, 2H), 1.36 (t, $J = 9.0$ Hz, 3H); $^{13}\text{C-NMR}$: δ 155.8, 151.3, 147.8, 127.8, 125.8, 125.2, 115.9, 115.2, 114.4, 112.7, 103.9, 64.4, 15.3; HRFABMS (%) 256.0947 [M^+] (calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_2$, 256.0960) (21), 219 (5), 165 (5), 154 (100), 138 (31), 136 (61), 120 (10), 107 (18).

(2Z)-2-Amino-3-[[*(1E)*-(2-chlorophenyl)methylene]amino]but-2-enedinitrile (**2g**). Yield: 79%; mp 201.4–202.4°C (from ethanol, lit. [7] 222.0–223.0°C); IR: $\nu_{\max}/\text{cm}^{-1}$: 3421, 3209, 3198, 2245, 2203, 1617, consistent with literature values [7]; $^1\text{H-NMR}$: δ 8.56 (s, 1H), 8.44 (dd, $J = 1.3, 7.9$ Hz, 1H), 8.19 (broad s, 2H), 7.55 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.50 (dt, $J = 1.6, 8.0$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H); $^{13}\text{C-NMR}$: δ 150.4, 135.1, 133.7, 133.3, 130.5, 129.5, 128.4, 127.9, 114.6, 114.0, 103.0.

(2Z)-2-Amino-3-[[*(1E)*-(2-nitrophenyl)methylene]amino]but-2-enedinitrile (**2h**). Yield: 76%; mp 224.0–225.0°C (from ethanol); IR: $\nu_{\max}/\text{cm}^{-1}$: 3420, 3298, 3200, 2247, 2204, 1616, 1574, 1521; $^1\text{H-NMR}$: δ 8.61 (s, 1H), 8.53 (d, $J = 7.9$ Hz, 1H), 8.27 (broad s, 2H), 8.08 (d, $J = 8.1$ Hz, 1H), 7.81 (t, $J = 7.5$ Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H); $^{13}\text{C-NMR}$: δ 150.9, 149.9, 134.3, 132.6, 130.4, 130.2, 129.4, 125.6, 114.9, 114.5, 103.0; HRFABMS (%) 242.0691 [$\text{M}+1$] $^+$ (calcd. for $\text{C}_{11}\text{H}_8\text{N}_5\text{O}_2$, 242.0678) (7), 219 (5), 166 (4), 154 (100), 138 (32), 136 (61), 124 (8), 120 (11), 107 (15).

(2Z)-2-Amino-3-[[*(1E)*-(3-nitrophenyl)methylene]-amino]but-2-enedinitrile (**2i**). Yield: 80%; mp 158.0–159.0°C (from methanol); IR: $\nu_{\max}/\text{cm}^{-1}$: 3465, 3425, 3348, 3294, 2237, 2200s, 1613, 1523, 1355; $^1\text{H-NMR}$: δ 8.87 (d, $J = 1.5$ Hz, 1H), 8.44 (d, $J = 7.9$ Hz, 1H), 8.39 (s, 1H), 8.29 (d, $J = 7.8$ Hz, 1H), 8.27 (broad s, 2H), 7.75 (t, $J = 7.8$ Hz, 1H); $^{13}\text{C-NMR}$: δ 153.2, 148.7, 137.7, 135.5, 130.6, 128.6, 125.8, 123.3, 114.6, 114.1, 102.0; HRFABMS (%) 241.0592 [M^+] (calcd. for $\text{C}_{11}\text{H}_7\text{N}_5\text{O}_2$, 241.0600) (3), 219 (5), 166 (4), 154 (100), 139 (12), 136 (64), 120 (11), 107 (19).

(2Z)-2-Amino-3-[[*(1E)*-(furfurylidyl)methylene]-amino]but-2-enedinitrile (**2j**). Yield: 96%; mp 158.0–159.0°C (from methanol); IR: $\nu_{\max}/\text{cm}^{-1}$: 3465, 3425, 3348, 3294, 2237, 2200, 1613; $^1\text{H-NMR}$: δ 8.08 (s, 1H), 7.96 (d, $J = 1.4$ Hz, 1H), 7.77 (broad s, 2H), 7.27 (d, $J = 3.5$ Hz, 1H), 6.73 (dd, $J = 1.5, 3.5$ Hz, 1H); $^{13}\text{C-NMR}$: δ 151.9, 147.5, 143.5, 126.7, 118.1, 114.9, 114.1, 113.5, 103.7.

(2Z)-2-amino-3-([*(1E)*]-[2-((*E*)-[[*(Z)*]-2-amino-1,2--dicyanovinyl]imino)methyl)phenylmethylene]-amino]but-2-enedinitrile (**2k**). A brown solid, yield: 83%; mp 158.0–159.0°C (from methanol); IR: $\nu_{\max}/\text{cm}^{-1}$: 3465, 3425, 3348, 3294, 2237, 2200, 1613; $^1\text{H-NMR}$: δ 8.85 (s, 1H), 8.28 (dd, $J = 3.4, 5.8$

Hz, 1H), 7.77 (broad s, 2H), 7.56 (dd, $J = 3.4, 5.8$ Hz, 1H); ^{13}C -NMR: δ 153.6, 134.8, 131.4, 130.0, 127.7, 114.8, 114.3, 103.7. HREIMS (%) 314.0998 [M^+] (calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_8$, 314.1028) (26), 222 (20), 206 (100), 181 (24); Anal. calc. for $\text{C}_{16}\text{H}_{10}\text{N}_8$: C, 61.14; H, 3.21; N, 35.65. Found: C, 61.18; H, 3.19; N, 35.63.

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Sample Availability: Samples of the compounds **2c** and **2k** are available from the authors.