Reaction of 2,3-Dichloro-5,6-dicyanopyrazine with Enamines and Some Tertiary Amines

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The reaction of 2,3-dichloro-5,6-dicyanopyrazine (**1**) with enamines as well as a few tertiary amines as enamine precursors was investigated. Both reactions gave aminovinyl-substituted pyrazine derivatives. During the attempted purification of **3c** or **3d** by column chromatography on silica gel, 2-chloro-5,6-dicyano-3-(1′-oxocyclopent-2′-yl)pyrazine (**4**) was obtained, apparently by hydrolytic cleavage. The products prepared are all of interest as potential pesticides.

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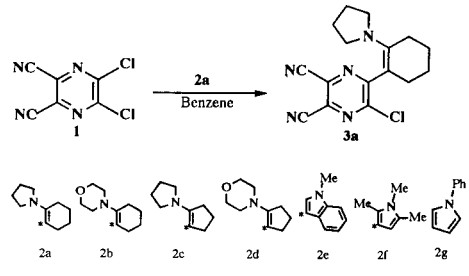
Treatment of 2,3-dichloro-5,6-dicyanopyrazine (**1**) with triethylamine afforded 3-chloro-5,6-dicyano-2-(2′-diethylaminoethenyl)pyrazine in 22% yield, and preliminary testing indicated that this compound has biological activity for controlling certain plant diseases [1]. Herbicidal properties of a series of 2,3-dicyanopyrazines have been studied by Nakamura and co-workers [2,3]. Recently Hodogaya patented the usefulness of diaminodicyanopyrazine derivatives as agricultural fungicides [4]. Compound **1** is available commerically [5], and we wished to explore new products of this class and to improve the yield of the reaction. With respect to the reaction mechanism, it has been reported that the reaction of chloranil with triethylamine gave the corresponding vinylamino product. In this case, triethylamine could be oxidized to diethylvinylamine by chloranil, and the reactive enamine should react with chloranil to give the vinylamino product [6]. In our case, **1** could be an oxidant also. In order to further clarify this mechanism and to improve the yield of this reaction, we selected some commercially available enamines and their parent amines, and investigated the reactivity of **1** with them.

Reaction of **1** with enamines **2** was easily realized, and the desired products **3** were obtained in good yields. The results are summarized in Scheme 1 and Table 1. Compound **1** reacted with (azacyclopent-1′-yl)-1-cyclohexene (**2a**) or (4′-oxyazacyclohepten-1′-yl)-1-cyclohexene (**2b**) to give the desired vinylamino products **3a** in 94% yield or **3b** in 53% yield, respectively (Runs 1 and 2, Table 1). On the other hand, reaction of **1** with (azacyclopent-1′-yl)-1-cyclopentene (**2c**) and (4′-oxyazacyclohepten-1′-yl)-1-cyclopentene (**2d**) gave the vinylamino products **3c** and **3d**, but these two products were unstable and upon attemped isolation by column chromatography on silica gel, hydrolysis of the products occurred in both cases to give the same ketone, 2-chloro-5,6-dicyano-3-(1′-oxocyclopent-2′-yl)pyrazine (**4**) in yields of 61% from **3c** and 57% from **3d** (Runs 3 and 4). We believe that this hydrolysis proceeds in reverse to the formation of enamines from ketones and amines [7]. The easier hydrolysis of the cyclopentenes **3c** or **3d** to give **4** upon column chromatography (Scheme 2) may be due to higher ring strain and easier access of the hydroxide.

Scheme 1



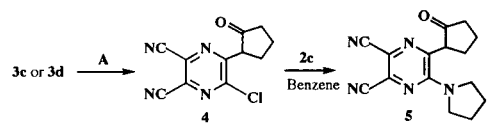
* Substitution position in 3.

Table 1
Reaction of **1** or **4** with Enamines [a]

Run	Reactant	Reagent	Time (hours)	Product	Yield (%)
1	**1**	**2a**	0.1	**3a**	95
2	**1**	**2b**	19	**3b**	53
3	**1**	**2c**	0.1	**4**	61
4	**1**	**2d**	0.1	**4**	57
5	**1**	**2e**	3	**3e**	64
6	**1**	**2f**	36	**3f**	81
7	**1**	**2g**	48	**3g**	0 [b]
8	**4**	**2c**	24	**5**	75

[a] A mixture of **1**or **4** (5 mmoles) and enamine (10 mmoles) in benzene (200 ml) was stirred at room temperature (Runs 1, 2, 3, 4 and 8) or under reflux (Runs 5, 6 and 7). [b] No reaction.

Scheme 2



A : Column chromatography on silica using chloroform as eluent.

Table 2
Spectral Data for **3a**, **3b**, **3e**, **3f**, **4** and **5**

Compound	ir/cm $^{-1}$ [a]	uv [b] λ max (log ε)	PMR (δ in ppm) [c]	MS (m/z, relative intensity %)
3a	2225.5 (CN) 2240.9 (CN)	376 (3.49) 327 (3.68) 277 (4.49)	4.31-4.26 (t, 2H), 3.61-3.57 (t, 2H), 2.94-2.89 (t, 2H), 2.86-2.82 (t, 2H), 2.10-1.76 (m, 8H).	315 (36, $[M+2]^+$), 313 (100, M^+), 278 (56), 236 (61), 195 (43)
3b	2229.3 (CN) 2235.1 (CN)	375 (3.44) 327 (3.53) 277 (4.49)	4.47-4.43 (t, 2H), 3.86-3.82 (t, 2H), 3.66-3.60 (t, 2H), 3.56-3.50 (t, 2H), 3.03-2.98 (t, 2H), 2.95-2.80 (t, 2H), 2.07-1.98 (m, 2H), 1.95.1.86 (m, 2H)	331 (32, $[M+2]^+$), 329 (100, M^+), 250 (8), 236 (36), 195 (17), 181 (10), 65 (7)
3e	2233.2 (CN)	413	8.95 (s, 1H), 8.43-8,39 (m, 1H) 7. 68-7.64 (m, 1H), 7.40-7.36 (m, 2H), 3.99 (s, 3H),	295 (32, $[M+2]^+$), 293 (100, M^+), 258 (8), 217 (27), 156 (95), 128 (13), 114 (21), 102 (12), 76 (21), 57 (17), 43 (20)
3f	2231.2 (CN)	407 (4.06) 343 (4.12)	6.65 (s, 1H), 3.50 (s, 3H), 2. 50 (s, 3H), 2.28 (s, 3H)	273 (25, $[M+2]^+$), 271 (73, M^+), 270 (75). 256(32). 236 (24). 133 (61) 108 (100), 76 (36)), 56 (29)
4	2248.6 (CN) 1729.8 (C=O)	312	4.25-4.17 (t, 1H), 2.62-1.98 (m, 6H)	248 (7, $[M+2]^+$), 246 (20, M^+), 233 (6), 231(18), 193 (9), 191 (26), 183 (11), 155 (15), 82 (22), 76, (13), 55 (100)
5	2225.5(CN) 1751.5 (C=O)	317, 363	3.93-3.86 (t, 1H), 3.83-3.76 (m, 2H) 3.68-3.59 (m, 2H), 2.56-2.22 (m, 5H) 209-1.89 (m, 5H)	281 (100, M^+), 264 (30), 253 (17), 238 (24). 226 (76). 224 (46). 210 (22), 196 (32), 182 (29), 169 (13), 142 (10), 129 (6), 103 (8)

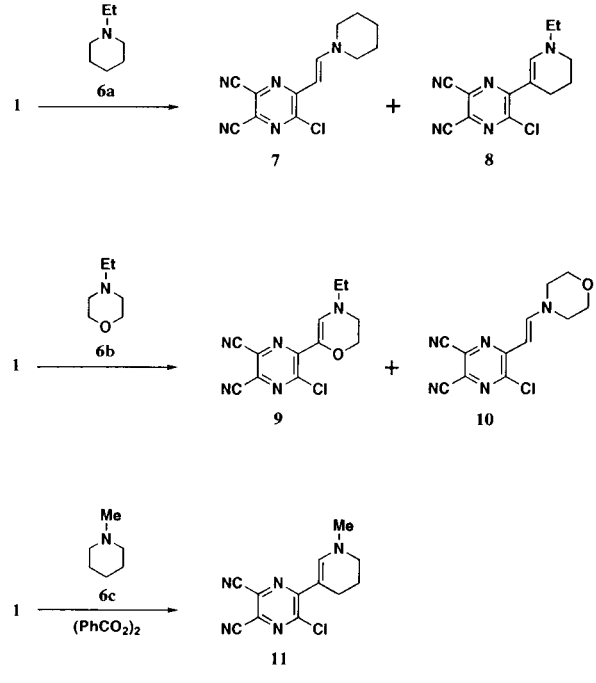
[a] On potassium bromide pellets. [b] In chloroform. [c] In chloroform-*d* with reference to TMS

In order to extend the scope of the reaction and to evaluate the reactivity of **1**, *N*-methylindole (**2e**), 1,2,5-trimethylpyrrole (**2f**) and *N*-phenylpyrrole (**2g**) were used as enamine equivalents. Reaction of **1** with **2e** or **2f** afforded the desired products **3e** or **3f** in good yield (Runs 5 and 6). However, reaction conditions were more severe than with the enamines (Runs 1-4), and zinc chloride had to be added as the catalyst to improve the yield. The reaction of **1** with **2g** did not afford **3g**, even in the presence of zinc chloride (Run 7). The reason for this failure may be the low electron density of **2g** in the "enamine" moiety. Further reaction of **4** with (azacyclopent-1′-yl)-1-cyclopentene (**2c**) gave unexpectedly 2-(azacyclopent-1′-yl)-5,6-dicyano-3-(1″-oxocyclopent-2″-yl)pyrazine (**5**) in 75% yield (Run 8). The mechanism for the formation of **5** has not been elucidated as yet, but nucleophilic substitution by pyrrolidine liberated by hydrolysis of **2c** is likely to occur. Another enamine substitution on **4** may be prevented by steric hindrance. The spectral data necessary for the identification of the products are summarized in Table 2.

The structures of the products are based upon pmr, ir and mass spectral data as well as microanalyses. Stretching vibrations of cyano groups for all of the products **3-5** were observed appearing as strong absorption bands between 2225 and 2240 cm^{-1}. In general, owing to the asymmetry of 2-substituted-3-chloro-5,6-dicyanopyrazines, characteristic stretching vibrations of two cyano groups should be seen. However, two different absorption were observed only in the cases of **3a** and **3b** (see Table 2). While a single peak appeared in other cases. The pmr and mass spectral data as well as elemental analyses are all in agreement with the structures described.

Reactions of **1** with the tertiary amine **6** as enamine precursors are summarized in Scheme 3 and Table 3. Reaction of **1** with *N*-ethylpiperidine (**6a**) or *N*-ethylmorpholine (**6b**) in DMF afforded a mixture of two products, that is, 3-chloro-5,6-dicyano-2-(1′-ethyl-1′-aza-2′-cyclohexen-3′-yl)-pyrazine (**7**), and 2-[2′-(azacyclohex-1″-yl)ethenyl]-3-chloro-5,6-dicyanopyrazine (**8**), or 3-chloro-5,6-dicyano-2-(1′-ethyl-

Scheme 3



1'-aza-4'-oxy-2'-cyclohexen-3'-yl)pyrazine (**9**), and 3-chloro-5,6-dicyano-2-[2'-(4''-oxy-1''-azacyclohex-1''-yl)ethenyl]-pyrazine (**10**) in very low yields of less than 6% (Runs 9 and 10). The reaction is thought proceed *via* the reactive vinylamine which could be generated from the amine by oxidation. Compound **1** could be an oxidant in this reaction [1], and addition of other oxidants improve the yield of the product considerably. Reaction of **1** with *N*-methylpiperidine (**6c**) in benzene was carried out in the presence of benzoyl peroxide as an oxidant. The yield was greatly improved to afford **11** in 51% yield (Run 10). The spectral data for **7-11** are summarized in Table 4.

The structural assignments for **7-11** were established on the basis of spectral data as well as microanalysis. From the ir spectra of **7-11**, stretching vibrations of cyano groups for all of the products were observed between 2213 and 2223 cm^{-1} as sharp single peaks.

In the cases of **7** and **8**, pmr spectra showed two sets of signals corresponding to two conformers (Figure 1). Chemical shifts of H-C(2') of the two conformers of **7** appear as singlet at 8.42 and 8.30 ppm, respectively. The H-C(6') also appear as two triplets with devised shifts of 2.65-2.70 ppm and 2.57-2.62 ppm, respectively. Chemical shifts of H-C(1') and H-C(2') for one conformer appeared as doublets in the range of 5.54-5.59 ppm (J = 12.2 Hz) and 8.02-8.06 ppm (J = 12.2 Hz), and those of another conformer appeared as doublets in the range of 5.48-5.52 ppm (J = 11.6 Hz) and 8.00-8.05 ppm (J = 11.6 Hz), respectively. From the results of the coupling constants of the ethylene protons (J > 11 Hz), **8** should exist in form of the *trans*-configuration and consequently, two conformers were proposed as indicated in Figure 1.

Table 3
Reaction of **1** with Tertiary Amine(**6**) as enamine precursor [a]

Run	Reactant	Reagent	Time (h)	Product (yield %)
9	**1**	**6a**	24	**7** (6) **8** (3)
10	**1**	**6b**	60	**9** (3) **10** (2)
11 [b]	**1**	**6c**	15	**11** (51)

[a] A mixture of **1** (5 mmoles) and enamine (**6**) (10 mmoles) in DMF (30 ml) was stirred at room room temperature. [b] Benzoyl peroxide (5 mmoles) was added.

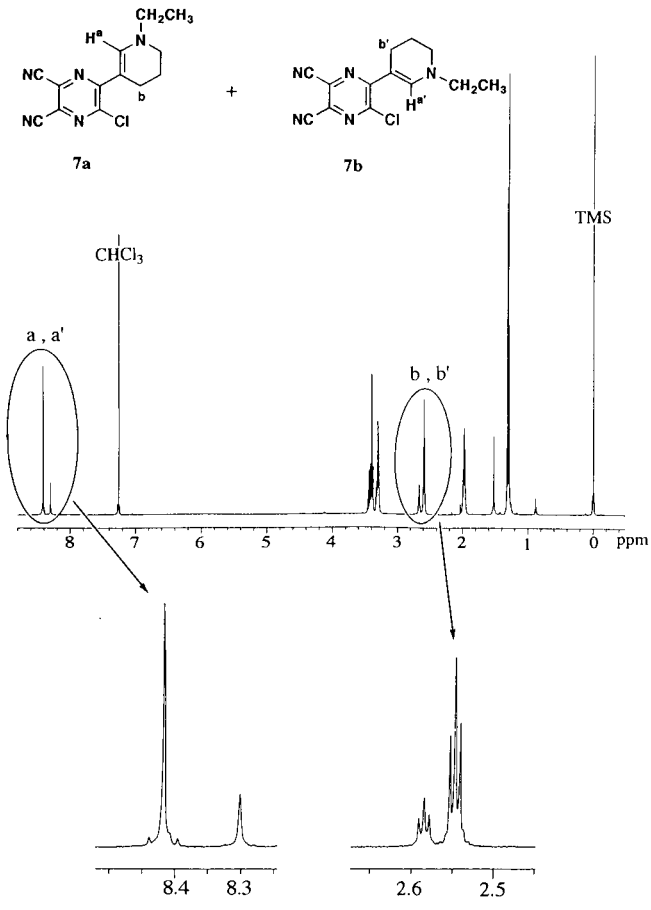


Figure 1. ^{1}H-NMR (500 MHz) spectra of two conformers for **7**.

Table 4
Spectral Data for **7-11**

Compound	ir/cm^{-1} [a]	uv [b] λ max (log ε)	pmr (δ in ppm) [c]	ms (m/z, relative intensity %)
7	2221 (CN)	429	8.31-8.24 [(s + s), 1H), 3.28-3.49 (m, 2H), 2.56-2.70 ((t + t), 2H), 1.93-2.17 (m, 2H), 1.27-1.34 ((t + t), 3H)	275 (26, $[M+2]^+$), 273 (83, M^+), 258 (100), 217 (8)
8	2223 (CN)	425	8.00-8.06 ((d + d), 1H); 5.48-5.59 ((d + d), 1H), 3.55 (s, 2H), 3.48 (s, 2H), 1.75 (s, 6H)	275 (6), $[M+2]^+$), 273 (15, M^+), 238 (22), 110 (21), 83 (100)
9	2213 (CN)	458	7.90 (s, 1H), 4.19-4.15 (t, 2H), 3.48-3.38 (m, 4H), 1.35-1.29 (t, 3H)	277 (6, $[M+2]^+$), 275 (17, M^+), 260 (29), 149 (32), 112 (49), 51 (100)
10	2223 (CN)	407	8.04-8.00 (d, J =12.82, 1H), 5.65-5.60 (d, J = 12.82, 1H), 3.85-3.81 (t, 4H); 3.55 (s, 4H)	277 (32, $[M+2]^+$), 275 (100, M^+), 240 (83), 218 (51), 182 (68), 155 (29), 129 (12), 85 (39)
11	2221 (CN)	432 (4.61)	8.37 (s, 1H), 3.32-3.27 (t, 2H), 3.21 (s, 3H), 2.60-2.55 (t, 2H), 2.05-1.94 (m, 2H)	261 (41, $[M+2]^+$), 259 (100, M^+), 215 (11), 196 (5), 96 (62), 81 (80), 57 (15), 42 (79)

[a] In potassium bromide pellet. [b] In chloroform . [c] In chloroform-*d* with reference to TMS.

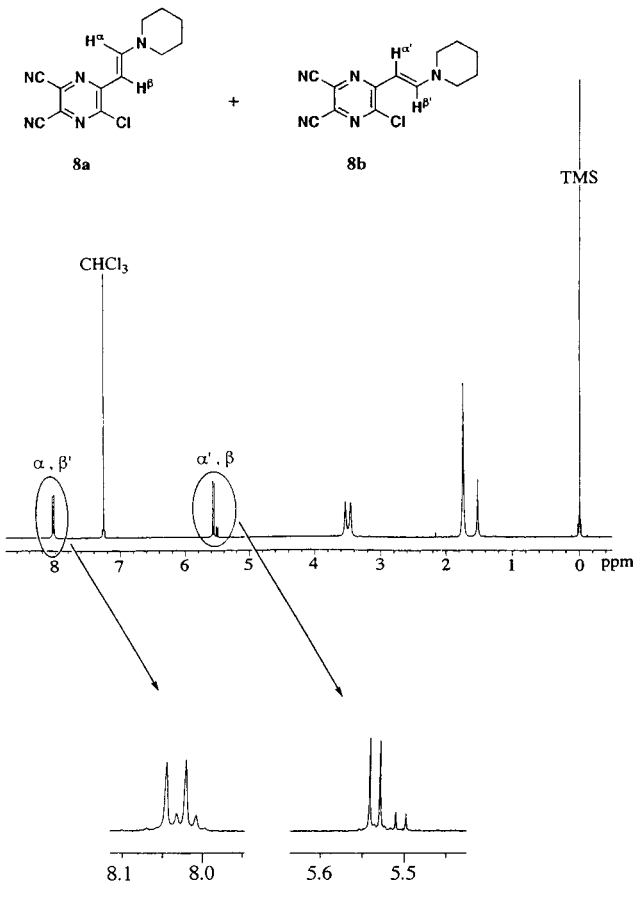


Figure 2. ^{1}H-NMR (500 MHz) spectra of two conformers for **8**.

Table 5
Analytical Data for all of the compounds prepared

Compound	Formula	mp (°C)	Calcd./Found(%) C	H	N
3a	$C_{16}H_{16}N_5Cl$	186-187	61.24	5.14	22.32
			61.44	5.05	22.50
3b	$C_{16}H_{16}N_5ClO$	127-129	58.27	4.89	21.42
			57.97	4.74	21.13
3c	$C_{15}H_8N_5Cl$	340-342	61.34	2.75	23.84
			61.15	2.40	23.88
3f	$C_{13}H_{10}N_5Cl$	213-214	57.47	3.71	25.78
			57.59	3.45	26.16
4	$C_{11}H_7N_4ClO$	119-121	53.56	2.86	22.71
			54.16	2.38	23.55
5	$C_{15}H_{15}N_5O$	155-156	64.04	5.37	24.89
			63.76	5.21	24.97
7	$C_{13}H_{12}N_5Cl$	128-129	57.04	4.42	25.59
			57.13	4.27	25.95
8	$C_{13}H_{12}N_5Cl$	163-167	57.04	4.42	25.59
			57.54	4.38	25.61
9	$C_{12}H_{10}N_5ClO$	151-153	52.28	3.66	25.40
			52.64	3.53	25.88
10	$C_{12}H_{10}N_5ClO$	209-210	52.28	3.66	25.40
			52.63	3.89	25.78
11	$C_{12}H_{10}N_5Cl$	158-160	55.50	3.88	26.97
			55.31	3.58	26.64

In the cases of **9** and **10**, only one conformer was observed. The signal for the H-C(2') of **9** appeared as a singlet at 7.90 ppm, and the resonances for the two N-CH_2 overlapped at 3.38-3.48 ppm while the O-CH_2 appeared as a triplet at 4.17 ppm. In case of **10**, H-C(1') and H-C(2') as an AB system were split into a doublet appearing in the range 5.60-5.65 ppm (J = 12.8 Hz) and 8.04-8.00 ppm (J = 12.8 Hz), respectively. According to this coupling constant, **10** should also exist in *trans*-configuration. The two N-CH_2 appeared as a triplet at 3.83 ppm. Splitting of the O-CH_2 into a triplet was not observed. In the case of **11**, the resonances of H-C(2') and N-CH_3) appeared as singlets at 8.37 and 3.21 ppm, respectively. Those of the N-CH_2 appeared as a triplet at 3.29 ppm. The signals for H-C(4') and H-C(5') overlapped at the range of 1.94-2.05 ppm. All of the spectral data as well as elemental analyses for **7-11** are in agreement with the structures depicted. The structural data and elemental analyses for all of the products prepared are summarized in Table 5.

In conclusion, the reaction of **1** with enamines or their aromatic analogues afforded the vinylamino products. In the case of aminocyclopentene as reagent, the initially formed enamino products were unstable, and were hydrolyzed to 2-chloro-5,6-dicyano-3-(1'-oxocyclopent-2'-yl)pyrazine (**4**) in the course of further purification by chromatography on silica gel. The biological activities of these new products will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-500D apparatus without correction. The ir spectra were recorded with Shimazu IR-420 and Horiba FT-200 spectrophotometers. The pmr spectra were taken on JOEL JNM-GX (270 MHz) and JOEL ALPHA-500 (500 MHz) spectrometers. The ms spectra were recorded on Shimazu LKB-9000 and Finnigan MAT TSQ-70 spectrometers. The visible spectra were measured on Shimazu UV-265FS and UV-3100 spectrophotometers. Microanalysis was conducted with a Yanaco CHN MT-3 recorder.

2-[2'-(Azacyclopent-1''-yl)-1'-cyclohexen-1'-yl]-3-chloro-5,6-dicyano-pyrazine (**3a**), 2-[2'-(4''-Oxy-1''-azacyclohex-1''-yl)-1'-cyclohexen-1'-yl]-3-chloro-5,6-dicyano pyrazine (**3b**) and 2-Chloro-5,6-dicyano-3-(1'-oxocyclopent-2'-yl)pyrazine (**4**).

To **1** (1.0 g, 5 mmoles) in benzene (200 ml) was added dropwise **2a-d** (10 mmoles), and then the mixture was stirred at room temperature until all of **1** disappeared by tlc (see Table 1 for reaction time). The precipitate formed was removed by filtration. The filtrate was evaporated to dryness. The residues were recrystallized from ethyl acetate for **3a** or ethyl acetate/*n*-hexane for **3b**, respectively. The separation of products **3c** and **3d** by column chromatography on silica gel using chloroform as eluent gave **4**.

3-Chloro-5,6-dicyano-2-(*N*-methylindol-3'-yl)pyrazine (**3e**) and 3-Chloro-5,6-dicyano-2-(1',2',5'-trimethylpyrrol-3'-yl)pyrazine (**3f**).

To **1** (1.0 g, 5 mmoles) and zinc chloride (5 mmoles) in benzene (200 ml) was added dropwise **2e** or **2f** (10 mmoles), and then the

mixture was heated under reflux until all of **1** disappeared by tlc. The precipitate formed was removed by filtration. The filtrate was evaporated to dryness. The residues were recrystallized from chloroform for **3e** or ethyl acetate/*n*-hexane for **3f**.

2-(Azacyclopent-1′-yl)-5,6-dicyano-3-(1″-oxocyclopent-2″-yl)pyrazine (**5**).

To **4** (2 mmoles) in benzene (50 ml) was added dropwise **2c** (4 mmoles), and then the mixture was stirred at room temperature until all of **4** completely disappeared by tlc. The precipitate formed was removed by filtration. The filtrate was evaporated to dryness to give **5** as pale yellow solids in 75% yield.

3-Chloro-5,6-dicyano-2-(1′-ethyl-1′-aza-2′-cyclohexen-3′-yl)pyrazine (**7**), 2-[2′-(Azacyclohex-1″-yl)ethenyl)]-3-chloro-5,6-dicyanopyrazine (**8**), 3-Chloro-5,6-dicyano-2-(1′-ethyl-1′-aza-4′-oxo-2′-cyclohexen-3′-yl)pyrazine (**9**), and 3-Chloro-5,6-dicyano-2-[2′-(4″-oxy-1″-azacyclohex-1″-yl)ethenyl]pyrazine (**10**).

To **1** (1.5 g, 7.5 mmoles) dissolved in DMF (30 ml) was added dropwise **6a-b** (15 mmoles) at room temperature, and then the mixture was stirred at room temperature until all of **1** completely disappeared by tlc. The salt formed was filtered out, and the filtrate was evaporated to dryness. The product was separated by column chromatography on silica gel. On recrystallization from acetone/*n*-hexane, **7-10** were obtained, respectively.

3-Chloro-5,6-dicyano-2-(1′-methyl-1′-aza-2′-cyclohexen-3′-yl)pyrazine (**11**).

To **1** (1.0 g, 5 mmoles) in benzene (200 ml) in the presence of benzoyl peroxide (1.37 g, 5 mmoles) was added dropwise **6c** (15 mmoles), and then the mixture was stirred at room temperature until all of **1** disappeared. The precipitate formed was removed by filtration. The filtrate was evaporated to dryness. The residues were recrystallized from ethyl acetate to give **11** in 51% yield.

Acknowledgement.

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