Regioselective Synthesis of 2(1*H*)-Pyridinones from *β*-Aminoenones and Malononitrile. Reaction Mechanism

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Received July 13, 1999

The identification of some intermediates of the reactions between *β*-aminoenones and malononitrile to give 2(1*H*)-pyridinones has allowed us to obtain valuable information concerning its mechanism. These reactions begin with a conjugated addition of the nitrile to the enone followed by elimination. The compounds thus obtained cyclize to nonisolable 2*H*-pyran-2-imine. This afforded 2(1*H*)-pyridinones by ring opening to unsaturated aminoamides followed by cyclization (Dimroth-type rearrangement).

Introduction

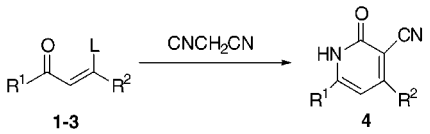
The reactions of *β*-dicarbonyl compounds or *β*-functionalized α,*β*-unsaturated ketones with malononitrile and related compounds have been described as a synthetic method of 2(1*H*)-pyridinones.[1−9] While the reaction mechanism with cyanacetamide seems to be firmly established,[9−13] the process by which malononitrile acts as a nucleophilic agent has been interpreted in according to different hypothetical mechanisms.[3,5,7,14−17]

In this paper, we have investigated the reaction pathway to 2(1*H*)-pyridinones from *β*-aminoenones and malononitrile, using the identification of their intermediates as a basic methodology.

Results and Discussion

Research has been carried out with *β*-aminoenones **1a**−**g**, **2a**,**g**,and **3a**, whose reactions with malononitrile (Scheme 1) afforded the results summarized in Table 1.

Scheme 1



1-3 **4**

1a: $R^1 = R^2 = Me$, L = NH_2
1b: R^1 = *i*-Pr, R^2 = Me, L = NH_2
1c: R^1 = Me, R^2 = *i*-Pr, L = NH_2
1d: R^1 = *t*-Bu, R^2 = Me, L = NH_2
1e: R^1 = Me, R^2 = *t*-Bu, L = NH_2
1f: R^1 = Et, R^2 = H, L = NH_2
1g: R^1 = *i*-Pr, R^2 = H, L = NH_2
2a: $R^1 = R^2$ = Me, L = NC_4H_8
2g: R^1 = *i*-Pr, R^2 = H, L = NC_4H_8
3a: $R^1 = R^2$ = Me, L = NHMe

4a: $R^1 = R^2$ = Me
4b: R^1 = *i*-Pr, R^2 = Me
4c: R^1 = Me, R^2 = *i*-Pr
4d: R^1 = *t*-Bu, R^2 = Me
4e: R^1 = Me, R^2 = *t*-Bu
4f: R^1 = Et, R^2 = H
4g: R^1 = *i*-Pr, R^2 = H

Table 1. Synthesis of 3-Cyano-2(1*H*)-pyridinones: Reaction Conditions

β-aminoenone	solvent	time (h)	*T* (°C)	pyridinone[a] (%)
1a	THF	2	65	**4a** (90)
1b	THF	72	20	**4b** (80)
1c	EtOH	70	80	**4c** (90)
1d	EtOH	24	20	**4d** (70)
1e	EtOH	24	80	**4e** (35)[b,c]
1f	EtOH	120	80	**4f** (70)[d]
1g	EtOH	120	80	**4g** (76)[d]
2a	THF	2	65	**4a** (90)
2g	EtOH	120	80	**4g** (65)[d]
3a	THF	1	65	**4a** (90)

[a] Isolated yield. [b] Basic catalysis (NH_4OH/Py) is necessary for reaction to be produced. [c] Other isolated products: 2-amino-6-*tert*-butyl-4-methylpyridine-3-carbonitrile **13** (38%) and 2-amino-4-*tert*-butyl-6-methyl-1,3-benzenedicarbonitrile **14** (14%). [d] See Scheme 5.

The processes are highly regioselective, and each *β*-aminoenone regioisomer leads to its corresponding 2(1*H*)-pyridinone (**1b** → **4b**, **1c** → **4c**, **1d** → **4d**, **1e** → **4e**).

The reaction rate between *β*-aminoenones and malononitrile depends on the nature of R^1, R^2, and L substituents and experimental conditions. Control of these factors has allowed us to reduce the rate of some of the steps and to identify the respective intermediates by spectro-

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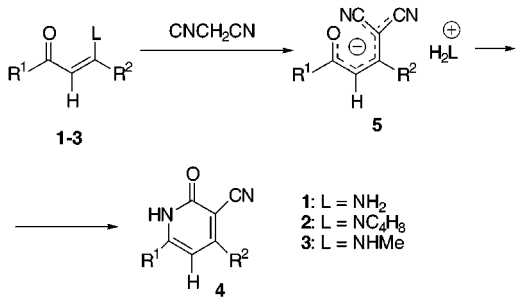
10.1021/jo991121o CCC: $18.00
Published on Web 12/03/1999

Scheme 2



scopic means in the reaction mixture or by prior isolation.

Monitoring of the reactions by ^{1}H NMR indicates that the process begins with a conjugated addition−elimination of the malonic dinitrile to the β-aminoenone to give the intermediate **5** (Scheme 2), whose concentration in the reaction mixture can reach values of between 30% and 90%, according to the nature of R^1, R^2, and L. The variations in the concentrations of the β-aminoenone (**1**), the intermediate **5**, and the final 2(1*H*)-pyridinone (**4**) have been determined according to the intensity of the signals due to their olefinic protons, which were recorded at δ = 4.87−5.12 (for **1**−**3**), 5.43−5.59 (for **5**), and 6.00−6.21 (for **4**).

The formation and disappearance rates of **5** depend on the size of the R^2 substituent: the more bulky this is, the more slowly the intermediate is produced and the more quickly it is transformed. In the case of the β-aminoenone**1g**, in which R^2 = H, the lifetime of **5g** allows its complete identification by means of its ^{1}H NMR and ^{13}C NMR spectra, which coincide with those of sodium salt **9** (Table 2), obtained and isolated from the reaction of the β-aminoenones **1g** or **2g** with malononitrile and sodium ethoxide in toluene.[18]

To establish the nature of the following steps of the process by which **1**−**3** gives rise to 2(1*H*)-pyridinones (**4**), we should point out that the transformations can be carried out in dry THF or other inert water-free solvents. This provides evidence that the oxygen atom at C-5 proceeds from the carbonyl group of the β-aminoenones and is not produced during the process by any external reagent. Consequently, **5** should be transformed by means of the reactions that involve a change of position of the initially ketonic oxygen and its integration in the amide group present in the pyridinone.This would be possible by the conversion of **5** in a 2*H*-pyran-2-imine intermediate **6** (Scheme 3), whose opening by action of a nucleophile (for example, that proceeding from the nitrogenate leaving group) would afford **7**, and this would give the 2(1*H*)-pyridinone (**4**) by cyclization.[9−13]

The transformation of **6** in **4** via **7** may be considered a Dimroth-type rearrangement.[19,20] When R^2 = H, **7g** (Scheme 4) may be isolated from the reaction mixture, as a stable solid, whose structure was confirmed by X-ray diffraction. The ^{1}H NMR and ^{13}C NMR spectra of **7g** coincided with those attributed to the other intermediates **7** in the monitoring of the reactions.

Compound **7a** (Scheme 4) was also obtained as the major product from **2a** and malononitrile in THF at −10 °C. When room temperature was reached, **7a** was transformed into the final 2(1*H*)-pyridinone (**4a**), with release of pyrrolidine. The comparative study of the evolution of **7a** by ^{1}H NMR (previously isolated) and, on the other hand, of the reaction of **2a** with malononitrile allowed us to deduce that **5a** is an intermediate prior to **7a** in the sequence (Scheme 3). The ^{1}H NMR spectral study of the reaction mixture also allowed us to confirm that the transformation of **7** into pyridinone is fast when R^2 is different from H and, consequently, that the concentration of the said intermediate in the reaction mixture is small. On the other hand, the conversion rate of **7** into **4** decreases with the volume of R^1.

The average life of the intermediate 2*H*-pyran-2-imine **6** must be very low. In the literature, we found described only those whose 2*H*-pyran-2-imine rings are stable to nucleophilic attack because they are integrated in condensated polycyclic systems.[5,21−24]

The rapid evolution of **6** prevented us from directly proving its presence in the reaction system. However, some complementary transformations carried out with β-aminoenones and their derivatives provide indirect proof of its existence:

(a) The reactions of **1f** and **1g** with malononitrile in excess yield type **8** compounds (Scheme 5), which afforded **4f**,**g**, by treatment with aqueous hydrochloric acid with release of malononitrile. The structure of **8f** was confirmed by X-ray diffraction.

(b) The reactions of **9** with ethanol or ethanethiol, in the presence of pyridinium 4-toluenesulfonate, yield **10** and **11**, respectively (Scheme 6), transformable in the pyridinone **4g** by treatment with aqueous hydrochloric acid.

The reaction mechanism proposed (Scheme 3) supposes the existence of an easily reversible equilibrium between the geometric isomers *Z* and *E* of **7** with respect to the double bond C2−C3. The opening of the iminopyrone **6** must lead to (2*Z*)-**7**, but the configuration of the intermediates **7**, isolated and identified by X-ray, is 2*E*. On the other hand, the formation of **4** starting from **7** demands that the last process of the conjugated addition−elimination takes place in the isomer (2*Z*)-**7**.

It has been described that those conjugated polyenes that possess one donor group and one electron-attracting group at their extremes (push−pull compounds) are easily isomerized.[25−29] This is due to the low energy barrier between their configurations *Z* and *E*, which allows an equilibrium between the isomers. The equilibrium is not shown in solutions of **7f**,**g** (R^2 = H) but is apparent in **7a** (R^2 = Me) and its analogue **12** (Scheme

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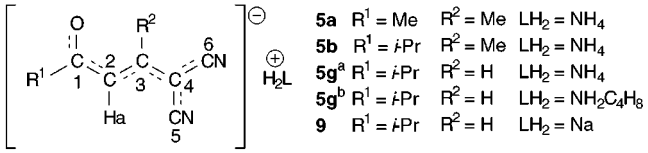
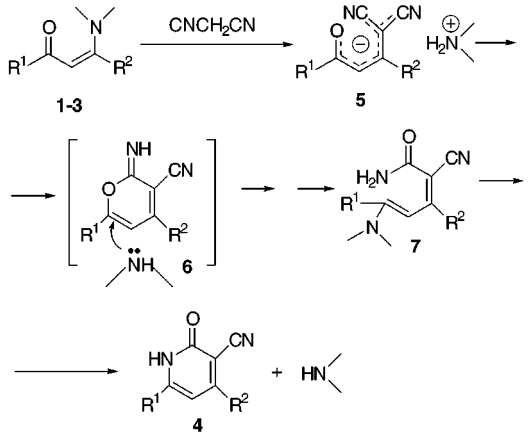
Table 2. Significant Data for Compounds 9 and for Some Type 5 Intermediates



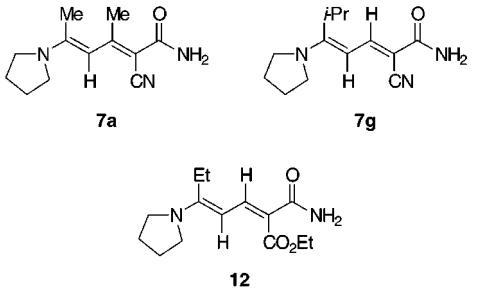
	^{1}H NMR δ (multiplicity, J, Hz)		^{13}C NMR δ					
compd	Ha	R^2	C-1	C-2	C-3	C-4	C-5	C-6
5a	5.53 (s)	2.22 (s)	190.8	102.5	167.1	159.5	121.3	122.6
5b	5.59 (s)	2.35 (s)	182.3	101.6	174.8	140.7	121.2	123.2
5g[a]	5.43 (d, 14.0)	7.19 (d, 14.1)	198.0	104.1	147.1	112.3	120.7	123.3
5g[b]	5.43 (d, 14.0)	7.20 (d, 14.0)	198.0	104.0	147.1	112.2	120.8	123.3
9	5.44 (d, 14.1)	7.19 (d, 14.1)	197.9	104.1	147.2	109.6	120.7	123.3

[a] From **1g**. [b] From **2g**.

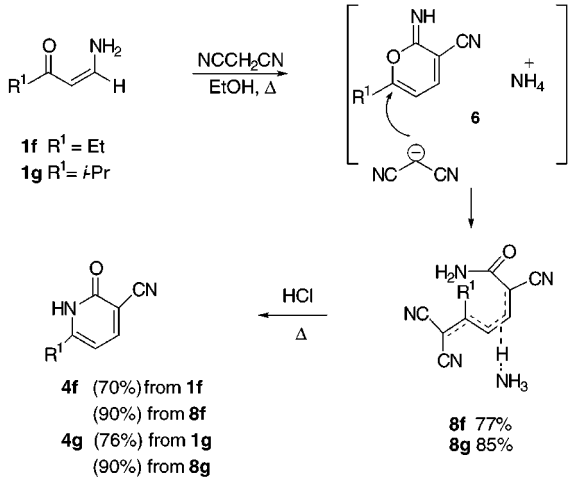
Scheme 3



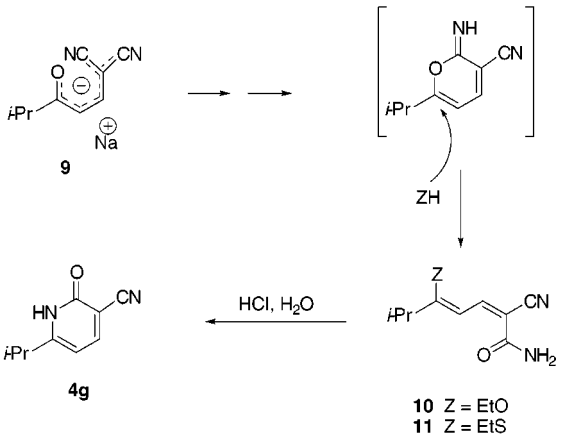
Scheme 4



Scheme 5



Scheme 6



4), which was obtained in the reaction of **1f** with ethyl cyanoacetate. The NMR spectra of **12**, starting from single crystalline compounds (by X-ray), gave duplicated signals.

Characterization of Reaction Intermediates. In this section, we give a structural description of intermediates and an outline of the methodology used for the structural assignment, especially for those intermediates that have only been detected by spectroscopy and not isolated as pure substances.

Type 5 Intermediates. Type **5** intermediates are an example of those that have not been isolated. Their structural assignment takes sodium salt **9** (R^2 = H) as a reference. It is a stable, yellow solid with a melting point of over 330 °C, soluble in water and insoluble in toluene and diethyl ether. Its ionic mass spectrum, recorded on a VG platform (Micromass Instrument) with electrospray ionization interphase, indicates a $M - 1 = 161$. Its ^{1}H NMR ^{13}C NMR spectra practically coincide with those of the intermediate **5g** (Table 2). The other type **5** intermediates, when $R^2 \neq$ H, have spectra referable to the previous ones.

The IR spectrum (KBr) of **9** indicates an important conjugation in all the molecules. It does not register the typical vibrations of enones at 1690−1630 cm^{-1}($\nu_{C=O}$) although it does show a broad, intense signal at 1500 cm^{-1}. On the other hand, the cyano groups, which undoubtedly contribute to the great stability of the anion, show four bands at frequencies characteristic of conjugated nitriles: 2207 (s), 2197 (s), 2180 (w), and 2166 cm^{-1} (m−w).

Type 7 Intermediates. The stability of these intermediates, when R^2 = H, allows them to be isolated as

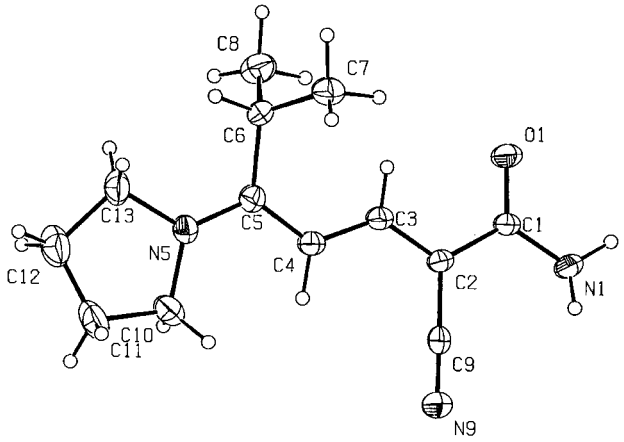


Figure 1.

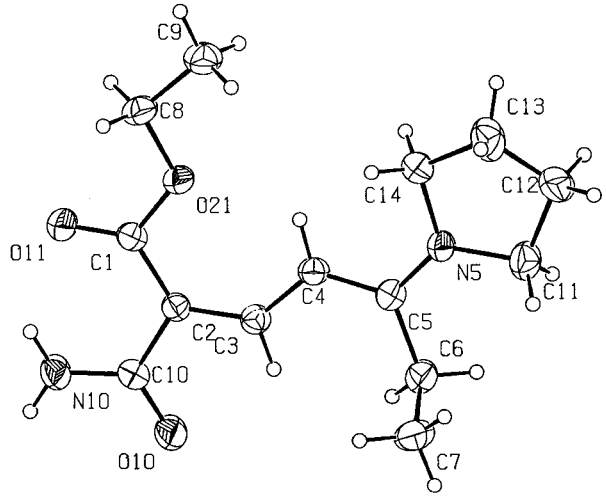


Figure 2.

stable solid compounds. The structure of these intermediates was established by X-ray diffraction of **7g** (Figure 1). This compound is a yellow solid with a melting point of 236−237 °C, soluble in acetone and ethanol and insoluble in diethyl ether.

^{1}H NMR and ^{13}C NMR spectra of intermediate **7g** indicate a single compound coinciding with the configuration 2*E*,4*E* of the solid state.

Other intermediates of the same type (when R^2 = H), which are single compounds in a solid state, present in solution ($CDCl_3$) two structures in equilibrium. This happens, for example, to ethyl 2-carbamoyl-5-(1-pyrrolidinyl)-2,4-heptadienate (**12**), which presents a 2*E*,4*E* configuration in the solid state (X-ray, Figure 2) but is seen in dissolution in equilibrium with the 2*Z*,4*E* isomer.

When R^2 is different from H, the intermediates **7** are less stable. They appear in low concentrations, and only the intermediate **7a** (R^1 = R^2 = Me) could be isolated as an unstable solid. It also appears in dissolution as two compounds in equilibrium: 2*Z*,4*E* and 2*E*,4*E* (push−pull effect).

Type 8 Intermediates. The unequivocal assignment of this compound was carried out by X-ray diffraction of **8f$_2$** (Figure 3). This is a cocrystallization adduct with a molecule of 4-hydroxy-4-methyl-2-pentanone and was obtained from the recrystallization of **8f** in acetone (Scheme 7). The NMR spectra of **8f$_2$** (or **8g$_2$**) are a

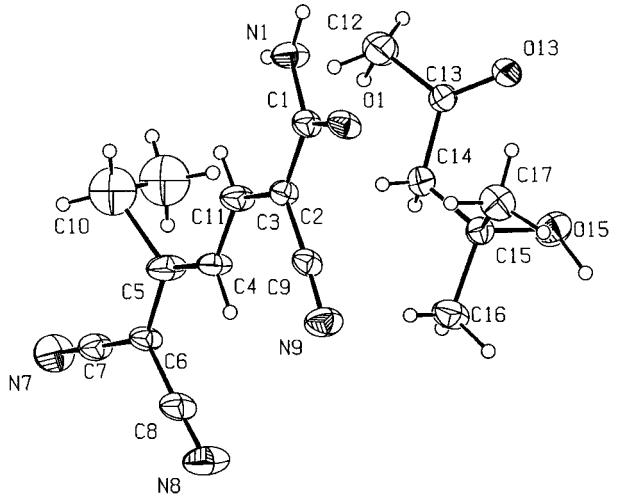
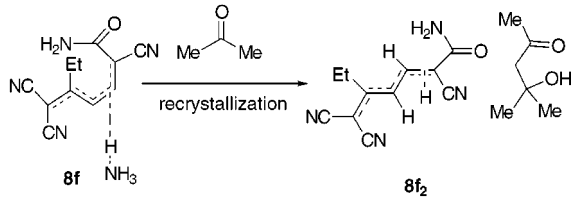


Figure 3.

Scheme 7



superimposition of those corresponding to **8f** (or **8g**) and to 4-hydroxy-4-methyl-2-pentanone.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 300.1 (^{1}H) and 75.0 MHz (^{13}C). The chemical shifts are reported as δ (ppm) referenced to the following: TMS as the internal standard, for experiments in DMSO-d_6 and $CDCl_3$. Definitive assignments of individual^{13}C resonance were supported by DEPT experiments. Mass spectra were recorded at an ionizing voltage of 70 eV by EI. All reactions were monitored by TLC, which was performed on precoated sheets of silica gel 60 F_{254}, and flash column chromatography was done in silica gel 60 (0.040−0.063 mm). Eluting solvents are indicated in the text. THF was distilled from sodium−benzophenone ketyl under argon, and toluene was distilled from sodium under argon. The starting compounds **1b**−**e** were prepared by catalytic hydrogenation[30,31] of isoxazoles, and these were regioselectively prepared by the procedure of Nitz et al.[32] from oximes and *N*-methoxy-*N*-methylalkylamides. The compounds **1**−**3a**, **1f**, **1g**, and **2g** have also been reported previously.[33]

General procedures for the synthesis of 2(1*H*)-pyridinones. Method A. To a solution of 10 mmol of β-aminoenone (**1**−**3**) in 10 mL of dry THF was added 10 mmol of malononitrile. The temperature for each reaction is indicated in Table 1. The reaction was monitored by TLC until the disappearance of starting materials. The pyridinone was precipitated from the reaction mixture by cooling, and the solid was separated by filtration and recrystallized from ethanol.

Method B. To a solution of 10 mmol of β-aminoenone in 10 mL of ethanol was added 10 mmol of malononitrile. The temperature for each reaction is indicated in Table 1. The reaction was monitored by TLC until the disappearance of

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starting materials. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (CH_2Cl_2/diethyl ether, 5:2).

Method C. A mixture of β-aminoenone (10 mmol), malononitrile (10 mmol), pyridine (11 mmol), and 25% aqueous NH_3 (1.7 mL) in 10 mL of ethanol was refluxed until TLC showed the disappearance of starting materials and the pyridinone was precipitated. The solid was separated by filtration and recrystallized from ethanol.

3-Cyano-4,6-dimethyl-2(1*H*)-pyridinone (4a) (method A): 90%; mp 291−92 °C; ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H), 2.31 (s, 3H), 6.13 (s, 1H), 11.89 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 18.8, 20.6, 99.3, 107.3, 115.9, 150.9, 160.2, 160.9; MS *m*/*z* (rel intensity) 148 (M^+, 77), 119 (100). Anal. Calcd for $C_8H_8N_2O$: C, 64.72; H, 5.46; N, 18.97. Found: C, 64.85; H, 5.44; N, 18.91.

3-Cyano-6-isopropyl-4-methyl-2(1*H*)-pyridinone (4b) (method A): 80%; mp 221−222 °C; ^{1}H NMR (DMSO-d_6) δ 1.21−1.23 (d, J = 7.6 Hz, 6H), 2.36 (s, 3H), 2.81 (m, 1H), 6.09 (s, 1H), 12.25 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.9, 21.0, 31.8, 100.2, 104.0, 115.0, 159.9, 160.3, 161.4; MS *m*/*z* (rel intensity) 176 (M^+, 31), 161 (100). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.07; H, 6.86; N, 15.95.

3-Cyano-4-isopropyl-6-methyl-2(1*H*)-pyridinone (4c) (method B): 90%; mp 285−86 °C; ^{1}H NMR (DMSO-d_6) δ 1.23−1.25 (d, J = 7.6 Hz, 6H), 2.31 (s, 3H), 3.11−3.20 (m, J = 7.6 Hz, 1H), 6.06 (s, 1H), 12.36 (s, 1H); ^{13}C NMR (DMSO-d_6) 19.4, 21.6, 33.0, 98.7, 103.1, 115.4, 151.2, 161.5, 169.6; MS *m*/*z* (rel intensity) 176 (M^+, 100), 161 (80). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.04; H, 6.89, N, 15.97.

6-*tert*-Butyl-3-cyano-4-methyl-2(1*H*)-pyridinone (4d) (method B): 70%; mp 285−286 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (s, 9H), 2.32 (s, 3H), 6.20 (s, 1H), 12.0 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.1, 28.3, 35.4, 100.2, 103.9, 116.1, 160.9, 161.5, 161.6; MS *m*/*z* (rel intensity) 190 (M^+, 24), 175 (100). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.43; H, 7.40; N, 14.74.

4-*tert*-Butyl-3-cyano-6-methyl-2(1*H*)-pyridinone (4e) (method C): 35%; mp 247−248 °C; ^{1}H NMR (DMSO-d_6) δ 1.38 (s, 9H), 2.4 (s, 3H), 6.1 (s, 1H), 12.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.5, 28.6, 35.6, 101.1, 104.8, 115.1, 160.7, 161.7, 163.0; MS *m*/*z* (rel intensity) 190 (M^+, 19), 175 (100).; Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.48; H, 7.44; N, 14.70.

3-Cyano-6-ethyl-2(1*H*)-pyridinone (4f) (method C): 38%; mp 255−256 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.28 (t, J = 7.6 Hz, 3H), 2.57−2.65 (q, J = 7.6 Hz, 2H), 6.09−6.12 (d, J = 7.4 Hz, 1H), 7.77−7.79 (d, J = 7.4 Hz, 1H), 12.55 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 12.5, 26.6, 101.2, 103.5, 116.3, 148.2, 158.4, 161.7; MS *m*/*z* (rel intensity) 148 (M^+, 64), 147 (100). Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.74; H, 5.46, N, 18.96.

3-Cyano-6-isopropyl-2(1*H*)-pyridinone (4g) (method C): 30%; mp 226−227 °C; ^{1}H NMR (DMSO-d_6) δ 1.18−1.20 (d, J = 6.9 Hz, 6H), 2.80−2.89 (m, 1H), 6.18−6.21 (d, J = 7.5 Hz, 1H), 7.97−8.00 (d, J = 7.5 Hz, 1H), 12.5 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 20.8, 31.7, 100.4, 101.2, 116.2, 148.5, 160.9, 162.2; MS *m*/*z* (rel intensity) 162 (M^+, 95), 147 (100). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.66; H, 6.21; N, 17.27. Found: C, 66.56; H, 6.23; N, 17.33.

2-Cyano-3-methyl-5-(1-pyrrolidinyl)-2,4-hexadienamide (7a). To a solution of 10 mmol of β-aminoenone **2a** in ethanol was added 10 mmol of malononitrile at −20 °C. The intermediate **7a** was precipitated from the reaction mixture and was separated by filtration as an unstable yellow solid, 90%. 2*E*,4*E* Isomer: ^{1}H NMR ($CDCl_3$) δ 1.83−1.95 (m, 4H), 2.23 (s, 3H), 2.50 (s, 3H), 3.41−3.49 (m, 4H), 5.43 (s, 1H), 5.89 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 19.5, 20.6, 24.7, 46.1, 48.7, 89.8, 100.0, 121.5, 161.0, 164.0, 166.4. 2*Z*,4*E* isomer: ^{1}H NMR ($CDCl_3$) δ 1.83−1.95 (m, 4H), 2.25 (s, 3H), 2.33 (s,3H), 3.41−3.49 (m, 4H), 5.97 (s, 2H), 7.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.8, 23.3, 25.0, 46.1, 49.0, 86.4, 100.8, 122.6, 157.1, 158.4, 166.9.

(2*E*,4*E*)-2-Cyano-5-(1-pyrrolidinyl)-2,4-heptadienamide (7f). A mixture of β-aminoenone **2f** (10 mmol) and malononitrile (10 mmol) in 10 mL of ethanol was refluxed until TLC showed the disappearance of starting materials. The intermediate **7f** was precipitated from the reaction mixture by cooling. The solid was separated by filtration and recrystallized from ethanol: 59%; mp 225−226 °C; ^{1}H NMR (DMSO-d_6) δ 1.08−1.12 (t, J = 7.5 Hz, 3H), 1.88−1.96 (m, 4H), 2.59−2.66 (q, J = 7.5 Hz, 2H), 3.30−3.36 (m, 2H), 3.46−3.61 (m, 2H), 5.17−5.22 (d, J = 13.0 Hz, 1H), 6.88 (s, 2H), 7.88−7.92 (d, J = 13.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 13.3, 22.8, 24.3, 24.8, 48.5, 48.7, 85.9, 94.5, 119.5, 149.2, 165.0, 166.0; MS *m*/*z* (rel intensity) 219 (M^+, 8), 175 (20), 44 (100). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.84; H, 7.79; N, 19.10.

2-Cyano-6-methyl-5-(1-pyrrolidinyl)-2,4-heptadienamide (7g). By a procedure analogous to the previous one, starting from **2g**, **7g** was obtained: 61%; mp 236−237 °C; ^{1}H NMR (DMSO-d_6) δ 1.24−1.27 (d, J = 7.1 Hz, 6H), 1.88−1.93 (m, 4H), 3.25−3.29 (m, 1H), 3.43−3.48 (m, 4H), 5.19−5.23 (d, J = 13.4 Hz, 1H), 6.63 (s, 2H), 8.08−8.13 (d, J = 13.4 Hz, 1H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$) δ 20.5, 24.3, 29.9, 49.7, 85.7, 94.4, 118.8, 149.9, 165.4, 167.8; MS *m*/*z* (rel intensity) 233 (M^+, 34), 44 (100). Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.97; H, 8.22; N, 17.94.

5-Ethyl-2,6,6-tricyano-2,4-hexadienamide Ammonium Salt (8f). A mixture of β-aminoenone **1f** (10 mmol) and malononitrile (20 mmol) in 10 mL of ethanol was refluxed until TLC showed the disappearance of starting materials. **8f** was precipitated from the reaction mixture by cooling, and the yellow solid was separated by filtration and recrystallized from ethanol: 50%; mp 195−196 °C; ^{1}H NMR (DMSO-d_6) δ 1.08−1.13 (t, J = 7.3 Hz, 3H), 2.45−2.53 (q, J = 6.9 Hz, 2H), 5.85−5.89 (d, J = 13.3 Hz, 1H), 6.69 (s, 2H), 7.10 (s, 4H), 7.78−7.82 (d, J = 13.5 Hz, 1H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$) δ 15.1, 23.7, 49.8, 83.4, 102.6, 119.6, 119.9, 120.3, 146.5, 166.5, 166.9. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.23; H, 5.65; N, 30.19.

Adduct of 5-Ethyl-2,6,6-tricyano-2,4-hexadienamide and 4-Hydroxy-4-methyl-2-pentanone ($8f_2$). This adduct was obtained by recrystallization of **8f** in acetone affording a stable yellow solid: mp 202−203 °C; ^{1}H NMR (DMSO-d_6) δ 1.02−1.07 (t, J = 7.4 Hz, 3H), 1.24 (s, 6H), 2.12 (s, 3H), 2.40−2.46 (q, J = 7.4 Hz, 2H), 2.79 (s, 2H), 5.79−5.83 (d, J = 13.3 Hz, 1H), 6.75 (s, 2H), 7.72 (s, 2H), 7.73−7.77 (d, J = 13.3 Hz, 1H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$) δ 15.1, 23.7, 25.3, 31.2, 49.6, 49.9, 51.7, 83.8, 102.6, 119.6, 119.9, 120.3, 146.5, 166.5, 166.9, 207.3. Anal. Calcd for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.78; H, 6.70; N, 16.94.

5-Isopropyl-2,6,6-tricyano-2,4-hexadienamide Ammonium Salt (8g). By a procedure analogous to that of **8f**, starting from **1g**, **8g** was obtained: 57%; mp 177−178 °C. 2*E*,4*E* isomer: ^{1}H NMR (DMSO-d_6) δ 1.21−1.24 (d, J = 6.9 Hz, 6H); 3.21−3.36 (m, 1H), 5.85−5.89 (d, J = 13.4 Hz, 1H), 6.78 (s, 2H), 7.12 (s, 4H), 7.91−7.95 (d, J = 13.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 20.8, 29.4, 48.3, 84.2, 102.9, 119.8, 120.1, 120.2, 145.7, 166.5, 170.2. Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.77; H, 6.16; N, 28.55. Found: C, 58.85; H, 6.15; N, 28.45.

Adduct of 5-Isopropyl-2,6,6-tricyano-2,4-hexadienamide and 4-Hydroxy-4-methyl-2-pentanone ($8g_2$). This intermediate was obtained by recrystallization of **8g** in acetone affording a stable yellow solid: mp 181−182 °C; ^{1}H NMR (DMSO-d_6) δ 1.21−1.24 (d, J = 6.9 Hz, 6H),. 1.31 (s, 6H), 2.09 (s, 3H), 2.83 (s, 2H), 3.20−3.35 (m, 1H), 5.85−5.89 (d, J = 13.4 Hz, 1H), 6.75 (s, 2H), 7.81(s, 2H), 7.90−7.94 (d, J = 13.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 20.8, 25.3, 29.3, 31.2, 50.0, 50.1, 51.7, 84.2, 102.9, 119.9, 120.1, 120.2, 120.3, 145.8, 166.5, 170.2. Anal. Calcd for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.74; H, 7.05; N, 16.24.

5-Methyl-4-oxo-2-hexene-1,1-dicarbonitrile Sodium Salt (9). To a solution of β-aminoenone **1g** (10 mmol) in dry toluene (100 mL) at 70 °C were added malononitrile (12 mmol) and sodium ethoxide (12 mmol). The mixture was stirred at 70 °C for 12 h, and new amounts of malononitrile (12 mmol) and sodium ethoxide (12 mmol) were added and stirred at the same temperature for another 12 h. The solid was separated by filtration and recrystallized from acetone−ether: 71%; mp >

330 °C; ^{1}H NMR (DMSO-d_6) δ 0.92−0.94 (d, J = 6.8 Hz, 6H); 2.52−2.54 (m, 1H), 5.41−5.46 (d, J = 13.3 Hz, 1H), 7.16−7.21 (d, J = 13.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 19.9, 37.9, 104.1, 109.6, 120.7, 123.3, 147.2, 197.9.

2-Cyano-5-ethoxy-6-methyl-2,4-heptadienamide (10). A mixture of sodium salt **9** (1 mmol) and pyridinium 4-toluenesulfonate (4 mmol) in dry ethanol was refluxed for 72 h. The resulting mixture was allowed to reach room temperature and, after dilution with CH_2Cl_2 (25 mL), was washed with a saturated solution of NaOH (25 mL), extracted with CH_2Cl_2 (3 × 25 mL), and dried with $MgSO_4$. The solvent was evaporated in vacuo, and **10** was isolated after flash chromatography (CH_2Cl_2): 44%; mp 130−131 °C; ^{1}H NMR (DMSO-d_6) 1.11−1.13 (d, J = 6.8 Hz, 6H); 1.34−1.39 (t, J = 7.4 Hz, 3H), 3.23−3.32 (m, 1H), 3.99−4.06 (q, J = 7.4 Hz, 2H), 5.69−5.76 (d, J = 12.5 Hz, 1H), 6.23 (s, 2H), 8.25−8.30 (d, J = 12.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) 14.0, 20.3, 30.0, 64.7, 96.6, 97.1, 117.0, 151.6, 164.4, 180.6; MS m/z (rel intensity) 208 (M^+, 25), 137 (100). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.45; H, 7.74; N, 13.45. Found: C, 63.49; H, 7.77; N, 13.41.

2-Cyano-5-ethylthio-6-methyl-2,4-heptadienamide (11). A mixture of sodium salt **9** (1 mmol) and pyridinium 4-toluenesulfonate (4 mmol) in dry ethanethiol was refluxed for 72 h. The resulting mixture was allowed to reach room temperature and, after dilution with CH_2Cl_2 (25 mL), was washed with a saturated solution of NaOH (25 mL), extracted with CH_2Cl_2 (3 × 25 mL), and dried with $MgSO_4$. The solvent was evaporated in vacuo, and **11** was isolated after flash chromatography (CH_2Cl_2): 65%; mp 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 1.21−1.23 (d, J = 6.8 Hz, 6H), 1.36−1.41 (t, J = 7.4 Hz, 3H), 2.87−2.94 (q, J = 7.4 Hz, 2H), 3.43−3.52 (m, 1H), 6.09 (s, 2H), 6.18−6.23 (d, J = 12.5 Hz, 1H), 8.22−8.27 (d, J = 12.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 22.5, 25.3, 32.3, 98.8, 113.6, 116.7, 146.6, 163.4, 173.4. Anal. Calcd for $C_{11}H_{16}N_2SO$: C, 58.90; H, 7.19; N, 12.49. Found: C, 58.81; H, 7.17; N, 12.52.

Ethyl 2-Carbamoyl-5-(1-pyrrolidinyl)-2,4-heptadienate (12). A mixture of β-aminoenone **2f** (10 mmol) and ethyl cyanoacetate (10 mmol) in 10 mL of ethanol was refluxed until TLC showed the disappearance of starting materials. **12** was precipitated from the reaction mixture by cooling. The solid was separated by filtration and recrystallized from ethanol: 42%; mp 181−182 °C. 2*E*,4*E* Isomer: ^{1}H NMR ($CDCl_3$) δ 1.01−1.07 (t, J = 7.1 Hz, 3H), 1.14−1.19 (t, J = 7.0 Hz, 3H), 1.81−1.86 (m, 4H), 2.44−2.51 (q, J = 7.0 Hz, 2H), 3.26−3.44 (m, 4H), 4.00−4.08 (q, J = 7.1 Hz, 2H), 5.36 (s, 1H), 6.85−6.89 (d, J = 13.4 Hz, 1H), 8.03−8.08 (d, J = 13.4 Hz, 1H), 8.37 (s,1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 14.4, 22.5, 24.4, 25.2, 48.5, 49.1, 59.6, 98.9, 100.7, 150.8, 166.8, 167.3, 169.5. 2*Z*,4*E* isomer: ^{1}H NMR (DMSO-d_6) δ 1.01−1.07 (t, J = 7.1 Hz, 3H), 1.21−1.26 (t, J = 7.1 Hz, 3H), 1.81−1.86 (m, 4H), 2.51−2.58 (q, J = 7.5 Hz, 2H), 3.26−3.44 (m, 4H), 4.06−4.13 (q, J = 7.1 Hz, 2H), 5.63 (s, 1H), 6.07−6.12 (d, J = 14.0 Hz, 1H), 8.37 (s, 1H), 8.38−8.43 (d, J = 14.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 13.6, 14.4, 22.7, 24.6, 25.2, 48.5, 48.8, 59.5, 98.7, 101.5, 150.4, 169.2, 169.5, 170.1; MS m/z (rel intensity) 266 (M^+, 11), 136 (100). Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.08; H, 8.35; N, 10.48.

2-Amino-6-*tert*-butyl-4-methylpyridine-3-carbonitrile (13): 38%; mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 2.41 (s, 3H), 5.04 (s, 2H), 6.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 29.6, 37.6, 89.0, 110.8, 116.7, 152.6, 159.0, 172.9; MS m/z (rel intensity) 189 (M^+, 20), 174 (100). Anal. Calcd for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.74; H, 7.97; N, 22.29.

2-Amino-4-*tert*-butyl-6-methyl-1,3-benzenedicarbonitrile (14): 14%; mp 109−110 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.48 (s, 3H), 5.21 (s, 2H), 6.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 29.8, 36.1, 92.8, 95.9, 115.5, 117.0, 117.4, 147.6, 153.3,-159.2; MS m/z (rel intensity) 213 (M^+, 40), 198 (100). Anal. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.23; H, 7.12; N, 19.65.

Acknowledgment. Financial support from Spanish CICYT (PB-1112) is gratefully acknowleged.

Supporting Information Available: X-ray characterization data for **7g**, **12,** and **8f$_2$**, including tables of experimental details, ORTEP drawings, and selected bond lengths and bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991121O