A Convenient Synthesis of 5-Acyl-6-substituted 3-Cyano-2(1*H*)-pyridinones

Winton D. Jones, Jr., Richard A. Schnettler and Edward W. Huber

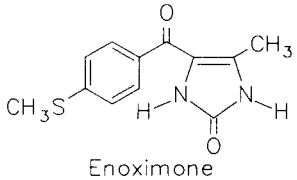
Merrell Dow Research Institute, 2110 E. Galbraith Road,
Cincinnati, Ohio 45215

Received September 13, 1989

2-Dimethylaminomethylidene-1,3-diketones are useful synthons for the construction of 5-acyl-6-substituted-3-cyano-2(1*H*)-pyridinones. The reaction of these 1,3-diketones and the anion of cyanoacetamide gave the title compounds. When the 1,3 diketone contained different alkyl or aryl groups, mixtures of regioisomers were formed. To circumvent this problem, dimethylaminomethylidene hydrazones, regioselectively prepared from dimethylhydrazino enones and dimethylformamide dimethyl acetal were reacted with cyanoacetamide anion followed by acid hydrolysis to give the title compounds.

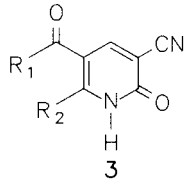
J. Heterocyclic Chem., **27**, 511 (1990).

As a continuation of a program directed toward the discovery of new inotropic agents, we sought to combine certain structural features of enoximone (**1**) [1] and milrinone (**2**) [2a], two compounds reported to be useful for the treatment of heart failure [2b]. Thus we elected to prepare a series of 5-acyl-6-substituted-3-cyano-2(1*H*)-pyridinones **3** [3].



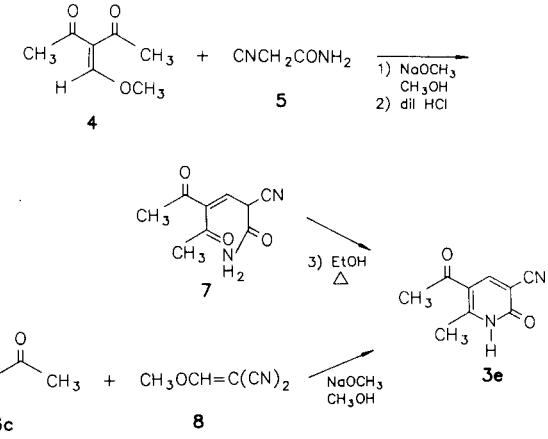
Enoximone
1

Milrinone
2



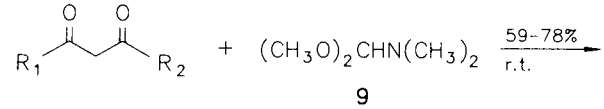
3

To the best of our knowledge at the time the project was initiated, the only example of this type of substituted 2(1*H*)-pyridinone was **3e**. Compound **3e** was prepared by Sunthankar and Vaidya [4] by condensation of methoxymethylene-2,4-pentanedione (**4**) with cyanoacetamide (**5**) using one equivalent of sodium methoxide in methanol. In order to limit side reactions, these workers isolated the intermediate **7** which was then cyclized in a separate operation. Crombie *et al.* [5] prepared **3e** in modest yield by a 15 minute condensation of 2,4-pentanedione **6c** and methoxymethylenemalononitrile **8**, using one equivalent of sodium methoxide in methanol. Higher concentrations of sodium methoxide and longer reaction times gave multiple side reactions thus limiting the synthetic potential of this route.



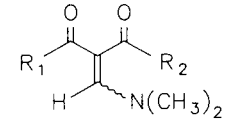
4 5 7 3e 6c 8

As an alternative to these syntheses, we investigated the reaction of 2-dimethylaminomethylidene-1,3-diketones **10** with cyanoacetamide (**5**). The requisite diketones **10** [6,7] were prepared in good yields by reaction of the appropriate 1,3-diketones **6** with dimethylformamide dimethyl acetal (**9**) at ambient temperature. In those instances where R_1 was not equivalent to R_2, these enamines were isolated as a mixture of geometrical isomers.



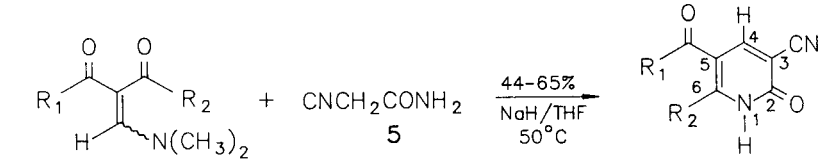
9

6a $R_1=C_4H_9; R_2=CH_3$
6b $R_1=Ph; R_2=CH_3$
6c $R_1=R_2=CH_3$



10a $R_1=C_4H_9; R_2=CH_3$
10b $R_1=Ph; R_2=CH_3$
10c $R_1=R_2=CH_3$

Condensation of enamines **10** with **5** using one equivalent of sodium hydride in tetrahydrofuran at 50° led to the rapid evolution of dimethylamine gas and formation of the target compounds **3a-3e** in modest to good



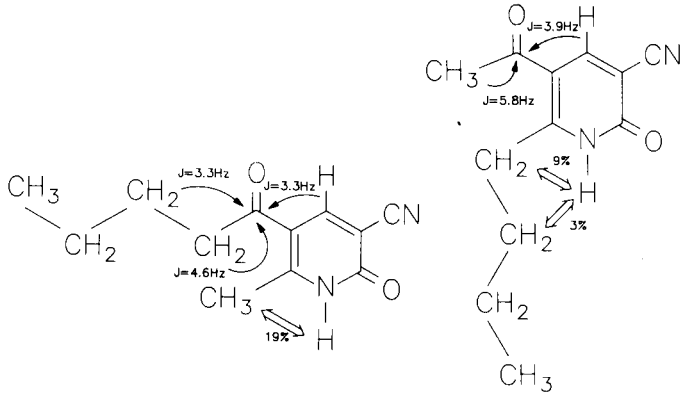
10a, $R_1 = C_4H_9$; $R_2 = CH_3$
10b, $R_1 = Ph$; $R_2 = CH_3$
10c, $R_1 = R_2 = CH_3$

10a → 3a+3b
10b → 3c+3d
10c → 3e

3a, $R_1 = C_4H_9$; $R_2 = CH_3$
3b, $R_1 = CH_3$; $R_2 = C_4H_9$
3c, $R_1 = Ph$; $R_2 = CH_3$
3d, $R_1 = CH_3$; $R_2 = Ph$
3e, $R_1 = R_2 = CH_3$

yields [8]. When R_1 and R_2 were different, the resulting regioisomers which formed were readily separated by flash chromatography.

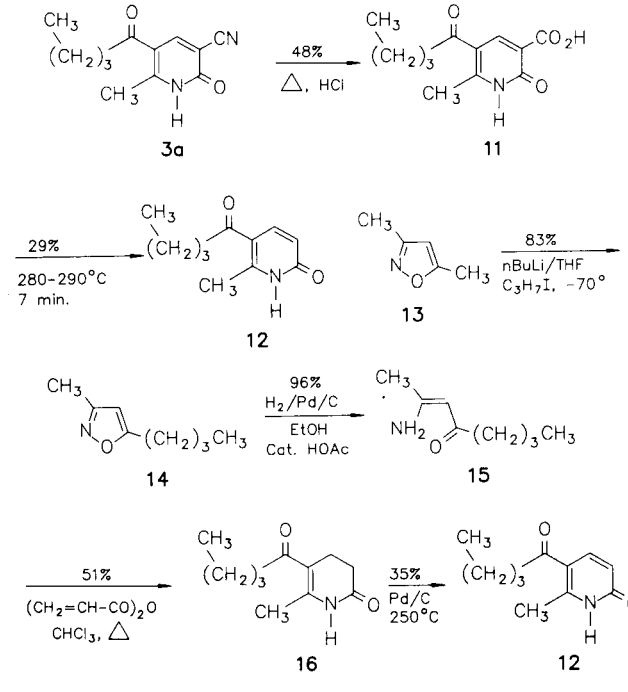
The structures of the regioisomers were assigned by ^1H and ^{13}C nmr spectroscopy. For example, **3a**, and **3b** were differentiated using a combination of NOE difference spectroscopy and long-range proton-carbon coupling information. More specifically in **3a**, a large NOE (19%) between the NH proton and the 6-methyl group established their close proximity. Similarly for **3b**, the NOE between the NH proton and both the α and β methylenes of the 6-butyl group established the assigned geometry. The NOE based assignments were supported by long range coupling between the ketone carbonyl and the R^1 alkyl group. Thus in **3a** the carbonyl at the 5-position was coupled to both the α and β-methylene protons of the 5-pentanoyl group. Similarly, in **3b**, the ketone carbonyl was coupled to the protons of the methyl group thus further establishing the presence of a 5-acetyl substituent. In both isomers ^{13}C-^1H couplings were observed between the ketone carbonyls and the proton at position 4 of the pyridinone ring.



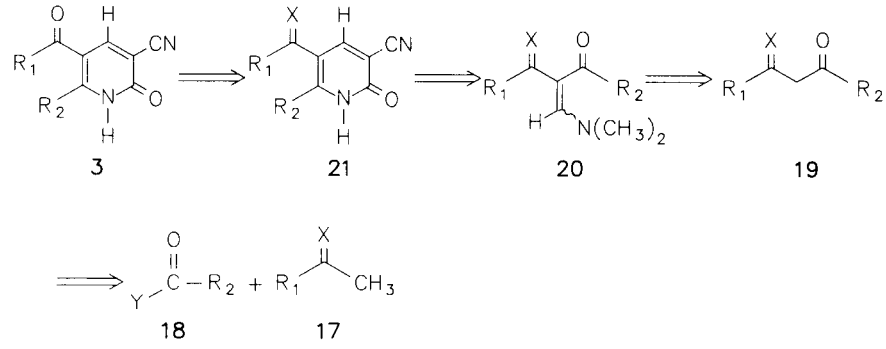
3a 3b

single arrow: ^1H-^{13}C coupling
double arrow: NOE

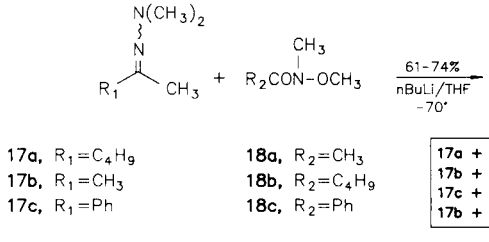
Further proof for the structural assignment of **3a** was provided *via* hydrolysis to the presumed acid **11** which was not characterized but immediately decarboxylated yielding **12**. It was then possible to prepare **12** in an unambiguous manner, and compare it to the product of the above decarboxylation. An unambiguous alternative synthesis of **12** was accomplished by selective alkylation of 3,5-dimethylisoxazole **13** at the 5-methyl group to give 3-methyl-5-butylisoxazole (**14**) [9,10]. Hydrogenation of **14** produced the amino ketone **15** in good yield. Cyclization of **15** with acrylic anhydride in chloroform gave the 3,4-dihydropyridinone **16** which when heated with palladium on carbon underwent aromatization to give the expected product **12**.



A way to circumvent the regioisomer problem is to chemically differentiate the carbonyls of the 1,3-diketone. Toward this end compounds of formula **21** where X is a ketone protecting group were utilized as the starting material. These derivatives could be prepared from **17** and **18** as indicated in the retrosynthetic scheme below. A dimethylhydrazone was our choice for the X protecting group.



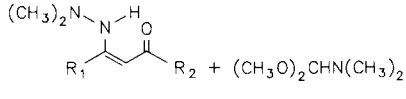
Thus, condensation of a suitable dimethylhydrazone of formula **17** [11,12,13] with the appropriate *N*-methoxy-*N*-methyl amide **18** [14] according to the method of Turner and Jacks [16] gave the dimethylhydrazino enones **19** [15, 16] in good yields. Subsequent reaction of compounds of formula **19** with dimethylformamide dimethyl acetal (**9**) gave the dimethylaminomethylidene hydrazones **20.**



17a, $R_1=C_4H_9$
17b, $R_1=CH_3$
17c, $R_1=Ph$

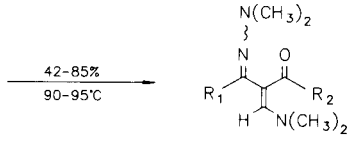
18a, $R_2=CH_3$
18b, $R_2=C_4H_9$
18c, $R_2=Ph$

17a + 18a —19a
17b + 18b —19b
17c + 18a —19c
17b + 18c —19d



9

19a, $R_1=C_4H_9;R_2=CH_3$
19b, $R_1=CH_3;R_2=C_4H_9$
19c, $R_1=Ph;R_2=CH_3$
19d, $R_1=CH_3;R_2=Ph$

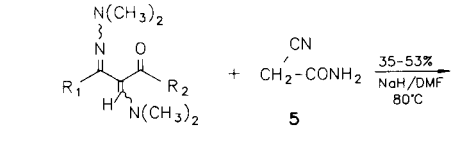


20a, $R_1=C_4H_9;R_2=CH_3$
20b, $R_1=CH_3;R_2=C_4H_9$
20c, $R_1=Ph;R_2=CH_3$
20d, $R_1=CH_3;R_2=Ph$

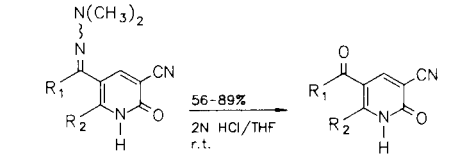
The ^1H nmr spectra of compounds of formula **20** at room temperature show broadened signal peaks [17] which decoalesce [18] at lower temperatures (5° in the case of **20c**). These results indicate a rapid interconversion between the various isomers at ambient temperature.

In contrast to the cyclization of **10** which readily occurred in tetrahydrofuran, the successful condensation of **20** requires the use of dimethylformamide. The dimethylhydrazonyl pyridinones **21b, 21c,** and **21d** appeared predominantly as a single *E* or *Z* isomer as evidenced by both tlc and ^{13}C nmr spectroscopy. Intermediate **21a** was a 45:55 mixture of unassigned *E* and *Z* isomers which were separable by flash chromatography.

Finally, deprotection of hydrazones **21** using dilute hydrochloric acid in tetrahydrofuran gave the desired ketones in good yields. These compounds were identical to the previously described samples of **3a-3d.**



20a, $R_1=C_4H_9;R_2=CH_3$
20b, $R_1=CH_3;R_2=C_4H_9$
20c, $R_1=Ph;R_2=CH_3$
20d, $R_1=CH_3;R_2=Ph$



20a, $R_1=C_4H_9;R_2=CH_3$
20b, $R_1=CH_3;R_2=C_4H_9$
20c, $R_1=Ph;R_2=CH_3$
20d, $R_1=CH_3;R_2=Ph$

3a, $R_1=C_4H_9;R_2=CH_3$
3b, $R_1=CH_3;R_2=C_4H_9$
3c, $R_1=Ph;R_2=CH_3$
3d, $R_1=CH_3;R_2=Ph$

In conclusion, an efficient regioselective synthesis of 5-acyl-6-substituted-3-cyano-2(1*H*)-pyridinones has been developed. This synthesis has given novel compounds for pharmacological evaluation.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover melting point apparatus and are uncorrected. The infrared spectra were obtained using a Perkin Elmer model 1800 spectrophotometer. Ultraviolet spectra were obtained on either a Cary Model 17 or Perkin Elmer Model Lambda 4C spectrophotometer. Proton (^1H) and carbon 13 (^{13}C) nuclear magnetic resonance measurements were performed on Varian FT-80A or VXR-300 spectrometers. The chemical shifts are

reported in parts per million (δ) downfield from tetramethylsilane. All spectra were acquired at ambient temperatures except where noted. NOE difference spectra were obtained in the following manner. The signal of interest was irradiated for 25 seconds and then a free induction delay acquired with the decoupler off. The signal was irradiated during the 25 second delay with sufficient power to saturate that signal. This process was repeated with the decoupler set for off resonance. This entire procedure was repeated for 8-12 hours. The resulting FID's were substracted and the spectra obtained after fourier transformation were displayed as the NOE difference spectra. Quantitation was obtained by measuring the integral of the enhanced signals and dividing by the integral of the signal being saturated. Mass spectra were obtained on a Finnegan MAT 6400 mass spectrometer. High pressure liquid chromatography (hplc) was performed on a Waters M6000A instrument using a model 440A 254 nm uv detector interfaced with a Waters 740 data module.

3-[(Dimethylamino)methylene]-2,4-octanedione (**10a**).

Compound **6a** (10.00 g, 70 mmoles) and **9** (9.60 g, 70 mmoles) were stirred in a dry 50 ml round bottom flask at ambient temperature overnight. The resulting mixture was concentrated on the rotary evaporator to give a red liquid. Distillation afforded 8.16 g (59%) of **10a** as an amber liquid bp 163-168 (0.15 mm-0.2 mm); ^{1}H nmr (deuteriochloroform): 300 MHz, δ 7.42 (b, 1H, vinyl H), 2.98 (b, 6H, $N(CH_3)_2$), 2.64 (m, 2H, CH_2), 2.29 (s, 3H, $COCH_3$), 1.60 (m, 2H, CH_2), 1.35 (m, 2H, CH_2), 0.92 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C nmr: δ 201.15, 197.44, 155.33, 114.79, 42.29, 42.22, 29.15, 27.36, 22.45 and 13.82; ir (neat): 2960, 2940, 2875, 1660, 1625, and 1580 cm^{-1} (broad band); uv (ethanol): λ max = 296 nm, ε = 12,800.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.10; H, 9.59; N, 6.97.

5-(1-Oxopentyl)-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**3a**) and 5-Acetyl-6-butyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**3b**).

Cyanoacetamide (4.20 g, 43 mmoles) was added to a stirred suspension of sodium hydride (50% in mineral oil) (2.40 g, 50 mmoles) in dry tetrahydrofuran (150 ml) under argon and the suspension was warmed briefly to 50°. Compound **10a** (8.60 g, 43 mmoles) dissolved in tetrahydrofuran (10 ml) was added dropwise and the heterogeneous reaction mixture was heated and stirred overnight at 50°. The reaction mixture was allowed to cool to ambient temperature then neutralized with glacial acetic acid. Concentration gave a semi-solid residue which was partitioned between dichloromethane and water. The organic layer was separated and dried with magnesium sulfate. Filtration through celite followed by concentration on the rotary evaporator gave 8.0 g (85%) mp 162-165°. Recrystallization from ethyl acetate gave the analytical sample of **3a** and **3b** mp 165-174°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.84. Found: C, 66.19; H, 6.46; N, 12.85.

Purification of 3.0 g by flash chromatography (35:65) ethyl acetate-dichloromethane gave first **3b** 0.60 g mp 223-225°; ^{1}H nmr (dimethylsulfoxide-d_6): 300 MHz, δ 12.94 (b, 1H, NH), 8.68 (s, 1H, pyridinone H), 2.92 (t, 2H, J = 7.6 Hz, CH_2), 2.47 (s, 3H, $COCH_3$), 1.50 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.33 (m, 2H, CH_2), 0.89 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): 75 MHz, δ 195.28, 162.41, 160.06, 150.48, 116.13, 115.14, 99.76, 31.84, 31.33, 29.35, 22.40, and 13.78; NOE difference (30°): irradiate 12.94 δ, NOES observed 2.92 (9%) and 1.50 (3%) δ; ^{13}C-^{1}H coupling experiments: fully coupled spectrum, 5-carbonyl 195.28 δ (d_6, $^2J_{CH}$ = 5.8 Hz, $^3J_{pyridinone\ H}$ = 3.9 Hz), irradiate δ 8.68 (carbonyl signal collapses to quartet), 2.92 (no change), 2.47 (carbonyl signal collapses to a doublet); ir (potassium bromide): 2958, 2934, 2232, 1690, 1652, and 1570 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 66.03; H, 6.46; N, 12.84. Found: C, 66.33; H, 6.94; N, 12.76.

Further elution gave **3a**, 1.80 g mp 195-197°; ^{1}H nmr (dimethylsulfoxide-d_6): 300 MHz, δ 12.94 (b, 1H, NH), 8.69 (s, 1H, pyridinone H), 2.85 (t, 2H, J = 7.3, $COCH_2$), 2.55 (s, 3H, CH_3), 1.51 (m, 2H, CH_2), 1.31 (m, 2H, CH_2), 0.89 (t, 3H, J = 7.3, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): 75 MHz, δ 197.21, 159.70, 158.30, 149.00, 115.89, 115.22, 99.20, 39.29, 25.80, 21.68, 19.83, and 13.79; NOE difference (30°): irradiate 12.94 δ, NOE observed at 2.55 δ (19%); ^{13}C-^{1}H coupling experiments: fully coupled spectrum, 5-carbonyl 197.21 δ (m, $^2J_{CH}$ = 4.6 Hz, $^3J_{pyridinone\ H}$ = 3.3 Hz, $^3J_{CH}$ = 2.3 Hz); irradiate (^{1}H) δ 8.69 (carbonyl signal collapses to multiplet), 2.85 (carbonyl signal collapses to doublet of triplets), 2.55 (no change), 1.51 (carbonyl signal collapses to doublet of triplets); ir (potassium bromide): 2962, 2938, 2230, 1686, 1654, and 1566 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}H_2N_2O_2$: C, 66.03; H, 6.46; N, 12.84. Found: C, 66.29; H, 6.42; N, 12.85.

5-Benzoyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (**3c**) and 5-Acetyl-1,2-dihydro-6-phenyl-2-oxopyridinecarbonitrile (**3d**).

Cyanoacetamide (2.50 g, 30 mmoles) was added to a stirred suspension of sodium hydride (50% in mineral oil) (1.5 g, 63 mmoles) in dry tetrahydrofuran (150 ml) under argon and the suspension was warmed briefly to 50°. Compound **10b** [7] (6.52 g, 30 mmoles) dissolved in dry tetrahydrofuran (50 ml) was added dropwise at ambient temperature. The resulting heterogeneous mixture was treated as described for **3a** and **3b**. Recrystallization from ethyl acetate gave a mixture of **3c** and **3d** (3.30 g 47%) 221-223°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.49; H, 4.03; N, 11.81.

Flash chromatography with (1:3) ethyl acetate-dichloromethane gave 1.1 g of **3d** mp 259-261°; ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz, δ 13.02 (b, 1H, NH), 8.53 (s, 1H, pyridinone H), 7.60-7.44 (m, 5H, aromatic), 2.02 (s, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): 75 MHz, δ 195.31, 159.81, 155.80, 148.74, 132.68, 130.72, 128.84, 128.45, 117.73, 115.80, 101.63, 29.35; NOE difference (27°): irradiate 13.02 δ, NOES observed 7.60-7.44 δ (19%); ^{13}C-^{1}H coupling experiments: fully coupled spectrum, carbonyl 195.31 δ (dq, $^2J_{CH3}$ = 6.2 Hz, $^3J_{pyridinone\ H}$ = 3.0 Hz), irradiate 8.53 δ (carbonyl signal collapses to q), 7.53 δ (no change), 2.02 δ (carbonyl signal collapses to d).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.77; H, 4.08; N, 11.73.

Continued chromatography gave compound **3c** 1.1 g mp 265-267°; ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz, δ 13.05 (b, 1H, NH), 8.10 (s, 1H, pyridinone H), 7.74-7.65 (m, 3H, aromatic), 7.59-7.52 (m, 2H, aromatic), 2.40 (s, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): 75 MHz, δ 192.24, 159.89, 157.37, 149.20, 137.44, 133.09, 129.47, 128.74, 115.87, 99.16, 18.84; NOE difference (27°): irradiate 13.05 δ, NOES observed 2.40 δ (21%); ^{13}C-^{1}H coupling experiments: fully coupled spectrum, 5-carbonyl 192.24 δ (dt, $^3J_{ArH}$ = 3.8 Hz, $^3J_{pyridinone\ H}$ = 3.6 Hz), irradiate 8.10 δ (car-

bonyl signal collapses to t, 7.73 δ (carbonyl signal collapses to d), 2.40 δ (no change in carbonyl).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.51; H, 4.23; N, 11.72.

5-Acetyl-6-Methyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**3e**).

Sodium hydride (50% in mineral oil) (2.50 g, 52 mmoles), cyanoacetamide (4.02 g, 50 mmoles) and **10c** (7.75 g, 50 mmoles) in dry tetrahydrofuran (125 ml) were treated as described for **3c** and **3d**. After neutralization with glacial acetic acid and concentration on the rotary evaporator, the insoluble residue was partitioned between dichloromethane-water. Filtration and workup of the dichloromethane layer gave a tan solid. Recrystallization from ethyl acetate gave the analytical sample of **3e** (3.84 g, 44%) mp 225-226° (lit mp 232°[3]); ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz, δ 12.90 (b, 1H, NH), 8.66 (s, 1H, pyridinone H), 2.56 (s, 3H, CH_3), 2.46 (s, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): 75 MHz, δ 194.99, 159.71, 158.58, 149.79, 115.89, 115.30, 90.06, 28.90, and 19.92.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.57; N, 15.90. Found: C, 61.08; H, 4.60; N, 16.17.

5-(1-Oxopentyl)-6-Methyl-2(1*H*)-pyridinone (**12**).

Compound **3a** (0.731 g, 3.3 mmoles) and concentrated hydrochloric acid (35 ml) were heated and stirred at reflux overnight. When the reaction mixture cooled to ambient temperature, crystals of acid **11** (0.47 g) precipitated. Acid **11** when heated and stirred at 280°-290° for 7 minutes gave crude **12**. Crude **12** was dissolved in dichloromethane (100 ml) and extracted with 5.0% sodium bicarbonate, separated, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to a residue which was recrystallized from cyclohexane to give **12**, 0.11 g (17%) mp 167-169°; ^{1}H nmr (dimethyl sulfoxide-d_6): 80 MHz, δ 11.97 (b, 1H, NH), 7.93 (d, 1H, J = 9.7 Hz, pyridinone H_4), 6.20 (d, 1H, J = 9.7 Hz, pyridinone H_3), 2.76 (t, 2H, J = 7.0 Hz, $COCH_2$), 2.47 (s, 3H, CH_3), 1.70-1.05 (m, 4H, $2CH_2$), 0.87 (t, 3H, J = 6.1 Hz, CH_3).

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.35; H, 7.84; N, 7.25. Found: C, 68.06; H, 7.83; N, 7.03.

Compound **16** (2.20 g, 110 mmoles) was heated and stirred with 0.32 g Pd/C for 20 minutes under an argon atmosphere at 250°. The reaction mixture was allowed to cool to ambient temperature then dissolved in dichloromethane (300 ml) and filtered through celite. The resulting light brown liquid when concentrated on the rotary evaporator gave a solid. Recrystallization from cyclohexane gave 0.75 g (35%) of **12** which was identical by tlc with the previous sample.

5-(1-Oxopentyl)-3,4-dihydro-6-methyl-2(1*H*)-pyridinone (**16**).

Compound **15** [10] (4.4 g, 31 mmoles) and acrylic anhydride (4.00 g, 37 mmoles) were heated and stirred in chloroform (50 ml) at reflux under argon for 1 hour. The resulting yellow solution was concentrated to give a yellow solid. The solid was dissolved in dichloromethane and extracted with 2 x 250 ml portions of 5.0% sodium bicarbonate, washed with brine and dried over anhydrous magnesium sulfate. Filtration followed by concentration and trituration with hexane gave a solid. Recrystallization from cyclohexane gave fluffy white needles of **16**, 2.0 g, (33%) mp 94-95°; ^{1}H nmr (deuteriochloroform): 80 MHz, δ 8.66 (b, 1H, NH), 2.75-2.30 (m, 6H, $3CH_2$), 223 (s, 3H, CH_3), 1.75-1.05 (m, 4H, $2CH_2$), 0.91 (t, 3H, J = 6.0 Hz, CH_3).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.82; H, 8.71; N, 6.95.

N-Methyl-*N*-methoxyvaleramide (**18b**).

Pyridine (43.0 ml, 0.53 mole) was added dropwise to a stirred mixture of valeryl chloride (29.67 ml, 250 mmoles), *N,O*-dimethylhydroxylamine hydrochloride (24.39 g, 250 mmoles) and 4-dimethylaminopyridine (6.79 g, 55 mmoles) in 400 ml of dry dichloromethane under argon at 0°. The reaction mixture was stirred overnight at ambient temperature. Concentration of the reaction mixture afforded a pasty tan semi-solid. The residue was partitioned in a mixture of dichloromethane-ether (1:1, 600 ml) and brine (300 ml). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a light brown liquid. Distillation at 101-103° on the aspirator gave 27.73 g (77%) of **18b**; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 3.69 (s, 3H, OCH_3), 3.18 (s, 3H, NCH_3), 2.42 (t, 2H, J = 7.0 Hz, CH_2), 1.68-1.55 (m, 2H, CH_2), 1.44-1.30 (m, 2H, CH_2), 93 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C nmr (deuteriochloroform): 75 MHz, δ 61.04, 31.47, 32.63, 22.39, 13.71; ir (neat): 1670 cm^{-1} (broad band).

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.93; H, 10.54; N, 9.54.

4-(2,2-Dimethylhydrazino)-3-octen-2-one (**19a**).

n-Butyllithium (2.5 *M*) (22.0 ml, 55 mmoles) was added to a stirred solution of **17a** [11] (7.11 g, 50 mmoles) in dry tetrahydrofuran (150 ml) at -70° under an argon blanket. To the resulting heterogeneous solution was added **18a** [12] (5.15 g, 50 mmoles) dissolved in tetrahydrofuran dropwise. The resulting solution was allowed to warm to 0° and quenched with a saturated solution of ammonium chloride. The resulting two phase mixture was stirred overnight. The organic phase was separated and dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate gave a pale yellow liquid. Distillation on the Kugelrohr at 90-110° (0.03 mm) afforded 6.58 g (71%) of **19a**; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 11.14 (b, 1H, NH), 4.85 (s, 1H, vinyl H), 2.54 (s, 6H, $2CH_3$), 2.37-2.30 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.59-1.48 (m, 2H, CH_2), 1.42-1.33 (m, 2H, CH_2), .93 (s, 3H, J = 7.0 Hz, CH_3); uv (ethanol): λ max = 309 nm, ε = 15.100; ir (deuteriochloroform): 1605 and 1570^{-1}.

Anal. Calcd. for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.94; N, 15.21. Found: C, 65.42; H, 10.94; N, 14.99.

4-(2,2-Dimethylhydrazino)-2-octen-4-one (**19b**).

n-Butyllithium (2.5 *M*) (56 ml, 140 mmoles) was added dropwise to a stirred solution of **17b** (11.90 g, 135 mmoles) in dry tetrahydrofuran (200 ml) at -70° under an argon blanket. The resulting heterogeneous mixture was stirred for 1 hour at -70° then **16b** (19.58 g, 135 mmoles) dissolved in tetrahydrofuran (20 ml) was added dropwise. The reaction mixture was then treated as described for **19a**. Distillation on the Kugelrohr at 85°, (0.015 mm) gave a colorless liquid. Fractional distillation gave **19b**, 15.17 g (61%), bp 70-74 (0.01-0.03 mm); ^{1}H nmr (deuteriochloroform): 300 MHz, δ 11.09 (b, 1H, NH), 4.77 (s, 1H, vinyl H), 2.46 (s, 6H, $2CH_3$), 2.16 (t, 2H, J = 8.0 Hz, CH_2), 1.94 (s, 3H, CH_3), 1.53-1.45 (m, 2H, CH_2), 1.30-1.22 (m, 2H, CH_2), 0.83 (t, 3H, J = 7.0 Hz, CH_3); uv (ethanol): λ max = 307 nm, ε = 15,900; ir (neat): 1610 and 1575 cm^{-1}.

Anal. Calcd. for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.94; N, 15.21. Found: C, 65.10; H, 10.98; N, 14.91.

4-(2,2-Dimethylhydrazino)-4-phenyl-3-buten-2-one (**19c**).

n-Butyllithium (2.5 *M*) (25.0 ml, 63 mmoles) was added dropwise to a stirred solution of **17c** (9.73 g, 60 mmoles) in dry tetrahydrofuran (200 ml) at -70° under an argon blanket. The resulting heterogeneous mixture was stirred for 1 hour at -70° then **18a** (6.73 g, 650 mmoles) dissolved in dry tetrahydrofuran (10 ml) was added dropwise. The reaction mixture was then treated as described for **19a**. The semi-solid resulting after workup was triturated with hexane (75 ml) and collected by filtration. Recrystallization from ether-hexane gave **19c** (9.02 g, 74%) as white needles mp 63.5-65.5°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 10.95 (b, 1H, NH), 7.46-7.32 (m, 5H, aromatic), 5.04 (s, 1H, vinyl H), 2.49 (s, 6H, $2CH_3$), 2.10 (s, 3H, CH_3); uv (ethanol): λ max = 237 nm, ε = 6,930), 318 nm, ε = 13,000); ir (neat): 1600, 1575, and 1510 cm^{-1}; ms: m/e 204 (M^+) (100), 146 (80).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.53; H, 8.06; N, 13.62.

3-(2,2-Dimethylhydrazino)-1-phenyl-2-buten-1-one (**19d**).

n-Butyllithium (2.5 *M*) (22.0 ml, 55 mmoles) was added dropwise to a stirred solution of **17b** (8.26 g, 50 mmoles) in dry tetrahydrofuran (200 ml) at -70° under argon. The resulting heterogeneous mixture was treated as described for **19c**. To this mixture was added **18c** (8.26 g, 50 mmoles) dissolved in dry tetrahydrofuran dropwise and the mixture treated as in **19c**. The yellow oil obtained after workup was subjected to flash chromatography on silica gel eluting with ethyl acetate-dichloromethane (35:65) to give **19d** 6.5 g (64%) as a yellow liquid; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 11.74 (b, 1H, NH), 7.88-7.81 (m, 2H, aromatic), 7.42-7.43 (m, 3H, aromatic), 5.64 (s, 1H, vinyl H), 2.58 (s, 6H, $2CH_3$), 2.15 (s, 3H, CH_3; ^{13}C nmr (deuteriochloroform): 75 MHz, δ 187.63, 164.74, 140.08, 130.45, 128.12, 126.91, 90.05, 77.54, 77.11, 76.69, 48.41 and 18.58; uv (ethanol): λ max = 341 nm, ε = 19,100; ir (neat): 1620, 1605, and 1570 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.65; H, 7.96; N, 13.80.

3-[(Dimethylamino)methylene]-2,4-octanedione-4-(dimethylhydrazone) (**20a**).

Compound **9** (4.77 g, 40 mmoles) and **19a** (5.94 g, 32 mmoles) were mixed together at ambient temperature under an argon blanket. The resulting liquid was heated and stirred at 95° overnight. Concentration on the rotary evaporator afforded brown liquid. Distillation on the Kugelrohr at 110-130° (0.3 mm) gave 5.42 g (71%) [19] of an amber liquid. Flash chromatography eluting with methanol-dichloromethane (7:5-92.5) gave 3.70 g (51%) of **20a**; uv (ethanol): λ max = 305 nm, ε = 18,000); ^{1}H nmr (deuteriochloroform): 300 MHz, 90:10 mixture of isomers, δ 7.35, 7.15 (each b, 1H, vinyl H), 2.97 (s, 6H, $2CH_3$), 2.54, 2.49 (each s, 6H, 2-CH_3), 2.39 (m, 2H, CH_2), 2.13, 2.12 (each s, 3H, $COCH_3$), 1.54 (m, 2H, CH_2), 1.36 (m, 2H, CH_2), 0.91 (t, 3H, J = 7.0 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{25}N_3O$: C, 65.23; H, 10.53; N, 17.56. Found: C, 65.26; H, 10.41; N, 17.22.

3-[(Dimethylamino)methylene]-2,4-octanedione-2-(dimethylhydrazone) (**20b**).

Compound **9** (10.0 ml, 75 mmoles) and **19b** (12.04 g, 65.3 mmoles) were allowed to react as described above. Distillation on the Kugelrohr at 88-120° (0.02 mm) gave 12.82 g (82%) [19] of an amber oil. Fractional distillation of a small amount of the oil gave **20b** bp 119-121° (0.01-0.015 mm); uv (ethanol): λ max = 303 nm, ε = 19,400); ^{1}H nmr (deuteriochloroform): 300 MHz, 50:50 mixture of isomers, δ 7.33-7.13 (each s, 1H, vinyl H), 2.97 (s, 6H, $2CH_3$), 2.56, 2.49 (each s, 6H, $2CH_3$), 2.39 (m, 2H, CH_2), 2.18, 2.14 (each s, 3H, CH_3), 1.59 (m, 2H, CH_2), 1.32 (m, 2H, CH_2), 0.907, 0.894 (each t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{25}N_3O$: C, 65.23; H, 10.53; N, 17.56. Found: C, 65.38; H, 10.34; N, 17.30.

2-[(Dimethylamino)methylene]-1-phenyl-1,3-butanedione-1-(dimethylhydrazone) (**20c**).

Compound **9** (6.5 ml, 40 mmoles) and **19c** (8.13 g, 40 mmoles) were heated and stirred under argon at 95° for 20 hours. The resulting mixture was concentrated and the resulting residue was stored in the refrigerator for 4 days. The resulting yellow semi-solid was triturated with hexane and collected by filtration. Recrystallization from hexane-ether gave 8.80 g (85%) of **20c** mp 91-92°; ^{1}H nmr (deuteriochloroform): 300 MHz, 22°, δ 7.72-7.61 (m, 3H, 2 aromatic, and 1 vinyl H), 7.35-7.26 (m, 3H, aromatic), 2.88 (b, 6H, $2CH_3$), 2.77 (s, 6H, $2CH_3$), 1.95 (s, 3H, $COCH_3$); ^{1}H nmr (deuteriochloroform): 300 MHz, 5°, δ 7.73-7.63 (m, 3H, 2 aromatic and vinyl H), 7.37-7.31 (m, 3H, aromatic), 2.90 (b, 6H, $2CH_3$), 2.76 (s, 6H, $2CH_3$), 1.96 (s, 3H, $COCH_3$); ^{1}H nmr (deuteriochloroform): 300 MHz, -30°, δ 7.74-7.68 (m, 3H, 2 aromatic and vinyl H), 7.39-7.35 (b, 3H, aromatic), 3.15 (s, 3H, CH_3), 2.77 (s, 6H, $2CH_3$), 2.67 (s, 3H, CH_3), 1.93 (s, 3H, $COCH_3$); ir (10% chloroform): 1645 and 1560 cm^{-1} (broad band); uv (ethanol): λ max = 309 nm, ε = 18,800); ms: (CI-CH_4), (260 MH^+).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.45; H, 8.21; N, 16.20. Found: C, 69.45; H, 8.21; N, 16.14.

2-[(Dimethylamino)methylene]-1-phenyl-1,3-butanedione-3-(dimethylhydrazone (**20d**).

Compound **9** (3.80 ml, 28 mmoles) and **19d** (4.90 g, 24 mmoles) were heated and stirred as previously described for **20c**. The liquid resulting from the workup was partially purified by chromatography on silica gel eluting with methanol-dichloromethane (7.55:92.5). The resulting liquid solidified when triturated with hexane. Recrystallization from ether-hexane gave the analytical sample of **20d**, 2.60 g (42%) mp 110-112°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 7.56-7.52 (m, 2H, aromatic), 7.39-7.36 (m, 3H, aromatic), 6.82 (s, 1H, vinyl H), 2.89 (s, 6H, $2CH_3$), 2.32 (s, 6H, $2CH_3$), 2.18 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 75 MHz, δ 190.13, 163.40, 149.82, 141.52, 129.52, 127.84, 127.71, 107.53, 45.75, 42.58, 23.92; ir (potassium bromide): 1630, 1620 (sh), 1580 and 1560 cm^{-1} (broad band); uv (ethanol): λ max = 309 nm, ε = 17,700).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.21; N, 16.20. Found: C, 69.28; H, 8.28; N, 16.23.

5-[1-(Dimethylhydrazono)pentyl)]-1,2-dihydro-6-methyl-2-oxo-3-pyridine carbonitrile (**21a**).

Compound **20a** (3.73 g, 156 mmoles) was added to a stirred mixture of **5** (1.68 g, 20 mmoles) and sodium hydride (80% suspension in mineral oil) (0.60 g, 20 mmoles) in dry dimethylformamide (40 ml) under argon. The mixture began to react immediately. After the initial reaction subsided the mixture was heated and stirred at 80° for 13 hours. The cooled reaction mixture was neutralized with 3.60 ml (60 mmoles) of glacial acetic acid. Concentration gave an orange residue which was dissolved in a 2-phase dichloromethane-water mixture. The dichloro-

methane layer was succesively washed with 2 x 200 ml water, 2 x 250 ml 5.0% sodium bicarbonate, brine and dried over anhydrous magnesium sulfate. Filtration followed by concentration on the rotary evaporator gave an orange oil. Trituraton of the oil with hexane afforded a solid (2.60 g, 64%) mp 91-104° [19]. Hplc (μ-porosil column, ethyl acetate) showed two major peaks (81.3%) of total were present. Flash chromatography of a small quantity of the *E* and *Z* mixture of **21a** with dichloromethane-ethyl acetate (1:1) gave the low melting isomer of **21a** (97.5% by hplc) mp 133-135°. ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz, δ 12.70 (b, 1H, NH), 8.03 (s, 1H, pyridinone H), 2.37 (t, 2H, J = 7.5 Hz, CH_2), 2.30 (s, 6H, $2CH_3$), 2.15 (s, 3H, CH_3), 1.40-1.21 (m, 4H, $2CH_2$), 0.85 (t, 3H, J = 7.0 Hz, CH_3); uv (ethanol): λ max = 252 nm, ε = 8,920).

Anal. Calcd. for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.42; H, 7.74; N, 21.71.

Further elution with methanol-dichloromethane (10:90) gave the more polar high melting isomer of **21a** which was 92.8% one isomer by hplc mp 144-145°; ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz, δ 12.65 (b, 1H, NH), 8.13 (s, 1H, pyridinone H), 2.73 (m, 2H, CH_2), 2.44 (s, 6H, $2CH_3$), 2.32 (s, 3H, CH_3), 1.26-1.19 (m, 4H, $2CH_2$), 0.84 (t, 3H, J = 7.0 Hz, CH_3); uv (ethanol): λ max = 253 nm, ε = 9,190).

Anal. Calcd. for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.54. Found: C, 64.55; H, 7.70; N, 21.66.

6-Butyl-5-[1-(dimethylhydrazono)ethyl]-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**21b**).

Sodium hydride (80% suspension in mineral oil) (0.86 g, 29 mmoles) was added to a stirred mixture of **20b** (3.73 g, 15.6 mmoles) amd **5** (1.68 g, 20 mmoles) in dry dimethylformamide (40 ml) under argon. The mixture began to react immediately. The mixture was then reacted and worked up as described for **21a**. Trituration with hexane (100 ml) followed by filtration gave a solid which was recrystallized from ethanol-water to give **21b**, 1.41 g (35%) mp 176-177°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 13.27 (b, 1H, NH), 7.85 (s, 1H, pyridinone H), 2.58 (s, 6H, $N(CH_3)_2$), 2.24 (s, 3H, CH_3), 1.76-1.64 (m, 2H, CH_2), 1.51-1.38 (m, 4H, $2CH_2$), .98 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C nmr (deuteriochloroform): 75 MHz, δ 162.28, 158.81, 156.00, 148.31, 119.19, 115.16, 101.16, 47.02, 32.00, 31.65, 22.98, 18.61, 13.63; ir (10% chloroform): 1660 cm^{-1} (broad band); uv (ethanol): λ max = 254 nm, ε = 8,980), 344 nm, ε = 9,190); ms: (CI-CH_4), 261 (MH^+).

Anal. Calcd. for: $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74, N, 21.52. Found: C, 64.73; H, 7.77; N, 21.56.

5-[(1-Dimethylhydrazono)phenylethyl]-1,2-dihydro-2-oxo-6-phenyl-3-pyridinecarbonitrile (**21c**).

Sodium hydride (80% suspension in mineral oil) (0.86 g, 29 mmoles), **20c** (4.02 g, 15.6 mmoles) and **5** (1.68 g, 20 mmoles) were reacted as described for **21b**. Trituration of the residue with hexane (100 ml) gave a solid. Recrystallization from ethanol-water gave 2.18 g (50%) of **21c** as yellow micro needles mp 226-227°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 7.80 (s, 1H, pyridinone H), 7.49-7.30 (m, 5H, aromatic), 2.63 (s, 6H, $2CH_3$), 2.31 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 75 MHz, δ 162.67, 151.43, 149.96, 149.60, 137.47, 129.72, 128.64, 126.79, 115.73, 115.07, 101.45, 47.03, 18.87; ir (potassium bromide): 1765 cm^{-1} (broad band); uv (ethanol): λ max = 243 nm, ε = 16,600), and λ max = 332 nm, (ε = 12,000); ms: (CI-CH_4), 280 (MH^+).

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.62; H, 5.76; N, 20.26.

5-[(1-Dimethylhydrazono)ethyl]-1,2-dihydro-2-oxo-6-phenyl-3-pyridinecarbonitrile (**21d**).

Sodium hydride (80% suspension in mineral oil) (0.24 g, 8.0 mmoles), **5** (0.67 g, 8.0 mmoles) and **20d** (1.89 g, 7.3 mmoles) were reacted as previously described for **21b**. Trituration with hexane (100 ml) gave a yellow solid. Recrystallization from ethanol-water gave 1.08 g (53%) of **21d** mp 209-211°; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 8.07 (s, 1H, pyridinone H), 7.55 (s, 6H, aromatic, NH), 2.56 (s, 6H, $2CH_3$), 1.70 (s, 3H, CH_3): uv (ethanol): λ max = 254 nm, ε = 11,900); ms: (CI-CH_4), 280 (MH^+).

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.66; H, 5.72; N, 19.99. Found: C, 68.66; H, 5.75; N, 19.92.

5-(1-Oxopentyl)-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**3a**).

To a stirred solution of **21a** (2.23 g, 8.6 mmoles) in tetrahydrofuran (50 ml), was slowly added 2*N* hydrochloric acid (100 ml). The resulting solution was stirred at ambient temperature under argon overnight. A flocculent white precipitate was collected by filtration and washed well with water to give a white solid. Recrystallization from ethanol-water afforded 1.26 g (67%) of **3a** mp 196-197° as fluffy white needles.

5-Acetyl-6-butyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**3b**).

To a solution of **21b** (2.23 g, 8.6 mmoles) dissolved in tetrahydrofuran (50 ml) was slowly added 2*N* hydrochloric acid (60 ml). The reaction mixture was treated as in **3a**. The precipitate was collected by filtration and washed well with water giving a solid. Recrystallization gave the analytical sample of **3b** 0.58 g (62%) mp 219-220°.

5-Benzoyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (**3c**).

Hydrochloric acid (2*N*) (15 ml) was slowly added to a stirred solution of **21c** (0.30 g, 1.1 mmoles) in tetrahydrofuran (15 ml) at ambient temperature. The resulting mixture was then stirred overnight under argon. Concentration of the reaction mixture on the rotary evaporator resulted in precipitation of a white solid. The solid was washed well with water and dried to give 0.148 g (56%) of **3c** identical by tlc with **3c** above.

5-Acetyl-6-phenyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**3d**).

Hydrochloric acid (2*N*) (36 ml) was slowly added to a stirred solution of **21d** (0.84 g, 3.0 mmoles) in tetrahydrofuron (36 ml). The resulting slightly yellow solution was stirred overnight at ambient temperature under argon. Concentration of the reaction mixture on the rotary evaporator resulted in precipitation of a lustrous white solid. The solid was washed well with water and dried giving 0.64 g (89%) mp 259-261°. The sample was identical by tlc with **3d** above.

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[19] The Compounds **17a** were sufficiently pure at this point to be used in the next step.