# Cyclization of Ylidenemalononitriles. VIII. Synthesis of Coumarins from *o*-Methoxybenzylidenemalonitriles (1)

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Received November 19, 1974

A new synthesis of coumarins, by direct cyclization of α-cyano-*o*-methoxycinnamates in sulfuric acid, is described. The reaction seems quite general, and alkoxy groups other than the *o*-methoxy group involved in lactone formation are not hydrolyzed during the reaction. The 3-cyano group on the resulting coumarin is not hydrated in concentrated sulfuric acid, but can be converted to the carbamido group in 90% sulfuric acid. In certain cases these conditions do cleave methoxy substituents on the coumarins. Although the sulfuric acid cyclization did not produce the usual indenones when an *o*-methoxy group was present, the corresponding indenones could be obtained by cyclizing the ylidenemalononitriles with boron trifluoride-etherate. Possible reasons for this selectivity are discussed, and new coumarins and indenones characterized.

Coumarins are widely documented in the literature and their preparation has received much attention due to the wide variety of biological activities they possess (3). Although coumarins are commonly prepared by lactonization of *o*-hydroxycinnamic acids, Baker *et al.* (4) were able to prepare 3-cyanocoumarin in 92% yield *via* condensation of malononitrile with *o*-hydroxybenzaldehyde followed by treatment with cold dilute hydrochloric acid. DeGraw (5) reported the synthesis of 6-hydroxycoumarin by cyclizing 2,5-dimethoxycinnamic acid in a chloroform solution containing boron tribromide. However, this reaction undoubtedly involved formation of the lactone from 2,5-dihydroxycinnamic acid, formed as an intermediate by ether cleavage. Indeed, treatment of 2,5-dimethoxycinnamic acid under the same conditions for a shorter period of time led to the isolation of 2,5-dihydroxycinnamic acid in nearly quantitative yield. *o*-Methoxycinnamates having a β-substituent, prepared by the Reformatsky reaction on *o*-methoxy ketones, have been cyclized to coumarins by first cleaving the methyl ether with hydrogen iodide (6). *O*-Methylcoumaric acid, however, did not cyclize under these conditions (7).

In the course of further work on the cyclization of ylidenemalononitriles (8) we have found that 2-methoxy substituted α-cyano-β-arylcinnamonitriles (**1**) are converted directly to 3-cyano-4-arylcoumarins (**2**) in good yield when warmed in concentrated sulfuric aicd. It is significant that other methoxy groups (*e.g.* **1**, Y = $CH_3O$) were not cleaved during the reaction. The cyanocoumarins obtained in this way are shown in Table II.

The reaction appears to be general for *o*-methoxybenzylindenemalononitriles. In addition to the various benzo-

Chart I

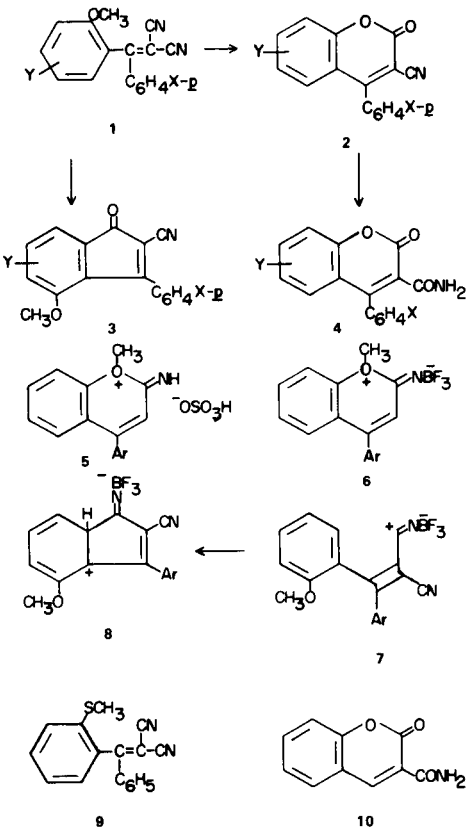

Table I

Some *o*-Methoxy Substituted Benzophenylidenemalononitriles (**1**)

| | X | Y | M.p. °C | % Yield | Method (a) | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N | NMR δ/$CDCl_3$ (b) 2-$OCH_3$ | NMR δ/$CDCl_3$ (b) Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | Cl | H | 103-104 | 43 | A | $C_{17}H_{11}ClN_2O$ | 69.27 | 3.76 | 9.50 | 69.22 | 3.79 | 9.23 (c) | 3.72 | |
| **1b** | H | H | 117-118 | 66 | B | $C_{17}H_{12}N_2O$ | 78.44 | 4.64 | 10.76 | 78.40 | 4.90 | 10.70 | 3.72 | |
| **1c** | Cl | 4-$OCH_3$ | 120-122 | 76 | A | $C_{18}H_{13}ClN_2O_2$ | 66.57 | 4.03 | 8.62 | 66.65 | 4.19 | 8.44 (d) | 3.68 | 4-3.80 |
| **1d** | Cl | 5-$OCH_3$ | 120-122 | 60 | A | $C_{18}H_{13}ClN_2O_2$ | 66.57 | 4.03 | 8.62 | 66.27 | 4.01 | 8.33 (e) | (3.70 & 3.73) | |
| **1e** | H | 3-$OCH_3$ | 106-107 | 65 | B | $C_{18}H_{14}N_2O_2$ | 74.46 | 4.86 | 9.64 | 74.94 | 4.78 | 9.50 | 3.82 | 3-3.42 |
| **1f** | H | 4-$OCH_3$ | 120-121 | 66 | B | $C_{18}H_{14}N_2O_2$ | 74.46 | 4.86 | 9.64 | 74.18 | 4.96 | 9.72 | 3.72 | 4-3.82 |
| **1g** | H | 5-$OCH_3$ | 82-84 | 54 | B | $C_{18}H_{14}N_2O_2$ | 74.46 | 4.86 | 9.64 | 74.70 | 4.85 | 9.55 | (3.70 & 3.72) | |

(a) Methods of preparation, see Experimental. (b) TMS standard. (c) Calcd: %Cl, 12.02. Found: 12.17. (d) Calcd: %Cl, 10.91. Found: 10.95. (e) Calcd: %Cl, 10.91. Found: 10.76.

phenone derivatives shown in Table I, α-cyano-*o*-methoxycinnamonitrile was converted to 3-carbamoylcoumarin (**10**) in high yield. The isolation of the intermediate 3-cyano-4-arylcoumarins (**2**) in all other cases reflects the hindrance to hydration of the cyano group by flanking bulky groups, already noted in the formation of 3-substituted-2-cyano-1-naphthylamines by cyclization of appropriate ylidenemalononitriles (9). As in these earlier cases, the hindered cyano groups could be hydrated by warming in 90% sulfuric acid for some time, thus converting **2** into the corresponding 3-carbamoyl derivatives, **4**. The 3-carbamoylcoumarins so formed are shown in Table III.

The direct cyclization of *o*-methoxycinnamonitriles to coumarins is synthetically advantageous, since frequently it is necessary to mask phenolic hydroxyl groups in order to synthesize the desired intermediates for coumarin syntheses. Thus the ether cleavage step can be omitted, which is particularly desirable when other alkoxy groups which are to be retained are present in the molecule. For example, all of the ylidenemalononitriles shown in Table I were synthesized by a convenient method recently described (10) in which a metal ketimate was formed by reaction of an aryllithium with a nitrile, and this quenched, without isolation, with malononitrile. This reaction could not be used to synthesize compounds with free phenolic groups.

In view of the facile cyclization of benzylidenemalononitriles to form indenones (11) in concentrated sulfuric acid, it is remarkable that no indenones **3** were isolated from the sulfuric acid treatment of **1**, even when the position for electrophilic attack was activated, as in α-cyano-β-phenyl-2,3-dimethoxycinnamonitrile (**1**, X = H, Y = 3-$OCH_3$) or α-cyano-β-aryl-2,5-dimethoxycinnamonitriles (**1**, X = H or Cl, Y = 5-$OCH_3$). However, several of these ylidenemalononitriles **1** were converted in good yield to the 4-methoxyindenones **3** by refluxing with boron trifluoride in ether. In these cases only traces of coumarins could be isolated, indicating a rather selective nature for the two reagents. The 4-methoxyindenones prepared by this reaction are reported in Table IV.

The different results obtained when different acidic catalysts were used may be the result of a deficiency of nucleophile present in the boron trifluoride cyclization. The reaction undoubtedly involved attack on the ether oxygen by the electrophilic nitrile-acid complex (protonated nitrile in sulfuric acid) leading to intermediate ionic species **5** (or **6** in boron trifluoride-etherate). In the case of **5**, however, there is bisulfate ion present, which can act as a nucleophile to displace the methyl group as methyl bisulfate, forming the lactone. The ionic intermediate **6** in ether solution has no nucleophile available for further reaction and must be in equilibrium with the nitrile-boron trifluoride complex (**7**). Attack of the electrophilic nitrile-boron trifluoride complex on the benzene ring will lead to

Table II

Substituted 3-Cyano-4-arylcoumarins (2)

| | X | Y | M.p. °C | % Yield | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N | NMR δ/CDCl$_3$ -OCH$_3$ (a) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | Cl | H | 213-214 | 73 | $C_{16}H_8ClNO_2$ | 68.22 | 2.86 | 4.97 | 68.00 | 3.10 | 4.88 (b) | |
| **2b** | H | H | 216-218 | 74 | $C_{16}H_9NO_2$ | 77.72 | 3.66 | 5.66 | 77.50 | 3.84 | 5.54 | |
| **2c** | Cl | 7-OCH$_3$ | 202-204 | 72 | $C_{17}H_{10}ClNO_3$ | 65.50 | 3.23 | 4.49 | 65.15 | 3.37 | 4.45 (c) | 3.98 |
| **2d** | Cl | 6-OCH$_3$ | 242-244 | 83 | $C_{17}H_{10}ClNO_3$ | 65.50 | 3.23 | 4.49 | 65.60 | 3.36 | 4.39 (d) | 3.72 |
| **2e** | H | 8-OCH$_3$ | 248-250 | 69 | $C_{17}H_{11}NO_3$ | 73.63 | 3.99 | 5.05 | 73.34 | 4.02 | 4.80 | 4.00 |
| **2f** | H | 7-OCH$_3$ | 200-201 | 63 | $C_{17}H_{11}NO_3$ | 73.63 | 3.99 | 5.05 | 73.34 | 4.12 | 4.84 | 3.93 |
| **2g** | H | 6-OCH$_3$ | 189-190 | 58 | $C_{17}H_{11}NO_3$ | 73.63 | 3.99 | 5.05 | 73.31 | 3.98 | 5.08 | 3.73 |

(a) TMS standard. (b) Calcd: %Cl, 12.58. Found: 12.59. (c) Calcd: %Cl, 11.37. Found: 11.25. (d) Calcd: %Cl, 11.37. Found: 11.55.

Table III

3-Carbamoyl-4-arylcoumarins (4)

| | X | Y | M.p. °C | % Yield | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | Cl | H | 230-232 | 75 | $C_{16}H_{10}ClNO_3$ | 64.12 | 3.36 | 4.67 | 63.89 | 3.31 | 4.58 (a) |
| **4b** | H | H | 191-192 | 90 | $C_{16}H_{11}NO_3$ | 72.44 | 4.17 | 5.28 | 72.59 | 4.22 | 5.25 |
| **4c** | Cl | 7-OCH$_3$ | 222-224 | 80 | $C_{17}H_{12}ClNO_4$ | 61.92 | 3.66 | 4.24 | 61.85 | 3.80 | 4.29 |
| **4d** | Cl | 6-OCH$_3$ | 209-212 | 70 (b) | $C_{17}H_{12}ClNO_4$ | 61.92 | 3.66 | 4.24 | 61.80 | 3.80 | 4.19 |
| **4e** | H | 8-OCH$_3$ | 195-197 | 75 | $C_{17}H_{13}NO_4$ | 69.14 | 4.43 | 4.74 | 69.21 | 4.70 | 4.58 |
| **4g** | H | 6-OH | 189-192 | 75 | $C_{16}H_{11}NO_4$ | 68.32 | 3.94 | 4.97 | 67.97 | 4.01 | 4.84 |
| **4h** | Cl | 6-OH | 149-151 | 90 | $C_{16}H_{10}ClNO_4$ | 60.87 | 3.19 | 4.43 | 60.71 | 3.25 | 4.27 |

(a) Calcd: %Cl, 11.82. Found: 11.90. (b) Overall yield from two step synthesis: see Experimental.

Table IV

Substituted Indenones (3)

| | X | Y | M.p. °C | % Yield | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3b** | H | H | 138-140 | 65 | $C_{17}H_{11}NO_2$ | 78.14 | 4.24 | 5.36 | 77.87 | 4.47 | 5.16 |
| **3c** | Cl | 6-OCH$_3$ | 212-214 | 60 | $C_{18}H_{12}ClNO_3$ | 66.36 | 3.71 | 4.29 | 66.35 | 3.91 | 4.21 |
| **3d** | Cl | 7-OCH$_3$ | 260-262 | 70 | $C_{18}H_{12}ClNO_3$ | 66.36 | 3.71 | 4.29 | 66.33 | 4.00 | 4.29 |
| **3e** | H | 5-OCH$_3$ | 161-162 | 60 | $C_{18}H_{13}NO_3$ | 74.21 | 4.49 | 4.80 | 74.05 | 4.67 | 4.55 |
| **3f** | H | 6-OCH$_3$ | 192-194 | 70 | $C_{18}H_{13}NO_3$ | 74.21 | 4.49 | 4.80 | 74.43 | 4.79 | 5.01 |
| **3g** | H | 7-OCH$_3$ | 248-250 | 75 | $C_{18}H_{13}NO_3$ | 74.21 | 4.49 | 4.80 | 73.93 | 4.72 | 4.76 |

intermediate **8**, which is readily converted to neutral keto-imine by proton transfer.

As previously noted, most of the 3-cyanocoumarins shown in Table II could be hydrated by warming in 90% sulfuric acid for several hours. When 3-cyano-4-*p*-chlorophenyl-6-methoxycoumarin and 3-cyano-4-phenyl-6-methoxycoumarin were heated on a steam-bath in 90% sulfuric acid for 12 hours, the corresponding 6-hydroxy-3-carbamido derivatives, **4h** and **4g**, were obtained. Compound **4h** was then realkylated to the methoxy derivative **4d**. Under the same conditions, the 8-methoxy group of 3-cyano-4-phenyl-8-methoxycoumarin was not cleaved. It is also surprising to note that little or no cleavage of any of the methoxy groups other than that involved in lactone formation occurred during the cyclization.

Attempted basic hydration of 3-cyano-4-*p*-chlorophenyl-6-methoxycoumarin, **2d** to the 3-carboxycoumarin resulted in hydrolysis followed by a retro-Knoevenagel reaction and the isolation of 2-hydroxy-5-methoxy-4′-chlorobenzophenone.

It was of interest to determine whether the corresponding 1-thiocoumarins could be prepared by cyclization of *o*-methylthiocinnamonitriles, and therefore α-cyano-β-phenyl-*o*-methylthiocinnamonitrile, **9**, was prepared. However, efforts to cyclize this material in sulfuric acid were unrewarding.

## EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. The infrared spectra were obtained on a Perkin-Elmer Model 137-B Infracord spectrometer using potassium bromide mulls. Nmr spectra were determined on a Varian Associates EM-360 60MHz spectrometer. Mass spectra were resolved on a Varian MAR CH-7 spectrometer. Elemental analyses were performed by Midwest Microlab, Inc. of Indianapolis, Indiana.

Starting Materials.

Most of the aromatic nitriles required for the preparations in Table I were synthesized from the corresponding aldehydes which were commercially available. 2,4-Dimethoxybenzonitrile (Aldrich) was the only nitrile obtained commercially. 2-Methoxybenzaldehyde (Matheson, Coleman and Bell), 2,3-dimethoxybenzaldehyde (J. T. Baker Industrial Co.) and 2,5-dimethoxybenzaldehyde (Aldrich) were converted into 2-methoxybenzonitrile, b.p. 73-76° @ 0.1 mm (lit. (12) 82° @ 0.4 mm), 2,3-dimethoxybenzonitrile, m.p. 42-43° (lit. (13) 41-43°) and 2,5-dimethoxybenzonitrile, m.p. 77-78° (lit. (14) 81-83°) respectively. These syntheses were carried out by the method described by T. van Es (15) in which an aldehyde was refluxed in hydroxylamine hydrochloride, sodium formate and formic acid. *o*-Methylthioaniline (Aldrich) was converted into the nitrile, m.p. 37-38° (lit. (16) 36-38°) *via* the Sandmeyer reaction (17).

α-Cyano-*o*-methoxycinnamonitrile.

In a 250 ml. round bottom flask fitted with a Dean-Stark water trap 40 g. (300 mmoles) of *o*-methoxybenzaldehyde, 19.8 g. (300 mmoles) of malononitrile, 125 ml. of benzene, 1.6 g. of benzoic acid and 4 ml. of piperidine were allowed to reflux for 15 hours. The reaction mixture was worked up by extraction with 100 ml. portions of water, 1*N* hydrochloric acid and conc. bicarbonate. The aqueous layers were extracted with 40 ml. portions of benzene and the benzene layers combined and dried over magnesium sulfate. Evaporation of the solvent yielded a crude solid which was recrystallized from methanol to give 48.2 g. (87%) of tan crystals, m.p. 83-85°; ir λ max, 4.50 μ (CN); nmr (deuteriochloroform): δ 3.94 (S, 3H, $-OCH_3$). This compound was reported to melt at 84° (18).

Preparation of the *o*-Methoxybenzophenylidenemalononitriles (**1**).

The compounds listed in Table I were prepared by condensing the appropriate aromatic nitrile with *p*-chlorophenyllithium, generated *in situ* from *p*-chlorobromobenzene and butyllithium (Method A), or with commercial phenyllthium (Method B).

Method A.

In a 3-neck round bottom flask equipped with a rubber septum, drying tube, dry nitrogen inlet and a magnetic stirrer, a solution of 38 mmoles (16.5 ml. of 2.3*M*) *n*-butyllithium in ether was cooled to -78°, and 5.73 g. (30 mmoles) of *p*-chlorobromobenzene added and stirred at -78° for 30 minutes. Then 30 mmoles of an *o*-methoxybenzonitrile in ether was injected into the solution, and after stirring for 10 minutes, 60 mmoles (4.0 g.) of malononitrile in ether was injected into the solution, and the mixture was allowed to warm to room temperature with stirring. The resulting ether suspension was washed with dilute hydrochloric acid, then several times with water, and dried over magnesium sulfate. Evaporation of the ether left a dark oil which usually solidified, and could be recrystallized from alcohol. In this manner compounds **1a**, **1c**, and **1d** were prepared.

Method B.

A dry round bottom flask containing a magnetic stirrer was flushed thoroughly with nitrogen gas and fitted with a rubber septum. A quantity of commercial phenyllithium (Alpha, 2.3*M* in hexane) was injected into the flask, and cooled to 0°. An equivalent of the desired nitrile was then injected slowly with stirring. Following this addition, the solution was cooled to -78° and two equivalents of malononitrile was added rapidly with stirring. The mixture was then allowed to warm to room temperature, poured over crushed ice, the ether layer separated, and the water layer extracted with ether. The combined ether layers were washed with dilute bicarbonate solution, dried and the ether layer evaporated to leave a crude yellow oil or solid, which could be recrystallized from methanol. Compounds, **1b**, **1e**, **1f**, and **1g** were prepared by this method.

The yields of these *o*-methoxy derivatives were generally lower than those previously reported (10), probably due to an *ortho*-effect.

α-Cyano-β-phenyl-*o*-methylthiocinnamonitrile (**9**).

Treatment of *o*-methylthiobenzonitrile with phenyllithium, as described under Method B above, led to the isolation of yellow crystals of **9**, m.p. 77-80°, in only 25% yield; nmr: δ 2.32 (S, 3H, $-SCH_3$).

*Anal.* Calcd. for $C_{17}H_{12}N_2S$: C, 73.88; H, 4.37; S, 11.60. Found: C, 73.67; H, 4.56; S, 11.56.

3-Carbamoylcoumarin (**10**).

A solution of 18.4 g. (0.1 mole) of α-cyano-*o*-methoxycinnamonitrile in 50 ml. of concentrated sulfuric acid was warmed on a steam bath for about 20 minutes, then poured over ice and let stand till all the ice melted. The crude solid which separated was collected and recrystallized from methanol, giving 17 g. (90%) of white crystals melting at 263-265°, as previously reported (19); ir: 5.85 (CO) and 6.10 (amide CO).

*Anal.* Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.32; H, 3.97; N, 7.27.

3-Cyano-4-arylcoumarins (**2**).

All of the compounds in Table II were prepared as described for Compound **10**. A quantity of the *o*-methoxybenzophenylidenemalononitrile (**1**), was added to 30 ml. of concentrated sulfuric acid and warmed gently at 75° for 20 minutes. At the end of this time, the mixture was poured over crushed ice and allowed to sit for approximately three hours, at which time the crude solid was filtered off and could be recrystallized from methanol.

All of the compounds in Table II showed characteristic ir max at 4.50 μ (CN) and 5.85-5.90 μ (C=O); and a complex aromatic multiplet δ 6.60-7.35 in the nmr. Chemical shifts for the substituent methoxy protons are given in Table II.

3-Carbamoyl-4-arylcoumarins (**4**).

A quantity of the 3-cyanocoumarin was added to 90% sulfuric acid and heated on a steam bath, usually overnight (20). At the end of this time, the mixture was poured over crushed ice and allowed

to stand for three hours, at which time the crude solid was filtered off and recrystallized from water. This procedure was used for the preparation of **4a**, **4b** and **4e**.

All of the compounds in Table III showed characteristic ir max at 5.85-5.90 $\mu$ (C=O) and 6.05-6.15 $\mu$ (amide C=O).

3-Carbamoyl-4-(*p*-chlorophenyl)-6-hydroxycoumarin (**4h**).

When **2d** was treated as above, the 6-methoxy group was hydrolyzed also, and the product isolated was the 6-hydroxy derivative, **4h**, which was recrystallized from water, and showed ir $\mu$ max (potassium bromide): 2.85 (-OH), 5.87 (lactone CO) and 6.08 (amide CO). Compound **4g** was prepared in the same manner from **2g**.

3-Carbamoyl-4-(*p*-chlorophenyl)-6-methoxycoumarin (**4d**).

An acetone solution (60 ml.) of 1.0 g. (3.17 mmoles) of **4h**, 0.44 g. (3.17 mmoles) of potassium carbonate and 0.40 g. (3.18 mmoles) of dimethyl sulfate, was allowed to reflux overnight, then 100 ml. of chloroform was added. The solid salts were filtered off and the filtrate evaporated to yield a crude white solid which was recrystallized from water to give 0.80 g. (80%) of white crystals of **4d**; nmr $\delta$ 3.72 (s, 3H, $OCH_3$).

2-Cyano-3-aryl-4-methoxyindenones (**3**).

The compounds listed in Table IV were obtained as follows: a mixture of 50 ml. of boron trifluoride-etherate (Eastman) and 0.05 mole of an ylidenemalononitrile, **1**, was allowed to reflux for one hour, then quenched by pouring over crushed ice. The crude mixture was extracted with four 100 ml. portions of chloroform, and the combined organic extracts dried over magnesium sulfate. Evaporation of the chloroform left an orange solid which was recrystallized from methanol. All compounds **3** listed in Table IV showed characteristics already noted for 2-cyano-3-arylidenones (11). The nmr data were consistent with structures shown, all compounds in Table IV having a peak at $\delta$ 3.85 (3H) for the 4-methoxy substituent. Compounds **3d** and **3g** showed a second peak at $\delta$ 3.98 (3H) for the 7-methoxy substituent, and compound **3e** two peaks at $\delta$ 3.80 (3H) and 3.85 (3H).

2-Hydroxy-5-methoxy-4′-chlorobenzophenone.

In an attempt to hydrate the nitrile group, 0.5 g. of **2d** was heated on a steam bath for four hours in 50 ml. of 10% potassium hydroxide, then poured over crushed ice. After two hours, the yellow precipitate was collected and recrystallized from water to yield 9.4 g. (95%) of yellow needles melting at 74-75°; ir: 2.9 $\mu$ (OH), 6.22 $\mu$ (CO); nmr (deuteriochloroform): $\delta$ 3.74 (s, 3H), 7.10 (m, 3H), 7.60 ($A_2B_2$dd, 4H) 11.00 (-OH, 1H).

*Anal.* Calcd. for $C_{14}H_{11}ClO_3$: C, 64.17; H, 4.22; Cl, 13.52; m.w. 262.0396. Found: C, 64.16; H, 4.25; Cl, 13.75; $M^+$ 262.0397.

The 2,4-dinitrophenylhydrazone melted at 264-265°.

*Anal.* Calcd. for $C_{20}H_{15}ClN_4O_6$: C, 54.24; H, 3.41; N, 12.65. Found: C, 54.44; H, 3.58; N, 12.54.

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