Aroylations of N,N-Dimethylglycinonitrile to Form α-Dimethylamino-β-ketonitriles. Cyclizations with Acetophenone to Give 3-Dimethylamino-2-pyridones[1]

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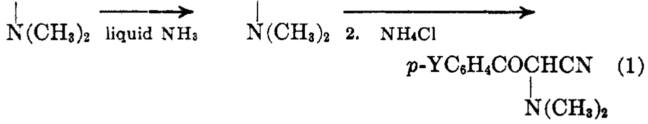
Similar to the earlier benzoylation of acetonitrile to form benzoylacetonitrile,[2] aroylations of dimethylaminoacetonitrile (**1**)[3] have now been accomplished with methyl benzoate, methyl anisate, and methyl *p*-chlorobenzoate by means of sodium amide in liquid ammonia to form aroyl N,N-dimethylglycinonitriles **2a–c**, respectively (eq 1) (Table I).

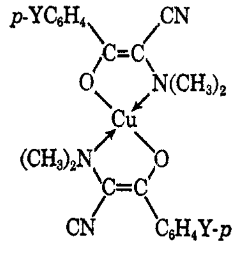


$$\underset{\displaystyle N(CH_3)_2}{CH_2CN} \xrightarrow[\text{liquid } NH_3]{NaNH_2} \underset{\displaystyle N(CH_3)_2}{NaCHCN} \xrightarrow[2.\ NH_4Cl]{1.\ p\text{-}YC_6H_4COOCH_3} p\text{-}YC_6H_4CO\underset{\displaystyle N(CH_3)_2}{CHCN} \quad (1)$$

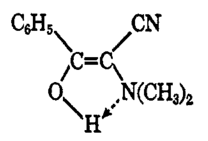
2a, Y = H
b, Y = OCH$_3$
c, Y = Cl

These new examples of the Claisen type of aroylation were effected in the presence of an extra equivalent of sodium amide,[4] and the products **2a–c** were isolated through their hydrochloride salts. The yield of **2a** was 65% when isolated in this manner but only 40% when isolated by direct recrystallization of the crude reaction product.

In contrast to benzoylacetonitrile, the corresponding α-dimethylamino compound **2a** evidently exists mainly in its enol form. Whereas benzoylacetonitrile gave a negative enol test and failed to form a copper chelate, **2a** produced a strong, positive enol test with ethanolic ferric chloride and readily yielded the copper chelate **3a**. The infrared spectrum of benzoylacetonitrile



3a, Y = H
b, Y = Cl



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showed a strong carbonyl peak but that of **2a** exhibited only a slight shoulder in this region. The nmr spectrum of **2a** showed an enol proton at 8.5 and a methinyl proton at 5.2 ppm, the intensities of which were, by integration, in the ratio of 3:2. These results suggest

TABLE I

AROYL N,N-DIMETHYLGLYCINONITRILES AND THEIR COPPER CHELATES

Compd	Mp, °C	Yield, %	Infrared spectrum, μ	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2a	85–86	65	3.3 (s) broad, 3.5 (s) broad, 4.6 (s), 6.0 (w) sh, 6.15 (m) Sh, 6.3 (s)	$C_{11}H_{12}N_2O$	70.2	6.43	14.9	70.26	6.50	14.87
2b	69–70	45	2.9 (w) broad, 3.35 (m), 3.5 (m) 4.5 (m), 5.9 (s), 6.2 (s), 6.35 (s)	$C_{12}H_{14}N_2O_2$	66.1	6.47	12.83	66.06	6.43	12.82
2c	84–85	60	3.1 (s) broad, 3.6 (s) broad, 4.55 (s), 5.95 (m) Sh, 6.25 (s) broad	$C_{11}H_{11}N_2OCl$	59.3	4.98	12.58	59.12	5.12	12.36
3a	181	48	3.4 (w) broad, 4.55 (s), 6.3 (m), 6.5 (s)	$C_{22}H_{22}N_4O_2Cu$	60.25	5.06	12.78	60.34	5.01	12.65
3b	184–185	53	3.4 (w) broad, 4.6 (s), 6.3 (m), 6.5 (s)	$C_{22}H_{20}N_4O_2Cl_2Cu$	52.15	3.97	11.05	52.07	4.32	10.84

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[1] Supported by the National Science Foundation and by Public Health Service Research Grant No. CA-04455 from the National Cancer Institute.

[2] C. J. Eby and C. R. Hauser, *J. Amer. Chem. Soc.*, **79**, 723 (1957).

[3] This compound is readily prepared from formaldehyde, dimethylamine, and sodium cyanide: A. Lespagnol, E. Cuingnet, and M. Derbaert, *Bull. Soc. Chim. Fr.*, **2**, 383 (1960).

[4] See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 114, 122 (1954).

TABLE II

3-DIMETHYLAMINO-4-*para*-SUBSTITUTED 6-PHENYL-2(1H)-PYRIDONES

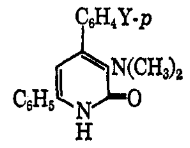
Compd	Mp, °C	Yield, %	Infrared spectrum, μ	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5a	231–234 dec	37	2.9 (w), 3.4 (s) broad, 6.1 (s), 6.35 (m), 6.5 (m), 12.9 (s), 13.1 (s), 14.3 (s)	$C_{19}H_{18}N_2O$	78.6	6.35	9.65	78.55	6.42	9.32
5b	259–262 dec	35[a]	2.9 (w), 3.5 (s) broad, 6.1 (s), 6.35 (m), 6.5 (m), 12.0 (s), 12.2 (m), 13.0 (s) doublet, 14.4 (s)	$C_{20}H_{20}N_2O_2$	75.0	6.3	8.75	74.89	6.26	8.56
5c	272–275 dec	30	2.9 (w), 3.4 (s) broad, 6.15 (s), 6.3 (m), 6.5 (m), 11.9 (s), 12.3 (m), 12.9 (s), 14.4 (s)	$C_{19}H_{17}N_2OCl$	70.20	5.35	8.62	70.36	5.23	8.53

[a] Also amide **6b**, mp 135–136°, was isolated in 35% yield. *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 61.0; H, 6.83; N, 11.86. Found: C, 61.22; H, 6.78; N, 12.10.

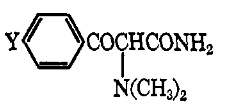
that about two-thirds of **2a** exists in the enol form which, in spite of distortion of the normal bond angles of the ethylene system, appears to be stabilized by hydrogen bonding as indicated in **4**. Such distortion may be mitigated somewhat by conjugation of the ethylniec double bond with both the phenyl and cyanide groups. Another possibility for stabilization of the enol form might arise through the enamine type of resonance. Molecular weight determinations by the Rast method in camphor and by the freezing point method in benzene indicated that the enol form did not exist as a dimer.

Although **2a** gave a strong enol test, the *p*-methoxy and *p*-chloro compounds **2b–c** produced weakly positive enol tests and their infrared spectra showed strong and medium peaks, respectively, for the carbonyl group. These results suggest predominance of the keto form; **2c** afforded copper chelate **3b**, but this may have arisen through shift in equilibrium to the side of the enol as the reaction proceeded.

Similar to the earlier cyclization of benzoylacetonitrile or benzoylacetamide with acetophenone to form a substituted 2-pyridone,[5] the ketoaminonitriles **2a–c** were cyclized with this ketone by means of polyphosphoric acid (PPA) to give the amino-2-pyridones **5a–c**, respectively (Table II). Presumably, the corresponding amides such as **6a–b** or PPA derivatives of them were intermediates; actually, amide **6b** was isolated from the reaction mixture (see note *a*, Table II). Moreover, nitrile **2a** was converted into amide **6a** by sulfuric acid, and subsequently cyclized with acetophenone to form pyridone **5a** by PPA. Benzoylacetonitrile has previously been converted into benzoylacetamide by PPA.[6]



5a, Y = H
b, Y = OCH_3
c, Y = Cl



6a, Y = H
b, Y = OCH_3

All of the products described above are new. Their structures are supported by analyses and infrared spectra (see Tables I and II and Experimental Section). The yields of the ketoaminonitriles **2a–c** were good (45–65%), but those of the amino pyridones **5a–c** were only fair (30–37%); these yields are probably not the maximum obtainable.

Experimental Section[7]

Aroyl N,N-Dimethylglycinonitriles (Table I).—Sodium amide was prepared by dissolving 10.7 g (0.466 mol) of sodium in approximately 350 ml of liquid ammonia containing a trace of ferric nitrate hexahydrate. To the stirred suspension of sodium amide in liquid ammonia was added N,N-dimethylglycinonitrile[3] (19.6 g, 0.233 mol). A yellow color developed. After stirring

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(5) C. R. Hauser and C. J. Eby, *J. Amer. Chem. Soc.*, **79**, 728 (1957).

(6) C. R. Hauser and C. J. Eby, *ibid.*, **79**, 725 (1957).

(7) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord in potassium bromide pellets. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer using deuteriochloroform solutions and tetramethylsilane as an internal standard. Elemental analyses were performed by Janssen Pharmaceutical Research Laboratories, Beerse, Belgium, and M-H-W Laboratories, Garden City, Mich.

for 15 min, 0.233 mol of the appropriate ester was added in 75 ml of ether. The reaction mixture was stirred for 20 min; then an excess of ammonium chloride was added. The ammonia was evaporated on the steam bath as an equal volume of ether was added. The resulting ethereal suspension was stirred with water to dissolve the inorganic salts. The layers were separated, and the aqueous layer was extracted twice with small portions of ether. The combined ethereal solution was dried over anhydrous sodium sulfate and saturated with anhydrous hydrogen chloride. The resulting precipitate was collected and dried to give the crude hydrochloride salts of the aroyl N,N-dimethylglycinonoitriles **2a–c** in yields of 80, 70, and 75%, respectively. The salts were neutralized with aqueous sodium bicarbonate to liberate the free base. Extraction of the aqueous mixture with ether, removal of the ether under reduced pressure, and recrystallization of the solid residue from hexane provided **2a–c** in the yields given in Table I.

To a solution of the aryl N,N-dimethylglycinonitrile in ethanol was added an excess of aqueous copper acetate solution with stirring. The mixture was stirred for about 20 min; then the precipitate was collected and recrystallized from 95% ethanol to give the copper chelate (see Table I).

Benzoyl N,N-Dimethylglycinamide (6a).—Benzoyl N,N-dimethylglycinonitrile (**2a**) (1 g) was dissolved in 5 g of concentrated sulfuric acid and heated on the steam bath for 30 min. The reaction mixture was poured onto crushed ice and the solution was neutralized with solid sodium bicarbonate. The mixture was extracted several times with ether; the combined ethereal extract was dried over anhydrous potassium carbonate and the ether was removed under reduced pressure. The residue was recrystallized from a benzene–hexane mixture giving 0.9 g (85%) of the amide **6a**: mp 93–94°; ir, 3.0 (s), 3.15 (s), 3.5 (m), 3.55 (m), 5.9 (s), 6.1 (w), and 6.25 (m) μ.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.84; N, 13.59. Found: C, 64.38; H, 6.75; N, 13.33.

3-Dimethylamino-4-*para*-Substituted 6-Phenyl-2(1H)-pyridones (Table II).—The aroyl N,N-dimethylglycinonitrile was stirred into five times its weight of polyphosphoric acid, and then an equivalent of acetophenone was added. The reaction mixture was placed in an oil bath and heated at 80–90° until a homogeneous solution was obtained. An additional equivalent of acetophenone was added and the temperature was raised to 140° and maintained at this temperature for 25 min. Upon addition of the solution to crushed ice, a precipitate formed. The resulting mixture was made basic with ammonium hydroxide and the precipitate was collected. Recrystallization of the product from benzene–ethanol gave the pyridone.

In a similar manner, N,N-dimethylbenzoylglycinamide (**6a**) was cyclized to give pyridone **5a** in 35% yield.

Registry No.—**1**, 926-64-7; acetophenone, 98-86-2; **2a**, 16607-55-9; **2b**, 16607-56-0; **2c**, 16607-57-1; **3a**, 16591-65-4; **3b**, 16591-66-5; **5a**, 16607-58-2; **5b**, 16607-18-4; **5c**, 16607-19-5; **6a**, 16622-18-7; **6b**, 16607-20-8.

A Convenient Preparation of Dimethyl Cyclohexa-1,3-diene-1,4-dicarboxylate. A Bicyclo[2.2.2]octane Precursor

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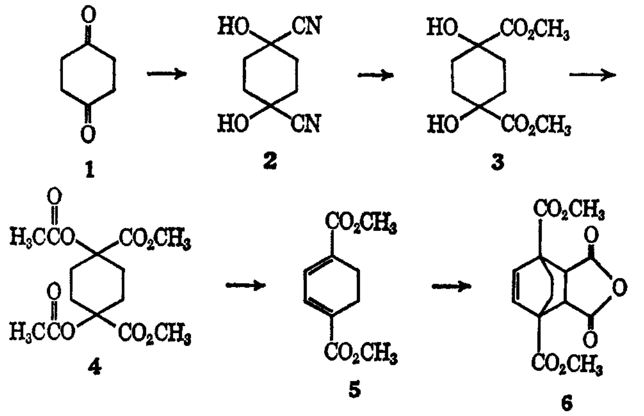
We wish to report a convenient synthesis of dimethyl cyclohexa-1,3-diene-1,4-dicarboxylate (**5**; see Chart I), a bicyclo[2.2.2]octane precursor. Bridgehead substituted bicyclo[2.2.2]octanes have been a subject of intensive study.[1] A time-consuming synthesis of these compounds was developed by Kauer and coworkers[2] which involves the dehydrohalogenation of dimethyl 1,4-dibromocyclohexane-1,4-dicarboxylate followed by addition of ethylene to the resulting 1,3-diene.

Chart I



Although 1,4-cyclohexanedione is available by other routes,[3] we found the oxidation of 1,4-cyclohexanediol with chromium trioxide to be a convenient source of this dione. Compound **1** reacts readily with acetone cyanohydrin to yield compound **2**. This material, in turn, is then converted in two steps into dimethyl 1,4-diacetoxy-1,4-dicarboxylate (**4**). Pyrolysis of this diacetate at 400° affords the desired diene (**5**) in 75% yield. The other major product, formed in 18% yield, is dimethyl terephthalate. The crude pyrolysate reacted readily with maleic anhydride to give 1,4-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-ene-*endo*-2,3-dicarboxylic anhydride (**6**). It is of interest to note the remarkable selectivity of the pyrolysis reaction under the conditions studied, especially since previous work strongly suggests that dimethyl cyclohexa-1,4-diene-1-4-dicarboxylate is the most stable of the methyl esters of the dihydroterephthalic acids.[4]

Experimental Section[5]

1,4-Cyclohexanediol.—This alcohol was prepared in 93% yield by the hydrogenation of hydroquinone according to the procedure of Owen and Robins.[6]

1,4-Cyclohexanedione (1)[3,7] was prepared by adding a solution of CrO_3 (9.1 g) and concentrated sulfuric acid (7.7 ml) in water (33.8-ml total volume)[8] to 1,4-cyclohexanediol (5.0 g, 0.043 mol) in acetone (300 ml) at 10°. After addition was completed (1 hr, voluminous precipitate), stirring for 0.5 hr, pouring into ice water, neutralizing with Na_2CO_3, continuous extraction with CH_2Cl_2, drying ($MgSO_4$), evaporating, and sublimation of the residue gave 4.1 g (84%) of **1**.

1,4-Dihydroxy-1,4-dicyanocyclohexane (2).—1,4-Cyclohexanedione (56 g, 0.5 mol) was mixed with acetone cyanohydrin[9] (750 ml, Matheson Coleman and Bell, practical grade) and heated to

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[1] See H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, **87**, 2404 (1965), and references cited therein.

[2] J. C. Kauer, R. E. Benson, and G. W. Parshall, *J. Org. Chem.*, **30**, 1431 (1965). These authors discuss the synthetic difficulties of previously reported approaches toward these compounds.

[3] A. T. Nielsen and W. R. Carpenter, *Org. Syn.*, **45**, 25 (1965).

[4] See ref 2, footnote 17.

[5] Melting points are corrected and were recorded on a Fisher–Johns apparatus. Microanalyses were done by H. C. Jones of this laboratory. Ultraviolet spectra were recorded on a Perkin-Elmer Spectracord Model 4000A. Infrared spectra were taken as KBr pellets using a Perkin-Elmer Infracord Model 137 spectrophotometer. Gas chromatographic analyses were done using an F & M Model 700 chromatograph. Recrystallizations were done in ethyl acetate.

[6] L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).

[7] J. R. Vincent, A. F. Thompson, Jr., and L. I. Smith, *J. Org. Chem.*, **3**, 603 (1939).

[8] C. Djerassi, R. R. Engle, and A. Bowers, *ibid.*, **21**, 1547 (1956).

[9] H. J. Ringold, *J. Amer. Chem. Soc.*, **82**, 961 (1960).