[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Conjugate Addition of α-Dimethylaminophenylacetonitrile with Benzalacetophenone and Ethyl Cinnamate by Means of Potassium Amide[1]

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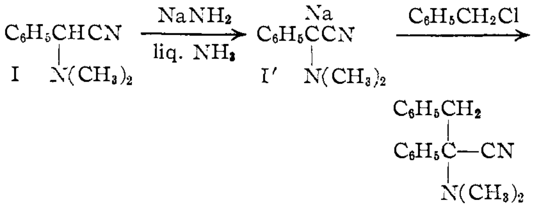
The conjugate additions of α-dimethylaminophenylacetonitrile with benzalacetophenone and with ethyl cinnamate were effected by means of catalytic and equivalent amounts of potassium amide in liquid ammonia. The structures of the products were determined by appropriate reactions.

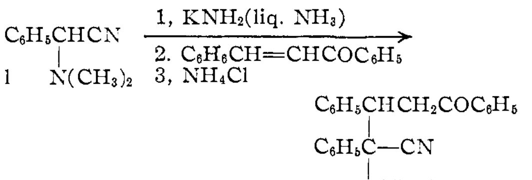
It has recently been shown that α-dimethylaminophenylacetonitrile (I) can be alkylated through the intermediate formation of carbanion I′, which was prepared by means of an equivalent of sodium amide or potassium amide in liquid ammonia.[2]

For example, the α-aminonitrile I was benzylated in 91% yield (equation 1).



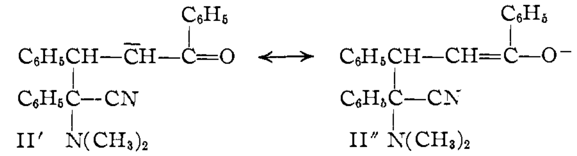
$$\underset{\text{I}}{C_6H_5CH(N(CH_3)_2)CN} \xrightarrow[\text{liq. }NH_3]{NaNH_2} \underset{\text{I}'}{C_6H_5C(Na)(N(CH_3)_2)CN} \xrightarrow{C_6H_5CH_2Cl} C_6H_5CH_2C(C_6H_5)(N(CH_3)_2)CN \quad (1)$$

It has now been found that α-dimethylaminophenylacetonitrile (I) can enter into conjugate addition with certain α,β-unsaturated carbonyl compounds through carbanion I′. Thus, when the α-aminonitrile I was added to an equivalent or a catalytic amount of potassium amide in liquid ammonia, followed by an equivalent of benzalacetophenone, the conjugate addition product II was obtained in yields of 80–84% (equation 2).



$$\underset{\text{I}}{C_6H_5CH(N(CH_3)_2)CN} \xrightarrow[\substack{2.\ C_6H_6CH=CHCOC_6H_5\\ 3,\ NH_4Cl}]{1,\ KNH_2(\text{liq. }NH_3)} \underset{\text{II}}{C_6H_5CH(CH_2COC_6H_5)C(C_6H_5)(N(CH_3)_2)CN} \quad (2)$$

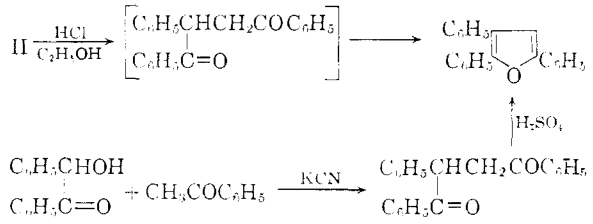
This condensation of intermediate carbanion I′ with the β-carbon of the α,β-unsaturated ketone would form carbanion II′, which would presumably be the end-product until acidification when an equivalent of potassium amide is employed.[3] On the other hand, carbanion II′ or its resonance form II″ should largely be neutralized by acquiring a proton from the medium to form II when a catalytic amount of the reagent is used, as in the common Michael type of condensation.



$$\underset{\text{II}'}{C_6H_5CH(C(C_6H_5)(N(CH_3)_2)CN)-\bar{C}H-C(C_6H_5)=O} \longleftrightarrow \underset{\text{II}''}{C_6H_5CH(C(C_6H_5)(N(CH_3)_2)CN)-CH=C(C_6H_5)-O^-}$$

The product obtained in 84% yield appeared to consist of a mixture of the two possible diastereoisomers of II since it melted over a range even after several recrystallizations. Its structure was indicated to be II by an analysis and by an infrared spectrum, which showed bands for the ketone and nitrile groups. This structure was established by an acid-catalyzed hydrolysis and cyclization to form 2,3,5-triphenylfuran, which was independently synthesized by the method of Smith[4] from benzoin and acetophenone (Scheme A).

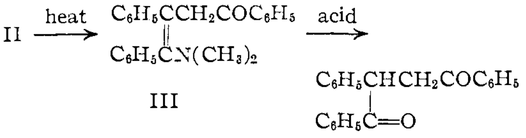
SCHEME A



Although the condensation of benzoin with acetophenone by means of potassium cyanide seems somewhat unusual,[5] the structure of the resulting 1,4-diketone, as well as that of the triphenylfuran produced on subsequent cyclization, appears to be well established.[4,6]

We have assumed that the 1,4-diketone is formed as an intermediate in the conversion of the ketone-aminonitrile II to the triphenylfuran, since acid-catalyzed hydrolyses of several α-aminonitriles have been shown to give the corresponding ketones.[2]

Ketone-aminonitrile II evidently underwent dehydrocyanation on heating to form the ketone-enamine III in low yield, since on subsequent treatment with hydrochloric acid the corresponding 1,4-diketone was obtained (equation 3).



$$\text{II} \xrightarrow{\text{heat}} \underset{\text{III}}{C_6H_5C(=C(C_6H_5)N(CH_3)_2)CH_2COC_6H_5} \xrightarrow{\text{acid}} C_6H_5CH(CH_2COC_6H_5)C(C_6H_5)=O \quad (3)$$

Such thermal dehydrocyanations of certain β-phenyl-α-aminonitriles and subsequent acid-catalyzed hydrolyses of the resulting enamines to form the corresponding ketones were described previously.[2] However, an attempt to effect the

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[1] Supported by a grant from Merck, Sharpe and Dohme, Rahway, N. J.

[2] C. R. Hauser, H. M. Taylor and T. G. Ledford, THIS JOURNAL, **82**, 1786 (1960).

[3] Under the conditions employed, there was no indication of the possible intramolecular displacement of the cyanide ion within carbanion II, or within resonance form II″ to give the cyclopropane or five-membered ring, respectively.

[4] A. Smith, *J. Chem. Soc.*, **57**, 643 (1890).

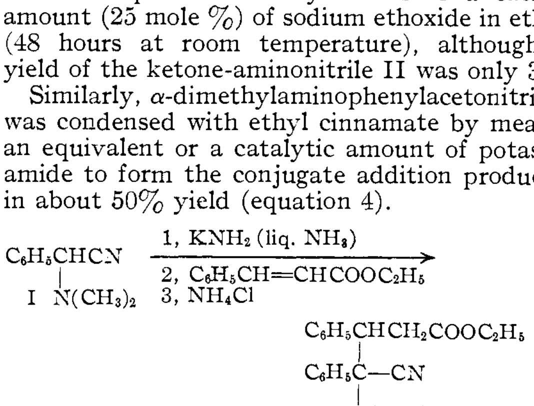
[5] Smith (ref. 4) states that carefully controlled conditions are required for success in this reaction.

[6] See T. Purdie and P. S. Arup, *J. Chem. Soc.*, **97**, 1545 (1910); and R. E. Lutz and W. R. Tyson, THIS JOURNAL, **56**, 1341 (1934).

dehydrocyanation of II by means of two equivalents of potassium amide in liquid ammonia (4 hr.) was unsuccessful, and 85% of II was recovered.

It should be mentioned that the conjugate addition of the aminonitrile I to benzalacetophenone was accomplished also by means of a catalytic amount (25 mole %) of sodium ethoxide in ethanol (48 hours at room temperature), although the yield of the ketone-aminonitrile II was only 38%.[7]

Similarly, α-dimethylaminophenylacetonitrile (I) was condensed with ethyl cinnamate by means of an equivalent or a catalytic amount of potassium amide to form the conjugate addition product IV in about 50% yield (equation 4).



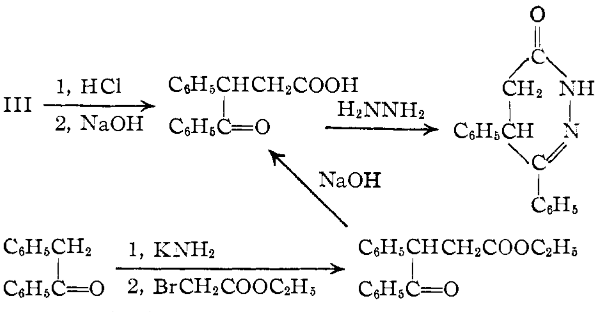
$$\underset{\text{I}}{\begin{array}{l}\mathrm{C_6H_5CHCN}\\ \quad|\\ \quad\mathrm{N(CH_3)_2}\end{array}} \xrightarrow[\substack{\text{2, } \mathrm{C_6H_5CH{=}CHCOOC_2H_5}\\ \text{3, } \mathrm{NH_4Cl}}]{\text{1, } \mathrm{KNH_2}\text{ (liq. } \mathrm{NH_3})} \underset{\text{IV}}{\begin{array}{l}\mathrm{C_6H_5CHCH_2COOC_2H_5}\\ \qquad|\\ \mathrm{C_6H_5C{-}CN}\\ \qquad|\\ \quad\mathrm{N(CH_3)_2}\end{array}} \qquad (4)$$

The condensation of the intermediate carbanion I′ with the β-carbon of the α,β-unsaturated ester presumably formed a carbanion analogous to II′ which either acquired a proton from the medium or remained as the end-product depending on the use of a catalytic or equivalent amount of the reagent (see above).

Since the product obtained in 50% yield melted rather sharply, it appeared to consist essentially of only one of the two possible diastereoisomers of III, although a second isomer was not isolated.

The structure of the product was indicated to be IV by an analysis and an infrared spectrum which showed both the ester and nitrile absorption bands. Its structure was established by hydrolysis to form the corresponding γ-keto acid which was independently synthesized from desoxybenzoin and ethyl bromoacetate; both samples of the keto-acid were converted to the pyridazinone with hydrazine (Scheme B).

SCHEME B



The alkylation of desoxybenzoin with ethyl bromoacetate by means of potassium amide is a modification of an earlier method in which sodium ethoxide was employed.[8]

Extensions of the conjugate addition of α-dimethylaminophenylacetonitrile (I) to ethyl acrylate and ethyl crotonate produced tarry materials from which derivatives of the expected products were evidently obtained in low yields (see Experimental).

Experimental[9]

α-Dimethylaminophenylacetonitrile (I) was prepared from benzaldehyde, 25% aqueous dimethylamine and sodium cyanide as described previously[2] except that anhydrous dimethylamine was employed in the earlier procedure. The product boiled at 88–90° at 1.8–2.1 mm., yield 88%.

Conjugate Addition of I with Benzalacetophenone to Form II. (A) With a Catalytic Amount of Potassium Amide.—To a stirred solution of 0.025 mole of potassium amide in 500 ml. of liquid ammonia[10] was added 0.3 mole of α-dimethylaminophenylacetonitrile (I) followed by 0.27 mole of solid benzalacetophenone. The solution was stirred for one hour, a solid being present in the reaction flask during the entire time. Excess ammonium chloride was added carefully, and stirring was continued for one-half hour. The ammonia was then replaced by ether. The ethereal suspension was filtered, and the solid was treated with hot benzene (some insoluble inorganic salts present). After filtering, an equal volume of hot hexane was added to the solution, and the mixture was allowed to cool to give 82.3 g. (84%) of α,β,δ-triphenyl-α-dimethylamino-δ-ketovaleronitrile (II), m.p. 161–165°. Several recrystallizations raised the melting point to 166–170°.

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.61. Found: C, 81.41; H, 6.60; N, 7.76.

The infrared spectrum contained a strong band at 1680 (carbonyl) and a weak band at 2230 cm.$^{-1}$ (nitrile).[11]

(B) With an Equivalent Amount of Potassium Amide.—The reaction was carried out as described above employing 0.1 mole of each of the reactants to give 29.7 g. (83%) of II melting at 158–164°. A mixed melting point with a sample of II obtained as described above was undepressed. The infrared spectra of the two products were superimposable.

Conversion of II to Form 2,3,5-Triphenylfuran.—To a solution of 100 ml. of 6 *M* hydrochloric acid in 200 ml. of ethanol was added 28.2 g. of II and the solution refluxed for 16 hours under the hood (caution, hydrogen cyanide evolved) The condenser was removed and about two-thirds of the solvent allowed to evaporate. On cooling, the oil that had separated solidified. The solid was recrystallized from ethanol to give 22.1 g. (96%) of 2,3,5-triphenylfuran, m.p. 90.5–91.5°. This melting point was not depressed on admixture with an authentic sample of 2,3,5-triphenylfuran prepared as described below. The infrared spectra of the two samples were identical.

Independent Synthesis of 2,3,5-Triphenylfuran.—1,2,4-Triphenylbutanedione-1,4 was prepared in 36% yield by the method of Smith[4] from benzoin and acetophenone in the presence of potassium cyanide. The product melted at 126–128°, reported 126°. Treatment of the diketone with sulfuric acid gave 78% of 2,3,5-triphenylfuran, m.p. 90.5–92°, reported[4] m.p. 92°.[4]

Thermal Dehydrocyanation of II.—Fifteen grams of II was refluxed in 100 ml. of toluene under the hood (caution, hydrogen cyanide evolved) for 20 hours using a drying tube. The toluene was removed under reduced pressure and the solid dissolved in hot benzene and filtered. An equal volume of hot hexane was added and on cooling, 8.5 g. (57%) of II separated. The filtrate was evaporated to dryness and the residue recrystallized from ethyl ether to give 3.2 g. of solid (III) melting at 82–115°. After two recrystallizations from methanol the product melted at 123.5–125°. The infrared spectrum contained a carbonyl band at 1680 cm.$^{-1}$, but showed no evidence of nitrile absorption. A mixed melting point of III with the diketone prepared by the method of Smith[4] showed a large depression.

Anal. Calcd. for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.55; H, 6.48; N, 4.25.

In another experiment, 15 g. of II was placed in a vacuum distillation system equipped with a Dry Ice–acetone trap

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(7) The product was identified by the mixed melting point method with a sample prepared by means of potassium amide. Much tarry material was obtained in the reaction with sodium ethoxide.

(8) J. Thiele and F. Straus, *Ann.*, **319**, 164 (1901).

(9) Analysis by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Melting points were determined on a Fisher-Johns apparatus. All melting points are uncorrected. Infrared spectra were obtained on a Perkin–Elmer model 21 instrument.

(10) See C. R. Hauser and T. M. Harris, THIS JOURNAL, **80**, 6360 (1958).

(11) See L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," second edition, John Wiley and Sons, Inc., New York, N. Y. 1958.

and a sodium hydroxide trap (hydrogen cyanide evolved). The solid was heated to 170–190° for 6 hours under a pressure of 0.6–1.0 mm. A small amount of liquid distilled over during this period. On working up the residue there was obtained 2.5 g. of solid melting at 80–118° which proved to be identical with III after several recrystallizations from methanol. The m.p. was not depressed on admixture with a sample prepared in toluene.

Hydrolysis of III.—To a solution of 5 ml. of concentrated hydrochloric acid in 15 ml. of water was added 0.75 g. of III and the suspension warmed on the steam-bath for one hour. The solid appeared to dissolve and reprecipitate simultaneously. The mixture was cooled, filtered and the solid recrystallized from methanol–water to give 0.61 g. (88%) of 1,2,4-triphenylbutanedione-1,4, m.p. 126–128°, undepressed on admixture with an authentic sample. A mixed melting point with III showed a large depression.

Conjugate Addition of I with Ethyl Cinnamate to Form IV. (A) With a Catalytic Amount of Potassium Amide.—To a solution of 0.0125 mole of potassium amide in 300 ml. of liquid ammonia was added 16 g. (0.1 mole) of α-dimethylaminophenylacetonitrile (I). After 5 minutes, 0.1 mole of redistilled ethyl cinnamate was added dropwise. When about three-fourths of the ethyl cinnamate had been added, a solid appeared in the reaction flask. The reaction was stopped 10 minutes after addition of the ester by careful addition of 4 g. of solid ammonium chloride. The ammonia was replaced by ether. The ethereal suspension was filtered and the solvent removed from the filtrate under reduced pressure. The mixture of solid and thick oil which remained was triturated with cold hexane and filtered, the solid being washed with more cold hexane. After 3 recrystallizations (one with Norite) there was obtained 14.0 g. of ethyl β,γ-diphenyl-γ-cyano-γ-dimethylaminobutyrate (IV) as a white crystalline solid melting at 90–91°. Concentration of the mother liquors and further purification gave an additional 3.45 g. of product to give a total yield of 17.45 g. (52%). For analysis a sample was recrystallized twice more from hexane, m.p. 91.5–92.5°. The infrared spectrum contained bands at 2215 (nitrile) and 1725 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 8.57; N, 8.33. Found: C, 75.10; H, 8.42; N, 8.32.

(B) With an Equivalent Amount of Potassium Amide.—The reaction was carried out as described above using 0.1 mole of each of the reagents. The reaction was stopped 5 minutes after addition of the ethyl cinnamate. There was obtained 12.5 g. (37%) of IV melting at 90.5–91.5° after 3 recrystallizations from hexane. A mixed m.p. with the product obtained above showed no depression. The infrared spectra of the two products were identical.

The mother liquors from the recrystallizations were concentrated and the solid obtained was hydrolyzed by the procedure described below to give 8.2 g. of desylacetic acid, m.p. 160.5–161.5°, undepressed on admixture with an authentic sample. Assuming the acid to arise from the hydrolysis of IV, the over-all yield of IV would be 69%.

Hydrolysis of IV to Form Desylacetic Acid, and Cyclization with Hydrazine.—To a solution of 20 ml. of hydrochloric acid, 50 ml. of water and 50 ml. of ethanol was added 12.5 g. of IV and the solution warmed on the steam-bath, under the hood (caution, hydrogen cyanide evolved) for 2 hours. A 5% excess of sodium hydroxide in 100 ml. of water and 100 ml. of ethanol was added and warming continued for 3 more hours, allowing the ethanol to evaporate. The solution was cooled, treated with Norite, filtered and acidified. The resulting oil solidified on cooling. The solid was recrystallized from ethanol–water to give 8.4 g. (88%) of desylacetic acid, m.p. 159–160°, which was undepressed on admixture with an authentic sample prepared below.

On warming with a slight excess of hydrazine, the desylacetic acid was converted to 2,3,4,5-tetrahydro-5,6-diphenylpyridazinone-3 melting at 219–221° (reported[12] 217–218°) undepressed on admixture with an authentic sample prepared below.

Independent Synthesis of Desylacetic Acid and Cyclization with Hydrazine.—This procedure is a modification of the method of Thiele and Straus.[8] To a solution of 0.1 mole of potassium amide in liquid ammonia was added 19.6 g. (0.1 mole) of desoxybenzoin to give a brownish suspension. After 15 minutes, 0.066 mole of ethyl bromoacetate was added and the solution allowed to stir for one-half hour and then 6 g. of ammonium chloride was carefully added. After one-half hour the ammonia was replaced by ether. The ethereal suspension was filtered and the solvent removed under reduced pressure to give a thick oil which was dissolved in 200 ml. of 60/40 ethanol–water solution containing 10 g. of sodium hydroxide. The solution was warmed on the steam-bath for 2 hours and the ethanol allowed to evaporate, water being added occasionally to maintain the volume. The solution was cooled, extracted with ether to remove any unreacted desoxybenzoin, and acidified to give an oil which soon crystallized. The solid was collected and recrystallized from ethanol–water to give 10.7 g. (63%) of desylacetic acid, m.p. 159.5–160.5° (reported[8] m.p. 162°).

The acid was converted to the pyridazinone by the method of Almström,[12] m.p. 219–221°.

The infrared spectra of both the acid and cyclization product were superimposable on those of the products obtained from the hydrolysis of IV.

Conjugate addition of I with ethyl acrylate was carried out according to the procedure for ethyl cinnamate. The ether and unreacted ethyl acrylate were removed under reduced pressure and the residual oil, which failed to crystallize, was hydrolyzed as described for ethyl cinnamate to give a tarry solid. This material was warmed on the steam-bath with a slight excess of hydrazine for 1 hour to give a solid, m.p. 144–149° after one recrystallization from ethanol. Further recrystallization gave 2.1 g. (12%) of presumably 2,3,4,5-tetrahydro-6-phenylpyridazinone-3, m.p. 149–152°, reported[13] m.p. 153°.

Conjugate Addition of I with Ethyl Crotonate.—The reaction was carried out on a 0.1-mole scale as described for ethyl cinnamate. The removal of the ether left an oil which failed to crystallize. This oil was hydrolyzed as described for ethyl cinnamate to give 15 g. of another oil which was refluxed with 9.1 g. of semicarbazide hydrochloride, 10 g. of sodium acetate trihydrate, 40 ml. of water and 100 ml. of ethanol. After 3 hours the alcohol was allowed to evaporate to give 4.3 g. (17%) of presumably β-benzoylbutyric acid semicarbazone, m.p. 174–176° after recrystallization from ethanol–water. The reported[14] m.p. is 177–178°.

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[12] G. K. Almström, *Ann.*, **400**, 137 (1913).

[13] S. Skraup and E. Schwamberger, *ibid.*, **462**, 135 (1928).

[14] L. Higginbotham, A. Lapworth and C. Simpson, *J. Chem. Soc.*, **125**, 2339 (1924).