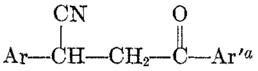
TABLE I

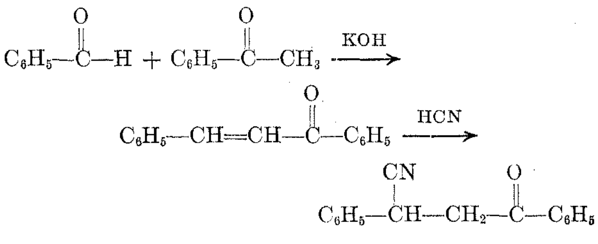


$$Ar{-}\overset{\overset{\displaystyle CN}{|}}{C}H{-}CH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Ar'^{a}$$

Ar	Ar′	Yield, %	M.P., °C.[b] Crude	M.P., °C.[b] Recrystd.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5	C_6H_5	77–82	124–126	126–127				
p-$CH_3OC_6H_4$	C_6H_5	72	115–117	116–118	76.96	76.94	5.70	5.68[c]
C_6H_5	p-$CH_3C_6H_4$	51	67–69	72–73	81.90	82.24	6.06	5.96[d]
o-ClC_6H_4	C_6H_5	76	106–108	107–109	71.25	71.54	4.48	4.63
p-ClC_6H_4	C_6H_5	89	116–118	117–119	71.25	71.35	4.48	4.49
p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$	67	95–99	103–105	77.39	77.49	6.13	6.22
o-ClC_6H_4	p-$CH_3OC_6H_4$	85	118–120	118–120	68.11	68.25	4.71	4.72

[a] Ar is from the aldehyde, $Ar{-}\overset{\overset{O}{\|}}{C}{-}H$. Ar′ is from the aryl methyl ketone, $Ar'{-}\overset{\overset{O}{\|}}{C}{-}CH_3$. [b] Melting points are uncorrected. [c] Nitrogen, Calcd. 5.28, found 5.18. [d] Nitrogen, Calcd. 5.62, found 5.74.

product of the reaction, however, was not the expected propionitrile. The preferred method for preparing 2-phenyl-3-benzoylpropionitrile has been by the addition of hydrogen cyanide to benzalacetophenone,[2] which in turn may be prepared by the base catalyzed condensation of benzaldehyde with acetophenone.[3] As was previously reported,[4] we have likewise found that hydrogen cyanide does not add to benzalacetophenone in the absence of a metal cyanide. Likewise the use of sodium or potassium cyanide alone, yields a mixture of products. The best method for adding hydrogen cyanide to benzalacetophenone employs an alkali cyanide and a weak acid such as acetic acid.[2,4] In search of a more convenient procedure for preparing 2-phenyl-3-benzoylpropionitrile, it occurred to us that there is no need to isolate the intermediate benzalacetophenone since it forms in excellent yield[3] in a basic medium. The addition of an excess of hydrogen cyanide to the original reaction mixture seemed, theoretically at least to constitute ideal conditions for the second step in the process.



$$C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}H + C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}CH_3 \xrightarrow{KOH}$$

$$C_6H_5{-}CH{=}CH{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5 \xrightarrow{HCN}$$

$$C_6H_5{-}\overset{\overset{CN}{|}}{C}H{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5$$

When benzaldehyde and acetophenone were reacted in the manner proposed, 2-phenyl-3-benzoylpropionitrile was obtained in 77 to 82% yields. Furthermore it was found that the procedure is general to the extent that other aromatic aldehydes and other aryl methyl ketones can be used. Employing this method a number of new 2-aryl-3-aroylpropionitriles were prepared. Table I will serve to illustrate the versatility of the procedure.

EXPERIMENTAL

Preparation of 2-phenyl-3-benzoylpropionitrile. Twenty-six grams of potassium hydroxide (assay 85%) was dissolved in 400 ml. of absolute acetone-free methanol by heating. The solution was cooled to room temperature on a water bath; 66 g. of acetophenone and then 53 g. of benzaldehyde were added with stirring. Gentle stirring was continued while the water bath was heated at 25–30° for 3 hr. The reaction mixture was then allowed to stand at room temperature overnight.

Hydrogen cyanide (caution[5]) was prepared[6] by adding a solution of 100 g. of sodium cyanide in 200 ml. water to a solution of 200 g. concentrated sulfuric acid in 120 ml. water over 25 min. The hydrogen cyanide evolved was collected in 200 ml. absolute acetone-free methanol cooled on an ice bath. The hydrogen cyanide solution was added to the original reaction mixture described above. While gentle stirring was maintained, the water bath was heated slowly to 50–55°, holding this temperature for 1 hr. Then 150 ml. water was added dropwise with stirring over 20 min. The reaction mixture was allowed to cool, was filtered, and the solid was washed with a solution of two parts methanol and one part water. Upon drying, 91–96 g. (77–82% yield) of 2-phenyl-3-benzoylpropionitrile was obtained, m.p. 124–126°, recrystallized from ethyl alcohol, m.p. 126–127° (lit.[2] 127°).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, IND.

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(2) G. F. H. Allen and R. K. Kimball, *Org. Syntheses*, **10**, 80 (1930).

(3) E. P. Kohler and H. M. Chadwell, *Org. Syntheses*, **Coll. Vol. I**, 78 (1941).

(4) A. C. O. Hann and A. Lapworth, *J. Chem. Soc.*, **85**, 1355 (1904).

(5) The preparation of hydrogen cyanide and all subsequent operations must be performed in a well ventilated hood.

(6) A. I. Vogel, "*Practical Organic Chemistry*," Longmans, Green and Co., London, 1954, p. 179.

Condensation of Aromatic Aldehydes with Methyl Aryl Ketones and Sodium Cyanide

R. B. DAVIS

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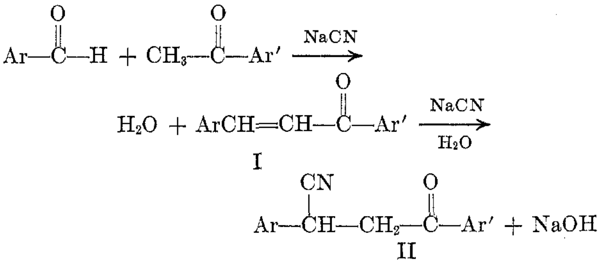
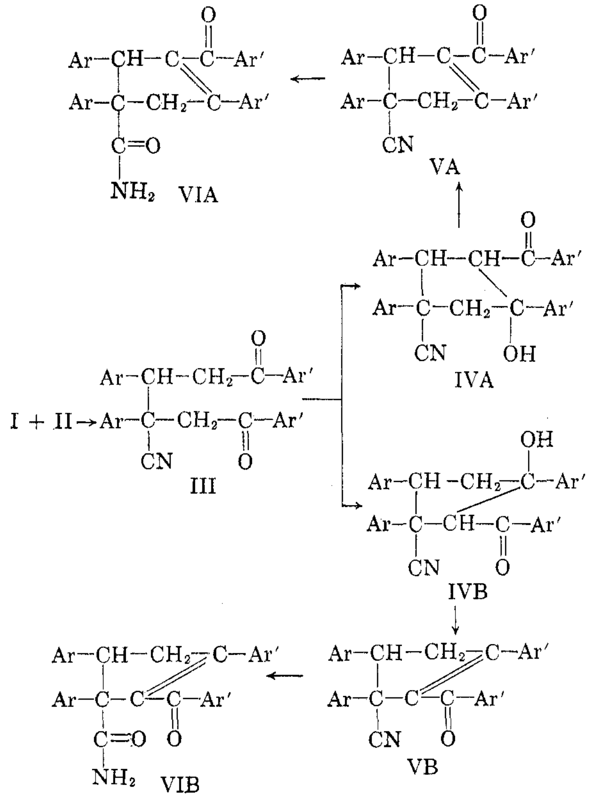
Previous work has shown that aromatic aldehydes condense with arylacetonitriles and sodium cyanide to produce 2,3-diarylsuccinonitriles.[1,2] It was proposed that similar reactions might be employed as a useful method for preparing 2-aryl-3-aroylpropionitriles(II) by using methyl aryl ketones in place of the arylacetonitriles.



$$\mathrm{Ar{-}\overset{O}{\overset{\|}{C}}{-}H + CH_3{-}\overset{O}{\overset{\|}{C}}{-}Ar' \xrightarrow{NaCN} H_2O + \underset{I}{ArCH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}Ar'} \xrightarrow[H_2O]{NaCN} \underset{II}{Ar{-}\overset{CN}{\overset{|}{C}}H{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}Ar'} + NaOH}$$

When benzaldehyde was reacted with acetophenone and sodium cyanide we obtained a solid product, $C_{31}H_{23}ON$. Infrared analysis indicated the presence of a nitrile group and a carbonyl group. The nitrile was converted to the corresponding amide by dissolving in concentrated sulfuric acid and then pouring the solution into water. Attempts to hydrolyze the nitrile and the amide to the corresponding acid were not successful. An examination of the literature indicated that other workers[3-5] had prepared the same compound, $C_{31}H_{23}ON$, the latter[4,5] having prepared it from benzalacetophenone and potassium cyanide. The following sequence of reactions in which all of the aryl groups are phenyl, has been adopted in large part from the reports of the previous workers[4,5] in an effort to rationalize the structure of the product.



These same authors were unsuccessful in their attempts to hydrolyze the compound, $C_{31}H_{23}ON$, and also in their attempts to prove the structure. While we have likewise been unsuccessful in our attempts to prove definitely the structure of the product, nevertheless our evidence is consistent with either VA or VB.

Upon reacting 2-thiophenaldehyde with acetophenone and sodium cyanide, a solid product, $C_{27}H_{19}S_2ON$, was obtained. Infrared analysis indicated the presence of a nitrile group and a carbonyl group. The evidence is consistent with either VA or VB in which the two Ar-groups are 2-thiophenyl and the two Ar′-groups are phenyl.

When benzaldehyde was reacted with methyl-*p*-tolyl ketone and sodium cyanide, the product obtained was $C_{33}H_{29}O_2N$. Infrared analysis indicated the presence of carbonyl and nitrile groups, and the absence of hydroxyl and amide groups. The evidence is consistent with structure III in which the Ar-groups are phenyl and the Ar′-groups are *p*-tolyl.

The reaction of *p*-methoxybenzaldehyde with actophenone and sodium cyanide produced $C_{33}H_{29}O_4N$. The compound gave infrared absorption peaks characteristic of the carbonyl group and either nitrogen to hydrogen or oxygen to hydrogen bonds. No evidence was obtained for the presence of a nitrile group. These facts are consistent with either VIA or VIB in which the Ar-groups are *p*-methoxyphenyl and the Ar′-groups are phenyl.

Upon treating *p*-methoxylbenzaldehyde with methyl-*p*-tolyl ketone and sodium cyanide, $C_{35}H_{33}O_4N$ was obtained. Again infrared analysis indicated the presence of carbonyl and either nitrogen to hydrogen or oxygen to hydrogen bonds, but no evidence for a nitrile group. The facts are consistent with either VIA or VIB in which the Ar-groups are *p*-methoxyphenyl and the Ar′-groups are *p*-tolyl.

In conclusion it may be stated that aromatic aldehydes react with aryl methyl ketones and sodium cyanide to produce complex compounds involving two molecules of the aldehyde, two molecules of the ketone and one molecule of hydrogen cyanide with the loss of two or three molecules of water.

EXPERIMENTAL[6,7]

Reaction of benzaldehyde, acetophenone and sodium cyanide. A mixture of 49 g. of sodium cyanide and 350 ml. of acetone-free methanol was heated with stirring to 55–60°, and 60 g. of acetophenone was added. A solution of 53

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(2) R. B. Davis, U. S. Patent **2,851,477** (1958).

(3) H. Rupe and F. Schneider, *Ber.*, **28**, 960 (1895).

(4) A. C. O. Hann and A. Lapworth, *Trans. J. Chem. Soc.*, **85**, 1355 (1904).

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(6) Analyses by Micro-Tech Laboratories, Skokie, Ill.

(7) All melting points are uncorrected.

g. of benzaldehyde, 20 g. of acetophenone and 50 ml. of acetone-free methanol was then added dropwise with stirring over 15 min. The reaction mixture was heated at 55–60° with stirring for an additional 1.5 hr., during which colorless solid precipitated. The mixture was cooled, filtered, and the precipitate was washed with methanol, water, again with methanol, and then ether. Upon drying, 49 g. of colorless solid was obtained, m.p. 244–248°, recrystallized from a large volume of acetone and also from benzene, m.p. 253–255°, (lit.[3] m.p. 249°). Infrared analysis showed significant absorption bands at 4.50 μ and 6.12 μ.

Anal. Calcd. for $C_{31}H_{23}ON$: C, 87.50; H, 5.45. Found: C, 87.67; H, 5.51.

Molecular weight. Calcd.[8] for $C_{31}H_{23}ON$: 425. Found: 427.

Hydrolysis of $C_{31}H_{23}ON$ to the corresponding amide. Ten grams of $C_{31}H_{23}ON$ was added portionwise with stirring to 200 g. of concentrated sulfuric acid at room temperature. Stirring was continued until all the solid dissolved. After standing at room temperature for 4 hr., the solution was poured with stirring into 2 l. water, solid precipitating. The mixture was filtered and the solid washed with water. Upon drying, 8.7 g. of colorless solid was obtained, m.p. 169–173° (dec.), recrystallized from acetone, m.p. 194–196 (dec.).

Anal. Calcd. for $C_{31}H_{25}O_2N$: C, 83.94; H, 5.68. Found: C, 83.88; H, 5.82.

Reaction of 2-thiophenaldehyde, acetophenone and sodium cyanide. A mixture of 3 g. of sodium cyanide and 30 ml. of acetone-free methanol was heated to 55–60° with stirring, 10 g. of acetophenone was added, and then 4 g. of 2-thiophenaldehyde over 5 min. with stirring. The reaction mixture was heated at 55–60° for an additional hour, cooled, filtered, and the solid washed with methanol, water, a second time with methanol, and dried. The colorless solid, 2.3 g., melted at 198–204°, recrystallized from acetone, m.p. 205–207°. Infrared analysis showed significant absorption peaks at 4.50 μ and 6.13 μ.

Anal. Calcd. for $C_{27}H_{19}S_2ON$: C, 74.13; H, 4.38. Found: C, 74.16; H, 4.46.

Reaction of benzaldehyde, methyl-p-tolyl ketone and sodium cyanide. In a similar manner, 53 g. of benzaldehyde was added over 20 min. at 55–60° to a mixture of 30 g. sodium cyanide, 400 ml. acetone-free methanol, 25 ml. water, and 90 g. of methyl-*p*-tolyl ketone. After stirring at 55–60° for 2 hr., the mixture was cooled, filtered, and solid washed with methanol, water, methanol, ether, and then dried. The colorless solid, 52.5 g., melted at 253–257°, recrystallized from dioxane, m.p. 263–266°. Infrared analysis showed significant absorption bands at 4.48 μ and 5.91 μ.

Anal. Calcd. for $C_{33}H_{29}O_2N$: C, 84.04; H, 6.20. Found: C, 84.16; H, 6.24.

Reaction of p-methoxybenzaldehyde, acetophenone and sodium cyanide. In like manner, the addition of 20 g. of *p*-methoxybenzaldehyde over 10 min. at 60–65° to 20 g. sodium cyanide, 200 ml. acetone-free methanol and 35 g. acetophenone produced 10.5 g. of colorless solid, m.p. 252–255°, recrystallized from acetic acid, m.p. 258–260°. Infrared analysis showed significant absorption bands at 2.95 μ, 3.06 μ, and 5.98 μ.

Anal. Calcd. for $C_{33}H_{29}O_4N$: C, 78.70; H, 5.80; N, 2.78. Found: C, 78.52; H, 5.94; N, 2.81.

Reaction of p-methoxybenzaldehyde, methyl-p-tolyl ketone and sodium cyanide. Similarly, the addition of 20 g. of *p*-methoxybenzaldehyde over 10 min. at 60–65° to a mixture of 20 g. sodium cyanide, 200 ml. acetone-free methanol and 40 g. methyl-*p*-tolyl ketone yielded 8.5 g. of solid, m.p. 231–233°, recrystallized from dioxane, m.p. 233–235°. Infrared analysis showed significant absorption bands at 2 95 μ, 3.05 μ, and 5.99 μ.

Anal. Calcd for $C_{35}H_{33}O_4N$: C, 79.07; H, 6.26; N, 2.63. Found: C, 78.82; H, 6.62; N, 2.67.

Department of Chemistry
University of Notre Dame
Notre Dame, Ind.

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Quaternary Hydroxamic Acids Derived from Pyridine[1]

D. G. Coe[2]

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Within the past few years several publications have appeared[3–12] in which hydroxamic acids and oximes have been described and tested as protecting cholinesterase (or alternatively reactivating it) from the inhibiting effects of such substances as tetraethyl pyrophosphate, di-isopropyl phosphorofluoridate and isopropyl methylphosphonofluoridate. It has been shown that while the hydroxamic acids exhibit little toxicity of their own to enzyme preparations, the oximes which are more potent prophylactically and therapeutically manifest inhibiting properties of their own.[13] Some of the most effective compounds described to date are nicotin- and picolinhydroxamic acids and their methiodides, and in particular pyridine-2-aldoxime methiodide.[14–25] It seemed of interest to determine

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[2] Present address: Jackson Laboratory, Box 525 Wilmington, Del.

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