[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Condensation Reactions. I. The Condensation of Ketones with Cyanoacetic Esters and the Mechanism of the Knoevenagel Reaction

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This paper describes a series of alkylidene cyanoacetic esters, $R_2C{=}C(CN)COOR$, prepared by condensing ten simple ketones with methyl cyanoacetate. Several unsaturated cyano esters of this type have been prepared previously by the Knoevenagel reaction, with secondary amines such as piperidine[1] and diethylamine[2] as catalysts. Sodium ethoxide[3] and the zinc chloride–aniline complex[4] have also been employed as condensing agents.

We have found that many salts catalyze the condensation of ketones with cyanoacetic esters, and that the ammonium and amine salts of organic acids are better catalysts than the free bases. The very weakly basic compound acetamide has been found to be an effective catalyst for these condensations, when used in acetic acid solution. Under these conditions, if the water formed during the condensation is removed continuously, the yields of unsaturated esters are from 80 to 90%. Knoevenagel[5] has employed amine salts in several condensation reactions of aldehydes and in the condensation of ketones with acids. Recently, Kuhn, Badstübner and Grundmann[6] have used secondary amine salts in condensing aldehydes with other aldehydes. Salts and amides have not been used previously in condensing ketones with esters, however. The activity of these catalysts appears to have some significance with regard to the mechanism of the Knoevenagel reaction, which is discussed in a later section.

Experimental Part

A. Condensation without Solvents or with Inert Solvents.—Data obtained concerning the condensation of methyl *n*-hexyl ketone with methyl cyanoacetate are useful in comparing the activity of the catalysts, since the condensation product boils much higher than the reactants, and fractionation, therefore, gives a fairly accurate measure of the extent of reaction. Methyl cyanoacetate (0.25 mole), methyl hexyl ketone (0.25 mole) and the catalyst were placed in a flask and allowed to stand for twelve hours at room temperature. The mixture was then heated for five hours in an oil-bath at 125° and allowed to stand overnight at room temperature. After washing with two 50-cc. portions of water, the mixture was distilled in vacuum. The recovered ketone and ester were collected together, b. p. 80–105° (24 mm.). The product, methyl 1-methylheptylidene cyanoacetate, boiled at 170–172° (24 mm.). The data are recorded in Table I.

TABLE I

CONDENSATIONS OF METHYL HEXYL KETONE WITH METHYL CYANOACETATE

Catalyst, moles	Yield of methyl 1-methylheptylidene cyanoacetate %	Recovery of ketone and ester, %
Piperidine (0.01)	39	37
Piperidine acetate (0.01)	52	28
Ammonium acetate (0.025)	52	26
Ethylenediamine diacetate (0.01)	52	32
Pyridine acetate (0.01)	28	55
Triethylamine acetate (0.01)	39	37
Acetamide (0.085)[a]	33	55

[a] Heated for nine hours at 140°.

The condensation of the ketone and ester to give an unsaturated ester and water is reversible. This was established by heating 0.25 mole of methyl 1-methylheptylidene cyanoacetate and 0.25 mole of water with 0.01 mole of piperidine acetate for five hours at 125°. The yield of methyl hexyl ketone and methyl cyanoacetate was 20%, and 70% of the unsaturated ester was recovered. It is improbable that equilibrium was reached either in the syntheses or in the above degradation, but longer heating was avoided, since the water present always produced an appreciable amount of hydrolysis. The addition

TABLE II

CONDENSATIONS OF METHYL AMYL KETONE WITH METHYL CYANOACETATE IN ACETIC ACID SOLUTION

Catalyst, moles	Yield of methyl 1-methylhexylidene cyanoacetate, %	Recovery of ketone and ester %
Acetamide (0.085)	91	5
Acetamide (0.042)	76	17
Acetamide (0.085)[a]	53	30
Ammonium acetate (0.04)	87	6
Ethylenediamine diacetate (0.03)	84	7
Piperidine acetate (0.02)	89	7
Triethylamine acetate (0.02)	37	50
Sodium acetate (0.025)	39	49
None	8	73

[a] In this preparation the solution was heated under reflux so that the water was not removed. The low yield shows that its removal is essential.

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(1) Harding, Haworth and Perkin, *J. Chem. Soc.*, **93**, 1943 (1908); Haworth and Fyfe, *ibid.*, **105**, 1663 (1914); Ingold and Thorpe, *ibid.*, **115**, 150 (1919); Vogel, *ibid.*, 2010 (1928); Barrett and Linstead, *ibid.*, 436 (1935).

(2) Komppa, *Ber.*, **33**, 3532 (1900).

(3) Gardner and Haworth, *J. Chem. Soc.*, **95**, 1955 (1909); Haworth, *ibid.*, **95**, 480 (1909); Harding, Haworth and Perkin, *ibid.*, **93**, 1956 (1908).

(4) Scheiber and Meisel, *Ber.*, **48**, 238 (1915).

(5) Knoevenagel, *Chem. Zentr.*, **76**, II, 179, 726 (1905).

(6) Kuhn, Badstübner and Grundmann, *Ber.*, **69B**, 98 (1936).

TABLE III

CONDENSATION PRODUCTS FROM KETONES AND METHYL CYANOACETATE

Ketone[a]	Methyl alkylidene cyanoacetate	B. p.,[b] °C.	Mm.	Formula	Analyses, % N (Kjeldahl) Calcd.	Analyses, % N (Kjeldahl) Found	n^{25}_D	d^{25}_{25}	Molecular refraction, M_D Calcd.	Molecular refraction, M_D Obsd.	Exaltation[c]	Yield, % Acetamide–acetic acid method	Yield, % Salt method[d]
Acetone	Isopropylidene[e]	99–101 (m. p. 20.3°)	9	$C_7H_9O_2N$			1.4696	1.0632	35.47	36.58	+1.11	30 (approx.)	
Methyl ethyl-	1-Methylpropylidene	105–106	9	$C_8H_{11}O_2N$	9.15	9.18	1.4705	1.0344	40.09	41.45	1.36	40 (approx.)	30 (approx.)
Methyl propyl-	1-Methylbutylidene	116–118	9	$C_9H_{13}O_2N$	8.38	8.66	1.4700	1.0115	44.71	46.27	1.56	73	31
Diethyl-	1-Ethylpropylidene	112–114	9	$C_9H_{13}O_2N$	8.38	8.27	1.4708	1.0130	44.71	46.23	1.52	64	12
Methyl isobutyl-	1,3-Dimethylbutylidene	119–123	9	$C_{10}H_{15}O_2N$	7.73	7.77	1.4696	0.9928	49.33	51.01	1.68	76	35
Methyl amyl-	1-Methylhexylidene	139–141	9	$C_{11}H_{17}O_2N$	7.18	7.43	1.4700	.9795	53.95	55.75	1.80	91	40
Dipropyl-	1-Propylbutylidene	129–130	9	$C_{11}H_{17}O_2N$	7.18	7.36	1.4701	.9779	53.95	55.85	1.90	73	20
Methyl hexyl-	1-Methylheptylidene	149–152	9	$C_{12}H_{19}O_2N$	6.69	6.69	1.4690	.9671	58.57	60.44	1.87	90	52
Cyclopentanone	Cyclopentylidene[f]	140–141 (m. p. 31°)	9	$C_9H_{11}O_2N$			1.5008	1.1042	42.51	44.16	1.65	72	
Cyclohexanone	Cyclohexylidene	146–147	9	$C_{10}H_{13}O_2N$	7.82	7.98	1.5035	1.0850	47.13	48.98	1.85	87	
Cyclohexanone	Cyclohexylidene[g]	150–151	9	$C_{11}H_{15}O_2N$			1.4950	1.0521	51.75	53.48	1.73	89	

[a] Acetone, methyl isobutyl ketone and methyl amyl ketone were obtained from Carbide and Carbon Chemicals Corp.; methyl ethyl ketone, methyl propyl ketone and cyclohexanone from Eastman Kodak Co.; methyl hexyl ketone from Röhm and Haas. Diethyl and dipropyl ketones were synthesized from propionic and butyric acids, passed over manganous oxide at 440°. Cyclopentanone was prepared from adipic acid.

[b] The products obtained from the unsymmetrical ketones should exist in two geometrically isomeric forms, and the presence of the two forms probably accounts for the 4° range in boiling point observed in several cases. The products were refractionated through a Widmer column, but no attempt was made to separate the isomers.

[c] These exaltations result from the conjugation of the α,β-double bond with the nitrile and ester carbonyl groups. They are somewhat larger than those noted for the condensation products of aldehydes with ethyl cyanoacetate by von Auwers, *Ber.*, **56**, 1178 (1923). However, several investigators have observed exaltations as large as these for the condensation products of several cyclic ketones with ethyl cyanoacetate; ref. Haworth and Fyfe, *J. Chem. Soc.*, **105**, 1664 (1914); Birch, Kon and Norris, *ibid.*, **123**, 1361 (1923); *cf.* Hugh and Kon, *ibid.*, 775 (1930); Vogel, *ibid.*, 2023 (1928).

[d] Since the water formed was not removed in these condensations, the yields depend upon the equilibria for each ketone–ester pair, as well as on the rates of reaction.

[e] Previously prepared by Schieber and Meisel.[4] Purified by fractional freezing after fractional distillation.

[f] Previously prepared by Harding and Haworth, *J. Chem. Soc.*, **97**, 490 (1910).

[g] Ethyl ester, prepared from ethyl cyanoacetate. Previously prepared by Harding, Haworth and Perkin.[1a] The physical constants reported here for this ester agree with those reported by Birch, Kon and Norris (*cf.* Hugh and Kon), and Vogel (footnote *c*). Other evidence for the α,β-unsaturation in this ester is given by Lapworth and McRae, *J. Chem. Soc.*, **121**, 2741 (1922), and Birch, Kon and Norris (*loc. cit.*, p. 1368). See also Lund, *Ber.*, **69**, 1621 (1936).

of a neutral drying agent such as calcium sulfate (Drierite) to the reaction mixture or the removal of water by the distillation of an inert solvent such as benzene improved the yield of condensation product.

Some of the other catalysts used in this and similar condensations with the other ketones gave the following results. Good yields were obtained with piperidine butyrate, piperidine oleate and diethylamine acetate, and fair yields with aniline acetate, glycine and diethanolamine acetate. Poor yields were obtained with several salts which were sparingly soluble in the reaction mixtures; among these were potassium acetate, sodium iodide, trimethylbenzylammonium chloride and tetramethylammonium iodide. The salts of organic and inorganic bases with phenols caused the formation of a relatively large proportion of high boiling polymeric material and are not suitable catalysts. Salts practically insoluble in the reaction mixtures gave from 2% to no condensation; among these were ammonium chloride, methylamine hydrochloride and sodium cyanide. Soluble substances giving similar low yields were mercuric chloride, acetanilide and N-acetylpiperidine. No condensation occurred in the absence of a catalyst.

Acetone did not give a pure product when condensed with methyl cyanoacetate in the presence of piperidine acetate, apparently due to the formation of mesityl oxide and its condensation product with the ester. All of the other methyl ketones condensed readily with methyl cyanoacetate using salts as catalysts (see column 13, Table III). Diethyl ketone and dipropyl ketone condensed much more slowly, however, the yields of the respective condensation products being only 12 and 20% after five to ten hours of heating.

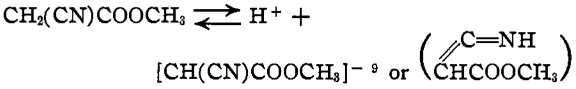
B. Condensation in Acetic Acid Solution.—Better yields were obtained by using acetic acid as a solvent and removing the water formed by distillation during the reaction. Data obtained concerning the condensation of methyl *n*-amyl ketone with methyl cyanoacetate illustrate the relative activity of the catalysts. Methyl cyanoacetate (0.25 mole), methyl amyl ketone (0.35 mole) and the catalyst were placed in a 250-cc. modified Claisen flask with 60 cc. of 99.8% acetic acid and the mixture distilled slowly for four hours, the heating being regulated so that the temperature of the vapor remained between 105 and 115°. The volume of the distillate (wet acetic acid plus a small amount of ketone) was 60 to 65 cc. The residue was then cooled, washed with two 50-cc. portions of water, and distilled in vacuum. The product, methyl 1-methylhexylidene cyanoacetate, boiled at 142–150° (12 mm.). The excess ketone was separated as a forerun, as was any unreacted methyl cyanoacetate. Representative data are recorded in Table II.

Qualitative observations of the rate of these condensations appear to be significant. Ammonium acetate and ethylenediamine diacetate caused a very rapid reaction; the reaction was slower when piperidine acetate and acetamide were used, and still slower with triethylamine acetate and sodium acetate. The most rapid reactions did not give the best yields, however, due to the formation of a small amount of high boiling products. The best yields were obtained with acetamide as a catalyst, in which case there was little if any high boiling material formed. The other ketones were condensed with methyl cyanoacetate in a similar manner, using acetamide in acetic acid as the catalyst. In some cases the reactions were complete in less than four hours. Thus two hours sufficed for the condensation of cyclohexanone with either methyl or ethyl cyanoacetate under these conditions. Dipropyl ketone condensed much more slowly than the methyl ketones and cyclic ketones; thus, after five hours, the yield of methyl 1-propylbutylidene cyanoacetate was only 20%; after twenty-two hours, 73%. The low boiling ketones, methyl propyl ketone and diethyl ketone, were condensed satisfactorily by the same method except that from 2 to 4 equivalents of ketone were used and the water distilled out with the excess ketone during eight to ten hours (b. p. of the distillate 80–100°). The condensation of acetone and methyl ethyl ketone with methyl cyanoacetate was effected by refluxing two equivalents of the ketones with the ester and acetamide in acetic acid solution for fifteen hours, since distillation would remove only the ketone. The yields of unsaturated esters from these two ketones were relatively low, both because the water formed was not removed during the condensation, and because it was difficult to separate these unsaturated esters from unreacted methyl cyanoacetate by fractional distillation. In all other cases the yield was about 90% if the recovered methyl cyanoacetate was allowed for, and was actually 90% with methyl amyl ketone, methyl hexyl ketone and cyclohexanone.

The properties of the unsaturated esters prepared by this method are recorded in Table III, together with the yields by the "salt method" using piperidine acetate or ammonium acetate, and by the acetamide–acetic acid procedure. Most of the preparations were in 0.25 mole lots, but runs of 1 to 2 moles in several cases have given exactly similar results. Acetamide was used in the ratio of 20 g. per mole of ester, and 99.8% acetic acid in the ratio of 240 cc. per mole. The excess of ketone was 100% with methyl isobutyl ketone and dipropyl ketone, 50% with cyclopentanone and 20% with methyl hexyl ketone and cyclohexanone. In each case practically all of the excess ketone was recovered either from the acetic acid distillate or from the ester forerun, or both, depending upon its boiling point.

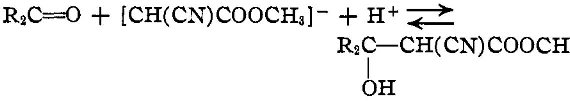
Discussion of Results

The data summarized in the "Experimental Part" support an aldol-like mechanism for the Knoevenagel reaction, first formulated (through intermediate ions) by Hann and Lapworth[7] and later supported by Kohler and Corson.[8] According to this mechanism, the reaction involves the following steps: (1) enolization of the adding methylene compound, probably through dissociation of a hydrogen ion



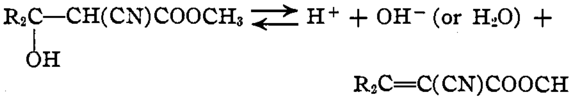
$$CH_2(CN)COOCH_3 \rightleftarrows H^+ + [CH(CN)COOCH_3]^{-\,[9]} \text{ or } \left(\begin{array}{l} \diagup\!\!\diagup C{=}NH \\ \diagdown CHCOOCH_3 \end{array}\right)$$

(2) addition of the enol, probably through its ions, to the carbonyl compound.



$$R_2C{=}O + [CH(CN)COOCH_3]^- + H^+ \rightleftarrows \underset{\displaystyle OH}{\underset{|}{R_2C}}{-}CH(CN)COOCH_3$$

(3) elimination of water from the aldol-like intermediate.[10]



$$\underset{\displaystyle OH}{\underset{|}{R_2C}}{-}CH(CN)COOCH_3 \rightleftarrows H^+ + OH^- \text{ (or } H_2O) + R_2C{=}C(CN)COOCH_3$$

The following facts are known in general about the above types of equilibria. The enolization equilibrium (1) is catalyzed by both acids and

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[7] Hann and Lapworth, *J. Chem. Soc.*, **85**, 46 (1904).

[8] Kohler and Corson, THIS JOURNAL, **45**, 1975 (1923). The earlier work on the mechanism of the Knoevenagel reaction is discussed by these authors, while references to recent work are given by Kuhn, Badstübner and Grundmann.[6]

[9] This formula is not intended to designate the position of the charge, *i. e.*, on nitrogen or carbon.

[10] The elimination of a hydroxyl ion from the anion $\left[\underset{\displaystyle O-}{\underset{|}{R_2C}}CH(CN)COOCH_3\right]^-$, probably formed as an intermediate in reaction (2) above, would lead to the same product as the elimination of water from the intermediate compound $\underset{\displaystyle OH}{\underset{|}{R_2C}}CH(CN)COOCH_3$. The ionic viewpoint is discussed in a recent paper by Arndt and Eistert, *Ber.*, **69**, 2386 (1936).

bases. Bases produce higher concentrations of the enolate anion, by removing the hydrogen ion. The rates of addition reactions such as (2) depend upon the degree to which addition to the carbonyl group is hindered, or upon the size of the alkyl groups. Reactions similar to (3) in which water is eliminated are catalyzed by both acids and bases, but in general more powerfully by acids.

The superior catalytic activity of salts finds a ready explanation in the above mechanism, modified in terms of Brönsted's extended theory of acid and basic catalysis.[11] Salts such as piperidine acetate, for example, furnish both the base, acetate ion, as a catalyst for reaction (1), and the acid, piperidinium ion, as a catalyst for (3). Acids or bases can catalyze the reaction only by the acid or basic mechanism, while an amine, amide or ammonium salt can function as both.

On the basis of this mechanism, optimum conditions for carrying out the condensation were selected. Acetic acid was chosen as an ionizing solvent which itself catalyzes enolization, and which by distillation allows the continuous removal of water, thus preventing reversal of the equilibria. The more active catalysts in acetic acid were the salts of the weaker bases, which give relatively acidic solutions. Acetamide acetate, ammonium acetate, and ethylenediamine diacetate were the most active catalysts. This may mean that the rate determining step in the over-all reaction is an acid catalyzed reaction, although the order of catalytic activity does not correspond exactly with the order of acidity. Certainly sodium acetate, which furnishes the most basic solution, is one of the poorest catalysts. This is attributed to the inability of the sodium ion to act as an acid, or proton donor. The number of hydrogen atoms capable of dissociation from the cations of the salt as protons, as well as their acidities, may influence the catalytic activity. This corresponds to the "statistical factor" in Brönsted's equation in which the catalytic activity of acids is related to their basicity. If the acidities are similar, this factor might invert the order of catalytic activity, and may explain, for example, why piperidine acetate is a better catalyst than triethylamine acetate, although the triethylammonium ion is slightly more acidic than the piperidinium ion.

The rates of condensation of the ketones with cyanoacetic esters are dependent on the structure of the ketones. Thus the cyclic ketones and methyl ketones condensed rapidly, while dipropyl ketone condensed much more slowly. This order of reactivity corresponds to the general behavior of these ketones in other addition reactions, and adds further evidence of the kind previously presented by Kohler and Corson[8] to show that an addition reaction (equation 2) is involved in the condensation.

Summary

Soluble salts and amides are shown to be active catalysts for the Knoevenagel condensation of ketones with cyanoacetic esters, which produces unsaturated cyano esters of the type $R_2C{=}C$—(CN)COOR. Eleven such esters are described. An effective method of bringing about such condensations is described, in which acetamide is used as the catalyst in an acetic acid solution which is kept dry by continuous distillation.

The experimental data reported are interpreted in favor of the aldol-like mechanism for the Knoevenagel reaction originally proposed by Hann and Lapworth. The effectiveness of the salts (and amides in acetic acid solution) as catalysts is attributed to their ability to act as both acid and basic catalysts, according to Brönsted's definition.

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[11] Brönsted, *Chem. Rev*, **5**, 231 (1928).