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AMINO ACID CATALYSIS OF THE KNOEVENAGEL REACTION

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Virtually any ketone will condense with ethyl cyanoacetate in a 1:1 Knoevenagel reaction when catalyzed by ammonium acetate (1–4) to give an alkylidenecyanoacetate. The mechanism postulated for this reaction by Cope (1) involves consecutive or simultaneous catalyses of a weak base and a weak acid. It seemed probable that amino acids or aminophenols would also catalyze this reaction, possibly more effectively if catalysis were a concerted reaction (*cf.* 5). The use of amino acids in alcoholic medium has been anticipated by Haley and Maitland (6).

Preliminary screening. The condensation of acetone with ethyl cyanoacetate (equation A) has been attempted using a variety of amino acids as catalysts.

$$(CH_3)_2C{=}O + CH_2(CN)COOC_2H_5 \rightarrow (CH_3)_2C{=}C(CN)COOC_2H_5 + H_2O \qquad (A)$$

Benzene was used as a solvent so that upon boiling the water formed by the reaction was azeotropically condensed and collected in a water trap (1–3). In preliminary runs one-gram portions of amino acid catalysts were used with 0.10-mole amounts of ethyl cyanoacetate. Then based solely on the water formation, the catalysts were divided into two categories: (a) ineffective, where little or no water was formed after 2–5 hours (Table I); and (b) effective, where water was collected, indicating the possibility of practical use (Table II).

All the aliphatic amino acids and the aminobenzenesulfonic acids cited in Tables I and II are sensibly insoluble in the reaction medium. However, four of them (ϵ-aminocaproic acid, α-aminophenylacetic acid, β-alanine, and *dl*-lysine) have apparently sufficient solubility and basic strength to be effective catalysts. Four other amino acids (L-leucine, *dl*-β-phenyl-α-alanine, glycine, and *dl*-methionine) are moderately effective but not practical catalysts. The other catalysts tested in Tables I and II were soluble in the reaction medium, at least at the boiling point.

Comparative condensations with effective catalysts. The condensations of acetone with ethyl cyanoacetate were repeated using 0.005 mole of the most effective catalysts (along with ammonium acetate and piperidine acetate) per mole of ethyl cyanoacetate. The yields (except for that of ammonium acetate) and quality of the products, as revealed by physical properties, were essentially the same in all cases (Table III).

The best catalysts were *p*-aminophenol, α-aminophenylacetic acid, β-alanine, and ϵ-aminocaproic acid. These catalysts were clearly superior to piperidine acetate. They were more effective than ammonium acetate because their loss through amide formation was slower (*cf.* 3). When adequate amounts of ammonium acetate were present, the condensation was very rapid (*cf.* Table III, footnote f). However, the amino acids are essentially nonvolatile and need not be removed

TABLE I

Catalyst Screening. Ineffective Catalysts for the Condensation of Acetone With Ethyl Cyanoacetate[a]

dl-α-Alanine
Aniline–Phenol
o-Aminobenzenesulfonic acid
m-Aminobenzenesulfonic acid
p-Aminobenzenesulfonic acid
p-Aminobenzenesulfonamide
o-Aminobenzoic acid
(+)-Glutamic acid
8-Hydroxyquinoline
Nicotinic acid
N-Phenylglycine

[a] A mixture of 11.3 g. of ethyl cyanoacetate, 6.9 g. of acetone, 2–7 g. of glacial acetic acid, and 25 cc. of benzene was added to 1 g. of catalyst for these condensation trials. No water was produced.

TABLE II

Catalyst Screening. Effective Catalysts for the Condensation of Acetone With Ethyl Cyanoacetate

CATALYST[a]	TIME[b]	
	Half-(Hours)	Total-(Hours)
ε-Aminocaproic acid	0.12	0.67
p-Aminophenol	.12	.67
Ammonium acetate	.17	.62
o-Aminophenol	.23	1.2
Piperidine	.25	1.1
m-Aminophenol	.37	1.5
α-Aminophenylacetic acid	.67	2.0
β-Alanine	.84	2.3
dl-Lysine[c]	1.0	3.0
p-Aminophenylacetic acid	1.2	3.75
m-Aminobenzoic acid	1.5	4.5
L-Leucine[d]	4.2	11.0
dl-β-Phenyl-α-alanine[d]	5.0	12.5
Glycine[d]	6.0	12
p-Aminobenzoic acid[d]	6.0	12
dl-Methionine[d]	7.0	16

[a] To 1 g. of catalyst a mixture of 11.3 g. of ethyl cyanoacetate, 6.9 g. of acetone, 2 g. of glacial acetic acid, and 25 cc. of benzene was added. Upon boiling the rate of condensation was assumed to parallel the rate of water collection. [b] Half-time was the period required to collect 1.0 cc. of water in the Barrett trap. (The theoretical amount of water was 1.8 cc. However, some acetic acid and acetone caused the volume of water to be 2.0–2.5 cc. when the reaction ceased.) [c] One gram of *dl*-lysine hydrochloride and an exactly equimolar amount of sodium acetate were dissolved in the reaction flask. The water was evaporated at 100° and the residue used as the catalyst. [d] An extra 5 g. of acetic acid was added to these runs.

prior to the fractionation of the product. Thus the usual extraction step can be eliminated.

Variation of the catalyst ratio. The effect of varying amounts of *o*-aminophenol and acetic acid was shown by the runs listed in Table IV. Runs A and B indicated that the acetic acid was unnecessary if enough *o*-aminophenol was used. An excess of acetic acid nevertheless seemed desirable, not only to accelerate the reaction (Runs C, D, and E), but also to prevent a small amount of hydrolysis of the nitrile (Runs B and F).

Scope of catalysis. In order to demonstrate the general utility of amino acid catalysis the procedure was adapted for the condensation of butanone and benzophenone with ethyl cyanoacetate; acetone with cyanoacetic acid; and acetone, cyclohexanone, and pinacolone with malononitrile. These results indicated that most condensations which can be effected with ammonium acetate or piperidine acetate can also be catalyzed with equal or better effect with certain amino acids.

TABLE III

CONDENSATION OF ACETONE WITH ETHYL CYANOACETATE USING VARIOUS EFFECTIVE CATALYSTS

CATALYST[a] (0.00125 Mole)	TIME[b]		PRODUCT		
	Half- (Hours)	Total- (Hours)	Yield, %	n_D (°C.)	F.P., °C.
m-Aminobenzoic acid[c]	4.5	10	77.3	1.4644 (21)	27
ε-Aminocaproic acid	0.33	1.25	78.1	1.4650 (23)	28
o-Aminophenol	2.08	5.25	76.2	1.4660 (18.5)	27.5
m-Aminophenol[d]	2.17	5.0	74.9	1.4663 (18)	27.5
p-Aminophenol	.60	2.5	79.7	1.4670 (18)	27.5
α-Aminophenylacetic acid	.67	2.5	74.5	1.4646 (23)	27
p-Aminophenylacetic acid	4.25	9.0	76.0	1.4646 (23)	27
β-Alanine	.87	3.0	78.1	1.4654 (21)	27
Piperidine[e]	3.0	13	78.3	1.4637 (25)	27
Ammonium acetate[f]	.80	3.0	38.3	1.4630 (25)	26

[a] In these runs 28.3 g. of ethyl cyanoacetate was condensed with 17.5 g. of acetone using 25 cc. of benzene as solvent and 5 g. of acetic acid and 0.00125 mole of amino acid as catalyst, except as noted. [b] Half-time was taken as that period required to collect 2.3 cc. of water. At total-time, 4.5–4.8 cc. of water had usually been collected (theoretical, 4.5 cc.) [c] In this run 0.86 g. (0.0063 mole) of *m*-aminobenzoic acid was required for effective catalysis. [d] Here 0.28 g. (0.0025 mole) of *m*-aminophenol was used. [e] For piperidine 0.106 g. (0.00125 mole) was insufficient; an additional 0.424 g. was added before condensation began. [f] Ammonium acetate (0.0013 mole) was prepared *in situ* by the action of the acetic acid in the mixture on 71 mg. of ammonium carbonate (30% NH_3, therefore 0.0013 mole of NH_3). This catalyst rapidly lost its activity for only 2.7 cc. of water was formed. However, by using larger amounts (354–425 mg.) of ammonium carbonate the half- and total-times were reduced to 0.25 and 1 hours, while the yield was raised to 76–79%.

However, the yield obtained when benzophenone was condensed with ethyl cyanoacetate was low. Furthermore, pinacolone was not condensed with ethyl cyanoacetate even though large amounts of amino acids were used (*cf.* 3). Acetone and ethyl malonate could not be condensed by these techniques with various amino acids (*cf.* 7).

EXPERIMENTAL

All melting and boiling points were uncorrected. All the fractionations (except one) were carried out through a 60-cm., Vigreux column with no head. The water formed by the reaction was collected in a Barrett trap (Corning #3622) when a lighter-than-water solvent was employed or in an oil dilution trap (Corning #3582) when chloroform or ethylene chloride were used. The nitrogen analysis was determined by Micro-Tech Laboratories, Skokie, Illinois.

Reagents. Ethyl cyanoacetate, cyanoacetic acid, and cyanoacetamide were obtained from Kay-Fries Chemicals, Inc. Malononitrile was obtained from the Matheson Co., Inc. or prepared from cyanoacetamide (8).

The *catalysts* were amino acids which were used in the form that they were obtained from The Matheson Co., Inc. or Distillation Products Industries, except for the following. ε-Aminocaproic acid (m.p. 195.5–199°; from 95% ethanol) was obtained by rearrangement of cyclohexanone oxime (9). The black aminophenols were purified: *o*-, m.p. 172–174.5°, from 95% ethanol; *m*-, m.p. 122–123°, from toluene; and *p*-, m.p. 177–180°, from 95% ethanol. *o*-Aminophenol acetate, m.p. 151.5–155°, resulted by crystallizing a mixture of the phenol and acetic acid from 95% ethanol.

Ethyl s-propylidenecyanoacetate. A. Preliminary catalyst screening. A mixture of 11.3 g. (0.10 mole) of ethyl cyanoacetate, 6.9 g. (0.12 mole) of acetone, 2 g. of glacial acetic acid, 25 cc. of benzene, and 1 g. of catalyst was placed in a flask. A benzene-filled Barrett trap and a condenser were attached to the flask. The mixture was heated briskly under reflux with a gas flame. With ineffective catalysts, no water resulted after 2–5 hours of boiling. With effective catalysts, the time of apparent half-reaction (after 1 cc. had been collected) and the time of completion (after 2.0–2.5 cc. of water had collected and water had ceased to form) were noted. (Some acetone and acetic acid contaminated the water which separated.) The results are assembled in Tables I and II.

TABLE IV

CONDENSATION OF ACETONE WITH ETHYL CYANOACETATE WITH VARIOUS CONCENTRATIONS OF ACETIC ACID AND *o*-AMINOPHENOL

RUN	MOLES OF CATALYST[a]		TIME		YIELD, %
	o-Aminophenol	Acetic Acid	Half-(Hours)	Total-(Hours)	
A	0.00125	—	No condensation		
B	.0125	—	1.67	5.0	74.2[b]
C	.00125[c]	0.00125[c]	6.0	18	75.2
D	.00125	.0167	2.17	6.0	78.8
E	.00125	.0833	2.08	5.25	76.2
F	.0125[d]	.0125[d]	0.67	2.25	68.9[b]

[a] In all these runs 28.3 g. (0.25 mole) of ethyl cyanoacetate was condensed with 17.5 g. of acetone using 25 cc. of benzene as solvent.
[b] In these runs there was an "ammoniacal" scent in the product.
[c] In this run 211 mg. (0.00125 mole) of *o*-aminophenol acetate, m.p. 151.5–155°, was used as catalyst.
[d] In run F, 2.11 g. of *o*-aminophenol acetate was used.

B. Comparative condensations with effective catalysts. The procedure above was repeated using mixtures of 28.3 g. (0.25 mole) of ethyl cyanoacetate, 17.5 g. (0.30 mole) of acetone, 5 g. of glacial acetic acid, 25 cc. of benzene, and 0.00125 mole of effective catalyst (Table III). The times required to collect 2.3 cc. and 4.5–4.8 cc. of water were noted as the half- and total-times. (The water yield was 92–99%, after deducting the acetic acid present, estimated by titration with standard base.)

After water had ceased to form, the reaction mixture was transferred to the fractionating column. The benzene was removed at atmospheric pressure. Distillation of the residue at reduced pressure furnished two fractions: (a) forerun, largely ethyl cyanoacetate, b.p. 95–115° (16 mm.), 5.8–7.6 g. and (b) ethyl s-propylidenecyanoacetate, b.p. 115–120° (16 mm.), 28.5–30.5 g. (74.5–79.7%). These trials are summarized in Table III.

One series of runs employed ammonium carbonate (30% NH_3) as catalyst (effectively, ammonium acetate). Using 71 mg. (0.0013 mole of NH_3) of ammonium carbonate the yield of ethyl *s*-propylidenecyanoacetate was only 38%; with 142 mg., 44%; with 284 mg., 67%; with 354 mg., 79%; with 425 mg., 76%.

Runs where the amounts of catalyst, *o*-aminophenol, and acetic acid, were varied are assembled in Table IV.

In another series, using β-alanine as catalyst, the effect of various azeotrope-forming solvents on the yield of product was tested: chloroform, 75%; benzene, 77%; ethylene chloride, 60%; toluene, 61%; and xylene, 37%. The higher-boiling solvents liquefied the catalyst, possibly forming the peptide, faster than condensation occurred (*cf.* 3).

One sample of product was crystallized from ethanol, m.p. 28.5–29.5°, n_D^{25} 1.4647 (supercooled). Komppa (10) and Vogel (11) reported m.p. 28° and m.p. 33°, respectively.

Other ethyl alkylidenecyanoacetates. Butanone (346 g.) was smoothly condensed with ethyl cyanoacetate (453 g.) in 400 cc. of benzene. Using 2.6 g. of ϵ-aminocaproic acid and 80 g. of acetic acid as catalysts a 79.6% yield (533 g.) of ethyl *s*-butylidenecyanoacetate was obtained: time of condensation, 7 hours; b.p. 115–120° (12 mm.); n_D^{25} 1.4638–1.4649. A 74% yield was obtained using *p*-aminophenol and 80% yield using β-alanine. Cope, Hofmann, Wyckoff, and Hardenbergh (2) reported 65–85% yields using ammonium acetate; b.p. 116–118° (11 mm.); n_D^{25} 1.4650.

Pinacolone has failed to condense with ethyl cyanoacetate using β-alanine and ϵ-aminocaproic acid as catalyst (*cf.* 3).

Benzophenone (45.6 g.), 33.9 g. of ethyl cyanoacetate, 12 g. of glacial acetic acid, 2 g. of ϵ-aminocaproic acid, and 50 cc. of benzene were heated under reflux for 11 hours while water was removed. Distillation from a Claisen flask gave 38.0 g. (54.9%) of ethyl 2-cyano-3,3-diphenylpropenoate; b.p. 185–195° (1 mm.); m.p. 82–93°. The literature (3) gives b.p. 175–182° (1 mm.); m.p. 95–97°.

Using chloroform, a 56% yield was obtained after 87 hours of reflux. Poor yields were obtained using β-alanine (37%), *p*-aminophenol (28%) and α-aminophenylacetic acid (0%).

s-Propylidenecyanoacetic acid. A mixture of 85 g. of cyanoacetic acid, 70 g. of acetone, 2 g. of α-aminophenylacetic acid and 200 cc. of benzene was placed in a flask. A Barrett trap and condenser were attached and the homogeneous solution was heated under reflux for 15 hours. The product was crystallized upon concentration of the reaction mixture to furnish two crops totalling 118 g. (94.4%) of product; m.p. 125–131.5°. Two recrystallizations of these heavy blades from acetone-benzene gave the purified acid; m.p. 132–134°; neut. equiv., 126.2 (calc'd, 125.11). Knoevenagel (12) reported m.p. 130° for this acid. β-Alanine catalyzed an 87–91% conversion in 22 hours.

s-Propylidenemalononitrile. A mixture of 49.5 g. of malononitrile, 52.2 g. of acetone, 0.5 g. of β-alanine, 10 cc. of acetic acid, and 140 cc. of benzene was heated under reflux for 1.5 hours while eliminating 16 cc. of water. The reaction mixture and a 35-cc. portion of benzene were washed successively with eight 75-cc. portions of water and 75 cc. of saturated sodium chloride solution. After drying with sodium sulfate and removal of the solvent and a small forerun, the product was fractionated: b.p. 100–102° (16 mm.); 73.0 g. (91.8%); n_D^{25} 1.4655. The literature (13) reports b.p. 107–108° (23 mm.); n_D^{25} 1.4662.

When acetic acid was omitted, the time for completion of reaction was 7.5 hours and the yield was 72%.

Cyclohexylidenemalononitrile. Cyclohexanone (25.5 g.) was condensed with 16.5 g. of malononitrile in 45 minutes following the procedure described for *s*-propylidenemalononitrile. Fractionation gave 33.7 g. (92.3%) of product; b.p. 147–150° (15 mm.); n_D^{25} 1.5100. Cope and Hoyle (13) gave b.p. 137–138° (10 mm.), n_D^{25} 1.5110.

2-Cyano-3,4,4-trimethyl-2-pentenenitrile. A mixture of 30 g. of pinacolone, 16.5 g. of malononitrile, 94 mg. of β-alanine, 5 g. of acetic acid, and 50 cc. of benzene was arranged with a benzene-filled trap and condenser and heated under reflux for 25 hours. Three additional 188-mg. amounts of β-alanine were added after 2, 8, and 20 hours of reflux. After removal of the solvent, the reaction mixture was fractionated: (a) 7.6 g., b.p. 105–115° (15–14 mm.), n_D^{24} 1.4442; (b) 2.0 g., b.p. 115–125° (14–13 mm.), n_D^{24} 1.4657; and (c) 17.8 g.

[48.0% conversion, 81.7% yield, correcting for recovered malononitrile in fraction (a)], b.p. 125–127° (13 mm.), n_D^{24} 1.4774. A purified center cut was obtained for analysis upon refractionation of the product through a 60-cm., heated, wire-spiral column (14): b.p. 137–138° (20 mm.), n_D^{25} 1.4772, d^{25} 0.9374.

Anal. Calc'd for $C_9H_{12}N_2$: N, 18.91. Found: N, 19.13.

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SUMMARY

A number of amino acids and aminophenols have been evaluated as possible catalysts in the Knoevenagel condensation of acetone with ethyl cyanoacetate. Four of them, ϵ-aminocaproic acid, α-aminophenylacetic acid, β-alanine, and *p*-aminophenol, have proved to be very efficient. In addition to efficient condensation, these catalysts allow the elimination of the extraction step usually required in the work-up of the reaction.

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REFERENCES

(1) COPE, *J. Am. Chem. Soc.*, **59**, 2327 (1937).
(2) COPE, HOFMANN, WYCKOFF, AND HARDENBERGH, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
(3) CRAIGOE, JR., ROBB, AND SPRAGUE, *J. Org. Chem.*, **15**, 381 (1950).
(4) WIDEQVIST, *Arkiv Kemi, Mineral., Geol.*, **B23**, No. 4 (1946).
(5) SWAIN AND BROWN, JR., *J. Am. Chem. Soc.*, **74**, 2534, 2538 (1952).
(6) HALEY AND MAITLAND, *J. Chem. Soc.*, 3155 (1951).
(7) COPE AND HANCOCK, *J. Am. Chem. Soc.*, **60**, 2901 (1938).
(8) CORSON, SCOTT, AND VOSE, *Org. Syntheses*, Coll. Vol. II, 379 (1943).
(9) ECK, *Org. Syntheses*, Coll. Vol. II, pp. 28, 77, 371 (1943). *Cf.* also MEYERS AND MILLER, *Org. Syntheses*, **32**, pp. 13–16 (1952).
(10) KOMPPA, *Ber.*, **33**, 3532 (1900).
(11) VOGEL, *J. Chem. Soc.*, 2010 (1928).
(12) KNOEVENAGEL, German Patent 162,281; *Chem. Centr.*, **II**, 726 (1905).
(13) COPE AND HOYLE, *J. Am. Chem. Soc.*, **63**, 733 (1941).
(14) CASON AND RAPOPORT, *A Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc. New York, N. Y., 1950, pp. 237–243.