Catalyst Study of the Knoevenagel Condensation

FRANKLIN S. PROUT, ATA A. ABDEL-LATIF and MARWAN R. KAMAL
Department of Chemistry, DePaul University, Chicago, Ill.

Several amino acids and aminophenols have been shown to be effective catalysts for the condensation of ketones with active methylene compounds (15). This study has now been extended to the condensation of seventeen aromatic and ten aliphatic aldehydes with ethyl cyanoacetate.

CONDENSATIONS of aldehydes with ethyl cyanoacetate were effected in boiling benzene. This followed the general procedure used by Pratt and Werble (*14*) for a heterogeneous kinetic study and by Cope (*5*) as a preparative method.

Amino acid catalysis gave yields of ethyl alkylidenecyanoacetate as good and often better than yields reported by other methods. Furthermore, the product could be distilled directly from the reaction flask.

Benzaldehyde can be easily condensed with ethyl cyanoacetate in the presence of sodium ethoxide (*3, 4*) and in alcohol without catalyst (*11*). However, no condensation resulted in benzene when the catalytic system was omitted. A slow condensation with poor yield (*12%*) resulted when a large amount of acetic acid only was present. Yields of 88–97.5% were obtained when, along with 0.3 moles of acetic acid, any one of five amino acids, three aminophenols or five salts were present to the extent of 0.02 mole per mole of benzaldehyde and ethyl cyanoacetate, Table I.

Since ϵ-aminocaproic acid was the most rapid amino acid it was used for the condensation of fifteen other substituted benzaldehydes with ethyl cyanoacetate. Table II.

The condensation of 2-ethylhexanal with ethyl cyanoacetate gave 69–88% yields of ethyl 2-cyano-4-ethyl-2-octenoate with fourteen catalysts, Table III. The best combination of high yield and short time were shown by β-alanine (88%, 7-min. half-time) and ϵ-aminocaproic acid (89.4%, 7-min. half-time). Piperidine acetate effected condensation, but also lead to polymerization.

Other aliphatic aldehydes with only one α-hydrogen, Table IV, were condensed successfully in excellent yield using β-alanine. Yields were lower (50–70%) with straight-chained aldehydes. Oddly, ϵ-aminocaproic acid caused the yields of ethyl *n*-alkylidenecyanoacetates to fall to 16–23% for butanal, 46% for hexanal and 8% for heptanal.

The straight-chained aldehydes gave large amounts of residue. These residues could be distilled, furnishing a fairly distinct high-boiling product. This product obtained from butanal was carefully examined and was largely ethyl 2-cyano-4-ethyl-2,4-octadienoate.

The identity of this product was demonstrated by its hydrogenation over platinum to ethyl 2-cyano-4-ethyloctanoate and hydrolysis of this cyanoester to 4-ethyloctanoic acid (*13*). The cyanoacetate and acid were also prepared when either 2-ethylhexanal or 2-ethyl-2-hexenal was initially condensed with ethyl cyanoacetate, hydrogenated and hydrolyzed, Table V.

EXPERIMENTAL PROCEDURES

Melting points and boiling points were uncorrected. Liquid aldehydes were distilled immediately prior to use. Solid aldehydes were recrystallized if melting points indi-

Table I. Condensation of Benzaldehyde with Ethyl Cyanoacetate[a]

Catalyst	Half-time[b,c] (Min.)	Total-time[c] (Min.)	Yield[c] %
ϵ-Aminocaproic Acid	1.5(7)	40(37)	92(83)
β-Alanine	7(40)	15(120)	95(83)
Glycine	12(150)	75(600)	96(85)
α-Aminophenylacetic Acid	15(195)	85(540)	91(81)
p-Aminophenylacetic Acid	33(100)	210(270)	93(88)
p-Aminobenzoic Acid	160–	900–	84–
p-Aminophenol	12(132)	130(360)	94(91)
m-Aminophenol	40(90)	360(360)	92(91)
o-Aminophenol	55(165)	360(720)	92(86)
Ammonium Acetate[d]	2(–)[e]	30–	97(18)
Potassium Acetate[f]	4(8)	90(45)	96(90)
Sodium Acetate[f]	8(240)	120(360)	73(72)
Potassium Fluoride[f,g]	10(16)	60(120)	91(86)
Piperidine	3(3)	60(120)	94(88)

[a] Benzaldehyde (0.25 mole), ethyl cyanoacetate (0.25 mole), 40 ml. of benzene, 5 ml. of glacial acetic acid (omitted in half the runs) and 0.005 mole of catalyst were used in these runs. Water was collected in a Barrett trap. [b] The half-time was the time required to collect 2.3 ml. of water. [c] Times and yields in parentheses refer to reaction omitting acetic acid. [d] Ammonium acetate was prepared in *situ* by adding 0.37 g. (0.0065 mole of NH_3) of ammonium carbonate to the mixture. [e] Only 1.6 ml. of water was produced after two hours. [f] These mixtures were filtered before distillation. [g] These were 0.5 mole runs (*16*).

Table II. Condensation of Aromatic Aldehydes with Ethyl Cyanoacetate Using ε-Aminocaproic Acid and Acetic Catalysis[a]

Compound	Time[b] Half-Min.	Time[b] Total-Min.	Yield %	Melting Point, ° C.[c] Obs.	Melting Point, ° C.[c] Ref.
Benzaldehyde	1.5	40	92	49–51	50–51 (*3,4*)
o-Nitro-	30	95	98	99–101	96 (*17*)
m-Nitro-	6	50	87	133–135	134 (*18*)
p-Nitro-	12	70	99	169–171	169–170(*6*)
p-Dimethylamino-	2	70	85	126–127[d]	...
2,3-Dimethoxy-	3	13	97	117–118	120 (*12*)
3,4-Dimethoxy-	3	30	97	152–153	155 (*7*)
p-Hydroxy-	10	55	72	171–172	162–163(*17*)
o-Methyl-	5	40	80	64–66	60 (*6*)
m-Methyl-	3	30	90	79–81	85 (*6*)
p-Methyl-	3	45	97	84–86	94 (*6*)
o-Chloro-	1.5	20	88	53–55	51–52 (*10*)
p-Chloro-	2	20	80	92–93	93 (*19*)
2,4-Dichloro-	10	60	96	81–82[e]	...
Cinnamaldehyde	3	15	92	110–111	114 (*6*)
α-Naphthaldehyde	2	45	87	81–82[f]	...
Mesitaldehyde	75	385	65	107–109[g]	...

[a] In general the aldehyde (0.25 mole), ethyl cyanoacetate (0.25 mole), 40 ml. benzene, 5 ml. of glacial acetic acid and 0.005 mole of ε-aminocaproic acid were used in these condensations. [b] *Cf.* Footnote b, Table I. [c] Observed m.p. was taken on product recrystallized from alcohol. [d] Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.82; H, 6.61. Found C, 69.26; H, 6.36. [e] Calcd. for $C_{12}H_9O_2NCl_2$: C, 53.33; H, 3.33. Found: C, 53.56; H, 3.35. [f] Calcd. for $C_{16}H_{13}O_2N$: C, 76.49: H, 5.20. Found: C, 76.67; H, 5.29. [g] Condensation catalysed with β-alanine. Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.05; N, 5.76. Found: C, 73.93; H, 6.90; N, 5.62.

cated lack of purity. Other reagents have been described previously (*15*). Products were fractionated through a 60 cm., heated Vigreux column.

The condensations were run in benzene as previously described (*15*). The water formed was separated with a Barrett (Corning No. 3622) or Stark and Dean (Corning No. 3602) trap. Results are assembled in Table I to IV.

Elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England. The infrared spectra were observed on a Perkin-Elmer Model 21 with samples on demountable salt plates, Table VI.

Table III. Condensation of Ethyl Cyanoacetate with 2-Ethylhexanal[a]

Catalyst	Time Half-min.	Time Total-min.	Time Terminal-min.	Forerun[b] g.	Product[c] g.	Product[c] %	Residue g.
β-Alanine	7	14	60	2.0	24.5	88.3	0.5
ε-Aminocaproic Acid	7	14	60	2.0	24.8	89.4	0.5
δ-Aminovaleric Acid	30	60	120	0.8	22.1	80.0	4.3
Glycine	30	60	120	1.0	25.1	90.5	1.0
p-Aminophenylacetic Acid	120	240	360	10.0	19.1	68.5	1.8
α-Aminophenylacetic Acid	20	40	80	3.4	19.1	68.9	5.0
p-Aminophenol	90	35	60	3.5	24.5	88.3	1.0
o-Aminophenol	15	180	240	1.2	23.0	81.9	1.0
o-Aminophenol[d]	180	360	480	5.0	16.4	59.1	5.0
m-Aminophenol	40	120	240	3.9	22.0	79.3	3.8
Ammonium Acetate	10	28	60	2.0	23.7	85.4	4.0
Potassium Acetate[e]	60	120	180	3.5	21.5	77.5	1.0
Sodium Acetate[e]	70	150	270	5.0	20.0	72.0	2.0
Potassium Fluoride[e]	25	65	120	2.3	23.4	83.8	1.9
Piperidine	5	10	15	2.0	20.0	72.0	7.5

[a] In these condensations 18.0 g. (0.125 mole) of 2-ethylhexanal, 14.5 g. (0.125 mole) of ethyl cyanoacetate, 25 ml. of benzene, 2.5 ml. of acetic acid and 0.0025 mole of catalyst were used. The times required to collect 1.5 ml. (half-time) and 2.9 ml. (total-time) in the Barrett trap were noted. Reflux continued to terminal-time. [b] Foreruns were usually collected at 90–91° C. (10 mm.). [c] Products were collected usually between 144–146° C. (10 mm.), n_D^{25} 1.4580. [d] Acetic acid was omitted. [e] Mixture filtered to remove salt prior to distillation.

Table IV. Condensation of Aliphatic Aldehydes and Ethyl Cyanoacetate[a]

$$RCHO + CH_2(CN)COOC_2H_5 \xrightarrow{\beta\text{-Alanine}} R{-}CH{=}C(CN)COOC_2H_5 + H_2O$$

	Products						
	Observed				Reported		
R	Half-time min.	B.p. ° C. (mm.)	Yield %	n_D (° C.)	B.p. ° C. (mm.)	Yield %	Method[b]
CH_3[c]		113–114(32)	50	1.4398(27)	112 (20)	52	E
C_2H_5	20	99–100(6)	70	1.4430(25)	112–122(20)	51	E
n-C_3H_7	15	109–111(17)[d]	47	1.4501(30)	...		
n-C_5H_{11}	10	140–142(12)	69	1.4538(25)	142–144(12)	59	I
n-C_6H_{13}	30	150–152(12)	66	1.4540(24)	144–145(13)	32	P
$(CH_3)_2CH$	6	110–111(9)[e]	84	1.4500(23)	...	..	.
$(C_2H_5)_2CH$	20	117–118(8)	88	1.4552(25)	122–123(8.5)	83	I
n-$C_4H_9(C_2H_5)CH$	7	140–142(8)	88	1.4580(25)	142–144(10)	70	I
n-$C_3H_7CH{=}C(C_2H_5)CH$	20	147–154(7)	73	1.5061(28)	...	..	.
Cl_3C	45	144–146(24)[f]	38	1.4990(30)	...	..	.

[a] Mixtures of 0.25 mole of aldehyde and ethyl cyanoacetate, 5 ml. of glacial acetic acid, 0.44 g. of β-alanine and 40 ml. of benzene were used for condensation. [b] E, esterification of cyanoacetic acids (*2*); I, ion exchange resin (*1*); P, piperidine acetate (*9*). [c] Condensation run in 95% ethanol instead of benzene at room temperature for 22 hours. [d] Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.83. Found: C, 64.37; H, 7.74. [e] Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.83. Found: C, 65.25; H, 7.46. [f] Calcd. for $C_7H_6O_2Cl_3N$: C, 34.67; H, 2.49. Found: C, 34.92; H, 2.63.

Table V. Values of Ethyl 2-Cyano-4-ethyloctanoate and 4-Ethyloctanoic Acid from Three Sources

	$C_4H_9CH(C_2H_5)CH_2CH(CN)COOC_2H_5$[a]			$C_4H_9CH(C_2H_5)CH_2CH_2COOH$[b]		
Source	B.p. ° C. (mm. of Hg)	n_D (° C.)	Sapon. Equiv.	B.p. ° C. (mm. of Hg)	n_D (° C.)	M.p. salt[c] ° C.
2-Ethylhexanal	142–143(11)	1.4368(30)	219	152–157(21)	1.4353(28)	110–112
2-Ethyl-2-hexenal	132–135(6)	1.4399(30)	214	126–132(13)	1.4420(25)	108.5–109.5
Butanal	110–113(2)	1.4408(28)	218	157–157(13)	1.4399(25)	110–112

[a] Purified cyano ester, b.p. 145–146° C. (7 mm.); n_D^{27} 1.4383. [b] The literature (*8, 13*) gives b.p. 253–256° C. (760 mm.); piperazine salt, m.p. 110° C. [c] Calculated saponification equiv., 225.3.

Table VI. Infrared and Analytical Data for Related Cyanoacetate Esters

	Infrared Stretch			Analysis, Calcd.		Analysis, Found	
Ester	C≡N	C=C	C=O	%C	%H	%C	%H
n-$C_3H_7CH{=}C(C_2H_5)CH{=}C(CN)COOC_2H_5$[a]	4.50μ	6.30μ	5.78μ	70.55	8.65	71.17	7.94
n-$C_3H_7CH{=}C(C_2H_5)CH{=}C(CN)COOC_2H_5$[b]	4.50	6.30	5.78	70.55	8.65	70.37	8.78
n-$C_4H_9CH(C_2H_5)CH{=}C(CN)COOC_2H_5$	4.47	6.14	5.75	...	...	...	...
n-$C_4H_9CH(C_2H_5)CH_2CH(CN)COOC_2H_5$	4.44	...	5.70	69.29	10.29	69.34	10.01
n-$C_3H_5CH{=}C(CN)COOC_2H_5$	4.48	6.13	5.76–5.83	64.65	7.83	64.37	7.74

[a] From butanal and ethyl cyanoacetate. [b] From 2-ethyl-2-hexenal and ethyl cyanoacetate.

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