140. *Carbonyl–Methylene Condensations. Part XIII.*[1] *Acid-catalysed Condensation of Ethyl Cyanoacetate with Aromatic Aldehydes.*

By Zvi Rappoport and Saul Patai.

In the reaction of aromatic aldehydes with ethyl cyanoacetate in acetic acid–perchloric acid, which gives *trans*-arylmethylenecyanoacetic acids, the relative reactivities of aromatic aldehydes deduced from the yields obtained in constant conditions were in the reverse order of those in base-catalysed condensations. The yields increase with increasing acidity of the medium. The reaction of anisaldehyde and ethyl cyanoacetate in the presence of aluminium chloride gave ethyl cyano-4-methoxybenzylideneacetate.

It is generally accepted that carbonyl condensations may be catalysed both by bases and by acids,[2] though the latter catalysis has been studied in detail only in relatively few cases.[3] An example of acid-catalysed carbonyl–methylene condensation, namely, that of benzaldehyde with diethyl malonate in the presence of Lewis acids, was studied by Hauser and his co-workers,[4] who also proposed a mechanism for the reaction.[5]

In this paper we present some results on the acid-catalysed condensation of aromatic aldehydes with ethyl cyanoacetate in acetic acid containing 33% (v/v) of 70% aqueous perchloric acid. This ester was chosen as the active methylene compound, as it is possible to obtain results with it concerning the stereochemistry of the products of the reaction. A low reaction temperature (25°) was used to decrease side reactions in the highly acidic and oxidising media. After 48 hr. products were isolated in 5—40% yield; they were arylmethylenecyanoacetic acids:

$$\mathrm{Ar{\cdot}CHO + CH_2(CN){\cdot}CO_2Et + AcOH \xrightarrow{HClO_4} Ar{\cdot}CH{:}C(CN){\cdot}CO_2H + EtOAc + H_2O}$$

Two reactions thus took place accordingly in the acid media, carbonyl–methylene condensation and transesterification (before or after the condensation).

Ethyl α-cyano-2-methoxybenzylideneacetate and ethyl cyanoacetate were then heated separately in acetic acid–perchloric acid. The former was recovered unchanged after 48 hr., the second gave ethyl acetate as one of the products. Thus, we believe that hydrolysis occurs before the condensation and that the active methylene compound in the condensation is actually the cyanoacetic acid which in identical conditions was found to give the same condensation product with *o*-methoxybenzaldehyde, although in somewhat lower yield.

To avoid transesterification, condensation of anisaldehyde and ethyl cyanoacetate was also carried out with aluminium chloride as catalyst in dioxan. This gave ethyl *trans*-cyano-4-methoxybenzylideneacetate, the same product as was obtained in the base-catalysed reaction.

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[1] Part XII, *J.*, 1961, 687.

[2] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, 1953, p. 684.

[3] Noyce and Pryor, *J. Amer. Chem. Soc.*, 1955, **77**, 1397; 1959, **81**, 618; Noyce, Pryor, and Bottini, *ibid.*, 1955, **77**, 1402; Noyce and Snyder, *ibid.*, 1958, **80**, 4033, 4324; 1959, **81**, 620; Noyce and Reed, *ibid.*, 1958, **80**, 5539.

[4] Breslow and Hauser, *J. Amer. Chem. Soc.*, 1940, **62**, 2385.

[5] Hauser and Breslow, *J. Amer. Chem. Soc.*, 1940, **62**, 2389.

Owing to the comparatively low yields the acid-catalysed reaction cannot compete seriously as a synthetic method with the base-catalysed one. Similar results were found for condensation of benzaldehyde with acetophenone, studied by Coombs and Evans[6] and by Noyce *et al.*,[3] where the rate of chalcone formation in the base-catalysed was much higher than in the acid-catalysed reaction.

We believe that the yields of products obtained in identical conditions can be taken, at least qualitatively, to parallel the reactivity of the various aldehydes in the acid-catalysed condensation. According to the yields recorded in the Table the aldehydes may be roughly divided into three groups. The first group (giving 15—40% yields) includes *o*- and *p*-anisaldehyde, which are among those giving the slowest reactions in the base-catalysed condensation,[7] as well as *p*-dimethylaminobenzaldehyde and vanillin, whose reactions can be estimated from the Hammett equation to be very slow. The second group of aldehydes (nos. 5—10, all giving yields of 5—10%) have medium rates in the base-catalysed condensation. The most active aldehydes in the base-catalysed condensation, *m*- and *p*-nitrobenzaldehyde, did not react at all in acid conditions.

Condensation of aldehydes (0·1 mole) with ethyl cyanoacetate (0·1 mole) in mixtures of acetic (30 ml.) and 70% aqueous perchloric acid (15 ml.) at 25° in 48 hr.

No.	R in R·CHO	Yield (%) of Ar·CH:C(CN)·CO_2H	Solvent for cryst.	M. p. Found	M. p. Recorded
1	*o*-MeO·C_6H_4	42	$CHCl_3$	211°	211—212° [a]
2	*p*-NMe_2·C_6H_4	21·5 [b]	$CHCl_3$	223—224 [c]	214 [d]
3	4,3-HO·C_6H_3(OMe)	18·5	95% EtOH	214	214 [e]
4	*p*-MeO·C_6H_4	15·5	C_6H_6–C_6H_{12}	228	227 [e]
5	Ph	10·5	C_6H_6	184 [c]	179—180 [e]
6	*o*-C_6H_4Cl	8·7	$CHCl_3$	208—209	208—209 [e]
7	*p*-C_6H_4Me	8·0	C_6H_6	215	214 [f]
8	*m*-C_6H_4Cl	5·8	C_6H_6	178—179 [g]	—
9	*p*-C_6H_4Cl	4·9	$CHCl_3$	196	196 [h]
10	1-$C_{10}H_7$	8·0	$CHCl_3$	224	225 [i]
11	*m*-NO_2·C_6H_4	0	—	—	167—168 [e]
12	*p*-NO_2·C_6H_4	0	—	—	—

[a] Baker and Howes, *J.*, 1953, 119. [b] Yield after 24 hr., 12·5%. A product of this m. p. was obtained by us also in the base-catalysed condensation. [d] Schonne, Braye, and Bruylants, *Bull. Soc. chim. belges*, 1953, **62**, 155. [e] Astle and Gergel, *J. Org. Chem.*, 1956, **21**, 493. [f] Fiquet, *Ann. Chim. Phys.*, 1883, 479. [g] Found: N, 6·2%; equiv., 205. $C_{10}H_6ClNO_2$ requires N, 6·7%; equiv., 207·5. [h] Walther and Raetze, *J. prakt. Chem.*, 1902, **65**, 258. [i] Hopkins, Chisholm, and Michael, *Canad. J. Res.*, 1945, **23**, *B*, 84.

The reactivity differences in the acid-catalysed condensation are not very great, in distinction to the large differences leading to a high ρ value (1·65) for the solvent-catalysed condensation.[7] This is in accordance with the results of Noyce *et al.*[3] for chalcone formation, in which the ρ value is very low (—0·25) for reaction in the acid medium, whereas large differences are observed in basic media, giving high ρ value (+3·5). Yates and Stewart[8] have shown that the dissociation constant of the conjugate acid of *p*-nitrobenzaldehyde is much higher than that of anisaldehyde, *i.e.*, the concentration of the oxonium ion of *p*- or *o*-anisaldehyde is much higher than that of *p*-nitrobenzaldehyde. This is probably the main factor which determines the reactivity of aldehydes in the acid-catalysed condensation. Accordingly, substituents operate in opposite directions in acid- and in base-catalysed (or solvent-catalysed) reactions. In the latter the polarity of the carbonyl bond, *i.e.*, the magnitude of the positive charge on the carbonyl-carbon atom, influences the rate of reaction with the carbanion formed from the active methylene compounds.

The only ketone studied, fluorenone, did not react.

The yields of α-cyano-2-methoxybenzylideneacetic acid obtained in 24 hr. from 0·1 mole

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[6] Coombs and Evans, *J.*, 1940, 1295.

[7] Patai and Zabicky, *J.*, 1960, 2030; Patai and Rappoport, unpublished results.

[8] Yates and Stewart, *Canad. J. Chem.*, 1959, **37**, 664.

each of *o*-anisaldehyde and ethyl cyanoacetate were 0, 2·5, 12·5, 24, and 28% in the presence of 0, 5, 10, 15, and 20 ml. of 70% aqueous perchloric acid, respectively, in 30 ml. of acetic acid. These results show that increasing the acidity of the medium results in higher yields of the product. At very high acidity (1 : 1 acetic acid–70% aqueous perchloric acid) which is known to promote decarbonylation of the aldehydes,[9] unidentified non-acidic by-products are formed in high yields. The increase in yield with acidity is in accordance with the parallel increase in the concentration of the aldehyde oxonium ions proposed by Noyce *et al.* for the chalcone formation.

The crude products obtained in the first precipitation by cyclohexane of the benzene extract of the reaction mixture had melting points very near to those claimed in the literature to be the *trans*-acids and gave the correct melting points for these after one crystallisation. In the two cases found in the literature (α-cyano-2-methoxybenzylideneacetic acid [10] and cyano-4-dimethylaminobenzylideneacetic acid [11]) in which the *cis*- and the *trans*-isomer of the same acid are known, the products obtained by us were identical with the *trans*-isomer of each pair as proved by melting point, mixed melting point, and in the first case also by the ultraviolet spectrum. However, the structure of the final product is not conclusive proof of the stereochemistry of the initial product of the reaction, as Baker has shown that isomerisation of the *cis*- to the *trans*-acid takes place in acid media, even though the same stable isomer (with aryl and carboxyl groups in *trans*-position) is the final product both in acid and in basic conditions.

Using aluminium chloride as catalyst also gives a *trans*-product (see above).

We believe that the mechanism proposed by Hauser *et al.*[4] and by Noyce *et al.*[3] for acid-catalysed condensations of aromatic aldehydes is applicable also to the present case.

EXPERIMENTAL

Acetic acid, 70% aqueous perchloric acid, ethyl cyanoacetate, and the aldehydes were pure commercial products.

Synthesis of Arylmethylenecyanoacetic Acids.—Ethyl cyanoacetate (0·1 mole) and the aromatic aldehyde (0·1 mole) were dissolved in acetic acid (30 ml.), and perchloric acid (15 ml.) was slowly added. In all the cases (except *o*-chlorobenzaldehyde) the solution became yellow or deep red after some hours at 25°. After 48 hr. the products were precipitated by pouring the solution into ice-water (400 ml.). If an oil separated it was extracted with benzene, from which addition of cyclohexane or low-boiling light petroleum precipitated the product. The products (see Table) crystallised from chloroform, chloroform–light petroleum, or benzene. This procedure is exemplified by the preparation of cyano-2-methoxybenzylideneacetic acid:

Ethyl cyanoacetate and *o*-anisaldehyde, reacting as above, gave a mixture from which a yellow solid (6 g.) was separated by filtration. The oily component was extracted with benzene (30 ml.), separated from the water layer, and treated with cyclohexane (100 ml.). A yellow solid (2·55 g.) was precipitated. The combined solid fractions (42%) crystallised from ethanol–benzene or from chloroform and then melted at 211° after preliminary sublimation. This compound was soluble in ethanol, slightly soluble in chloroform, and insoluble in light petroleum. A mixed m. p. with a sample obtained by Baker and Howes's method [10] for the *trans*-acid was also 211° and the two samples had the same ultraviolet absorption spectrum.

The arylmethylenecyanoacetic acids for mixed m. p. determinations were prepared by condensing cyanoacetic acid (2 g.) with an equimolar amount of the aromatic aldehyde in 0·1M-ethanolic sodium hydroxide (20 ml.). Acidification of the mixture after 6 hr. at room temperature and crystallisation from chloroform gave the arylmethylenecyanoacetic acids with the m. p.s reported in the literature (see Table).

Reaction in the Presence of Aluminium Chloride.—On addition of anhydrous aluminium chloride (7 g.) to *p*-anisaldehyde (8 g.) in dioxan (20 ml.) heat was evolved. After cooling, ethyl cyanoacetate (8 g.) was added, heat was again evolved and the red solution became yellow.

[9] Schubert and Zahler, *J. Amer. Chem. Soc.*, 1954, **76**, 1.

[10] Baker and Howes, *J.*, 1953, 119.

[11] Schonne, Braye, and Bruylants, *Bull. Soc. chim. belges*, 1953, **62**, 155.

After 48 hr. the mixture (containing some red crystals) was poured into ice-water. A yellow oil separated which on addition of ethanol (20 ml.) gave a solid (4·9 g., 60%), m. p. 67°. Crystallisation from benzene–light petroleum gave yellow needles, m. p. 84° alone or mixed with ethyl *trans*-cyano-4-methoxybenzylideneacetate.[12]

Reaction of Cyanoacetic Acid with o-*Methoxybenzaldehyde.*—Cyanoacetic acid (5 g.) and *o*-anisaldehyde (7 g.) in acetic acid (30 ml.) and 70% perchloric acid (15 ml.) were left for 24 hr. at 25°, poured into water and treated as above. Cyano-2-methoxybenzylideneacetic acid (1·8 g., 15%) was obtained.

Control Experiments.—From ethyl cyano-2-methoxybenzlideneacetate (9 g.) in acetic acid (30 ml.) and 70% perchloric acid (15 ml.), after 48 hr., 91% (8·2 g.) of starting material was recovered and no base-soluble material was obtained. Ethyl cyanoacetate in the same conditions gave, after neutralisation with sodium hydrogen carbonate, ether-extraction, and distillation, 35% of ethyl acetate.

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[12] Zabicky, *J.*, 1961, 683.