[Contribution from the Department of Chemistry and Chemical Engineering, Case Institute of Technology]

Ion-exchange Resin Catalysis of the Knoevenagel Condensation of Ketones[1]

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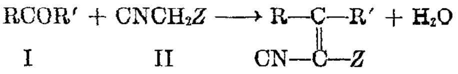
A weakly basic ion-exchange resin, Dowex 3, and its acetate salt are shown to be effective catalysts for the Knoevenagel condensation of various unhindered ketones with various cyano active-methylene compounds. The acetate salt of Dowex 3 is as effective as the better homogeneous catalysts reported in the literature. A concerted type mechanism is postulated.

Ion-exchange resin catalysis of the Knoevenagel condensation of aldehydes has been studied by Astle and co-workers[4,5] and by Mastagli and co-workers.[6] It had been thought that ketones would not, satisfactorily, undergo this resin-catalyzed reaction, but it is now shown that weakly basic ion-exchange resins and their organic salts are effective catalysts for the Knoevenagel condensation of unhindered ketones(I) with cyano active methylene compounds(II).



$$\underset{\text{I}}{\text{RCOR}'} + \underset{\text{II}}{\text{CNCH}_2Z} \longrightarrow \text{R—}\underset{\text{CN—C—}Z}{\overset{}{\underset{\|}{\text{C}}}}\text{—R}' + \text{H}_2\text{O}$$

(R and R′ = alkyl or aryl; *Z* = an electron-withdrawing group.)

In studying the Knoevenagel condensation of acetophenone and ethyl cyanoacetate, it was found that mixtures of acetic acid and the weakly basic resin, Dowex 3, were as effective as, and in some cases more effective than, the better homogeneous catalysts reported in the literature—*e.g.*, piperidine acetate and ammonium acetate–acetic acid mixtures[7] (Table I).

The acetate salt of Dowex 3 gives a faster rate of reaction than does the free basic form of the resin. The acetate salt of Dowex 1 × 4, a strongly basic exchanger, gives only a slightly faster rate than the free basic form. Also, Dowex 3 is much more effective than Dowex 1 × 4. The structures of these resins are described in the Experimental section.

TABLE I

Acetophenone with Ethyl Cyanoacetate; Variation of the Catalyst[a]

Catalyst	% Conversion[b] 1.5 hr.	2.5 hr.	4 hr.	6 hr.	8 hr.
Dowex 3[c]	8	14	21	26	31
Dowex 3[d]	7	14	26	32	42
Dowex 3[c] and HOAc	10	19	31	38	43
Dowex 3[d] and 0.032 mole HOAc	13	22	33	42	47
Dowex 1 × 4[c]	1	3	6	8	11
Dowex 1 × 4[d]	0	3	4	8	11
Dowex 1 × 4[c] and HOAc	8	8	13	14	17
Piperidine	7	8	10	13	14
Piperidine acetate	11	17	25	36	42
n-Amylamine acetate	53	67	78	86	90
Di-*n*-propylamine acetate	3	4	4	6	7
Triethylamine acetate	3	3	3	4	4
t-Ocylamine acetate	3	3	3	3	3
p-Aminophenol	13	15	29	39	46
Glycine	3	6	10	15	19
Ammonium acetate	7	7	10	10	11
Ammonium acetate and 0.04 mole HOAc	36	42	44	46	46

[a] 0.2 mole of each reactant, 0.013 mole of catalyst, and 0.013 mole of each component of a catalyst mixture, unless otherwise stated. [b] Based on volume of water of reaction from benzene-water azeotrope. [c] Free basic form. [d] Acetate salt form.

n-Amylamine acetate is by far the best catalyst in Table I. The acetate salts of di-*n*-propylamine and triethylamine are quite ineffective, however. This would seem to indicate that the primary amine groups in Dowex 3 are most effective in promoting the condensation reaction. However, *t*-octylamine acetate, a neopentyl type primary amine acetate, was very ineffective and the acetate salt of a cyclic secondary amine, piperidine, was effective. Thus, it is evident that the steric environment of the amine group is an important factor. The basic strengths of these amines could not be correlated with their catalytic ability.

By treating twenty-eight different ketones with ethyl cyanoacetate (Table II) and using the acetate salt of Dowex 3 as the catalyst, it was found that the percent conversion to product decreases as the alkyl or aryl groups increase in size or bulkiness. Branching at the *alpha* carbons of the ketones markedly reduces the percent conversion. In general, the increasing steric and inductive

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[2] Present address: Escambia Chemical Corp., Wilton, Conn.

[3] Present address: Lubrizol Corp., Cleveland, Ohio.

[4] M. J. Astle and W. C. Gergel, *J. Org. Chem.*, **21**, 493 (1956).

[5] M. J. Astle and J. A. Zaslowsky, *Ind. Eng. Chem.*, **44**, 2867 (1952).

[6] P. Mastagli, *Compt. rend.*, **241**, 1313 (1955); P. Mastagli, *Compt. rend.*, **242**, 1031 (1956); P. Mastagli, P. Lambert, and N. Andric, *Bull. soc. chim. France*, 796 (1956); P. Mastagli and N. Andric, *Bull. soc. chim. France*, 792 (1957).

[7] A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937); A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

electron-releasing effects of the hydrocarbon alkyl and aryl groups of the ketones studied affect the reaction rates in the same manner.

Experiments with a few substituted acetophenones indicate that the inductive and resonance effects of some hetero groups influence the reaction rates. As might be expected *p*-nitroacetophenone reacts at a faster rate than acetophenone itself, which in turn reacts faster than *p*-chloro or *p*-methoxyacetophenone. This also indicates that the resonance effect is more important for *p*-chloro and *p*-methoxyacetophenone than the inductive effect.

TABLE II

VARIOUS KETONES WITH ETHYL CYANOACETATE[a]

	% Conversion[b]					
Ketone	1.5 hr.	2.5 hr.	4 hr.	6 hr.	8 hr.	24 hr.
Cyclopentanone	90	99	100	100	—	—
Cyclohexanone	67	93	99	100	—	—
4-Methylcyclohexanone	65	92	100	100	—	—
3-Methylcyclohexanone	61	88	99	100	—	—
Acetone	75	92	96	97	—	—
Methyl ethyl ketone	60	76	88	93	97	—
Phenylacetone	49	72	85	92	—	—
Methyl *n*-amyl ketone	36	64	82	90	96	—
Methyl *n*-propyl ketone	33	61	75	85	90	—
Methyl *i*-butyl ketone	32	50	65	79	85	—
Diethyl ketone	19	33	47	64	72	—
Methyl *i*-propyl ketone	15	31	46	56	65	—
2-Methylcyclohexanone	11	28	40	50	58	—
p-Nitroacetophenone	14	28	38	47	54	—
Acetophenone	10	21	32	40	46	—
p-Chloroacetophenone	8	17	25	33	38	—
p-Methoxyacetophenone	7	11	17	21	24	—
1,3-Diphenylacetone	1	10	15	21	26	35
Propiophenone	3	7	10	13	14	21
Di-*i*-butyl ketone	3	6	8	10	10	13
α-Tetralone	3	3	6	8	—	14
i-Butyrophenone	1	3	4	4	4	6
Methyl *t*-butyl ketone	0	1	3	3	4	7
2,4-Dimethylacetophenone	0	0	0	3	3	4

[a] 0.2 mole of each reactant and 0.0245 mole (5.000 g.) of Dowex 3, acetate salt. No reaction was observed with anthrone, benzophenone, camphor, or fenchone. [b] Based on volume of water of reaction from benzene-water azeotrope.

The only active methylene compounds which undergo resin-catalyzed reaction with ketones are those in which one of the activating groups on the methylene is a nitrile group (Table III). The reason for the necessity of at least one nitrile group on the methylene appears to be tied to its small size rather than to its great electron-withdrawing power. For example, the difference in electron-withdrawing power between a nitrile and a carbethoxy group is not great enough to explain the fact that ethyl cyanoacetate reacts very rapidly with cyclohexanone and diethyl malonate does not react at all.

There have been a number of mechanisms suggested for the Knoevenagel condensation and it appears that any one of them may be operative depending primarily on the nature of the systems studied.

Patai, Zabicky, *et al.*[8,9] recently studied the reaction of malononitrile and aromatic aldehydes with and without catalysts and found first-order kinetics in water solutions and second order in ethanol solution. It was postulated that ionization of the malononitrile to a proton and a carbanion was the first step, the second being nucleophilic attack by the carbanion on the carbonyl carbon.

TABLE III

CYCLOHEXANONE WITH VARIOUS ACTIVE METHYLENE COMPOUNDS[a]

	% Conversion[b]				
Active Methylene	1.5 hr.	2.5 hr.	4 hr.	6 hr.	8 hr.
Malononitrile	94	94	100	100	—
Ethyl cyanoacetate	67	93	99	100	—
Benzoylacetonitrile	36	58	72	83	89
2,4-Dimethylbenzoylacetonitrile[c]	47	58	72	81	86
Pivaloylacetonitrile[c]	36	56	69	83	89
Cyanoacetamide	17	29	44	58	63
Cyanoacetic acid	0	13	31	46	54
p-Nitrophenylacetonitrile	3	3	14	22	31
p-Cyanophenylacetonitrile[c]	0	0	3	3	3

[a] 0.2 mole of each reactant and 0.0245 mole (5.000 g.) of Dowex 3, acetate salt. No reaction was observed with the following active methylenes: diethyl malonate, ethyl acetoacetate, acetylacetone, ethyl chloroacetate, chloroacetonitrile, phenylacetonitrile, *p*-methylphenylacetonitrile,[c] methyl α-cyano-*p*-toluate[c], and caprylonitrile. [b] Based on volume of water of reaction from benzene-water azeotrope. [c] Prepared according to the procedure used by Ipatieff *et al.*[5]

Supporting evidence for this mechanism is observed if one compares the rates of reaction of ethyl cyanoacetate with methyl ethyl ketone and cyclohexanone (Table IV).

Only a small difference in the rates is observed with resin catalysis, but a large difference is observed using piperidine acetate. It appears that the steric factor is more important for methyl ethyl ketone in solution than for cyclohexanone, but the steric requirements using resin catalysis are similar for both ketones. This suggests that a complex or a transition state is being formed on the resin, which is similar for both ketones. This has also been postulated for ester hydrolysis catalyzed by acidic exchange resins.[10,11]

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(8) S. Patai, S. Saltiel, and J. Zabicky, *Bull. Research Council, Israel*, **7A**, 186 (1958); Y. Ysraeli and S. Patai, *Bull. Research Council, Israel*, **7A**, 100 (1958).

(9) S. Patai and Y. Israeli, *J. Chem. Soc.*, 2020 and 2025 (1960); S. Patai and J. Zabicky, *J. Chem. Soc.*, 2030 (1960); S. Patai, J. Zabicky, and Y. Israeli, *J. Chem. Soc.*, 2039 (1960).

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TABLE IV

VARIOUS KETONES WITH ETHYL CYANOACETATE; COMPARING PIPERIDINE ACETATE WITH A RESIN CATALYST[a]

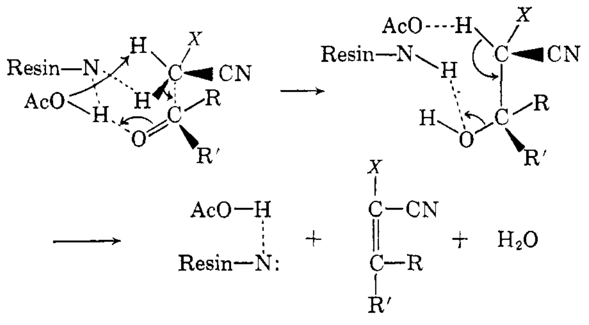
Ketone	% Conversion[b] 1.5 hr.	2.5 hr.	4 hr.	6 hr.	8 hr.
Cyclohexanone[c]	50	71	83	90	96
Cyclohexanone[d]	81	93	100	100	100
Methyl ethyl ketone[c]	51	69	81	86	92
Methyl ethyl ketone[d]	47	71	85	94	100

[a] 0.2 mole of each reactant and 0.013 mole of catalyst. [b] Based on volume of water of reaction from benzene-water azeotrope. [c] Dowex 3, acetate salt, is the catalyst. [d] Piperidine acetate is the catalyst.

Sprinzak and co-workers[12] recently proposed a concerted mechanism for the Triton B-catalyzed condensation of fluorene with aldehydes and ketones in ethanol, but in pyridine the carbanion mechanism is favored. Ogata and Tsuchida[13] have suggested a concerted mechanism for the tertiary amine catalyzed Perkin reaction.

Several workers[14] have proposed that Schiff bases are formed as intermediates, but this would only occur with primary amines and ammonia. Enolization is another possible intermediate reaction, but this also is limited to special cases.[15]

The experimental results suggest that the following concerted mechanism is the principal mode of reaction using ion-exchange resins as catalysts.



The acetate salt of Dowex 3 is not as effective as a mixture of the free basic form of Dowex 3 and acetic acid (Table I). With the former catalyst, almost all the acetic acid is associated with a nitrogen atom in the resin, but not necessarily so in the latter case. This means that in the latter case free acetic acid molecules may be associated with the carbonyl compound and the nitrogen atoms may then be associated with a proton from the active methylene compound. Also it is shown that if acetic acid is added to the acetate salt form of Dowex 3 the reaction is promoted.

With resin catalysis no aldol type intermediates were detected at any time in the reaction mixtures, thus indicating that the reactants are fixed on the resin until the final carbon-carbon double bond is formed.

When the free basic form of a resin is used the carbonyl group would not be activated by acetic acid, as indicated above, and the attack by Resin-N:· · ·H—CH(X)CN is much slower as is demonstrated. Also, the acetic acid, being close to the nitrogen on the resin, brings the carbonyl in close proximity to the species Resin-N:· ·H—CH(X)CN, thus facilitating the reaction sterically.

The reason for the fact that Dowex 1 × 4 is much less effective than Dowex 3 is not quite clear. However, it may be pointed out that in strongly basic resins the quaternary nitrogen is quite sterically hindered with four groups around it, thus making association with the carbonyl oxygen difficult.

Although it was not the authors' objective to obtain kinetic data, if one examines the data reported here one finds that the fast reacting ketones in Table II give first-order kinetics. With the slower reacting ketones, however, the order is not clearly defined. The data is not precise enough to make a choice at this time, but there seems to be a change in kinetics and it would seem most probable to be to second- or mixed-order kinetics. Mechanistically, the rate of activation of the active methylene compound is the limiting factor in the first-order reactions, whereas as the carbonyl of the ketone becomes more sterically hindered the rate of carbon-carbon bond formation becomes rate determining. These observations are similar to those of Patai, Zabicky, *et al.*[8,9]

The fact that all the reactions in Table IV give first-order kinetics indicates that diffusion of the reactants into the resin is not rate determining, but rather the chemical reaction is rate determining. Bernhard and Hammett[10] have shown this to be the case in the ion-exchange resin catalysis of the hydrolysis of esters.

EXPERIMENTAL

Materials. The highest purity chemicals that were commercially available were used. The ethyl cyanoacetate and cyclohexanone were redistilled before using. The cyanoacetic acid and the ammonium acetate were dried under vacuum before using. The ion-exchange resins were supplied by the Dow Chemical Company. Dowex 3 is a polystyrene-polyamine resin[16] containing primary, secondary, and tertiary amine groups in the ratio 2:1:2[17] with a capacity (see below) of 4.9 meq./dry g. Dowex 1 × 4 is a type I polystyrenequater-

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[12] E. Ghera and Y. Sprinzak, *J. Am. Chem. Soc.*, **82**, 4945 (1960); M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **82**, 4953 (1960).

[13] Y. Ogata and M. Tsuchida, *J. Org. Chem.*, **24**, 78 (1959).

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[15] E. L. May, *J. Org. Chem.*, **22**, 593 (1957).

[16] C. M. McBurney (to Rohm and Haas Co.), U. S. Patent **2,591,573** (April 1, 1952) and U. S. Pat. **2,591,574** (April 1, 1952); *Chem. Abstr.*, **46**, 7364 (1952).

[17] P. A. Jones, The Dow Chemical Co., Midland, Mich., Dec. 13, 1960, private communication.

TABLE V

PHYSICAL PROPERTIES OF PRODUCTS OF THE TYPE $R'(R)C{=}C(CN)COOC_2H_5$ FROM THE KNOEVENAGEL CONDENSATION OF $CNCH_2COOC_2H_5$ WITH VARIOUS KETONES[a]

Ketone	B.P./Mm.	n_D^t	Nitrogen, %		Ref.
			Calcd.	Found	
Cyclopentanone[b]	131–131.5/0.05	—	7.82	7.91	20
Cyclohexanone[c]	98–99/0.10–0.12	$1.4939^{25.0}$	7.25	7.55	7, 20
4-Methylcyclohexanone	126–128/0.09–0.11	$1.4938^{19.1}$	6.76	7.06	21
Acetone[d]	60–65/1	$1.4578^{25.0}$	9.14	9.26	22, 23
3-Methylcyclohexanone	122–123/0.08–0.10	$1.4944^{19.5}$	6.76	6.72	21
Methyl ethyl ketone[e]	92.5/0.12	$1.4634^{23.8}$	8.38	8.62	7, 23
Phenylacetone	160–164/0.11–0.13	$1.5343^{20.2}$	6.11	6.38	7
Methyl *n*-amyl ketone	121–123/0.07	$1.4680^{19.9}$	6.69	6.96	7
Methyl *n*-propyl ketone	107–110/0.09	$1.4682^{19.9}$	7.73	7.54	7
Methyl *i*-butyl ketone	109.5/0.07	$1.4670^{20.0}$	7.17	7.14	7, 22
Diethyl ketone	80–81.5/0.06	$1.4636^{27.5}$	7.73	7.70	7
Methyl *i*-propyl ketone	103/0.07	$1.4677^{19.9}$	7.73	7.29	24
2-Methylcyclohexanone	128–129/0.08	$1.4948^{19.2}$	6.76	7.12	25
Acetophenone	135–137/0.07–0.08	$1.5456^{27.0}$	6.51	6.76	7
p-Chloroacetophenone	154–158/0.08–0.10	$1.5610^{23.0}$	5.61	5.87	—
p-Methoxyacetophenone	171–173/0.12	$1.5700^{23.2}$	5.71	6.03	26
1,3-Diphenylacetone	177/0.08–0.09	$1.5705^{19.3}$	4.59	4.55	27
Propiophenone	121–122/0.07	$1.5382^{20.4}$	6.11	6.12	7, 28
Di-*i*-butyl ketone	108–109/0.10–0.11	$1.4681^{19.8}$	5.90	6.09	7
α-Tetralone	149/0.09	—	5.81	5.90	29
Methyl *t*-butyl ketone	83/0.1–0.2	$1.4690^{20.3}$	7.17	7.56	28

[a] Products of this type gave an infrared adsorption peak at 2222–2228 cm.$^{-1}$ because of the conjugated nitrile. A Beckman model IR-7 infrared sphectrophotometer with sodium chloride cells was used. All these products have a freezing point below −35° except as noted. [b] M.p. 56.4–57.0° (corr.). [c] M.p. 0.0°. [d] M.p. 6.8–7.6°. [e] M.p. −37 ± 1°.

nary ammonium resin[18] with a capacity of 3.8 meq./dry g.

Modification of resins. About 200 g. of Dowex 3 (or Dowex 1 × 4) was slurried with a filtered 5% sodium hydroxide solution and placed in a large chromatographic tube, which was fitted with a fritted glass plate. More 5% sodium hydroxide, 1–2 gal., was passed over the resin until the eluate had the same normality as did the 5% sodium hydroxide solution by titration with standard 0.1*N* hydrochloric acid solution and phenolphthalein indicator. The resin was washed free of excess sodium hydroxide with deionized water. The washing was stopped when the *p*H of the eluate became constant, which was usually within one *p*H unit of the *p*H of the deionized water; 8–12 gal. of water was required. A Beckman Model H-2 *p*H meter was used. A portion of the free basic resin was then filtered off and placed in a vacuum desiccator to dry at about 1 mm. pressure and at room temperatures under a nitrogen atmosphere. The resin was placed in a bottle under nitrogen when no more water was observed in the Dry Ice trap between the desiccator and the vacuum pump. A 10% acetic acid solution, 1–2 gal, was passed over the second portion of the resin in the chromatographic tube until the eluate had the same normality (phenolphthalein) as did the 10% acetic acid. The resin was then washed free of excess acetic acid with deionized water. The washing was stopped when the *p*H of the eluate was constant, which was usually within 1–2 *p*H units of the pH of the deionized water; 5–8 gal. of water was required. The resin was then filtered and air dried in a hood at room temperature for 3–5 days.

Capacity of resins. Dried Dowex 3 (5.000 g.), free basic form, and 50.00 ml. of standardized 1.800*N* hydrochloric acid solution were placed in a 100 ml. stoppered flask. The mixture, after standing for 20 hr., was placed on a Burrell wrist-action shaker for 2 hr. and then let settle for 0.5 hr. before titrating the solution with standard 0.1*N* sodium hydroxide solution and phenolphthalein indicator. From the observed 1.310*N* hydrochloric acid remaining the capacity is calculated to be 4.9 meq./dry g. In the same manner the capacity of Dowex 1 × 4 was found to be 3.8 meq./dry g.

Reaction procedure. The general procedure for the reactions cited in this work can be illustrated by the following example. A mixture of 20.7 ml. (0.2 mole) of cyclohexanone, 21.3 ml. (0.2 mole) of ethyl cyanoacetate, 5.000 g. (0.0245 mole) of Dowex 3, acetate salt, and 75 ml. of benzene was heated with constant stirring in a flask fitted with a reflux condenser and a graduated Dean-Stark azeotrope trap.[19] A "Glas-Col" heating mantle was used and was controlled by a "Variac" to ± 2 volts so that check runs indicated a reproducibility of results within ± 3%. (The overall error is within about 5%.) The water-benzene azeotrope separated in the trap and the water collected at the bottom of the trap. The volume of the water was read directly at intervals. A run was made with the ketone omitted in order to determine the water content of the resin so as to correct for it; 1.35 ml. of water was obtained from 5.000 g. of Dowex 3, acetate salt, by the end of the first hour of heating and no additional water was collected in 3 additional hr. of heating. After 6 hr. of heating the

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(18) *Dowex: Ion Exchange,* The Dow Chemical Co., Midland, Mich., 1959.

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(24) Eli Lilly and Co., Brit. Patent **613,705** (Dec. 2, 1948); *Chem. Abstrs.,* **43,** 4692 (1959).

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(27) H. Le Moal, *Ann. chim. (Paris),* **8,** 841 (1953); *Chem. Abstr.,* **49,** 7525 (1955).

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TABLE VI

PHYSICAL PROPERTIES OF CYCLOHEXYLIDENE PRODUCTS FROM THE KNOEVENAGEL CONDENSATION OF CYCLOHEXANONE WITH VARIOUS CYANO ACTIVE METHYLENE COMPOUNDS

				Carbon, %		Hydrogen, %		Nitrogen, %		
Active Methylene	B.P./P., Mm.	M.P.	n_D^t	Calcd.	Found	Calcd.	Found	Calcd.	Found	Ref.
Malononitrile	98–101/0.08–0.09	−3.5 to −4.5	$1.5091^{26.6}$	73.94	73.80	6.89	6.71	19.16	19.32	23
Cyanoacetamide	—	110.5–111.5[a]	—	65.83	65.77	7.37	7.37	17.06	17.08	30
Pivaloylacetonitrile	103–105/0.13–0.14	<−35	$1.4911^{19.4}$	76.05	76.00	9.33	9.31	6.82	6.70	—
Benzoylacetonitrile	145–147/0.05	69–71.5[a]	$1.5687^{30.5}$	79.97	79.25	6.71	6.64	6.22	6.35	—

[a] Corrected.

reaction mixture was cooled, filtered to separate the resin, and vacuum distilled to give ethyl cyclohexylidenecyanoacetate in 95–100% yield. See Tables V and VI for the physical properties of the products of the reactions cited in this work.

Fresh catalyst was used in each experiment described in this work. All the Dowex 3 used was from the same lot. The amine acetate catalysts were formed *in situ* from equimolar quantities of the amine and acetic acid. Blank runs were made with all resins as well as with the ammonium acetate and the cyanoacetic acid to determine their water content, so as to correct for it.

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(30) M. Nakamura, Japan. Pat. **2,176** (April 23, 1954); *Chem. Abstr.*, **49**, 14802 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

Partial Asymmetric Synthesis in the Darzens Reaction

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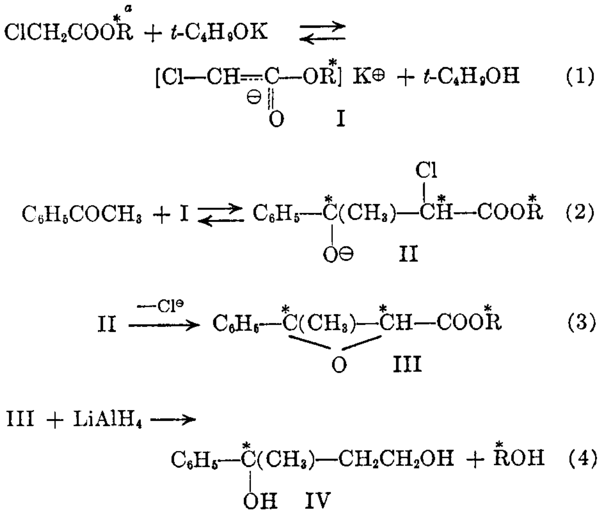
The Darzens reaction of either (−)-menthyl or (+)-bornyl chloroacetate with acetophenone is accompanied by a partial asymmetric synthesis, as this is shown by reduction of the resulting ester with lithium aluminum hydride to (−)-3-phenylbutane-1,3-diol of varying optical activities. Interestingly the predominant configuration of the asymmetric center newly formed has been found to be the same in both cases. Ethanolysis of menthyl or bornyl glycidate thus prepared affords the corresponding ethyl ester, which is dextrorotatory and can be transformed into (−)-3-phenylbutane-1,3-diol in optical yields comparable to those in direct hydride reduction. Possible mechanism leading to this asymmetric synthesis is discussed.

Evidence has been accumulated in favor of the aldolization mechanism of the Darzens reaction between α-halo esters and aldehydes or ketones, involving the initial formation of halohydrin anions (I) (Equations 1 and 2) followed by the loss of halide anion (Equation 3).[1,2] On the other hand the aldol type condensation of ketones and esters[3] has been shown to afford optically active β-hydroxy acids, when (−)-menthyl or (+)-bornyl acetate is allowed to react with unsymmetrically substituted ketones and the resulting β-hydroxy esters are hydrolyzed.[4] This paper comprises the Darzens reaction of optically active chloroacetates and the subsequent removal of asymmetric carbons initially introduced. These reactions are accompanied by partial asymmetric syntheses and are summarized as follows:



$$\mathrm{ClCH_2COO\overset{*a}{R}} + t\text{-}\mathrm{C_4H_9OK} \rightleftarrows [\mathrm{Cl{-}CH{=}\underset{\ominus O}{C}{-}O\overset{*}{R}}]\,\mathrm{K^{\oplus}} + t\text{-}\mathrm{C_4H_9OH} \quad \text{(1)}$$

$$\text{I}$$

$$\mathrm{C_6H_5COCH_3} + \text{I} \rightleftarrows \mathrm{C_6H_5{-}\underset{O^{\ominus}}{\overset{*}{C}}(CH_3){-}\overset{Cl}{\overset{*}{C}H}{-}COO\overset{*}{R}} \quad \text{II} \quad \text{(2)}$$

$$\text{II} \xrightarrow{-\mathrm{Cl^{\ominus}}} \mathrm{C_6H_5{-}\overset{*}{C}(CH_3){-}\overset{*}{C}H{-}COO\overset{*}{R}}\ (\text{epoxide } \mathrm{O}) \quad \text{III} \quad \text{(3)}$$

$$\text{III} + \mathrm{LiAlH_4} \longrightarrow \mathrm{C_6H_5{-}\underset{OH}{\overset{*}{C}}(CH_3){-}CH_2CH_2OH} + \mathrm{\overset{*}{R}OH} \quad \text{IV} \quad \text{(4)}$$

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