somewhat more subtle than a simple change in mechanism.[11]

Position of Reaction in the Condensation of Aromatic Aldehydes with Methyl Ethyl Ketone.—It has been pointed out that the kinetic results observed are inconsistent with the formation of any appreciable amounts of the linear β-hydroxyketone. These results strongly suggest that in acid solution, selectivity enters into the condensation step. The situation in alkaline medium is discussed in the following paper.

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[11] H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Carbonyl Reactions. IX. The Rate and Mechanism of the Base-catalyzed Condensation of Benzaldehyde and Acetone. Factors Influencing the Structural Course of Condensation of Unsymmetrical Ketones

BY DONALD S. NOYCE AND WILMER L. REED

RECEIVED AUGUST 11, 1958

The rate of condensation of benzaldehyde and acetone has been studied in aqueous sodium hydroxide solution. It is concluded that the reaction is first order in each component and also shows first-order dependence upon the hydroxide ion concentration. The rates of reaction of the intermediate ketol, 4-phenyl-4-hydroxy-2-butanone (I), in alkaline media have been examined; I undergoes two competitive reactions: dehydration to form benzalacetone II, and cleavage to form benzaldehyde and acetone. The base-catalyzed reactions of 4-(p-methoxyphenyl)-4-hydroxy-2-butanone (III) and 4-(p-methoxy phenyl)-4-hydroxy-3-methyl-2-butanone (V) have also been examined; III likewise undergoes competitive dehydration and cleavage; V is rapidly and completely cleaved by base to give anisaldehyde and methyl ethyl ketone. Consideration of the results supports the conclusion that the structurally definitive process in the acid-catalyzed reaction is the condensation step, but that dehydration of the intermediate ketol is the structurally determining process in the base-catalyzed reaction involving methyl ethyl ketone.

Introduction

In recent papers[1-5] we have pointed out the important kinetic role of β-hydroxyketones in the acid-catalyzed aldol condensation. It is the purpose of the present report to examine the base-catalyzed condensation reaction and the behavior of β-hydroxyketones in basic solution.

The base-catalyzed condensation of benzaldehyde and acetone has been studied by Nikitin[6] and by Gettler and Hammett[7] utilizing different methods of measuring the rate. Nikitin found the reaction to be second order with respect to benzaldehyde in the presence of excess acetone and first order with respect to acetone in excess benzaldehyde. The order in base was not determined. The description of the method leads one to consider that the colorimetric determination was involved with the benzopyrylium salts of the type studied by Wizinger.[8]

Gettler and Hammett found the reaction to be first order in benzaldehyde and acetone with an apparent half-order dependence on the sodium hydroxide concentration in the 70% aqueous dioxane solvent system employed.

We have shown[5] that the ketol 4-phenyl-4-hydroxy-2-butanone (I) is an intermediate in the base-catalyzed condensation reaction. In aqueous sulfuric acid solution I dehydrates to yield 4-phenyl-3-buten-2-one (II) (benzalacetone). However, in aqueous sodium hydroxide solution we have found that I undergoes competitive reactions, one leading to the formation of II and the second resulting in cleavage to form benzaldehyde and acetone. The product II is unstable in aqueous sodium hydroxide and cleaves slowly to benzaldehyde and acetone. We are thus dealing with an equilibrium process analogous to the acetone–diacetone alcohol–mesityl oxide equilibrium studied by Koelichen,[9] La Mer and Miller,[10] and Brewer.[11]

Experimental

Preparation of Materials.—The preparation of 4-phenyl-4-hydroxy-2-butanone (I), 4-phenyl-3-buten-2-one (II), 4-(p-methoxyphenyl)-4-hydroxy-2-butanone (III) and 4-(p-methoxyphenyl)-3-buten-2-one (IV), has been described previously.[5] 4-(p-Methoxyphenyl)-3-methyl-3-buten-2-one (VI) was prepared by the method of Woodruff and Conger,[12] m.p. 28°. Benzaldehyde was purified by the method of Noyce and Pryor.[1]

Preparation of 4-(p-Methoxyphenyl)-4-hydroxy-3-methyl-2-butanone.—A mixture of 11.2 g. of freshly distilled anisaldehyde and 200 ml. of methyl ethyl ketone was cooled to 0° and 10 ml. of 1 M NaOH was added. The reaction mixture was maintained between 0 and $-5°$ for three hours with stirring and then neutralized with dilute H_2SO_4. The organic material was extracted with ether, the extract concentrated and dried by addition of benzene and distillation of the water azeotrope. The excess anisaldehyde was removed by distillation at reduced pressure. The material remaining was indicated to be mainly ketol by the infrared spectrum. Attempts to achieve crystallization failed.[13]

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[1] D. S. Noyce and W. A. Pryor, THIS JOURNAL, **77**, 1397 (1955).

[2] D. S. Noyce, W. A. Pryor and A. T. Bottini, *ibid.*, **77**, 1402 (1955).

[3] D. S. Noyce and L. R. Snyder, *ibid.*, **80**, 4033 (1958).

[4] D. S. Noyce and L. R. Snyder, *ibid.*, **80**, 4324 (1958).

[5] D. S. Noyce and W. L. Reed, *ibid.*, **80**, 5539 (1958).

[6] J. K. Nikitin, *J. Gen. Chem. USSR*, **7**, 71 (1937); *Chem. Zentr.*, **108**, II, 2333 (1937).

[7] J. D. Gettler and L. P. Hammett, THIS JOURNAL, **65**, 1824 (1943).

[8] R. Wizinger, S. Losinger and P. Ulrich, *Helv. Chim. Acta*, **39**, 5-15 (1956).

[9] K. Koelichen, *Z. physik. Chem.*, **33**, 129 (1900).

[10] V. K. La Mer and M. L. Miller, THIS JOURNAL, **57**, 2674 (1935).

[11] L. Brewer, Doctoral Dissertation, University of California, 1943.

[12] E. H. Woodruff and T. W. Conger, THIS JOURNAL, **60**, 465 (1938).

[13] A previous preparation of this material was distilled under reduced pressure to yield a small amount of a pale yellow oil (b.p. 73–75° at 0.3 mm.) which was indicated to be ketol by the infrared spectrum. By repeated distillation of this oil we were unable to obtain crystalline material.

A sample of the crude ketol, 2.06 g., was chromatographed on 62 g. of Florisil (60/100 mesh, The Floridin Co., Tallahassee, Fla.). Elution with ether–benzene, 1:4, afforded 530 mg. of V as a white crystalline solid, m.p. 38.2–39.2°, after sublimation.

Anal.[14] Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74. Found: C, 69.40; H, 7.93.

Kinetic Procedures.—Measurements were carried out essentially as described previously.[5] Data were taken at the 250 mμ absorption band for benzaldehyde and at 290 mμ for benzalacetone. In all condensation reactions the acetone concentration was compensated for by placing a solution of the same concentration in the reference cell. The base concentration does not affect the optical properties of the solutions. The rate constants were determined graphically from data covering approximately 70% reaction.

The Acid-catalyzed Dehydration of V.—The sulfuric acid-catalyzed dehydration of V was determined as we have reported previously.[5] The data are reported in Table I and are to be compared to the results of Noyce and Snyder.[4]

TABLE I

THE RATE OF DEHYDRATION OF 4-(*p*-METHOXYPHENYL)-4-HYDROXY-3-METHYL-2-BUTANONE (V)

Concentration of Ketol = 5.5×10^{-5} *M*, *T* = 25.0°

H_2SO_4, *M*	H_0[15]	$k_2 + k_3 \times 10^5$, sec.$^{-1}$	$k_2 \times 10^5$, sec.$^{-1}$	$k_3 \times 10^5$, sec.$^{-1}$
1.03	−0.28	0.361 ± 0.013	0.1685	0.1925
1.03 (44.75°)	−0.28	3.54 ± 0.1	1.85	1.69
4.63	−2.12	13.56	8.20	5.36
5.62	−2.58	38.3	21.9	16.4
6.27	−2.90	75.8	33.1	42.7

The rate constants in Table I were determined from the ultimate production of anisaldehyde and 4-(*p*-methoxyphenyl)-3-methyl-3-buten-2-one (VI). Comparison with Table IV of reference 4 reveals the near superposition of the data. In the region of 4 to 5.5 molar sulfuric acid, Noyce and Snyder observed 40.6 ± 1.5% dehydration, and in the present instance there is obtained 41.2 ± 1.7% dehydration. It is thus clear that some of branched chain ketol is produced under alkaline condensation conditions.

The activation parameters calculated from the data of Table I (for k_2, $\Delta H^{\ddagger} = 22.8 \pm 1$ kcal., $\Delta S^{\ddagger} = -8.3 \pm 2$ e.u.; for k_3, $\Delta H^{\ddagger} = 20.1 \pm 1.2$ kcal., $\Delta S^{\ddagger} = -17 \pm 5$ e.u.) differ somewhat from those previously obtained by Noyce and Snyder by extrapolation from rate data at higher acidities, assuming linear dependence on H_0.

The Hydrolysis of 4-(*p*-Methoxyphenyl)-4-acetoxy-3-methyl-2-butanone (VII).—This material was prepared by Snyder[3] utilizing the acid-catalyzed condensation of anisaldehyde and methyl ethyl ketone in acetic acid.

To a solution of 1.345 g. of the acetate dissolved in 100 ml. of 95% ethanol was added 200 ml. of 1.05 *M* H_2SO_4 and the reaction mixture was placed in a 25° thermostated bath. After 4 hours the reaction mixture was neutralized with 67 ml. of 1 *M* NaOH and the resulting solution was made up to a volume of 1 liter with *p*H 7 buffer solution ($NaHPO_4$–Na_2PO_4). The solution was extracted with ether in a continuous liquid–liquid extractor. The extract was concentrated, benzene was added and distilled to dry the product which was a yellow oil.

The product was placed on a 40-g. Florisil chromatography column with pentane–benzene 1:1. Elution with this solvent was continued until very little material could be removed, using successive 50-ml. volumes of elution solvent. The solvent mixture was changed to ether–benzene, 1:4, when a fluorescent band had progressed down the column. The first fraction with this solvent yielded 161 mg. of unreacted acetate. The next fraction contained 461 mg. of a yellow oil which was indicated to be mainly ketol by the infrared spectrum. This material was rechromatographed on the same type of column using benzene containing increasing amounts of ether to yield 30 mg. of a white crystalline solid, m.p. 37.8–39° after sublimation. The infrared spectrum of this material is identical with that of the ketol V prepared by base-catalyzed condensation of anisaldehyde and methyl ethyl ketone.

Production Isolation from the Base-catalyzed Dealdolization of V Under Kinetic Conditions.—A solution of 80 mg. of V in 100 ml. of 0.01 *M* NaOH was maintained at 25° for a period of time calculated to be 10 half-lives. The reaction mixture was neutralized with 0.05 *M* sulfuric acid and 1.5 g. of sodium acetate and 1.0 g. of semicarbazide–HCl was added and the mixture heated at 45° for 16 hours. The mixture was heated briefly to boiling and allowed to cool. The reaction mixture was extracted with 300 ml. of methylene chloride and the extract concentrated. The white crystalline solid obtained was chromatographed on 10 g. of Grade I Alumina using chloroform–methanol as the eluting solvent.

The chromatographic behavior of this material was identical with that of a known mixture of anisaldehyde semicarbazone and methyl ethyl ketone semicarbazone. No other semicarbazones were found or indicated. A pure fraction of each compound was isolated from the chromatography, but there was a certain amount of overlap of the bands due to the limitations of the method.

Results

The Condensation of Benzaldehyde and Acetone.—The results for the condensation are given in Table II. It is to be noted that the condensation does not proceed to completion under these experimental conditions, but only to the extent of 76 ± 5% at 0.01192 *M* acetone concentration and to the extent of 87% where the acetone concentration is 0.02384 *M*. That equilibrium is established is demonstrated by the fact that the optical density of the solutions remain constant over a period of 50 half-lives.

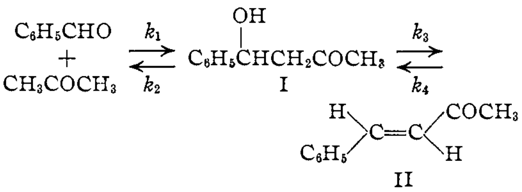
TABLE II

THE CONDENSATION REACTION AT 25.0°

(C_6H_5-CHO), *M* × 10^5	(CH_3-$COCH_3$), *M*	(OH^-), *M*	$k_1 + k_4 \times 10^5$, sec.$^{-1}$	k_4[a] × 10^5, sec.$^{-5}$	k_1[b]	Reaction, %
2.60	0.01192	0.0503	4.62	1.15	3.47	70.7
3.15	.01192	.145	13.51	3.26	10.25	81.8
2.60	.01192	.304	27.73	6.85	20.88	71.2
4.03	.01192	.490	46.21	10.80	35.41	80.0
3.85	.02384	.188	31.49	4.23	27.26	86.8
		.188[c]	17.33[c]	4.23	13.10[c]	

[a] Interpolated values of k_4 from data of Table III. [b] By difference. [c] Values taken from Fig. 1 to determine the order with respect to acetone.

The rate of approach to equilibrium is the sum rate constant $k_1 + k_4$ as shown in equation 1.



$$C_6H_5CHO + CH_3COCH_3 \underset{k_2}{\overset{k_1}{\rightleftarrows}} C_6H_5CH(OH)CH_2COCH_3\ (I) \underset{k_4}{\overset{k_3}{\rightleftarrows}} (H)(C_6H_5)C{=}C(COCH_3)(H)\ (II) \qquad (1)$$

The rate constants may be separated by determining the extent of reaction (column 7 of Table II). However, any difficulties encountered in the benzaldehyde concentration will magnify uncertainties in the rate constants. More satisfactory is the determination of one of the constants separately. By measuring the rate of destruction of II in dilute solution, k_4 may be determined. Data are given in Table III. The average degree of completion calculated by both methods is in good agreement. However, the data of Table III give a more accurate value for k_4.

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[14] Analysis by the Microanalytical Laboratory, University of California.

[15] Values interpolated from M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

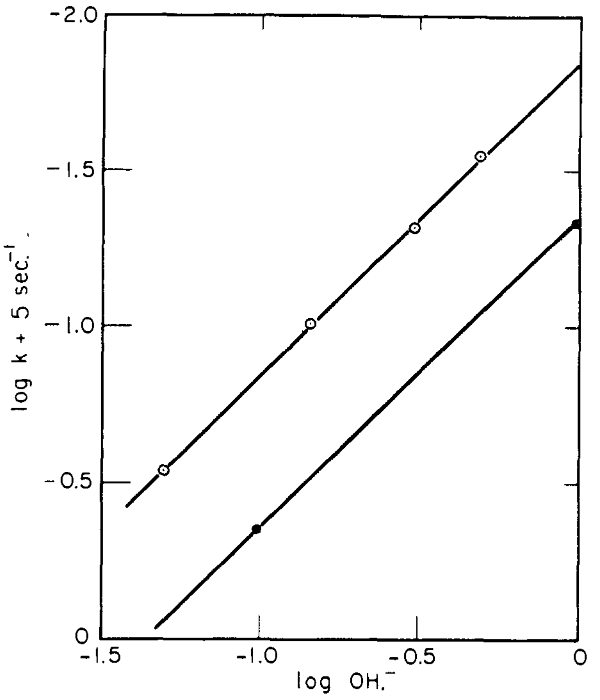


Fig. 1.—Condensation of benzaldehyde and acetone: —○—, k_1 rate of condensation; —●—, k_4 rate of cleavage of benzalacetone.

In Table IV we present the results of a kinetic investigation of the behavior of the ketol I with hydroxide. The reaction proceeds to an ultimate formation of 40% of benzalacetone (II), and the rate constants for k_2 and k_3 which are tabulated may thus be calculated.

TABLE III

THE RATE OF REVERSION OF 4-PHENYL-3-BUTEN-2-ONE (II) AT 25.0°

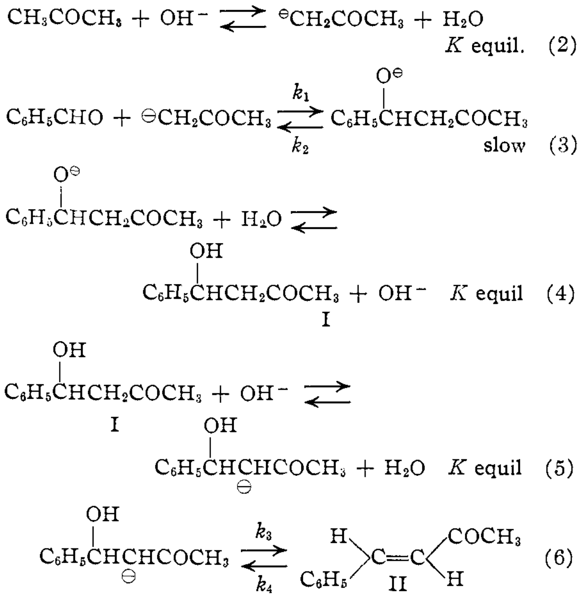
($C_6H_5CH{=}CH$-$COCH_3$), $M \times 10^5$	(OH^-), M	$k_4 \times 10^5$, sec.$^{-1}$
3.99	0.0980	2.24
2.92	0.977	21.76

TABLE IV

THE DEHYDRATION OF 4-PHENYL-3-HYDROXY-2-BUTANONE (I) AT 25.0°

($C_6H_5\overset{OH}{C}HCH_2$-$COCH_3$) $\times 10^5$, M	(OH^-), M	$k_2 + k_3$ $\times 10^5$, sec.$^{-1}$	k_2 $\times 10^5$, sec.$^{-1}$	k_3 $\times 10^5$, sec.$^{-1}$
3.45	0.00433	13.19	7.94	5.25
3.45	.00936	27.29	16.42	10.87
3.45	.0191	50.41	30.35	20.06

The data of Table II demonstrate that the reaction is first order in benzaldehyde, in acetone and in hydroxide ion. The rate of the condensation step is slower than the rate of halogenation of acetone,[16] and thus k_1 represents the condensation step (equation 3). Similar considerations apply to k_3 (equation 6). The reaction scheme is shown in equations 2–6.



$$CH_3COCH_3 + OH^- \rightleftarrows {}^{\ominus}CH_2COCH_3 + H_2O \qquad K \text{ equil.} \qquad (2)$$

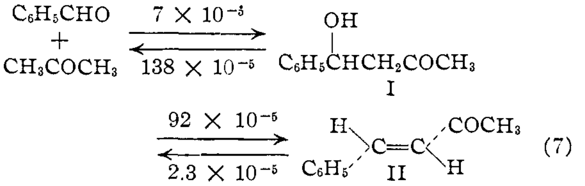
$$C_6H_5CHO + {}^{\ominus}CH_2COCH_3 \underset{k_2}{\overset{k_1}{\rightleftarrows}} C_6H_5\overset{O^{\ominus}}{C}HCH_2COCH_3 \qquad \text{slow} \qquad (3)$$

$$C_6H_5\overset{O^{\ominus}}{C}HCH_2COCH_3 + H_2O \rightleftarrows \underset{\text{I}}{C_6H_5\overset{OH}{C}HCH_2COCH_3} + OH^- \qquad K \text{ equil} \qquad (4)$$

$$\underset{\text{I}}{C_6H_5\overset{OH}{C}HCH_2COCH_3} + OH^- \rightleftarrows C_6H_5\overset{OH}{C}H\underset{\ominus}{C}HCOCH_3 + H_2O \qquad K \text{ equil} \qquad (5)$$

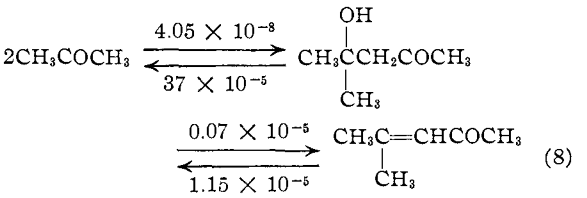
$$C_6H_5\overset{OH}{C}H\underset{\ominus}{C}HCOCH_3 \underset{k_4}{\overset{k_3}{\rightleftarrows}} \underset{\text{II}}{\overset{H}{\underset{C_6H_5}{}}\!\!C{=}C\!\!\overset{COCH_3}{\underset{H}{}}} \qquad (6)$$

Selecting values of the rate constants at 0.1 M NaOH concentration and 0.01192 M acetone, we note that the ketol I is only a transient intermediate.



$$\begin{matrix} C_6H_5CHO \\ + \\ CH_3COCH_3 \end{matrix} \underset{138 \times 10^{-5}}{\overset{7 \times 10^{-5}}{\rightleftarrows}} \underset{\text{I}}{C_6H_5\overset{OH}{C}HCH_2COCH_3} \underset{2.3 \times 10^{-5}}{\overset{92 \times 10^{-5}}{\rightleftarrows}} \underset{\text{II}}{\overset{H}{\underset{C_6H_5}{}}\!\!C{=}C\!\!\overset{COCH_3}{\underset{H}{}}} \qquad (7)$$

This may be compared to diacetone alcohol in 0.1 M NaOH. The data are taken from Koelichen,[9] La Mer and Miller,[10] and Brewer.[11]



$$2CH_3COCH_3 \underset{37 \times 10^{-5}}{\overset{4.05 \times 10^{-8}}{\rightleftarrows}} CH_3\overset{OH}{\underset{CH_3}{C}}CH_2COCH_3 \underset{1.15 \times 10^{-5}}{\overset{0.07 \times 10^{-5}}{\rightleftarrows}} CH_3\underset{CH_3}{C}{=}CHCOCH_3 \qquad (8)$$

For the comparable reactions involving benzaldehyde and acetophenone the results of Walker and Young[17] combined with the observations of Noyce, Pryor and Bottini[2] indicate an entirely comparable situation.

For 0.1 M NaOH the bimolecular rate constant, k_1', of the condensation reaction is 5.8×10^{-3} liter moles^{-1} sec.$^{-1}$ at 25°. This may be compared with the value of 7.8×10^{-4} liter moles^{-1} sec.$^{-1}$ found by Barton, Head and May[18] for the condensation of benzaldehyde with lanost-8-enone at 25° in 0.1 M KOH–90% ethanol.

The ketol III derived from anisaldehyde and acetone shows completely analogous behavior. The fraction of dehydration is 45%. The rates of reaction are larger for III than for I, which is easily understood since both processes k_2 and k_3 lead to more effectively resonance stabilized products. The data are given in Table V.

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[16] P. D. Bartlett, THIS JOURNAL, **56**, 967 (1934).

[17] E. A. Walker and J. R. Young, *J. Chem. Soc.*, 2045 (1957).

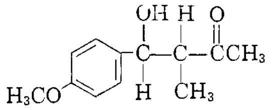
[18] D. H. R. Barton, A. J. Head and P. J. May, *ibid.*, 935 (1957)

TABLE V

THE DEHYDRATION OF 4-(*p*-METHOXYPHENYL)-4-HYDROXY-2-BUTANONE (III) AT 25.0°

(III) × 10^5, *M*	(OH$^-$), *M*	$k_2 + k_3$ × 10^5, sec.$^{-1}$	k_2 × 10^5, sec.$^{-1}$	k_3 × 10^5, sec.$^{-1}$
1.46	0.0054	31.7	17.5	14.2
5.74	.0093	48.1	26.5	21.6
2.87	.0196	103.4	56.9	46.5

The Behavior of 4-(*p*-Methoxyphenyl)-4-hydroxy-3-methyl-2-butanone (V) in Hydroxide.—The most significant contrast is observed when the ketol derived from anisaldehyde and methyl ethyl ketone is examined. Under alkaline conditions a small amount of V may be isolated.



V

Compound V reacts extremely rapidly with dilute hydroxide to form anisaldehyde and methyl ethyl ketone. The spectrum at completion of the reaction is that of anisaldehyde and precludes the possibility that more than 2% of the unsaturated ketone, 4-(*p*-methoxyphenyl)-3-methyl-3-buten-2-one (VI), is formed. From a reaction mixture it was possible to isolate only anisaldehyde and methyl ethyl ketone as semicarbazones. The relevant rate data are given in Table VI.

TABLE VI

THE RATE OF CLEAVAGE OF 4-(*p*-METHOXYPHENYL)-4-HYDROXY-3-METHYL-2-BUTANONE (V) AT 25.0°

(V) × 10^6, *M*	(OH$^-$), *M*	k_1 × 10^5, sec.$^{-1}$
5.5	0.0051	104.2
5.5	.0095	204.5
5.5	.0137	277.3

Discussion

A survey of the literature relating to condensation reactions of unsymmetrical ketones, with special attention to methyl ethyl ketone, reveals that reaction occurs at both the methyl and methylene positions to α to the carbonyl group. Royals[19] has pointed out that the course of the base-catalyzed reaction of methyl ethyl ketone with aldehydes is dependent upon the structure of the aldehyde. In acid-catalyzed reactions condensation at the methylene position is the general rule, whereas in base-catalyzed condensations involving aromatic aldehydes, condensation at the methyl carbon is generally observed.

Considering the reaction of benzaldehyde with methyl ethyl ketone, it is found that the product of the base-catalyzed reaction is exclusively 1-phenyl-1-penten-3-one and that the acid-catalyzed reaction produces only 4-phenyl-3-methyl-3-buten-3-one. The structural assignments have been carefully reviewed by Gettler and Hammett.[7] Stiles and Wolf[20] attributed the selectivity in acid solution to the relative rates of condensation, while in basic solution the relative rates of dehydration of the intermediate ketols are product determining.

There are a number of exceptions to the generalizations involving base-catalyzed reactions, however. Kasiwagi[21] has investigated the base-catalyzed condensation of furfural with methyl ethyl ketone, and has shown that the methylene adduct is a product of the reaction when the β-hydroxy ketone is formed. When the unsaturated ketone is formed, reaction at the methyl carbon is observed.[22] Mariella and Godar[23] have shown that ethyl formate condenses with methyl ethyl ketone to yield a mixture of the two condensation products and have pointed out that the difficulty with past chemical evidence is that various steps were involved in which one of the isomers may have been lost during the purification process. Kyrides[24] has reported that acetaldehyde condenses at the methylene position to yield 3-methyl-3-penten-2-one.

Bruson and Riener[25] observed that the base-catalyzed cyanoethylation of methyl ethyl ketone takes place at the methylene carbon. Mangus and Levine[26] report that 4-vinylpyridine condenses under the action of sodium to yield only 3-methyl-5-(4-pyridyl)-2-pentanone.

In addition to the mixture demonstrated by Mariella and Godar,[23] the condensation with isobutyraldehyde is reported to yield a mixture of products.[27]

It is also observed that a mixture of ketols arises from the condensation of aromatic aldehydes with methyl ethyl ketone. Evidence supporting this conclusion may be derived from the work of Midorikawa[28] on benzaldehyde and methyl ethyl ketone, the work of Stiles and Wolf[21] on *p*-nitrobenzaldehyde and methyl ethyl ketone, and the present report regarding anisaldehyde and methyl ethyl ketone.

It is thus concluded that condensations under alkaline conditions lead to the initial formation of a mixture of products resulting from condensation at the methylene carbon and the methyl carbon, or primarily to condensation at the methylene carbon. One may suggest that these reactions arise from the competitive reactions of the two enolate ions formed in a prior equilibrium step. In cases where a single stage reaction leads to the formation of a reasonably stable product (β-hydroxyketone, acrylonitrile product, formate condensation) the conclusions above are in agreement with the facts.

For a reaction which involves a further stage, such as dehydration, the second step exerts a decisive influence upon the nature of the product. The results with 4-(*p*-methoxyphenyl)-4-hydroxy-3-methyl-2-butanone (V) show that cleavage is the sole reaction. In other words, the rate of dehydration of V is less than one-fiftieth the rate of

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[19] E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Inc., Engelwood Cliffs, N. J., 1954, p. 767.

[20] M. Stiles and D. Wolf, Abstracts of Papers Presented at the 133d Meeting of the American Chemical Society, San Francisco, Calif., April 1958, 106N; M. Stiles, G. Wolf and G. V. Hudson, THIS JOURNAL, **81**, 628 (1959).

[21] I. Kasiwagi, *Bull. Chem. Soc., Japan*, **2**, 310 (1927).

[22] H. Midorikawa, *ibid.*, **27**, 149 (1954).

[23] R. P. Mariella and E. Godar, *J. Org. Chem.*, **22**, 566 (1957).

[24] L. P. Kyrides, THIS JOURNAL, **55**, 3431 (1933).

[25] H. A. Bruson and T. W. Riener, *ibid.*, **64**, 2850 (1942); *cf.* J. Cason and M. P. Chang, *J. Org. Chem.*, **21**, 449 (1956).

[26] G. Mangus and R. Levine, *ibid.*, **22**, 270 (1957).

[27] H. Haeussler and J. Dijkema, *Ber.*, **77B**, 601 (1944).

[28] H. Midorikawa, *Bull. Chem. Soc., Japan*, **27**, 131 (1954).

cleavage, and is only about one-tenth or less of the rate of dehydration of the isomer 1-(*p*-methoxyphenyl)-1-hydroxy-3-pentanone. This fact, coupled with the facile dehydration of 4-(*p*-methoxyphenyl)-4-hydroxy-2-butanone (III), makes it clear that the structural course of the aldol type condensation (the Claisen–Schmidt condensation) is determined in the latter stages of the reaction.

In contrast, the acid-catalyzed condensation of anisaldehyde and methyl ethyl ketone gave results[3,4] consistent *only* with the conclusion that the structure of the product is determined by the condensation step itself. Particularly pertinent is the observation that III undergoes dehydration more rapidly than V. Analogously, 1-(*p*-methoxyphenyl)-1-hydroxy-3-pentanone should undergo similar rapid dehydration were it formed during the course of the acid-catalyzed reaction. However, Noyce and Snyder[3,4] excluded the formation of 1-(*p*-methoxyphenyl)-1-hydroxy-3-pentanone in their kinetic investigations.

The conclusions presented in this paper are therefore in complete accord with the deductions of Stiles and Wolf[20] and supplement their observations with additional quantitative information.

BERKELEY 4, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF MICHIGAN]

Catalyst Selectivity in the Reactions of Unsymmetrical Ketones; Reaction of Butanone with Benzaldehyde and *p*-Nitrobenzaldehyde

BY MARTIN STILES, DANIEL WOLF AND GWYN V. HUDSON

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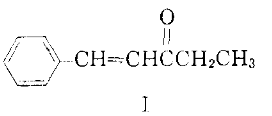
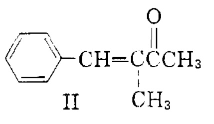
The hydroxy ketone intermediates III and IV from the reaction between benzaldehyde and butanone have been prepared by the Schöpf method. Treatment of either the straight-chain isomer III or the branched isomer IV with dilute alkali produced the straight-chain unsaturated ketone I. Treatment of III and IV with acid afforded I and II, respectively, with no evidence of rearrangement. The reaction between *p*-nitrobenzaldehyde and butanone in alkali yielded three hydroxy ketones (V, VIa and VIb) indicating that both methyl and methylene positions were attacked to a comparable extent. These results support a mechanism for the alkaline condensation in which the dehydration of the intermediate hydroxy ketones is a slow step and thus responsible for the exclusive formation of I. The formation of II in acid results from selectivity at the addition step (2) of the reaction.

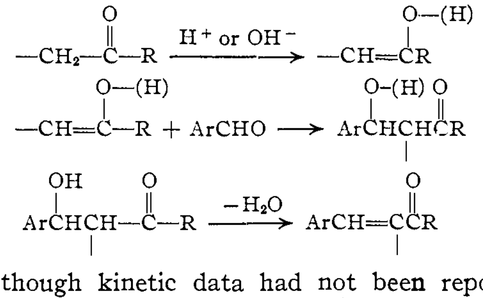
The replacement of hydrogen atoms adjacent to a carbonyl group normally proceeds through enolization and is therefore frequently catalyzed by either acidic or basic reagents. An unsymmetrical dialkyl ketone may allow substitution at either of two positions which differ in the extent of substitution already present. Much investigation has been directed at determining the position of attack upon such unsymmetrical ketones, and several important reactions have been encountered in which acidic reagents favor attack at the more substituted, and basic reagents at the less substituted, of two α-carbons. Thus butanone undergoes bromination predominantly at the methyl group in alkali and at the methylene group in acid[1]; it is acylated by boron trifluoride–acetic anhydride largely at the methylene group and by sodium ethoxide–ethyl acetate at the methyl group[2]; and it reacts with benzaldehyde to give exclusively 1-phenyl-1-penten-3-one (I) when dilute sodium hydroxide is used as catalyst and exclusively 3-methyl-4-phenyl-3-buten-2-one (II) with hydrogen chloride as catalyst.[3]


I


II

Since enolization is the rate-controlling step in the bromination of ketones at moderate catalyst concentrations,[4] it may be concluded that the first of these examples of catalyst selectivity is due to rate differences at the enolization step, acid favoring formation of the more highly branched enol and base preferentially removing the primary hydrogens. However, most other substitution reactions in which such catalyst selectivity is observed require much more vigorous conditions, and the selectivity must be due to other causes. We have chosen to examine in detail the reaction of butanone with aromatic aldehydes, with the aim of understanding those factors which are responsible for the catalyst selectivity.

The generally accepted reaction sequence for the aldehyde–ketone condensation is



$$\mathrm{-CH_2-\overset{\overset{O}{\|}}{C}-R \xrightarrow{H^+ \text{ or } OH^-} -CH{=}\overset{\overset{O-(H)}{|}}{C}R} \qquad (1)$$

$$\mathrm{-CH{=}\overset{\overset{O-(H)}{|}}{C}-R + ArCHO \longrightarrow Ar\overset{\overset{O-(H)}{|}}{C}H\underset{|}{C}H\overset{\overset{O}{\|}}{C}R} \qquad (2)$$

$$\mathrm{Ar\overset{\overset{OH}{|}}{C}H\underset{|}{C}H-\overset{\overset{O}{\|}}{C}-R \xrightarrow{-H_2O} ArCH{=}\underset{|}{C}\overset{\overset{O}{\|}}{C}R} \qquad (3)$$

Although kinetic data had not been reported for the acid-catalyzed condensation[5] it was clear that the conditions under which it is usually car-

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[1] H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 2430 (1951); H. M. E. Cardwell, *ibid.*, 2442 (1951).

[2] C. R. Hauser, F. W. Swanson and J. T. Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 59.

[3] (a) C. Harries and G. H. Müller, *Ber.*, **35**, 966 (1902); (b) J. D. Gettler and L. P. Hammett, THIS JOURNAL, **65**, 1824 (1943); (c) for a summary of many reactions between butanone and aldehydes see H. Haeussler and C. Brugger, *Ber.*, **77**, 152 (1944–1946).

[4] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 96–97.

[5] Such data for this reaction and related ones have now been presented; D. S. Noyce and L. R. Snyder, THIS JOURNAL, **80**, 4033, 4324 (1958).