Organic Reactions

VOLUME 16

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the investigator will be able to use the

tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter.   In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters.   They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work.   The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

PREFACE TO VOLUME 16

Volume 16 is a departure in pattern from its predecessors for it deals with a single reaction.   The original plan for a chapter on a limited aspect of the Aldol Condensation was abandoned when it became clear that a single long chapter would be more useful and less repetitious than several short chapters.   It is not the intention of the editors to follow the pattern of Volume 16 regularly.

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THE ALDOL CONDENSATION

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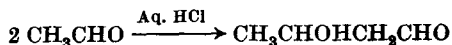
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INTRODUCTION

The aldol condensation takes its name from aldol (3-hydroxybutanal), a
name introduced by Wurtz who first prepared this β-hydroxy aldehyde
from acetaldehyde in 1872.[1]   The aldol condensation includes reactions
producing β-hydroxy aldehydes (β-aldols) or β-hydroxy ketones (β-ketols)

$$2 \text{ CH}_3\text{CHO} \xrightarrow{\text{Aq. HCl}} \text{CH}_3\text{CHOHCH}_2\text{CHO}$$

[1] A. Wurtz, *Bull. Soc. Chim. France*, [2] **17**, 436 (1872); *Ber.*, **5**, 326 (1872); *Compt. Rend.*,
74, 1361 (1872).

by self-condensations or mixed condensations of aldehydes and ketones, as well as reactions leading to α,β-unsaturated aldehydes or α,β-unsaturated ketones, formed by dehydration of intermediate β-aldols or β-ketols. Formation of mesityl oxide by self-condensation of acetone, a reaction discovered by Kane in 1838, is the first known example of ketone self-condensation.[2]

$$2\ CH_3COCH_3 \xrightarrow{H_2SO_4} (CH_3)_2C{=}CHCOCH_3 + H_2O$$

The Claisen-Schmidt condensation is an aldol condensation discovered by Schmidt[3] in 1880 (condensation of furfural with acetaldehyde or acetone) and developed by Claisen (1881–1899).[4-6] It is most often taken to be the condensation of an aromatic aldehyde with an aliphatic aldehyde or ketone to yield an α,β-unsaturated aldehyde or ketone, usually in the presence of a basic catalyst.

$$\text{furyl}{-}CHO + CH_3CHO \xrightarrow{NaOH} \text{furyl}{-}CH{=}CHCHO + H_2O$$

$$C_6H_5CHO + CH_3COCH_3 \xrightarrow{NaOH} C_6H_5CH{=}CHCOCH_3 + H_2O$$
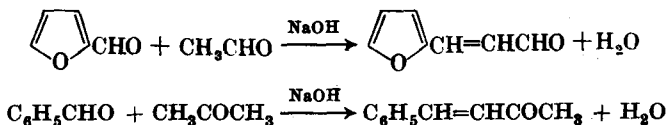
However, the term has been extended to include many types of aldehyde-ketone condensations (e.g., chalcone formation[5]) employing either acidic

$$C_6H_5CHO + CH_3COC_6H_5 \xrightarrow{H^{\oplus}\ or\ OH^{\ominus}} C_6H_5CH{=}CHCOC_6H_5 + H_2O$$
$$\text{Chalcone}$$
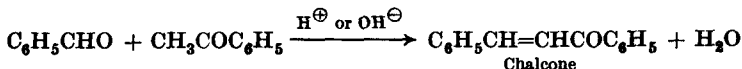
or basic catalysts. Schmidt was first to employ a basic catalyst for the aldol condensation.[3]

The term aldol condensation has sometimes been applied to many so-called "aldol-type" condensations involving reaction of an aldehyde or ketone with a substance R_2CHX or $RCH(X)Y$ (X or Y = an activating group such as CO_2R, $CONHR$, CN, NO_2, SO_2CH_3; R = alkyl, aryl or hydrogen). Mechanistically, of course, these reactions are like aldol condensations. They produce a hydroxyl compound or its dehydration product and include the Claisen,[7, 8] Knoevenagel,[9, 9a] Doebner,[9, 9a]

[2] R. Kane, Ann. Physik Chem., [2] 44, 475 (1838); J. Prakt. Chem., 15, 129 (1838).
[3] J. G. Schmidt, Ber., 13, 2342 (1880); 14, 1459 (1881).
[4] L. Claisen and A. Claparède, Ber., 14, 349 (1881).
[5] L. Claisen, Ber., 20, 655 (1887).
[6] L. Claisen, Ann., 306, 322 (1899).
[7] C. R. Hauser and B. E. Hudson, Jr., Org. Reactions, 1, 266–302 (1942).
[8] C. R. Hauser, F. W. Swamer, and J. T. Adams, Org. Reactions, 8, 59–196 (1954).
[9] J. R. Johnson, Org. Reactions, 1, 210–265 (1942).
[9a] G. Jones, Org. Reactions, 15, 204–599 (1967).

Perkin,[9] Stobbe,[10] and Reformatsky[11] reactions.[12] However, since the products are not aldols or ketols or dehydration products thereof, it is believed that the term aldol condensation should not be applied to reactions forming them. The present review includes examples where X and Y = CHO or COR only, i.e., solely condensation reactions of aldehydes and ketones. Included are 1,3-diketones, β-keto aldehydes, and α- and γ-ω-keto compounds (e.g., RCH_2COCO_2H and $RCH_2CO(CH_2)_nX$; $n > 1$, X = any group); some of these reactions might be described as both Knoevenagel and aldol condensations.

Excluded arbitrarily from this review, with few exceptions, are certain Knoevenagel-aldol condensations involving β-keto compounds, $RCOCH_2X$, where the α-methylene group of a ketone is activated *additionally* by some activating group other than the carbonyl group (e.g., β-keto esters). With few exceptions, reaction sequences starting with aldehydes or ketones which involve transient aldol intermediates that are not isolated are excluded; an example would be the formation of certain heterocyclic compounds as in the Robinson-Schöpf reaction.[13] Most reactions of aldehydes or ketones leading indirectly through other reactions to an aldol condensation product are also arbitrarily excluded. One exception is the Michael reaction[14] which may generate 1,5-diketones or keto aldehydes which, *in situ*, undergo an aldol condensation to a cyclic product. Except for a few important and closely related methods, syntheses of β-aldols and β-ketols and their dehydration products by alternative methods of preparation are not discussed. One such method is the Wittig reaction[15] which may be applied to syntheses of α,β-unsaturated aldehydes and ketones.

In France, the term *β-hydroxycarbonylation*[16] has been applied to condensations leading to β-aldols and β-ketols. However, this terminology has not been used extensively elsewhere.

MECHANISM

Simple Base Catalysis. The aldol condensation is catalyzed by acids and bases, the latter being more frequently employed. The

[10] W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1–73 (1951).

[11] R. L. Shriner, *Org. Reactions*, **1**, 1–37 (1942).

[12] For recent summaries of aldol condensation and related reactions, cf. H. O. House, *Modern Synthetic Reactions*, pp. 216–256, Benjamin, New York, 1965; R. L. Reeves, in *The Chemistry of the Carbonyl Group*, ed. by S. Patai, pp. 580–600, Interscience, New York, 1966.

[13] L. A. Paquette and J. W. Heimaster, *J. Am. Chem. Soc.*, **88**, 763 (1966).

[14] E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179–555 (1959).

[15] A. Maercker, *Org. Reactions*, **14**, 332–334 (1965).

[16] H. Gault, *Bull. Soc. Chim. France*, 302 (1955); "L'Hydroxycarbonylation," *Colloques Internationaux du Centre National de la Recherche Scientifique*, Paris, May 31–June 5, 1954. A group of 26 papers published in *Bull. Soc. Chim. France*, 250–302 (1955).

base-catalyzed mechanism, which has received much study,[17, 18] may be pictured by the following steps (R and R″ = alkyl or aryl; R′ and R‴ = alkyl, aryl, or hydrogen).

$$\text{RCH}_2\text{COR}' + \text{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\substack{| \\ \text{O}^{\ominus}}}{\text{RCH=CR}'} + \text{BH}^{\oplus} \qquad \text{(Eq. 1)}$$

$$\mathbf{1} \qquad \qquad \mathbf{2}$$

$$\text{R}''\text{COR}''' + \underset{\substack{| \\ \text{O}^{\ominus}}}{\text{RCH=CR}'} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{R}'\text{—}\underset{\substack{| \\ \text{R}'''}}{\overset{\text{O}^{\ominus}}{\text{C}}}\text{—CH(R)COR}' \qquad \text{(Eq. 2)}$$

$$\mathbf{3} \qquad \mathbf{2} \qquad \qquad \mathbf{4}$$

$$\mathbf{4} + \text{BH}^{\oplus} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{R}'\text{—}\underset{\substack{| \\ \text{R}'''}}{\overset{\text{OH}}{\text{C}}}\text{—CH(R)COR}' + \text{B} \qquad \text{(Eq. 3)}$$

$$\mathbf{5}$$

$$\mathbf{5} + \text{B} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \text{R}'\text{—}\underset{\substack{| \\ \text{R}'''}}{\overset{\text{HO}}{\text{C}}}\text{—}\underset{\substack{| \\ \text{O}^{\ominus}}}{\overset{\text{R}}{\text{C}}}\text{=C—R}' + \text{BH}^{\oplus} \qquad \text{(Eq. 4)}$$

$$\mathbf{6}$$

$$\text{R}'\text{—}\underset{\substack{| \\ \text{R}'''}}{\overset{\text{HO}}{\text{C}}}\text{—}\underset{\substack{| \\ \text{O}^{\ominus}}}{\overset{\text{R}}{\text{C}}}\text{=C—R}' + \text{BH}^{\oplus} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \text{R}'\text{—C=}\underset{\substack{| \\ \text{R}'''}}{\text{C}}\text{—}\underset{\substack{| \\ \text{O}}}{\overset{\text{R}}{\text{C}}}\text{—R}' + \text{H}_2\text{O} + \text{B}$$

$$\mathbf{6} \qquad \qquad \qquad \mathbf{7} \qquad \qquad \text{(Eq. 5)}$$
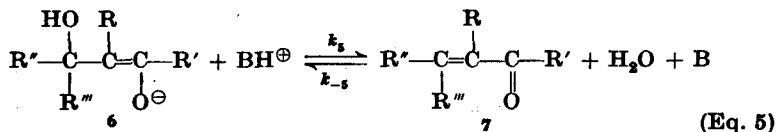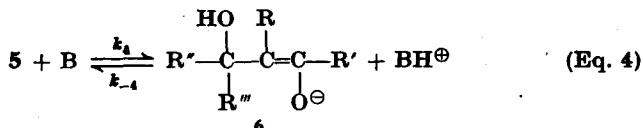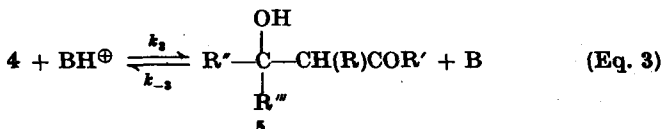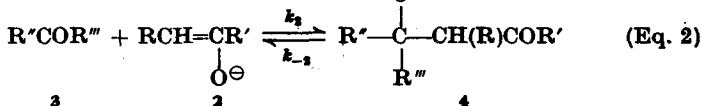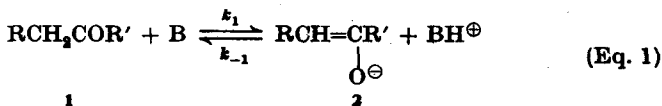
The question of the rate-limiting step for aldol and ketol formation has been examined.[17-20] For formation of an aldol in concentrated solutions (from acetaldehyde,[19, 21] propanal,[22] and butanal[23]) the proton removal step (Eq. 1) is rate-limiting ($k_1 < k_2$). However, at low aldehyde concentrations the rate of ionization is not much greater than the rate of condensation, and the reaction becomes second order in aldehyde.[19-27]

[17] C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, pp. 676-699, Cornell University Press, Ithaca, New York, 1953.

[18] A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, 2nd ed., pp. 335-350, Wiley, New York, 1961.

[19] R. P. Bell, *The Proton in Chemistry*, pp. 137-138, Cornell University Press, Ithaca, New York, 1959.

[20] J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **87**, 5050 (1965).

[21] A. Broche and R. Gibert, *Bull. Soc. Chim. France*, 131 (1955).

[22] J. Jiminez and A. Broche, *Bull. Soc. Chim. France*, 1499 (1961).

[23] S. E. Rudakova and V. V. Zharkov, *Zh. Obshch. Khim.*, **33**, 3617 (1963) [*C.A.*, **60**, 7883 (1964)].

[24] H. Matsuyama, *Proc. Japan Acad.*, **27**, 552 (1951) [*C.A.*, **46**, 3838 (1952)].

[25] J. Hine, J. G. Houston, and J. H. Jensen, *J. Org. Chem.*, **30**, 1184, 1328 (1965).

[26] R. P. Bell and M. J. Smith, *J. Chem. Soc.*, 1691 (1958).

[27] R. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 2983 (1960).

For condensations of certain aldehydes with ketones the reaction is first order in aldehyde at low concentrations, but zero order in aldehyde at high concentrations: examples are the reaction of p-nitrobenzaldehyde with 2-butanone, cyclohexanone, and desoxybenzoin.[28, 29] However, for many condensations involving ketones, at a wide range of concentrations, the slow step is the condensation step in which the new carbon-carbon bond is formed (Eq. 2); $k_1 > k_2$. Kinetic evidence supporting this view has been presented for the formation of diacetone alcohol from acetone,[26, 30] and for the condensations of aromatic aldehydes with acetophenone,[31] of formaldehyde[32, 33] and acetaldehyde[33] with 1,3-diketones, and of formaldehyde[34] with acetone. When the first step (Eq. 1) is rate-limiting, general base catalysis may be important.[35] When the second step (Eq. 2) is relatively slow, specific solvent anion (hydroxide, ethoxide) catalysis is observed.

The α,β-unsaturated aldehydes and ketones (7) often found as reaction products can arise from the aldol or ketol 5 by a carbanion elimination (E1cb) mechanism which requires an initial proton removal, followed by elimination of hydroxide ion (Eqs. 4 and 5). The equilibrium of Eq. 4 may lie far to the left ($k_{-4} \gg k_4$; $K_{eq}^{(4)} \ll 1$) and deuterium exchange into 5 would be expected to occur readily during formation of 7 in cases where $k_{-4} \gg k_5$.[36, 37] In certain examples, rates k_4 and k_5 appear to be of the same order of magnitude. Factors met in certain aldol condensations (R = alkyl, R″ = aryl; protic solvents) and favoring facile loss of hydroxide ion[37] from 6 could also disfavor proton removal[38, 39] from 5. A comparison of the overall rate of base-catalyzed dehydration (5 → 7; rate = $K_{eq}^{(4)}k_5$) for 1-hydroxy-1-phenyl-3-pentanone (5a)[40] with rates of proton removal of certain aliphatic ketones under similar reaction

[28] S. F. Nelsen and M. Stiles, unpublished results. We are indebted to Professor Stiles for making some of his results available to us prior to publication.

[29] This situation is illustrated by the lack of deuterium incorporation into *threo*- and *erythro*-4-O$_2$NC$_6$H$_4$CHOHCH(C$_6$H$_5$)COC$_6$H$_5$ in D$_2$O—NaOD during their interconversion; L. Traynor, Ph.D. thesis, University of Michigan, 1964; *Dissertation Abstr.*, 25, 6972 (1965).

[30] D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, 81, 624 (1959).

[31] E. Coombs and D. P. Evans, *J. Chem. Soc.*, 1295 (1940).

[32] P. Rumpf and M. Diard, *Compt. Rend.*, 248, 823 (1959).

[33] M. Laloi, *J. Rech. Centre Natl. Rech. Sci. Lab. Bellevue (Paris)*, 55, 141 (1961) [*C.A.*, 58, 4393 (1963)].

[34] S. Nagase, *Kogyo Kagaku Zasshi*, 64, 1008 (1961) [*C.A.*, 57, 2064 (1963)].

[35] D. C. Gutsche, R. S. Buriks, K. Nowotny, and H. Grassner, *J. Am. Chem. Soc.*, 84, 3775 (1962).

[36] R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 75, 2439 (1953).

[37] J. F. Bunnett, *Angew. Chem., Intl. Ed. Engl.*, 1, 225 (1962).

[38] A. K. Mills and A. E. Wilder Smith, *Helv. Chim. Acta*, 43, 1915 (1960).

[39] H. Shechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Am. Chem. Soc.*, 84, 2905 (1962).

[40] M. Stiles, D. Wolf, and G. V. Hudson, *J. Am. Chem. Soc.*, 81, 628 (1959).

conditions[38] suggests that k_4 and k_5 could be comparable. The observation that 3-methyl-4-hydroxy-4-phenyl-2-butanone (5b) undergoes retrogression to reactants rather than dehydration in basic medium[40] suggests

$$C_6H_5CHOHCH_2COCH_2CH_3 \qquad \overset{\textstyle CH_3}{\underset{\textstyle 5b}{C_6H_5CHOHCHCOCH_3}}$$
$$\underset{5a}{}$$
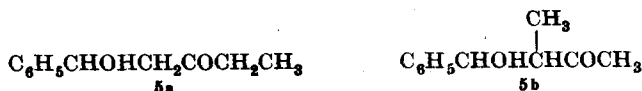
that k_4 is relatively slow ($k_4 \ll k_{-3}k_{-2}/k_3$) in this case; k_5 is not, however, necessarily slow relative to k_4.[40a] The rate of retrogression of 5b to reactants is about four times faster than that of 5a,[40] under conditions where the rate of proton removal (k_4) from 5b would be expected to be 10^2 to 10^3 times slower than from 5a.[29, 36,.39] Although α,β-unsaturated ketones may be hydrated in basic media, their formation is effectively irreversible in most instances ($k_5 \gg k_{-5}$). This circumstance may offset previous unfavorable equilibria and allow the condensation to proceed to completion (formation of 7). A detailed understanding of the mechanism of the base-catalyzed dehydration of aldols and ketols awaits further study.

In protic solvents (water, ethanol) the aldol condensation is reversible and the various equilibria are often quite sensitive to the nature of substituents.[40–42] Since in practice the preparations are generally so conducted that thermodynamic control determines the products, the effects of substituents on the several equilibria are of great importance. In aprotic solvents (ethers, hydrocarbons) equilibration occurs exceedingly slowly, particularly with lithium and magnesium enolates.[43–45] Thus kinetically controlled aldol condensations should be more favorable under these conditions.

Amine Catalysis. Primary and secondary amines (especially in the presence of added acid) exert a pronounced catalytic effect on condensation of aldehydes and ketones with active methylene compounds (Knoevenagel condensation).[9a, 46] Pyrrolidine and piperidine are very effective. Tertiary amines are without effect or are very poor aldol catalysts except when general base catalysis is observed.[35, 47, 48] Because of their weak base strength most amines provide only low concentrations

[40a] P. Carsky, P. Zuman, and V. Horak, *Collection Czech. Chem. Commun.*, **30**, 4316 (1965).

[41] J. E. Dubois and H. Viellard, *Tetrahedron Letters*, 1809 (1964).

[42] D. S. Noyce and L. R. Snyder, *J. Am. Chem. Soc.*, **81**, 620 (1959).

[43] H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

[44] H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

[45] H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

[46] E. Knoevenagel, *Ann.*, **281**, 25 (1894).

[47] F. H. Westheimer and H. Cohen, *J. Am. Chem. Soc.*, **60**, 90 (1938).

[48] T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Letters*, 3889 (1965).

of solvent anion base (hydroxide, ethoxide), and the marked catalytic effect of primary and secondary amines must be explained on another basis.

At least two mechanisms appear to be operative for most amine-catalyzed aldol condensations. Many of these reactions, especially those involving secondary amines and reactive aldehydes or ketones capable of forming enamines, require an enamine intermediate in the condensation step leading to an aldol, as well as in the step leading to an α,β-unsaturated carbonyl compound.[49-56] Evidence supporting an enamine mechanism has been presented for the self-condensation of propanal to 2-methyl-2-pentenal[50, 54-56] and for certain Robinson annelation reactions.[48] Enamines have been condensed with aldehydes and ketones to give aldol condensation products.[53a-56b] An acid catalyst (preferably acetic acid), usually employed in an amount equivalent to the amine, is required to effect the condensation. It is reported that enamines fail to undergo aldol condensation with aldehydes in the absence of an added acid catalyst.[56]
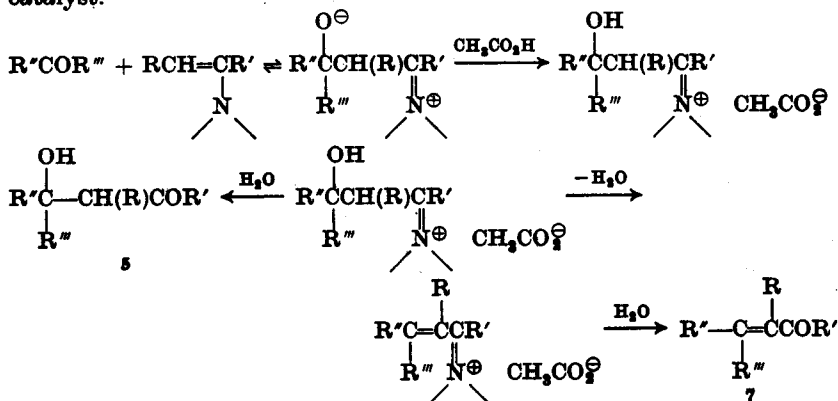
[49] T. A. Spencer and K. K. Schmiegel, *Chem. Ind.* (*London*), 1765 (1963).

[50] I. V. Mel'nichenko and A. A. Yasnikov, *Ukr. Khim. Zh.*, 30, 838 (1964) [*C.A.*, 61, 14490 (1964)].

[51] D. J. Goldsmith and J. A. Hartman, *J. Org. Chem.*, 29, 3520, 3524 (1964).

[52] J. Szmuszkovics, *Advan. Org. Chem.*, 4, 1-114 (1963).

[53] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell. *J. Am. Chem. Soc.*, 85, 207 (1963).

[53a] L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.*, 95, 1495 (1962).

[54] A. A. Yasnikov and K. I. Matkovskii, *Ukr. Khim. Zh.*, 28, 210 (1962). [*C.A.*, 58, 3306 (1963)].
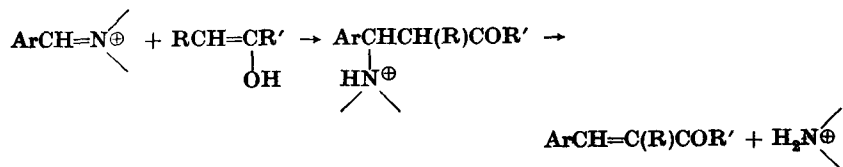
[55] T. S. Boiko, N. V. Volkova, and A. A. Yasnikov, *Ukr. Khim. Zh.*, 29, 1179 (1963) [*C.A.*, 60, 3964 (1964)].

[56] N. V. Volkova and A. A. Yasnikov, *Dokl. Akad. Nauk SSSR*, 149, 94 (1963) [*C.A.*, 59, 5011 (1963)].

[56a] L. A. Paquette and H. Stucki, *J. Org. Chem.*, 31, 1232 (1966).

[56b] F. T. Bond and W. E. Musa, *Chem. Ind.* (*London*), 1380 (1966).

A second amine-catalyzed mechanism, involving attack of an imine or immonium ion on the methylene group (enol) of an aldehyde or ketone, is important in certain aldol condensations (Knoevenagel-aldol);[9a] see p. 43.[12, 13, 56c-e] This process is favored by use of primary amines with aldehydes or ketones which readily form imines and in condensations with carbonyl compounds of high enol content such as 1,3-diketones.[56, 57] Aldimines[58] and ketimines[59] condense readily with certain active methylene compounds, including ketones[58] ("alkylidenation reaction"[59]); α,β-unsaturated ketones may be prepared by this reaction which is catalyzed by acids.[58]

$$\text{ArCH=N}^{\oplus}\diagdown \ + \ \text{RCH=CR}' \ \rightarrow \ \text{ArCHCH(R)COR}' \ \rightarrow$$
$$\underset{\text{OH}}{|} \qquad \underset{\text{HN}^{\oplus}}{|}\diagup\diagdown$$

$$\text{ArCH=C(R)COR}' + \text{H}_2\text{N}^{\oplus}\diagup$$

A third mechanism is possible, that of condensation of an immonium ion with an enamine. An immonium ion-dienamine reaction step is postulated in the pyrrolidinium perchlorate-catalyzed self-condensation of 2-cyclohexen-1-one.[59a] The formation of α,β-unsaturated ketones by self-condensation of enamines derived from methyl alkyl ketones may involve such a reaction (see p. 20);[60] a dienamine intermediate can be isolated. An immonium ion-enamine reaction may occur in the condensation of acetone with 1-propenylpiperidine (added acetic acid) to yield 2,4,5-trimethyl-2,4-hexadienal (see p. 27).[54]

Acid Catalysis. The mechanism of the acid-catalyzed reaction[17, 18] is similar to that of the base-catalyzed reaction in that an initial proton removal step (Eq. 7) is involved, though from a protonated intermediate 8 (R and R″ = alkyl or aryl; R′ and R‴ = alkyl, aryl, or hydrogen). The intermediate enol 9 reacts in a rate-limiting step (Eq. 8)[42] with a second (protonated) carbonyl molecule to produce an aldol or ketol 5. However, α,β-unsaturated carbonyl compounds 7 (rather than aldols

[56c] J. Hine, B. C. Merron, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **88**, 3367 (1966).

[56d] M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2502 (1966).

[56e] J. Hine, F. C. Kokesh, K. G. Hampton, and J. Mulders, *J. Am. Chem. Soc.*, **89**, 1205 (1967).

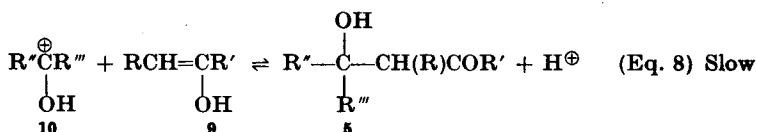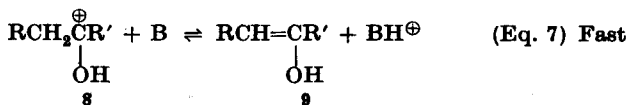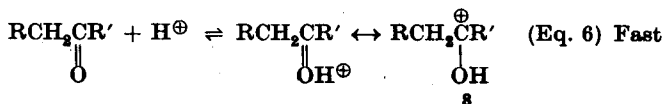[57] A. A. Yasnikov, K. I. Matkovskii, and E. M. Gaivoronskaya, *Ukr. Khim. Zh.*, **28**, 88 (1962) [*C.A.*, **58**, 1326 (1963)].

[58] A. H. Blatt and N. Gross, *J. Org. Chem.*, **29**, 3306 (1964).

[59] G. Charles, *Bull. Soc. Chim. France*, 1559 (1963).

[59a] N. J. Leonard and W. J. Musliner, *J. Org. Chem.*, **31**, 639 (1966).

[60] G. Bianchetti, P. Dalla Croce, and D. Pocar, *Tetrahedron Letters*, 2039 (1965).

$$\text{RCH}_2\text{CR}' + \text{H}^{\oplus} \rightleftharpoons \underset{\overset{|}{\text{O}}\text{H}^{\oplus}}{\text{RCH}_2\text{CR}'} \leftrightarrow \underset{\overset{|}{\text{O}}\text{H}}{\text{RCH}_2\overset{\oplus}{\text{C}}\text{R}'} \qquad \text{(Eq. 6) Fast}$$
$$\underset{\text{O}}{\overset{\|}{}} \qquad\qquad\qquad\qquad\qquad\qquad\qquad 8$$

$$\underset{\overset{|}{\text{O}}\text{H}}{\text{RCH}_2\overset{\oplus}{\text{C}}\text{R}'} + \text{B} \rightleftharpoons \underset{\overset{|}{\text{O}}\text{H}}{\text{RCH}=\text{CR}'} + \text{BH}^{\oplus} \qquad \text{(Eq. 7) Fast}$$
$$\qquad 8 \qquad\qquad\qquad 9$$

$$\underset{\overset{|}{\text{O}}\text{H}}{\text{R}''\overset{\oplus}{\text{C}}\text{R}'''} + \underset{\overset{|}{\text{O}}\text{H}}{\text{RCH}=\text{CR}'} \rightleftharpoons \text{R}''\!\!\underset{\overset{|}{\text{R}'''}}{\overset{\overset{\text{OH}}{|}}{\text{C}}}\!\!\text{—CH(R)COR}' + \text{H}^{\oplus} \qquad \text{(Eq. 8) Slow}$$
$$\qquad 10 \qquad\qquad 9 \qquad\qquad\qquad 5$$

or ketols) are the most frequently encountered products, because acid-catalyzed dehydration is very rapid and in most instances not easily reversed. The dehydration step (Eq. 9) involves protonation of the hydroxyl group, followed by loss of water and then loss of a proton. The dehydration may proceed, in kinetically distinguishable paths, via a carbonium ion or enol intermediate (Eqs. 9a and 9b).[61-62a] Dehydration

$$\text{(Eq. 9a) Fast}$$
$$\text{(Eq. 9b) Fast}$$
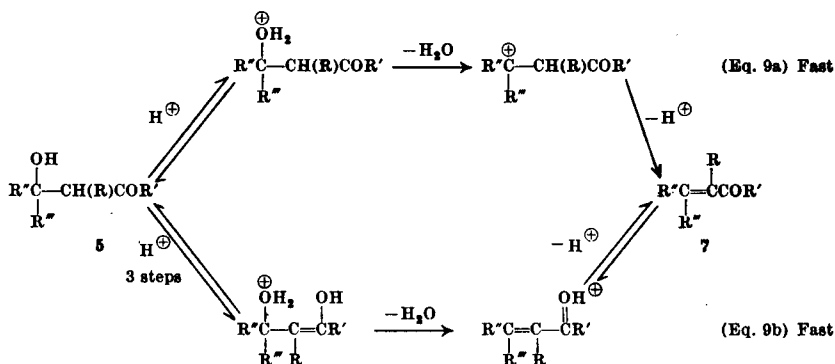
is generally more rapid than reversal of the rate-determining condensation step (Eq. 8).[42] The course of the acid-catalyzed reaction, unlike the base-catalyzed process, is not characterized by the influence of reversibility in all steps, but principally by reactivity and stability of intermediate enols.[42]

An important and useful acid-catalyzed procedure employs hydrogen chloride in the absence of solvent, or in an aprotic solvent such as benzene,

[61] D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, **80**, 5539 (1958).

[62] M. Stiles and A. Longroy, *Tetrahedron Letters*, 337 (1961).

[62a] S. Cabani and N. Ceccanti, *J. Chem. Soc., Phys. Org.*, 77 (1966).