Anal. Calcd. for $C_{11}H_{14}O_2N_2$: N, 13.6. Found: N, 13.7.

When α,α-diacetaminophenylacetic acid was heated with acetamide under the above conditions for as long as five hours, no evidence of decarboxylation could be obtained, and only the starting material could be isolated from the reaction mixture.

Summary

1. The condensation of the following α-keto acids with acetamide has been studied: pyruvic, phenylpyruvic, α-ketoglutaric, and benzoylformic acids.

2. The condensation takes place in the following steps: (a) addition of acetamide to the carbonyl group of the keto acid with the formation of an α-acetamino-α-hydroxy acid, and (b) replacement of the hydroxyl group by a second acetamino group, either directly or by dehydration followed by addition of acetamide to the unsaturated intermediate.

3. Phenylpyruvic acid forms only α-acetaminocinnamic acid, and the latter does not add acetamide to its double bond under the experimental conditions chosen.

4. The opening of a lactone ring by addition of acetamide was observed with the lactone of α-acetamino-α-hydroxyglutaric acid.

5. In the condensation of benzoylformic acid with acetamide a secondary reaction analogous to the Erlenmeyer–de Jong reaction was observed. A mechanism is suggested to explain the formation of α-acylamino acids from α-keto acids by this reaction.

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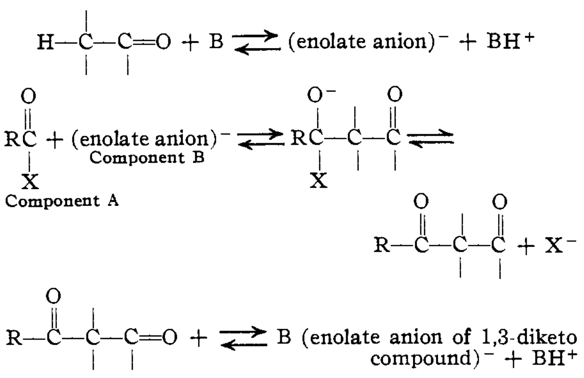
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

Condensations Brought about by Bases. III. The General Course of the Claisen Type of Condensation

BY CHARLES R. HAUSER

The equations proposed recently[1] for the Claisen condensation of ethyl esters may be generalized to include other carbon–carbon condensations in which a metallic enolate condenses with a compound of the general type RCOX, where X is an atom or group that is removed as an anion during the reaction. The general course for this type of condensation may be represented by the following ionic equations, in which B represents a base.



$$\mathrm{H{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{C}{=}O + B \rightleftarrows (enolate\ anion)^- + BH^+}$$

$$\underset{\text{Component A}}{\mathrm{R\overset{O}{\overset{\|}{C}}\underset{X}{\underset{|}{}}}} + \underset{\text{Component B}}{\mathrm{(enolate\ anion)^-}} \rightleftarrows \mathrm{R\underset{X}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{\overset{O}{\overset{\|}{C}}}} \rightleftarrows \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{\overset{O}{\overset{\|}{C}}} + X^-}$$

$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{C}{=}O} + \rightleftarrows \mathrm{B}\ \text{(enolate anion of 1,3-diketo compound)}^- + \mathrm{BH^+}$$

The first equation represents an acid–base reaction in which a new acid and a new base (the enolate anion) are formed. The second equation represents a carbon–carbon condensation between the enolate anion, designated component B, and a compound of the type RCOX, which is designated component A.[2] This reaction gives an intermediate organic anion, which releases X as anion, forming the 1,3-diketo compound. The last equation represents another acid–base reaction in which the 1,3-diketo compound is converted into its enolate anion. This reaction can occur, of course, only if the 1,3-diketo compound contains an enolizable hydrogen, and if a sufficiently strong base is present.

A number of apparently diverse condensations, as, for example, the condensation of two molecules of an ethyl ester in the presence of a base, and the condensation of a molecule of acetoacetic ester (as enolate) with a molecule of an acid chloride are represented by these general equations. It is proposed that any reaction that is represented by the above equations be classified as a Claisen type of condensation.

While there is little doubt that the general mechanism of the Claisen type of condensation involves the formation of a metallic enolate as an active intermediate, the detailed mechanism by which this enolate condenses with a compound

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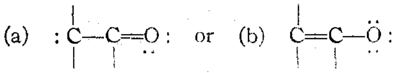
(1) (a) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937); (b) Renfrow and Hauser, *ibid.*, **60**, 463 (1938).

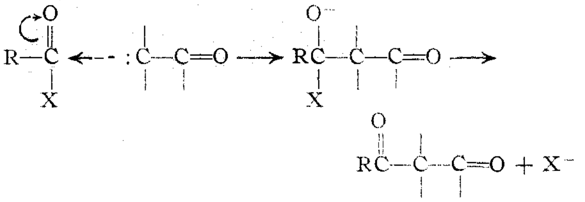
(2) In this connection see Arndt and Eistert, *Ber.*, **69**, 2383 (1936).

of the type RCOX is not entirely clear. Metallic enolates are capable of reacting as if their anions possessed either of the resonance forms

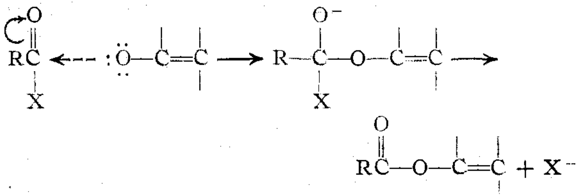


$$(a)\quad :\overset{|}{\underset{|}{C}}-\underset{|}{C}=\ddot{O}: \quad \text{or} \quad (b)\quad \overset{|}{\underset{|}{C}}=\underset{|}{C}-\ddot{\underset{\cdot\cdot}{O}}:$$

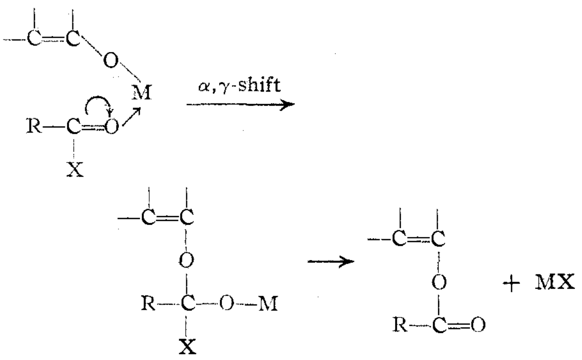
giving both carbon and oxygen derivatives. The carbon–carbon condensation represented by the above equations may be considered to involve an attack of resonance form (a) of the enolate anion on the potentially positive carbon atom of the carbonyl group in component A, thus

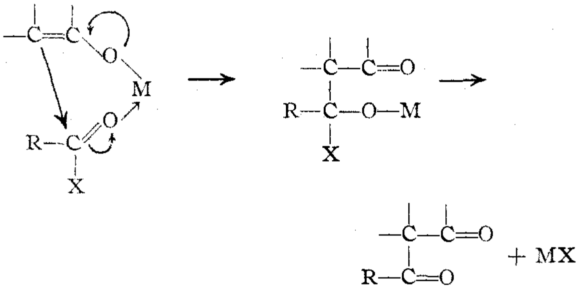


An oxygen–carbon condensation may be considered to involve a reaction of resonance form (b) of the enolate anion, thus



This simple representation, however, does not indicate the effect that component A may have on the course of the condensation as exhibited, for example, in the reactions of the sodium enolate of acetoacetic ester with certain acid chlorides; this enolate with acetyl or benzoyl chloride gives mainly the carbon derivative, but with chloroformic ester, mainly the oxygen derivative.[3] In the similar phenomena of oxygen- and carbon-alkylation of metallic enolates Johnson[4] assumes that a coördination complex is first formed: an α,γ-shift leads to oxygen ethers, and a cyclic mechanism leads to carbon alkylation. On the basis of these ideas the alternative courses of reaction of metallic enolates (especially those that would not be ionized appreciably) with compounds of the type RCOX might be represented as follows[5]





Whether or not further data will support these mechanisms remains to be determined. At the present time the ionic point of view of the Claisen condensation seems preferable. It is not only simpler but at least certain metallic enolates appear to be ionized; certain other enolates which may not be ionized appreciably, may be regarded as possessing potential ions. It is possible that a coördination complex between component A and the metallic enolate might lead to the transient formation of resonance structures (a) or (b). Regardless of the intimate mechanism, however, a carbon–carbon condensation between a metallic enolate and a compound of the type RCOX may be classified as a Claisen type of condensation.

The types[6] of component A of the condensation include esters, anhydrides,[7] acid chlorides,[7] and N-diphenylacetamide,[8] where X is OR, OOCR, Cl, and $(C_6H_5)_2N$, respectively. The types[6] of component B include the enolate anions of esters, aldehydes, ketones, N-diphenylacetamide,[8] and 1,3-diketo compounds.[9] Component B could also be the enolate anions of other types of compounds. A general formula for compounds whose anions might function as com-

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[3] See, for example, Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Company, New York, N. Y., 1936, p. 105, or Richter, "Organic Chemistry," Blakiston, Philadelphia, Pa., 1934, Vol. I, p. 474.

[4] See Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1651.

[5] The general formula $-\overset{|}{C}=\overset{|}{C}-O-M$ represents a metallic enolate. The enolic form of the enolate is shown because this, rather than the ketonic form, probably more nearly approximates the structure of the compound.

[6] It should be pointed out that not all of these types of components A and B have been condensed with each other.

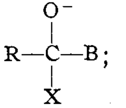
[7] See Hudson, Dick and Hauser, THIS JOURNAL, **60**, 1960 (1938).

[8] Chelintzev and Osetrova, *Ber.*, **69B**, 374 (1936).

[9] The reaction of the enolate of a 1,3-diketo compound, such as acetoacetic ester, with an acid chloride (component A) will form a triketo compound of the type $RCOCH(COR)\underset{|}{C}O$.

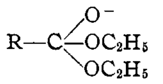
ponent B is represented by the system $\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\underset{|}{A}{=}X}$, where A is carbon or nitrogen and X oxygen or nitrogen. It should be pointed out also that the condensation of many basic anions or of Grignard reagents with a compound of the type RCOX may follow a course similar to that represented above, but it is probably best to classify as examples of the Claisen type of condensation only those reactions in which a carbon–carbon condensation occurs, and in which a metallic enolate or its anion serves as component B.

The types of base B that may be used to effect the Claisen condensation include the anions, $^{-}OC_2H_5$, $^{-}NH_2$, and $(C_6H_5)_3C^{-}$, and certain Grignard reagents.[10] The base that will effect a condensation between a particular set of components A and B is limited by several factors. In the first place, the base B, as well as the enolate anion, may condense with the carbonyl group of component A, giving the intermediate anion



$$\mathrm{R{-}\overset{\overset{\large O^-}{|}}{\underset{\underset{\large X}{|}}{C}}{-}B}$$

; the latter on decomposition may form RCOB and X^-. This competing reaction should be expected especially when the equilibrium of the first equation above is on the left side (*i. e.*, when there is a high concentration of the base B), and when X of component A corresponds to a weaker base than B. In the common condensations of ethyl esters effected by sodium ethoxide the equilibrium of the first step is probably on the left side, but here the base B, which is ethoxide ion, is the same group as X of component A; consequently, any anion of the type



$$R{-}C(O^-)(OC_2H_5)(OC_2H_5)$$

that might be formed by reaction of ethoxide ion with component A, would on decomposition regenerate the original component A (ethyl ester) and original base B (ethoxide ion). On the other hand, if X of component A is chlorine, the ethoxide ion probably would convert most of the acid chloride into the corresponding ethyl ester and chloride ion. The very low yield of acetoacetic ester obtained from ethyl acetate in the presence of sodamide[11] is probably due to the predominance of a similar competing reaction between the amide ion $(NH_2)^-$ and the carbonyl group of the ester. In certain cases it is possible to minimize the competing reaction of the base B with component A by first converting the system $\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\underset{|}{C}{=}O}$ into its enolate anion, and then allowing this anion to react with component A. Esters may be enolized by sodium triphenylmethyl,[12] and ketones by sodamide.[13] β-Keto esters, such as ethyl acetoacetate,[9] are commonly enolized by sodium ethoxide.

Other factors that limit the type of base B that may be used to effect a Claisen condensation are not well understood at the present time. One of the requirements appears to be that a weaker base must be formed than the one used to initiate the reaction. In all known condensations of ethyl esters by sodium ethoxide the β-keto ester that is formed is converted into its enolate; it should be noted that in this way only can a base (enolate anion) be formed that is weaker than the one (ethoxide ion) used to initiate the reaction. On the other hand, when sodium triphenylmethyl is used in condensations of ethyl esters it is not necessary[1b] for the β-keto ester that is formed to be converted into its enolate, because a weaker base, the ethoxide ion, is formed during the reaction. It should be pointed out, however, that condensation does not always occur even when it appears possible to form a weaker base.[14] Solubility relationships or perhaps other factors may play an important role in these condensations.

Summary

1. The general course of the Claisen type of condensation is outlined.

2. It is proposed that any reaction that involves the carbon–carbon condensation of a metallic enolate with a compound of the type RCOX, where X is an atom or group that is removed as an anion, be classified as a Claisen type of condensation.

3. Certain aspects of this type of condensation are discussed.

DURHAM, NORTH CAROLINA

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[10] Spielman and Schmidt, THIS JOURNAL, **59**, 2009 (1937).

[11] See Bergstrom and Fernelius, *Chem. Rev.*, **12**, 146 (1933).

[12] The anion of sodium triphenylmethyl is a base which readily enolizes the hydrogen on the α-carbon atom of an ester, but which appears to attack the carbonyl group of the ester only at a relatively slow rate. Apparently the latter reaction occurs only when it is not possible for an ester to be enolized. In this connection see Schlenk and Ochs, *Ber.*, **49**, 610 (1916).

[13] See Bergstrom and Fernelius, *Chem. Rev.*, **12**, 107 (1933).

[14] Roberts and McElvain [THIS JOURNAL, **59**, 2007 (1937)] have shown that ethyl isovalerate and ethyl *t*-butylacetate are not condensed by sodium ethoxide even though the β-keto esters that would be formed have hydrogen on the α-carbon atom.