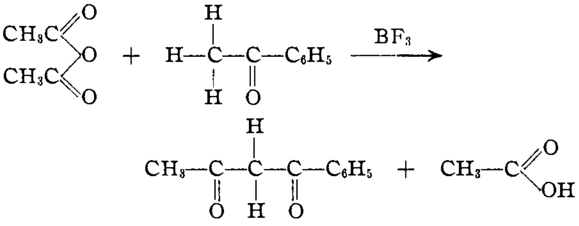
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

# Condensations.[1] XI. Condensations of Certain Active Hydrogen Compounds Effected by Boron Trifluoride and Aluminum Chloride[2]

BY DAVID S. BRESLOW[3] AND CHARLES R. HAUSER

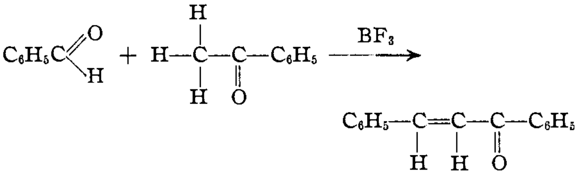
It is well known that the alkylation of a reactive methylenic compound, as well as the Claisen, Perkin, Knoevenagel and Michael condensations, are generally effected by means of bases. The purpose of the present investigation has been to study the possibility of effecting the analogs of these reactions by means of the acidic reagents, boron trifluoride and aluminum chloride.

Actually, certain of these analogs have been effected previously by means of acidic reagents. Meerwein and Vossen[4] showed that ketones, acetophenone for example, condense with acetic anhydride in the presence of boron trifluoride; also, acetic anhydride undergoes self-condensation in the presence of this reagent. We have confirmed this result with acetophenone, the reaction being represented as follows



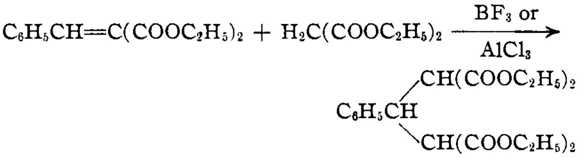
This reaction (and also the self-condensation of acetic anhydride) may be regarded as an analog of the generalized Claisen type of condensation.[5] Apparently, ethyl acetate does not undergo the Claisen type of condensation with acetophenone in the presence of boron trifluoride.

The Perkin and Knoevenagel reactions belong to the "aldol" type of condensation, many of which are commonly effected by acids. The self-condensation of acetone to form mesityl oxide[6] or mesitylene[7] in the presence of acids is a well-known example. The self-condensation of certain ketones has been effected also by aluminum chloride.[8] We have found that acetophenone condenses with benzaldehyde in the presence of boron trifluoride to give a good yield of benzalacetophenone.



Ethyl malonate condenses with benzaldehyde in the presence of boron trifluoride or aluminum chloride, but the product formed, ethyl benzalmalonate, undergoes a Michael type of condensation with unchanged ethyl malonate giving ethyl benzaldimalonate. When the reaction was effected by aluminum chloride, both ethyl benzalmalonate and ethyl benzaldimalonate were obtained, but when the condensation was effected by boron trifluoride, only the latter was obtained. These reactions may be represented as follows

$$C_6H_5CHO + H_2C(COOC_2H_5)_2 \xrightarrow[AlCl_3]{BF_3 \text{ or}} C_6H_5CH{=}C(COOC_2H_5)_2$$



The condensation of ethyl malonate with benzaldehyde is obviously an analog of the Knoevenagel reaction. The analog of the classic Perkin reaction, involving the condensation of acetic anhydride[9] with benzaldehyde, has been effected by means of boron trifluoride, but only a small yield of cinnamic acid could be isolated from the reaction products, much tar being obtained. An attempt to condense ethyl acetate

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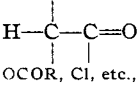
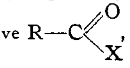
[1] Previous papers of this series are entitled "Condensations Brought about by Bases." For paper X, see THIS JOURNAL, **62**, 1763 (1940).

[2] This paper was presented before the Division of Organic Chemistry at the Cincinnati meeting of the American Chemical Society, April, 1940.

[3] This paper embodies a part of the material presented by David S. Breslow to the Graduate School of Duke University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[4] Meerwein and Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

[5] The condensation of an active hydrogen compound of the type  with an acid derivative , where X is OR, OCOR, Cl, etc., is regarded as a Claisen type of condensation. See Hauser, THIS JOURNAL, **60**, 1957 (1938).

[6] Freer and Lachman, *Am. Chem. J.*, **19**, 887 (1897).

[7] Adams and Hufferd, "Organic Syntheses," Vol. II, John Wiley and Sons, New York, N. Y., 1922, p. 41.

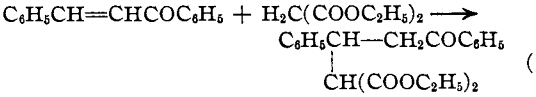
[8] Courtot and Ouperoff, *Compt. rend.*, **191**, 416 (1930).

[9] The classic Perkin reaction undoubtedly involves the condensation of the anhydride and not the sodium salt. See Breslow and Hauser, THIS JOURNAL, **61**, 786 (1939).

with benzaldehyde was unsuccessful; at 30° no condensation occurred while at 100° tar resulted.

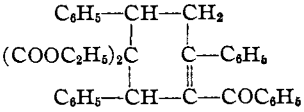
Apparently no analog of the Michael condensation effected by acidic reagents has been reported previously. We have condensed ethyl malonate with ethyl benzalmalonate by means of boron trifluoride to give a good yield of the Michael product, ethyl benzaldimalonate, the reaction being represented above. This result indicates that the formation of ethyl benzaldimalonate from ethyl malonate and benzaldehyde in the presence of boron trifluoride very probably involves the intermediate formation of ethyl benzalmalonate as shown and not the elimination of water from the "aldol" and another molecule of ethyl malonate as sometimes represented.

Ethyl malonate also has been condensed with benzalacetophenone in the presence of boron trifluoride, but as previously found by Michael and Ross[10] using the basic catalyst, sodium ethoxide, a complex mixture of products is formed. Although the primary addition compound was not isolated, there seems little doubt that the initial reaction took place as follows

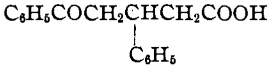


$$C_6H_5CH{=}CHCOC_6H_5 + H_2C(COOC_2H_5)_2 \longrightarrow \underset{\displaystyle CH(COOC_2H_5)_2}{C_6H_5CH}\text{—}CH_2COC_6H_5 \qquad (I)$$

A small amount of a crystalline substance melting at 234–235° was isolated; this was apparently the cyclic compound (II), which was obtained previously by Michael and Ross. On hydrolysis of the reaction mixture the acid (III) was obtained in fair yield. This product could have resulted by hydrolysis and decarboxylation of either the ester (I) or other reaction products present in the mixture.



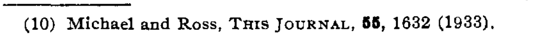
(II)



$$C_6H_5COCH_2\underset{C_6H_5}{CH}CH_2COOH$$

(III)

There are apparently no cases known of the successful alkylation of enolizable hydrogen compounds, such as ethyl acetoacetate or ethyl malonate, in the presence of acidic reagents. We have succeeded in alkylating ethyl acetoacetate with benzyl chloride in the presence of boron trifluoride, ethyl α-benzylacetoacetate being formed.



$$C_6H_5CH_2Cl + CH_3COCH_2COOC_2H_5 \xrightarrow{BF_3} CH_3CO\underset{CH_2C_6H_5}{CH}COOC_2H_5$$

The condensation of ethyl acetoacetate with certain compounds which will react in the presence of acidic reagents but not in the presence of basic reagents will be discussed in the following paper.

## Experimental

**Preparation and Purification of Materials.**—Boron trifluoride (supplied by the Harshaw Chemical Co., Cleveland, Ohio, as the compressed gas) was passed through a solution of boric oxide in concentrated sulfuric acid to remove hydrogen fluoride and then through an empty trap.

Acetophenone (Eastman Kodak Co.) was recrystallized; m. p. 20.5°.

Ethyl acetoacetate (Eastman Kodak Co.) was extracted with dilute sodium carbonate solution, washed with water until neutral, dried over "Drierite" and distilled through a short Widmer column; b. p. 180–181°.

Acetic anhydride, benzaldehyde, ethyl acetate and ethyl malonate were purified as previously described.[9,11]

Ethyl benzalmalonate was prepared according to the method of Knoevenagel[12]; b. p. 163–164° at 6 mm.

Other compounds were Eastman Kodak Co. best grade and were used without further purification: anhydrous aluminum chloride, benzyl chloride and benzalacetophenone (m. p. 57.0–57.5°).

**Method of Saturating Solutions with Boron Trifluoride.**—The reacting substances were placed in a 200-cc. three-necked flask equipped with a mercury-sealed stirrer,[13] the other two necks closed off with stoppers and the flask weighed. One stopper was replaced by a calcium chloride drying tube and the other by a delivery tube which did not dip into the liquid. The flask was cooled in an ice-bath, the solution stirred vigorously and a slow stream of purified boron trifluoride passed over the surface of the liquid until saturated and for a short time thereafter. The saturation point was indicated by evolution of boron trifluoride fumes from the calcium chloride tube. The calcium chloride and delivery tubes were replaced by stoppers and the flask dried and weighed.

**Condensation of Benzaldehyde with Acetophenone in the Presence of Boron Trifluoride.**—Benzaldehyde (10.6 g., 0.10 mole) was chilled and saturated with boron trifluoride, 6.0 g. (0.089 mole) being added. The yellow solid, formed in the reaction with boron trifluoride, was allowed to warm up to room temperature and to it was added 24.0 g. (0.20 mole) of acetophenone. The reaction mixture became warm and formed a clear deep-red solution. After being stirred at room temperature for three hours, the reaction mixture was hydrolyzed with sodium acetate solution and extracted with ether. The ether solution was extracted with sodium bicarbonate and the ether distilled off after drying over "Drierite." The residue was distilled at reduced pressure. The first fraction (9.4 g.) consisted apparently of impure acetophenone and was collected at 90–94° at 10 mm. The second fraction (12.7 g.) boiled at 218–222° at 4 mm. and solidified to a pale yellow solid on standing. It was identified as benzalacetophenone by its melting point (56–57° after one recrystallization from alcohol)

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[10] Michael and Ross, THIS JOURNAL, **55**, 1632 (1933).

[11] Hauser and Breslow, *ibid.*, **61**, 793 (1939).

[12] Knoevenagel, *Ber.*, **31**, 2591 (1898).

[13] Rubber stoppers are attacked by boron trifluoride less rapidly than cork.

and by a mixed melting point with an authentic sample of benzalacetophenone. The boiling point[14] of benzalacetophenone is given in the literature as 208° at approximately 25 mm. and the melting point[15] as 56–57°. A large non-distillable residue (8.9 g.) was obtained. Four recrystallizations of this residue from alcohol yielded a small amount of solid, m. p. 81–84°, which was probably the Michael condensation product, benzaldiacetophenone (m. p. 85°[16]), but not enough of it was obtained for further identification.

The yield of crude benzalacetophenone (b. p. 218–222° at 4 mm.) was 12.7 g. (61.0% of the theoretical based on the benzaldehyde used as starting material).

**Condensation of Benzaldehyde with Ethyl Malonate in the Presence of Boron Trifluoride.**—A solution of 10.6 g. (0.10 mole) of benzaldehyde and 16.0 g. (0.10 mole) of ethyl malonate was saturated with boron trifluoride, the mixture taking up 12.5 g. (0.18 mole). The reaction mixture, yellow and almost completely solid, partially liquefied and turned a deep red on standing at room temperature. After being stirred at room temperature for six hours, the reaction mixture was hydrolyzed with sodium acetate solution and extracted with ether. The ether solution was extracted with potassium carbonate until alkaline and dried over "Drierite." The ether was distilled off from the dried ethereal solution and the residue distilled under reduced pressure. The first fraction (9.0 g.) was collected at 61–81° at 12 mm. and yielded 3.1 g. (29.2%) of benzaldehyde recovered as the sodium bisulfite addition product, the remainder of the distillate being presumably recovered ethyl malonate. The second fraction (11.3 g.) boiled at 170–215° at 6 mm., most of it distilling at 208–209°. A dark red oil (2.4 g.) was obtained as residue.

The second fraction was refluxed for twenty-four hours with 100 cc. of 45% hydrobromic acid. The resulting solution was evaporated to dryness on a water-bath, the residue dissolved in hot water, filtered and the clear aqueous solution evaporated to small volume. The precipitate obtained on cooling (3.4 g.) melted at 115–120°. The filtrate was evaporated further and a small amount of hydrochloric acid added; 1.3 g. of crystals, m. p. 139–141°, was obtained on cooling and filtering. The filtrate was evaporated to dryness, the residue obtained combined with the low-melting precipitate mentioned above and the combined precipitates treated with a small amount of hot benzene. A portion of the solid remained undissolved. The mixture was cooled and filtered, 3.2 g. of β-phenylglutaric acid being obtained, m. p. 140–141° (identical with melting point recorded in the literature[17]). Neutral equivalent calculated for $C_{11}H_{12}O_4$: 104.0. Found: 104.6.

The total yield of β-phenylglutaric acid was 4.5 g., which is equivalent to 8.9 g. of ethyl benzaldimalonate (43.6% of the theoretical amount based on the ethyl malonate used as starting material).

**Condensation of Benzaldehyde with Ethyl Malonate in the Presence of Aluminum Chloride.**—To a solution of 10.6 g. (0.10 mole) of benzaldehyde, 16.0 g. (0.10 mole) of ethyl malonate and 75 cc. of 30–60° ligroin was added, with stirring, 40.0 g. (0.30 mole) of aluminum chloride. The solution refluxed gently. After all the aluminum chloride had been added, the mixture was refluxed for an additional five hours, during which time it turned semi-solid and green-brown. The reaction mixture was chilled and hydrolyzed with ice and a small amount of hydrochloric acid. It was then extracted with ether, the ether solution extracted with dilute potassium carbonate until alkaline and dried over "Drierite." The residue remaining after distilling the ether from the dried ethereal solution was distilled at 7 mm. The first fraction (2.3 g.), boiling at 57–60°, was presumably recovered benzaldehyde and ethyl malonate and yielded 1.5 g. (14.1%) of benzaldehyde as the sodium bisulfite addition complex. The second fraction (10.4 g.) was collected at 167–195° and the third (6.8 g.) at 204–220°. About 2 g. of residue remained.

The second fraction was redistilled from a 25-cc. Claisen flask with an attached column. It was collected at 161–164° at 6 mm., 8.1 g. of ethyl benzalmalonate being thus obtained. It was identified by hydrolysis to benzalmalonic acid[11]; m. p. 195–196° with decomposition. A mixed melting point with an authentic sample of benzalmalonic acid was the same.

The residue obtained from the redistillation of fraction two was combined with fraction three and hydrolyzed with hydrobromic acid, the hydrolysis and purification of the resulting β-phenylglutaric acid being carried out as described in the preceding experiment. In this way 2.8 g. of β-phenylglutaric acid, m. p. 140–141°, was obtained.

The yield of ethyl benzalmalonate was 8.1 g. and that of ethyl benzaldimalonate was 5.5 g. (calculated from pure β-phenylglutaric acid), the total yield being 59.7% of the theoretical (based on the ethyl malonate used as starting material).

**Condensation of Benzaldehyde with Acetic Anhydride in the Presence of Boron Trifluoride.**—A solution of 10.6 g. (0.10 mole) of benzaldehyde and 10.2 g. (0.10 mole) of acetic anhydride was saturated with boron trifluoride. The reaction mixture was allowed to stand at 0° for fifteen minutes, during which time it turned black and tarry. It was transferred to a 500-cc. flask with the aid of sodium acetate solution and steam-distilled until no more oil was obtained in the distillate. The distillate was extracted with ether and the ether solution extracted with dilute sodium carbonate until alkaline. The alkaline solution yielded 0.06 g. of cinnamic acid, m. p. 132.5–133.5°, on acidification and subsequent recrystallization of the precipitate from hot water. The ethereal solution yielded only 0.3 g. of benzaldehyde as the sodium bisulfite addition complex.

The residue from the steam-distillation contained a solid resin. The hot liquid was poured off from the resin and allowed to cool. It was made strongly acid with hydrochloric acid and filtered. The precipitate consisted of 0.6 g. of cinnamic acid (m. p. 133–134° after recrystallization from hot water) and a small amount of an unknown solid. The total yield of cinnamic acid was 0.66 g. (4.5% of theoretical based on benzaldehyde used as starting material).

This experiment was repeated several times under widely varying conditions. In certain cases up to 50% of the benzaldehyde could be recovered unchanged, but some tar was always formed. The experiment was also run in the presence of aluminum chloride, but no cinnamic acid could be isolated.

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[14] Wieland, *Ann.*, **328**, 221 (1903).

[15] Pfeiffer, *ibid.*, **383**, 145 (1911).

[16] Von Kostanecki and Rossbach, *Ber.*, **29**, 1493 (1896).

[17] Avery and Bouton, *Am. Chem. J.*, **20**, 511 (1898).

The experiment was also run substituting ethyl acetate for the acetic anhydride. At 30° most of the benzaldehyde (about 75%) was recovered unchanged, while at 100° a great deal of tar was obtained. Neither run yielded any ethyl cinnamate.

**Condensation of Ethyl Benzalmalonate with Ethyl Malonate in the Presence of Boron Trifluoride.**—A solution of 24.8 g. (0.10 mole) of ethyl benzalmalonate and 16.0 g. (0.10 mole) of ethyl malonate was saturated with boron trifluoride; 11.0 g. (0.16 mole) of boron trifluoride was absorbed by the solution, a clear, orange, viscous oil being formed. The reaction mixture was allowed to stand for six hours at room temperature, during which time it turned deep red. Ether was added and the mixture hydrolyzed with sodium acetate solution. The ethereal solution was dried over sodium sulfate, the ether distilled off and the residue distilled at reduced pressure. The first fraction (4.4 g.), boiling at 75–87° at 10 mm., was presumably recovered ethyl malonate. The second fraction (3.7 g.), boiling at 170–198° at 8 mm., was probably impure ethyl benzalmalonate, while the third fraction (28.2 g.), boiling at 198–223° at 8 mm., was impure ethyl benzaldimalonate. A negligible small residue remained.

The third fraction was redistilled from a 50-cc. Claisen flask with an attached column. The fraction (18.5 g.) boiling at 214–217° at 8 mm. was collected. It was identified as ethyl benzaldimalonate by hydrolysis to β-phenylglutaric acid with hydrobromic acid as described above; m. p. 139–141° (mixed melting point unchanged). Hydrolysis of the low-boiling fraction from the redistillation of ethyl benzaldimalonate yielded 1.6 g. of β-phenylglutaric acid, m. p. 139–140°, equivalent to 3.1 g. of ethyl benzaldimalonate. The total yield of ethyl benzaldimalonate was 21.6 g. (53.0% of the theoretical based on ethyl benzalmalonate used as starting material).

An attempt to condense ethyl cinnamate with ethyl malonate in the presence of boron trifluoride was unsuccessful under the conditions used.

**Condensation of Benzalacetophenone with Ethyl Malonate in the Presence of Boron Trifluoride.**—A solution of 20.8 g. (0.10 mole) of benzalacetophenone, 16.0 g. (0.10 mole) of ethyl malonate and 25 cc. of 30–60° ligroin was saturated with boron trifluoride. An orange-colored precipitate formed, which turned deep red on refluxing the reaction mixture for twenty-four hours. The mixture was then hydrolyzed with 150 cc. of 5% sodium hydroxide solution and extracted with ether. The alkaline solution yielded a negligible precipitate on acidification. A precipitate formed in the wet ether solution on standing. The precipitate was filtered off, the filtrate partially evaporated and ligroin (b. p. 30–60°) added. This procedure was repeated several times, 0.78 g. of yellow crystals with melting points about 227–233° being obtained. They were identified as 1,3,5-triphenyl-2-benzoyl-4-dicarbethoxycyclohexene (II) by recrystallization from chloroform; m. p. 234–235°, which agrees with that given by Michael and Ross.[10]

Since further treatment of the ether–ligroin solution yielded an oil, the solvent was evaporated and the residue distilled at 8 mm. Only 0.5 g. of distillate was obtained with a bath temperature up to 160°, showing the absence of any appreciable amount of unreacted ethyl malonate. The residue from the vacuum distillation was refluxed for eight hours with 100 cc. of a 20% potassium hydroxide solution containing 50% alcohol. Water was added and the alkaline solution partially evaporated to remove the alcohol. An unidentified precipitate insoluble in alkali and ether was filtered off from the alkaline solution and the filtrate extracted with ether to remove unsaponified material. The alkaline solution was then acidified with hydrochloric acid and the acidified solution extracted with ether. The ether solution was dried and evaporated. The residue was recrystallized from a mixture of ether and petroleum ether (b. p. 30–60°), 3.2 g. of white crystals being obtained in several fractions, m. p. 151–154°. The crystals were identified as β-phenyl-γ-benzoylbutyric acid (III) by recrystallization from hot water; m. p. 156–156.5° identical with that recorded in the literature.[18] Neutral equivalent calculated for $C_{17}H_{16}O_3$: 268.1. Found: 267.5.

The total yield of condensation product calculated as ethyl α-carbethoxy-β-phenyl-γ-benzoylbutyrate (I) from the impure cyclohexene derivative (II) and the impure acid (III) was 4.9 g. (13.3% of the theoretical based on benzalacetophenone).

**Alkylation of Ethyl Acetoacetate with Benzyl Chloride in the Presence of Boron Trifluoride.**—A solution of 26.0 g. (0.20 mole) of ethyl acetoacetate and 12.7 g. (0.10 mole) of benzyl chloride was saturated with boron trifluoride, 24.0 g. (0.35 mole) being absorbed. After stirring at room temperature for eight hours, the dark-red oily mixture was hydrolyzed with sodium acetate solution. Ether was added to the hydrolyzed solution and the ethereal solution separated, washed with dilute sodium bicarbonate solution and dried over "Drierite." The ether was distilled off from the dried ethereal solution and the residue distilled at 12 mm. The first fraction (8.7 g.), boiling at 45–74°, consisted presumably of a mixture of ethyl acetoacetate and benzyl chloride. These were separated by treating the distillate with 5% sodium hydroxide, extracting with ether, drying the ether solution and evaporating to dryness; 1.2 g. of benzyl chloride was left as a residue. The second fraction (4.6 g.) was collected at 155–167°, most of it boiling at 164–167°. The boiling point recorded in the literature[19] for ethyl α-benzylacetoacetate is 164–165° at 12 mm. The second fraction was shown to be chiefly this compound by preparation of the amide; m. p. 149–150° (literature, m. p. 150–151°[20]). A large non-distillable residue (9.2 g.) was obtained.

The yield of crude ethyl α-benzylacetoacetate (b. p. 155–167° at 12 mm.) was 4.6 g. (23.1% of the theoretical based on benzyl chloride used minus that recovered).

## Summary

1. Condensations analogous to the base-induced Claisen, "aldol" and Michael reactions have been effected by means of the acidic reagent, boron trifluoride or aluminum chloride.

2. The alkylation of ethyl acetoacetate with benzyl chloride has been effected by means of boron trifluoride.

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[18] Vorländer and Knötzsch, *Ann.*, **294**, 332 (1897).

[19] Fittig and Christ, *ibid.*, **268**, 122 (1892).

[20] Meyer, *Monatsh.*, **27**, 1090 (1906).