[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensations. XIX. The Alkylation of β-Keto Esters with Alcohols and Ethers in the Presence of Boron Trifluoride[1,2]

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It was shown recently in this Laboratory that ethyl acetoacetate is alkylated by isopropyl alcohol or ether in the presence of boron trifluoride to form ethyl α-isopropylacetoacetate.[3] The present paper reports the results of a further study of this type of alkylation.

General Procedure.—All of the materials were purified before use. A mixture of one mole of the alcohol, or one-half mole of the ether, and one-half mole of the β-keto ester was placed in a three-necked flask equipped with a mercury-sealed stirrer, a drying tube (a condenser, with a drying tube attached, was used for volatile liquids) and a delivery tube about 1 cm. above the surface of the liquid. The mixture was chilled to approximately 0° by immersing the flask in an ice-bath. A stream of boron trifluoride was passed over the surface of the rapidly stirred solution until the reaction mixture was saturated[4] (usually one to three hours was required) and then for an additional fifteen minutes. The saturation point was indicated by the copious evolution of boron trifluoride fumes from the drying tube. The reaction flask was removed from the iced bath and allowed to stand at room temperature for an appropriate time.[5] The mixture was poured with stirring into a solution of excess sodium acetate containing ice, and the resulting mixture extracted (generally after a few hours) with ether. The ether solution was washed with saturated sodium bicarbonate solution to remove the acetic acid, and dried over sodium sulfate followed by Drierite. After distilling off the ether and unreacted alkylating agent, the residue was distilled *in vacuo* through a twelve-inch Vigreux column and appropriate fractions were collected. Refractionation was sometimes required to give an essentially pure product.

Results.[6]—Before presenting the results it seems best to consider the side-reactions (and consecutive reactions) that might be expected when a mixture of an alcohol or ether and ethyl acetoacetate is treated with boron trifluoride. The alcohol may be dehydrated (or the ether dealcoholated) to form unsaturated hydrocarbons which may polymerize. The β-keto ester may undergo an ester–alcohol exchange or may react with boron trifluoride to form higher boiling products[7]; the alkylated product also may undergo these changes. Apparently, all of these reactions occurred in the present investigation.

At the time of the earlier work[3] the importance of controlling the time and temperature of the reaction was not fully appreciated. The previous yield of ethyl α-isopropylacetoacetate of 40%, obtained with isopropyl alcohol and ethyl acetoacetate, has now been increased to 67% of essentially pure product (b. p. 97–98° at 20 mm. *Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 63.03; H, 9.17). This yield of alkylated product was obtained by allowing the reaction flask to stand (after the reaction mixture had been saturated with boron trifluoride at 0°) at the room temperature of 28° for two and one-half hours. The use of 0.5 mole each of the alcohol and β-keto ester under similar conditions gave a 48% yield of the alkylated product. The previous yield of 70% of the alkylated product obtained with isopropyl ether and the β-keto ester has been found difficult to duplicate; unfortunately the exact temperature at which the reaction was carried out was not recorded. A 61% yield of alkylated product (b. p. 90–91° at 15 mm.) has been obtained by allowing the reaction mixture to stand at 33° for twelve hours; seventeen hours of standing reduced the yield to 30%, while standing at 29° for two and one-half hours resulted in a 50% yield of product.

Ethyl acetoacetate has been alkylated with cyclohexanol to form ethyl α-cyclohexylacetoacetate (b. p. 146–148° at 20 mm. *Anal.* Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 67.92; H, 9.26). The yield of alkylated product was 32–34% when the reaction mixture was allowed to stand at 30° for one to two hours. On ketonic hydrolysis with 5% sodium hydroxide

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(1) This paper was supported in part by a grant from the Duke University Research Council.

(2) Part of this paper has been taken from a Ph.D. thesis by B. Abramovitch, Duke University, 1942.

(3) Hauser and Breslow, THIS JOURNAL, **62**, 2389 (1940).

(4) For one mole of isopropyl alcohol and one-half mole of ethyl acetoacetate, approximately one and six-tenths mole of boron trifluoride was absorbed. In one experiment the addition of boron trifluoride was stopped after only one mole had been absorbed; on working up the mixture no alkylated product was obtained.

(5) In most of the experiments some high boiling residue was obtained even when a portion of the β-keto ester remained unalkylated and attempts were made to determine the conditions that would yield minimum amounts of both high boiling residues and unalkylated β-keto esters. In most cases, the change of color during the reaction served as a rough indication of the amount of high boiling material being formed, the reaction mixture becoming deep red or brown when a considerable amount of it was present.

(6) Boiling points and melting points are uncorrected. Micro analyses are by Saul Gottlieb and William Saschek, New York, N. Y.

(7) See Monacelli and Hennion, THIS JOURNAL, **63**, 1722 (1941).

solution, the product gave a 55% yield of cyclohexylacetone (b. p. 196–200°); the semicarbazone of the ketone melted at 166.0–166.5°.[8]

With *t*-butyl alcohol or ethyl *t*-butyl ether and ethyl acetoacetate, *t*-butyl α-*t*-butylacetoacetate has been obtained but the yields were low (6–14%); obviously the alkylation was accompanied by an ester alcohol exhange. Some unchanged ethyl acetoacetate was recovered but no *t*-butyl acetoacetate could be isolated. Mixtures of unsaturated hydrocarbons were also obtained. The best yield of alkylated product was obtained with *t*-butyl alcohol under the conditions described previously.[9] On ketonic hydrolysis with a mixture of acetic and sulfuric acids,[10] the alkylated product gave a 23% yield of methyl neopentyl ketone (b. p. 123–126°); the ketone semicarbazone melted at 173–175°.[11] With *t*-amyl alcohol and ethyl acetoacetate a fraction was obtained which, on ketonic hydrolysis with a mixture of acetic and sulfuric acids,[10] yielded a small amount of 4,4-dimethylhexanone-2 identified as its semicarbazone (m. p. 167.5–168.5°).[12]

Under special conditions ethyl acetoacetate has been alkylated with dibenzyl ether to form ethyl α-benzylacetoacetate. An 18% yield of the alkylated product (b. p. 164–166° at 12 mm., m. p. of its amide 149–150°)[13] was obtained when the reaction mixture was saturated with boron trifluoride at −70°, allowed to stand for thirty minutes (the temperature rising to −10°) and then worked up. Only a trace or no alkylated product was obtained under the usual conditions. Monacelli and Hennion[7] obtained no alkylated product from ethyl acetoacetate and benzyl *n*-propyl ether.

Ethyl α-methylacetoacetate has been alkylated with isopropyl ether to form ethyl α-methyl-α-isopropylacetoacetate (b. p. 98.0–98.5° at 15 mm.). The yield was 55% when the reaction mixture was allowed to stand at 24° for fourteen hours. Ketonic hydrolysis of the alkylated product gave a 70% yield of 3,4-dimethylpentanone-2 (b. p. 134–137°)[14]; the semicarbazone of the ketone melted at 107.0–107.5° (*Anal.* Calcd. for $C_8H_{17}ON_3$: N, 24.6. Found: 25.0).

No alkylated product could be isolated in experiments with the following components: ethyl acetoacetate with *n*-butyl, isobutyl or *s*-butyl alcohols; ethyl acetoacetate with ethyl or *n*-propyl ethers; ethyl benzoylacetate with isopropyl alcohol or ethyl or isopropyl ethers; ethyl α-isopropylacetoacetate with isopropyl ether; ethyl malonate with isopropyl ether or *t*-butyl alcohol; nitromethane with isopropyl ether or *t*-butyl alcohol. In the experiments with ethyl benzoylacetate there was formed a heavy crystalline precipitate, presumably the addition complex between the β-keto ester and the boron trifluoride. In the experiments with ethyl acetoacetate and *n*-butyl and isobutyl alcohols the ester–alcohol exchange occurred yielding, respectively, *n*-butylacetoacetate (b. p. 105–107° at 20 mm., ketonic hydrolysis yielding acetone and *n*-butyl alcohol) and isobutyl acetoacetate (b. p. 98–101° at 20 mm., ketonic hydrolysis yielding acetone and isobutyl alcohol).

The method of synthesis of ethyl α-isopropylacetoacetate and ethyl α-cyclohexylacetoacetate described above is considered superior to the more common method of alkylation in which the sodium derivative of ethyl acetoacetate is treated with the appropriate alkyl halide. The boron trifluoride method is the more convenient and gives the better yield of alkylated product in these cases.[15] The boron trifluoride method is probably also to be preferred for the synthesis of ethyl α-methyl-α-isopropylacetoacetate from ethyl α-methylacetoacetate, although a slightly better yield of the alkylated product has been obtained from the sodium derivative of ethyl α-methylacetoacetate and isopropyl iodide.[16] It is noteworthy that even a low yield of a *t*-butyl derivative may be obtained by the boron trifluoride method, since, as it is well known, the use of a base with *t*-butyl halides gives little if any of the alkylated derivative.

Discussion

The results presented above are considered to be in agreement with the mechanism of alkylation discussed previously.[3] This consists essentially in the formation of a coördination complex between the alcohol or ether and boron tri-

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[8] Wallach, *Ann.*, **353**, 300 (1907).

[9] Hauser and Adams, THIS JOURNAL, **64**, 728 (1942).

[10] Hudson and Hauser, *ibid.*, **63**, 3163 (1941).

[11] Whitmore and Mixon, *ibid.*, **63**, 1460 (1941).

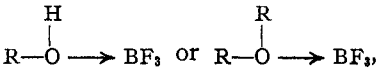
[12] Drake, Kline and Rose, *ibid.*, **56**, 2076 (1934).

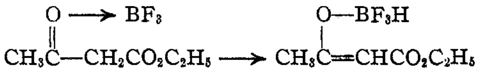
[13] Meyer, *Monatsh.*, **27**, 1090 (1906).

[14] Van Romburgh, *Rec. trav. chim.*, **5**, 233 (1886).

[15] The alkylation of the sodium derivative of ethyl acetoacetate has been reported to give with isopropyl iodide a 49% yield of ethyl α-isopropylacetoacetate [Bischoff, *Ber.*, **28**, 2620 (1895)] and with cyclohexyl iodide, only a 6% yield of ethyl α-cyclohexylacetoacetate [Hell and Schaal, *Ber.*, **42**, 2232 (1909)].

[16] Willstätter and Hatt, *Ann.*, **418**, 151 (1919).

fluoride,  $\mathrm{R}-\overset{\mathrm{H}}{\mathrm{O}} \longrightarrow \mathrm{BF_3}$ or $\mathrm{R}-\overset{\mathrm{R}}{\mathrm{O}} \longrightarrow \mathrm{BF_3}$, which (with or without the intermediate formation of carbonium ions) alkylates the β-keto ester. Complexes are probably also formed between ethyl acetoacetate and boron trifluoride; the complex involving the ketone oxygen should facilitate the conversion of the β-keto ester into the "enol" form



$$\mathrm{CH_3\overset{O \rightarrow BF_3}{\overset{\|}{C}}-CH_2CO_2C_2H_5 \longrightarrow CH_3\overset{O-BF_3H}{\overset{|}{C}}=CHCO_2C_2H_5}$$

It is not known whether or not this is a prerequisite to the alkylation.[17]

As with the similar Friedel–Crafts type of reaction,[18] the alkylation of β-keto esters depends upon the reactivities of both components. Thus, the secondary and tertiary alcohols or ethers (and benzyl ether) are capable of alkylating ethyl acetoacetate, whereas the purely aliphatic primary alcohols or ethers, which are known to be less reactive,[18] fail to alkylate this β-keto ester under similar conditions. The failure of *s*-butyl alcohol to alkylate ethyl acetoacetate, and the low yields obtained with the tertiary alcohols, appear to be due to the predominance of side reactions. The relatively reactive compounds, ethyl acetoacetate and its methyl derivative are readily isopropylated whereas the less reactive compounds, ethyl α-isopropylacetoacetate and ethyl malonate, fail to be alkylated under similar conditions. It should be noted that not all relatively reactive compounds yielded alkyl derivatives. Ethyl benzoylacetate formed an insoluble boron trifluoride complex and failed to be alkylated. Nitromethane also failed to be alkylated.

Summary

A study has been made of the alkylations of β-keto esters and certain other active hydrogen compounds with alcohols and ethers in the presence of boron trifluoride. Certain of the reactions are of synthetic value. The results are considered in the light of the theory of condensations.

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(17) Results, which will be published shortly, on the acylation of ketones with anhydrides indicate that the enol form of the ketone is acylated.

(18) See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 309–310.

[CONTRIBUTION FROM THE IOWA AGRICULTURAL EXPERIMENT STATION]

The Configuration of Starch and the Starch–Iodine Complex. I. The Dichroism of Flow of Starch–Iodine Solutions[1]

BY R. E. RUNDLE AND R. R. BALDWIN

Introduction

The X-ray diffraction studies of Bear and French,[2] and the optical studies of Frey-Wyssling,[3] have established rather conclusively that native, granular starches and retrograded starches, both of which exhibit "A" or "B" X-ray diffraction patterns, have essentially linearly extended-chain configurations. Hanes[4] has, nevertheless, suggested a helical configuration for the starch chain, and this suggestion has been adopted and extended by Freudenberg and co-workers.[5] The reason for suggesting this configuration and almost the entire evidence for it, is that it will explain certain properties of starch which as yet are not well understood. These may be summarized as follows:

(1) Various enzyme actions suggest that glucose residues, six apart down the starch chain, are quite close to each other. For example, the enzyme from *B. macerans* converts starch into cycloamyloses of six or more glucose residues per molecule,[6] and α-amylase, according to Hanes,[4,7] degrades starch into a dextrin containing six glucose residues per molecule.

(2) Starch and its degradation products form highly colored addition products with iodine, the achroic point coming at about six glucose residues; that is, dextrins of less than six glucose residues show little or no intensification of the color of an iodine solution. Hanes[4] believes

(1) Journal Paper No. J-1037 of the Iowa Agricultural Experiment Station, Ames. Project No. 660. Supported in part by a grant from the Corn Industries Research Foundation.

(2) R. S. Bear and D. French, THIS JOURNAL, **63**, 2298 (1941).

(3) A. Frey-Wyssling, *Naturw.*, **28**, 78 (1940); *Ber. Schweiz. Bot. Ges.*, **59**, 321 (1940).

(4) C. S. Hanes, *New Phytologist*, **36**, 101, 189 (1937).

(5) K. Freudenberg, E. Schaaf, G. Dumpert and T. Ploetz, *Naturw.*, **27**, 850 (1939).

(6) D. French and R. E. Rundle, THIS JOURNAL, **64**, 1651 (1942).

(7) This is probably incorrect; see K. Meyer, "Adv. in Colloid Science," Interscience Pub. Inc., New York, N. Y., 1942, p. 171.