[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Mesitylmagnesium Bromide as a Reagent in the Acetoacetic Ester Condensation[1]

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An investigation recently completed in this Laboratory[2] has revealed that neither ethyl isovalerate nor ethyl *t*-butylacetate undergoes the acetoacetic ester condensation in the presence of sodium ethoxide, either under equilibrium conditions or when provision is made for removal of alcohol from the reaction mixture. Both of these esters contain an α-methylene group, but their non-reactivity places them in a category with ethyl isobutyrate, which is similarly recalcitrant, although generally held to be so because of the presence of only a single α-hydrogen atom. Any reagent capable of bringing these anomalous compounds to react is of considerable interest in developing a general theory of acetoacetic ester condensations.

In connection with a different project we were engaged in preparing certain alkyl aryl ketones by the use of the Grignard reagent, and, as usual in such experiments, we were confronted with the problem of stopping the reaction at the ketone stage to prevent the formation of excessive amounts of carbinol. The well-known inability of acetomesitylene to react except by enolization prompted us to investigate mesitylmagnesium bromide as a parent to the aryl part of the ketone body. It reacted readily with ethyl stearate, but the products were ethyl α-stearylstearate and mesitylene. The result, while surprising, is not without precedent, as Conant and Blatt[3] have found that isopropylmagnesium bromide promotes the acetoacetic ester type of condensation with ethyl phenylacetate in yields above 90%. Indication is made in a table of their paper that ethyl propionate undergoes condensation in the presence of *t*-butylmagnesium chloride, but the nature and extent of the reaction are not noted. Ivanov and Spasov[4] have extended the reaction of Conant and Blatt to ethyl *p*-chlorophenylacetate.

At Professor McElvain's suggestion, we treated the above mentioned unreactive esters with mesitylmagnesium bromide, and in each case there resulted considerable amounts of β-keto ester. Ethyl isovalerate gave a 51% yield of ethyl isovalerylvalerate; ethyl *t*-butylacetate gave 32% of ethyl α,γ-di-*t*-butylacetoacetate; and ethyl isobutyrate gave 26% of ethyl tetramethylacetoacetate. None of these β-keto esters gives a ferric chloride test, although the first two contain the necessary α-hydrogen atom for enolization. All were characterized by hydrolysis to the corresponding ketones. In carrying out the Grignard reactions, best yields were obtained by inverse order of addition, that is, by adding the reagent to the ester.

These experiments and those of Roberts and McElvain raise two problems for explanation: first, why the esters involved undergo no acetoacetic ester condensation with sodium ethoxide but do react thus with mesitylmagnesium bromide; and, second, why the ferric chloride test should be negative for only these two monosubstituted β-keto esters among a host of similar compounds. The conclusion seems inescapable that the phenomena are related, and the following interpretation is suggested to bring the observations into line. In every known case of the acetoacetic ester condensation the end-product is a metal enolate of the β-keto ester; therefore the condensing agent must be able to form such an enolate, regardless of the intimate mechanism by which it is formed. This implies that the reagent must be the salt of an acid which is *weaker* than the condensate. Such a condition is fulfilled by mesitylmagnesium bromide because the halomagnesium is given up irreversibly with the formation of the hydrocarbon mesitylene. The failure of sodium ethoxide and the success of mesitylmagnesium bromide are due to the disparate acidity of alcohol and mesitylene relative to the β-keto-esters involved. Ethyl tetramethylacetoacetate is a very weak acid because it can form only a β,γ-enolate, thus

$$(CH_3)_2CHCOC(CH_3)_2COOC_2H_5 \rightleftarrows (CH_3)_2C{=}C(OH)C(CH_3)_2COOC_2H_5$$

The disinclination of the other esters to exist in enolic forms is shown by negative ferric chloride tests. It is to be understood that the above in-

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[2] Roberts and McElvain, THIS JOURNAL, **59**, 2007 (1937).

[3] Conant and Blatt, *ibid.*, **51**, 1227 (1929).

[4] Ivanov and Spasov, *Bull. soc. chim.*, [4] **49**, 375 (1931).

terpretation does not presuppose the formation of the metal enolate by enolization of the β-keto ester.

Experimental Part

Ethyl α-Isovalerylisovalerate.—In a 3-necked flask equipped with condenser, stirrer and dropping funnel was placed 24 g. of ethyl isovalerate in two volumes of ether. To this was added slowly through the dropping funnel 0.189 mole of mesitylmagnesium bromide in 170 cc. of ether. The titer of the Grignard reagent was determined immediately before use. The reaction was mildly exothermic, and refluxing ceased soon after the last of the reagent was added. The mixture was stirred for an hour and then decomposed in the usual fashion. Distillation yielded 26 g. of mesitylene boiling at 70–75° at 32 mm. and 10.0 g. (51%) of ethyl isovalerylisovalerate, b. p. 128–133° at 32 mm.[5]

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.3; H, 10.3. Found: C, 67.4; H, 10.5.

An experiment was performed in which the normal order of addition was followed; that is, the ester was added to the Grignard reagent. The yield was substantially the same, but the product was much more difficult to purify. Isopropylmagnesium bromide was also tried. The yield of β-keto ester from a half-mole run was 1.3 g. or 1.2%.

Hydrolysis of ethyl isovalerylisovalerate was attended with extreme difficulty. The result was finally achieved by placing 20 g. of ester and 30 cc. of 5% sodium carbonate solution in a steel bomb and heating to 225° for eight hours. The diisobutyl ketone boiled at 163–164° and formed a semicarbazone melting at 122°. These figures agree with the literature values.[6]

Ethyl α,γ-Di-*t*-butylacetoacetate.—As above, 0.194 mole of mesitylmagnesium bromide was added to 27 g. or 1 equivalent of ethyl *t*-butylacetate.[7] The yield of β-keto ester was 7.3 g. or 32% of the theoretical; b. p. 138–140° at 32 mm.; $n^{25}\text{D}$ 1.4389. As usual with compounds containing the *t*-butyl group, combustion was very difficult, and the rather erratic carbon values obtained seemed to approach correctness as a maximum.

Anal. Calcd. for $C_{14}H_{26}O_3$: C, 69.4; H, 10.8. Found: C, 68.9, 68.9; H, 10.8, 11.1.

Hydrolysis was carried out in a steel bomb at 200° for five hours with 8% potassium hydroxide in 50% alcohol. The dineopentyl ketone which was obtained boiled at 185° at 740 mm.; $n^{25}\text{D}$ 1.4210.

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.6; H, 13.0. Found: C, 77.5; H, 12.7.

Dineopentyl ketone semicarbazone forms very slowly. After several crystallizations it yields soft leaflets melting at 178–179°.

Anal. Calcd. for $C_{12}H_{25}N_3O$: N, 18.5. Found: N, 18.8.

Ethyl Tetramethylacetoacetate.—As above, 0.19 mole of Grignard reagent was added to 22 g. or 0.19 mole of ethyl isobutyrate. The yield of the β-keto ester was 4.7 g. or 26.5% of the theoretical; b. p. 105–109° at 33 mm. This sample refluxed at 195° (uncorr.) at 740 mm. Salkind[8] gives the boiling point as 199–201°.

Hydrolysis with 8% potassium hydroxide gave diisopropyl ketone; b. p. 123–124°.[9] The semicarbazone melted at 149°. Literature values range from 123 to 157°.[9]

Ethyl α-Stearylstearate.—A 0.1-mole run was made in the usual way using carefully purified ethyl stearate (m. p. of free acid 69–70°). The product was a waxy solid which after several crystallizations from acetone melted at 48–49°. The melting point was not raised by distillation at 0.030 mm.; yield, 27%. Fröschl and Harlass[10] mention briefly the same compound, but give its melting point as 28–29°. It is soluble in benzene and dry ether, and very sparingly soluble in acetone and wet ether.

Anal. Calcd. for $C_{38}H_{74}O_3$: C, 78.8; H, 12.9. Found: C, 79.3; H, 13.1.

Hydrolysis with alcoholic alkali gave stearone; m. p 88–89°.

Summary

Ethyl isovalerate, ethyl *t*-butylacetate, and ethyl isobutyrate, three esters which do not undergo the acetoacetic ester type of condensation with sodium ethoxide, do so with mesitylmagnesium bromide. Since the resulting β-keto esters give no coloration with ferric chloride, their failure to be formed in the presence of sodium ethoxide is attributed to their inability to enolize as do ordinary β-keto esters.

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(5) Hamonet, *Bull. soc. chim.*, [3] **2**, 343 (1889); Zeltner, *Ber.*, **41**, 594 (1908).

(6) Skita and Ritter, *Ber.*, **43**, 3396 (1910); Kubota and Yoshikawa, *Jap. J. Chem.*, **2**, 45 (1925); *C. A.*, **20**, 860 (1926).

(7) Homeyer, Whitmore and Wallingford, THIS JOURNAL, **55**, 4209 (1933).

(8) Salkind, *Chem. Centr.*, **77**, II, 315 (1906).

(9) Henderson, Henderson and Heilbron, *Ber.*, **47**, 887 (1914); Beilstein, Suppl. Vol. I, p. 361.

(10) Fröschl and Harlass, *Monatsh.*, **59**, 294 (1932).