

third day up to the end of the sixth day of the dialysis, both solutions (I) and (II) lost no copper. Since most copper proteins lose copper in dilute acid solutions,¹⁶ at the end of the sixth day both solutions were made pH 3.5 with hydrochloric acid, and under these conditions the copper belonging to the milk protein was lost in the dialysis.

The authors wish to express their thanks to the Borden Company for their generous supply of milk which made this study possible.

(16) Kubowitz, *Biochem. Z.*, **299**, 32 (1938).

Summary

A procedure is described for isolation of a copper bearing protein from cow's milk.

The copper in the protein is non-ionic and cannot be removed by dialysis at pH 6.5.

Up to the present, no chemical reactions have been found which are catalyzed by this milk protein.

NEW YORK CITY, N. Y.

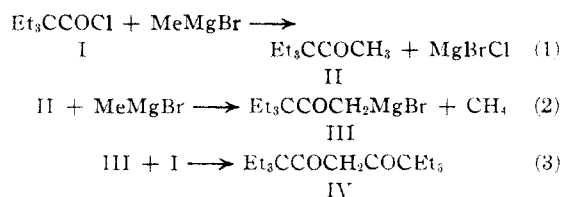
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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Abnormal Grignard Reactions. XIV.¹ Sterically Hindered Aliphatic Carbonyl Compounds. IV. Methyl Triethylcarbinyl Ketone and its Bromomagnesium Enolate

BY FRANK C. WHITMORE AND C. E. LEWIS²

An attempt to prepare 2-methyl-3,3-diethyl-2-pentanol by the reaction of methylmagnesium bromide with triethylacetyl chloride was unsuccessful. The action of the Grignard reagent with the acid chloride caused the evolution of one-half mole of methane for each mole of Grignard reagent used. The liquid products were methyl triethylcarbinyl ketone and bis-triethylacetyl-methane.



Such a series of reactions is not new. Methyl-*t*-butylneopentylacetyl chloride³ and dineopentylacetyl chloride⁴ have both been found to give good yields of the corresponding methyl ketones with methylmagnesium bromide. These ketones give bromomagnesium enolates which react as true Grignard reagents.^{3,4,5} Fuson and co-workers⁶ had earlier shown that mesityl alkyl ketones give halomagnesium enolates which also react as true Grignard reagents.

Methyl triethylcarbinyl ketone gave 94% enolization and no addition when run in the

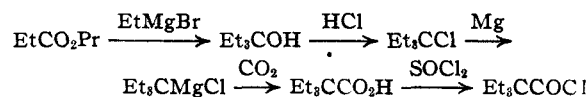
Grignard machine⁷ with methylmagnesium bromide. Thus, it is the lowest molecular weight ketone known which gives only enolization with the methyl Grignard reagent. The bromomagnesium enolate of methyl triethylcarbinyl ketone acts as a true Grignard reagent. Treatment of the enolate with carbon dioxide and formaldehyde gave the corresponding beta-keto acid and beta-ketol, respectively.

The few reactions studied indicate that the carbonyl of methyl triethylcarbinyl ketone is almost as sterically hindered as that of methyl methyl-*t*-butylneopentylcarbinyl ketone,³ methyl dineopentylcarbinyl ketone⁴ and acetomesitylene.⁶ This is interesting when it is remembered that the reactions of pinacolone indicate only slight steric influence on the carbonyl. Thus, the remarkable difference in steric influence of the methyl and ethyl groups is clearly demonstrated.

We thank R. S. George of this Laboratory for his help on this paper.

Experimental

The Grignard reagents for this work were prepared in the usual manner. All fractionations were done with the usual type of column⁸ having 12-18 theoretical plates. The triethylacetyl chloride was prepared by standard reactions as follows:



The chloride had b. p. 98° (65 mm.); n_D^{20} 1.4438.

(7) Kohler, Stone and Fuson, *THIS JOURNAL*, **49**, 3181 (1927).

(8) Whitmore and Lux, *ibid.*, **54**, 3451 (1932).

(1) XIII, Whitmore and Lester, *THIS JOURNAL*, **64**, 1251 (1942).

(2) Present address: Calco Chem. Div., American Cyanamide Co., Bound Brook, New Jersey.

(3) Whitmore and Randall, *THIS JOURNAL*, **64**, 1242 (1942).

(4) Whitmore and Lester, *ibid.*, **64**, 1247 (1942).

(5) Whitmore and Lester, *ibid.*, **64**, 1251 (1942).

(6) Fuson and co-workers, *ibid.*, **52**, 5036 (1930); **61**, 2362 (1939); *J. Org. Chem.*, **4**, 111 (1939).

Action of Methylmagnesium Bromide with Triethylacetyl Chloride (I).—To a solution of 157 g., 0.95 mole, of triethylacetyl chloride in ether was added 2 moles of 1.52 molar methylmagnesium bromide. About 0.5 mole of gas was evolved per mole of Grignard reagent added. The material was worked up as usual. Fractionation gave 45.6 g., 0.32 mole, or 34% of methyl triethylcarbonyl ketone (II), b. p. 90° (60 mm.), n_D^{20} 1.4318–9, and 39.9 g., 0.15 mole, or 32% of bis-triethylacetyl-methane (IV), b. p. 135–6° (8 mm.), n_D^{20} 1.4769–70. The 2,4-dinitrophenylhydrazones and the oxime of the monoketone, both of which were prepared with difficulty, melted at 93–94.5° and 97–101°, respectively. The diketone gave a chelate copper derivative with ammoniacal cupric acetate. The derivative was a brilliant purple compound with m. p. 143–144°. The monoketone gave 94% enolization and no addition when run in the Grignard machine with methylmagnesium bromide.⁷

3-Keto-4,4-diethylhexan-1-ol.—To 16 g., 0.65 gram-atom, of magnesium in 200 cc. of dry ether was added 70 g., 0.65 mole, of ethyl bromide. When the reaction was completed 80 g., 0.56 mole, of methyl triethylcarbonyl ketone was added. The reaction mixture was stirred for twenty-four hours. Formaldehyde gas was then passed into the reaction flask until an excess had been added. The reaction mixture became viscous as the reaction proceeded, and heating was necessary to keep it fluid enough for adequate stirring. The material was worked up as usual. Fractionation gave 37.7 g., 0.22 mole, or 34% of 3-keto-4,4-diethylhexan-1-ol, b. p. 86° (2 mm.), n_D^{20} 1.4554–8; alpha-naphthylurethan, m. p. 120–122°.

Mol. wt. Calcd. for $C_{10}H_{20}O_2$: mol. wt., 172. Found: mol. wt. (cryoscopic), 171.

3-Keto-4,4-diethylhexanoic Acid.—To 0.07 mole of ethylmagnesium bromide was added 10 g., 0.07 mole, of methyl triethylcarbonyl ketone. The reaction mixture was stirred three hours. Gas was evolved during the reaction. An excess of carbon dioxide gas was passed into the reaction mixture with continuous stirring. The material was worked up as usual. The oil layer was extracted with dilute sodium carbonate. The alkaline extract was acidified with sulfuric acid and the solid beta-keto acid was filtered off. The yield was 2.5 g., 0.014 mole, or 21%. The acid, m. p. 63–65°, decomposed on heating to give carbon dioxide and methyl triethylcarbonyl ketone.

Anal. Calcd. for $C_{10}H_{18}O_2$: neut. equiv., 186. Found: neut. equiv., 183, 185, 190.

Summary

1. The presence of three ethyl groups on the carbon adjacent to a carbonyl group has been found to have a pronounced influence on the reactions of the carbonyl.

2. The reaction of methyl triethylcarbonyl ketone with a Grignard reagent gives an enolate which reacts as a true Grignard reagent.

3. Methyl triethylcarbonyl ketone is the lowest molecular weight aliphatic ketone found to give only enolization with the methyl Grignard reagent.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Grignard Reactions. XV.¹ Sterically Hindered Aliphatic Carbonyl Compounds. V. Enolization Studies. I

BY FRANK C. WHITMORE AND L. P. BLOCK²

Methylmagnesium halides have long been used as reagents for the determination of active hydrogen in organic compounds. Early work on such determinations has been reviewed by Courtot,³ who pointed out that the method is applicable to the study of keto-enol tautomerism.

Kohler and co-workers⁴ devised a new type of apparatus with which one can determine the amount of gas evolved with the methylmagnesium halide, and also measure the amount of reagent used in the reaction.

Enolization studies until recently have been confined almost entirely to ketones containing an aromatic group. The reason for this is prob-

ably because hindered ketones which would contain conjugated double bonds in the enol form almost invariably give enolization.⁵ Thus acetomesitylene and related compounds⁶ have been studied rather extensively.

A definite correlation between the branching in aliphatic ketones and the amount of enolization given with the methyl Grignard reagent is not yet entirely clear. The literature indicates that such ketones show little tendency to give enolization with simple Grignard reagents. However, several new aliphatic sterically hindered ketones⁷ prepared in this Laboratory give as high as 100%

(5) (a) Fuson, Fisher and Fugate, *J. Org. Chem.*, **4**, 111 (1939); (b) Fuson, Fugate and Fisher, *THIS JOURNAL*, **61**, 2382 (1939).

(6) (a) Kohler and Baltzly, *ibid.*, **54**, 4015 (1932); (b) Smith and Guss, *ibid.*, **59**, 804 (1937).

(7) (a) Whitmore and Randall, *ibid.*, **64**, 1242 (1942); (b) Whitmore and Lester, *ibid.*, **64**, 1247 (1942); (c) Whitmore and Lewis, *ibid.*, **64**, 1618 (1942).

(1) Whitmore and Lewis, *THIS JOURNAL*, **64**, 1618 (1942).

(2) Present address: E. I. du Pont de Nemours and Co., Waynesboro, Va.

(3) Courtot, "Le Magnesium en Chemie Organique," 1926.

(4) Kohler, Stone and Fuson, *THIS JOURNAL*, **49**, 3181 (1927).