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Abnormal Grignard Reactions. X.¹ Enolizing and Reducing Action of Grignard Reagents upon Diisopropyl Ketone

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Since Tschugaeff,² in 1902, described a process for determining active hydrogen in organic compounds with methylmagnesium iodide, enolization measurements³ have been made on many carbonyl compounds using the methyl Grignard reagent. In contrast to the large amount of work done on the enolization of different carbonyl compounds by methylmagnesium halides only Grignard and co-workers⁴ have attempted a systematic investigation of the enolization of certain carbonyl compounds by different Grignard reagents. From a study of the reactions of several Grignard reagents with dibutyl ketone, in particular, Grignard and Blanchon^{4b} made several generalizations regarding the different amounts of enolization products given by the reaction of primary, secondary and tertiary Grignard reagents with the same ketone. However, Kohler and Thompson⁵ have shown that Grignard and Blanchon confused enolization with reduction.

The work of Kohler and Thompson led Smith and Guss^{6c} to make an observation regarding the enolization of ketones by Grignard reagents which seems to have been generally accepted. Their observation may be stated as follows: Enolization of ketones by Grignard reagents

is primarily a function of hindrance in the ketone. Branching of the chain in the reagent is of relatively minor importance. The present work invalidates the last statement.

The reduction of ketones by Grignard reagents has been more extensively studied.^{1,6}

The present study has covered the reactions of diisopropyl ketone with six different Grignard reagents. The amounts of enolization products found vary from 0% with methylmagnesium bromide to 90% with neopentylmagnesium chloride. The yields of reduction products vary from 0% with methylmagnesium bromide and neopentylmagnesium chloride to 78% with isobutylmagnesium bromide.

It has been pointed out^{3e,6a} that the reaction between ketones and Grignard reagents most frequently consists in addition of the reagent to the carbonyl group. However, when the speed of the addition reaction is greatly reduced due to steric conditions either around the carbonyl or in the Grignard reagent, the slower reactions of enolization, reduction and condensation may occur. In this study condensation is excluded by the structure of the ketone.^{6a} The results of the study are summarized in Table I.

In the reaction of diisopropyl ketone with methylmagnesium bromide the addition reaction is not sufficiently retarded by steric factors to allow time for the competing reactions to take

(1) Paper IX, Whitmore, *et al.*, *THIS JOURNAL*, **63**, 643 (1941).

(2) Tschugaeff, *Ber.*, **35**, 3912 (1902).

(3) (a) Hibbert and Sudborough, *J. Chem. Soc.*, 933 (1904); (b) Zerevitinov, *Ber.*, **41**, 2233 (1908); (c) Bhagvat and Sudborough, *J. Indian Inst. Sci.*, **2**, 187 (1919); (d) Bhagvat, *J. Chem. Soc.*, 1803 (1923); (e) Smith and Guss, *THIS JOURNAL*, **59**, 804 (1937).

(4) (a) Grignard and Savard, *Bull. soc. chim. Belg.*, **36**, 97 (1927); (b) Grignard and Blanchon, *Bull. soc. chim.*, [4] **49**, 23 (1931).

(5) Kohler and Thompson, *THIS JOURNAL*, **55**, 3822 (1933).

(6) (a) Conant and Blatt, *ibid.*, **51**, 1227 (1929); (b) Blatt and Stone, *ibid.*, **54**, 1495 (1932); (c) Stas, *Bull. soc. chim. Belg.*, **34**, 188 (1925); (d) Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

TABLE I
REACTION OF DIISOPROPYL KETONE WITH GRIGNARD REAGENTS

Grignard reagent	Enoliza- tion	Percentage yields		
		Reduc- tion	Addition	Total
MeMgBr	0	0	95	95
EtMgBr	2	21	77	100
<i>n</i> -PrMgBr	2	30	36	98
<i>i</i> -PrMgBr	29	65	0	94
<i>i</i> -BuMgBr	11	78	8	97
NpMgCl ⁷	90	0	4	94

place. Methyl-diisopropylcarbinol, the result of simple addition, was the only product found. The action of the ketone with ethylmagnesium bromide, however, gives addition, reduction and enolization products. In this case the combined steric hindrance of the ketone and the ethyl Grignard reagent retards the addition reaction sufficiently to make the reduction and enolization reactions possible. When the ketone is allowed to react with *n*-propylmagnesium bromide steric factors retard the addition reaction even more than in the reaction with the ethyl Grignard reagent. Thus it is not surprising that the yield of addition product is much lower while reduction takes place to a larger extent. When isopropylmagnesium bromide was used no addition product was obtained, apparently because steric factors prohibit the addition reaction completely. Enolization and reduction products were the only ones found. This result was predicted by Conant and Blatt.^{6a} Aliphatic carbinols of the triisopropylcarbinol type are still unknown. The action of the ketone with isobutylmagnesium bromide gives addition, enolization and reduction products with the reduction product predominating. The steric hindrance of the isobutyl group is thus shown to be less than that of the isopropyl group. With neopentylmagnesium chloride the ketone gives a very small yield of addition product and 90% of enolization product. No reduction could be detected. This fact is significant.

A study of reduction in these reactions, as summarized in Table I, shows a correlation between the amount of reduction and the primary, secondary or tertiary character of the hydrogen atoms attached to the beta-carbon of the Grignard reagent. If the Grignard reagent has no hydrogen on the beta-carbon no reduction takes place. Among the reagents used in this study which give reduction, the highest yield is given by the isobutyl reagent which has a tertiary hydrogen on

(7) Np is neopentyl, (CH₃)₃CCH₂.

the beta-carbon. The lowest yield is given by the ethyl reagent which has primary hydrogens on the beta-carbon. An intermediate yield is given by the *n*-propyl reagent having two secondary hydrogens in this position. The fact that the amount of reduction given by the isopropyl Grignard reagent is somewhat higher than with the *n*-propyl reagent may be attributed to two causes, (1) steric hindrance prohibits addition entirely thus increasing the possible amount of reduction, and (2) the isopropyl reagent contains two beta-carbons to which are attached six primary hydrogens.

With diisopropyl ketone *t*-butyl Grignard reagent gives 65% reduction.⁸ The *t*-butyl reagent has nine primary hydrogens in the critical beta position.

Although the increase in yield of reduction products in several of the above reactions parallels a decrease in yield of addition products, a comparison of the reactions of the ketone with the isobutyl and the neopentyl reagents shows that the presence of hydrogen on the beta-carbon of the Grignard reagent is necessary for reduction. Thus isobutyl and neopentyl reagents give similar small yields of addition products, but show 78 and 0% reduction, respectively.

The present study covers the following points:
1. Further evidence is given that in the reaction of a particular ketone with aliphatic Grignard reagents the amount of addition is determined by the steric conditions in the alkyl group of the Grignard reagent.

2. It has been shown for the first time that enolization of a ketone by a Grignard reagent is not an inherent property of the ketone. Thus the enolization of a given ketone may vary from 0% to over 90% depending upon the Grignard reagent used.

3. It has been definitely established⁹ that in the reaction of a ketone with an aliphatic Grignard reagent a beta-hydrogen in the latter is necessary for reduction. The extent of the reduction depends on the number and character of such beta-hydrogen atoms.

The authors are greatly indebted to Dr. F. E. Williams for his assistance in this work.

Experimental

The Grignard reagents used in this study were all prepared and titrated¹⁰ according to standard procedures.

(8) Unpublished work by Dr. T. S. Oakwood of this Laboratory.

(9) Cf. ref. 1, pp. 645-646.

(10) (a) Whitmore and Badertscher, *THIS JOURNAL*, **55**, 1559 (1933); (b) Gilman, Wilkinson, Fishel and Meyers, *ibid.*, **45**, 150 (1923).

The diisopropyl ketone used was a selected cut from the fractionation of the crude ketone supplied by the du Pont Co. It had b. p. 123° (733 mm.) and n_D^{20} 1.4002. The products of the reactions of the ketone with the Grignard reagents were poured on cracked ice. The oil layers were steam distilled from the alkaline mixture, dried with anhydrous potassium carbonate or by distillation with benzene and then fractionated. All fractionations were done with packed columns¹¹ of 15-20 theoretical plates. A complete fractionation of the products from ethylmagnesium bromide and diisopropyl ketone is given. The results of the other fractionations are given only in summary form. The refractive indices of known mixtures of the pure products from the reactions studied were plotted. The indices of the enolization product (diisopropyl ketone) and the reduction product (diisopropylcarbinol) were found to be additive as were those of diisopropylcarbinol and the addition product (the tertiary alcohol). Thus, the composition of the intermediate cuts from each fractionation was calculated. Recovered diisopropyl ketone (from enolization) was identified by b. p. (123° at 733 mm.) and n_D^{20} (1.4002) and by its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 94.5-95.5°. Diisopropylcarbinol (from reduction) was identified by b. p. (87.5° at 125 mm.) and n_D^{20} (1.4246) and by its phenylurethan, m. p. and mixed m. p. 94-95°. The structure of the addition products, the tertiary alcohols, was shown by dehydration and ozonolysis¹² of the resulting olefins.

Addition of Diisopropyl Ketone to Methylmagnesium Bromide.—To 2.47 moles of methylmagnesium bromide in anhydrous ether was added 184 g. (1.6 moles) of diisopropyl ketone. The products were worked up as described above. Fractionation of the dried oil layer gave 197.4 g. (1.52 moles) or 95% of methyl-diisopropylcarbinol, b. p. 101° (125 mm.), n_D^{20} 1.4350. No reduction or enolization products could be found. Diisopropyl ketone was also run in a Kohler type Grignard machine¹³ with methylmagnesium bromide. No enolization was found.

Addition of Diisopropyl Ketone to Ethylmagnesium Bromide.—To 2.7 moles of ethylmagnesium bromide in anhydrous ether was added 2.5 moles of diisopropyl ketone. Considerable gas was evolved during the reaction. After addition of the ketone the reaction mixture gave a positive Gilman test.¹⁴ Decomposition and fractionation gave the following cuts: 1, 9.9 g., b. p. 77-83° (125 mm.), n_D^{20} 1.4126; 2-3, 26.1, 83-87° (125 mm.), 1.4225-1.4240; 4-5, 26.0, 87-87.5° (125 mm.), 1.4246; 6, 14.9, 87.5-116° (125 mm.), 1.4372; 7-8, 28.1, 116-117° (125 mm.), 1.4410-1.4438; 9-15, 244.9, 117-117.5° (125 mm.), 1.4440. The composition of the intermediate cuts was determined from their refractive indices as given above. The yields of products may be summarized as follows: diisopropyl ketone, 6.1 g. (0.054 mole) or 2%; diisopropylcarbinol, 63.7 g. (0.54 mole) or 21%; ethyl-diisopropylcarbinol, 280.1 g. (1.95 moles) or 77%, b. p. 117.5° (125 mm.), n_D^{20} 1.4440.

Addition of Diisopropyl Ketone to *n*-Propylmagnesium Bromide.—The diisopropyl ketone, 2.5 moles, was added to 3.43 moles of *n*-propylmagnesium bromide in anhydrous ether. Gas was evolved during the reaction. The reac-

tion mixture, after addition of the ketone, gave a positive Gilman test. Decomposition and fractionation as usual gave the following products: diisopropyl ketone, 6.2 g. (0.054 mole) or 2%; diisopropylcarbinol, 175 g. (1.51 moles) or 60.3%; *n*-propyl-diisopropylcarbinol, 141.7 g. (0.897 mole) or 35.8%, b. p. 132° (125 mm.), n_D^{20} 1.4445.

Addition of Diisopropyl Ketone to Isopropylmagnesium Bromide.—The diisopropyl ketone (two moles) was added to 2.65 moles of isopropylmagnesium bromide in anhydrous ether. The gases evolved during the reaction were collected. Decomposition and fractionation as usual gave the following products: diisopropyl ketone, 66.0 g. (0.58 mole) or 29%; diisopropylcarbinol, 151 g. (1.30 moles) or 65%. No addition product could be found. The total volume of gas collected was 43.6 liters at standard conditions or 97.2% of the theoretical. Analysis of the gas mixture in an Orsat apparatus, using 82.5% sulfuric acid,¹⁵ showed that it contained 63.4% propylene and 33.8% saturated hydrocarbon. Combustion analyses of the saturated hydrocarbon proved it to be propane.

Addition of Diisopropyl Ketone to Isobutylmagnesium Bromide.—The diisopropyl ketone 4.5 moles was added to 5.22 moles of isobutylmagnesium bromide. All of the gas evolved was collected. Decomposition and fractionation as usual gave the following products: diisopropyl ketone, 54.2 g. (0.476 mole) or 10.6%; diisopropylcarbinol, 407.9 g. (3.52 moles) or 78.2%; isobutyl-diisopropylcarbinol, 61.3 g. (0.357 mole) or 7.9%, b. p. 140° (125 mm.) and 118.5° (60 mm.), n_D^{20} 1.4426. The volume of gas collected was 90.3 liters at standard conditions which represents a yield of 98.4% isobutylene and isobutane based on the amounts of ketone and secondary alcohol isolated. Analysis of the gas mixture in an Orsat apparatus, using 82.5% sulfuric acid, showed that it contained 88.4% of isobutylene and 9.6% of saturated hydrocarbon which was identified as isobutane by combustion analysis. The theoretical amounts of isobutylene and isobutane, based on the yields of ketone and secondary alcohol, are 88% and 12%, respectively.

Addition of Diisopropyl Ketone to Neopentylmagnesium Chloride.—Since this reaction involves several departures from the conventional procedure it will be described in detail. In a 2-liter flask, equipped with a dropping funnel, a mercury-seal stirrer and a condenser to which was attached a Gilman trap, an ice-hydrochloric acid trap and a dry-ice-acetone trap in the order named, was placed 46.2 g. (1.9 gram atoms) of magnesium turnings. To this was added 200 cc. of anhydrous ether. Neopentyl chloride,¹⁶ b. p. 84° (733 mm.), n_D^{20} 1.4046, was added slowly. There was no evidence of reaction. After an appreciable amount of the chloride had been added with no reaction taking place, 1 cc. of ethyl bromide was added. The reaction then started and 250 cc. of anhydrous ether was added to the flask and 200 cc. was added to the chloride. A total of 181.1 g. (1.7 moles) of neopentyl chloride was added over a period of two and one-half hours. After all of the chloride was added, warm water was placed around the flask and refluxing and stirring was continued for one hour. The water was removed, the stirrer was stopped and the reaction mixture was allowed to stand overnight. Nothing collected

(11) Whitmore and Lux, *THIS JOURNAL*, **54**, 3451 (1932).

(12) Church, Whitmore and McGrew, *ibid.*, **56**, 176 (1934).

(13) Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927).

(14) Gilman and Schulze, *THIS JOURNAL*, **47**, 2002 (1925).

(15) Hurd and Spence, *ibid.*, **51**, 3353 (1929).

(16) Whitmore and Fleming, *ibid.*, **55**, 4161 (1933).

in the traps. Titration^{10b} showed 1.52 moles of neopentylmagnesium chloride, a yield of 89.4%.

To the neopentylmagnesium chloride, 1.52 moles, was added, over a period of two hours, 231 g. (2.02 moles) of diisopropyl ketone. It took considerable time for the reaction to start. After about 35 cc. of the ketone had been added there was still no evidence of reaction. The reaction flask was heated until refluxing started. More ketone was added at this point, and the reaction between the ketone and the Grignard reagent started. The heat was removed and the rest of the ketone was added slowly. After all of the ketone had been added slow refluxing continued, without heating, for about five hours. The reaction mixture was allowed to stand overnight, and it was then stirred for twelve hours with enough heat to keep it refluxing. A sample of the reaction mixture was removed and a Gilman test¹⁴ was run on it. The test was negative. A check test gave the same result. Neopentylmagnesium chloride, itself, gives a positive Gilman test. The reaction being completed, a 220 cc. fraction was distilled from the reaction flask and carefully collected in a well-trapped system. This fraction contained neopentane. The products were

treated as usual. Fractionation of the oil layer gave the following products: diisopropyl ketone, 213.3 g. (1.87 moles); neopentyl-diisopropylcarbinol, 13.2 g. (0.071 mole) or 4%, b. p. 127° (60 mm.), n_D^{20} 1.4472. No reduction product could be found. The yield of enolization product, after correcting for the excess ketone used, was 90%.

Summary

1. The reactions of diisopropyl ketone with six Grignard reagents have been studied.

2. It has been shown that the enolization of a ketone in the Grignard reaction is not an inherent property of the ketone. The amount of enolization given by a particular ketone depends upon the Grignard reagent used.

3. A relation between the reduction given by the Grignard reagent and the presence and character of beta-hydrogen atoms in the Grignard reagent has been pointed out.

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Abnormal Grignard Reactions. XI.^{1a} Sterically Hindered Aliphatic Carbonyl Compounds. I. Ketones Containing the Methyl-*t*-butylneopentylcarbinyl Group and their Bromomagnesium Enolates

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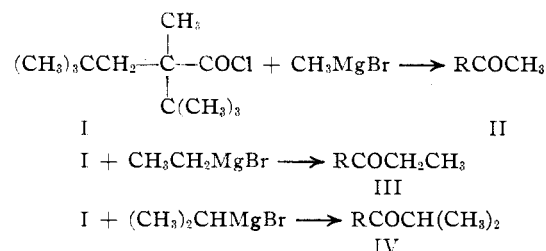
The effect of an adjacent mesityl group on the reactivity of the carbonyl of a ketone has been the subject of considerable interest during recent years. The investigations of this effect have been particularly centered around the behavior of mesityl ketones toward Grignard reagents.² In a few cases other ketones containing an aromatic group have been studied as to steric effects.^{2c} Until the present study no such sterically hindered ketones of the purely aliphatic series have been investigated.

There has now been made in this Laboratory a series of aliphatic sterically hindered ketones containing the methyl-*t*-butylneopentylcarbinyl group. When methyl-*t*-butylneopentylacetyl chloride (I)³ was added to an excess of methylmagnesium bromide, methyl methyl-*t*-butylneopentyl ketone (II) was the only product isolated.

(1) (a) Paper X. Whitmore and George, *THIS JOURNAL*, **64**, 1239 (1942). (b) Present address, Eastern Laboratory, Gibbstown, N. J. (2) (a) Kohler, Fuson and Stone, *THIS JOURNAL*, **49**, 3181 (1927); (b) Kohler and Baltzly, *ibid.*, **54**, 4017 (1932); (c) Fuson, Fisher and Oakwood, *ibid.*, **52**, 5036 (1930); (d) Fuson, *et al.*, *J. Org. Chem.*, **4**, 111 (1939); (e) Smith and Guss, *THIS JOURNAL*, **59**, 804 (1937). These papers contain leading references to all other important work in this field.

(3) Whitmore and Laughlin, *ibid.*, **56**, 1129 (1934).

Ethylmagnesium bromide and isopropylmagnesium bromide reacted with methyl-*t*-butylneopentylacetyl chloride in the same way to give the corresponding alkyl methyl-*t*-butylneopentylcarbinyl ketones (III and IV).



R is the alkyl radical of I.

It is surprising that the action of methyl-*t*-butylneopentylacetyl chloride with isopropylmagnesium bromide gave no methyl-*t*-butylneopentylacetaldehyde or the corresponding primary alcohol. It will be recalled that the addition of this chloride to *t*-butylmagnesium chloride gave only methyl-*t*-butylneopentylacetaldehyde and its primary alcohol, with the former predominating.⁴

These ketones, like acetomesitylene,² show

(4) Whitmore, *et al.*, *ibid.*, **63**, 643 (1941).