[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Factors Determining the Course and Mechanisms of Grignard Reactions. II. The Effect of Metallic Compounds on the Reaction between Isophorone and Methylmagnesium Bromide

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In an earlier study in this Laboratory[2] it was demonstrated that small amounts of certain metallic halides profoundly influence the course of the reaction between isobutylmagnesium bromide and benzophenone. The effect of such traces of metallic halides upon the course of reactions with Grignard reagents has now been investigated for many classes of organic compounds. This paper describes the remarkable effect on the reaction between isophorone and methylmagnesium bromide.

Reaction of Isophorone and Methylmagnesium Bromide.—The reaction of isophorone with methylmagnesium bromide has not been studied previously. However, many other additions of Grignard reagents to the carbonyl group of conjugated cyclic unsaturated ketones are recorded in the literature. Thus, Kohler[3] stated that diphenylhexenone and ethylmagnesium bromide yield 80% of the 1,2 and 20% of the 1,4 addition product. Carvone appears to behave in a similar manner.[4] On the other hand, benzaldiketohydrindene[5] gives exclusively the 1,4-addition product and 7-ketocholesteryl acetate[6] exclusively the 1,2 addition product when treated with various Grignard reagents.[7]

The above representative examples have been selected from a comprehensive collection of data on addition of Grignard reagents to α,β unsaturated ketones and aldehydes. However, an exhaustive literature review appears, at this time, superfluous. Suffice to say that no worker has ever been able to alter appreciably (for the same Grignard reagent) the ratio of the 1,2 and 1,4 addition products. Furthermore, it must be admitted, in spite of the very large amount of work done in this field, that no successful correlation of the findings has been made. Predictions based on the hypotheses in vogue are so uncertain as to be practically useless.[8]

Our experience with isophorone and methylmagnesium bromide confirms the results obtained by others with similar substances. The Grignard reagent adds to the carbonyl group to give the tertiary alcohol Δ^1-1,3,5,5-tetramethylcyclohexene-3-ol (I) and its dehydration product 1,3,5,5-tetramethylcyclohexadiene-1,3 (II). The total yield of the two products is uniformly about 91%. Strikingly different results are obtained, however, when isophorone is added to methylmagnesium bromide mixed with about one mole per cent. of a metallic halide. The structures of the major products isolated are indicated below, and a complete statement of the experimental results is given in Table I.

Obviously, the mechanism of the reaction of the Grignard reagent with the unsaturated ketone is altered by the addition of these minute amounts of metal halides. Previously, it has been shown that when certain metal halides are added to a Grignard reagent RMgX (where R is an aromatic radical) the hydrocarbon RR is formed.[9] But to produce this result stoichiometric amounts of the metal halide must be used. This reaction thus differs essentially from the ones here described, which are significant because of the minute amounts of the metal halides necessary to produce them. Furthermore, the effects noted have to do with reactions between the Grignard reagent and other molecules rather than with the reaction between two molecules of a Grignard reagent itself.

As indicated in Table I, whenever 1,2 addition predominates, the total yield of addition products (carbinol and diene) remains fairly constant at

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[1] The authors wish to express to the Sherwin-Williams Company of Cleveland, Ohio, their appreciation for aid which made this work possible.

[2] Kharasch, Kleiger, Martin and Mayo, THIS JOURNAL, **63**, 2305 (1941).

[3] Kohler, *Am. Chem. J.*, **37**, 369 (1907).

[4] Kohler, *ibid.*, **37**, 369 (1907); Rupe and Liechtenhan, *Ber.*, **39**, 1119 (1906); Klages and Sommer, *ibid.*, **39**, 2309 (1906).

[5] Kohler, *Am. Chem. J.*, **37**, 369 (1907).

[6] Bann, Heilbron and Spring, *J. Chem. Soc.*, 1274 (1936); Weinhouse and Kharasch, *J. Org. Chem.*, **1**, 491 (1936).

[7] The ratio of the 1,2 and 1,4 addition products of Grignard reagents to α,β unsaturated ketones does not depend upon which geometric isomer is employed. Colonge, *Bull. soc. chim.*, [5] **3**, 413 (1936); [5] **2**, 754 (1935).

[8] For a summary of the literature on the addition of Grignard reagents to α,β unsaturated ketones see Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., Vol. I, 1938, pp. 581–584, 598, 604–605, 1690.

[9] Supniewski, *Roczniki Chem.*, **7**, 172 (1927); Kharasch and Isbell, THIS JOURNAL, **52**, 2919 (1930); Gardner, Joseph and Gollub, *ibid.*, **59**, 2583 (1937).

TABLE I

EFFECTS OF METALLIC CATALYSTS ON THE REACTION BETWEEN ISOPHORONE AND PURE METHYLMAGNESIUM BROMIDE

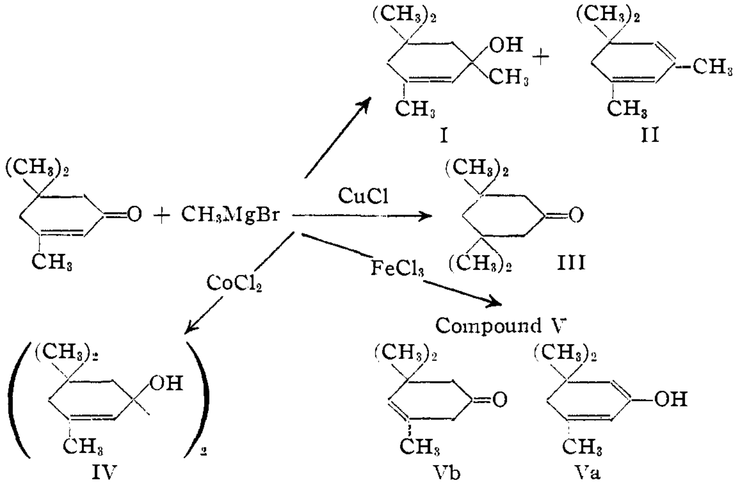
Mole % of metal or metal salt added	1,2-Addition, % Diene	1,2-Addition, % Carbinol	Compound V, %	Pinacol, %	1,4-Addition, %	Total, %
None	48.2	42.6	..	...	...	90.8
None[a]	23.6	67.2	..	...	...	90.8
0.2 $FeCl_3$	8.85	5.7	66.4	5.26	...	86.2
1.0 $FeCl_3$	2.2	...	81.6	9.46	...	94.0
1.0 CuCl	6.96	...	..	...	82.5	89.5
1.0 $NiCl_2$	7.3	22.6	..	61.1	4.73	96.0
1.0 $CoCl_2$[b]	...	...	16.1	78.5	...	94.6
1.0 $CoCl_2$[c] Unfiltered	20.0	9.6	..	67.0	...	96.6
1.0 $CoCl_2$[c] Filtered	12.2	13.8	..	73.0	...	99.0
20 Excess Mg	55.5	22.7	..	1.45	...	80.0
1.0 Copper powder	78.0	...	..	...	8.0	86.0
1.0 AgCl	57.7	35.0	..	...	...	92.7
1.0 $PbCl_2$	85.7	...	..	Trace	...	86.0
1.0 $CrCl_3$	56.8	27.4	..	Trace	...	87.0
1.0 VCl_2	33.1	56.7	..	...	...	89.8
1.0 $MnCl_2$	56.0	28.5	..	...	...	84.5
Ordinary Mg[d]	85.5	4.35	..	...	1.45	91.3

[a] Grignard solution added to the isophorone. In all other runs, the ketone was added to the Grignard reagent. [b] $CoCl_2$ added to the filtered Grignard solution. [c] $CoCl_2$ added at the beginning of the Grignard preparation; one-half of the resulting Grignard solution was filtered. [d] Eastman Kodak Co. grade magnesium ribbon.

about 90%. Under these conditions, there are, however, significant differences in the relative yields of carbinol and diene which make up the total.

The carbinol (I), namely, Δ^1-1,3,5,5-tetramethylcyclohexene-3-ol, is stable only when pure and preserved in a sealed tube; otherwise within a few weeks at room temperature it is converted into the diene by the loss of water. This dehydration can be accomplished by distillation of the carbinol at ordinary pressure, or, still more satisfactorily, by distillation over a small amount of anhydrous potassium bisulfate.

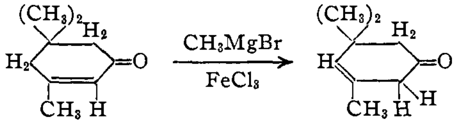
The diene structure (II) (1,3,5,5-tetramethylcyclohexadiene-1,3) is assigned the compound formed from the carbinol because of the well established tendency of carbinols like (I) to dehydrate in the manner indicated. The substance absorbs bromine in the cold, and the crystalline addition product decomposes at room temperature, evolving large quantities of hydrogen bromide. The supposed diene forms an adduct with maleic anhydride and with α-naphthoquinone. It is stable when preserved *in vacuo*, but slowly becomes colored in air. The concomitant increase in viscosity of the solution indicates considerable polymerization.



The structure of the product formed by the 1,4 addition of methylmagnesium bromide to isophorone, namely, 3,3,5,5-tetramethylcyclohexanone (III) has not been established by independent synthesis, but there can be little doubt as to the correctness of the structure indicated. Thus, the analyses of the substance and of its oxime, semicarbazone, *p*-nitrophenylhydrazone and 2,4-dinitrophenylhydrazone agree well with the calculated values. The fact that the substance is unaffected by cold neutral 5% potassium permanganate is further corroboration of the structure assigned.

The structure of compound (II) has been confirmed by the fact that it melts at the same temperature as does the compound which Hess and Munderloh[10] obtained by reduction of isophorone with sodium amalgam, and that the two substances do not depress each other's melting points.

On the basis of chemical data, we believe compound V to be either the enol form of isophorone V(a) or the isomer of isophorone in which the double bond is in β,γ position—namely, Δ^3-3,5,5-trimethylcyclohexenone (Vb). We are fully aware that previous claims for the isolation of enol forms of ketones[11] have been questioned and presumably disproved.[12] Yet, in the light of the results recorded in this paper, a summary dismissal of the claims of Grignard and Blanchon is perhaps unjustified. Much further work in this field is necessary. On the other hand, if compound V is in reality Vb then a remarkable rearrangement takes place when isophorone is treated with methylmagnesium bromide in the presence of two mole per cent. of ferric chloride. No example of this type of tautomerism appears to be on record. However, a closely related, but not necessarily pertinent, series of examples is the one carefully studied by Linstead and co-workers.[13] These investigators showed that the cyclohexylidene and cyclohexenylacetic acids can be converted into one another by chemical agents and by heat. A similar interconvertibility was noted for the ketones corresponding to the above acids. It was further shown that nuclear methylation of the cyclohexane ring displaces the equilibrium toward the β,γ form. It would, therefore, be in accord with experience if in isophorone (containing three methyl groups) the double bond should show a great tendency to migrate away from the carbonyl group. The isomer thus formed Vb should be quite stable.



The evidence for the existence of compound V (as distinct from isophorone) is as follows:

(1) Analyses for carbon and hydrogen indicate an empirical formula $C_9H_{14}O$, the same as that of isophorone. The molecular weight in triphenylmethane and in camphor is 150 as compared with a calculated 138. Because of the behavior indicated in (3) this value is acceptable.

(2) The physical properties of compound V are different from those of isophorone.

	B. p., °C.	B. p. (atm.), °C.	n^{20}_D	d^{20}_4
Isophorone	69–69.3 (5 mm.)	210–211	1.4775	0.9215
Compound V	38–38.4 (4 mm.)	181–185	1.4620	0.9083

(3) Compound V absorbs oxygen much faster than isophorone. This great avidity for oxygen explains our early difficulties in securing satisfactory carbon and hydrogen analyses. Constant results were obtained only from samples distilled and kept in high vacuum. The analyses of samples distilled and kept in air for six days were about 2% low in carbon.

(4) Compound V slowly changes into isophorone at room temperature. The rate of change is accelerated slightly by a trace of acetic acid and considerably by potassium bisulfate. In the presence of the latter reagent the change at 150° is complete within an hour. At ordinary pressures Compound V boils at 181–185° and its index of refraction is n^{20}_D 1.4620. However, when distilled over potassium bisulfate, it boils at 210–211°. The index of refraction of the distillate is n^{20}_D 1.4775. These latter constants correspond to those of pure isophorone.

The index of refraction of a mixture of Compound V and pure isophorone is a linear function of its composition. When the pure compound V is mixed with about 20% of its weight of potassium bisulfate and heated to 150°, the conversion to isophorone can be followed by the change in refractive index. The change is complete in about sixty minutes (Fig. 1). Since the curve is essentially a straight line, a reaction of zero order is indicated. This order suggests that the rapid transformation of compound V to isophorone takes place at the surface of the catalyst. These conclusions have been further confirmed by a study of the transformation at room temperature. The graphs (Fig. 2) show the conversion of compound V at ordinary temperatures when pure, and when mixed with either 1% acetic acid or 2% of potassium bisulfate. A more comprehensive study of these phenomena is now under way in this Laboratory.

(5) The possibility that compound V is in

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[10] Hess and Munderloh, *Ber.*, **51**, 377 (1918).

[11] Grignard and Blanchon, *Roczniki Chem.*, **9**, 547 (1929); *Bull. soc. chim.*, [4] **49**, 23 (1931).

[12] Kohler and Thompson, THIS JOURNAL, **55**, 3822 (1933); Hückel and Radszat, *J. prakt. Chem.*, **140**, 247 (1934).

[13] Linstead, *J. Chem. Soc.*, 1603 (1930). For an exhaustive review and references to this type of tautomerism see *Ann. Reports*, 108 (1931). An unsubstantiated claim that isophorone is a mixture of two isomeric products Va and Vb is made by Wolff, *Ann.*, **322**, 379 (1902).

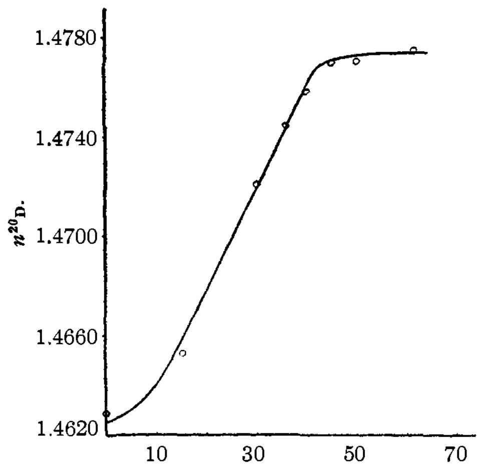

Fig. 1.—Isomerization of compound V to isophorone at 150° in the presence of potassium bisulfate.

reality the alcohol Δ^2-3,5,5-trimethylcyclohexenol formed by reduction of the isophorone by the methylmagnesium bromide, was disproved by comparison of the two substances. Isophorone was reduced to the alcohol by aluminum isopropylate.

	B. p., °C.	n^{20}_D	d^{20}_{20}
Compound V	38–38.4 (4 mm.)	1.4620	0.9083
Δ^2-3,5,5-Trimethylcyclohexenol	69 (5 mm.)	1.4717	0.9144

Furthermore, the alcohol is transformed by heating with potassium bisulfate to a diene. This behavior is in marked contrast to that of compound V which under similar conditions is not dehydrated but transformed to isophorone. The alcohol does not react with carbonyl reagents; compound V, as indicated below, reacts with semicarbazide and hydroxylamine.

(6) A comparison of the reactivity of compound V and isophorone toward semicarbazide was carried out under the following conditions. Two ml. of each of the substances was added to a solution of 2 g. of semicarbazide hydrochloride and 3.0 g. of potassium acetate in 20 ml. of water; sufficient alcohol (20 ml.) was then added to produce a homogeneous solution. Compound V gave a copious precipitate of the semicarbazone immediately, whereas one to three hours was required for the formation of a precipitate from isophorone. Both semicarbazones melt at 186–187°; they do not depress each other's melting points.[14]

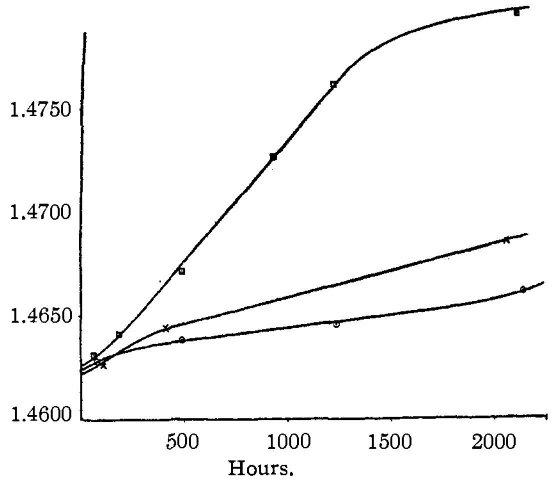

Fig. 2.—Isomerization of compound V to isophorone at 25°: ⊡, compound V + 2% KHSO$_4$; ⊙, compound V; ×, compound V + 1% acetic acid.

(7) The evidence thus far adduced is strongly in favor of the existence of a stable isomeric form of isophorone. It is possible that this isomer is the enol. But since no such stable enols of cyclic ketones or cyclic unsaturated ketones have hitherto been known, the evidence for the first case should be overwhelming. There are items which, at first glance, might be considered to exclude Va (the enol) as a possibility. In the first place, compound V does not give a color with either aqueous or alcoholic ferric chloride. However, it is well established that not all enols give color reactions under these conditions. Second, both enol and keto forms react slowly with hydroxylamine. Each of the oximes thus produced melts at 78–79°, but an equimolecular mixture of the two melts at 50–52°. These two oximes may however be *syn* and *anti* forms of isophorone oxime. There is, therefore, no really conclusive evidence against the existence of a stable enol form of isophorone. The recent work of Mel'nikow and Rokitskaya[15] dealing with the effect of methyl groups in the 3-position on the enolization of alicyclic ketones is of interest in this connection.

On the other hand, the experiments presented are compatible with the hypothesis that compound V and isophorone differ with respect to the position of the double bond in the ring. We in fact favor this view, which is fairly well supported by molecular refraction of compound V. The experimental value of this constant is 41.75, the value calculated for V(b) is 41.17. The slight ex-

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[14] Compound V is to be represented as Vb; then no assignment of structure to the semicarbazones is possible on the basis of chemical evidence. The slow formation of the semicarbazone from isophorone and its practically instantaneous formation from compound V might indicate that the rate determining step is the rate of tautomerization of isophorone to compound V.

[15] Mel'nikow and Rokitskaya, *J. Gen. Chem.* (U. S. S. R.), **8**, 1369 (1938), also **7**, 2738 (1937).

cess of the observed over the calculated value is, however, not surprising. For 3,3,5,5-tetramethylcyclohexanone the calculated value is 46.19; the observed 46.60. Probably the atomic refraction of oxygen is somewhat larger in cyclic than in straight chain ketones. Calculation of the molecular refraction of isophorone (in either the enol or the keto form) is unsatisfactory because of the unknown correction for conjugation which must be applied.

The data at hand do not, however, permit a final decision between formulas V(a) and V(b). Investigation of the absorption spectrum seems to be the best way of deciding the question since the infrared should reveal the presence of an hydroxyl group, and the ultraviolet should show the presence of conjugation. Spectrographic work is now under way.

Numerous other questions also remain unanswered:

(a) Is isophorone a pure substance (enol or keto), a tautomeric enol-keto mixture, or a tautomeric mixture of two keto forms?

(b) If it is a tautomeric mixture what is the value of the equilibrium constant, and how is the equilibrium affected by changes of temperature, solvent, etc.?

Further work on these points is contemplated.

Experimental

Materials.—The magnesium used in this work was the 99.98% Radio grade Mazlo rolled ribbon supplied by the Aluminum Company of America. The impurities present are claimed to be 0.01–0.015% of combined iron and aluminum with the balance taken up by silicon and traces of copper and nickel.

Isophorone, secured from the Carbide and Carbon Corporation, was carefully fractionated, first through a 24-inch column packed with Raschig rings and finally through a 40 cm. Vigreux column under diminished pressure: b. p. 69–69.3° (7 mm.), $n^{20}{}_D$ 1.4775; $d^{20}{}_{20}$ 0.9215; semicarbazone m. p. 186–187°.

The silver chloride and cuprous chloride were freshly prepared and dried over phosphorus pentoxide *in vacuo*. The ferric chloride was the usual anhydrous salt of analytical grade, and the vanadous chloride was a sample supplied by the Vanadium Corporation of America. The manganese, chromic, nickelous, and cobaltous chlorides were prepared from their hydrated forms by careful heating in a stream of dry hydrogen chloride. A stream of dry nitrogen was then employed to sweep out the excess hydrogen chloride and the anhydrous salts were preserved in a vacuum desiccator over phosphorus pentoxide.

Preparation of the Grignard Reagent.—The Grignard reagents were prepared in a three-necked flask equipped with a mercury-sealed stirrer, reflux condenser, a dropping funnel, and an inlet tube extending to the bottom of the flask for methyl bromide.

In a typical run, 40 g. of pure magnesium was covered with 230 ml. of dry ether and methyl bromide gas passed into the solution. The reaction commenced at once. The methyl bromide was introduced at a rate to keep the ether refluxing. More ether was added at the end of fifteen minutes (230 ml.) and one hour (160 ml.). The magnesium was all dissolved in seventy to eighty minutes from the starting time but refluxing and stirring were continued ten minutes longer.

The Grignard reagent was filtered (under nitrogen pressure) and collected in a graduated dropping funnel, and the flask washed with sufficient ether to make a total of 770 ml. Samples of 4 to 5 ml. of the Grignard reagent were used for analyses.

Addition of Isophorone to Methylmagnesium Bromide.[16]—(Pure magnesium was used in the preparation of the reagent.) To 390 ml. of 2.09 molar Grignard reagent[15] placed in a 1-liter, round-bottomed flask equipped with a mercury-sealed stirrer, a thermometer, a dropping funnel and a reflux condenser, and cooled to 5°. Isophorone (94.5 g., 0.685 mole) diluted with 135 ml. of ether was added in the course of one hour. The mixture was stirred and maintained at 10–12° during the addition. At the end of that time, a semi-solid white addition complex had separated. The mixture was heated for an hour, after which it was permitted to stand overnight. The reaction mixture was decomposed with 380 g. of chipped ice and 49 g. of glacial acetic acid and the ether layer separated. The water layer was extracted with 75 ml. of ether and the two extracts combined. The ether extracts were washed twice with sodium carbonate solution and twice with water, and dried over anhydrous sodium carbonate. Upon filtration, the ether was removed on a water-bath and the residual colorless oil distilled *in vacuo* through a 40-cm. Vigreux column.

Two fractions were obtained: (a) 45 g. (42.6%) was identified as Δ^1-1,3,5,5-tetramethylcyclohexene-3-ol (I); b. p. 59–60° at 5 mm.; $n^{20}{}_D$ 1.4690; $d^{20}{}_{20}$ 0.9075; *M*R calcd., 47.24; found, 47.30. *Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.92; H, 11.68. Found: C, 77.81; H, 11.82.

(b) 45 g. (48.2%) which was identified as 1,3,5,5-tetramethylcyclohexadiene-1,3 (II); b. p. 24–25° at 7 mm., 151–155° at 760 mm.; $n^{20}{}_D$ 1.4698; $d^{20}{}_{20}$ 0.8152; *M*R calcd., 46.34; found, 46.54.

Anal. Calcd. for $C_{10}H_{16}$: C, 88.23; H, 11.77. Found: C, 88.64; H, 11.13.

Maleic Anhydride Adduct of II.—To 13.6 g. (0.1 mole) of the diene was added a solution of 9.8 g. (0.1 mole) of maleic anhydride in 11 ml. of benzene. The mixture was heated to 47°. A deep yellow color developed and the heat of the reaction raised the temperature of the mixture to 90°. The reaction mixture was then refluxed for thirty minutes during which time the yellow color faded. Upon cooling a mass of crystals formed which were collected upon a filter and crystallized twice from a mixture of petroleum ether and benzene (3:1), yield 18 g. (77%), m. p. 98–99°.

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[16] In all experiments a 19% mole excess of Grignard reagent over isophorone was used.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.96; H, 8.03.

The dibasic acid corresponding to the above anhydride was obtained by dissolving the anhydride in sodium carbonate solution, and acidifying with hydrochloric acid. Upon crystallization from dilute alcohol it melted at 154–155°.

α-Naphthoquinone Adduct of II.—To 5 g. of α-naphthoquinone was added 10 ml. of the diene in 20 ml. of 95% alcohol. The mixture was heated for three hours, and the hot solution filtered. Upon cooling the filtrate in an ice-bath, a copious mass of leaflets formed which were collected on a filter and crystallized twice from methanol; colorless needles, m. p. 133.5–134.5°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.62; H, 7.48. Found: C, 81.18; H, 7.62.

An experiment was carried out in which the Grignard reagent was added to the cold ethereal solution of isophorone. The only change in products obtained by this reversal of procedure was in the relative amounts of diene (II) and carbinol (I) obtained. An experiment carried out as above, except substituting ordinary Eastman Kodak Co. magnesium for the pure grade, gave the diene in 85% yield. In the experiment employing 20 mole per cent. excess magnesium, the latter was added directly to the unfiltered Grignard reagent and the reaction carried on from this point as usual.

When a salt or metallic catalyst was used in an experiment, the necessary amount of catalyst (1 mole %) was added to the filtered Grignard solution at room temperature, and the mixture stirred forty-five minutes before it was cooled and the isophorone added. The procedure, otherwise, was made to conform as closely as possible to that of the control given above. The individual variations produced by the addition of these catalysts are as follows:

Addition of Isophorone to Methylmagnesium Bromide in the Presence of Cuprous Chloride (1 mole %).—The addition of the cuprous chloride to the clear, filtered Grignard solution produced a bluish-green color. Upon working up the reaction product, three fractionations gave 6.5 g. (6.9%) of 1,3,5,5-tetramethylcyclohexadiene-1,3 (II) (identified by the maleic anhydride adduct) and 84 g. (82.5%) of 3,3,5,5-tetramethylcyclohexanone (III), b. p. 59–61° at 5.5 mm.; 196–197° at 760 mm.; m. p. 11–12°; n^{20}_D 1.4520; d^{20}_{20} 0.8914; *M*R calcd. 46.19, found 46.60.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.92; H, 11.68. Found: C, 77.48; H, 11.71.

A number of derivatives of III were prepared.

(a) **Oxime.**—The oxime forms readily upon heating (forty minutes) of III, hydroxylamine hydrochloride, sodium hydroxide and alcohol. Upon cooling long needles separate, m. p. 144–145°. It can be crystallized from 60% alcohol.

(b) **Semicarbazone, m.** p. 217–218° (dec.).

Anal. Calcd. for $C_{11}H_{21}N_3O$: C, 62.55; H, 9.95; N, 19.89. Found: C, 63.09; H, 9.69; N, 20.15.

(c) **2,4-Dinitrophenylhydrazone,** yellow needles, m. p. 133–134° from 95% ethanol.

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.48; H, 6.59; N, 16.78. Found: C, 57.87; H, 7.15; N, 17.07.

(d) ***p*-Nitrophenylhydrazone,** yellow needles from ethanol, m. p. 176.5–177.2°.

Anal. Calcd. for $C_{16}H_{23}N_3O_2$: C, 66.43; H, 7.95; N, 14.53. Found: C, 66.68; H, 7.70; N, 14.28.

Addition of Isophorone to Methylmagnesium Chloride in the Presence of Ferric Chloride (1 mole %).—The addition of the ferric chloride produced an immediate black-colored solution and considerable heat evolution. The first fractionation of the reaction product left a residue of 9 g. (9.5%) of pinacol. Three fractionations of the distillate through a 40-cm. Vigreux column gave less than 1% of the diene and 77 g. (81.6%) of the compound V; b. p. 32° at 3.5 mm., 181–185° at 750 mm., n^{20}_D 1.4620, d^{20}_{20} 0.9083. It is important to keep the apparatus free of oxygen during the preparation and particularly during the distillation of this substance.

Anal. Calcd. for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 78.14; 78.40; H, 9.78; 9.82.

(a) **Semicarbazone.**—The semicarbazones described in this paper were usually prepared by the procedure described in detail for the semicarbazone of Compound V.

To a mixture of 2 g. of semicarbazide hydrochloride, 3 g. of potassium acetate and 20 ml. of water, 2 ml. of pure compound V was added. A precipitate formed instantaneously. After standing for twenty-five minutes, the crystals were collected on a filter and crystallized from dilute ethanol (m. p. 186–187°).

Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.53; H, 8.72; N, 21.53. Found: C, 61.84; H, 8.37; N, 21.29.

This semicarbazone was compared with a sample of the semicarbazone of isophorone which melted at 186–187°[17] and gave the following analyses.

Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.53; H, 8.72; N, 21.53. Found: C, 61.61; H, 8.38; N, 21.01.

A 50:50 mixture of the two semicarbazones melted sharply at 186–187°, indicating their identity. Although the semicarbazones of V and isophorone are identical there are significant differences in their rates of formation. Thus, under the conditions described, the former is obtained almost at once, while a lapse of four hours is required before any precipitation is noted with isophorone.

The experiment using 0.2 mole per cent. of ferric chloride was carried out essentially as above and the results are recorded in Table I.

The Addition of Isophorone to Methylmagnesium Bromide in the Presence of Nickelous Chloride (1 mole %).—The addition of nickelous chloride to the Grignard solution produced a dark red brown color and considerable heat. Upon working up the product, 3 g. of pinacol separated from the ether solution. The rest of the reaction product was subjected to distillation *in vacuo* through a 40-cm. Vigreux column. After 34 g. of liquid distillate had been collected at 6–10 mm., the residue suddenly crystallized while the flask was still in the hot oil-bath. This residue amounted to 52.5 g. and consisted entirely of pinacol (IV), m. p. 161–162°. The total yield of pinacol was 61%.

Fractionation of the distillate yielded 6.5 g. (7.3%) of 1,3,5,5-tetramethylcyclohexadiene-1,3 (II) (identified as

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[17] Knoevenagel, *Ann.*, **297**, 185 (1897), gives 186–187° also as the melting point of isophorone semicarbazone.

the maleic anhydride adduct) and 27.5 g. of a mixture of tertiary alcohol (I) and 3,3,5,5-tetramethylcyclohexanone (III). Through semicarbazone separation, this fraction was shown to consist of 4.7 g. (4.7%) of ketone and 22.7 g. (22.6%) of tertiary alcohol.

Addition of Isophorone to Methylmagnesium Bromide in the Presence of Cobaltous Chloride (1 mole %).—The addition of cobaltous chloride to the filtered Grignard solution produced the same effects as the ferric and nickelous chlorides, that is, a dark colored solution and gentle refluxing of the ether. After the isophorone was added, the reaction mixture was worked up as described previously. Only the pinacol (IV) (79%) and compound V (16%) were isolated under these conditions. The effect produced by alterations in the order of addition of the cobaltous chloride are indicated in Table I.

Preparation of Δ^2-3,5,5-Trimethylcyclohexenol (VI).—A solution of aluminum isopropylate was prepared by dissolving 18 g. of aluminum turnings in 900 ml. of isopropanol, with the aid of 0.07 g. of mercuric chloride. After adding 150 g. (1.08 moles) of isophorone, the mixture was heated for seven hours. At the end of that time the excess isopropanol was removed under reduced pressure and the residue decomposed with water and steam-distilled. The upper layer of the distillate was extracted with 300 ml. of ether, washed once with saturated sodium chloride solution, and dried over anhydrous sodium carbonate.

Removal of the ether on the water-bath left a colorless oil which distilled entirely at 63–68°, at 5.5 mm. This mixture (140 g.) of isophorone and secondary carbinol could not be separated readily by distillation and was therefore treated with benzoyl chloride.

Preparation of the Benzoate of VI.—132 g. of the above mixture was dissolved in 500 ml. of dry pyridine, the mixture cooled (15°) and 160 g. of benzoyl chloride slowly added to it. The whole mixture was warmed to 50° in a water-bath (thirty minutes), then poured into 2 liters of water and the heavy oil which settled to the bottom was separated by decantation. The oil was taken up in 400 ml. of ether and the decanted water layer extracted once with 100 ml. of ether. The combined ether solutions were washed successively with 5% hydrochloric acid, then 5% sodium carbonate solution, and finally with water. After drying over sodium sulfate, the ether was removed on the water-bath, and the residual oil distilled under reduced pressure. The first fraction, b. p. 63–98°, $n^{20}\text{D}$ 1.4775, consisted of 51 g. and represented a 39% recovery of the isophorone. The benzoate of VI (129 g.) distilled at 134–136° (5 mm.), $n^{20}\text{D}$ 1.5198, with slight decomposition. There was a residue of 36 g. of heavy yellow oil (b. p. 150–151°, 4.5 mm.; $n^{20}\text{D}$ 1.5698) which presumably is a condensation product of the benzoate and of the diene resulting from decomposition of the benzoate. It was not further investigated. The benzoate was not redistilled. The yield of 129 g. represents 74 g. of Δ^2-3,5,5-trimethylcyclohexenol (VI), a yield of 48.6% (or 73.5% considering the isophorone recovered).

Saponification of the Benzoate of (VI) and Isolation of (VI).—To 73 g. of the benzoate was added a solution consisting of 30 g. of sodium hydroxide in 300 g. of ethanol and 100 g. of water, and the mixture refluxed for four hours. The ethanol was removed from the water-bath and the residue poured into 800 ml. of water. The carbinol was extracted with three 125-ml. portions of ether. After washing once with water and drying over sodium carbonate, the ether was removed on the water-bath and the residual colorless oil distilled *in vacuo* through a 40-cm. Vigreux column. The product was pure carbinol (36 g.). Redistillation did not change the refractive index; b. p. 69°, 5 mm.; 74.8°, 8 mm.; $n^{20}\text{D}$ 1.4717; $d^{20}{}_{20}$ 0.9144.

Anal. Calcd. for $C_9H_{16}O$: C, 77.14; H, 11.42. Found: C, 77.02; H, 11.21; M_R calcd. 42.62; found 42.82.

***p*-Nitrobenzoate of (VI).**—The *p*-nitrobenzoate was prepared by dissolving the carbinol in pyridine and adding *p*-nitrobenzoyl chloride. After warming for five minutes the mixture was poured into water and the solid which separated collected on a filter. After three crystallizations from dilute methanol, colorless plates were obtained, m. p. 68.5–69.5°.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.50; H, 6.50; N, 4.83.

Upon heating 10 g. of Δ^2-3,5,5-trimethylcyclohexenol with 10 g. of anhydrous potassium bisulfate for three hours at 120°, dehydration occurred, leading to 6 g. of diene (b. p. 132–135°). The latter readily reacted with maleic anhydride forming a resinous product which was not investigated.

Reaction of Isophorone and Methylmagnesium Bromide in the Presence of Metallic Copper.—To 400 ml. of the filtered 1.96 molar Grignard solution (0.785 mole of CH_3MgBr) was added 0.50 g. (1 mole %) of copper bronze. No visible reaction seemed to take place. The mixture was stirred forty-five minutes at room temperature, then cooled to 0°, and 91.2 g. (0.660 mole) of isophorone in 137 ml. of ether added in the course of forty-six minutes. The temperature was maintained at 3° during the addition. From this point on the procedure, including decomposition and working up of the product, was identical to that described above.

Vacuum distillation of the residual oil gave 70 g. of the diene (II) resulting from 1,2-addition. The diene was practically pure after the first distillation and upon redistillation at atmospheric pressure boiled at 151–155°. It was identified as the maleic anhydride adduct; m. p. 98–99°. A yield of 70 g. was obtained (78%).

There was also obtained 9 g. of pure 3,3,5,5-tetramethylcyclohexanone, b. p. 47–51°, at 3 mm., resulting from 1,4-addition. This substance readily formed a yellow 2,4-dinitrophenylhydrazone, m. p. 133–134°; when this was mixed with authentic 2,4-dinitrophenylhydrazone (from the previous cuprous chloride experiment) the melting point was unchanged. The yield represents 8% of 1,4-addition.

Summary

1. The reaction between pure methylmagnesium bromide and isophorone leads entirely to 1,2-addition. The course of the reaction is practically unaffected by silver chloride, vanadous chloride, manganous chloride, or chromic chloride in concentrations of 1.0 mole per cent. The following metal halides had a pronounced effect when added to the Grignard reagent.

a. Cuprous chloride in a concentration of 1.0 mole per cent. leads almost entirely to 1,4-addition.

b. Ferric chloride in a concentration of 1.0 mole per cent. leads mainly to the formation of an isomer of isophorone, probably Δ^3-3,5,5-trimethylcyclohexenone, and a small amount of the pinacol of isophorone.

c. Cobaltous chloride in a concentration of 1.0 mole per cent. gave mainly the pinacol of isophorone. Nickelous chloride gave 60% of the pinacol, and appreciable amounts of 1,2- and 1,4-additions as well.

2. The unsaturated alcohol Δ^2-3,5,5-trimethylcyclohexenol has been prepared by reduction of isophorone by means of aluminum isopropylate.

3. A number of new compounds and many derivatives have been prepared. This work on the effect of metal halides on the course of Grignard reactions is being extended into other systems in which the double bond is conjugated with an aldehyde or ketone group (cyclic and otherwise) and in other reactions involving condensations and reductions with Grignard reagents.

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Factors Determining the Course and Mechanisms of Grignard Reactions. III. The Effect of Metallic Halides on the Reaction between Benzophenone and Methylmagnesium Bromide

BY M. S. KHARASCH AND FRANK L. LAMBERT[1]

Methylmagnesium bromide reacts with benzophenone to yield only one product, namely, diphenylmethylcarbinol.[2a] This reagent is thus unlike many other Grignard reagents which usually reduce benzophenone to benzhydrol.[2b] However, in view of the recent results in this Laboratory on the effect of metallic halides on the interaction of Grignard reagents with many classes of organic compounds,[3] a reinvestigation of this reaction appeared in order. Table I shows that with the aid of minute quantities (2 mole %) of some metallic halides the course of the reaction can be altered to yield either benzopinacol or diphenylmethylcarbinol in quantitative yields.

TABLE I

EFFECT OF METALLIC HALIDES ON THE REACTION OF BENZOPHENONE WITH METHYLMAGNESIUM BROMIDE

2 Mole % of metallic halide or metal used	Yield, % of calcd. Benzopinacol	Yield, % of calcd. Diphenylmethyl carbinol
Mg	0	95
Cu_2Cl_2	0	93
$MnCl_2$	0	93
$FeCl_3$	65	21
$CoCl_2$	93	2

Experimental

The benzophenone was obtained from the Eastman Kodak Company, Sublimed magnesium[3a] and radio grade magnesium[3b] were used in the preparation of the Grignard. Cuprous chloride, manganous chloride, and cobaltous chloride were reagent grade salts; the latter two were dehydrated by heating. The anhydrous ferric chloride was prepared by passing chlorine over standardizing grade iron wire and drying the product over sodium hydroxide.

Preparation of the Grignard Reagent.—The methylmagnesium bromide was prepared in a three-necked flask equipped with mercury-sealed stirrer, reflux condenser, and inlet tube.

In a representative experiment a 10% excess of sublimed magnesium was placed in the flask, and approximately 50 cc. of anhydrous ether was added. Dry methyl bromide was passed into the flask until the reaction started, at which time the remainder of the dry ether was added (sufficient to make a 2 molar solution of the Grignard). The methyl bromide was passed in at such a rate as to maintain a gentle reflux of the ether until the magnesium had been almost completely consumed. The Grignard reagent was then filtered through glass wool or glass cloth into a brown storage bottle.

Reaction of Methylmagnesium Bromide with Benzophenone.—The Grignard reagent was filtered from the storage bottle (to remove any magnesium hydroxide which may have formed) into a graduated dropping funnel, and two five-milliliter aliquot portions were removed for titration. Usually 0.2 mole of Grignard reagent was placed in a three-necked flask equipped with a mercury-sealed stirrer, a thermometer, and a two-necked adapter fitted with a reflux condenser and dropping funnel. Two mole per cent. of catalyst was added, and the resultant solution was stirred while cooling to 10°. One-tenth of a mole of benzophenone, dissolved in 40 g. of benzene, was placed in the dropping funnel and added at such a rate as to maintain the temperature of the solution between 10 and 20°. After completion of the addition, the temperature was allowed to rise to that of the room. The solution was then refluxed gently for one to two hours and left overnight.

The magnesium alcoholate was decomposed by an ice-hydrochloric acid mixture, and the ethereal layer was separated. After the aqueous layer had been extracted several times, the ethereal extracts were combined, washed with sodium carbonate solution, and with distilled water, and then dried over anhydrous sodium sulfate. The ether was removed on a steam-bath. The carbinol produced in the eexpriments with magnesium, cuprous chloride, and manganous chloride was crystallized from high-boiling ligroin. It melted at 79–81°.

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[1] The authors wish to express their appreciation to the du Pont Company for support which made this work possible.

[2] (a) Blicke and Powers, THIS JOURNAL, **51**, 3378 (1929); (b) Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

[3] (a) Kharasch, Kleiger, Martin and Mayo, THIS JOURNAL, **63**, 2305 (1941). (b) Kharasch and Tawney, *ibid.*, **63**, 2308 (1941). (c) Other work in progress includes the reaction of aromatic and aliphatic Grignard reagents with alkyl and aryl halides, aldehydes, acid chlorides, esters, unsaturated ketones and aldehydes, nitriles, etc.

In the cobalt chloride experiment a solid residue remained after removal of the ether. The solid was leached with hot ligroin until half the substance had dissolved, and the remainder was then dissolved in hot 95% alcohol. The two portions were fractionally crystallized. All fractions from the alcohol produced benzopinacol, 178-180° (dec.). The first fractions from ligroin produced pinacol, succeeding fractions giving a mixture of pinacol and 1,2-addition product. The two compounds were separated by fractional crystallization from ligroin.

The product of the ferric chloride experiment was fractionally crystallized from 95% alcohol. Pure pinacol crystallized at first. A mixture of pinacol and carbinol appeared in the last fractions. The substances were separated by fractional crystallization from ligroin.

In the experiment in which magnesium was added to the Grignard reagent, a red to red-violet coloration appeared during and shortly after the addition of the benzophenone. However, only diphenylmethylcarbinol was obtained, although a careful search was made for benzopinacol.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Factors Determining the Course and Mechanisms of Grignard Reactions. IV. The Effect of Metallic Halides on the Reaction of Aryl Grignard Reagents and Organic Halides[1]

BY M. S. KHARASCH AND E. K. FIELDS

Introduction

The interesting effects of metallic halides on the reaction between Grignard reagents and benzophenone[2,3] or isophorone[4] prompted us to extend our studies to other systems. This paper describes the results obtained when aryl Grignard reagents are treated with organic halides in the presence of small quantities (3-5 mole per cent.) of the halides of copper, manganese, nickel, chromium and cobalt.

Previous Work

The coupling of Grignard reagents by metallic halides in accordance with scheme (I) has been

$$2RMgX + MX_2 \longrightarrow R{-}R + 2MgX_2 + M \quad \text{(I)}$$

the subject of numerous investigations.[5] Chromic chloride, cupric chloride, aurous chloride carbonyl, and silver bromide are the halides most thoroughly investigated. The Grignard reagents studied are those of bromobenzene, benzyl chloride, bromonaphthalene, the bromotoluenes, *p*-bromoanisole, cyclohexyl bromide, and the butyl bromides. The yields of the R—R compounds vary from 25-100%.

In all cases, however, at least one mole of the metallic halide was used. Their function is best understood by assuming that they act as electron acceptors. In the reaction they are reduced, in some cases, to the metallic state.

Arylmagnesium Halides with Organic Halides in the Presence of Metallic Halides.—To appreciate the tremendous effect of small quantities of metallic halides on the reaction between aryl Grignard reagents and organic halides, the following facts must be borne in mind: (1) arylmagnesium halides do not react with monosubstituted aryl halides; (2) the metallic halides, such as cobaltous chloride, nickelous chloride, ferric chloride, etc., do not react with aryl halides; (3) arylmagnesium halides react with the above-mentioned metallic halides to yield the biaryl compounds. Thus, phenylmagnesium bromide reacts with cobaltous chloride to yield biphenyl. Furthermore, it follows from Scheme I that for each mole per cent. of the cobaltous chloride used, no more than two mole per cent. of the Grignard reagent can be utilized and no more than one mole per cent. of biphenyl (on the basis of the Grignard reagent) can be formed. A large number of our experiments has confirmed the validity of this principle. Similar results were obtained by Gilman and Lichtenwalter.[5]

However, when bromobenzene (one mole) is dropped into a mixture consisting of one equivalent of phenylmagnesium bromide and three mole per cent. of cobaltous chloride, a vigorous reaction ensues; considerable heat is liberated, and biphenyl is formed in excellent yield. Further-

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(1) The writers are indebted to Eli Lilly and Company for support which made this work possible.

(2) Kharasch, Kleiger, Martin and Mayo, THIS JOURNAL, **63**, 2305 (1941).

(3) Kharasch and Lambert, *ibid.*, **63**, 2315 (1941).

(4) Kharasch and Tawney, *ibid.*, **63**, 2308 (1941).

(5) For an exhaustive series of references see Gilman and Lichtenwalter, *ibid.*, **61**, 957 (1939).