[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF MICHIGAN]

THE REDUCING ACTION OF ALIPHATIC GRIGNARD REAGENTS

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RECEIVED APRIL 20, 1929 PUBLISHED NOVEMBER 8, 1929

During the course of an investigation, we wished to prepare a number of tertiary carbinols from the interaction of alkylmagnesium halides and benzophenone. Methyl- and ethyldiphenylcarbinol can be obtained in good yields from methylmagnesium iodide and ethylmagnesium bromide, respectively, and benzophenone. Klages and Heilmann[2] state that *n*-propylmagnesium bromide reacts with the above ketone to form a compound which melts at 65°; this material they considered to be *n*-propyldiphenylcarbinol. When the carbinol was treated with hydrogen chloride a substance was formed which was described as propyldiphenylchloromethane. By reduction of the carbinol, diphenylbutane was supposed to have been produced. We found that the propyldiphenylcarbinol of Klages and Heilmann was, in reality, benzhydrol and that their propyldiphenylchloromethane and diphenylbutane were actually diphenylchloromethane and diphenylmethane, respectively.

In order to prepare propyldiphenylcarbinol Masson,[3] as well as Skraup and Freundlich,[4] allowed phenylmagnesium bromide to react with ethyl butyrate. The former investigator obtained an oil which boiled at 185° under 15-mm. pressure; the latter isolated a product, after distillation under greatly diminished pressure, which melted at 36°. Inasmuch as tertiary carbinols of the type under discussion lose water very readily, with the formation of an ethylene derivative, especially when subjected to heat, we decided to investigate further the compound obtained by Skraup and Freundlich. After the interaction of phenylmagnesium bromide and ethyl butyrate, at a low temperature, we were able to isolate, without distillation, a crystalline compound which melted at 33–35°. The carbinol nature of this substance was shown by the fact that it reacted with ethylmagnesium bromide with the evolution of ethane. Finally, we found that the compound obtained by the action of phenylmagnesium bromide on phenylpropyl ketone, undoubtedly propyldiphenylcarbinol, melted at 33–34°.

It seems remarkable that no secondary carbinol should be formed from the interaction of methylmagnesium iodide and benzophenone, very little from ethylmagnesium bromide and the ketone, while in the case of *n*-propylmagnesium bromide at least 50% of the benzophenone is converted

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[1] Parke, Davis and Company Fellow, 1926–1927.

[2] Klages and Heilmann, *Ber.*, **37**, 1451 (1904).

[3] Masson, *Compt. rend.*, **135**, 533 (1902).

[4] Skraup and Freundlich, *Ber.*, **55**, 1078 (1922).

into benzhydrol, even though the reaction is carried out at 0°, as a result of the reducing action of the Grignard reagent.

A number of isolated instances of the reducing action of Grignard compounds have been reported from time to time.[5] However, since a systematic study to determine the relative reducing power of an homologous series of alkylmagnesium halides, especially with respect to a given ketone,[6] has not been made, we began an investigation of the action of various alkylmagnesium halides on benzophenone. This ketone is especially adapted for the purpose in view since it cannot enolize and the reduction product, benzhydrol, is a crystalline substance which can be purified and identified without difficulty. Our results are described in the experimental part of this paper.

It seems to us that the reducing action of aliphatic Grignard reagents toward various compounds can be accounted for if the assumption is made that trivalent carbon radicals are produced as intermediate reaction products.[7] It would be expected that these trivalent carbon radicals would be very unstable and that they might undergo, spontaneously, one of the types of transformation which have been found to be characteristic for trivalent carbon radicals of the triarylmethyl type, namely, addition, mutual oxidation and reduction, and polymerization.[8]

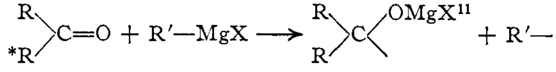
[5] The first observation of this type is that of Grignard (Doctor's "Dissertation," Annales de L'Université de Lyon, **1901**, p. 48), who obtained not only phenyl*iso*-amylcarbinol but also benzyl alcohol from *iso*-amylmagnesium bromide and benzaldehyde. Sabatier and Mailhe, *Compt. rend.*, **139**, 343 (1904); *Bull. soc. chim.*, [3] **33**, 79 (1905); *Ann. chim. phys.*, [8] **10**, 540 (1907), noted that benzophenone and cyclohexylmagnesium chloride yielded benzhydrol and cyclohexene.

[6] Stas, *Bull. soc. chim. Belg.*, **34**, 188 (1925); *ibid.*, **35**, 379 (1926), has studied the action of a number of Grignard reagents on several aliphatic ketones; however, since aliphatic ketones may react in the enolic form with alkylmagnesium halides, these ketones are not entirely suitable for a study of the reducing action of Grignard compounds. Recent contributions to somewhat different phases of this subject have been made by the following investigators: Meisenheimer and Casper, *Ber.*, **54**, 1655 (1921); Hess and Rheinboldt, *ibid.*, **54**, 2043 (1921); Hess and Wustrow, *Ann.*, **437**, 256 (1924); Meisenheimer, *ibid.*, **442**, 180 (1925); Rheinboldt and Roleff, *J. prakt. Chem.*, **109**, 175 (1925); Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).

[7] Späth, *Monatsh.*, **34**, 1967 (1913), and also Schlubach and Goes, *Ber.*, **55**, 2897 (1922), have already proposed such an explanation to account for the products which are formed when an alkyl- or arylmagnesium halide reacts with an organic halogen compound. Bachmann and Clarke, THIS JOURNAL, **49**, 2089 (1927), have assumed the formation of radicals in the Wurtz–Fittig reaction and Wieland and co-workers, *Ber.*, **48**, 1098 (1915); *ibid.*, **55**, 1816 (1922); *Ann.*, **446**, 31, 49 (1925); *ibid.*, **452**, 1 (1926), have made an extensive study in order to determine, in certain instances, whether or not radicals are intermediate reaction products. Quite recently Gilman and Fothergill, THIS JOURNAL, **50**, 3334 (1928), and Gilman and Kirby, *ibid.*, **51**, 1571 (1929), have made several observations on the mutual oxidation and reduction (disproportionation) of radicals.

[8] In some instances it has been found that triarylmethyls also undergo internal rearrangement.

In conformity with this hypothesis the interaction of a ketone and a Grignard reagent would be formulated as follows[9,10]



$$\mathrm{R(^*R)C{=}O + R'{-}MgX \longrightarrow R_2C(OMgX)^{11}{-} + R'{-}}$$

I II

The radicals I[12] and II may unite (addition) to form the addition product $R_2C(OMgX)R'$ which, upon the addition of water, would yield a tertiary carbinol; they may undergo mutual oxidation and reduction with the production of $R_2C(OMgX)H$, the magnesium halide derivative of a secondary carbinol, and the unsaturated hydrocarbon R'_{-H}; or, finally, they may polymerize to dimolecular forms $R_2C(OMgX)—R_2C(OMgX)$ and $R'—R'$; the former when treated with water would yield a pinacol,[13] the latter product represents a saturated hydrocarbon.[14]

Experimental Part

Propyldiphenylcarbinol.—Ethyl butyrate, dissolved in benzene, was added to approximately three molecular equivalents of phenylmagnesium bromide which had been cooled to 0°. After twenty-four hours the reaction mixture was decomposed with ice and ammonium chloride. The oily product which was obtained became crystalline after it had been cooled to a low temperature for some time. The material was so soluble that it could not be recrystallized but after it had been washed with petroleum ether (20–40°) it melted at 33–34°.

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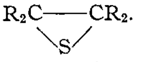
[9] This mechanism applies also to the reaction between a Grignard compound and an aldehyde or an ester. If an aldehyde is used R* is to be replaced by H, in the case of an ester by OR.

[10] It is possible that a molecular addition product may be formed first in all instances.

[11] Radicals of this type have been formulated by Lagrave, *Ann. chim.*, [10] **8**, 372 (1927).

[12] Compounds of Type I seem to be formed by the action of iodine and magnesium on ketones [Gomberg and Bachmann, This Journal, **49**, 238 (1927); *ibid.*, **50**, 2762 (1928)] and sodium analogs have been described by Schlenk and co-workers [*Ber.*, **44**, 1182 (1911); *ibid.*, **46**, 2840 (1913); *ibid.*, **47**, 486 (1914); *Ann.*, **463**, 1 (1928)]; and by Blicke [This Journal, **46**, 2560 (1924); *ibid.*, **47**, 229 (1925)].

[13] An example of what appears to be pinacol formation in the Grignard synthesis has been recorded by Barnett, Cook and Nixon [*J. Chem. Soc.*, **131**, 505 (1927)]. It has been shown by Schönberg and co-workers [*Ber.*, **58**, 1796 (1925); *ibid.*, **60**, 235 (1927); *Ann.*, **454**, 37 (1927)] that thioketones react with Grignard reagents to form sulfides of the type



$R_2C—CR_2$ (bridged by S). These sulfides, analogs of α-pinacolines, are formed, undoubtedly, through loss of XMg—S—MgX from the compound $R_2C(SMgX)—C(SMgX)R_2$, the dimolecular form of the initial reaction product $R_2C(SMgX)—$.

[14] The radical R′— instead of polymerizing might also undergo oxidation and reduction with the formation of equivalent amounts of the saturated hydrocarbon R'_{+H} and the unsaturated hydrocarbon R'_{-H}.

Phenylpropyl ketone,[15] dissolved in benzene, was added in small portions to a cold ether solution of phenylmagnesium bromide which had been prepared from 1.2 molecular equivalents of bromobenzene. After twenty-four hours the liquid was decanted from the precipitate and the latter was treated with ice and ammonium chloride. After the oily reaction product had been cooled for several days it became solid. The material was washed with low-boiling petroleum ether; m. p. 32–33°.

Reducing Action of Alkylmagnesium Halides.—It is not a simple matter to determine quantitatively the relative reducing power of a series of alkylmagnesium halides. The yields of the latter compounds vary greatly, depending upon the nature of the alkyl halide and other factors, and a complete separation of the secondary carbinol from the tertiary carbinol and other products present in the reaction mixture is a difficult process. In order to isolate benzhydrol we made use of the fact that the MgBr derivative of this carbinol is quite insoluble in a mixture of benzene and ether. To ethylmagnesium bromide, prepared from 13.1 g. of ethyl bromide, 2.9 g. of magnesium and 25 cc. of ether, there was added 9.2 g. of benzhydrol dissolved in 25 cc. of benzene. After twelve hours the precipitate was separated from the ether–benzene layer and decomposed with ice and ammonium chloride. There was obtained 7.5 g. of benzhydrol or 81% of that used originally, which melted at 64–66° without recrystallization.

Procedure.—The ketone, dissolved in the smallest possible amount of dry benzene, was added in small portions with vigorous agitation to an ether solution of the Grignard reagent which had been thoroughly cooled with ice. After twenty-four hours the reaction mixture was treated with ice and ammonium chloride. In those instances in which a precipitate had formed the latter was isolated and decomposed separately. The ether–benzene solution was dried with fused sodium sulfate and the solvents were then allowed to evaporate spontaneously.

In addition to the crystalline secondary carbinols there were obtained in most cases oils from which some solid material deposited after a number of days.

Undoubtedly the reduction of the ketones took place to a greater extent than is indicated in the above table. Some of the secondary carbinol was lost during the final purification and a certain amount could not be separated from other products formed in the reaction. The five-degree range in the melting point of the benzhydrol, obtained from benzophenone and *iso*butylmagnesium iodide, shows that the material was impure; hence the yield recorded is somewhat too high. In all other instances it can be seen from the melting points that the yields of the secondary carbinols are based on quite pure material.

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[15] Sorge, *Ber.*, **35**, 1073 (1902).

TABLE I

RESULTS OF EXPERIMENTS

Alkylmagnesium halide prepared from		Yield of secondary carbinol based on ketone, %	M. p., °C.		Mixed m. p., °C.
			Found	Literature	
Methyl iodide	Benzophenone	97[a]	...	...	...
Ethyl bromide	Benzophenone	80[b]	...	...	...
n-Propyl bromide	Benzophenone	50[c]	67–68	68[d]	67–68
*Iso*propyl bromide	Benzophenone	22	65–66	...	...
n-Butyl iodide	Benzophenone	27	65–67	...	...
*Iso*butyl iodide	Benzophenone	74	61–66	...	...
Iso-amyl bromide	Benzophenone	30	63–67	...	...
n-Propyl bromide	*p*-Bromobenzophenone[e]	24	62–64	63[f]	63–64
n-Propyl bromide	Phenyl-α-naphthyl[g]	65	84–86	86[h]	84–86
n-Propyl bromide	Phenylbiphenyl[i]	48	94–96	96[j]	95–96
n-Propyl bromide	Phenylbenzyl[k]	9	64–66	66–67[l]	64–65

[a] Tertiary carbinol. There was used 0.025 mole of benzophenone and 0.100 mole of methyl iodide. The tertiary carbinol melted at 81–82°. Klages [*Ber.*, **35**, 2646 (1902)] recorded the melting point as 81°. Schmalfuss [*J. prakt. chem.*, **108**, 88 (1924)] reported a 98% yield of this carbinol.

[b] Tertiary carbinol. 0.025 mole of benzophenone and 0.100 mole of ethyl bromide. The tertiary carbinol was recrystallized from a mixture of benzene and low-boiling petroleum ether; m. p. 92–94°. Masson [*Compt. rend.*, **135**, 533 (1902)] prepared ethyldiphenylcarbinol from phenylmagnesium bromide and ethyl propionate; m. p. 91°. Hell and Bauer [*Ber.*, **37**, 231 (1904)] obtained the compound from ethylmagnesium bromide and benzophenone but did not report the yield; m. p. 94–95°.

[c] In this experiment, as well as in those which follow, there were used 0.100 mole of ketone and 0.120 mole of the alkyl halide.

[d] A sample of benzhydrol was prepared from phenylmagnesium bromide and ethyl formate Masson [*Compt. rend.*, **135**, 533 (1902)]. A part of the benzhydrol obtained as a reduction product was converted by hydrogen chloride into benzhydryl chloride. The latter was dissolved in benzene and shaken with silver benzoate. The benzhydryl benzoate formed melted at 86–88°. Linnemann [*Ann.*, **133**, 20 (1865) prepared this benzoate by another method; m. p. 87–89°.

[e] Montagne, *Rec. trav. chim.*, **27**, 335 (1908).

[f] Montagne, *ibid.*, **27**, 342 (1908).

[g] Phenyl-α-naphthyl ketone was prepared by the addition of 20.6 g. of phenyl cyanide, drop by drop, to α-naphthylmagnesium bromide which had been prepared from 49.6 g. of α-bromonaphthalene and 5.8 g. of magnesium. The mixture was heated for one hour on a water-bath, the heavy precipitate removed by filtration and decomposed in the usual manner. The ketone imine was boiled for several hours with a mixture composed of water, acetic acid and sulfuric acid. The crude ketone which was formed was subjected to steam distillation in order to remove traces of naphthalene and phenyl cyanide and was then distilled under diminished pressure. The product melted at 71–73°.

[h] A much better procedure for the preparation of phenyl-α-naphthylcarbinol than that described by Acree [*Ber.*, **37**, 2757 (1904)] is as follows: 10.6 g. of pure benzaldehyde, diluted with four volumes of absolute ether, was added slowly to the Grignard reagent obtained from 24.8 g. of α-bromonaphthalene and 2.9 g. of magnesium. After twenty-four hours the precipitate was filtered and decomposed with ice and ammonium chloride. The crude product was recrystallized from a mixture of benzene and petroleum ether. The yield of pure carbinol was 16 g.

[i] Montagne, *Rec. trav. chim.*, **27**, 356 (1908).
[j] Montagne, *ibid.*, **27**, 358 (1908).
[k] Sudborough, *J. Chem. Soc.*, **71**, 219 (1897).
[l] Hell, *Ber.*, **37**, 456 (1904).

In one instance 36.4 g. of benzophenone, dissolved in benzene, was allowed to react with 1.2 molecular equivalents of *n*-propylmagnesium bromide at approximately 0°. The gas evolved during the reaction was collected over mercury and then passed through bromine dissolved in carbon tetrachloride. Nine and four-tenths g. of propylene bromide was obtained which corresponds to a 23% yield. The bromide boiled from 135–140°. Undoubtedly a considerable part of the propylene remained dissolved in the reaction mixture.

An attempt was made to obtain the carbinol chloride from methyldiphenylcarbinol. The latter was dissolved in absolute ether and the solution was saturated with dry hydrogen chloride. After several days the solvent was removed at ordinary temperature by means of a stream of dry air. An oily residue was obtained, a part of which eventually became crystalline. The oil possessed a penetrating, camphoraceous odor. The crystalline material, after recrystallization from low-boiling petroleum ether, melted at 113–114°. This compound seems to be a polymerized form of 1,1-diphenylethylene and has been obtained by other investigators by a different method.[16]

Summary

It has been shown that a number of diarylalkylcarbinols cannot be made satisfactorily by the interaction of an alkylmagnesium halide and an aromatic ketone because of the reducing action of the Grignard reagent.

A mechanism has been suggested to account for the formation of the compounds produced in the above-mentioned reaction.

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[16] Lebedew, Andreewsky and Matyuschkina, *Ber.*, **56**, 2349 (1923); Kauffmann [*Z. physik. Chem.*, **55**, 557 (1905)] made a number of substituted ethylenes by the action of hydrogen chloride on tertiary carbinols.