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

Factors Determining the Course and Mechanisms of Grignard Reactions. X. The Oxidation of Grignard Reagents—Effect of Metallic Catalysts

BY M. S. KHARASCH AND W. B. REYNOLDS

It is recorded that aliphatic Grignard reagents are readily oxidized by oxygen to give satisfactory (60–80%) yields of the corresponding alcohols,[1] whereas similar oxidations of aromatic Grignard reagents give poor (8–30%) yields of the corresponding phenols.[2] The reported[2b] by-products in the oxidation of phenylmagnesium bromide are benzene, much biphenyl, terphenyl, a little ethyl alcohol and considerable quantities of phenylmethylcarbinol. Wuyts postulates the formation of a Grignard peroxide (ROOMgX) as the first step in the reaction. Porter and Steele suggest the following oxidation mechanism

(A) $R—MgX + O_2 \longrightarrow ROOMgX$

(B) $ROOMgX + R—MgX \longrightarrow 2ROMgX$

This mechanism, however, does not explain the differences between alkyl and aryl Grignard reagents under oxidation. Gilman[3] states that there is no satisfactory explanation for these significant differences.

The present study had two objectives: (1) to determine the effect of cobaltous chloride upon the oxidation of Grignard reagents by oxygen, and (2) to account for the large differences between alkyl and aryl Grignard reagents with respect to the yields of the hydroxy derivatives formed when these reagents are oxidized.

If ethyl bromide is added to an ether solution of phenylmagnesium bromide at ordinary temperatures, no appreciable reaction occurs. However, in the presence of cobaltous chloride (1–5 mole per cent.), an energetic reaction takes place, and biphenyl, ethane and ethylene are obtained in good yields.[4] The reaction is best explained as a chain reaction in which the cobalt subhalide (CoCl) is the chain carrier. The organic halide, in this instance, acts as the oxidizing agent. Table I summarizes the results obtained in the oxidation of Grignard reagents in the presence of five mole per cent. of cobaltous chloride. The oxygen was introduced into a gently refluxing ether solution of the reagents.

The experiments recorded in Table I demonstrate that, in the presence of cobaltous chloride, the normal oxidation of aryl reagents is suppressed, probably because the catalyst brings about a faster reaction, which leads to the formation of biaryls. Cobaltous chloride, however, has less effect on the oxidation by oxygen of aliphatic Grignard reagents.

Competitive reaction rates would account for these unexpected results. The findings are thus intimately connected with the explanation of the differences between alkyl and aryl Grignard reagents when these reagents are oxidized in the absence of a catalyst.

In the mechanism suggested by Porter and Steel[2c] step B must depend upon the reducing tendency of the Grignard reagent. Higher yields should, therefore, be obtained from Grignard reagents which are good reducers. The reducing tendency of Grignard reagents was thoroughly investigated by Kharasch and Weinhouse.[5] In the ordered series obtained by them, the aryl Grignard reagents are shown to be greatly inferior to the alkyl Grignard reagents as reducers. These facts account for the good yields of cyclohexanol or butyl alcohol, and the poor yields of phenol or naphthol, obtained when the respective Grignard reagents are oxidized with oxygen. Furthermore, if the difficulty in obtaining good yields of phenol or naphthol (under these conditions) lies in step B rather than in step A, then the oxidation of an aryl Grignard reagent in the presence of an aliphatic Grignard reagent should result in improved yields of the aryl hydroxyl compound, since the alkyl Grignard reagent would function as a reducer[6]

$$C_6H_5OOMgX + C_6H_{11}MgBr \longrightarrow C_6H_5OMgBr + C_6H_{11}OMgBr$$

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[1] (a) Wuyts, *Bull. soc. chim. Belg.*, **36**, 222 (1927); (b) Bouveault, *Bull. soc. chim.*, **29**, 1051 (1903); (c) Bodroux, *ibid.*, **31**, 33 (1904); (d) Grignard, *Comp. rend.*, **138**, 1048 (1904); (e) Goebel and Marvel, THIS JOURNAL, **55**, 1693 (1933).

[2] (a) Bodroux, *Bull. soc. chim.*, **31**, 33 (1904); (b) Wuyts, *Compt. rend.*, **148**, 930 (1909); (c) Porter and Steele, THIS JOURNAL, **42**, 2650 (1920); (d) Ivanoff, *Bull. soc. chim.*, (4), **39**, 47 (1926); (e) Gilman and Wood, THIS JOURNAL, **48**, 806 (1926); (f) Meisenheimer and Schlichtenmaier, *Ber.*, **61B**, 2029 (1928).

[3] Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, Vol. I, p. 424.

[4] Kharasch, Lewis and Reynolds, THIS JOURNAL, **65**, 493 (1943).

[5] Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

[6] The converse of this mechanism where the aryl Grignard reagent exerts a reducing effect, as postulated by Ivanoff, is considered unlikely (see ref. 5). For this reason, an excess of an aliphatic Grignard reagent is required. Independently of the above reaction, the cyclohexyl Grignard reagent reacts directly with oxygen.

TABLE I

EFFECT OF COBALTOUS CHLORIDE UPON OXIDATION OF GRIGNARD REAGENTS

Grignard reagent	Yield of alcohol or phenol (% Calcd.)		Yield R—H (% Calcd.)		Yield RCH(OH)CH$_3$ (% Calcd.)		Yield R—R or disp. products (% Calcd.)		Yield (R)$_n$ (% Calcd.)	
	Control	CoCl$_2$	Control	CoCl$_2$	Control	CoCl$_2$	Control	CoCl$_2$	Control	CoCl$_2$
Cyclohexyl-MgCl	93	71	..	..	..	..	6	16	..	..
Benzyl-MgBr	65	68	..	..	..	..	31	29	..	..
n-Butyl-MgBr	88	56	..	..	..	..	tr.	30[a]	..	..
Phenyl-MgBr	27	3	10	0	10	tr.	28	80	6	6
α-Naphthyl-MgBr	25	4	34	13	30	10	tr.	61	..	2

[a] A mixture of butane and butylene was evolved in quantity sufficient to account for 30% of the Grignard reagent used. The cobaltous chloride used would account for about 25% of the gas formed.

In the experiments here recorded (Table II), where two Grignard reagents were employed, gratifying increases in yields of phenols were obtained.[7] The absence of high percentages of by-products (biaryls, tars, arylmethylcarbinols) indicates that in the usual oxidation of aryl Grignard reagents, these products are formed either by thermal decomposition of the Grignard peroxide or by reaction of the peroxide with the solvent. If the peroxide is removed by step B as rapidly as it is formed in step A, such by-products are not observed.

TABLE II

OXIDATION OF MIXTURES OF ALIPHATIC AND AROMATIC GRIGNARD REAGENTS

Aryl Grignard	Alkyl Grignard	Yield of phenol, %	Control yield of phenol (no alkyl Grignard), %
Phenyl-MgBr	Isopropyl-MgBr (1.5 mole)	64	28
Phenyl-MgBr	Isopropyl-MgBr (1.1 mole)[a]	43	28
Phenyl-MgBr	*n*-Butyl-MgBr (1.5 mole)	47	28
Phenyl-MgBr	Cyclohexyl-MgBr (1.2 mole)	74	28
α-Naphthyl-MgBr	Isopropyl-MgBr (1.7 mole)[b]	70	25

[a] Only 0.1 mole added at beginning of oxidation. Balance dropped in slowly throughout the entire period of oxidation. [b] One mole added at beginning; 0.5 mole added after 50% of the calculated amount of oxygen had been added, and 0.2 mole added after 75% of the calculated amount of oxygen had been added.

The fact that cobaltous chloride does not catalyze the oxidation of the aliphatic Grignard reagents appreciably is possibly due to a combination of two factors: (1) The reducing tendency of the aliphatic Grignard reagents and the instability of the aliphatic cobaltous halides (RCoCl) at the temperature of boiling ether. Kharasch and Fields[8] found that an aliphatic Grignard reagent to which cobaltous chloride has been added loses its catalytic activity when refluxed for one-half hour, whereas similar refluxing of an aromatic Grignard reagent with cobaltous chloride does not completely destroy the catalytic activity of the mixture. (2) The relative reaction rates of oxygen with aliphatic Grignard reagents and with the cobalt subhalide. Aliphatic Grignard reagents appear to react with oxygen more rapidly than do aryl Grignard reagents. Both of these factors favor an effect of cobaltous chloride in the oxidation of aryl Grignard reagents and mitigate such an effect in the oxidation of an alkyl Grignard reagent.

Experimental Part

Preparation of the Grignard Reagents.—All of the Grignard reagents were prepared (in an atmosphere of oxygen-free nitrogen) from freshly distilled organic halides, Mallinckrodt magnesium and anhydrous ether. The α-naphthylmagnesium bromide crystallized near the end of the preparation and was redissolved with anhydrous benzene. The finished reagents were filtered under nitrogen into brown bottles and stored under nitrogen in tightly stoppered containers. Samples of the solutions were titrated for normality and halogen content. Stock solutions were never used after standing more than two weeks, although experience has shown that most Grignards can safely be stored as described for much longer periods.

Oxidation of the Grignard Reagents.—Dry oxygen (free of carbon dioxide) was bubbled into an agitated solution of the Grignard reagent at a rate sufficient to maintain gentle boiling (approximately 50 cc./min.). When 0.2 mole of reagent was used, the evolution of heat usually ceased after one and one-half to two hours; the introduction of oxygen was discontinued after an additional hour. The oxidized mixtures were always allowed to stand overnight before being decomposed with aqueous sulfuric acid. In those experiments where a catalyst was used, the Grignard solution was cooled to 0°, and five mole per cent. of anhydrous cobaltous chloride was added. The solution was then warmed to room temperature. and the oxidation and decomposition carried out under agitation, as described. In the oxidations of mixtures of aryl and alkyl Grignard reagents, oxygen was bubbled into a mixture of the two Grignard reagents, and additional quantities of alkyl Grignard reagent were added as the reaction proceeded (Table II). Slightly less than molar quantities of sulfuric acid

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(7) Ivanoff (2d) reports a 53% yield of phenol in the oxidation of a mixture of one mole of phenylmagnesium bromide and two moles of benzylmagnesium bromide. For the reasons given in this paper, the mechanism here suggested to account for this observation is preferred to the one given by Ivanoff.

(8) Kharasch and Fields, THIS JOURNAL, **63**, 2316 (1941).

were added to decompose the oxidized mixtures. The water used was just sufficient to keep the magnesium salt in solution. The water layer was extracted three times with ether. The combined ether layers were extracted with a small amount of saturated bicarbonate solution and dried over anhydrous sodium sulfate.

Oxidation of Cyclohexylmagnesium Chloride.—Cyclohexylmagnesium chloride (0.18 mole) was oxidized as described above. Fractionation of the ether layer gave 0.85 g. of a mixture of cyclohexane and cyclohexene together with 16.7 g. of cyclohexanol b. p. 158–162°; f. p. 22–24°.

In a similar experiment in which the oxidation was carried out in the presence of 5 mole per cent. of cobaltous chloride, 2.4 g. of the cyclohexane cyclohexene mixture and 12.8 g. of cyclohexanol were obtained.

Oxidation of Benzylmagnesium Bromide.—Benzylmagnesium bromide (0.15 mole) was oxidized as described above. Fractionation of the ether layer gave 10.5 g. of benzyl alcohol (b. p. 204–207°) and a residue (8.17 g.) which boiled above 240°. This residue solidified when cooled. Steam distillation of the solid gave pure bibenzyl (m. p. 51.5–52.5°). Analysis of the Grignard reagent used showed 3.9 g. of bibenzyl to be present in the quantity of reagent used. From a similar experiment where cobaltous chloride was used as a catalyst, 11.1 g. of benzyl alcohol and 7.9 g. of bibenzyl were obtained.

Oxidation of *n*-Butylmagnesium Bromide.—*n*-Butylmagnesium bromide (0.2 mole) was oxidized by the standard procedure. From the ether layer, 13.0 g. of butyl alcohol (b. p. 116–120°) was obtained. No octane could be isolated. In a similar experiment where cobaltous chloride was used as a catalyst, the yield of butyl alcohol was 8.4 g. In both of these experiments, the top of the reflux condenser on the outlet side of the reaction vessel was connected to a trap immersed in an acetone–dry-ice-bath. No detectable amount of gas was condensed in the experiment without the catalyst. From the catalyzed experiment, approximately 1200 ml. of an unsaturated gas was collected. The molecular weight of this gas was 53 (Dumas). The molecular weight of a 50-50 mixture of butane and butylene should be 57, but the sample tested probably contained enough air to account for the low result. Direct interaction of cobaltous chloride (5 mole per cent.) with butylmagnesium bromide would account for about one-third of the gas collected.

Oxidation of Phenylmagnesium Bromide.—Phenylmagnesium bromide (0.23 mole) was oxidized and worked up by the standard procedure. The ether layer so obtained (150 ml.) was extracted with 0.2 mole of sodium hydroxide in 200 ml. of water. The water layer was titrated with bromate–bromide solution according to the procedure in Scott's "Standard Analyses," Vol. II, p. 2253. The yield of phenol was 6 g. The ether layer was dried and the ether carefully removed through an efficient column. When the residue was steam distilled, it yielded 5.9 g. of biphenyl and 5.2 g. of an oil which separated readily from the biphenyl in the receiving vessel. Fractionation of the oil gave benzene (1.8 g.) and phenylmethylcarbinol (2.8 g., b. p. 195–208°). The acid phthalate of this carbinol melted at 80–81°. The residue from the steam distillation was a tar weighing 1 g.

In a similar experiment where cobaltous chloride was used as a catalyst, the yield of phenol was only 0.65 g. Steam distillation of the product yielded 15 g. of biphenyl with no more than a trace of benzene or phenylmethylcarbinol. There was 1 g. of polyphenyl, non-volatile with steam.

Oxidation of Mixtures of Phenylmagnesium Bromide with Aliphatic Grignard Reagents.—The products from the experiments recorded in Table II were worked up essentially as described for the oxidation of phenylmagnesium bromide. In these experiments, very little biphenyl was formed. The ether layers, after being extracted with sodium hydroxide to remove the phenol, were fractionated to recover any alcohol formed. Good recovery of cyclohexanol and butanol was attained by extracting the sodium phenolate solution several times with ether and then combining the extracts with the original ether layer. It was not possible to extract isopropyl alcohol completely in this way. Where this alcohol was present, the ether–isopropyl alcohol mixture was removed before the extraction with sodium hydroxide. The alkaline phenol solution was later extracted with fresh ether.

Oxidation of α-Naphthylmagnesium Bromide.—α-Naphthylmagnesium bromide (0.15 mole) was oxidized and decomposed as already described. The ether was removed from the ether layer, and the residue treated with 0.15 mole of sodium hydroxide in 200 ml. of water. The alkaline solution was extracted three times with fresh ether, warmed to 50° for a few minutes, and clarified with activated charcoal. The clarified solution was cooled to 0–5° and treated with dry-ice to precipitate the α-naphthol. The yield of α-naphthol was 5.5 g. The ether was removed from the extract, and the residue steam distilled. In this way 6.5 g. of naphthalene was obtained. The residue (8 g.) from the steam distillation (except for a very small amount of binaphthyl) was soluble in cold alcohol. The product distilled from 165° to 173° at 12 mm. pressure and solidified upon standing several days in a refrigerator. Two recrystallizations from ligroin gave pure α-naphthylmethylcarbinol, m. p. 65–66°. The acid phthalate of this carbinol melted at 130–131.5°.

The product from a similar experiment, where the oxidation was carried out in the presence of five mole per cent. of cobaltous chloride, was worked up in the manner described. The yield of naphthol was only 0.8 g. Steam distillation gave naphthalene (2.6 g.). The residue (14 g.) from the steam distillation proved to be mostly 1,1′-binaphthyl (11.5 g. insoluble in cold alcohol), with a smaller amount of α-naphthylmethylcarbinol (2.4 g. soluble in cold alcohol). The material, insoluble in cold alcohol, distilled between 200 and 220° at 5 mm. pressure to give a solid substance which was recrystallized twice from 95% alcohol (leaflets, m. p. 155–156°). The alcohol-soluble material was identified as carbinol as in the previous experiment.

Oxidation of Mixture of α-Naphthylmagnesium Bromide and Isopropylmagnesium Bromide.—In this experiment a mixture of 0.15 mole of α-naphthylmagnesium bromide and 0.15 mole of isopropylmagnesium bromide was oxidized as usual. After 0.025 mole of oxygen had been passed into the mixture, an additional 0.075 mole of the aliphatic Grignard was added. Then, after a total of 0.15 mole of oxygen had been passed into the mixture, a further 0.03 mole of aliphatic Grignard was added, and the oxidation carried to completion. The reaction mixture was decomposed as usual. No attempt was made to recover the isopropyl alcohol. The α-naphthol was obtained as in the previous experiments. The yield was 15.2 g. or 70% of the amount calculated. Small amounts of naphthalene and carbinol were also present; these products were not worked up quantitatively.

Summary

1. The catalytic effect of cobaltous halide upon the oxidation of aliphatic and aromatic Grignard reagents has been studied. With aliphatic Grignard reagents, the effect is small; but with aromatic Grignard reagents, high yields of biaryls are obtained instead of the normal oxidation products.

2. Aromatic Grignard reagents have been oxidized in the presence of aliphatic Grignard reagents to give high yields of the corresponding phenols.

3. Mechanisms for the normal and catalyzed oxidations and for the oxidation of mixtures are suggested.

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Factors Influencing the Course and Mechanisms of Grignard Reactions. XI. The Effect of Metallic Halides on the Reaction of Grignard Reagents with Vinyl Halides and Substituted Vinyl Halides

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The results obtained by the action of Grignard reagents on organic halides, aromatic ketones, unsaturated ketones, etc., in the presence of small quantities of the halides of cobalt, nickel, chromium and iron, have been described.[2] The present paper describes a new type of catalytic effect exercised by cobalt and chromium halides in the condensation of Grignard reagents with vinyl and substituted vinyl halides.

No reference to condensations of vinyl halides with Grignard reagents is recorded in the literature, and numerous attempts in this Laboratory to effect such condensations without catalysts have been of little avail. It has been found, however, that, in the presence of small quantities (5 mole per cent.) of the metallic halides mentioned above (cuprous salts have only a slight effect), reactions of the following type readily take place.

$$C_6H_5MgBr + HC{=}CH{\cdot}Cl \xrightarrow{CoCl_2} C_6H_5{\cdot}CH{=}CH_2 + MgBrCl$$

In the particular reaction cited, the yield of styrene is 50–75%. At the same time biphenyl (6–18%) and some polymeric hydrocarbons (7–25%) are formed. In similar reactions, corresponding biaryls are produced.

According to experience so far obtained, the given reaction is applicable to the condensation of vinyl halides (or substituted vinyl halides) with most aromatic or aryl-aliphatic Grignard reagents (phenylmagnesium bromide, naphthylmagnesium bromide, benzylmagnesium chloride). Small to negligible yields are obtained from cyclohexylmagnesium chloride and aliphatic Grignard reagents (Table I). Comparison of the reactions of vinyl bromide, of vinyl chloride, of 1-bromopropene-1, 2-bromopropene-1, of trimethylbromoethylene, and triphenylbromoethylene leads to the conclusion that condensation occurs readily when the unsaturated carbon atom carrying the halogen atom also carries a hydrogen atom, but not when this carbon atom carries a hydrocarbon radical. With the halides of the latter type, because of the catalytic effect of the metallic halides, the rate of the competitive chain-reaction which results in the formation of biaryls[3] is greater than the rate of the so-called normal condensation, and accordingly large quantities of biaryls, but no terphenyl or other phenylated benzene derivatives, are formed. This last finding is in complete agreement with previous observations that biaryls (but no higher phenylated benzene hydrocarbons) are formed from aromatic Grignard reagents and alkyl halides in the presence of the metallic halides mentioned.[3]

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(1) The authors are indebted to Dr. S. Archer for some preliminary studies here recorded.

(2) For earlier references, see Kharasch, Lewis and Reynolds, THIS JOURNAL, **65**, 493 (1943)

(3) Kharasch and Fields, *ibid.*, **63**, 2316 (1941)