TABLE I

COMPARISON OF YIELDS

Hours of digestion	Without pyridine: Actual yield, g.	Without pyridine: % of the theoretical	With pyridine: Actual yield, g.	With pyridine: % of the theoretical
4	10.3	36.7	18.8	67.1
6	15.00	53.6	23.2	83
8	17.00	60.7	23.8	85

between 53.6 and 70% of the theoretical; furthermore, after a digestion period of eight hours, the yield is similar to the one obtained in four hours when pyridine is used. When the digestion is continued for eight hours in the experiment with pyridine, the yield becomes 85% of the theoretical and considering also that no charcoaling is necessary, we may say that we have here a decided improvement.

Summary

A substantially increased yield (up to 85%) of cinnamic acid in the Perkin synthesis has been produced by using pyridine as a catalyst at the rate of 8 drops for 20 g. of benzaldehyde, the time of reaction being eight hours. Additional pyridine and longer heating do not increase the yield. The product is obtained in very pure condition.

NEW YORK CITY

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

SOME SIDE REACTIONS IN THE PREPARATION OF ALKYLMAGNESIUM HALIDES

BY HENRY GILMAN AND ROBERT E. FOTHERGILL

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Introduction

In connection with studies concerned with the analysis of gases evolved in Grignard reactions it is necessary to know the nature and extent of gas evolution *during the preparation* of several typical organomagnesium halides. The present paper discusses some results obtained in the preparation of methyl-, ethyl- and *n*-butylmagnesium halides.

It has long been known that in addition to the formation of RMgX compound in the reaction between RX compound and magnesium in ether, the following side reaction occurs

$$2RX + Mg \longrightarrow R{\cdot}R + MgX_2 \qquad (1)$$

Until recently this side reaction was supposed to increase markedly with the weight of the R-group and its greater branching (particularly with tertiary groups), so that with a hexyl or octyl group the extent of Reaction 1 equaled or exceeded the yield of RMgX compound.[1] Even in the

[1] Grignard, *Ann. chim. phys.*, [7] **24**, 433 (1901).

preparation of benzylmagnesium chloride the yield of dibenzyl has equaled 30%;[1] and in the reaction between allyl bromide and magnesium it has long been thought impossible to prepare allylmagnesium bromide because of the quantitative formation of di-allyl.[2] As a consequence, practically all reactions involving "allylmagnesium bromide" have been carried out in accordance with Barbier's original procedure: namely, allyl bromide and the other reactant have been added to magnesium in ether so that the allylmagnesium bromide is brought into reaction simultaneously with its formation.

However, studies in this Laboratory have shown that under suitable conditions excellent yields of Grignard reagents are generally obtainable,[3] and that Reaction 1 takes place to but a minor extent in most cases. In particular it has been possible to prepare *tert.*-butylmagnesium chloride in satisfactory yields (70%),[4] and to prepare allylmagnesium bromide directly and in excellent yields (over 90%).[2] There is little doubt but that the improved methods of Gilman and Zoellner[4] and Gilman and McGlumphy[2] will make it possible to obtain satisfactory yields with other RX compounds where the halogen is very highly active and, therefore, favorable to Reaction 1 at the expense of RMgX compound. Two such RX compounds are benzohydryl chloride, $(C_6H_5)_2CHCl$, and cinnamyl chloride.[5] The most recent[6] reaction between benzohydryl chloride and magnesium gave an extraordinarily large quantity of coupling product (Reaction 1), namely, 95.5% of tetraphenylethane.

The formation of R·R compound as illustrated in Reaction 1 has been variously interpreted. In addition to the usual Würtz–Fittig reaction, some have proposed Reaction 2

$$RMgX + RX \longrightarrow R{\cdot}R + MgX_2 \qquad (2)$$

Some splendid studies by Fuson[7] show that under certain conditions the coupling reaction is best interpreted as follows

$$2RX + 2R'MgX \longrightarrow R{\cdot}R + R'{\cdot}R' + 2MgX_2 \qquad (3)$$

In Fuson's articles there is a review of related work by Späth,[8] Gomberg

[2] Gilman and McGlumphy, *Bull. soc. chim.*, **43** (1928).

[3] Gilman and McCracken, THIS JOURNAL, **45**, 2462 (1923); and *Rec. trav. chim.*, **46**, 463 (1927). Completed studies by E. A. Zoellner have shown that it is possible to get distinctly superior yields to those reported by Gilman and McCracken. Marvel and coworkers have recently determined the yields of some Grignard reagents prepared in di-*n*-butyl ether (THIS JOURNAL, **50**, 2810 (1928)).

[4] Gilman and Zoellner, THIS JOURNAL, **50**, 425 (1928); also, Puntambeker and Zoellner, "Organic Syntheses," **8**, 104 (1928).

[5] Gilman and Harris, *ibid.*, **49**, 1825 (1927).

[6] Gilman and Kirby, *ibid.*, **48**, 1733 (1926).

[7] Fuson, *ibid.*, **48**, 830, 2681, 2937 (1926).

[8] Späth, *Monatsh.*, **34**, 1965 (1913).

and Cone,[9] Schmidlin and Massini,[10] Schmidlin,[11] Gomberg and Kamm,[12] Binaghi and Oddo[13] and Binaghi.[14]

We are inclined to agree with Gomberg and Bachmann[15] that the R·R compound results, at least in part, as a consequence of the initial formation of free radicals.

$$2RX + Mg \longrightarrow 2R- + MgX_2 \quad (4)$$

$$2R- \longrightarrow R{\cdot}R \quad (5)$$

$$2R- \longrightarrow R(+H) + R(-H) \quad (6)$$

The free radicals so formed may then combine with the magnesium halide (MgX) of Gomberg and Bachmann[15] to give the RMgX compound; or with itself to give the R·R compound according to Reaction 5; or it may disproportionate, and if it is an alkyl group the products of such disproportionation would be a saturated and an olefinic hydrocarbon. Admittedly there is no convincing experimental proof as yet for the preliminary formation of such free radicals.[16] We are nevertheless led to such an opinion, first, because of the formation of small quantities of di-*p*-tolyl in the preparation of benzylmagnesium chloride, and, second, because of the disproportionation evidenced by the evolution of saturated and olefinic hydrocarbons, see Reaction 6 in the preparation of alkylmagnesium halides. The formation of free radicals from the Grignard reagent in reactions of it *after* it has been prepared has been suggested by several.[8,17]

The side reactions leading to the formation of R·R, R(+H) and R(−H) are undoubtedly the chief reactions when the oxygen, carbon dioxide and moisture of the atmosphere are excluded. Some other side reactions that can take place to a minor extent when the Grignard reagent is prepared in an inert atmosphere like nitrogen or hydrogen are due to contaminations of the ether (dissolved oxygen and water, and peroxides[18]) and the

[9] Gomberg and Cone, *Ber.*, **39**, 1463 (1906).

[10] Schmidlin and Massini, *ibid.*, **42**, 2384 (1909).

[11] Schmidlin, *ibid.*, **43**, 1141 (1910).

[12] Gomberg and Kamm, THIS JOURNAL, **39**, 2009 (1917).

[13] Binaghi and Oddo, *Gazz. chim. ital.*, [II] **51**, 330 (1921).

[14] Binaghi, *ibid.*, **53**, 879 (1923).

[15] Gomberg and Bachmann, THIS JOURNAL, **49**, 236 (1927). A review of related theories of the activation of magnesium for the Grignard reaction is given on pages 255–256 of this reference.

[16] A preliminary report indicating the capture of these free radicals by preparing organomagnesium halides in the presence of (1) olefins, like ethylene, (2) other free radicals like triphenylmethyl and diphenyl nitrogen and (3) hydrogen was read by Gilman, Fothergill, Kirby and McGlumphy at the September, 1928, meeting held at Swampscott.

[17] Bachmann and Clarke, THIS JOURNAL, **49**, 2089 (1927); Blicke, *ibid.*, **48**, 738 (1926); **49**, 2843 (1927); Rheinboldt and Kirberg, *J. prakt. Chem.*, **118**, 1 (1928); Gilman and Fothergill, THIS JOURNAL, **50**, 867 (1928).

[18] Unless the ether is of an extreme degree of purity it contains small amounts of ether peroxide. See Gilman and Wood, THIS JOURNAL, **48**, 806 (1926), and Gilman and Adams, *ibid.*, **47**, 2816 (1925).

splitting[19] of the ether by the RMgX compound or by MgX_2 and MgX formed as by-products in the preparation of the Grignard reagent. We assume here that the RX compound and magnesium are pure.

The reactions already considered are not the only ones that take place, because minute quantities of hydrogen were detected in some preparations.

Related studies have been made by Jolibois,[20] Job, Reich and Dubien,[21] Chelinzev,[22] Chavanne and DeGraef,[23] Leroide,[24] Bouveault,[25] Madelung and Volker,[26] Grignard,[1] and Gilman and Zoellner.[4]

Experimental Part

The alkylmagnesium halides were prepared in the customary manner, essentially after the general procedure followed by Gilman and McCracken[3] in determining the yields of some typical Grignard reagents. The apparatus used in the experiments with 0.2 and 0.5 mole of reagents consisted of a 150-cc. wide-necked flask having a tight-fitting rubber stopper provided with a small dropping funnel, a 6-inch condenser and a mechanical stirrer with a mercury seal. The condenser outlet was connected, through a drying tube filled with calcium chloride, to a 2-liter eudiometer containing water. A small crystal of iodine was used as a catalyst in each experiment. The preparations were carried out in carefully dried apparatus and after the alkyl halide had been added the solution was refluxed for at least one hour to expel dissolved gases.

The gas evolved was analyzed by standard procedures. Diethyl ether vapor was removed by absorption in water; unsaturated gases were removed by bromine water followed by washing with 30% potassium hydroxide; carbon dioxide by 30% potassium hydroxide; oxygen by alkaline pyrogallate; hydrogen by palladium black at 100°; and the saturated hydrocarbons were analyzed by combustion with oxygen in an explosion pipet. Check analyses were obtained with aliquots from a given experiment. Some inherent errors in such gas analyses were minimized by uniformity of procedure and by corrections for dissolved gases. The quantities of gas obtained in the several runs were too small to permit of careful fractionation by the use of liquid air. In a few cases the volume of hydrogen measured was close to the experimental error. However, from Table I it is evident that the volume of hydrogen in other cases is unquestionably beyond any experimental error. The total gas collected was the volume obtained after the removal of ether and includes the air displaced by the gas. In order to have a basis for comparison with earlier studies, all yields are expressed as percentages of alkyl halide used.

Two Mole Experiments. (a) **Methyl Iodide.**—This large run was carried out in a

[19] Such splitting of diethyl ether takes place, if at all, to a negligible extent under ordinary conditions. However, methylmagnesium iodide will split di-*n*-butyl ether to an appreciable extent if, during its preparation, the solution is allowed to become too warm.

[20] Jolibois, *Compt. rend.*, **155**, 213 (1912); **156**, 712 (1913).

[21] Job, Reich and Dubien, *Bull. soc. chim.*, **37**, 976 (1925).

[22] Chelinzev, *J. Russ. Phys.-Chem. Soc.*, **36**, 549 (1904); *J. Chem. Soc.*, **86**, 641 (1904).

[23] Chavanne and DeGraef, *Bull. soc. chim. Belg.*, **33**, 366 (1924).

[24] Leroide, *Ann. chim.*, **16**, 354 (1921).

[25] Bouveault, *Compt. rend.*, **138**, 1108 (1904).

[26] Madelung and Volker, *J. prakt. Chem.*, **115**, 24 (1927).

500-cc. three-necked flask in order positively to identify the olefin by the preparation of a derivative. The dilute solution of bromine in carbon tetrachloride that was used to absorb the olefin was carefully fractionated and the ethylene bromide was characterized

TABLE I

GASES OBTAINED IN THE PREPARATION OF SOME ALKYLMAGNESIUM HALIDES

Alkyl halide	Moles	Olefin	Yield, %	Hydrogen %	Saturated Hydrocarbons R·H	Yield, %	R·R	Yield, %
CH_3I	0.25	Ethylene	0.43		Methane	2.35	Ethane	1.34
CH_3I[a]	.5	Ethylene	.69	0.0324	Methane	1.82	Ethane	1.87
CH_3I[b]	.2	Ethylene	4.76[b]	.0	Methane	4.84	Ethane	1.16
CH_3I[c]	.2	Ethylene	0.14	.0104	Methane	2.12	Ethane	0.24
C_2H_5Br	.2	Ethylene	.12	...	Ethane	1.53	Butane	.577
C_2H_5Br	.2	Ethylene	.118	...	Ethane	1.46	Butane	.497
C_2H_5Br[d]	.2	Ethylene	.116[d]	.0112	Ethane	0.753	Butane	.0
n-C_4H_9Br[e]	.5	α-Butylene	.823	.0	Butane	1.505	.....	...
n-C_4H_9Br[e]	.2	α-Butylene	.308	.0	Butane	1.16	.....	...

[a] The methyl iodide was added rapidly in this experiment in order to increase the volume of evolved gas. However, the addition was so rapid that part of the methyl iodide was vaporized and collected in the eudiometer; 42% of unused magnesium was recovered. The total volume of gas collected was 535.1 cc., of which 7.24% was ethylene, 0.34% hydrogen, 36.5% methane and 18.93% ethane. The yields given in the table are based on the total quantity of methyl iodide used.

[b] In this experiment 130 cc. of di-*n*-butyl ether was used as the solvent and after the addition of halide over a thirty-minute period, the mixture was refluxed for one hour. The total gas collected was 561 cc., of which 19.03% was unsaturated, 38.7% was methane and 4.64% was ethane. The high yield of unsaturated gas is probably due to a splitting reaction of the butyl ether by methylmagnesium iodide. This finds confirmation in other studies on the Zerewitinoff analysis, where it has been shown that gases are evolved when the methylmagnesium iodide solution in butyl ether is heated to 140–150°. Ethylmagnesium bromide is stable at 175° in boiling cymene.

[c] In this experiment, 130 cc. of di-*n*-butyl ether was again used as the solvent. However, the reaction flask was cooled below 70° during the addition of methyl iodide and when all of the iodide had been added the reaction mixture was stirred at 70° for two hours. The total gas evolved was 269.1 cc. and the percentage of hydrogen determined in this case was too near the experimental error to warrant its serious consideration as one of the evolved gases.

[d] One hundred and thirty cc. of di-*n*-butyl ether was used as the solvent in this experiment and after adding the ethyl bromide the mixture was stirred and heated at 70° for 2.25 hours.

[e] In the analysis of the saturated hydrocarbons in the two *n*-butylmagnesium bromide experiments, the contraction after explosion of a sample was always slightly greater than that calculated for the quantity of butane present as based on the volume of carbon dioxide formed. This corresponds with values obtained by Fuson[7] in the analysis of ethane by the same method. If free radicals are formed (see Discussion of Results) then according to Taylor [*Proc. Am. Phil. Soc.*, **65**, 90 (1926)] and Bates and Taylor [THIS JOURNAL, **49**, 2439 (1927)] such free radicals may under some conditions add to the ethylenic compounds (see Ref. 16) to give hydrocarbons of higher molecular weight. It is apparent that such mixtures of higher hydrocarbons would affect the gas analysis. If disproportionation is the true explanation for the formation of R(+H) and R(−H) compounds, then the excess of R(+H) compound is to be expected in view of traces of moisture and ether peroxide[18] in the already carefully prepared ether.

by the formation of ethylene di-*p*-tolylsulfone prepared from sodium *p*-toluenesulfinate. A mixed melting-point determination with an authentic specimen showed no depresssion. Only a part of the gas evolved was collected and it had the following composition: 31.0% methane, 12.1% ethane, 0.417% ethylene and 0.326% hydrogen.

(b) *n*-Butyl Bromide.—The gases evolved in a 2-mole run were first passed into a dilute solution of bromine in carbon tetrachloride and almost all dissolved in this solution. From this solution there was obtained 1640 cc. of gas of which 65.13% was butane and 4.0 g. of α-butylene bromide, which agreed in b. p., density and refractive index with the compound reported in the literature.

Gases Evolved on the Hydrolysis of Methylmagnesium Iodide

The analysis of 409.6 cc. of gas evolved from the dil. sulfuric acid hydrolysis of an ether solution of methylmagnesium iodide showed 77.8% methane, 0.515% ethylene and a negligible quantity (0.095%) of hydrogen. The analysis of 393.9 cc. of gas evolved from the hydrolysis of methylmagnesium iodide prepared in di-*n*-butyl ether showed 69.3% methane, 2.6% ethylene and 0.285% hydrogen. The higher percentages of ethylene and hydrogen in the experiment where di-*n*-butyl ether was used as a solvent are probably due, in part, to the collection of the gases over water which had previously been saturated with ethylene and hydrogen. In the diethyl ether experiment, the gas was collected over fresh water.

The gas explosion values of the saturated hydrocarbons obtained in these two experiments did not entirely agree for methane. The combustions gave a greater contraction than that required for the methane present as based on the volume of carbon dioxide formed.

Discussion of Results

Entirely apart from the future consideration of the evolved gases on the possibility of the initial formation of free radicals and their disproportionation,[16] the results have a direct bearing on some problems concerned with the Grignard reagent. First, the extent of gas evolution accounts, in part, for the 90% and greater yields of most RMgX compounds.[2,3,27] Second, one of the five methods investigated by Gilman, Wilkinson, Fishel and Meyers[28] for the quantitative estimation of Grignard reagents was a gas analysis based on the following reaction

$$RMgX + HOH \longrightarrow RH + Mg(OH)X \qquad (7)$$

Obviously, in any determinations carried out without refluxing the solution to expel dissolved gases before hydrolysis, the results of the gas analysis would be too high. Also, the gases evolved on hydrolysis (see Experimental Part) show that Reaction 1 is not the only one that takes place.

Third, the Zerewitinoff[29] method for the estimation of active hydrogen

[27] Gilman and Meyers, THIS JOURNAL, **45**, 159 (1923).

[28] Gilman, Wilkinson, Fishel and Meyers, *ibid.*, **45**, 150 (1923); Gilman and Meyers, *Rec. trav. chim.*, **45**, 314 (1926); Job and Reich, *Bull. soc. chim.*, **33**, 1414 (1923); Job, Reich and Dubien, *ibid.*, **37**, 976 (1925).

[29] In one of the most recent studies on this method, Kohler, Stone and Fuson [THIS JOURNAL, **49**, 3181 (1927)] have described an ingenious, workable and accurate method for determining simultaneously the amount of gas evolved and the amount of reagent consumed in reactions of methylmagnesium iodide.

is affected not only by the gases evolved during the preparation of the Grignard reagent but also by the gases evolved when a compound having an active hydrogen is treated with an RMgX compound. The danger of dissolved gases formed during the preparation of the Grignard reagent in solutions like amyl and butyl ether is slight if the customary procedure of heating to remove excess methyl iodide is followed, but active hydrogen determinations with diethyl ether as a solvent may introduce larger errors because of the low boiling point of this ether.[30] The gas measured in a Zerewitinoff analysis where methylmagnesium iodide, for example, is used may not be pure methane, for if the disproportionation of free radicals should be the true explanation for the formation of olefins on hydrolysis of RMgX compounds, then it is reasonable to assume that free radicals are formed transitorily in all decompositions with active hydrogen compounds.

Fourth, the mixture of gases obtained on the hydrolysis of Grignard reagents shows that this reaction cannot be used directly for the preparation of *pure* hydrocarbons and related derivatives. This, however, is not peculiar to this method for it is quite probable that no method of preparation of hydrocarbons will give pure compounds without some subsequent rectification. With the Grignard reaction, the extent of such impurities is not large.

Fifth, many reactions involving reduction by the Grignard reagent are accompanied by the evolution of olefins. Allowances should be made, therefore, for any olefins formed during the preparation of RMgX compounds or as a result of subsequent treatment with active hydrogen compounds.

The evolution of ethylene and hydrogen in the preparation of methylmagnesium iodide indicates that the methyl radical undergoes secondary reactions in a manner contrary to the predictions of some. Of course, it is possible that these gases may owe their formation to other reactions like that involving the direct removal of hydrogen iodide.

$$2CH_3I + 2Mg \longrightarrow CH_2{=}CH_2 + 2MgHI \qquad (8)$$

If this were the case, and if no disproportionation took place, one would expect equal volumes of ethylene and hydrogen. The nearest approach to this in the results so far obtained is in the 2-mole run with methylmagnesium iodide where the percentage of ethylene was 0.417, and that of hydrogen, 0.326. The hydrogen evolved on hydrolysis may be due to a reaction between magnesious bromide and water.

Both the nature of the gases and the extent of their formation appear to vary with the solvent.

[30] References to this method are contained in an article by Gilman and Fothergill, THIS JOURNAL, **49**, 2815 (1927).

Summary

A study has been made of the gases formed during the preparation and in the hydrolysis of some alkylmagnesium halides. From the nature of these gases it appears that the free radicals that are probably formed prior to the formation of organomagnesium halides undergo disproportionation and coupling to varying degrees.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE SYNTHESIS OF MESOXALATES BY INTERACTION OF NITROGEN TETROXIDE WITH ESTERS OF MALONIC ACID[1]

BY ELIZABETH GILMAN[2] AND TREAT B. JOHNSON

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Only a few examples of organic compounds are known in which two hydroxyl groups appear to exist in stable union with a single carbon atom. What influence such linkages have on physiological activity is not well understood. Although the physiological action of chloral hydrate is not definitely linked with the property of hydrate formation, and while the effect of this drug is regarded as due to the organic radical containing chlorine, yet the prevalence of activity among hydrated constructions of the type which we are investigating (alloxan, for example) leads the writers to suppose that mesoxalates may be of pharmacological interest. As far as we have been able to ascertain, mesoxalates have never been investigated physiologically. They are admirably suited to intravenous injection. The diethyl ester is soluble in its own weight of water and it has been our experience that even the esters of higher molecular weight are surprisingly soluble in water. Diethyl mesoxalate is also a valuable reagent for synthetic work and any method that can be devised for preparing it more easily and cheaply will undoubtedly find important applications.

Bouveault and Wahl,[3] in 1903, provided the basis for the present method of preparing mesoxalates when they succeeded in obtaining diethyl mesoxalate from diethyl isonitrosomalonate by the action of oxides of nitrogen generated from sodium nitrate and nitrosyl-sulfuric acid. The principal oxide generated in this manner is nitrogen tetroxide (N_2O_4). They made their isonitrosomalonate from diethyl malonate in alcoholic sodium ethylate solution by interaction with methyl nitrite. Treatment with an ex-

[1] Constructed from a dissertation presented by Elizabeth Gilman in June, 1927, to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Holder of the Alice Freeman Palmer Fellowship of Wellesley College in 1926–27.

[3] Bouveault and Wahl, *Compt. rend.*, **137**, 196 (1903).