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A Quantitative Study of the Addition of *n*-Butylmagnesium Bromide to Acetone

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The normal addition reaction of a Grignard reagent to an aldehyde or ketone is always accompanied by side reactions of oxidation and reduction.[1] In the present instance acetone and *n*-butylmagnesium bromide yield dimethyl-*n*-butylcarbinol, isopropyl alcohol and pinacol.

$$n\text{-}C_4H_9MgBr + (CH_3)_2C{=}O \longrightarrow n\text{-}(C_4H_9)(CH_3)_2C{-}O{-}MgBr \quad (1)$$

$$n\text{-}C_4H_9MgBr + (CH_3)_2C{=}O \longrightarrow C_4H_8 + (CH_3)_2CH{-}O{-}MgBr \quad (2)$$

$$2n\text{-}C_4H_9MgBr + 2(CH_3)_2C{=}O \longrightarrow C_4H_8 + C_4H_{10} + (CH_3)_2C(OMgBr){-}C(OMgBr)(CH_3)_2 \quad (3)$$

The ratios of these competitive reactions have been determined. The reaction was carried out in ether at 0°, at initial concentrations of about 1 *M* of each reactant, in the presence and absence of oxygen both during the Grignard formation and during the coupling.

In order to clarify the variable yields of tertiary alcohol, a material balance of reactants and products has been made as accurately as possible, including the autoöxidation products.

The acetone solution was added during one hour, and the mixture stood for an additional half hour. The completion of the reaction was tested by passing dry carbon dioxide. This reaction

$$n\text{-}C_4H_9MgBr + CO_2 \longrightarrow n\text{-}C_4H_9CO_2MgBr \quad (4)$$

is known to be very rapid; the product, valeric acid, lends itself to quantitative measurement in small amount.[2,3] After the time allowed passage of carbon dioxide produced no acid.[4]

A further reason for testing the completion of the reaction in this way lay in the possibility that the type of ketone complex first proposed by Hess[5] as an unstable intermediate might instead stabilize either the ketone or the Grignard. These complexes were merely coördination compounds of uncertain composition, in which the oxygen of the ketone has entered the coördinate sphere of magnesium ion, replacing the ether oxygen. Such a system, $R{-}MgBr{\cdot}(O{=}CR_2)$ or $R{-}MgBr{\cdot}2(O{=}CR_2)$, could form the final products by rearrangement or by reaction with other ketone or Grignard molecules. With two possible paths for the net reaction, *i. e.*, direct reaction or *via* the coördinate complex, and with two or more

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[1] For a recent discussion, see Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

[2] Gilman and others, THIS JOURNAL, **45**, 150 (1923), discuss the estimation of the Grignard reagent and (*ibid.*, p. 159) the optimum conditions for preparing the reagent.

[3] In two preliminary experiments the valeric acid obtained corresponded to 87 and 91%, respectively, based upon the Grignard reagent present as determined by titration with acid. This latter was actually high by a few per cent. due to peroxides in the ether as discovered later; normally the reaction with carbon dioxide yields some ketone or tertiary alcohol which vitiates its use as a quantitative tool [Bodroux, *Compt. rend.*, **137**, 710 (1903)].

[4] Usually there was a slight excess of ketone, but in one experiment the Grignard solution was divided and to one portion half the required acetone was added while to the other the full amount was added. The yields of tertiary alcohol were, respectively, 32.8 and 66.7%, of valeric acid 45.6 and 1.0%, of unsaturated hydrocarbon 3.9 and 9.9%; total accounted for 82.3 and 77.6% (of the initial amounts). The remainder was octane and oxidation products common to both. The valeric acid is about 10% high if one assumes completely parallel courses with respect to acetone in the two parts of the experiment and suggests further examination of the effect of excess of one reagent.

[5] (a) Hess and Rheinboldt, *Ber.*, **54**, 2043 (1921); Meisenheimer, *Ann*, **442**, 180 (1925); Johnson, THIS JOURNAL, **55**, 3029 (1933).

TABLE I

YIELD OF PRODUCTS EXPRESSED AS PERCENTAGE OF STARTING MATERIALS

Product	Expt. I Air present, peroxide present		Expt. II Nitrogen, present		Expt. III Air present during addition of acetone		Expt. IV Air present during formation of Grignard	
Grignard (by titration), %	92.0		93.1		93.5		..	
Dimethylbutylcarbinol		64.8		73.6		62.2		62.9
Methylbutylcarbinol (×1.5)		7.7		0		2.34		3.15
Isopropyl alcohol	7.5	11.4	6.6	11.6	6.8	10.8	8.1	12.6
Pinacol (×2)	3.9		5.0		4.0		4.5	
Heptylene (from tertiary alcohol)		2.5		4.1		4.3		2.1
Butyl alcohol		1.2		0		10.0		10.3
Valeric acid		0		0		0		0
Octane		6.5		6.0		6.2		5.5
Totals		94.1		95.3		96.9		96.55
Butene	9.4		7.9		7.6		9.4	
Butene ($\times F$)[8]	11.3		10.0		9.3		11.4	
i-Pr alc./pinacol	3.9		2.65		3.4		2.9	
Addn. reacn./redn. reacns.	5.9		6.7		6.1		5.2	

products formed, it seemed desirable to look for evidences of anomalous stability in a part of the reactants. While the time and temperature used have not been a drastic test of difference in reaction rate, certainly no undue stability of part of the reactants has been noted. Similarly complete reaction at 0° was observed in experiments with acetaldehyde and propionaldehyde.

Table I gives the results of the experiments, expressed as the percentage of starting materials used up in the production of each substance formed. In Expt. I the ether was decanted from sodium wire after standing over the sodium in a 2-liter bottle for six weeks without special precaution as to exclusion of air. A mercury-sealed stirrer was used but dry air filled the reaction vessel. In Expt. II the ether was freshly distilled and air replaced by pure nitrogen to the rigid exclusion of oxygen. In Expts. III and IV the ether was freshly distilled, but in the former the Grignard was formed in nitrogen and dry air passed through the ethereal solution for one hour at 0° while the acetone was being added. In the latter dry air was passed through the ether for one hour while the Grignard derivative was in preparation at 0°, and then displaced by nitrogen before the acetone was added.

Methylbutylcarbinol is derived from the reaction

$$(C_2H_5)_2O + O_2 \longrightarrow \text{Ether peroxide} \longrightarrow 2CH_3CHO + H_2O \quad (5)$$

Ether peroxide is assigned the formula $C_2H_5—O—CH(OOH)—CH_3$ by Clover,[6] who found it to liberate two equivalents of iodine per mole and to be reasonably stable.[7] In the present instance it does not react as two equivalents of an oxidizing agent upon the Grignard reagent, since butyl alcohol is not produced in Expt. I in amount equal to the butylmethylcarbinol as demanded by the equation

$$C_2H_5—O—CH(OOH)CH_3 + 3C_4H_9MgBr \longrightarrow C_2H_5OMgBr + C_4H_{10} + C_4H_9OMgBr + C_2H_5(CH_3)CHOMgBr \quad (6)$$

The peroxide is too stable to have decomposed prior to the condensation and apparently reacted with the butylmagnesium bromide as follows

$$C_2H_5—O—CH(OOH)CH_3 + 3C_4H_9MgBr \longrightarrow 2C_4H_9(CH_3)CHOMgBr + C_4H_{10} + Mg(OH)Br \quad (7)$$

It is interesting, as shown in Expts. III and IV, that in the presence of the Grignard reagent there is a relatively rapid reaction of air with ether to produce peroxide.

As a method of analysis the fractional distillation employed is not accurate. The octane is low by at least one unit. Losses are probably in proportion to volatility and amount of each constituent, and do not affect seriously the ratios recorded. It is entirely possible that other reactions such as enolization and condensation are responsible for a part of the Grignard reagent not accounted for.[9]

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(6) Clover, THIS JOURNAL, **44**, 1107 (1922).

(7) Gilman and Adams, *ibid.*, **47**, 2816 (1925), mention the reaction of this peroxide with Grignard reagents but give no quantitative results. Wuyts, *Compt. rend.*, **148**, 930 (1909), and Gilman and Wood, THIS JOURNAL, **48**, 806 (1926), observed acetaldehyde derivatives during oxidation of Grignard reagents by oxygen in ether solution.

(8) By F is meant a factor based upon Equations 2 and 3, taken in the proportion for each experiment indicated by the analysis for isopropyl alcohol and pinacol. This offers a qualitative check upon the distillation; it was suspected that in Expts. II, III and IV the butene found was low, due to permanent gas passing through the liquid air trap.

(9) Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).

From a practical standpoint, the use of a nitrogen atmosphere is warranted largely by the greater ease of fractionation of the products. Distillation of the ether from fresh sodium suffices to remove nearly all the aldehyde and peroxide, but in the presence of the strongly basic Grignard reagent peroxide is reformed rapidly upon contact with air. A calculation of the yields of tertiary alcohol based upon the amount of butylmagnesium bromide actually present when the acetone was added, and including heptylene formed during the fractionation gives: Expt. I, 81%; II, 83%; IV, 82%, indicating consistency in experimental error and essential constancy in the ratio of the competing reactions of addition and reduction.

Experimental Part

Materials.—**Ether** was dried over calcium chloride for two weeks, then over sodium wire for one week, and distilled from sodium twice. After standing it was tested for peroxides with both the ferric chloride–ferricyanide and the ferrous sulfate–thiocyanate reagents. ***n*-Butyl bromide** was distilled and the fraction of b. p. 101–101.5° used. **Carbon dioxide** was dried over calcium chloride and concentrated sulfuric acid. **Magnesium** turnings were washed with dry ether and dried for two hours at 110°. **Acetone** was dried over calcium chloride for one month and distilled once; the middle fraction of b. p. 56.1 ± 0.1° was collected and diluted with ether to a concentration of 1 *M*. **Nitrogen** was passed through alkaline pyrogallol; exclusion of oxygen was tested by passing effluent nitrogen through fresh pyrogallol without coloration.

Procedure.—The optimum conditions found by Gilman[2] were used. One mole of magnesium covered with ether was kept below 15° and stirred vigorously with a mercury-sealed stirrer while one mole of butyl bromide in ether was added. The final concentration was between 0.6 and 0.8 *M*. A small crystal of iodine served to initiate the reaction. Opening to the air was through a liquid air trap to condense butene.

An aliquot part of the Grignard reagent was extracted for titration and after cooling to 0° (thermometer in the reaction mixture) a cooled ethereal solution of acetone was added in amount indicated by the titration. Stirring was vigorous and the temperature kept at 0°. About one hour was used for the addition of acetone, after which the ice-bath was removed and the mixture stood for half an hour (warming to 5–10°). It was then again cooled to 0° and carbon dioxide passed through for twenty minutes.

The reaction product was hydrolyzed by the addition of ice, one equivalent of dilute hydrochloric acid added, and the ether and water layers separated. The latter was washed with three portions of fresh ether and the combined ether layers were washed twice with sodium carbonate solution. The carbonate solution was treated with fresh ether twice.

The ether solution was dried over sodium sulfate and potassium carbonate and distilled through a Widmer column During the distillation of the ether the same liquid air trap was used to condense any butylene as was used during the reaction to close the system. Careful fractionation followed removal of the ether, using a semi-micro Widmer. The aqueous layers above were acidified and steam distilled for valeric acid.

Butylene was determined in the liquid-air trap and in the first 20% of the ether distillate, by adding excess bromine dissolved in carbon tetrachloride, standing for one hour and back-titrating the excess with potassium iodide and thiosulfate. Acid formed in the reaction was used to correct the result, assuming that one mole of bromine produced one equivalent of acid. The correction was small. The 1,2-dibromobutane was isolated, b. p. 166°.

The higher fractions were titrated similarly for unsaturated hydrocarbons (heptylene). These fractions, upon which Table I is based, were collected as follows: dimethylbutylcarbinol, b. p. 141–142°; *n*-butyl alcohol, b. p. 115–119°; *n*-butylmethylcarbinol, b. p. 130–134°; isopropyl alcohol, b. p. 80–84°; pinacol, b. p. 170–175°, m. p. 38°; hydrate, m. p. 46°. The octane was of b. p. 124–127°. Equivalent weights of the alcohols were taken by acetylation: isopropyl alcohol, found 63.5, calcd. 60; *n*-butyl alcohol, found 76, calcd. 74; butylmethylcarbinol, found 108, calcd. 102. The agreement indicates in the case of isopropyl alcohol that the fraction contained little or no ethyl alcohol.

Summary

1. The ratio of the reduction products, isopropyl alcohol to pinacol, formed in the reaction studied is about 3:1. The ratio of the addition reaction giving tertiary alcohol to the reduction reactions yielding secondary alcohol and pinacol is about 6:1.

2. Ether peroxide is formed rapidly in an ethereal solution of *n*-butylmagnesium bromide upon contact with air. The peroxide reacts with the Grignard reagent not as an oxidizing agent but as acetaldehyde.

3. There is no essential difference in the reaction of air for one hour with a Grignard reagent in process of formation as compared to its reaction with the same amount of Grignard in process of reaction with acetone.

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