[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

PREPARATION OF NORMAL-BUTYLMAGNESIUM BROMIDE

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Introduction

In the course of preparing certain compounds in fairly large amounts by means of the Grignard synthesis, it seemed of interest to make a study of the conditions giving the best yields of the Grignard reagent formed from *n*-butyl bromide, especially with a view to determining the extent to which the results of Gilman and Meyers[1] obtained with 0.05 molar quantities would hold for runs made on a large scale.

When *n*-butyl bromide and magnesium are brought together in ether solution, it is well known that at least three reactions may occur[2]

$$C_4H_9Br + Mg \longrightarrow C_4H_9MgBr \qquad (a)$$
$$C_4H_9MgBr + C_4H_9Br \longrightarrow MgBr_2 + \text{hydrocarbons} \qquad (b)$$
$$C_4H_9Br + Mg + BrC_4H_9 \longrightarrow MgBr_2 + \text{hydrocarbons} \qquad (c)$$

It is the conditions favoring the first of these reactions and minimizing the other two which are of interest in securing as high yields as possible of the Grignard reagent.

Materials, Apparatus and Procedures

The *n*-butyl bromide used was prepared from *n*-butyl alcohol (b. p. 117.2–117.5°) by the hydrobromic–sulfuric acid method,[3] and had a boiling point of 101.2–101.5°. An average of 300 cc. of absolute ether per mole of *n*-butyl bromide was used in each run. The magnesium was in the form of moderately fine turnings.

All of the runs, except No. 5 for which a 12-liter flask was used, were made in 5-liter, three-necked flasks fitted with stirrer, reflux condenser and dropping funnel. The top of the flask was packed in ice during all of the runs. By this means cooling the contents of the flask by an ice-water bath to prevent too rapid refluxing was avoided, except for brief periods in one or two of the fastest runs. Usually no refluxing occurred.

Samples for analysis were taken at the end of each run (except 14–17) by means of sampling tubes having a capacity of about 5 cc. A weighed sample was taken at the completion of Runs 14–17 by means of a thin-walled sampling bulb, and the weight of the whole contents of the flask was determined; the weight of the bromide added being known, the percentage recovery of bromide could be calculated. The analysis of the sample taken with the sampling tubes determined only the amount of bromide which had reacted, called in the tables "Recovered Br." Samples were taken after the addition of each mole of butyl bromide in Runs 6 and 17 in order to follow the course of the reaction.

Analysis for the amount of Grignard reagent present was by the acid titration method,[4] using *N*/5 nitric acid and *N*/10 sodium hydroxide. Some of the analyses for

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[1] Gilman and Meyers, THIS JOURNAL, **45**, 159, 2462 (1923).

[2] For a discussion of the side reactions occurring and their possible mechanism see Gilman and Fothergill, *ibid.*, **50**, 3334 (1928).

[3] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1921**, Vol. I, p. 5.

[4] Gilman, Wilkinson, Fishel and Meyers, THIS JOURNAL, **45**, 150 (1923).

bromide were made by the Volhard method, while others were done gravimetrically; both methods were used in several cases as checks.

The experimental results are given in Tables I and II.

TABLE I

FINAL RESULTS FROM SIXTEEN RUNS IN THE PREPARATION OF *n*-BUTYLMAGNESIUM BROMIDE

Run	Moles BuBr	At. wts. of Mg	Time per mole, minutes	Grignard on basis of Br recov. OH:Br recov., %	Run	Moles BuBr	At. wts. of Mg	Time per mole, minutes	Grignard on basis of Br recov. OH:Br recov., %
1	6	6	20	85.8	10	6	6.5	40	95.0
2	6	6	20	85.3	11	6	6.5	40	95.0
3	5	5	24	84.8	12	6	6.5	52	95.6
4	7	7	26	85.1	13	6	6	45	95.6
5	10	10.5	24	90.9	14	4.5	5	18	87.5
7	6	6	20	68.5	15	4.5	5	48	94.9
8	2	2	45	91.6	16	6	6.5	48	93.4
9	5.5	6	49	93.1	17	6	6.5	57	94.5

The percentages of Grignard reagent formed on the basis of bromide used were determined for Runs 14–17 as follows: Run 14, 87.6; Run 15, 93.9; Run 16, 91.7; Run 17, 91.9. The percentages of bromide recovered in these runs were: Run 14, 100.1; Run 15, 98.9; Run 16, 98.2; Run 17, 97.0.

TABLE II

INTERMEDIATE AND FINAL RESULTS FROM TWO RUNS IN THE PREPARATION OF *n*-BUTYLMAGNESIUM BROMIDE

BuBr, moles	1 Mole added in, minutes	Start to taking of sample, hr., min.	% Grig. on basis of Br rec. OH:Br recov.	BuBr moles	1 Mole added in, minutes	Start to taking of sample, hr., min.	% Grig. on basis of Br rec. OH:Br recov.
Run 6; 6 atomic weights of magnesium				6a	..	18–30	84.0
1	30	1–0	85.5	6b	..	69–30	83.90
a	..	1–30	91.9	Run 17; 6.5 atomic weights of magnesium			
2	30	2–15	90.4	2	83	2–45	90.1
3	8	3–0	87.0	3	55	3–40	92.9
4	27	3–45	87.4	4	50	4–30	93.6
5	12	4–30	87.3	5	40	5–10	95.2
6	33	5–20	87.1	6	25	5–35	94.5

Discussion of Results

Rate of Addition of Butyl Bromide.—Runs 1–4, in which the rate of addition of the bromide did not vary markedly, agree closely in their yields of Grignard reagent. Run 4 developed marked turbulence after the addition of the fourth mole, though the rate of addition was slightly slower than in any previous run. No explanation of this which seemed adequate could be formulated. It was, however, a somewhat larger run than those preceding, so the amounts used in Run 5 were larger still, the object being to determine whether a large amount of magnesium present in the early stages of the reaction had a definite accelerating effect and whether runs on a ten-mole scale could be made satisfactorily. The run proved to be a quiet one with a markedly increased yield. The quantities of materials used were not employed again as the large amounts were unsatisfactory in further manipulations. The increased yield led to the procedure adopted for Run 6, in which a sample was taken after the addition of each mole of butyl bromide in order to find out the quantities of Grignard reagent present in successive stages of the reaction. The results, shown in Table II, were disappointing in that, through accident, the rates of addition of the third and fifth moles were so much greater than the thirty-minute rate desired. The marked drop in the OH:Br ratio after the addition of the third mole in place of the rise shown in Run 17 shows very plainly the bad results obtained by adding the alkyl halide too rapidly.

Runs 8–17 show, with the exception of Number 14, a reasonable uniformity of yield; it will be noted that the molar rate of addition was in every case forty minutes or more and that no marked gain in yield is secured by any increase over this time—a complete verification of the conclusions of Gilman and Meyers. Further evidence might be found in the results of Run 17, in which a progressively decreasing time of addition of each successive mole of butyl bromide was used, finally getting, for the sixth mole, below the forty-minute limit, with resultant decrease in the OH:Br ratio. Run 14 was intentionally made at a rapid rate as a final confirmation of the lowered yield to be expected from increased rate of addition.

Reverse Process of Addition.—Run 7 was carried out with the suspicion—amply justified by the results—of poor yields to be obtained by adding magnesium to the alkyl halide, since by this procedure the latter is present in excess throughout the reaction. The completeness with which the results of this run justified the suspicions entertained may be seen from the figure for percentage yield given in Table I.

Excess of Butyl Bromide.—A consideration of the reactions given in an introductory paragraph will afford an explanation of why an unduly high concentration of butyl bromide results, as has been found always to be the case, in reduced yields of Grignard reagent. Any reaction, such as b and c, which uses up butyl bromide while producing no butylmagnesium bromide, obviously reduces the amount of the latter which can be secured from a given amount of the former by Reaction a. To the fact that a slow addition rate of butyl bromide to magnesium keeps the concentration of butyl bromide at a minimum may be ascribed the high yields obtained by this method of operation. The drop in the OH:Br ratio after the addition of the third mole in Run 6 shows the bad effect of an excess of butyl bromide, brought about by its introduction at a rate greater than that at which it could react according to Equation a, and reacting instead according to one or both of Equations b and c. The further drop of 3% in the sample taken in this run after eighteen and one-half hours further indicates that this same factor is at work. Sample 6 had been taken in the evening after only fifteen minutes' stirring subsequent to the addition of the sixth mole. When the stirrer was started the next morning enough heat was spontaneously developed to cause active refluxing, indicating the presence of unchanged butyl bromide which further stirring had caused to react, chiefly again according to one or both of Reactions b and c. It might be noted in passing that analyses made on this run on further standing show that the reaction was completed at this time and also point to the permanence of the Grignard reagent, already noted by others.[5] The very low yield obtained in Run 7 has already been given as essentially due to the constant presence of an excess of butyl bromide throughout the reaction. Just what amount constitutes an "excess" is not known; it has been repeatedly found, however, that when the ratio of the amount of free alkyl halide to the amount of active magnesium present in the reaction mixture exceeds a certain definite small value, low yields of Grignard reagent are obtained. In practice the value of this ratio is kept low by the slow addition of the alkyl halide. What has been said previously about the effects of the rate at which the butyl bromide is added and of the reverse process of addition are essentially corollaries of the effect of the presence of excess of butyl bromide.

Excess of Magnesium.—Comparison of results from Runs 8–17 shows no advantage in the half-mole excess of magnesium present in most of the runs, the highest yields (Runs 12 and 13) being obtained one with it and one without. It was used in most of the runs to make sure that the necessary slight excess would always be present. Equimolecular proportions of alkyl halide and magnesium will usually insure a sufficient excess, as pointed out by the investigators previously mentioned.

Yields.—An average of the percentage yields of Grignard reagent from the runs from which good yields could be expected (8–13, 15–17) gives 94.3% on the basis of the *n*-butyl bromide taking part in the reaction, or "recovered." An average of the yields based on the whole amount of *n*-butyl bromide used gives 92.5% for Runs 15–17 (the figure for Run 14 is omitted as being somewhat anomalous); while the average for the same runs on the basis of bromide recovered is 94.3%, which is 1.8% higher than the average based on bromide used. If this difference obtained in all the runs, the average percentage yield on the basis of bromide used would be 94.3 − 1.8 = 92.5%. This is somewhat (1.2%) higher than the figure given by Gilman and McCracken[6] as obtained with *n*-butyl bromide in their small quantitative runs but the agreement seems excellent

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[5] Gilman and Meyers, *Ind. Eng. Chem.*, **15**, 61 (1923).

[6] Gilman and McCracken, THIS JOURNAL, **45**, 2462 (1923).

between experiments in which the quantities of reactants in one series were usually 120 times as great as in the other.

Summary

1. A study has been made of the following conditions affecting the yield of Grignard reagent formed from *n*-butyl bromide: rate of addition of butyl bromide, reverse process of addition, excess of butyl bromide and excess of magnesium.

2. The yields obtained on the large scale are in close agreement with those obtained by Gilman and co-workers in quantitative work on the small scale.

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PHENOL-HALO-PHTHALEINS. PRELIMINARY PAPER[1]

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Extensive practical use has been made of the fact that the halogens, chlorine, bromine and iodine, when introduced into certain synthetic organic compounds, greatly increase the hypnotic activity in some cases and in other instances augment the antiseptic power of the parent substance; chlorine and bromine are used especially for the former purpose, iodine for the latter.

It would be of considerable interest to know just what change could be effected by the introduction of fluorine instead of the other halogens. At present very little information is to be found in the literature regarding the physiological activity of any type of organic fluorine compounds;[2] to a large extent our lack of knowledge of these substances may be attributed to the fact that comparatively few organic fluorides have been prepared.

Phenolphthalein and various tetra-halogen substitution products have found extensive use in medicine, the former as a laxative, the latter as diagnostic agents. Fluoro derivatives of phenolphthalein have never been described. Since the effect of fluorine can be determined only by comparison of the fluoro compound with the corresponding chloro, bromo and iodo derivatives, we decided to attempt the preparation of the complete series of substances—phenol-fluoro-, -chloro-, -bromo- and -iodo-phthalein.

We prepared, first, five mono-halogenated phthalic acids, the 4-fluoro-,

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[2] Frankel, "Die Arzneimittel-Synthese," J. Springer, Berlin, **1927**, p. 616.