A Study of the Grignard Reaction as Applied to Student Preparations

KENNETH WHELAN and FRANK J. WELCHER, Indiana University Extension Division

The use of Grignard reagents as intermediates in organic synthetic chemistry has become increasingly more important in the forty-three years which have elapsed since V. Grignard (1) succeeded in resolving Barbier's (2) original synthesis of dimethylheptenol from methyl iodide, magnesium and methylheptenone into its now familiar two steps, consisting (a) of the formation of the methyl magnesium iodide, and (b) the coupling of this compound with the carbonyl group of methylheptenone. In the period from 1900 to 1920, following this discovery, there appeared in the literature more than 1500 articles concerning the use and application of Grignard reagents. No present day organic chemist needs to be shown justification of the importance of Grignard reagents, since their versatility is forcibly demonstrated in everyday synthetic work.

The importance of these reagents is duly stressed in lectures in elementary organic chemistry and is frequently somewhat neglected in the laboratory course which accompanies these lectures. The same may be true of other reactions of organic chemistry, such as the Wurtz synthesis, the Friedel-Craft reaction, and others; but justification may be made that these latter syntheses are often difficult for the student to perform properly. Grignard reagents, and compounds formed from them, may, however, be easily prepared with only the reagents and equipment usually available in laboratories devoted to instruction in elementary organic chemistry. In laboratory courses in elementary organic chemistry, one typical Grignard reaction is usually included. Even with adequate experimental directions, however, student yields are frequently very low and in some cases the desired product is not obtained. Since the separative procedures are not difficult, nor different from many others students perform with good results, it appears that the difficulty lies in the formation of the Grignard reagent, or in the coupling reaction which follows. With this thought in mind, the desirability of studying the conditions necessary for a good yield of a Grignard reagent became apparent. To this end, the following experiments were planned.

A typical student preparation of phenyl ethyl carbinol from an ethyl halide, magnesium, and benzaldehyde, by the method of Grignard (1-3), was used as a standard procedure. Conditions were carefully controlled, and in each series of experiments only one variation was permitted in order to show the effect, in terms of percent theoretical yield, on the result. Among the factors affecting the yield are: (a) use of the proper halide, (b) purity or dryness of the ether, (c) manipulation of the reagents during the formation of the Grignard reagent, and (d) exclusion

of atmospheric moisture. With proper attention to these four details, it is shown that an average yield as high as 82.5% of theory can be obtained in this preparation. Careful attention on the part of instructors to these four details should show organic students that the Grignard reaction is a very useful laboratory procedure and not "just another textbook or theoretical reaction."

Experimental

The equipment consisted of a one liter Florence flask fitted with a two-hole stopper and carrying a separatory funnel and water condenser arranged at an angle of 45° for reflux. A small calcium chloride tube was fitted to the upper end of the condenser to exclude atmospheric moisture.

Reagents:

24.4 grams of ethyl bromide or equivalent quantity of ethyl iodide or ethyl chloride.

5.4 grams of magnesium turnings which were new and bright.

150 ml. ethyl ether.

25 grams of freshly distilled benzaldehyde.

The following method, described by Grignard (1-3) was used throughout:

The magnesium is placed in the liter flask, and a solution of the alkyl halide in 100 ml. of ether is placed in the separatory funnel. One-quarter of the alkyl halide-ether solution is then run into the flask, and a period of 5 minutes is allowed for the reaction to start. If, after this time, there is no indication that the reaction has begun, such as a cloudy appearance of the mixture, or a gentle boiling of the ether, a small crystal of iodine is added to the flask. If after another 5 minutes the reaction still has not started, a piece of the magnesium is rubbed with the flattened end of a glass rod; and if this fails, the mixture is gently warmed until the ether just begins to boil. When the initial violence of the reaction has subsided, the remaining ether-alkyl halide solution is allowed to drip in just fast enough to maintain the reaction. Approximately 40 drops per minute is adequate for this operation. After the addition of the alkyl halide, add 25 ml. of ether to the separatory funnel to wash the last traces of the alkyl halide into the flask. Reflux the mixture for 30 minutes. Cool in an ice-bath, and allow the benzaldehyde, mixed with an equal volume of ether, to flow in slowly from the separatory funnel with constant shaking. This should require approximately 20 minutes. Cork and allow the mixture to stand overnight.

Hydrolyze the mixture with 3 N. HCl, adding a sufficient excess to dissolve any unattacked magnesium. Separate the ether layer, wash with 25 ml. of 10% sodium bicarbonate, and then with 25 ml. of 10% sodium bisulfite, and finally with another 25 ml. portion of 10% sodium

bicarbonate solution. Dry the ether solution with anhydrous potassium carbonate, and then distill off the ether and fractionate the residue. Collect the fraction boiling at 200-215° C. as phenyl ethyl carbinol. The theoretical yield, based upon the alkyl halide, is 30.5 grams.

Effect of alkyl halide upon yield. (Series 1)

Since the variety of alkyl halides usually available in the average organic laboratory is somewhat limited, it is frequently necessary to use a chloride, bromide or iodide when one of the other halides is specifically called for by a given procedure. In order to determine whether a resulting increase in yield would justify the additional work of preparing the required halide, the following series of experiments was carried out: Samples of phenyl ethyl carbinol were prepared using as starting materials ethyl chloride, ethyl bromide and ethyl iodide, with all other conditions exactly as described above. Ethyl bromide gave 82.5% of theory, while ethyl chloride gave 78.9% of theory and ethyl iodide gave 68.6% of theory. (All percentage results are averages of at least three experiments.)

Effect of grade of ether upon yield. (Series 2)

In the many procedures examined, various directions were found for preparing the ether. Some of these were time consuming and wasteful, or otherwise undesirable, and so to determine exactly the effect of various grades of ether on the yield, ether samples of different quality were used. These were:

(a) Ether dried over metallic sodium and distilled over metallic sodium.

(b) Ether dried over calcium chloride for two weeks.

(c) Ether dried over calcium chloride for 24 hours.

(d) Ether dried over calcium chloride for 1 hour.

(e) Ether used as purchased. (Contained water and about 3.5% ethyl alcohol.)

(f) Absolute ether which had been saturated with water.

The results are given in Table I.

Effect of improper manipulation of reagents on yield. (Series 3)

The procedure for preparing phenyl ethyl carbinol described above may be made somewhat simpler, both in amount of time required and in the complexity of equipment needed, by mixing all the alkyl halide with the ether, and then adding the magnesium and refluxing or controlling the reaction by suitably cooling the mixture. The following experiments were conducted to determine the justifiability of the longer method. Ethers of the same grades as used in Series 2 were used and all conditions remained the same with the exception that the entire quantity of the

alkyl halide-ether solution was added to the magnesium at once, and, if the reaction became violent, the mixture was cooled with an ice-bath. The results are given in Table I.

Effect of atmospheric moisture on yield. (Series 4)

In this series of experiments all of the conditions of the second series were duplicated with the exception that the calcium chloride tube was removed from the upper end of the condenser, thus allowing the reaction mixture to be in contact with atmospheric moisture during the time of addition of the alkyl halide, refluxing, and addition of the benzaldehyde (about 1½ hours in all). The results are given in Table I.

Discussion

Under the best conditions of the procedures used, an average yield of 82.5% of theory was obtained. The experiments clearly show: (a) The choice of the proper alkyl halide is essential to good yield. In these experiments the iodide gave a low yield probably because of the tendency of one mole of the alkyl magnesium iodide to react with another mole of the alkyl iodide to form an alkane as suggested by Gilman and West (4). The chloride and the bromide gave essentially the same yields but the handling of the volatile ethyl chloride makes its use impractical in a student preparation. (b) Improperly dried ether, or ether containing ethyl alcohol, was found to cause a serious depression in the yields. With ether which had been saturated with water the desired product was never obtained, and with ethers which had been dried over calcium chloride yields were at least 20% lower than those obtained under an ideal condition of absolute ether. With absolute ether, it was found unnecessary to resort to catalytic devices, such as iodine, to start the reaction, except in the case of the unreactive chloride. Many such devices are suggested in the literature (5, 6, 7, 8, 9, 10, 11) and the three most common are incorporated in the procedure to be used if necessary. Since the use of iodine was found unnecessary in experiments using absolute ether, the washing of the ether solution of phenyl ethyl carbinol with sodium bisulfite could have been eliminated and the yields probably increased. For the sake of uniformity in these experiments, all samples were washed with sodium bisulfite solution. With even traces of water present in the ether, it was necessary to use iodine, and, in some instances, the other two catalytic methods to start the reaction. (c) Proper manipulation of the reagents was found to be another essential feature. For example, if all of the alkyl halide, in its ether solution, was added to the magnesium at one time and the reaction controlled with cooling, the reaction at times was too vigorous to control. Flooding of the condenser with considerable loss of ether sometimes resulted, and at other times, the reaction would stop completely and the mixtures would have to be warmed gently to start again. Yields in every instance were some 20% lower than those experiments in which the alkyl halide-ether mixture was added slowly to the magnesium. (d) The exclusion of atmospheric moisture, by the use

of a calcium chloride tube fitted to the upper end of the condenser, was found essential, since yields dropped from 10 to 20% when this item of equipment was eliminated.

All of the above experiments were controlled so that they could be completed in two three-hour laboratory periods.

The above experimental results constitute a summation of research which has been presented before by many authors. It is hoped, however, that from these results, instructors of elementary organic chemistry will find some helpful facts which will enable them to show the student more satisfactorily the value of the Grignard reaction.

TABLE I.

Grade of Ether	Average % of Theoretical Yield* *Series 2*	*Series 3*	*Series 4*
Ether dried over metallic sodium	82.5	58.7	52.7
Ether dried over calcium chloride for two weeks	60.4	42.6	40.8
Ether dried over calcium chloride for 24 hours	59.7	44.7	39.4
Ether dried over calcium chloride for 1 hour	58.4	35.6	36.5
Ether as purchased (contained approx. 3.5% ethyl alcohol)	42.8	22.7	28.9
Absolute ether which had been saturated with water	0.0	0.0	0.0

* All percentages are averages of at least three experiments.

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