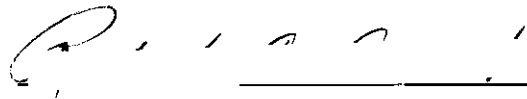


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b

THE MECHANISM OF THE NORMAL GRIGNARD ADDITION
REACTION WITH KETONES AND NITRILES

A THESIS

Presented to

The Faculty of the Graduate Division

by

Robert Charles Arnott

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Chemistry

Georgia Institute of Technology

June, 1967

THE MECHANISM OF THE NORMAL GRIGNARD ADDITION
REACTION WITH KETONES AND NITRILES

Approved:

[Handwritten signature]

Chairman *[Handwritten initials]* _____
[Handwritten initials] _____

Date Approved by Chairman: May 10, 1967

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I wish to express my appreciation to Dr. Eugene C. Ashby who suggested the problem and whose encouragement and enthusiasm were a constant driving force. I also wish to convey my thanks to the other members of the reading committee, Dr. Leon H. Zalkow and Dr. Charles L. Liotta, for their helpful comments and criticisms during the preparation of this thesis.

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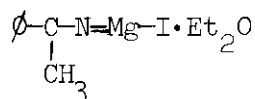
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SUMMARY

The normal addition reaction of a ketone with a Grignard reagent, followed by hydrolysis of the reaction mixture results in the formation of a tertiary alcohol. The intermediates resulting from the reaction of benzophenone with methyl and phenyl Grignard compounds in 1:2 stoichiometry have been isolated, prior to hydrolysis, by fractional crystallization of the reaction mixtures. As the solvent was removed from the reaction mixture under vacuum, a precipitate resulted which was filtered in the dry box. Further stepwise removal of solvent from the reaction mixture resulted in several fractions. In all cases the first fractions obtained were found to contain an alkoxymagnesium halide. This was true regardless of which Grignard compound was used or whether the initial Grignard compound concentration was 0.1M or 1.0M in diethyl ether. The final fraction resulting from the removal of the last traces of solvent, was found to contain unreacted Grignard compound.

Redistribution has been found to occur readily between methylmagnesium 1,1-diphenylethoxide and magnesium iodide dietherate in diethyl solution to form methylmagnesium iodide in 1,1-diphenylethoxymagnesium iodide quantitatively. Thus, it has been shown that alkylmagnesium alkoxides can also be intermediates in the reaction of Grignard compounds with ketones. When inverse addition (e.g. the addition of the Grignard compound to the ketone) was used, employing a 1:1 ratio of reactants the product was again 1,1-diphenylethoxymagnesium iodide.

The intermediate resulting from the reaction of benzonitrile with methylmagnesium iodide in 1:2 stoichiometry, was isolated and found to be (I), with unreacted Grignard compound again found in the last fraction.



I

A kinetic investigation was attempted in order to determine the mechanism whereby a ketone reacts with a Grignard compound. 2-Methyl-4-mercaptomethylbenzophenone and methylmagnesium chloride was found to be a satisfactory system for the study. No suitable data was obtained with which to determine the kinetic order of the reaction. A system of analysis was developed, utilizing ultraviolet spectroscopy, with which it was possible to reproduce values for the initial concentration of the ketone to within one per cent. Initial difficulty in preparing stable Grignard solutions at low concentration was overcome. The best method found for preparing Grignard compounds in triethylamine consisted of running the reaction in triethylamine solvent which was previously distilled from a triethylamine solution of the Grignard compound to be prepared in the reaction.

CHAPTER I

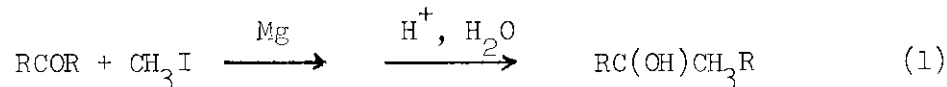
INTRODUCTION AND HISTORICAL BACKGROUND

Grignard reagents have been the subject of much interest and controversy since their discovery in the year 1900¹. Since then many attempts have been made to determine the structure and composition of the reagent and to understand the mechanisms by which Grignard compounds react with various classes of organic compounds. A great many contributions have been made in these areas, particularly in the 1950's and early 1960's, however, many are conflicting and lead to confusion and speculation.

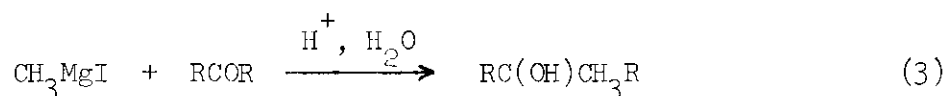
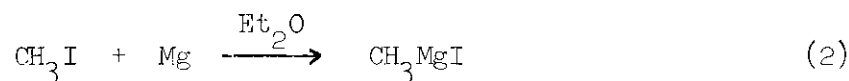
It would appear that an exact description of a reaction mechanism is impossible unless the reacting species are known with certainty. Therefore, one must forego consideration of the mechanism whereby a Grignard reagent reacts with an organic functional group until the composition of the Grignard compound in solution is well understood. Before discussing the ultimate objective of this research, which concerns the mechanism of Grignard compound addition to ketones, it is necessary first to consider the nature of the species present in ether solutions of Grignard compounds.

Barbier² first discovered in 1899 that alkyl halides and ketones react with magnesium metal to produce, on hydrolysis, tertiary alcohols.

-
1. V. Grignard, Compt. rend., 130, 1322 (1900).
 2. P. Barbier, Compt. rend., 128, 110 (1899).



In 1900 Victor Grignard¹, after whom the reagent is named, discovered that the reaction is actually a two step process involving the formation of an alkylmagnesium halide followed by subsequent reaction with the ketone, to yield on hydrolysis the tertiary alcohol.



Although " CH_3MgI "* is not the only species in solution, it is most often used to predict the products of the reaction.

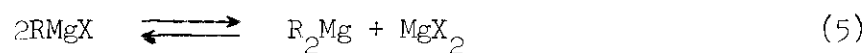
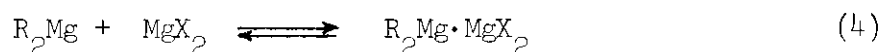
Several early workers reported on the composition of Grignard compounds in solution. Perhaps the best known is that of Jolibois³, who in 1912 proposed a dimeric structure ($\text{Et}_2\text{Mg} \cdot \text{MgBr}_2$) for the Grignard compound, ethylmagnesium bromide. He based his conclusion on the following facts: (1) $\text{MgI}_2 \cdot 2\text{Et}_2\text{O}$ was already known, (2) Et_2Mg is soluble in a diethyl ether solution of $\text{MgI}_2 \cdot 2\text{Et}_2\text{O}$, and (3) " EtMgBr " like Et_2Mg decomposes at elevated temperature (~ 175) in the absence of air to give MgH_2 and ethylene. Further support for a dimeric structure was proposed

*The quotation marks, as in " CH_3MgI ", will be used not to indicate the RMgX species, but merely the Grignard compound formed in the reaction of the alkyl halide with magnesium.

3. P. Jolibois, Compt. rend., 155, 353 (1912).

by Terentiev⁴ in 1926, who showed by ebullioscopic measurements that methylmagnesium iodide was dimeric in diethyl ether solution using a .34 M concentration of the Grignard compound.

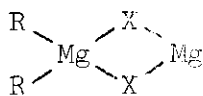
Schlenk and Schlenk⁵ in 1929 proposed the equilibria (4) and (5) to explain the composition of Grignard compounds in diethyl ether solutions. They observed that the addition of dioxane to a Grignard solu-



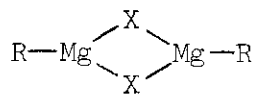
tion precipitated the magnesium halide as the bis-dioxanate, whereas the dialkylmagnesium compound remained in solution. From this, they also attempted to derive equilibrium constants, but later workers showed that the equilibrium is mobile and that the amount of magnesium halide that precipitates is a function of the reaction time. It is apparent that all the halogen does not exist in diethyl ether solution as MgX_2 since the solubility of the Grignard compounds, exceeds the solubility of pure magnesium halide. Therefore, the magnesium halide must be associated as represented by the unsymmetrical dimer (I) or it may exist in the form $RMgX$, and the associated symmetrical dimer (II).

4. A. P. Terentiev, Z. Anorg. Chem., 156, 73 (1926).

5. W. Schlenk and W. Schlenk, Jr., Ber., 62B, 920 (1929).

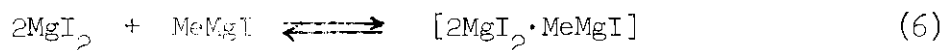


I



II

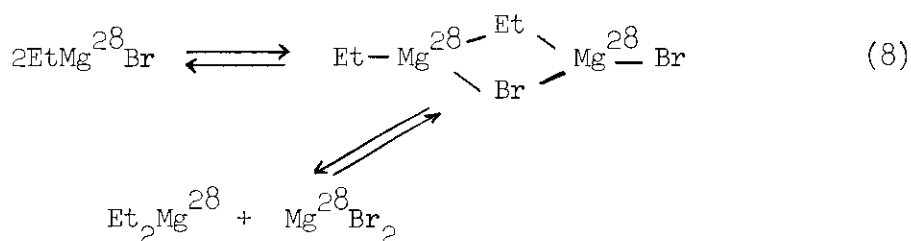
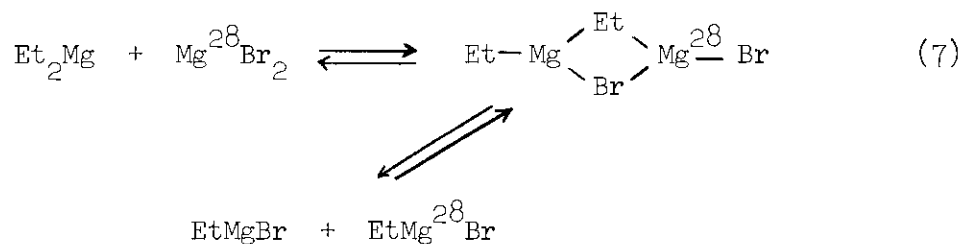
Stewart and Ubbelode⁶ studied the equilibrium in a system containing methylmagnesium iodide and magnesium iodide in diethyl ether. They evaluated the magnesium iodide concentration from freezing point data, and their results can be accounted for on the basis of an equilibrium.



Dessy⁷, in his classical exchange experiments of 1957, attempted to either prove or disprove the presence of RMgX species in solution. He mixed Et_2Mg and isotopically labeled $\text{Mg}^{28}\text{Br}_2$ and allowed the mixture to reach equilibrium. He then precipitated the magnesium bromide with dioxane and found that all of the activity remained with the magnesium bromide. The conclusion of this experiment was that no exchange took place, and hence monomeric EtMgBr did not exist in a Grignard solution. If exchange had taken place it should have occurred through an RMgX species, thus resulting in a loss of activity for the precipitated magnesium bromide and a gain in activity for the Et_2Mg remaining in solution.

6. R. Stewart and A. R. Ubbelode, J. Chem. Soc., 2649 (1949).

7. R. E. Dessy, G. S. Handler, J. H. Wotiz and C. A. Hollingsworth, J. Am. Chem. Soc., 79, 3476 (1957).

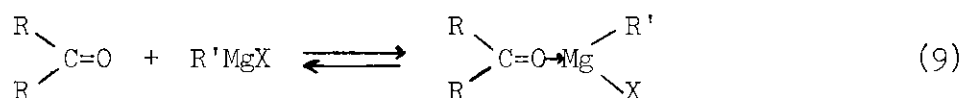


Dessy observed only six to ten percent exchange after thirty-six hours using Mg^{28} and concluded that this was not due to the formation of RMgX species in solution. However, using Mg^{25} he did observe exchange. This result was largely deemphasized and attributed to impurities in the Mg^{25} . Thus, the absence of monomeric RMgX became accepted and mechanisms describing reactions of Grignard compounds were proposed on the basis of an attacking unsymmetrical dimeric species (I).

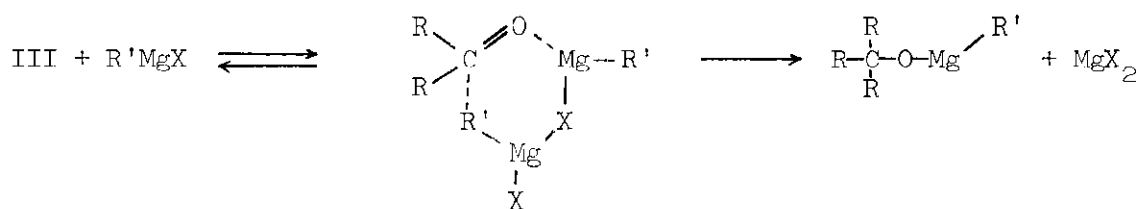
It should be noted here that in 1951 prior to Dessy's isotope experiment, Swain⁸ proposed a mechanism (9), for Grignard compound addition to ketones involving complexation by a monomeric RMgX species, followed by subsequent attack by a second molecule of the same type. Transfer of the alkyl group from the magnesium atom to the carbonyl carbon was pictured as taking place via a six centered transition state.

8. C. G. Swain and H. B. Boyles, J. Am. Chem. Soc., 73, 870 (1951).

This mechanism would involve overall third-order kinetics, second-order in monomeric RMgX and first-order in ketone, if the second step were rate controlling. By adding an equivalent amount of MgBr_2 to the ketone Swain found that he was able to increase the yield of addition product from 35 to 65 percent, with a corresponding decrease in the amount of reduction product. He concluded that MgBr_2 must complex first with the ketone, (10), decreasing the amount of (III) that forms when the Grignard compound is added, and thereby decreasing the amount of reduction product.

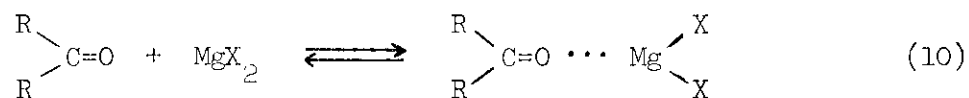


III

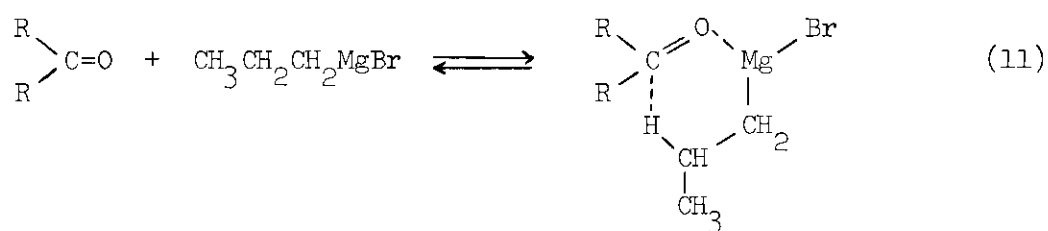


IV

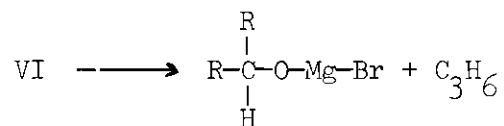
V



The reduction of ketones by Grignard compounds was also represented by a six-centered transition state (11) involving a monomeric RMgX species complexed to the ketone, and showing migration of a β -hydrogen from the alkyl group on the Grignard compound to the carbonyl carbon. The reduction mechanism referred to by Swain, was first proposed by Whitmore⁹. This mechanism was later substantiated by Dunn and Warkentin¹⁰



VI



VII

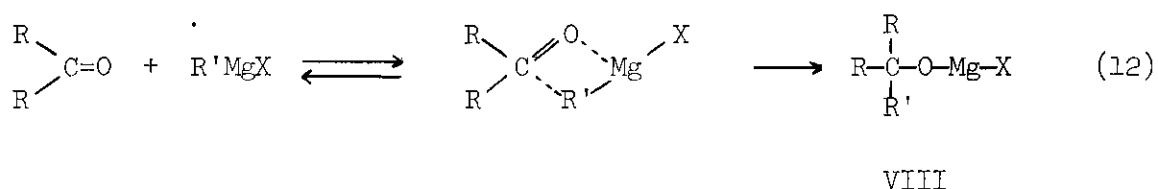
who studied the reduction of ketones by Grignard compounds, in which the β -hydrogens were replaced by deuterium atoms. They found that a deuterium atom migrated to the carbonyl carbon, in agreement with the above mechanism. It is also important that reduction does not occur

9. F. C. Whitmore and R. S. George, J. Am. Chem. Soc., 64, 1239 (1942).

10. G. E. Dunn and J. Warkentin, Can. J. Chem., 34, 75 (1956).

unless there is a β -hydrogen present in the Grignard molecule⁹.

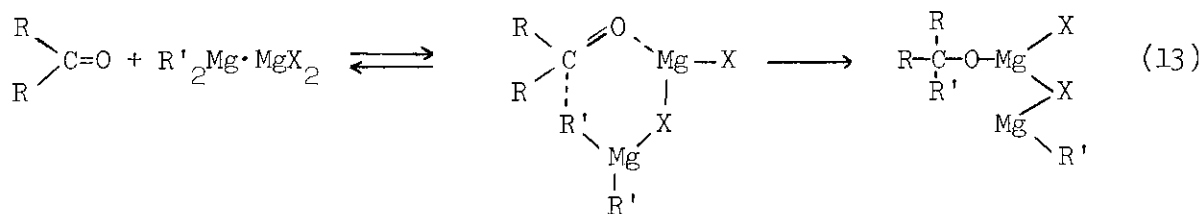
Meisenheimer¹¹ proposed a mechanism for the addition reaction involving the rearrangement of a Werner type complex via a four centered transition state to give intermediate (VIII). The Meisenheimer mechanism involves second-order overall kinetics, first-order in monomeric Grignard compound and first-order in ketone. In lieu of Dessy's exchange experiments both the Swain and Meisenheimer mechanism were judged to be incorrect.



Influenced by the new Grignard composition proposed by Dessy, Miller, et al.¹² proposed a mechanism involving attack by the unsymmetrical Grignard dimer (I). They studied the system diisopropyl ketone and "EtMgBr", and found the reaction to be first-order in ketone and first-order in Grignard dimer. Transition state (IX), in which the carbonyl oxygen is complexed to the magnesium containing the halogen, leads to addition and (X), while (XI) leads to reduction and (XII). A second molecule of ketone could undergo attack by either intermediate (X) or (XII), in a similar manner, generating more addition or reduction product.

11. J. Meisenheimer, Ann., 442, 180 (1925).

12. J. Miller, G. Grigoriou and H. S. Mosher, J. Am. Chem. Soc., 83, 3966 (1961).



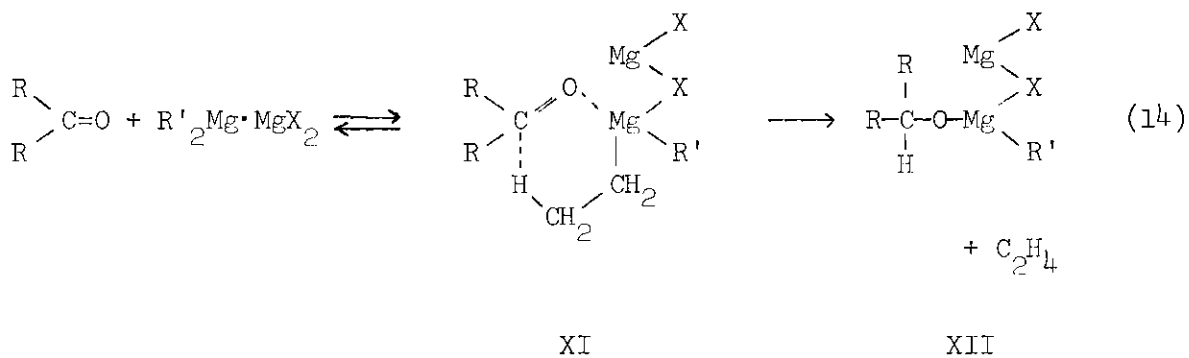
R=isopropyl

IX

X

R'=ethyl

X=bromide



XI

XII

Regardless of whether the symmetrical or unsymmetrical Grignard dimer is used to describe the reaction mechanism, two alkyl groups are attached to each molecule of the Grignard dimer. Bikales and Becker¹³ had shown earlier that the reactivity of these two alkyl groups is vastly different. When fifty percent of the alkyl groups present in a Grignard solution (e.g. one-half the number of equivalents of magnesium) and undergone reaction, the rate decreased eighty-five fold in the case of a ketone. With a nitrile, the reaction essentially halted completely after one-half of the available alkyl groups had

13. N. M. Bikales and E. I. Becker, Chem. Ind., 1831 (1961).

reacted¹⁴. Addition of benzaldehyde to the Grignard-nitrile mixture produced the products expected in the normal reaction of benzaldehyde with a Grignard compound. This indicated that the remaining alkyl group is still capable of undergoing the expected reaction but that its reactivity is in some way hampered. The mechanism of Miller, et al. appears to be consistent with these results, since the reactivity of the intermediates prior to reaction with the second molecule of ketone would be expected to be less than that of the original Grignard compound.

Cowan and Mosher¹⁵ found in 1962 that changing the halogen had more effect on the rate of addition than on the rate of reduction. This would be expected from the above mechanism, in which the halogen plays more of a role in the addition intermediate, than in the reduction intermediate. It is now known that the halogen also influences the composition of the Grignard compounds in diethyl ether solution.

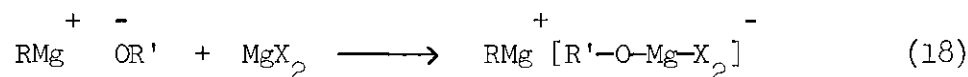
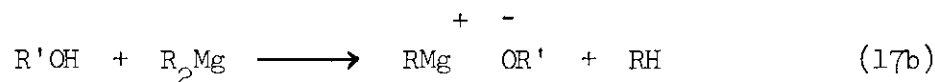
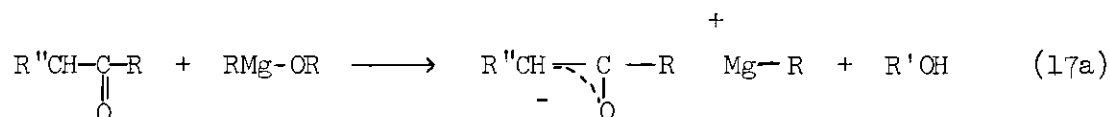
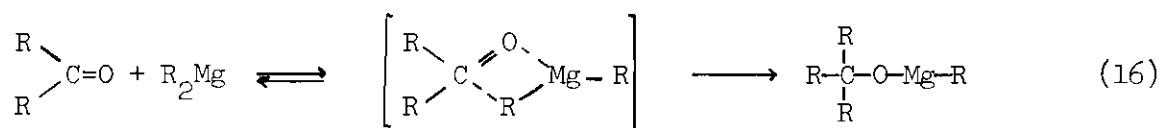
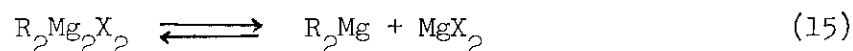
House and Traficante¹⁶ proposed a mechanism for the Grignard compound addition reaction involving attack by only the dialkyl magnesium. They studied the reaction of diethylmagnesium with diethyl ketone and found the rate of reaction to be 50 times greater than the rate of reaction when ethylmagnesium bromide was used. Furthermore, they observed that when only diethylmagnesium was used that the amount of enolization and reduction products was greater than when a Grignard compound was used. Unlike the mechanisms proposed earlier

14. S. J. Storfer and E. I. Becker, J. Org. Chem., 27, 1868 (1962).

15. D. O. Cowan and H. S. Mosher, J. Org. Chem., 27, 1 (1962).

16. H. O. House and D. O. Traficante, J. Org. Chem., 28, 355 (1963).

by other workers^{8,12,15} they did not propose that magnesium halide present in a Grignard compound in solution played any part in the transition state leading to the normal addition product, but that the magnesium halide depressed the ability of the intermediate alkylmagnesium alkoxide to catalyze the enolization of the ketone (17a, b, 18). For the normal addition reaction House and Traficante concluded that their

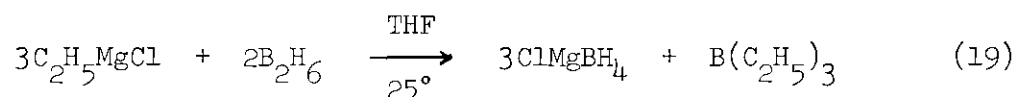


data best fit second-order kinetics, first-order in ketone and first-order in dialkylmagnesium. It is probable that the transfer of the alkyl group from the magnesium atom to the carbonyl carbon takes place

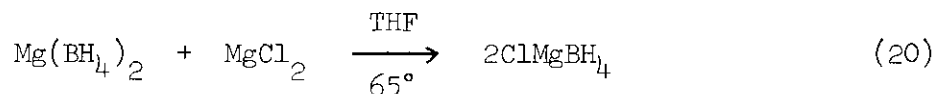
via a four centered transition state.

From consideration of all of these reports it was not possible to draw any satisfactory conclusion concerning the mechanism of the reaction. No one had obtained indisputable kinetic data which presented a clear cut picture.

Ashby and Becker¹⁷, studied the reaction of diborane with "EtMgCl" in tetrahydrofuran solution. They found that quantitative yields of chloromagnesium borohydride were produced.



Chloromagnesium borohydride was shown to be stable to disproportionation and monomeric in boiling tetrahydrofuran. If, the Grignard had appreciable amounts of dialkylmagnesium, either associated or unassociated, the product isolated should have been magnesium borohydride. However, $\text{Mg}(\text{BH}_4)_2$ and MgCl_2 were found to redistribute to chloromagnesium borohydride, and the results are therefore, inconclusive.

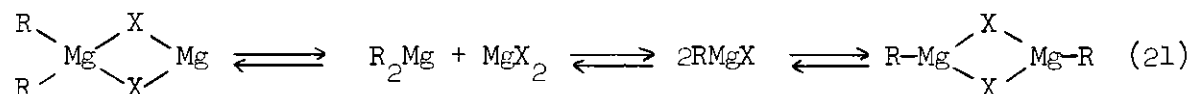


Ashby¹⁸, in further work on a similar Grignard compound in tetrahydrofuran solution, concluded that monomeric RMgX species do exist.

17. W. E. Becker and E. C. Ashby, J. Inorg. Chem., 4, 1816 (1965).

18. E. C. Ashby and W. E. Becker, J. Am. Chem. Soc., 85, 118 (1963).

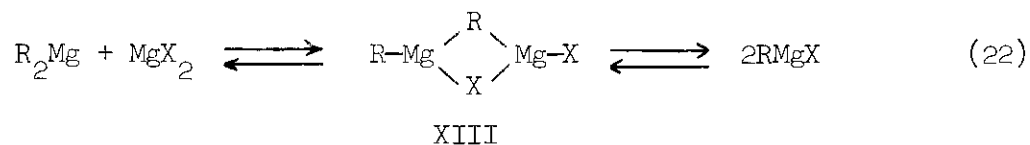
Fractional crystallization of a Grignard, "EtMgBr", produced a quantitative yield of the species EtMg_2Br_3 and Et_2Mg . When put back into tetrahydrofuran, the EtMg_2Br_3 showed an i factor of 0.5 indicating that it dissociated to two species which could only be EtMgBr and MgBr_2 . The concentration was not given. Similar results were found in diethyl ether but the RMg_2X_3 compounds were not soluble and association studies could not be made. Association studies of ethylmagnesium chloride in diethyl ether solution did show the presence of dimeric species over a concentration range measured from .05 M to .2 M. The Schlenk equilibrium (5) was suggested to describe Grignard compound composition in tetrahydrofuran and an expanded Schlenk equilibrium involving dimeric species to represent the Grignard compounds in diethyl ether.



Further evidence for the presence of monomeric RMgX was found by Ashby¹⁹ when he quenched an ether solution of ethylmagnesium bromide with a large volume of triethylamine. Fractional crystallization of the resulting triethylamine solution resulted in seven fractions all analyzing for the species $\text{EtMgBr} \cdot \text{Et}_3\text{N}$, showing a Mg:Br:N ratio of 1:1:1. If MgBr_2 existed to any extent in the diethyl ether solution of "EtMgBr", it is being the strongest Lewis acid should have complexed first with the

19. E. C. Ashby, J. Am. Chem. Soc., 87, 2509 (1965).

triethylamine and having a very low solubility, crystallized in the early fractions. In the same report it was shown that if EtMgBr was prepared directly in triethylamine, and the reaction mixture fractionally crystallized, the species isolated was again EtMgBr·Et₃N in all fractions giving a Mg:Br:N ratio of 1:1:1. Molecular association studies of these fractions showed them to be monomeric. Et₂Mg and MgBr₂ were shown not to redistribute to EtMgBr in triethylamine, the solvent being a strong enough base to tie up the magnesium orbitals and prevent the formation of the dimer (XIII). The data implied that the first formed species in the reaction of an alkyl halide with



magnesium must be monomeric RMgX, and that this species is definitely present in appreciable amounts in diethyl ether solution.

Stucky and Rundle²⁰ reported that X-ray studies of phenylmagnesium bromide, obtained by evaporation of the solvent from an ether solution of "ϕMgBr", showed the crystal to be made up of monomeric ϕMgBr units with the coordination around the magnesium atom satisfied by two molecules of diethyl ether.

20. G. D. Stucky and R. E. Rundle, J. Am. Chem. Soc., 85, 1002 (1963).

In 1964 Dessy, et al.²¹ repeated the exchange work reported earlier involving Et_2Mg and $\text{Mg}^{28}\text{Br}_2$. They found that exchange occurred in all cases except when "Dow atomized shot" grade magnesium was used. This was also the most impure sample of magnesium in the study. Shortly thereafter, Cowen, et al.²² reported exchange in the system $\text{Et}_2\text{Mg}\cdot\text{MgBr}_2$. In light of these findings the proposed mechanisms representing the attacking species by the unsymmetrical dimer no longer appeared as likely. The possibility of attack by a monomeric RMgX species was again introduced to explain the mechanism of Grignard compound addition to ketones.

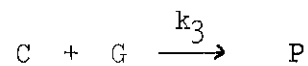
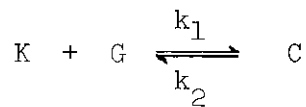
Anteunis²³ performed several experiments in the early 1960's which showed that Grignard compound addition to ketones proceeds by third order kinetics. A Hammett study indicated that the rate controlling step was the transfer of the alkyl group from the magnesium atom to the carbonyl carbon²⁴. The mechanism proposed was the same as the Swain mechanism represented by equation (9). To explain the kinetic results Anteunis applied a steady state approximation to the complex obtained prior to the transfer of the alkyl group. A steady state treatment showed that if k_3 , the transfer of the alkyl group from the

21. R. E. Dessy, S. Green and R. M. Salinger, Tetrahedron Letters, 8, 1369 (1964).

22. D. O. Cowen, J. Hsu and J. D. Roberts, J. Org. Chem., 29, 3688 (1964).

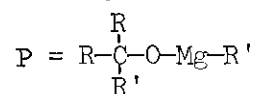
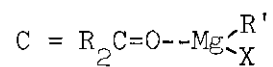
23. M. Anteunis, J. Org. Chem., 26, 4211 (1961).

24. M. Anteunis and T. Van Schoote, Bull. Soc. Chim. Belg., 72, 776, (1963).



K = ketone

G = monomeric Grignard, R'MgX



magnesium atom to the carbonyl carbon was rate controlling the reaction would obey overall third-order kinetics, second-order in Grignard monomer and first-order in ketone.

$$\text{Rate} = \frac{-dK}{dt} = \frac{k_1 k_3 [G]^2 [K]}{k_2 + k_3 [G]}$$

$$\text{if: } k_2 \gg k_3 [G]$$

$$\frac{-dK}{dt} = \frac{k_1 k_3 [K] [G]^2}{k_2}$$

One of the most significant contributions to the mechanism of Grignard compound addition to ketones, was published by Smith^{25,26} in 1963. Smith used substituted benzophenone system in his study, and was able to observe new bands in the ultraviolet region of the spectrum for complex formation when he added the various ketones to different species present in a Grignard solution. Smith showed that distinction could be made between a complex formed on the addition of Me_2Mg , MeBr_2 or "MeMgBr". The complex bands attributed to Me_2Mg were not in the same position as those attributed to the normal Grignard. Smith found that the complex band and the ketone band disappeared at the same rate, giving good pseudo first-order kinetics for the normal addition reaction. Smith plotted the concentration of an ether solution of methylmagnesium bromide versus the observed pseudo first-order rate constant and found that the curve was not linear, but tapered off at higher Grignard concentrations (Fig. 1). However, applying the results of Ashby's²⁷ molecular weight studies, and plotting the concentration of monomeric species, the graph is linear at all concentrations. This seems to indicate that the attacking species is probably monomeric CH_3MgBr . Since Smith's data is given in terms of molal concentration the assumption was made that the density of the Grignard solution was the same as the density of ether and the conversion to molal concentration was made.

25. S. G. Smith, Tetrahedron Letters, 7, 409 (1963).

26. S. G. Smith and G. Su, J. Am. Chem. Soc., 86, 2750 (1964).

27. E. C. Ashby and M. B. Smith, J. Am. Chem. Soc., 86, 4363 (1964).

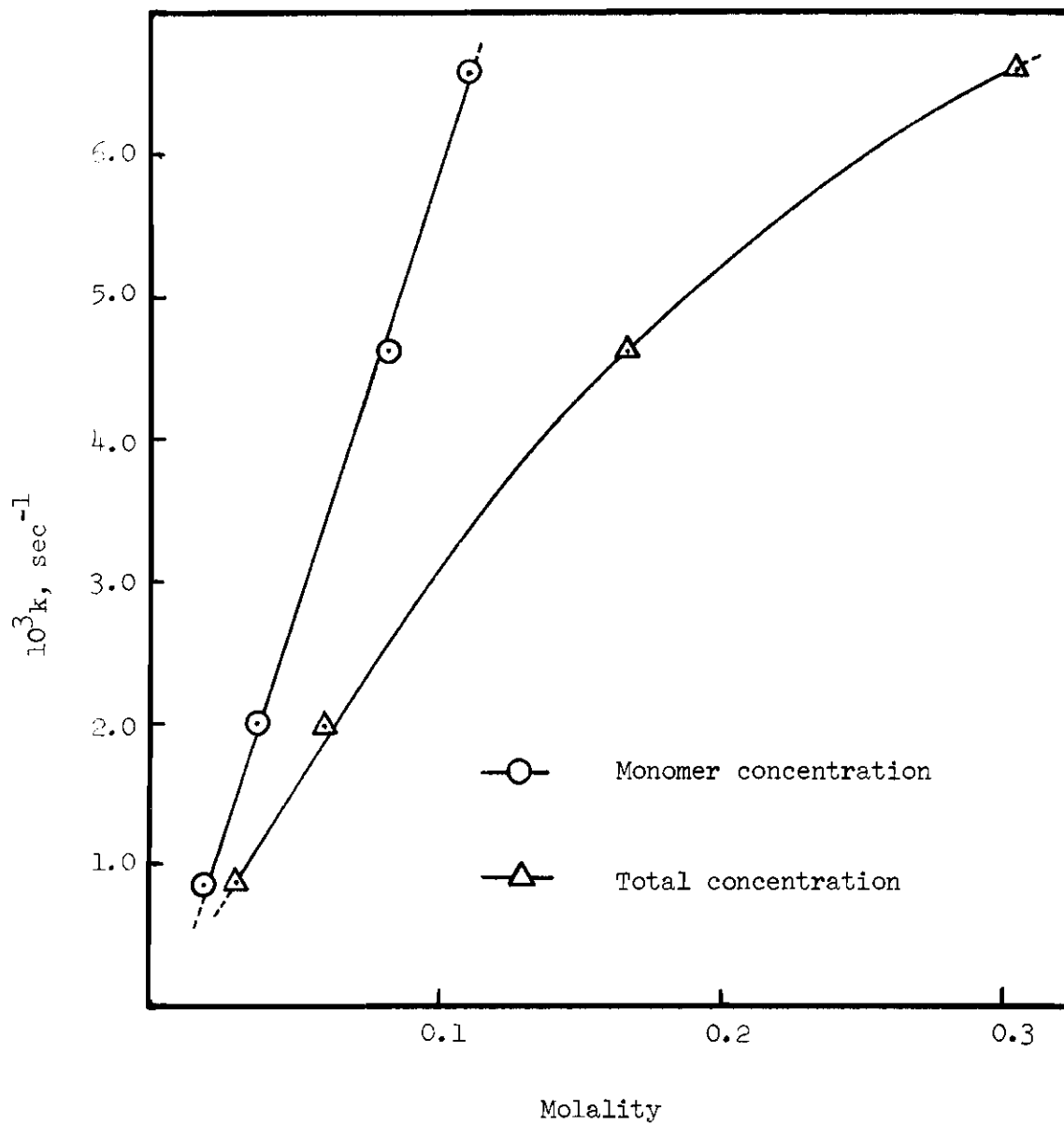


Figure 1. Graph of the Pseudo-first Order Rate Constant versus Concentration of the Grignard Compound from the Reaction of 2,4-Dimethyl-4'-mercaptomethylbenzophenone with Methylmagnesium Bromide in Diethyl Ether.

After reviewing the prior art in this area some logical approaches to further study became apparent. Since several of the proposed mechanisms postulate different intermediates, the first consideration was to isolate and determine the composition of the intermediate formed when a Grignard reagent and ketone react. In all cases, systems were chosen to eliminate side reactions, such as enolization and reduction, thereby limiting the formation of intermediates to only the addition reaction. Benzophenone, with no α hydrogens capable of enolization, and methyl and phenyl Grignard compounds were used predominantly in this study.

Since the results of this work were informative, but inconclusive a kinetic study was then undertaken, in an attempt to determine the kinetic order of the reaction with respect to ketone and Grignard compound. The carbonyl absorption band in the ultraviolet region for the ketones made spectroscopy a useful tool with which to follow the extent of the reaction. Triethylamine, a solvent in which the Grignard compound is known to be represented only by monomeric RMgX was chosen. Thus, any rate constants obtained were the rate constants only for the reaction of one species in the Grignard solution and not a summation of rate constants due to several species reacting competitively.

CHAPTER II

EXPERIMENTAL

All reactions involving organometallic compounds were carried out under a nitrogen atmosphere (unless otherwise stated to be argon), in a system flamed and flushed with nitrogen prior to the addition of the organometallic compound. The conventional apparatus for most of the reactions consisted of a three necked reaction vessel equipped with appropriate dropping funnels and condensers. All fittings were ground glass.

All diethyl ether used, other than what was used for extraction purposes, was freshly distilled over lithium aluminum hydride, unless otherwise specified. All triethylamine was distilled over sodium aluminum hydride directly prior to use unless otherwise stated. All alkyl and aryl halides were distilled prior to use through a column packed with glass helices. Organomagnesium compounds used in the synthetic work were prepared using Grignard grade magnesium turnings. Triply sublimed magnesium was obtained from the Dow Chemical Company in ingot form and milled with a cutting tool. These magnesium turnings were then washed with diethyl ether several times to remove any contamination due to oil resulting from the milling operation. All solid samples were dried on a vacuum manifold.

All vapor phase chromatographic analyses were carried out using an F and M 720 Dual Column Programmed Temperature Gas Chromatograph. All ultraviolet spectra were obtained on a Cary 14 Recording

Spectrophotometer. All infrared spectra were obtained on a Perkin Elmer 237B Grating Infrared Spectrophotometer. The nmr spectra were obtained on a Varian A-60 Spectrograph.

The dry box used in these studies was a Kewaunee Scientific Company inert atmosphere box, maintained under an atmosphere of dry nitrogen. Prior to the kinetic study this system was improved considerably. A little giant pump was used to recirculate the box atmosphere continuously, through a dry ice trap to remove any solvent vapor, followed by passage through molecular sieve (type 4-A, 1/16 inch pellets). The atmosphere was then passed through a column containing MnO suspended on vermiculite to remove oxygen from the system. Entry into this dry box involved flushing the entry port for a period of at least 15 minutes prior to opening the inside door, or if conditions permitted, a vacuum of one millimeter was obtained in the entry port itself, and the atmosphere replaced by nitrogen that had passed through the purification train.

Samples were prepared for analysis in the following manner. Liquid samples (e.g. 5 ml of a Grignard compound in diethyl ether solution) were hydrolyzed with isopropyl alcohol and the resulting hydroxides were acidified with dilute sulfuric acid. The ether was then removed with a water aspirator and the aqueous solutions diluted to the appropriate volumes with distilled water. Solid samples (approximately 1 g) were covered with diethyl ether and hydrolyzed with diethyl ether to which a small quantity of distilled water had been added. After hydrolysis the mixture was acidified with sulfuric acid and the ether removed prior to dilution to 250 ml with distilled water. Two 25 ml aliquots

were withdrawn, buffered to pH 10 and a small quantity of eriochrome black T and methyl red indicators added. The samples were then warmed and titrated to the end point with standard ethylenediaminetetraacetic acid. The analysis for halogen was carried out using another 25 ml aliquot to which 5 ml of ethanol had been added. The solution was adjusted to a pH of about 2 using nitric acid and titrated to the potentiometric end point using a standard silver nitrate solution.

Preparation of Methylmagnesium Iodide in Diethyl Ether

Methyl iodide was distilled through a packed column (glass helices) and the fraction taken boiling at 42.9°. Methyl iodide (284 g, 2.0 moles) was then added to 400 ml of diethyl ether in a dropping funnel. Triply sublimed magnesium (49.8 g, 2.05 moles) was placed in a 3 necked reaction flask equipped with a stirrer, condenser and solvent addition funnel containing an additional 400 ml of diethyl ether. The methyl iodide solution was added dropwise with stirring to the magnesium and the reaction proceeded readily. Diethyl ether was added during the course of the reaction and the temperature kept at the point of mildly refluxing ether. The resulting Grignard solution was colorless and clear after filtration. Analysis by the Gilman method showed the solution to be 2.07M in magnesium.

Preparation of Magnesium Bromide in Diethyl Ether

Magnesium metal (26.0 g, 1.07 moles) was added to a reaction vessel equipped with a stirrer, dry ice condenser and thermometer. Bromine (160 g, 1.0 moles) was added to a 125 ml dropping funnel and placed in the apparatus, as was a solvent funnel containing an additional 500 ml

of ether. The bromine was added slowly, with the ether, keeping the temperature between 10 and 20° with an ice bath. After the reaction had gone to completion two layers were observed, a straw colored upper layer and a dark lower layer. The solution was filtered to remove excess magnesium and the solvent removed in vacuo.

Anal: Calcd. for $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$	Mg, 9.42; Br, 61.9
Found	Mg, 9.33; Br, 60.2
Mg/Br	1.0/1.96

Preparation of Magnesium Iodide in Diethyl Ether

Magnesium metal (36.48 g, 1.5 moles) was placed in a 3 necked flask equipped with a stirrer, thermometer, dry ice condenser and addition funnel. Iodine (381 g, 1.5 moles) was dissolved in about 1500 ml of freshly distilled diethyl ether and added to the magnesium over a period of three hours, maintaining the temperature of the reaction at the point of mildly refluxing ether. The reaction was run under a nitrogen atmosphere and shielded from light. After stirring for twelve hours, the solution appeared to contain unreacted iodine, and more magnesium was added, continuing the stirring for several hours. After this time the solution was two phase, a light colored upper layer and a dark red, opaque lower layer. The solvent was removed in vacuo and the sample dried on a vacuum manifold. A portion of the resulting solid (50.0 g) was redissolved in 500 ml of diethyl ether and the solution cooled to 0° precipitating a white crystalline material which after filtration from the cold solvent and drying on the vacuum manifold gave the following analysis.

Anal: Calcd. for $\text{MgI}_2 \cdot 2\text{Et}_2\text{O}$	Mg, 5.70; I, 59.5
Found	Mg, 5.68; I, 57.5
Mg/I	1.0/1.95

Preparation of Dimethylmagnesium in Diethyl Ether

An apparatus was assembled, consisting of a 2 liter 3 necked flask equipped with a stirrer, thermometer, dry ice condenser, solvent addition funnel and a second 500 ml addition funnel over which another dry ice condenser was placed. Methyl chloride (151.5 g, 3.0 moles) was distilled from a Matheson lecture bottle through a column packed with solid NaOH and drierite, and condensed on the dry ice condenser, dropping into the halide addition funnel. The methyl chloride, diluted with 350 ml of freshly distilled diethyl ether was added slowly along with pure solvent into the reaction flask containing magnesium metal (75.0 g, 3.08 moles) with rapid stirring. After 24 hours a white precipitate was observed which was thought to be MgCl_2 . Analysis showed the Grignard solution to be 1.63M in magnesium. p-Dioxane (159 g, 1.8 moles) was added to the Grignard compound to precipitate the magnesium chloride. With the addition of the dioxane a thick white slurry was obtained which was removed by filtration in the dry box. The reaction was maintained under nitrogen at all times and the resulting dialkylmagnesium solution was found to be 0.863M in magnesium. No chloride was detected on addition of silver nitrate to a hydrolyzed sample of the ether solution.

Preparation of Methylmagnesium Chloride in Triethylamine

An apparatus was assembled similar to the one previously described for the preparation of methylmagnesium chloride in diethyl ether. Triply

sublimed magnesium (18.2 g, 0.75 moles) was placed in the reaction vessel. Methyl chloride was distilled into the halide dropping funnel through solid NaOH and drierite, and diluted with 40 ml of freshly distilled triethylamine. A 10 ml portion of the halide solution was added to the magnesium and the mixture heated to 50° to initiate the reaction, during which an additional 300 ml of triethylamine was added. After 24 hours a solid was observed in the reaction flask. This solid was removed by filtration in a dry box and redissolved in benzene to remove the excess magnesium and any ammonium salts formed in the reaction. The benzene solution was fractionally crystallized into two parts (1 and 2) and the triethylamine filtrate fractionally crystallized into two additional parts (3 and 4). The solid materials were dried on a vacuum manifold for 24 hours (72 hours in the case of fraction 1), and gave the following analysis:

Table 1. Fractional Crystallization of Methylmagnesium Chloride from Triethylamine

Fractions	Sample Weight (g)	Mg(%)	Cl(%)	Mg/Cl Ratio
1	6.60	22.4	33.1	1.0/1.01
2	11.60	17.7	24.7	1.0/.96
3	4.60	13.6	19.7	1.0/.99
4	3.88	14.1	18.7	1.0/.91
Calcd. for $\text{CH}_3\text{MgCl}\cdot\text{N}(\text{C}_2\text{H}_5)_3$		13.8	20.2	1.0/1.0

Preparation of Methylmagnesium Chloride in Triethylamine for the
Kinetic Study

A method analogous to the above was employed with the exception that the triethylamine was distilled first from NaAlH_4 and then from a triethylamine solution of methylmagnesium chloride in triethylamine. In this case argon was used instead of nitrogen to supply an inert atmosphere.

Preparation of Phenylmagnesium Bromide in Diethyl Ether

Magnesium (20.0 g, 0.8 moles) was added to a 3 necked flask equipped with two dropping funnels and a dry ice condenser. Bromobenzene (78.0 g, 0.50 moles) was diluted with 150 ml of diethyl ether in one of the dropping funnels and 200 ml of ether was added to the other. The system was kept under a nitrogen atmosphere at all times. The bromobenzene solution was added slowly, at the same rate as the ether, and the reaction started in one minute. The resulting solution was clear and colored. Analysis for Mg and Br showed the solution to be 1.14M in Mg and a Mg/Br ratio of 1.0/1.0.

Preparation of Phenylmagnesium Bromide in Triethylamine

The method used was similar to the preparation in ether with the exception that the temperature was kept at 40 to 50° during the reaction and a 100 percent excess of magnesium was used.

Preparation of 1,1-Diphenylethanol

Methylmagnesium iodide (935 ml of a 2.14M solution in diethyl ether, 2.0 moles) was added to a 2 liter, 3 necked flask equipped with a

stirrer, dry ice condenser and addition funnel for the ketone, which had been previously flamed and flushed with nitrogen. The Grignard solution was cooled to 10° with an ice bath. Benzophenone (182 g, 1.0 moles) was dissolved in just enough dry benzene to effect solution and added to the Grignard solution, maintaining the temperature between 10 and 20°. The addition required two hours and the solution was then allowed to reflux for an additional two hours. At the end of this time a white solid was observed in the flask. After stirring for 24 hours the mixture was hydrolyzed by pouring it on a mixture of ice and NH₄Cl in a large beaker, followed by acidification with dilute HCl. The organic layer was separated and the aqueous layer extracted with several portions of ether. The ether extract was washed with a solution of sodium thiosulfate to remove the iodine and dried over anhydrous MgSO₄. The liquid was decanted from the MgSO₄ and the solvent removed in vacuo. The resulting product was recrystallized from n-hexane to a melting point of 78.5-79.0°. (Lit.²⁸ mp 79-81°). A mixed melting point with Eastman 1,1-Diphenylethanol showed no depression. NMR gave signals at δ 1.83 (3H, singlet), δ 2.2 (1H) and δ 6.8-7.5 (10H, from the aromatic ring).

Preparation of 9-Methyl-9-Fluorenone

9-Fluorenone was recrystallized from n-hexane to give yellow needles melting at 82.2-82.6°. (Lit.²⁹ mp 84°). 9-Fluorenone (6.0 g, 0.033 moles) was dissolved in 200 ml of diethyl ether and added to a 500 ml

28. M. S. Kharasch and F. L. Lambert, J. Am. Chem. Soc., **63**, 2315 (1941).

29. J. Schmidt, Wagner, Ber., **43** 1798 (1910).

3 necked reaction flask equipped with a stirrer and dry ice condenser. Methylmagnesium iodide (61.5 ml of a 1.63M solution in diethyl ether, 0.1 moles) was added dropwise with stirring, and the resulting mixture was allowed to reflux for two hours and then cooled to room temperature. The mixture was hydrolyzed by pouring it onto ice and NH_4Cl , acidified with dilute HCl, and the organic layer separated. The aqueous layer was extracted with several portions of fresh ether. The combined extract was dried over anhydrous MgSO_4 , decanted and the solvent removed in vacuo. The product was recrystallized from benzene to a melting point $173.6\text{-}174^\circ$ (Lit.³⁰ mp $173\text{-}174^\circ$), giving 5.2 g of the alcohol and corresponding to 80 percent yield.

Preparation of Methylmagnesium 1,1-Diphenylethoxide in Diethyl Ether

Method A:

To 1,1-diphenylethanol (9.9 g, 0.05 moles) dissolved in 150 ml of diethyl ether, in a 500 ml, 3 necked flask equipped with a stirrer and dry ice condenser, was added dropwise, dimethylmagnesium (59.7 ml of a 0.862M solution in diethyl ether, 0.05 moles). The reaction was not noticeably exothermic and gas evolution was observed during the course of the addition. The temperature was maintained at 25° during the 20 minutes required for the addition and then allowed to attain room temperature. After 24 hours the mixture was fractionally crystallized into three fractions and analyzed for magnesium, giving the results shown in Table 2.

30. G. M. Badger, J. Chem. Soc., 535 (1941).

Method B:

Dimethylmagnesium (116 ml of a 0.862M solution in diethyl ether, 0.1 moles) was added to 750 ml of freshly distilled diethyl ether, in a 2 liter, 3 necked flask equipped with a stirrer, thermometer and addition funnel, and the mixture cooled to 2-3°. To this solution was added 1,1-diphenylethanol (19.8 g, 0.1 moles) dissolved in 200 ml of diethyl ether. The mixture was allowed to warm to room temperature after the evolution of gas had ceased, and was allowed to sit overnight under a nitrogen atmosphere. The mixture was then fractionally crystallized into three fractions and analyzed for magnesium giving the results shown in Table 3.

Reaction of Methylmagnesium 1,1-Diphenylethoxide with Magnesium
Iodide Dietherate in Diethyl Ether Solution

Methylmagnesium 1,1-diphenylethoxide (0.05 moles) was prepared in diethyl ether solution by method B, to give a final concentration of 0.1M at the completion of the reaction. Magnesium iodide dietherate (21.25 g, 0.05 moles) was dissolved in 250 ml of diethyl ether and added to the reaction mixture at 28°. No evolution of heat was observed. The reaction mixture was left stirring overnight and a white precipitate resulted which was filtered as fraction 1. The remainder of the mixture was fractionally crystallized into 3 more fractions and analyzed for Mg and I, giving a total recovery of Mg corresponding to 88 percent.

Table 2. Fractional Crystallization of Methylmagnesium 1,1-diphenylethoxide from diethyl ether (Method A)

Fractions	Sample Weight (g)	Mg(%)
1	7.30	8.30
2	2.40	8.75
3	2.80	9.40
Calcd. for $\phi_2\text{C}(\text{CH}_3)\text{OMgCH}_3 \cdot \text{Et}_2\text{O}$		7.85

Table 3. Fractional Crystallization of Methylmagnesium 1,1-diphenylethoxide from diethyl ether (Method B)

Fractions	Sample Weight (g)	Mg(%)
1	7.20	8.51
2	3.90	8.10
3	16.04	8.25
Calcd. for $\phi_2\text{C}(\text{CH}_3)\text{OMgCH}_3 \cdot \text{Et}_2\text{O}$		7.85

Table 4. Products from the Reaction of Methylmagnesium 1,1-Diphenylethoxide with Magnesium Iodide Dietherate in Diethyl Ether.

Fractions	Sample Wt. (g)	Mg(%)	I(%)	Mg/I Ratio
1	17.50	5.91	28.29	1.0/.92
2	1.25	9.02	31.14	1.0/.67
3	.40	6.11	27.60	1.0/.89
4	10.20	9.35	48.34	1.0/1.0
Calcd. for $\phi_2C(CH_3)OMgI \cdot Et_2O$		5.78	30.05	1.0/1.0
Calcd. for $CH_3MgI \cdot Et_2O$		10.10	52.83	1.0/1.0

Preparation of 4,4'-Dimethoxybenzophenone

The distillation of p-bromoanisole was carried out at 104.5° and 15 mm using a packed column. p-Methoxyphenylmagnesium bromide was prepared in the usual manner (see preparation of phenylmagnesium bromide) by adding p-bromoanisole (37.4 g, 0.2 moles) to triply sublimed magnesium (6.1 g, 0.25 moles) in diethyl ether under a nitrogen atmosphere. Cadmium chloride dihydrate (~100 g) was placed in a round bottom flask and heated with an oil bath in vacuo at 120° to remove the water of hydration. Anhydrous CdCl₂ (21.1 g, 0.11 moles) was then added to the previously prepared Grignard compound over a period of 4 hours, in powder form. The distillation of anisoyl chloride was carried out at 127° and 6 mm. The diarylcadmium compound was added without further purification to anisoyl chloride (34.0 g, 0.20 moles) in diethyl ether. The resulting mixture was hydrolyzed after 48 hours by pouring it onto a mixture of ice and solid NH₄Cl in a large beaker, and acidified with dilute HCl. The

organic layer was removed and the aqueous layer extracted with 600 ml of diethyl ether. The combined extract was washed with aqueous NaHCO_3 to remove anisic acid. Recrystallization of the resulting product was carried out in EtOH in which the other two compounds, anisole and p-bromoanisole, are soluble, to a melting point 140.5-141°. (Lit.³¹ mp 143-144°).

Preparation of 2-Methyl-4' mercaptomethylbenzophenone

A 500 ml 3 necked flask equipped with a stirrer and Friedrich condenser was flushed with nitrogen. To this was added thionyl chloride (77.3 g, 0.65 moles) and o-toluic acid (65 g, 0.5 moles). The reaction was observed to be very slow at room temperature, and the mixture was then heated to 40° in a fume hood, bringing about the evolution of HCl. The reaction required four hours and the excess thionyl chloride was distilled from the mixture. The acid chloride was distilled in vacuo at 42° and 0.5 mm. Redistillation through a packed column gave a product boiling at 56.3-56.4° at 1.10 mm. The yield of the acid chloride was 80 percent based on o-toluic acid.

Carbon disulfide (~375 ml) was then added to a liter 3 necked flask, along with o-toluoyl chloride (61.5 g, .40 moles) and thioanisole (46.5 g, 0.375 moles). The mixture was cooled to 15° with an ice bath, and anhydrous aluminum chloride was added slowly, keeping the temperature between 15-20°. During the two hours required for the addition HCl gas was evolved. The mixture was then acidified and the organic layer separated. The aqueous layer was extracted with an additional 100

31. H. Schnackenberg and R. Scholl, Ber., 36, 654 (1903).

ml of CS_2 . The combined extract was washed with aqueous NaHCO_3 and dried over MgSO_4 . The solution was then decanted and the CS_2 removed in a fume hood with a water aspirator. The resulting solid was recrystallized from a large volume of n-hexane to a melting point of 38.2-39.2, yielding 38 g of pure product. VPC (2 ft. SE-30 columns) showed only one peak. $\lambda_{\text{max}}^{\text{ether}} = 312 \text{ m}\mu$ ($\epsilon = 2.5 \times 10^4$). NMR showed signals at $\delta 2.45$ (3H, singlet attributed to SCH_3), $\delta 2.26$ (3H, singlet attributed to O-CH_3), $\delta 7.0-7.7$ (8H, attributed to the ring protons).

Preparation of 1(o-tolyl),1(p-mercaptomethylphenyl)ethanol

2-Methyl-4'-mercaptomethylbenzophenone (10.0 g, 0.0414 moles) was dissolved in 250 ml of freshly distilled diethyl ether and placed in a 3 necked reaction flask equipped with a stirrer, dry ice condenser and addition funnel. Methylmagnesium chloride (100 ml of a 1.1M solution in diethyl ether, 0.11 moles) was added slowly over a period of two and one-half hours, and the mixture left stirring overnight. After this time a white precipitate was observed which was filtered in the dry box and hydrolyzed by pouring it slowly on a mixture of ice and solid NH_4Cl in a beaker. After acidification the organic layer was separated and the water layer extracted with an additional 50 ml of ether. The combined extract was dried over anhydrous MgSO_4 , decanted and the solvent removed in vacuo. The solid product gave a total yield of 8.5 g melting at 81.2-81.8°. Ultraviolet analysis showed no absorption at the λ_{max} of the starting material using a 0.01M solution, indicating that no residual ketone remained. Infrared analysis showed a sharp peak at 3610 cm^{-1} indicating a tertiary alcohol, and no absorption

in the carbonyl range. NMR of the product showed signals at δ 2.35 (3H, singlet attributed to 3CH_3), δ 2.92 (3H, singlet attributed to O-CH_3), δ 2.78 (3H, singlet attributed to the terminal CH_3), δ 1.97 (1H, attributed to alcohol), and signals at δ 6.9-7.7 (8H, attributed to aromatic protons).

Reaction of Methylmagnesium Iodide with Benzonitrile in Diethyl Ether

Methylmagnesium iodide (145 ml of a 2.07 M solution in diethyl ether 0.3 moles) was diluted to 750 ml with freshly distilled diethyl ether and placed in a 3 necked reaction vessel equipped with a stirrer, dry ice condenser and addition funnel. Benzonitrile was distilled through a column packed with glass helices and the fraction collected boiling at $82.2\text{-}82.8^\circ$ at 4.4 mm. A solution of benzonitrile (15.5 g, 0.15 moles) in 15 ml of diethyl ether was added slowly to the Grignard solution and the mixture was allowed to reflux for 20 hours. The resulting mixture, 0.4M in Grignard compound was allowed to cool to room temperature and fractionally crystallized into four fractions giving the following analysis.

Table 5. Products from the Reaction of Methylmagnesium Iodide with Benzonitrile in Diethyl Ether (using a 0.4M solution of the Grignard compound)

Fractions	Sample Wt. (g)	Mg (%)	I (%)	Mg/I Ratio
1	27.60	7.03	37.2	1.0/1.01
2	8.70	7.56	37.3	1.0/.95
3	5.10	7.64	38.6	1.0/.97
4	24.10	10.70	50.3	1.0/.91
Calcd. for $\phi\text{C}(\text{CH}_3)\text{NMgI}\cdot\text{Et}_2\text{O}$		7.08	36.9	1.0/1.0
Calcd. for $\text{CH}_3\text{MgI}\cdot\text{Et}_2\text{O}$		10.10	52.83	1.0/1.0

The same reaction was also carried out using 1M methylmagnesium iodide and benzonitrile. The reaction product was fractionally crystallized and the fractions analyzed for magnesium and iodide, excepting fraction 3*. The results of this study are shown in Table 6.

Table 6. Products from the Reaction of Methylmagnesium Iodide with Benzonitrile in Diethyl Ether (using a 1.0M solution of the Grignard Compound)

Fractions	Sample Wt (g)	Mg (%)	I (%)	Mg/I Ratio
1	25.20	6.92	41.1	1.0/1.1
2	4.40	7.17	39.0	1.0/1.03
3	24.80	--	--	

Reaction of Methylmagnesium Iodide with Benzophenone

Methyl magnesium iodide (72.5 ml of a 2.07M solution in diethyl ether, 0.15 moles) was added to 1400 ml of freshly distilled diethyl ether to give a final concentration 0.1M in Grignard compound. The solution was placed in a 2 liter 3 necked flask equipped with a stirrer, thermometer, dry ice condenser and addition funnel and cooled to 10° with an ice bath. Benzophenone (14.0 g, 0.078 moles) was dissolved in 125 ml of diethyl ether and added to the Grignard compound keeping the temperature between 10 and 20°. The solution was allowed to reflux for

*Fraction 3 was not analyzed to oxidation of the sample. It may be reasonably assumed that it was unreacted Grignard compound since fraction 1 and 2 would account for 89 percent of the nitrile and the weight of sample 3 corresponds to .102 moles, one half of the CH_3MgI added. There is an analogy to the other nitrile experiments and to the various experiments using benzophenone in which Grignard compound was always found in the last fraction.

two hours after the addition and a white precipitate was observed in the reaction vessel. The solid was filtered in the dry box and the filtrate fractionally crystallized into two more fractions. The final fraction was very soluble in diethyl ether. Analysis for magnesium and iodide gave the results shown in Table 7.

Table 7. Products from the Reaction of Methylmagnesium Iodide with Benzophenone (using normal addition and a 0.1M solution of the Grignard compound)

Fractions	Sample Wt. (g)	Mg (%)	I (%)	Mg/I Ratio
1	29.90	6.10	29.50	1.0/.93
2	3.0	--	39.80	--
3	13.45	8.76	53.30	1.0/1.14
Calcd. for $\phi_2C(CH_3)OMgI \cdot Et_2O$		5.78	30.05	1.0/1.0
Calcd. for $CH_3MgI \cdot Et_2O$		10.10	52.83	1.0/1.0

The same reaction was also carried out using 1M methylmagnesium iodide and benzophenone. The reaction product was fractionally crystallized and analyzed for magnesium and iodide, giving the results shown in Table 8.

A further modification of this reaction was made using inverse addition (adding the Grignard compound to the ketone) employing a 1:1 ratio of Grignard to ketone. The mixture was allowed to reflux for one hour after the addition and was fractionally crystallized after sitting for six hours under a nitrogen atmosphere. Only two fractions were obtained giving the following analyses shown in Table 9.

Table 8. Products from the Reaction of Methylmagnesium Iodide with Benzophenone (using normal addition and a 1.0M solution of the Grignard compound)

Fractions	Sample Wt (g)	Mg (%)	I (%)	Mg/I Ratio
1	30.85	6.09	29.2	1.0/1.0
2	18.80	10.2	50.8	1.0/.95

Table 9. Products from the Reaction of Methylmagnesium Iodide with Benzophenone

Fractions	Sample Wt. (g)	Mg (%)	I (%)	Mg/I Ratio
1	18.06	5.92	29.9	1.0/.97
2	1.40	5.02	26.1	1.0/.99
Calcd. for $\phi_2C(CH_3)OMgI \cdot Et_2O$		5.78	30.05	1.0/1.0
Calcd. for $CH_3MgI \cdot Et_2O$		10.10	52.83	1.0/1.0

VPC analysis of a hydrolyzed portion of fraction 1 (2 ft. silicone rubber, SE-30) showed the presence of only 1,1-diphenylethanol and no benzophenone.

Reaction of Phenylmagnesium Bromide with Benzophenone in Diethyl Ether

Benzophenone (9.1 g, 0.05 moles) and phenylmagnesium bromide (87.7 ml of a 1.14 M solution in diethyl ether, 0.1 moles) were mixed, using normal addition in the manner previously described using methylmagnesium iodide. Fraction 1 was obtained by filtering an insoluble intermediate and fraction 2 resulted when the solvent was removed in vacuo. Analyses for magnesium and bromide gave the following results.

Table 10. Products from the Reaction of Phenylmagnesium Bromide with Benzophenone

Fractions	Sample Wt. (g)	Mg (%)	Br (%)	Mg/Br Ratio
1	16.30	5.80	19.3	1.0/1.01
2	12.60	8.30	27.2	1.0/1.00
Calcd. for $\phi_3\text{COMgBr}\cdot\text{Et}_2\text{O}$		5.56	18.3	1.0/1.0
Calcd. for $\phi\text{MgBr}\cdot\text{Et}_2\text{O}$		9.52	31.30	1.0/1.0

Method for Making a Kinetic Run and Subsequent Analysis

The reaction vessel used for a kinetic run consisted of a 25 ml volumetric flask, equipped with a small sidearm approximately 1 cm above the graduation line. These flasks were flamed and flushed with dry nitrogen and placed in a dry box prior to loading with the Grignard compound and ketone solutions. A 5 ml sample of the Grignard compound in solution was placed in the bottom of the flask and a sample of the ketone in the same solvent introduced in the side arm of the flask using a Hamilton micro syringe. One flask contained only Grignard reagent and was hydrolyzed and acidified, to give a solution used in the reference beam of the Cary 14 spectrophotometer. A second sample was hydrolyzed prior to mixing the ketone and Grignard compound and after the work up was used to establish the absorption at the initial time, t_0 . The remaining samples were mixed by shaking the flask and allowing the solutions to react for a given time before hydrolysis of the mixture. The work-up procedure consisted of hydrolyzing the sample with 2 ml of distilled water, acidification with 7 ml of 6N hydrochloric acid, and dilution

of this mixture to 25 ml with distilled diethyl ether. Prior to acidification the mixture was frozen in a dry ice-acetone bath, and the heat of the acid-base reaction brought the mixture to room temperature. During the actual kinetic run the samples were maintained at 25° in a constant temperature bath. The extinction coefficient used to determine the concentration of ketone in each sample was obtained directly in the water-ether solution using known concentrations of ketone, and was not the extinction coefficient obtained in pure ether. This was done to compensate for the fact that some of the ether added was miscible in the salt water layer.

CHAPTER III

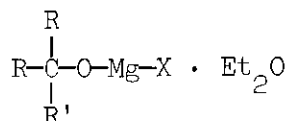
DISCUSSION AND RESULTS

The mechanism of the normal Grignard compound addition to ketones is quite complex, as exemplified by the numerous reports in the literature. To study the normal addition reaction it is necessary to choose a system in which the known side reactions cannot occur. If the ketone has a hydrogen atom α to the carbonyl group, enolization can occur, a side reaction in which the Grignard compound is destroyed and the ketone remains unchanged after hydrolysis. If the Grignard compound contains a β -hydrogen atom, reduction can occur to give a secondary alcohol. For these reasons this study was limited to those ketones without enolizable hydrogens, such as benzophenone, and methyl and phenyl Grignard compounds.

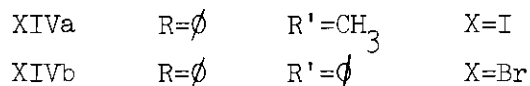
Since many of the proposed mechanisms describing Grignard compound addition to ketones predict different intermediates, the first step was to isolate and identify the intermediates which are obtained prior to hydrolysis of the reaction mixture. Hopefully, knowledge about the composition of these intermediates would allow the exclusion of some of the proposed reaction mechanisms.

The reaction of benzophenone with methyl and phenyl Grignard compounds was studied at different Grignard compound concentrations, where either monomeric or dimeric species were known to predominate in diethyl ether solutions. The reaction mixtures were then fractionally crystallized prior to hydrolysis. The results are given in Tables 7-9. In all

cases the first fraction consisted of a slightly soluble species and the last fraction consisted of a very soluble species. The first fractions were analyzed for magnesium and halogen and had the following general formula (XIV). The analysis of the last fractions corresponded to that



XIV



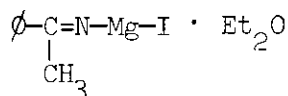
calculated for unreacted Grignard compound.

No association study was made on the above intermediate. If monomeric, two molecules of ether would be expected to satisfy the coordination around magnesium. However, it is known that one ether of solvation can be removed readily in vacuo. The extent of the loss of solvation sometimes caused a difference between weight percentages calculated for the intermediate and those actually found, but in all cases the Mg/X ratio was very good, this being independent of the degree of solvation.

In most cases a ratio of Grignard compound to ketone of 2:1 was used employing the normal addition mode (i.e. addition of ketone to the Grignard compound in solution). In the one case where a Grignard compound to ketone ratio of 1:1 was used, employing inverse addition (i.e. addition of the Grignard compound to ketone) the intermediate was

identical to those previously isolated. A sample of one of the fractions from this experiment was hydrolyzed and examined by VPC and no residual ketone was observed. The quantitative production of the tertiary alcohol on hydrolysis showed that the intermediate was not just a complex between the Grignard compound and ketone, as once reported by Pfeiffer and Blank³².

The reaction of benzonitrile with methylmagnesium iodide was then examined to see if this trend persisted. Once again, halogen was found in the intermediate and analysis of the last fraction indicated that it was unreacted Grignard compound, as shown by Tables 5 and 6. The general composition of the intermediate isolated in this case is given by (XV).



XV

There are five reaction mechanisms that predict the composition of the intermediate isolated in the reaction of benzophenone with a Grignard compound. The kinetic interpretation of each of these is different, but all are first-order in benzophenone. Three of these involve the redistribution of the first-formed intermediate with magnesium halide in order to rationalize the isolated intermediate.

In equation (1) the reaction is first-order in Grignard monomer

32. P. Pfeiffer and H. Blank, J. prakt. Chem., [2], 153, 242 (1939).

and involves a four-centered transition state, to obtain directly the intermediate isolated experimentally. Equation (2), first order in dialkylmagnesium, involves attack by dialkylmagnesium and again a transfer of the alkyl group from the magnesium atom to the carbonyl via a four-centered transition state. Redistribution would then have to occur to agree with the intermediate isolated, (VIII). Equation (3) involves attack by monomeric Grignard reagent, 2 molecules per molecule of ketone, to give a six centered transition state. Again redistribution would have to occur, but here the reaction is third order overall, second order in Grignard monomer. Equation (4) requires the reaction to be first order in the symmetrical Grignard dimer and after the transfer of the alkyl group is identical to (3). Equation (5) requires the reaction to be first order in the unsymmetrical dimer. In view of the present accepted composition of the Grignard reagent in solution this is possible but not probable. In all cases the transfer of the alkyl is thought to be the rate controlling step in the reaction.

To test the theory of redistribution and the fact that the intermediate isolated experimentally may not be the first formed intermediate, methylmagnesium 1,1-diphenylethoxide was prepared and mixed with magnesium iodide dietherate in diethyl ether under the reaction conditions used for the normal Grignard reaction. It was found that redistribution did take place to give the same intermediate isolated in the normal Grignard reaction, and methylmagnesium iodide was again found in the last fraction. If redistribution had not occurred, then the results would have been more informative. Since redistribution did occur no choice could be made to favor any one mechanism over another.

In lieu of these results a kinetic study was attempted to determine the kinetic order of the normal Grignard compound addition to ketones. The first consideration was again to simplify the system as much as possible, to avoid a multitude of competing reactions. It is conceivable that all of the components in a Grignard compound in solution will react with benzophenone, but at different rates.

Ashby²⁰ had shown that the Grignard compound "EtMgBr" in triethylamine contains only the monomeric species EtMgBr. Lewis and Wright³³ showed that the reaction of a Grignard compound with a ketone is slower in a more basic solvent such as triethylamine, than in diethyl ether. Bikales and Becker¹³ had shown that the reaction of CH_3MgBr with benzophenone was rapid, with 30-40 percent of the reaction complete in about 40 seconds, using a Grignard compound concentration 0.08M in tetrahydrofuran, with a stoichiometric amount of ketone. For these reasons triethylamine was chosen as the solvent for this study, using again benzophenone and methyl and phenyl Grignard compounds.

The first attempt to follow the decrease in ketone concentration, to determine the kinetic order of the reaction was made using vapor phase chromatography. It had been shown in this work that when benzophenone and methylmagnesium iodide react only one product is produced, 1,1-diphenylethanol. Hence, by following either the disappearance of the ketone or the appearance of the alcohol, it should be possible to determine the extent of the reaction, and thereby determine the rate constant. In the presence of triethylamine, however,

33. R. N. Lewis and J. R. Wright, J. Am. Chem. Soc., 74, 1253 (1952).

1,1-diphenylethanol dehydrates in the VPC to give 1,1-diphenylethylene, limiting the study to the disappearance of ketone.

Two methods of preparing samples for analysis were considered. Either (a) aliquots for analysis could be withdrawn at specified time intervals from one reaction vessel and hydrolyzed or (b) the reaction could be run in serum bottles and each one hydrolyzed at some specific time in the reaction. The reaction of benzophenone and methylmagnesium bromide had been reported to be quite fast¹³ and in order to get data early in the reaction it was necessary to use dilute solutions of Grignard reagent and even more dilute solutions of ketone, by a factor of 50 to 100 fold. In either case (a) or (b) it was necessary to acidify the samples after hydrolysis, extract from the water layer and then concentrate the samples in order to see the peaks on the VPC, using a thermal conductivity detector. In lieu of the small quantities of ketone used and the number of manipulations involved in this method, the accuracy was doubtful and this method was dropped from further consideration.

Triethylamine absorbs strongly in the region 200-300 μ . Benzophenone, in diethyl ether solution exhibits two bands in the ultraviolet region of the spectrum due to the carbonyl absorption, a $\pi \rightarrow \pi^*$ transition at 251 μ ($\epsilon=1.92 \times 10^4$) and an $n \rightarrow \pi^*$ transition at 343 μ ($\epsilon=128$). Since the study involved the use of dilute reagents to slow down the reaction and maintain pseudo first-order conditions the band at 251 μ was chosen. This made it necessary to acidify the triethylamine solution prior to ultraviolet analysis. The salt-water layer was then extracted to volume with diethyl ether to ensure that the ketone was in solution, and the

extract examined. When distilled triethylamine was subjected to this treatment, it showed no absorption in the region 200-300 μ .

Phenylmagnesium bromide was prepared in triethylamine yielding a solution 0.164M in magnesium, with a Mg/Br ratio of 1.0/1.2. A sample of this Grignard solution was prepared for ultraviolet analysis and showed strong absorption in the vicinity of 250 μ where benzophenone also shows major carbonyl absorption. A VPC study indicated the presence of biphenyl, the coupling product in the formation of the phenylmagnesium bromide. Biphenyl was found to absorb in the region 200-300 μ and hence, phenyl Grignard compounds were excluded from further study.

An attempt was made to prepare methylmagnesium bromide in triethylamine which resulted mainly in salt formation. A sample of $\text{MeMgBr}\cdot\text{Et}_3\text{N}$ was obtained by quenching an ether solution of the Grignard compound as previously described. When this sample was examined in the ultraviolet region it exhibited absorption in the region 200-290 μ . A sample of methylmagnesium bromide was prepared in diethyl ether and a sample prepared for study in the UV. It showed no absorption indicating that impurities in the methyl bromide did not cause this absorption, nor did it result from the work-up since the same amount of HCl was added, as was added to the amine solution. When another sample of the Grignard compound in triethylamine was prepared and used in the reference beam, the absorption was minimized, but not totally excluded.

Methylmagnesium chloride was prepared directly in triethylamine and it also showed absorption in the region 200-290 μ . When the triethylamine used in the preparation of the Grignard solution was distilled from a Grignard solution in triethylamine the absorption of a hydrolyzed, acidified solution was considerably decreased but still observable. The

addition of a mild reducing agent, SnCl_2 , did not remove the unknown species causing absorption, nor did the addition of NaS_2O_3 . The latter, in the presence of the acid used in the work-up procedure resulted in the formation of colloidal sulfur.

The results of this work indicated some unknown species produced absorption in the 200-290 μ region. In an attempt to clean up the triethylamine prior to Grignard compound formation a study was carried out in which the triethylamine was distilled from several drying agents and the distillate examined by VPC. Distillation from LiAlH_4 , P_2O_5 , and $\text{MeMgCl}\cdot\text{Et}_3\text{N}$ showed that the water was removed in all cases but that traces of other components found in a drum sample of triethylamine were not. No attempt was made to determine the identity of these impurities, which corresponded to about 0.1 percent, but secondary amines were ruled out because they would have reacted with the Grignard compound and been removed in that distillation.

Since the unknown absorption could not be eliminated the next step was to find a suitable ketone with its major carbonyl absorption above the range of interference. Several ketones were examined and gave the results shown in Table 11.

The $\pi\rightarrow\pi^*$ transition for 4-methoxybenzophenone, and 4,4'-dimethoxybenzophenone did not fall beyond the range of interference of the Grignard compound and were not suitable for the study. Preliminary work with fluorenone, showed that the reaction was quite fast, comparable to benzophenone. Also, the product of the reaction, 9-methyl-9-fluorenone absorbed very close to the ketone, at 319 μ . The shoulder of this peak interfered with the peak attributed to the $n\rightarrow\pi^*$ transition.

Table 11. Ultraviolet Absorption Bands for Ketones

Ketone	λ ether max	ϵ
4-methoxybenzophenone	283	1.9×10^4
4,4'-dimethoxybenzophenone	283	2.45×10^4
fluorene ($n \rightarrow \pi^*$)	328	765
2-methyl-4'-mercaptomethylbenzophenone	312	2.5×10^4

The reaction of 2-methyl-4'-mercaptomethylbenzophenone with methylmagnesium chloride in triethylamine was then studied. The $\pi \rightarrow \pi^*$ transition ($\epsilon = 2.5 \times 10^4$) for this ketone was removed from the range of Grignard interference. The product of the reaction, 1-(o-tolyl)-1-(p-methylmercaptophenyl)ethanol was shown not to absorb at the λ max of the ketone, even when present in a 0.01M solution, more than 100 times the maximum concentration of this species resulting from the reaction of the ketone with the Grignard compound.

The high extinction coefficient of this ketone required the concentration in the ether extract after work-up to be 4×10^{-5} M. To maintain pseudo first-order conditions the desired Grignard compound concentration in triethylamine must be approximately 1×10^{-3} M. To prepare a stable solution of Grignard compound at this low concentration it was necessary to carefully distill the solvent used for the dilution of a previously prepared Grignard standard solution. This was achieved by distilling the triethylamine directly into a 100 ml. volumetric flask equipped with a 24/40 ground glass joint, after first evacuating

the receiver and replacing the atmosphere with nitrogen. Any impurity that was capable of reacting with the Grignard solution after dilution was removed by distilling the amine from a Grignard solution.

It was also necessary to test the reproducibility of the addition of the ketone standard to the side arm of the reaction flask. Several flasks were prepared by adding 5 ml of a 1×10^{-3} M solution of the Grignard solution in the lower portion and 10 μ l of a 0.1M standard ketone solution to the side arm. The Grignard was first subjected to hydrolysis and the ketone solution then mixed by shaking the flask. The resulting mixture was acidified and diluted to volume with diethyl ether. The initial absorption due to the carbonyl group was found to be reproducible to within one percent. The stability of the ketone in triethylamine was also checked over a period of time and gave the results shown in Table 12.

Table 12. Stability of 2-Methyl-4'-mercaptomethylbenzophenone in Triethylamine

Time	Temperature	Absorbance	Average Absorbance
initial	26°	.900	.906
		.911	
1 day	24°	.909	.904
		.898	
5 days	27°	.898	.889
		.880	
10 days	25°	.902	.904
		.907	

During this study the Cary 14 instrument was not jacketed. The ketone solution in triethylamine was shielded from light during the time required for this study. If the standard solution was exposed to light over a period of two weeks or more a dark, viscous, oily material was observed in the bottom of the flask.

Several kinetic runs were attempted with 2-methyl-4'-mercapto-methylbenzophenone, most of which resulted in a "shotgun" scattering of points (e.g. run No. 1) when pseudo first-order conditions were maintained. One run, (No. 2) was attempted in which the Grignard compound was in only 10 fold excess and in this run better agreement was reached than in any previous case. In view of the scattering of points, rate constants were not calculated for the early runs. In the last kinetic run, a pseudo first-order rate constant was obtained, $15.52 \pm 14.66 \times 10^{-4} \text{ sec}^{-1}$, using an initial ketone concentration of $1 \times 10^{-4} \text{ M}$ and a Grignard compound concentration of $1 \times 10^{-3} \text{ M}$. The results of this work are given in Table 13.

In the following table, Table 13, the value of k, the pseudo first-order rate constant is calculated from the following expression.

$$k = \frac{2.3 \log(A_0/A)}{t}$$

Table 13. Kinetic Data on the Reaction of 2-Methyl-4'-mercapto-
methylbenzophenone with Methylmagnesium Chloride in
Triethylamine

Run No. 1		Run No. 2		
$G_o = .118M$	$K_o = 1.10^{-4}M$	$G_o = 1 \times 10^{-3}M$	$K_o = 1 \times 10^{-4}M$	
<u>time (sec)</u>	<u>Absorbance</u>	<u>time (sec)</u>	<u>A</u>	<u>$k \times 10^4 \text{ sec}^{-1}$</u>
0.0	.924	0.0	1.01	
24.5	.186	0.0	.99	
50.0	.207	30.2	.97	9.76
99.4	.243	70.3	.89	16.11
100.5	.235	100.8	.81	20.53
204.1	.382	200.3	.73	15.71

CHAPTER IV

CONCLUSIONS AND RECOMMENDATIONS

Although the isolation of intermediates from the normal addition reaction of a ketone with a Grignard compound did not allow a choice to be made as to the correct mechanism, several important observations were made. The intermediate was the same regardless of what the concentration of the Grignard compound in solution was when a 2:1 ratio of Grignard compound to ketone was used. Furthermore, the intermediate was the same regardless of whether an alkyl or aryl Grignard compound was used, and was independent of the halogen in the Grignard. There is also a marked similarity between the reaction of a Grignard compound with a ketone or nitrile.

The experiment in which inverse addition was used, with the ketone in excess during the addition of the Grignard reagent, proved that the species isolated is not just a complex between the ketone and Grignard reagent, but a species in which the alkyl group has already been transferred, from the magnesium atom to the carbonyl carbon.

No suitable data was obtained from which a reliable rate constant could be calculated in the kinetic portion of this work, however, several problems were overcome. The ketone standard was shown to be stable. The alcohol product from the reaction of 2-methyl-4'-mercapto-methylbenzophenone with methylmagnesium chloride was shown not to interfere with the absorption due to the carbonyl group of the ketone. The impurity

to which absorption at the lower wavelength was attributed could not be eliminated but was at least minimized. The dilution of the Grignard compound in triethylamine did not show any visible evidence that the Grignard reagent had been destroyed at the low concentration, leading to the observed scattering of the data. At this point the study was abandoned.

Since there is no apparent reason why the system studied did not give good kinetic data, it may be fruitful to carry out further work in this area. The last kinetic run attempted gave the best results. In the future the author recommends that no attempt be made to obtain pseudo first-order conditions, but that the investigator work under conditions that will allow the determination of the order with respect to the Grignard compound. Since it is known that the reaction is first-order in ketone, it should be possible to determine the order of the reaction with respect to monomeric methylmagnesium chloride in triethylamine.

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