REACTIONS OF ACETYLENE AND ITS DERIVATIVES WITH ALDEHYDES AND KETONES

by

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1940

Signature of Author

Department of Chemistry, May 16, 1940

Signature of Professor
in Charge of Research

Signature of Head of Department...
ACKNOWLEDGEMENT

I wish to thank Dr. Alberto F. Thompson for suggesting the problem for this thesis and for being of inestimable help in solving it.
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INTRODUCTION

Since no satisfactory method, in the sense of being short, simple, and resulting in high yields, has been found for the condensation of acetylene with aliphatic aldehydes, it was the purpose of this thesis to find such a method. In attempting to solve the problem two aldehydes, form-aldehyde and n-butyraldehyde were used. The former because, if the reaction proceeded in the desired manner, the result would be propargyl alcohol, and the latter because it was considered a representative saturated aliphatic aldehyde.

Our interest in propargyl alcohol (HC=C-CH_2OH) was aroused because its structure is such that it would be very useful as a building block for many compounds, since, although it contains only three carbon atoms, it is acetylenic at one end and alcoholic at the other. Propargyl alcohol has been prepared by various methods, but these are quite tedious and thus far only small yields have been reported. ¹

A possible method of attacking this problem was suggested by the work of several research men who have worked on the condensation of sodium acetylide with ketones and aldehydes. ² Campbell, Campbell, and Elby²a have used the

¹ a) Henry, B., 5, 453, 564; 6, 729; 14, 404; Ann. Scient. Brux. (1878)
   b) Paal, Heupel, B., 24, 3039
² a) Campbell, Campbell, and Elby J. A. C. S. 60, (1938), 2282
   b) Moreau and Desmots Bull. Soc. Chim. 27, (1902), 360
method of preparing sodium acetylide in liquid ammonia and adding their ketone or aromatic aldehyde directly to the resultant solution. Hess and Munderloh\(^3\) made the modification of evaporating off the liquid ammonia and using a little ether to moisten the sodium acetylide before adding the liquid aldehyde. Other researchers have reported similar condensations with varying degrees of success.\(^4\)

Another method of attack was suggested by several other chemists\(^5\) who prepared the mono grignard of acetylene. Dr. Thompson working during the summer of 1939 prepared some mono grignard of acetylene and reacted it with p-formaldehyde, obtaining small yields of propargyl alcohol by this very long and tedious method.

It was decided then to use metallic acetylides in order to determine if, and under what conditions, these could be caused to react with aldehydes to yield the corresponding alcohols in satisfactory amounts. Formaldehyde was the aldehyde mainly used, but butyraldehyde was also used.

Sodium acetylide was used in the main and it was reacted under various conditions of temperature with gaseous formaldehyde and its solid polymer, p-formaldehyde.

\(^3\) Hess and Munderloh B., 51, 380
\(^4\) a) Iotisch Bull. Soc. Chim. (3) 24, (1905), 181
   b) Nef Ann. 308, (1899), 264
   c) F.G. Fischer and Lowenburg Ann. 475, (1929), 183
\(^5\) a) V. Grignard, L. Lapayne, T. Faki, Comptes Rendues (187) 517 (1928)
   b) B. Oddo Gazz. Chim. Ital. 34, (1904), 429
   c) Salkind, Rosenfeld B., (1924), 57, 1690
and also various solvents, liquid ammonia, ether, and dioxane, were used. One trial was also made using calcium acetyl-
ylide instead of sodium acetylide, reacting this with gas-
seous formaldehyde. An attempt to make propargyl alcohol
by means of the mono grignard of acetylene, dioxane as the
solvent was also made. The result of these reactions was
a 12% maximum yield, as shown by hydrogenation, of propargyl
alcohol, and this yield was obtained using sodium acetylide,
gaseous formaldehyde, dioxane as the solvent, and with the
temperature uncontrolled.

Several trials were made with n-butyraldehyde, using
sodium acetylide, dioxane as the solvent, and varying
conditions of temperature. These trials gave no measurable
amount of the desired alcohol \((\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}==\text{CH})\), but did
give indications of high yields, especially at -5 degrees,
of aldol condensation products, only two molecules being
condensed. (i.e. evidently no polymers of long chains with
more than two butyraldehyde units were obtained.)
GENERAL PROCEDURE

In order to prepare the sodium acetylide the method suggested by Campbell\textsuperscript{2a} as modified by Miss Rovno\textsuperscript{6} was used. This method consists of dropping pellets of sodium into liquid ammonia through which a stream of dry acetylene is being constantly passed, the reaction mixture being mechanically stirred continuously. When the solution completely loses its dark blue color it is considered complete.

No references could be found for a method of reacting formaldehyde with sodium acetylide, but, as stated previously, Campbell, whose method proves quite satisfactory when aromatic aldehydes are used, suggested adding the aldehyde directly to a liquid ammonia solution of sodium acetylide.

It was decided to use this method with necessary modifications. Since it was soon found that liquid ammonia was not a suitable solvent, it was necessary to turn to other solvents.

The method used for the Grignard synthesis was a modification of the work done by V. Grignard.\textsuperscript{5a} He suggests preparing phenyl magnesium/bromide in ethyl ether and passing in acetylene for long periods of time at one half an atmosphere pressure. Several men working at the Institute have found it impossible to reproduce his work, obtaining almost entirely

\textsuperscript{6} I. Rovno Thesis M.I.T. 1939
the di magnesium bromide compound. It was therefore decided since dioxane is often a good solvent for inorganic substances, perhaps it would bring the di magnesium bromide compound into solution to allow further reaction with acetylene. Acetylene was passed in at atmospheric pressure.

EXPERIMENTAL

A- Method when using mono sodium, or calcium, acetylide.

This discussion will be limited to working with half molal quantities of acetylide, but it is applicable to larger quantities, the only difference being that proportionately larger amounts of liquid ammonia and solvent must be used.

Sodium* acetylide was made in the set-up labeled "Apparatus A" (page 6a). The three necked flask was surrounded by a dry-ice-toluene bath, and with the only opening to the atmosphere being the soda-lime drying tube, the three-necked flask was surrounded by a dry-ice-toluene bath, and with the only opening to the atmosphere being the soda-lime drying tube, (I) 300 cc. of liquid ammonia were led into the flask through the T tube. One half a mol (11.5 grams) of sodium in the form of pellets of such a size that they will not clog the tube when attempting to shake them into the reaction mixture, were now placed in the sodium addition tube (M). The

* Whenever the word "sodium" is used, "calcium" may be substituted.
mechanical stirrer was set into operation, turning at quite a rapid rate, the water turned on in the gas washer, and acetylene passed into the reaction chamber at a rapid rate.*

Several pellets of sodium were dropped into the reaction chamber by tilting the addition tube. After the blue color, caused in the reaction mixture by such addition, disappeared, a few more pellets were added. Such addition and waiting for the color to be discharged were continued until all the sodium had been added. This took from fifteen to twenty minutes.

Acetylene was bubbled through the reaction mixture for from five to ten minutes longer to insure formation of the mono- rather than the di- acetylide.

The acetylene washing and drying train was now shut off from the reaction flask by means of a screw clamp placed on the rubber tubing connecting the T tube (H) with the phosphorous pentoxide drying tube (F). When liquid ammonia was used as a solvent for the subsequent reaction, the substitutions (mentioned below) for the sodium addition tube (N) were made immediately. At other times the liquid ammonia was evaporated off on a warm water bath (40-50 degrees) through the soda-lime drying tube (I) with the mechanical

* When the incoming stream of water flows at a steady and not too rapid rate, the height of the water level is automatically adjusted, since it can not rise above the level of the tube labeled "wash water out".
A - GAS WASHER (WATER USED)
B - SMALL PIECES OF GLASS TUBING
C - TRAP
D - DRYING TUBE
E - GLASS WOOL TRAP
F - DRYING TUBE
G - GLASS WOOL
H - GLASS WOOL
I - GLASS WOOL
J - SCREW CLAMPS
K - CALCIUM CHLORIDE
L - SULFURIC ACID GAS DRYER
M - GLASS WOOL TRAP
N - GLASS WOOL TRAP
O - DRYING TUBE
P - DRYING TUBE
Q - GLASS WOOL TRAP
R - DRYING TUBE
S - GLASS WOOL TRAP
T - DRYING TUBE
U - GLASS WOOL TRAP
V - DRYING TUBE
W - GLASS WOOL TRAP
X - DRYING TUBE
Y - GLASS WOOL TRAP
Z - DRYING TUBE
stirrer kept in operation to avoid bumping. When the liquid ammonia was entirely evaporated, 100-150 c.c. of solvent were put in the reaction chamber.

When the reaction with aldehyde was carried out at an elevated temperature, a reflux water condenser, protected by a soda-lime drying tube, was substituted for the soda-lime drying tube (I).

The sodium addition tube was removed and, depending upon the state of the aldehyde, the following were substituted:

1. If liquid aldehyde (butyraldehyde), a drying tube protected dropping funnel.

2. If gaseous aldehyde (formaldehyde), a formaldehyde gas generator. (Three types were used. For when each was used, see table on pages 10a and b)

3. If solid aldehyde (p-formaldehyde), a large filter funnel.

In case 1, half a mol of butyraldehyde was used, and it was added in such a manner that the temperature variation of the reaction was never more than one or two degrees.

In cases 2 and 3, a threefold excess (1.5 mols) of formaldehyde was used, usually. When p-formaldehyde was used, it was added all at once, the funnel removed, and the opening stoppered. An alternative method of reacting with p-formaldehyde, that of washing the sodium acetylide into a bottle with between 100 c.c. and 150 c.c. of solvent
stoppering the bottle tightly and shaking, was also tried. This mixture gave a high initial heat of reaction which, however, was of short duration.

When gaseous formaldehyde was used, three formaldehyde generators were employed. These are shown on page 8a. The first of these was unsatisfactory because the formaldehyde formed by depolymerizing p-formaldehyde repolymerized in the U tube, clogging it and causing explosions. The second of these was so constructed that clogged material could theoretically be pushed out manually, but this too was unsatisfactory because explosions occurred anyhow and moist air was admitted to the reaction chamber. The third of these eliminated the previous difficulties since the addition tube could be kept above 180 degrees and so prevent repolymerization.

The stirring rod was kept going continuously during the aldehyde addition.

When the reaction was complete the solution was made slightly acid with concentrated sulfuric acid in ice, adding the acid as rapidly as possible with mechanical stirring. Two layers, organic and water, appeared at this point.

The three necked flask was removed from the rest of the apparatus and its contents treated in the following manner:

The reaction mixture was neutralized with sodium
GENERATOR 1  
A-OIL BATH  
B-PFORMALDEHYDE  
C.RUBBER CONNECTOR  
D-STOPPER  
E-RESISTANCE WIRE 

GENERATOR 2  

GENERATOR 3  

A-OIL BATH  
B-PFORMALDEHYDE  
C.RUBBER CONNECTOR  
D-STOPPER  
E-RESISTANCE WIRE 

Which can be removed to push out the repolymerized CH₂O
bicarbonate. The excess bicarbonate was filtered off and washed two or three times with 10-15 cc. portions of ether, washings being returned to solution. To form the bisulfite addition product, an amount of sodium bisulfite, dissolved in the minimum amount of water, equivalent to all the aldehyde was shaken thoroughly with the organic layer (this was done only in those cases indicated by an asterisk (*) in table 1, pages 10-11).

The water layer was saturated with sodium chloride and the organic layer separated. The water layer was extracted 4-5 times with 50-60 cc. portions of ether, the extracted material being added to the organic layer. The organic layer was now dried with anhydrous magnesium sulfate, the magnesium sulfate then being filtered off and washed 3-4 times with 15-20 cc. of ether. The washings were added to the filtered organic layer. The ether was removed from the organic layer by distilling to 55 degrees using column "1" (page 9a). The residue was fractionated on the column labelled "2", page 9a.

The water layer was continuously extracted with ethyl acetate for periods of 18-24 hours in several runs without further recovery of alcohol.

At first ethyl ether was the solvent used, but later dioxane, because it was found that the latter was a better solvent for p-formaldehyde and sodium acetylide.
The product was tested for free acetylenic hydrogen with ammoniacal silver nitrate in almost every case and with cuprous chloride in several cases. Its unsaturation was determined by hydrogenation, using platinum oxide catalyst, whenever the silver acetylide test showed it worth while.

It was found that if much dioxane was present when attempting to make this silver acetylide test, no characteristic curdy white precipitate was obtained. Silver acetyldes seem to be soluble in dioxane.

The solvents used, conditions maintained, and the results of all the runs, together with any other pertinent data are listed in table 1, pages 10-11.

The 12% yield, as shown by hydrogenation, was made under non-reproducible conditions of explosions and foreign materials getting into the reaction chamber. Attempts to reproduce this yield under controlled conditions proved unsuccessful.

B- Attempted Grignard Synthesis

Ethyl magnesium bromide was prepared as follows in the apparatus shown on page 22a. Magnesium turnings (7.8 gms, .32 mols) were placed in the three necked flask and 50 cc. of dry ether were added and the mechanical stirrer was started. Ethyl bromide (40 grams, .37 mols) was mixed with 200 cc. dry ether and placed in the dropping funnel. The
<table>
<thead>
<tr>
<th>Run #</th>
<th>Solvent + NaC6H7</th>
<th>Reactant + How Introduced</th>
<th>How Run</th>
<th>Temp. Control</th>
<th>Observations</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Liquid Ammonia + 1 mol</td>
<td>2 mol CH₂O as p-formaldehyde + Na addition tube</td>
<td>In 3 necked flask</td>
<td>None</td>
<td>Addition tube heated up and the p-formaldehyde became gummy. Reaction time = 1 hour</td>
<td>Positive test for hexamethylene tetramine Slight AgCEC-R test</td>
</tr>
<tr>
<td>2</td>
<td>Ether + 1 mol</td>
<td>4 mol CH₂O as p-formaldehyde + filter funnel</td>
<td>II</td>
<td>II</td>
<td>When temperature of distillation reached 41° only 20cc of material remained Reaction time = 1/2 hour</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ether + 1 mol</td>
<td>CH₂O gas 1/2 mol generator</td>
<td>II</td>
<td>II</td>
<td>Distilled to 44°. little remained. Many explosions</td>
<td>Faint AgCEC-R test</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane + 1 mol</td>
<td>CH₂O gas 3 mol generator</td>
<td>II</td>
<td>II</td>
<td>Explosions occur. Final fraction = 18 gm. BP: 103-107 (Theor = 114-115) Reaction time: generation = 3 1/2 hrs Additional = 1/2 hr</td>
<td>Strong AgCEC-R test Hydrogenation = 11.9-12.9% yield</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane + 2 mol</td>
<td>2 mol CH₂O as p-formaldehyde</td>
<td>Bottle</td>
<td>II</td>
<td>BP = 103-107 Reaction time = 20 mins. of shaking</td>
<td>Strong AgCEC-R test Hydrogenation = 5-7% yield</td>
</tr>
<tr>
<td>6</td>
<td>Dioxane + 3 mol</td>
<td>6 mol CH₂O as p-formaldehyde + filter funnel</td>
<td>In 3 necked flask</td>
<td>II</td>
<td>Distilled to 100°. only 10 cc remained. Reaction time = 1 3/4 hours</td>
<td>Faint AgCEC-R test</td>
</tr>
<tr>
<td>7</td>
<td>Dioxane + 1/2 mol</td>
<td>1½ mol CH₂O as p-formaldehyde</td>
<td>Bottle</td>
<td>II</td>
<td>Shaken for 12 hours. Everything boiled below 101°</td>
<td>No AgCEC-R test</td>
</tr>
<tr>
<td>Run#</td>
<td>Solvent + # Mols of NaC≡CH</td>
<td>Reactant</td>
<td>How Run</td>
<td>Temp Control</td>
<td>Observations</td>
<td>Results</td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>8</td>
<td>Dry Dioxane + 1/2 mol CH₂O as aldehyde</td>
<td>In 3 necked flask</td>
<td>Hot water bath</td>
<td>Everything boiled below 110°C</td>
<td>Reaction time = 2 hours</td>
<td>No AgC≡CR test</td>
</tr>
<tr>
<td>12</td>
<td>Dry Ether + 1/2 mol CH₂O</td>
<td>Distilled to 36°C</td>
<td>Reaction time = 2 1/2 hours</td>
<td>No AgC≡CR test</td>
<td>Hydrogenation = 3.5% yield</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Dry Dioxane + 1/2 mol CH₂O</td>
<td>Distilled to 36°C</td>
<td>Reaction time = 2 1/2 hours</td>
<td>No AgC≡CR test</td>
<td>Hydrogenation = 3.5% yield</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Dry Dioxane + 1/2 mol CH₂O</td>
<td>Distilled to 36°C</td>
<td>Reaction time = 2 1/2 hours</td>
<td>No AgC≡CR test</td>
<td>Hydrogenation = 3.5% yield</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Dry Dioxane + 1/2 mol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Dry Dioxane 50 parts Dry Ether 15 parts 1/2 mol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In those runs marked with an asterisk*, the reaction mixture was shaken with NaHSO₃ to remove any unreacted aldehyde.
mixture was dropped into the flask at such a rate as to cause slow refluxing. Time required for this was \( \frac{3}{4} \) of an hour. The reaction was completed by refluxing slowly for \( \frac{1}{2} \) hour on a warm water bath.

The reaction flask was now connected to the acetylene washing and drying trains (see "Apparatus A", p. 6a), and 200 cc. dry dioxane were added. A finely divided white precipitate probably consisting of \( \text{C}_2\text{H}_5\text{MgBr} \) and \( \text{MgBr}_2 \) appeared immediately.

The mechanical stirrer was set in motion and acetylene bubbled slowly through the washing and drying train into the reaction mixture for 12 hours.

The acetylene train was then shut off from the reaction chamber by means of a screw clamp, and 45 grams of formaldehyde gas were passed in over a period of 1½ hours using generator #3, page 8a. The reaction mixture was now made slightly acidic with concentrated sulfuric acid in ice and treated as described in the sodium acetylide runs.

Nothing distilled above 102 degrees, and the final cc. of distillate gave no silver acetylide test.
CONCLUSIONS

We have observed that when using formaldehyde no product other than that corresponding to propargyl alcohol was separated. The alkalinity of the reaction mixture probably caused side reactions of formaldehyde polymerizing to ether insoluble carbohydrates, thus explaining the failure to recover by-products. This premise seems to be substantiated by the fact that when p-formaldehyde is shaken with sodium acetylide for 12 hours, no sodium acetylide is left, as shown by the very small heat of neutralization with sulfuric acid and the completely negative silver acetylide test. In spite of the fact that the 12% yield could not be reproduced, the results of the various runs seemed to indicate that in order to make this reaction proceed in the desired manner, the following conditions should be maintained:

1- High concentration of formaldehyde gas.

2- Use of a solvent which will not react with sodium acetylide or formaldehyde, but will dissolve these substances to a considerable extent.

3- Acidification of the reaction mixture as soon as possible after the heat of reaction has ceased.

The reasons for specifying these conditions are several. In the first place the only runs in which yields were obtained at all were those in which formaldehyde gas was used, or in which the high heat of reaction depolymerized the p-formaldehyde. Secondly dioxane gave much better re-
results than any other solvent used. And finally, when the reaction mixture was acidified very soon after reaction heat had ceased the highest yields of propargyl alcohol were obtained, but when allowed to react for a long time afterwards, no measurable yields were obtained.

While the yields of alcohol from the butyraldehyde runs were insignificant, if extant at all, the results showing aldol condensation may be quite significant. We have several reasons for saying that condensations took place to give the dimolecular aldol compounds. It is known that in dilute solutions of alkali, which condition is met by the dioxane solution of sodium acetylide, aldol condensations are prone to occur. Also, although when fractionating the organic layer no fraction corresponding to butyraldehyde was obtained, the organic layer always gave a sodium bisulfite addition product, indicating the presence of an aldehyde, and a fraction was obtained with a boiling point corresponding approximately to the aldol condensate of butyraldehyde. In one case the fraction gave a 78% yield, and in all cases it gave a very definite sodium bisulfite addition product. The significance of all this is that in those cases where it is difficult to make the dimolecular aldol condensation product of an aldehyde, it might be useful to go through the sodium acetylide procedure, since it is quite simple and gives no extraneous products.
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   b) Paal, Heupel, B., 24, 3039

2. a) Campbell, Campbell, and Elby J. A. C. S. 60, (1938), 2282
   b) Moreau and Desmots Bull. Soc. Chim. 27, (1902), 360

3. Hess and Munderloh B., 51, 380

4. a) Iotisch Bull. Soc. Chim. (3) 34, (1905), 181
   b) Nef Ann. 308, (1899), 264
   c) F. G. Fischer and Lowenburg Ann. 475, (1929), 183

5. a) V. Grignard, L. Lapayne, T. Faki Comptes Rendues (187) 517 (1928)
   b) B. Oddo Gazz. Chim. Ital. 34, (1904), 429
   c) Salkind, Rosenfeld B., 57, (1924), 1690

6. I. Rovno Thesis M. I. T. 1939
REACTION OF CERTAIN GRIGNARD REAGENTS
WITH α-IONONE
INTRODUCTION

Although much work has been done with β-ionone, it has not been established whether Grignard reagents react with it to give 1,2 or 1,4 addition. Knowledge of this is quite important, especially for synthetical work on Vitamin A, since if 1,4 addition predominates, there will always result a difficultly separable mixture. It was the purpose then of this research to attempt to cast more light on the subject.

Since β-ionone is an α,β-unsaturated ketone, it is difficult to tell beforehand just how Grignard reagents will behave with it. From the great amount of work that has been done with α,β-unsaturated ketones and aldehydes, some knowledge of the peculiarities of their reactions may be gleaned. It has been found that some Grignard reagents add 1,2 to the carbonyl group, others 1,4, to the conjugated system, still others 3,4, and finally some add both 1,2 and 1,4. Unsaturated ketones give either saturated ketones or unsaturated alcohols.¹

Kohler has done a great deal of research on α,β-unsaturated ketones and the following table of his covers some of the most significant points.²

¹ Gilman-Organic Chemistry- 1938 ed., Vol 1, p. 581
² Kohler, Am. Chem. J., 38, (1907), 511
"It will be noted", says Gilman, "that as the activity of the carbonyl group decreases, the amount of 1,4 addition increases." The mode of such addition depends upon the number, kind, and position of the substituents in the ketone and upon the Grignard reagent. 3

Karrer tells us further that with α-ionone, allyl magnesium bromide gives us an alcohol (1,2 addition), but the reaction with β-ionone is not analogous (1,4 addition?) 4

From all this it will be seen that it is not so

<table>
<thead>
<tr>
<th>Substance</th>
<th>% 1,4 addition with</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C₆H₅MgBr*</td>
<td>C₂H₅MgBr*</td>
</tr>
<tr>
<td>C₆H₅CH=CHO</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C₆H₅CH=CHCOCH₃</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>C₆H₅CH=CHCOC₂H₅</td>
<td>40</td>
<td>71</td>
</tr>
<tr>
<td>C₆H₅CH=CHCOCH(CH₃)₂</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>C₆H₅CH=CHCOC(CH₃)₃</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>C₆H₅CH=CHCOC₆H₅</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>(C₆H₅)₂C=CHCOC₆H₅</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>C₆H₅CH=C(C₆H₅)COC₆H₅</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>C₆H₅C(CH₃)=CHCOC₆H₅</td>
<td>44</td>
<td>41</td>
</tr>
</tbody>
</table>

* The remainder is to be accounted for by 1,2 addition.

3 Smith and Hanson, J. Am. Chem. Soc., 57, (1935), 1326

easy to tell just how various magnesium halides will react with \( \beta \)ionone. It was attempted, therefore, to take various Grignard reagents, especially those of types similar to those which will probably be used in Vitamin A syntheses, and determine if these added 1,2 or 1,4 to the ionone.

The following Grignard reagents were used: \( \text{C}_2\text{H}_5\text{MgBr} \), \( (\text{CH}_3)_2\text{CH-CH}_2\text{-MgBr} \), \( \text{CH}_3(\text{CH}_2)_3\text{C}=\text{C-MgBr} \), \( \text{CH}_3(\text{CH}_2)_4\text{C}=\text{C-MgBr} \), \( \text{CH}_2=\text{CH-CH}_2\text{-MgBr} \). To determine the amount of 1,2 addition which had occurred, a Grignard apparatus for the determination of hydroxyl and carbonyl groups proposed by Assaf and Gladding was used.\(^5\)

The crude products were separated into three fractions under vacuum, using an oil pump. It was deemed reasonable that the highest boiling fractions should contain no ionone and consist essentially of a mixture of 1,2 and 1,4 addition products. This was born out by the practically quantitative yields of alcohols when acetylene magnesium bromide compounds were used, as shown by Grignard analysis. The percent of 1,2 addition and the percent of crude product represented by the highest boiling fractions are summarized below.

<table>
<thead>
<tr>
<th>Substance Reacted With ( \beta )ionone</th>
<th>% of Crude Product Represented by High Boiling Fraction</th>
<th>% 1,2 Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}_2\text{H}_5\text{MgBr} )</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>( (\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{MgBr} )</td>
<td>12</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substance Reacted With α-Ionone</th>
<th>% of Crude Product Represented by High Boiling Fraction</th>
<th>% 1,2 Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂=CHCH₂MgBr</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>CH₃(CH₂)₂C≡CMgBr</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>CH₃(CH₂)₄C≡CMgBr</td>
<td>36</td>
<td>89</td>
</tr>
<tr>
<td>* CH₂=CHC≡CMgBr</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>* CH₂=C(CH₃)C≡CMgBr</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>* CH₂=CH=C(CH₃)C≡CMgBr</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

* Previously prepared and tested by Dr. Thompson

**GENERAL PROCEDURE**

The ethyl and isoamyl magnesium bromides were prepared by the standard methods. N-butyl and n-amyl acetylene were prepared by a slight modification of the method suggested by Vaughn et al.⁵ Their MgBr compounds were prepared by standard methods. The allyl magnesium bromide was prepared by a modification of the method suggested by Gilman.⁷ Gilman suggested placing 30 mesh magnesium metal in a long column and pouring the allyl bromide mixed with dry ether over it, but J. Burr found that he could obtain sat-


⁸ J. Burr Thesis M.I.T. 1940
isfactory yields by using 60 mesh magnesium and a "Morton" baffled flask equipped with a high speed stirrer. Allyl bromide, magnesium, and ether were used in the molal ratio of 1:3:7.5 as suggested by Gilman, and allowed to reflux at a very slow rate.

The reaction of G ionone with the Grignard reagents were carried out by adding the ionone dropwise to give moderately slow refluxing, and completing by refluxing on a warm water bath.

EXPERIMENTAL

A- Preparation of the acetylene derivatives.

Both hexine-1 and heptine-1 were prepared in the same way. In this discussion we will limit ourselves to the preparation of the former.

Sodium acetylide (½ mol) was prepared in the same manner as before (see page 5). The Y tube (J) with its rubber connector and the sodium addition tube with its rubber connector were removed. In their places were substituted a reflux condenser and a dropping funnel, both protected by soda-lime drying tubes and set in tin foil-collodion painted stoppers. Such stoppers are necessary because the acetylene derivatives are very volatile, and rubber absorbs many times its volume of such substances.

Then n-butyl bromide (\( \frac{3}{4} \) mol) was dropped into the well stirred liquid ammonia solution for a period \( \frac{3}{4} \) of an hour. The liquid ammonia was then evaporated off through the water condenser and enough cold water added to dissolve the sodium bromide. The organic layer was separated from the water layer, and the water layer extracted with six 20-25 cc. portions of cold ether. The extracts were added to the organic layer, and the organic layer washed twice with ice cold 15 cc. portions of 6 N HCl and once with ice water (20 cc.).

The organic layer was now dried with anhydrous magnesium sulfate, the magnesium sulfate filtered off and washed twice with ether. This layer was then distilled through a three foot fractionating column.

Six grams of a material boiling at 71.5 degrees were collected. This is a 14\( \frac{1}{2} \) % yield.

B- Preparation of the Grignard compounds of hexine-1 and heptine-1.

Ethyl magnesium bromide was prepared in the apparatus illustrated on page 22a. Magnesium turnings (3.6 grams = .15 mols) were placed in the three necked flask and 50 cc. dry ether added. Ethyl bromide (16.5 grams = .15 mols) was mixed with 120 cc. of dry ether and put into the dropping funnel. The mechanical stirrer was started and the mixture added dropwise so that slow refluxing occurred. Addition
took \( \frac{1}{2} \) hour and the reaction was completed by stirring and refluxing slowly on a warm water bath for one hour after the last addition of \( \text{EtMgBr} \).

The acetylene compound (.15 mols) was introduced into the dropping funnel and added dropwise to the ethyl magnesium bromide so that slow refluxing occurred. The reaction mixture was stirred and refluxed (water bath) for \( \frac{1}{2} \) hour after the last addition of the acetylene derivative.

C- Preparation of Ethyl and Isoamyl Magnesium Bromides.

Ethyl magnesium bromide and isoamyl magnesium bromide were prepared by the method for ethyl magnesium bromide given in the previous paragraphs. 15 grams (.14 mols) of ethyl bromide and 20 grams (.13 mols) of isoamyl bromide were used together with 150 cc. of dry ether for the former and 175 cc. for the latter.

D- Preparation of Allyl Magnesium Bromide

This compound was prepared in an apparatus similar to that shown on page 22 except that a "Morton" flask was used.

28 grams (.23 mols) of allyl bromide were placed in the dropping funnel together with 95 cc. (.865 mols = \( 3.75 \times \) # mols of allyl bromide) of dry ether. 18 grams (.73 mols = 3 times # mols of allyl bromide) of ground \( \text{Mg} \) turnings were
APPARATUS FOR CARRYING OUT GRIGNARD REACTIONS

A-Calcium chloride drying tubes
B-Reflux water condenser
C-Mechanical stirring rod
D-Dropping funnel
E-Mercury seal
F-Three necked flask
were placed in the flask together with 95 cc. (.865 mols = 3.75 times the # mols of allyl bromide) of dry ether.

The motor was started at high speed and the allyl bromide dropped in at such a rate as to give very slow refluxing. Time for such addition was two hours and 50 minutes. The reaction mixture was stirred for 4 hours longer to complete the reaction. After stopping the motor and allowing the Mg to settle for 4 hour, the liquid was decanted into a 1 liter three necked flask with a reflux condenser and a dropping funnel.

E- Reactions of the Grignard Reagents With $\beta$ Ionone

$\beta$ ionone was added to each of the Grignard reagents in the same manner.

That amount of $\beta$ ionone necessary to react with the magnesium bromide compound (one mol of ionone per mol of reagent) was placed in the dropping funnel (Apparatus p.22) and added at such a rate, with good stirring, that slow refluxing occurred. Time for adding 0.1 mol was approximately 20 minutes. After the last drop of ionone had been added, stirring and refluxing slowly on a water bath were continued for 1 hour. The flask was then surrounded by an ice-water bath and the reaction mixture decomposed by making slightly acid with ice cold sulfuric acid (1 part in 50 parts of water).

The resultant solution consisting of two layers was treated in the following manner. After having saturated
<table>
<thead>
<tr>
<th>Substance Reacted with (3'Ionone</th>
<th>Theoretical Yield (mg)</th>
<th>Fraction #</th>
<th>Actual Yield (mg)</th>
<th>Vacuum Fractionation with Oil Pump</th>
<th>Refractive Index*</th>
<th>% 1,2 Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_2H_5MgBr$</td>
<td>30</td>
<td>1</td>
<td>15</td>
<td>160°C 105-120</td>
<td>1.5042</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>5</td>
<td>160 120</td>
<td>1.5012</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>2</td>
<td>160 120</td>
<td>1.5000</td>
<td>42</td>
</tr>
<tr>
<td>$(CH_3)_2CHCH_2CH_2MgBr$</td>
<td>34</td>
<td>1</td>
<td>14</td>
<td>150 130</td>
<td>1.4993</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>8</td>
<td>165 130-135</td>
<td>1.4968</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
<td>165 135-138</td>
<td>1.4880</td>
<td>30</td>
</tr>
<tr>
<td>$CH_2=CH-CH_2MgBr$</td>
<td>53</td>
<td>1</td>
<td>17</td>
<td>150 110-115</td>
<td>1.5175</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>12</td>
<td>160 115</td>
<td>1.5210</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>10</td>
<td>160 115-122</td>
<td>1.5220</td>
<td>27</td>
</tr>
<tr>
<td>$CH_3(CH_2)_3C≡CMgBr$</td>
<td>41</td>
<td>1</td>
<td>8</td>
<td>160-170 118-130</td>
<td>1.5020</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>7</td>
<td>170 130-138</td>
<td>1.5056</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>15</td>
<td>190 145-155</td>
<td>1.5160</td>
<td>90</td>
</tr>
<tr>
<td>$CH_3(CH_2)_4C≡CMgBr$</td>
<td>27</td>
<td>1</td>
<td>4</td>
<td>150-155 105-123</td>
<td>1.5042</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>4</td>
<td>155-190 123-152</td>
<td>1.5060</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>8</td>
<td>190-200 152-158</td>
<td>1.5170</td>
<td>89</td>
</tr>
<tr>
<td>$CH_2=CHC≡CMgBr$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>$CH_2=C(CH_3)C≡CMgBr$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>$CH_3CH_2=C(CH_3)C≡CMgBr$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

*Refractive Index of (3'Ionone at same temp = 1.5110

† Substances previously prepared by R. Thompson
the water layer with sodium chloride, the organic layer was separated. The water layer was extracted 4 times with 30-40 cc. portions of ether, the extracted material being added to the organic layer which was now dried with anhydrous magnesium sulfate. The magnesium sulfate was filtered off and washed with 15-20 cc. portions of ether three times, the washings being added to the organic layer. The ether was removed from the organic layer through column "l", p. 4a, up to such a temperature that decomposition began to occur.

The resultant residues were fractionated under vacuum, using an oil pump. Data on the fractionations are given in table II, page 23a.

In all cases the third fraction was analyzed to determine if 1,2 or 1,4 addition had occurred. A Grignard apparatus for the determination of the hydroxyl and carbonyl groups was used. The vinyl acetylene products were those which Dr. Thompson had previously prepared. All the results are summarized in table II, page .

CONCLUSIONS

The results obtained from the experimental work and from the analyses of the vinyl acetylene derivatives of ßionone indicate several interesting conclusions.
The evidence presented points strongly toward 1,2 addition occurring when β-ionone is treated with acetylene magnesium bromide compounds, and 1,4 addition when treated with alkyl magnesium bromide compounds. It is interesting to note that while Karrer says allyl magnesium bromide probably does not give 1,2 addition at all, but probably does give a dimolecular hydrocarbon, it was found that 27% 1,2 addition was obtained by the method given in this paper. It seems reasonable to assume that the remainder of the product obtained is the 1,4 isomer because the physical properties of the products presumably eliminate any other possibilities.

The results of the various reactions carried out show further that acetylenic Grignard reagents are more reactive with reference to β-ionone than alkyl reagents. It will be seen from table II that the third fractions of the former were a larger percent of the total yield than those of the latter, although conditions of reaction in each case were the same.
BIBLIOGRAPHY

2. Kohler, Am. Chem. J., 38, (1907), 511
3. Smith and Hanson, J. Am. Chem. Soc., 57, (1935), 1326
8. J. Burr, Thesis M.I.T. 1940