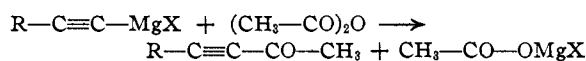[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

The Synthesis of Acetylenic Ketones from Acetylenic Grignard Reagents[1]
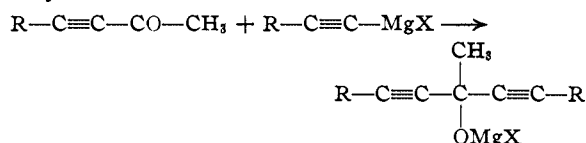
BY J. W. KROEGER AND J. A. NIEUWLAND[2]

In connection with some of the work carried on in this Laboratory[3] it was found necessary to prepare acetylenic ketones of the type $R—C\equiv C—CO—CH_3$. The principal method reported in the literature consists in treating the sodium salt of an acetylenic hydrocarbon with an acyl halide.[4] This method was found to be unsatisfactory from the point of view both of yields and quality of products since traces of halogen were always present in the resulting ketone. This report concerns an entirely successful solution of the problem involving the use of acetylenic Grignard reagents.

A number of compounds have been reported to react with Grignard reagents to form ketones.[5] Of these, acetonitrile, acetamide, acetyl chloride and acetic anhydride were investigated. The first two compounds were found to be inert toward acetylenic Grignard reagents while, of the latter two, acetic anhydride gave the best results.

The ketone which is formed in accordance with the reaction

$$R—C\equiv C—MgX + (CH_3—CO)_2O \longrightarrow$$
$$R—C\equiv C—CO—CH_3 + CH_3—CO—OMgX$$

may react further, as follows

$$R—C\equiv C—CO—CH_3 + R—C\equiv C—MgX \longrightarrow$$

$$R—C\equiv C—\underset{\underset{OMgX}{|}}{\overset{\overset{CH_3}{|}}{C}}—C\equiv C—R$$

The usual method of avoiding this last reaction is to ensure the presence of a large excess of acetic anhydride by slow addition *to* it of the Grignard reagent. Better results, however, were obtained by cooling the Grignard reagent to at least $-25°$ and then adding the acetic anhydride.

For purposes of comparison alkynylmagnesium chlorides, bromides and iodides were investigated

and of the three the chlorides were found most suitable. While the bromides and iodides invariably gave considerable amounts of carbinol and higher boiling polymeric material, the reaction product from an alkynylmagnesium chloride and acetic anhydride usually contained only the desired ketone and a small amount of unreacted alkyne. Occasionally the iodide yielded some iodine-containing material which exploded violently on heating.

Acetylenemagnesium chlorides are apparently rather insoluble in ether. Within the concentration range used, that is, 0.5 to 1.0 mole per liter, the bromides and iodides were always completely soluble whereas the preparation of an acetylenemagnesium chloride always resulted in the formation of a heavy, white precipitate. This was found to be mainly undissolved Grignard reagent.

Acetylenic Grignard reagents apparently are much more stable as well as less reactive than the Grignard reagents from the corresponding saturated hydrocarbons. Arylacetylenemagnesium halides occupy an intermediate position. Indications of this stability may be found in the facts that no reaction was obtained with acetonitrile or acetamide under the ordinary conditions of refluxing the ether solution. In addition, oxygen reacts only to a negligible extent with alkynylmagnesium halides at $-25°$. In spite of this fact, however, the reactions described below were always performed in an atmosphere of nitrogen as recommended by Gilman and Hewlett.[6]

Experimental

Reagents.—The alkylacetylenes were prepared by a modified Picon synthesis.[7] Phenylacetylene was prepared from ethylbenzene as suggested by Friedel and Balsohn.[8] The acetyl chloride, acetic anhydride and methyl iodide were redistilled shortly before use. Ethyl bromide was obtained from the Eastman Kodak Company. The ethyl chloride was supplied through the kindness of E. I. du Pont de Nemours and Company. Anhydrous ether was stored over phosphorus pentoxide and small quantities were distilled off when needed.

Analysis of Grignard Reagents.—The acetylenemagnesium chlorides prepared as described below always con-

(1) Paper XVII on the chemistry of alkylacetylenes and their addition compounds. Previous papers, in this series; XVI, THIS JOURNAL, **58**, 1609 (1936); XV, *ibid.*, **58**, 1806 (1936); XIV, *ibid.*, **58**, 1658 (1936).

(2) The major portion of the research herein reported was completed before the death of Dr. Nieuwland in June, 1936.

(3) Kroeger, Sowa and Nieuwland, *J. Org. Chem.*, 1, 163 (1936).

(4) Nef, *Ann.*, **308**, 264 (1899); Moureu, *et al.*, *Bull. soc. chim.*, **25**, 302 (1901); *ibid.*, **31**, 343 (1904); *Ann. chim. phys.*, [7] **25**, 239 (1902); Andre, *ibid.*, [8] **29**, 540 (1913).

(5) Runge, "Chimie in Einzeldarstellungen," Vol. XVI, Part I, "Organomagnesiumverbindungen," Stuttgart, Wissenschaftliche Verlagsgesellschaft m. b. H., 1932, pp. 180–195.

(6) Gilman and Hewlett, *Rec. trav. chim.*, **48**, 1124 (1929).

(7) Picon, *Compt. rend.*, **158**, 1346 (1914); **169**, 32 (1919).

(8) Friedel and Balsohn, *Bull. soc. chim.*, **35**, 55 (1881).

tained considerable amounts of powdery, white, insoluble material which was analyzed as follows.

Three half-mole samples of ethylmagnesium chloride were prepared in ether, each having a volume of 250 ml. A 2-ml. sample of each was dropped into 50 ml. of ice cold, 0.1 N hydrochloric acid and back-titrated with 0.1 N sodium hydroxide. All three samples corresponded to 0.50 ± 0.02 mole of Grignard reagent.

One-half mole each of amyl-, butyl- and phenylacetylene, respectively, was dropped into the prepared Grignard reagents and the solutions were refluxed until no more ethane was evolved. The contents of each flask was then diluted with anhydrous ether to a volume of 500 ml. and 2-ml. samples were taken while the material in the flasks was being stirred vigorously. This last precaution was to ensure, as nearly as possible, representative samples. Titration of the samples showed that all three flasks contained 0.50 ± 0.01 mole of basic magnesium.

The solid material in each of the three samples was allowed to settle and the supernatant liquid was decanted under nitrogen. The solid was washed twice with 200-ml. portions of anhydrous ether which were then added to the original liquid. The three ether solutions were then diluted to 1000 ml. and 5-ml. samples were taken. They represented 0.20, 0.17 and 0.09 mole of amyl-, butyl-, and phenylacetylenylmagnesium chlorides, respectively.

Although these results give only a rough estimate of the solubilities of the acetylenemagnesium chlorides, they show definitely that the solid material is not magnesium chloride etherate, as it was first supposed, but that it consists largely, if not entirely, of active Grignard reagent.

At similar concentrations the acetylenemagnesium bromides and iodides were completely soluble.

Preparation of Acetylenic Grignard Reagents.—Methyl iodide, ethyl bromide or ethyl chloride was converted to the Grignard reagent in the usual manner. Ethyl chloride was diluted with twice its volume of ether and then added to the metallic magnesium. The preparations were carried out in nitrogen[6] and with mechanical stirring.

The calculated quantity of an acetylenic hydrocarbon was dissolved in ether and added to the prepared Grignard after which the solution was refluxed until no more ethane was evolved. In the case of quarter-mole runs, this required a half-hour for phenylacetylene and about two hours for the alkylacetylenes. Finally the apparatus was again flushed out with nitrogen. The volume of the solution at this point was about 500 ml.

Reaction of Hexynylmagnesium Bromide with Acetonitrile.—One-fourth mole of acetonitrile was added to 0.25 mole of hexynylmagnesium bromide, which was prepared from 21 g. of hexyne-1, and the solution was refluxed for eight hours. After hydrolysis with dilute acid in the usual way and drying, fractionation gave only hexyne-1, b. p. 70–71° (19.5 g.). Similarly, 20 g. of phenylacetylene was recovered from a quarter-mole run of phenylethynylmagnesium bromide.

Reaction of Heptynylmagnesium Bromide with Acetamide.—One mole of heptynylmagnesium bromide was prepared from 96 g. of heptyne-1. To this was added 0.33 mole of acetamide (20 g.) dissolved in warm ether. The acetamide had been previously fused to free it from water. A slight reaction was apparent and the solution was re-

fluxed for four hours. Only heptyne-1 was recovered, b. p. 99–101° (90 g.).

Addition of Grignard Reagent to Acetic Anhydride.—One-half mole of hexynylmagnesium bromide in ether was slowly dropped into one mole of acetic anhydride cooled in an ice–salt mixture. The addition required three hours. Stirring was continued for two hours, then the product was hydrolyzed with ice water and steam distilled. From the steam distillate 20 g. of 3-octyne-2-one, b. p. 90–95° (30 mm.) was obtained. Fractionation of the tarry residue in the steam distillation flask gave 8 g. of bis-hexynylmethylcarbinol, b. p. 125–130° (5 mm.).

Phenylethynylmagnesium bromide (0.25 mole) when treated similarly gave 3 g. of 4-phenyl-3-butyne-2-one, b. p. 105–108° (5 mm.), and 30 g. of a yellow-brown powder, m. p. 108–111°. This material was extracted with hot alcohol and the extract diluted with an equal volume of water. The material so obtained was recrystallized six times from aqueous alcohol finally giving fine, white needles of bis-phenylethynylmethylcarbinol,[9] m. p. 111.5–112.0°.

Reaction of Hexynylmagnesium Chloride with Acetic Anhydride.—One-fourth mole of hexynylmagnesium chloride was prepared in the usual manner and cooled to −30° in a bath of liquid ammonia. One-half mole of acetic anhydride in ether was added at such a rate that the temperature of the mixture remained below −25°, vigorous stirring being maintained. The addition required two and one-half hours. Stirring was continued for two hours at −30° and then for two hours at −5° in an ice–salt bath. After hydrolysis with ice-water and drying, fractionation gave 8 g. of hexyne-1 and 18 g. of 3-octyne-2-one, b. p. 76–77° (15 mm.). This represents a 58% over-all yield or a 98% yield based on the amount of acetylene reacted.

Under similar conditions, 0.25 mole of heptynylmagnesium chloride gave 22 g. of 3-nonyne-2-one, b. p. 86–87° (13 mm.) and 10 g. of heptyne-1. In contrast to the practically quantitative yields from alkynes, only 40–45% yields of 4-phenyl-3-butyne-2-one were obtained. Considerable amounts of carbinol were always formed in this case.

Alkynylmagnesium bromides and iodides, when treated as outlined above, gave 10 to 20% yields of ketones.

TABLE I
PHYSICAL PROPERTIES OF THE COMPOUNDS
R—C≡C—CO—CH₃

R-	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	MRD Calcd.	MRD Found
C₄H₉-	76–76.5	15	1.4446	0.8631	37.16	38.23
C₅H₁₁-	89–89.5	15	1.4463	.8616	41.77	42.73
C₆H₅-	101–102	3	1.5735	1.0239	42.79	46.40

TABLE II
PHYSICAL PROPERTIES OF THE COMPOUNDS
(R—C≡C)₂(CH₃)C—OH

R-	B. p., °C. (2 mm.)	nD	d_4	MRD Calcd.	MRD Found
C₄H₉-	123–125	1.4660 (24°)	0.8840 (24°)	64.38	64.60
C₅H₁₁-	134–136	1.4678 (29°)	.8785 (29°)	73.62	74.09
C₆H₅-	M. p. 111.5–112.0°				

(9) Salkind, *J. Russ. Phys.-Chem. Soc.*, **50**, 24 (1917); *Chem. Zentr.*, **94**, 1391 (1923).

When acetyl chloride was substituted for acetic anhydride, the yields varied from 8 to 15% in the case of bromides and chlorides while the iodides gave nothing but a viscous tar which exploded on attempted vacuum distillation and gave off iodine vapor.

The Action of Oxygen on Hexynylmagnesium Bromide.—The inertness of acetylenic Grignard reagents is well illustrated by the following experiment.

During eight hours dry oxygen was bubbled rapidly through a solution of hexynylmagnesium bromide (0.25 mole) cooled to $-30°$. A 5-ml. sample was then hydrolyzed with dilute hydrochloric acid and the organic layer allowed to evaporate. A slight film of oil remained which had a faint odor of caproic acid.

While the Grignard reagent was still in the liquid ammonia bath, 0.25 mole of acetic anhydride was added and the product was worked up as usual. Fractionation gave 5 g.

of 3-octyne-2-one and 16 g. of bis-hexynylmethylcarbinol, b. p. 123–125° (2 mm.).

Acknowledgment.—We are indebted to Mr. G. M. Wolf for carrying out several of these preparations.

Summary

1. Acetylenic ketones of the type $R—C\equiv C—CO—CH_3$ have been prepared from acetylenic Grignard reagents.

2. Alkynylmagnesium chlorides, when cooled to $-25°$ and treated with acetic anhydride, gave almost quantitative yields of acetylenic ketones.

Sedimentation and Electrophoresis of the Tobacco-Mosaic Virus Protein

BY INGA-BRITTA ERIKSSON-QUENSEL AND THE SVEDBERG

The isolation by W. M. Stanley[1] of a crystalline protein showing the properties of the tobacco-mosaic virus has attracted much attention both in physiological and chemical circles. Stanley's substance is really the first example of a chemically well-defined virus, all previous preparations having been defined by means of biological tests only.

A quantity of the crystalline virus protein was kindly put at our disposal by Dr. Stanley for the purpose of an ultracentrifugal study. In view of the vivid discussion centering around the question whether a virus is a living being with the faculty of propagation or a high-molecular compound with the property of multiplication by autocatalysis a determination of the molecular weight and the degree of homogeneity of this virus protein seemed of great interest. Preliminary measurements by Dr. Stanley of the diffusion and osmotic pressure gave molecular weight values of the order of millions.

The object of our ultracentrifugal study was to determine by means of sedimentation velocity runs the sedimentation constant, and by sedimentation equilibrium runs the molecular weight as well as the dependence of the sedimentation constant on pH, i. e., the pH stability region. Further we wanted to subject the material to a homogeneity test with regard to molecular weight by means of velocity scale runs and, should the virus

protein prove inhomogeneous, to determine the distribution curve.

Previous work on proteins in this Laboratory has demonstrated the great sensitivity of the isoelectric point against chemical differences in the protein molecule. Thus the measurements carried out by K. O. Pedersen[2,3] on respiratory proteins have shown that the isoelectric point varies from species to species although the molecular weight is the same. For example the isoelectric point of the hemocyanin from Helix pomatia is 5.05 while that from Helix nemoralis is 4.63, both proteins possessing near the isoelectric point the molecular weight 6,400,000. On the other hand, the blood pigment of a certain species often contains several components all of which have the same isoelectric point and the same mobility in an electric field. For example, at pH 8.2 the hemocyanin of Helix pomatia has three well-defined components of molecular weight 6,400,000, 3,200,000, and 800,000, all of which are identical in electrophoretic respect. Subjected to a centrifugal field this particular protein system, therefore, is resolved into three components, while exposed to an electric field it moves with a single boundary. In view of this fact it was desirable to carry out a series of electrophoresis determinations on the virus protein.

(1) W. M. Stanley, Science, **81**, 644 (1935).

(2) K. O. Pedersen, Kolloid.-Z., **63**, 268 (1933).

(3) Cf. T. Svedberg, J. Biol. Chem., **103**, 311 (1933).