vinylestradiol methyl ether (Vb) with osmium tetroxide followed by acetylation and Serini reaction of the 20,21-diacetate (VI). The second method consisted of partial aromatization of ring A with the elimination of the angular methyl group of an appropriately substituted etiocholanic acid derivative (VII) and subsequent introduction of the ketol side-chain *via* the diazoketone.

The diazoketone synthesis was also employed in the preparation of an aromatic cortical hormone analog (XI) with a methyl group at C-1. Neither product showed estrogenic or life maintenance activity in rats at the dosage tested.

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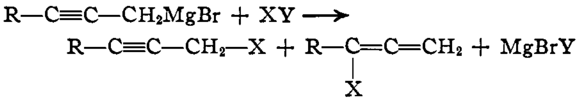
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF ANTIOCH COLLEGE]

Beta Acetylenic Grignard Reagents. I. Hydrolysis and Carbonation of γ-Phenylpropargylmagnesium Bromide

BY GERALD R. LAPPIN*

An earlier investigation of the reaction of β-acetylenic halides with magnesium[1] reportedly showed that no Grignard reagent was formed and only coupling occurred. It has now been found that certain of these halides do yield an organometallic derivative with magnesium, at least one, γ-phenylpropargyl bromide, giving an excellent yield under the ordinary conditions of this reaction.[2]

The structural similarity of β-acetylenic Grignard reagents to those derived from allylic halides led to the question of whether the former would undergo rearrangement similar to the well-known rearrangement of allylmagnesium halides, yielding both acetylenic and allenic products. Rearrangement of β-acetylenic compounds to allenes has been observed[3] but under conditions totally unlike those of the Grignard reaction. When it was found that these new organomagnesium compounds could be prepared it was decided to investigate this possible rearrangement. Because it required no special method and was obtained in high yield γ-phenylpropargylmagnesium bromide was chosen for this study[4] and the reactions chosen were hydrolysis and carbonation.



$$R-C\equiv C-CH_2MgBr + XY \longrightarrow R-C\equiv C-CH_2-X + R-\underset{\substack{|\\ X}}{C}=C=CH_2 + MgBrY$$

Discussion of Results

Hydrolysis.—The hydrolysis of γ-phenylpropargylmagnesium bromide (I) under oxygen and peroxide free conditions gave up to an 87% yield of monomeric hydrocarbon product. On distillation through a high efficiency fractionating column this gave phenylpropadiene (II) as well as 1-phenyl-1-propyne (III) along with a considerable amount of polymeric residue. Both products were identified by comparison with the previously reported characteristics, II being identified by its boiling point,[5,6] refractive index,[6] rapid polymerization[5,6] and rapid uptake of oxygen from the air to form a ketone, presumably methyl phenyl diketone.[5] Identification of III was made through its boiling point and refractive index.[7] Final confirmation was obtained from the oxidation of these hydrocarbons with potassium permanganate in pyridine solution,[8] II yielding only benzoic acid while III gave both benzoic and acetic acids.

An attempt was made to determine the ratio of acetylene to allene formed by oxidation followed by analysis for the ratio of benzoic to acetic acid formed.[8] Because of the rapid polymerization of II consistent results were not obtained, the amount of II present in the monomeric product ranging from 6 to 37% in various experiments. However, in those experiments which gave a low yield of monomeric II a high yield of polymer was obtained and if the polymer consisted only of phenylpropadiene this must have made up more than half of the total hydrolysis product. Since in at least one experiment practically no volatile monomer was obtained it is evident that copolymerization between II and III can occur so that any estimate of the composition of the total reaction mixture is very doubtful. It was clearly shown, nevertheless, that an allylic-like rearrangement did occur, whether during the formation of the organomagnesium bromide or during the subsequent hydrolysis it is, at present, impossible to say.

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(1) Lai, *Bull. soc. chim.*, **53**, 1543 (1933).

(2) Since the completion of the work herein described, Newman and Wotiz, THIS JOURNAL, **71**, 1292 (1949), have briefly mentioned the preparation in 95% yield of a Grignard reagent from 1-bromo-2-heptyne using a special "high dilution technique" which was not described. Carbonation was said to yield an unidentified mixture of acids. In this Laboratory the Grignard reagent has been prepared from 1-bromo-2-octyne in about 30% yield by a method which will be described in a subsequent publication.

(3) For a summary of such rearrangements see Johnson, "Acetylenic Compounds," Edward Arnold and Company, London, 1946, Vol. I, p. 63 ff.

(4) Later results have shown this choice to be a poor one for the phenylpropadiene derivatives polymerize much more rapidly than purely aliphatic allenic compounds. Further work on these rearrangements is being carried out with octynylmagnesium bromide.

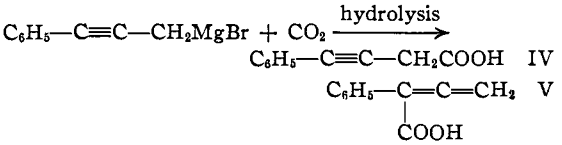
(5) Bourguel, *Compt. rend.*, **192**, 686 (1931).

(6) Ginsberg, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1029 (1938).

(7) Truchet, *Ann. chim.*, **16**, 309 (1931).

(8) Young, Ballou and Nozaki, THIS JOURNAL, **61**, 12 (1939).

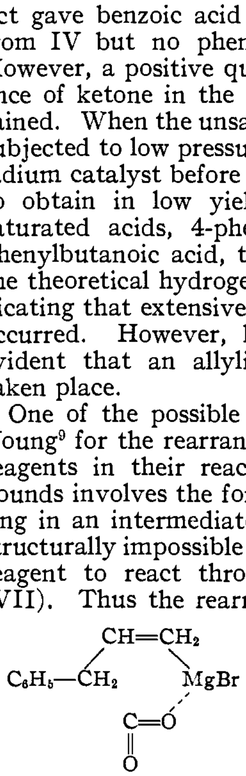
Carbonation.—The carbonation of I was carried out in the usual fashion but in the absence of oxygen and peroxides. An acidic product was obtained but all attempts to isolate either of the expected products, 1-phenyl-1-propyne-3-carboxylic acid (IV) or 1-phenylpropadiene-1-carboxylic acid (V), failed because of complete polymerization of the product either on distillation or even on standing in the refrigerator for a few hours. Oxidation of a portion of the acidic product gave benzoic acid and malonic acid derived from IV but no phenylglyoxylic acid from V. However, a positive qualitative test for the presence of ketone in the oxidation product was obtained. When the unsaturated acidic product was subjected to low pressure hydrogenation over palladium catalyst before distillation, it was possible to obtain in low yield the two corresponding saturated acids, 4-phenylbutanoic acid and 2-phenylbutanoic acid, though only about 40% of the theoretical hydrogen uptake was observed indicating that extensive polymerization must have occurred. However, here again it was clearly evident that an allylic-like rearrangement had taken place.



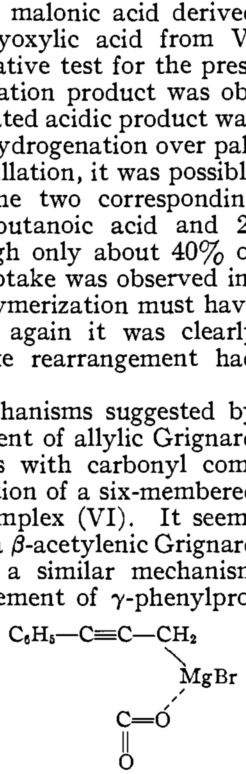
$$C_6H_5—C{\equiv}C—CH_2MgBr + CO_2 \xrightarrow{\text{hydrolysis}} C_6H_5—C{\equiv}C—CH_2COOH \quad \text{IV}$$

$$\underset{\displaystyle COOH}{C_6H_5—\overset{}{C}}{=}C{=}CH_2 \quad \text{V}$$

One of the possible mechanisms suggested by Young[9] for the rearrangement of allylic Grignard reagents in their reactions with carbonyl compounds involves the formation of a six-membered ring in an intermediate complex (VI). It seems structurally impossible for a β-acetylenic Grignard reagent to react through a similar mechanism (VII). Thus the rearrangement of γ-phenylpropargylmagnesium bromide on carbonation may constitute some evidence against this mechanism. However, considerably more study will be required before it can be known whether this new type of rearrangement is fundamentally or only superficially similar to that of allylic Grignard reagents.



VI



VII

Experimental[10]

Preparation and Hydrolysis of γ-Phenylpropargylmagnesium Bromide.—The reaction was carried out in a special indented flask fitted with a high speed stirrer giving extremely vigorous agitation and under the usual anhydrous conditions using an atmosphere of dry nitrogen throughout the entire experiment. To 2.88 g. (0.12 g. atom) of magnesium turnings in 150 ml. of dry ether was added dropwise over a period of four hours a solution of 24 g. (0.12 mole) of γ-phenylpropargyl bromide[11] in 200 ml. of anhydrous ether. After addition of all the bromide the solution was warmed on the water-bath for one hour. Titration of a 1-ml. aliquot with standard acid indicated a yield of 92% of RMgBr. Hydrolysis was carried out by adding to the ether solution dropwise a cold 5% sulfuric acid solution while cooling the flask in an ice-salt-bath. The ethereal layer was separated, washed with water, 5% sodium bicarbonate solution, and with water again. After drying over Drierite the ether was removed under reduced pressure at 20° and the residue was flash distilled at 1 mm. pressure and an oil-bath temperature of 65° to separate the monomeric product from polymerization products. The yield of volatile product was 12.9 g. (87% based on the product being C_9H_8). The non-volatile residue was a soft brown material resembling closely the description of phenylpropadiene polymer.[5]

Fractionation of the Volatile Product.—Still maintaining the atmosphere of dry nitrogen, 10 g. of the volatile product was distilled through a 50-plate distilling column[12] at 15 mm. pressure. Three fractions were collected. The first, b. p. 68–69°, $n^{20}D$ 1.563, 1.7 g., was colorless when first collected but rapidly turned deep yellow on exposure to air and polymerized to a soft brown solid on standing for a few hours. The freshly distilled material gave a scarlet sodium salt when warmed with sodium in dry benzene. This is a reported reaction of phenylpropadiene.[6] After short exposure to air this fraction gave a positive carbonyl test with 2,4-dinitrophenylhydrazine and alcoholic potassium hydroxide.[13] These properties and reactions agree well with those reported for phenylpropadiene.[5,6] The second fraction, b. p. 69–72°, $n^{20}D$ 1.561, 3.8 g., was colorless when collected, slowly turned pale yellow on standing for a few hours, but did not polymerize after being exposed to air for several weeks. A weak positive test for carbonyl was obtained from the yellowed fraction. This was presumed to be a mixture of II and III. The third fraction, b. p. 72–73°, $n^{20}D$ 1.560, 2.8 g., was colorless even after standing exposed to air for several hours and gave a negative ketone test after being exposed to the air for two days. Its properties agree well with those of 1-phenyl-1-propyne (III).[7] A soft polymeric residue of about 1.5 g. remained in the pot.

Oxidation of the Volatile Product and the Fractions from Distillation.—Samples (0.3–0.5 g.) of the volatile product and of each of the above-mentioned fractions were oxidized in pyridine solution with potassium permanganate by the method of Young, Ballou and Nozaki.[8] The oxidation products were analyzed for the ratio of benzoic acid to acetic acid produced as described by these authors. The volatile product analyzed for a mixture of 37% II and 63% III, but the volatile products from other similar reactions ranged from a low of 6% II to this high value. However, in those experiments which gave a low proportion of II the amount of non-volatile product was larger indicating that, while the allene was formed, it had polymerized before the flash distillation. The first fraction from the distillation analyzed for 93% II and 7% III, the second fraction for 25% II and 75% III, the third for 98% III and 2% II thus confirming the identity of these fractions.

Carbonation of γ-Phenylpropargylmagnesium Bromide.—The Grignard reagent was prepared as previously described from 24 g. (0.12 mole) of the bromide and 2.88 g.

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[9] Young and Roberts, THIS JOURNAL, **68**, 649 (1946).

[10] The ether used herein was carefully freed from peroxides and stored under nitrogen. The use of ether containing 0.005% peroxide in a carbonation experiment resulted in complete polymerization of the product.

[11] This was prepared from the corresponding alcohol by reaction with phosphorus tribromide using the method of Lai [*Bull. soc. chim.*, **53**, 1533 (1933)]. However, yields of 90–95% were obtained consistently in contrast to the reported yield of about 70%.

[12] Precise Fractionation Assembly manufactured by Todd Scientific Company, Springfield, Pa.

[13] Clark and Lappin, unpublished research, Antioch College.

(0.12 g. atom) of magnesium turnings in 250 ml. of anhydrous ether using a nitrogen atmosphere. Titration of a 1-ml. aliquot indicated an 81% yield of RMgX. A large excess of air-free carbon dioxide, dried by bubbling through sulfuric acid followed by passing through anhydrous alumina, was passed into the solution of the organomagnesium bromide while cooling the reaction flask in an ice-bath. Hydrolysis was carried out immediately by adding dropwise about 50 ml. of cold 5% sulfuric acid to the cooled reaction mixture. All subsequent operations were carried out under a carbon dioxide atmosphere. The ether layer was separated and washed three times with 20-ml. portions of cold water. The acidic product was extracted with three 20-ml. portions of ice-cold 5% aqueous sodium hydroxide solution and the basic extract was washed twice with small portions of ether. The basic extract was covered with 50 ml. of ether and, while cooling in an ice-bath, acidified with cold dilute sulfuric acid. After separating the ether layer the aqueous layer was again extracted with a 25-ml. portion of ether. The combined ether extracts were dried over Drierite and the ether was removed under reduced pressure. The sirupy residue was dissolved in 100 ml. of absolute ethanol and the solution was filtered through a 1-cm. bed of decolorizing charcoal. To it was added 0.5 g. of 5% palladium-on-charcoal and hydrogenation was carried out at 60 lb. pressure and room temperature in a Parr low pressure hydrogenation apparatus. The hydrogen uptake was 6 lb. over a period of three hours, theory requiring 15.2 lb. assuming a quantitative yield of C_9H_7COOH from the organomagnesium bromide. After removal of the catalyst and distillation of the ethanol the brown sirupy residue was distilled through a small spiral-packed column at atmospheric pressure. No decomposition occurred and two main fractions were collected. The first, b. p. 268–272°, 0.8 g., was a thick yellow sirup which would not crystallize even after long standing in the refrigerator. The second, b. p. 290–294°, 3.1 g., was a thick sirup which crystallized after several weeks at 0°, m. p. 49–50° after two recrystallizations from ethanol. The reported properties of the two expected isomeric phenylbutanoic acids are: 2-phenylbutanoic acid,[14] b. p. 270–272°, m. p. 41–42°; 4-phenylbutanoic acid,[15] b. p. 290°, m. p. 51°, m. p. of amide 84–85°. Inasmuch as no solid derivative was reported for 2-phenylbutanoic acid and time did not permit the preparation of an authentic sample of this substance the neutral equivalent and molecular weight of the first fraction were determined. Calcd. for $C_{10}H_{12}O_2$: neut. equiv., 164; mol. wt., 164. Found: neut. equiv., 168; mol. wt., (cryoscopic in benzene) 170. On the basis of its boiling point, neutral equivalent and molecular weight fraction one was identified with reasonable certainty as 2-phenylbutanoic acid. Fraction two was converted to the amide in the usual manner, m. p. 83–85°, thus confirming its identity as 4-phenylbutanoic acid.

In another identical experiment an attempt was made to separate the expected acetylenic and allenic acids before hydrogenation by distillation at 0.1 mm. pressure. No distillate was obtained and the material became hard and resinous. A 3-g. sample of the unsaturated acidic product was oxidized in pyridine solution with potassium permanganate at 50° for four hours. To the mixture was added 50 ml. of water and the precipitated manganese dioxide was removed by filtration. The solution was evaporated to dryness under vacuum and the residue was redissolved in 50 ml. of water. A small portion was neutralized with dilute sulfuric acid and tested for presence of ketone,[13] a strongly positive test being obtained. However, all attempts to isolate a derivative of phenylglyoxylic acid failed. The basic solution was cooled to 5° and passed through a cation exchange resin column to convert the salts to the free acids. Evaporation of the solution to 5 ml. *in vacuo* resulted in the crystallization of 1.1 g. of benzoic acid, identified by mixture melting point with an authentic sample. The filtrate was evaporated to dryness and the residue taken up in ether. Evaporation of the ether solution to a volume of about 3 ml. *in vacuo* resulted in the crystallization of 0.3 g. of malonic acid, identified by mixture melting point with an authentic sample. No phenylglyoxylic acid was isolated.

Summary

1. The preparation of a Grignard reagent from a β-acetylenic halide, γ-phenylpropargyl bromide, is described for the first time.

2. Hydrolysis of γ-phenylpropargylmagnesium bromide has been shown to give not only the expected 1-phenyl-1propyne but also phenylpropadiene, indicating that an allylic-like rearrangement occurred.

3. Carbonation of this Grignard reagent gave a mixture of unsaturated acids which could not be separated because of the rapid polymerization which occurred. However, immediate hydrogenation of this mixture gave a low yield of both 4-phenylbutanoic acid and 2-phenylbutanoic acid, indicating that here, too, rearrangement of an allylic nature had occurred.

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[14] Ruber, *Ber.*, **36**, 1406 (1903).

[15] Willgerodt and Merck, *J. prakt. Chem.*, [2] **80**, 197 (1909).