[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

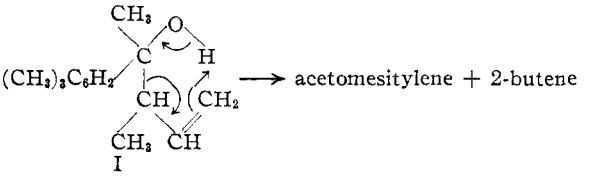
Allylic Rearrangements. XXI. Further Studies Related to the Nature of the Butenyl Grignard Reagent[1]

BY WILLIAM G. YOUNG AND JOHN D. ROBERTS[2]

Cleavage of the butenyl Grignard reagent by water[3] gives a mixture of butenes, although the products from a variety of addition[4] and coupling[5] reactions are almost exclusively α-methylallyl derivatives. To gain further information regarding the butenyl Grignard reagent we have turned to the study of some reactions expected to cleave the reagent to butenes through the operation of mechanisms different from that involved with water.

For the cleavage of butenylmagnesium bromide by an enolizable ketone, acetomesitylene was chosen since several investigators[6] have shown that organometallic compounds such as ethylmagnesium bromide, *n*-butyllithium and phenylsodium do not add to the carbonyl group of this compound but give enolization products exclusively. Contrary to expectation, the reaction of butenylmagnesium bromide with acetomesitylene gave a negligible amount of enolization products (less than 3% of the calculated amount of butenes was detected). From the reaction mixture was recovered about 12% of the original ketone and the principal product was the tertiary alcohol, α-methylallylmesitylmethylcarbinol (I). The yield was 83%.

The addition product was found to have some unusual properties. The assigned structure was based on ozonization which gave large quantities of formaldehyde, indicating the presence of a terminal double bond. Propionaldehyde and acetomesitylene were also present in the ozonization products and probably resulted from the dealdolization of the anticipated α-methyl-β-hydroxy-β-mesitylbutyraldehyde during the process of reducing the ozonide and steam distilling the products. On heating at atmospheric pressure, α-methylallylmesitylmethylcarbinol cleaved smoothly to butenes and acetomesitylene. The butene mixture consisted of *cis* (72%) and *trans*-2-butene (28%) and contained no detectable 1-butene. A mechanism for this cleavage reaction may be formulated which is quite similar to that proposed for the Claisen allyl ether rearrangement.[7]



acetomesitylene + 2-butene

I

The striking behavior of butenylmagnesium bromide in forming an addition product with acetomesitylene suggested that other β,γ-unsaturated Grignard reagents might give similar results. This was found to be the case and the reaction of acetomesitylene with benzylmagnesium chloride resulted in yields of addition and enolization products to the extent of 38 and 52%, respectively. The structure of the addition product was established as that of a benzyl rather than an *o*-tolyl derivative by oxidative degradation with potassium permanganate in pyridine. Benzoic acid was obtained. Pyrolysis of the addition product resulted in dehydration rather than the cleavage noted with α-methylallylmesitylmethylcarbinol. If, as indicated by the earlier experiments, the cleavage reaction proceeds through a cyclic mechanism similar to the Claisen rearrangement, the failure of this mechanism to operate when the α-methylallyl group is replaced by a benzyl group is not unexpected in view of the fact that benzyl phenyl ether does not undergo the Claisen rearrangement under the usual conditions.[7]

Although the excellent yield of addition product obtained from the reaction of butenylmagnesium bromide with acetomesitylene might be ascribed to the operation of a special type of cyclic addition mechanism available to β,γ-unsaturated organomagnesium halides, the operation of such a mechanism is clearly not a necessary condition for addition since benzylmagnesium chloride gives the "normal"[8] addition product. A general explanation for the difference in behavior of saturated and unsaturated Grignard reagents has been proposed by Dr. S. Winstein of this Laboratory, who suggests that the *ratio* between the rates of addition and enolization for a given carbonyl compound may vary with the basicity of the organic radical (considered as a free carbanion) of the attacking Grignard reagent much in the same way as the ratio between substitution and

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society at New York City, September, 1944. Preliminary report, THIS JOURNAL, **66**, 2131 (1944).

(2) Abbott Laboratories Fellow, 1943-1944.

(3) (a) Young, Winstein and Prater, THIS JOURNAL, **58**, 289 (1936); (b) Young and Eisner, *ibid.*, **63**, 2113 (1941).

(4) (a) Ou Kuin-Houo, *Ann. chim.*, (11), **13**, 175 (1940); (b) Lane, Roberts and Young, THIS JOURNAL, **66**, 543 (1944); (c) Young and Roberts, *ibid.*, **67**, 148 (1945); (d) *ibid.*, **67**, 319 (1945); (e) *ibid.*, **68**, 649 (1946).

(5) Young, Roberts and Wax, *ibid.*, **67**, 841 (1945).

(6) (a) Kohler and Baltzly, *ibid.*, **54**, 4015 (1932); (b) Kohler, Jacobs and Sonnichsen, *ibid.*, **62**, 785 (1940); (c) Gilman and Jones, *ibid.*, **63**, 1162 (1941).

(7) *Cf.* Tarbell, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 16.

(8) (a) Tiffeneau and Delange, *Compt. rend.*, **137**, 573 (1903); (b) Gilman and Kirby, THIS JOURNAL, **51**, 3475 (1929); (c) Austin and Johnson, *ibid.*, **54**, 647 (1932); (d) Young and Siegel, *ibid.*, **66**, 354 (1944); (e) Gilman, "Organic Chemistry," 2nd. ed., John Wiley and Sons, Inc. New York N. Y., 1943, p. 1880.

elimination for a particular alkyl halide varies with the basicity of the attacking anion.

Turning to other types of active hydrogen compounds, we investigated the reactions of phenylacetylene, quinaldine and fluorene with butenylmagnesium bromide. The experiments with quinaldine and fluorene were unsuccessful as the Grignard reagent was not appreciably cleaved by these compounds in refluxing ether solutions over periods of several hours. With phenylacetylene cleavage occurred readily and the resulting butene mixture consisted of at least 93% 1-butene.

Discussion[9]

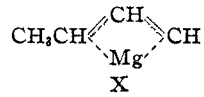
Three general proposals may be made as to the nature of the butenyl Grignard reagent, depending on the fundamental character of the C-Mg bonds involved. First, the C-Mg bond might be considered to be essentially ionic and the Grignard solution to contain significant concentrations of carbanions produced by direct ionization. Second, the C-Mg bond might be essentially covalent but readily broken so that the isomeric forms of the reagent would be capable of rapid interconversion. Such a process would not necessarily involve ionization of the C-Mg bond. Finally, the bond might have considerable stability so that the isomeric forms of the reagent could react independently with or without rearrangement depending on the conditions and nature of the reactants much in the same way as is observed with the butenyl chlorides.[10]

Assuming the butenyl Grignard reagent to be considerably ionized, it is certain that the butenyl anion would exist as a resonance hybrid of the forms, $CH_3CH{=}CHCH_2^- \longleftrightarrow CH_3\bar{C}HCH{=}CH_2$. If this is the case, no more specific structure can be assigned to the reagent than is possible for potassium cyanide or the salt of a carboxylic acid where the metallic ion cannot be regarded as being "bonded" to any particular atom of the anion. Considerable evidence may be cited to show that, in general, primarily ionic linkages are not involved in the C–Mg bonds of organomagnesium halides and that no appreciable concentration of free carbanions is ever present in a normal Grignard solution[11]: (1) the C–Mg bond has but 34% ionic character as calculated according to Pauling[12]; (2) ether has no good way of solvating a carbanion and this fact would tend to inhibit ionization; (3) free carbanions, if present in ethereal solution, would be expected to attack the solvent to give hydrocarbons and ethoxide ion[13]; (4) the conductance and transference data, as well as the products of the electrode reactions,[11] can be explained without necessity for direct ionization of the C-Mg bond by the following equilibra involving species, all of which can conceivably be solvated by ether.

$$RMgX + R_2Mg \rightleftarrows R_2MgX^- + RMg^+$$
$$2RMgX \rightleftarrows RMgX_2^- + RMg^+$$
$$RMgX + MgX_2 \rightleftarrows RMgX_2^- + MgX^+$$
$$2R_2Mg \rightleftarrows R_3Mg^- + RMg^+$$

The second proposal, on which basis the forms of the butenyl Grignard reagent are regarded as being essentially covalent but rapidly interconvertible, permits only an equilibrium mixture of the isomeric forms to have other than a transitory existence. The composition of a mixture of this type could probably be determined only by physical methods as it would seem unlikely that any chemical reagent could be found which would react with each of the allylic isomers of the butenylmagnesium halides at identical rates. To explain the results of the hydrolysis,[3] carbonyl addition,[4] and coupling[5] reactions it is necessary to assume that the different species react at suitably different rates and that the equilibrium between the forms is established more rapidly than reaction occurs. It is to be noted that if a rapidly established equilibrium exists between the forms of the Grignard reagent, it must be capable of being established independently of equilibria such as $2RMgX \leftrightarrows MgX_2 + R_2Mg$ since dibutenylmagnesium behaves like butenylmagnesium bromide in giving a mixture of butenes with water[14] and pure 2-methyl-3-butenoic acid with carbon dioxide.[4c]

An alternative but similar hypothesis would have the magnesium atom bonded substantially to both the α and the γ-carbon atoms of the organic moiety of the reagent in a resonance hybrid structure.



The principal objection to these proposals lies in their failure to account for the striking specificity of the formation of addition and coupling products. In particular, considerably more than the observed amount of product containing the crotyl group would be expected with diisopropyl ketone and acetomesitylene because of the large difference in steric factor between the paths leading to the crotyl and α-methylallyl products.

On the basis of the third hypothesis for the nature of the butenyl Grignard reagent it is suggested that the isomeric forms are capable of independent existence and reaction. If that is the case, butenylmagnesium halides as commonly prepared are best formulated as being almost exclusively either one or the other of the isomeric

(9) See Ref. 4c for a discussion of earlier work on the nature of allylic Grignard reagents.

(10) (a) Roberts, Young and Winstein, THIS JOURNAL, **64**, 2157 (1942); (b) Young and Andrews, *ibid.*, **66**, 421 (1944).

(11) For an opposing point of view see Evans and Pearson, *ibid.*, **64**, 2865 (1942).

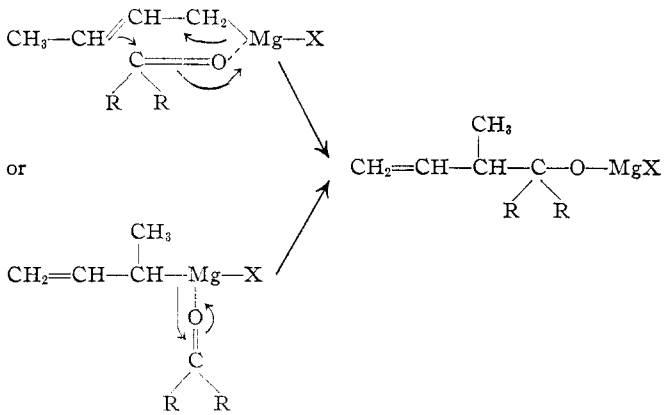
(12) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 64.

(13) This behavior is noted with compounds such as ethylsodium, see Schorigin, *Ber.*, **43**, 1931 (1910).

(14) Young and Pokras, *J. Org. Chem.*, **7**, 233 (1942).

forms as it would appear improbable that a mixture of primary and secondary allylic isomers could react in addition, coupling and cleavage processes with a wide range of substances to give predominantly, if not exclusively, α-methylallyl derivatives. In fact, those reactions, *i. e.*, with water[3] and oxygen,[15] which give mixtures of products, are just those in which the character of the reactants is such that resonating ionic[16] or radical intermediates would be expected to be important and lead to mixtures.

If it is assumed that the butenyl Grignard reagent exists almost exclusively as either crotyl or α-methylallylmagnesium bromide, it remains to decide between the two possible structures. The results of addition, coupling and cleavage reactions do not offer a definite choice since the operation of either of two mechanisms would account for the formation of α-methylallyl derivatives as the reaction products. Choosing a carbonyl addition reaction as an example we have:



Similar mechanisms may be written for the other reactions. At present, only indirect evidence is available to aid in a decision as to the structure of the butenylmagnesium halides. Perhaps the most cogent argument is concerned with the situation with respect to benzylmagnesium chloride. With formaldehyde the benzyl Grignard reagent gives *o*-tolylcarbinol.[8] Conceivably, benzylmagnesium chloride, in common with other Grignard reagents, could react with formaldehyde in the customary fashion and yet the abnormal process is favored. With butenylmagnesium halides the activation energy required to effect reaction by a mechanism analogous to that postulated[8e] for abnormal reaction in the benzyl system should be far less than in the case of benzylmagnesium halides as the double bond is not part of an aromatic ring and, certainly, if for formaldehyde this process is favored in the aromatic system, it should be the expected path for simple allylic Grignard reagents. Therefore, since the operation of this abnormal mechanism in the reaction for formaldehyde with α-methylallylmagnesium bromide would be expected to lead to 3-pentenol-1 and with crotylmagnesium bromide to 2-methyl-3-butenol-1, the exclusive formation of the latter product[4c] indicates that the formulation of the butenyl Grignard reagent as a crotylmagnesium halide is to be preferred. A similar conclusion was reached from the results of experiments directed toward effecting the 1,4-addition of the butenyl Grignard reagent to α,β-unsaturated carbonyl compounds.[4e]

(15) Siegel, Master's Thesis, University of California at Los Angeles, 1940.

(16) See ref. 10 for references to the role of ionic intermediates in nucleophilic reactions of allylic systems.

Experimental Part

Reaction of Butenylmagnesium Bromide with Acetomesitylene.—In order to eliminate any butenes dissolved in a standardized ethereal solution (360 ml.) containing 0.36 mole of butenylmagnesium bromide,[4b] the solution was heated until about 100 ml. of ether was distilled. Acetomesitylene (49 g., 0.30 mole) dissolved in 100 ml. of ether was then added dropwise with stirring over a half-hour period. After an additional half-hour at room temperature, 125 ml. of ether was distilled into a Dry Ice-cooled trap. The distillate was titrated with liquid bromine from a microburet. Less than 0.35 ml. (0.007 mole) of bromine was required to give a permanent deep red color to the solution. Less than 3% of the theoretical amount of butene was thus detected. The Grignard complexes were decomposed by pouring the mixture into iced ammonium chloride solution and the products were isolated in the usual way. Fractionation through a 35 × 0.9 cm. column packed with glass helices gave several cuts (see table below). The distillation curve indicates an upper limit to the recovery of acetomesitylene as 12% and the yield of addition product as 52.8 g. (81%). The pure addition product, Fractions 6–9, amounted to 49.8 g. (76%).

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.54; H, 10.16. Found: C, 82.36, H, 10.23.

Fraction 8 (2.036 g.) was hydrogenated in ethyl alcohol over platinum oxide. The absorption of hydrogen was 0.00950 mole and assuming one double bond the molecular weight found was 214 (calcd. for $C_{15}H_{22}O$, 218).

Frac.	B. p., °C., 2 mm.	Wt., g.	$n^{20}D$
1–3	86–103	6.0	1.5140–1.5207
4–5	103–119	3.0	1.5240–1.5276
6–9	119–122.5	48.8	1.5328–1.5321
10	122.5–123	1.3	1.5321
11	123–127	0.7	1.5218
Residue		4.2	

Fraction 8 (10.0 g.) was heated at atmospheric pressure in a distilling apparatus. The outlet of the system was connected to a Dry Ice trap. Gas was evolved very slowly when the temperature of the liquid reached 120–140° and at 200° the decomposition proceeded briskly. No charring or discoloration was noted. A small amount of water was evolved. The temperature rose finally to 240° and no further decomposition occurred. The residue was distilled, giving 7.1 g. (95%) of acetomesitylene, b. p., 124–127.5° (19 mm.), $n^{20}D$ 1.5171. The butenes were distilled from the trap through a calcium chloride tube and sealed in an ampoule. An infra-red spectroscopic analysis[17] revealed the butenes to have the composition: 1-butene, 0%; *cis*-2-butene, 72%; and *trans*-2-butene, 28%. The acetomesitylene in the distillate

(17) We are grateful to Dr. O. Beeck of the Shell Development Company for this analysis.

was identified by conversion to mesitoyldibenzoylmethane, m. p. 193–194° (lit.[6a] 192°) and 3,5-dinitroacetomesitylene, m. p. 138–139.5° (lit.[18] 138–139°).

Fraction 8 (2 ml.) was ozonized at −70° in 15 ml. of dichlorodifluoromethane. A modification of the method of Whitmore and Church[19] was used for the reduction and isolation of the products. Formaldehyde and propionaldehyde were identified as their methone derivatives of m. p. 189–191° and 155–156°, respectively. Acetomesitylene was identified by conversion to *m*-nitrobenzalacetomesitylene, m. p. 98–99° (lit.[20] 98°).

Benzylmagnesium Chloride with Acetomesitylene.—To a solution of benzylmagnesium chloride prepared from 2.4 g. (0.10 gram atom) of magnesium, 9.5 g. (0.075 mole) of freshly distilled benzyl chloride (b. p. 93.5° (50 mm.)) and 100 ml. of ether was added dropwise with stirring 8.0 g. (0.05 mole) of acetomesitylene dissolved in 100 ml. of ether. A brilliant orange-red color developed, which faded to light yellow after all of the ketone had been added. The mixture was poured into iced ammonium chloride solution and the ethereal layer separated and dried. The ether was removed through a column and remainder of the low-boiling material was then distilled into a Dry Ice trap at 50° (5 mm.). Fractionation of this distillate gave 3.7 g. (0.040 mole) of toluene, b. p. 109–110°. The residue (10.3 g.) from the reduced pressure distillation was distilled in a molecular still.

Frac.	Bath temp., °C.	Press., mm.	Wt., g.	$n^{20}D$
1	63–65	3.5×10^{-4}–1.5×10^{-4}	2.7	1.5242
2	65–100	1.5×10^{-4}–3.0×10^{-4}	0.8	1.5520
3	100–110	3.0×10^{-4}	5.9	1.5689
Residue			0.2	

Fraction 1 appeared to be mainly acetomesitylene. Fraction 3 was the addition product. If Fraction 2 is considered to be roughly two-thirds addition product and one-third ketone, the amount of enolization and addition on the basis of the theoretical yields were 38 and 52%, respectively, giving a recovery of 90%. Concordant analyses were not obtained with the addition product. The material apparently absorbed oxygen or water continuously from the air, to judge from the trend of the analytical values.

Anal. Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.91. Found: (Fraction 3) C, 85.23, 84.09, 82.97; H, 9.12, 8.67, 8.50.

Fraction 3 (1 g.) was distilled at atmospheric pressure. Water was given off and after the moisture had passed over the product distilled at about 300°. The material was very little discolored in this process and the distillate showed $n^{20}D$ 1.5603.

Fraction 3 (1.51 g.) was oxidized in pyridine[21] solution with potassium permanganate. The acidic products were separated by the procedure of Gilman and Kirby.[22] No phthalic acid was detected. Benzoic acid was isolated and crystallized from a water–alcohol mixture; m. p. and mixed m. p. 117–121°; yield 0.10 g. (32%).

Butenylmagnesium Bromide with Phenylacetylene.—To an ethereal solution of butenylmagnesium bromide (0.094 mole) was added a solution of 11 g. (0.11 mole) of phenylacetylene (b. p. 80.5°, 100 mm.). The resulting butenes were distilled into a Dry Ice trap and purified as previously described.[23]

The butene mixture was analyzed by the infra-red method[17] and found to consists of 1-butene, 93.6%; *cis*-2-butene, 5.4% and *trans*-2-butene, 1.0%.

Summary

Butenylmagnesium bromide was found to add to acetomesitylene to give α-methylallylmesitylmethylcarbinol in 83% yield. Less than 3% of the theoretical quantity of butene was evolved. The addition product was cleaved on heating to give *cis*- and *trans*-2-butene and acetomesitylene.

Benzylmagnesium chloride also added to acetomesitylene to give benzylmesitylmethylcarbinol in 38% yield.

Butenylmagnesium bromide was cleaved by phenylacetylene to give a mixture of butenes, of which at least 93% was 1-butene.

Existing evidence appears to favor the formulation of the butenylmagnesium halides as crotylmagnesium halides.

(18) Fisher, Snyder and Fuson, THIS JOURNAL, **54**, 3665 (1932).

(19) Whitmore and Church, *ibid.*, **54**, 3710 (1932).

(20) Barnes and Spriggs, *ibid.*, **67**, 134 (1945). In our first experiments this material was isolated in an unstable form as pale yellow prisms, m. p. 82–83°. A solution of the compound seeded with a crystal of the stable form kindly furnished by Dr. Barnes gave the bright lemon-yellow crystals of the stable form, m. p. 98–99°.

(21) (a) Bucher, *ibid.*, **32**, 374 (1910); (b) Smith and Spoehr, *J. Biol. Chem.*, **86**, 87 (1930).

(22) Gilman and Kirby, THIS JOURNAL, **54**, 345 (1932).

(23) Young and Roberts, *ibid.*, **67**, 1040 (1945).

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[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

Esterification of Galacturonic Acid and Polyuronides with Methanol–Hydrogen Chloride

BY EUGENE F. JANSEN AND ROSIE JANG

A simple method for the preparation of the methyl ester of α-D-galacturonic acid became desirable in our investigations of the specificity of pectinesterase. Furthermore the ester, as opposed to the free acid, has been shown to inhibit the growth of many dysentery bacteria *in vitro*.[2] Esterification in acidic methanol would be expected to lead to partial or complete formation of the methyl glycoside as well as the methyl ester. For this reason the methyl ester of α-D-galacturonic acid has been prepared by the laborious and somewhat hazardous diazomethane method.[3] Fraenkel-Conrat and Olcott[4] found, in the course of studies of esterification of carboxyl groups of proteins and model substances, including acetic, lactic, benzoic and galacturonic acids, that galacturonic acid is readily esterified at room temperature in methanol containing 0.02 to 0.1 *N* mineral acid. This observation raised

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) Steinhaus and Georgi, *J. Infectious Diseases*, **69**, 1 (1941).

(3) Morell and Link, *J. Biol. Chem.*, **108**, 763 (1935).

(4) Fraenkel-Conrat and Olcott, *ibid.*, **161**, 259 (1945).