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Allylic Rearrangements. XVIII. Coupling Reactions of Butenylmagnesium Bromide

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In connection with our work on the nature of the butenyl Grignard reagent it was desirable to study the coupling reactions of butenylmagnesium bromide. Henne, Chanan and Turk[2] have coupled butenyl chlorides in the presence of magnesium while Lespieau and Heitzmann[3] have reported similar experiments with crotyl bromide, but the results of these investigators are not in agreement. Furthermore, it is not clear whether or not the butenyl Grignard reagent is truly involved under conditions where the organometallic compound couples as rapidly as it forms. Indeed, valuable information might be expected from a comparison of the products resulting from the rapid coupling of two halide molecules with magnesium and from the coupling of a preparation of the Grignard reagent with a suitable halide. We have, therefore, made a study of the coupling reactions of butenylmagnesium bromide. After the completion of this work a paper by Levy and Cope[4] appeared describing a number of similar experiments but without comment as to the significance of the results.

TABLE I

PRODUCTS FROM THE COUPLING REACTIONS OF ALLYLIC HALIDES WITH BUTENYLMAGNESIUM HALIDES

Allylic halide	2,6-Octadiene, %	3-Methylheptadiene-1,5, %	3,4-Dimethylhexadiene-1,5, %	2,6-Heptadiene, %	3-Methylhexadiene-1,5, %	Yield, %	Ref.
Crotyl bromide[a,b]	50	50	Trace	..	..	90	3
Crotyl bromide[a]	10	88	2	..	..	58	This paper
Methylvinylcarbinyl bromide	50	35	15	..	..	75	This paper
Allyl bromide	..	..	..	50	50	68	This paper
Allyl bromide	..	..	..	22	78	62	4
Crotyl chloride[b]	Trace	92.5	7.5	..	..	54	2
Crotyl chloride	12	82	6	..	..	72	This paper
Methylvinylcarbinyl chloride[b]	4.5	85	10.5	..	..	67	2
Methylvinylcarbinyl chloride	3	86	11	..	..	76	This paper
Allyl chloride	..	..	..	<8	>92	49	This paper

[a] Equilibrium mixture of the bromides (87% primary, 13% secondary). [b] Grignard reagent not prepared separately.

The compositions of the products of coupling reactions of butenylmagnesium halides with allylic halides are presented in Table I. It is evident that allylic bromides generally give quite different products than the corresponding chlorides. This may be due to a greater tendency of the bromides to undergo an ionic type[5] reaction involving an electrophilic attack of magnesium on halogen. However, the operation of such a mechanism in itself would not explain the experimental results, as rearrangements of both the Grignard reagent and halide molecules appear to be involved in these reactions. As yet no definite explanation can be offered for the differences between the products obtained by coupling crotyl bromide with the Grignard reagent and the rapid coupling of the bromide with magnesium. It is uncertain whether or not exchange reactions between the Grignard reagent and halide molecules are involved but no products were isolated in significant amounts in the present work which could be attributed to exchange reactions alone.

In contrast to the complex results obtained with allylic bromides, the coupling of butenylmagnesium halides with allylic chlorides appears to result in the predomination of but one of the possible products. Furthermore, substantially the same composition of isomers is obtained either by direct coupling of the halides or through the prior formation of the Grignard reagent. The fact that both crotyl and methylvinylcarbinyl chlorides give as the principal product 3-methylheptadiene-1,5 (I), leads to speculation as to which half of the diene molecule is derived in each case from the Grignard reagent and which from the halide. Evidence on this point is furnished by the results (Table II) of the coupling reactions of butenyl chlorides with allylmagnesium halides. The product from the reaction of crotyl chloride with allylmagnesium bromide was 2,6-heptadiene, while the coupling of the secondary chloride gave

TABLE II

PRODUCTS FROM THE COUPLING REACTIONS OF BUTENYL CHLORIDES WITH ALLYLMAGNESIUM HALIDES

Butenyl chloride	2,6-Heptadiene, %	3-Methylhexadiene-1,5, %	Yield, %	Ref.
Primary	>94	<6	54	This paper
Primary	100	0	54	4
Secondary	77	24	55	This paper
Secondary	67	33	54	4

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(1) Abbott Laboratories Research Fellow, 1943–1944.

(2) Henne, Chanan and Turk, THIS JOURNAL, **63**, 3474 (1941).

(3) Lespieau and Heitzmann, *Bull. soc. chim.*, [5] **3**, 273 (1936).

(4) Levy and Cope, THIS JOURNAL, **66**, 1684 (1944).

(5) Roberts, Young and Winstein, *ibid.*, **64**, 2163 (1942).

a mixture of products which was mostly 2,6-heptadiene. This result indicates that *both* chlorides tend to furnish mainly primary butenyl groups in coupling reactions and, hence, that the origin of the secondary butenyl group in I may be traced to the Grignard reagent.

The generality of the appearance of the organic radical of the butenyl Grignard reagent as the methylvinylcarbinyl group in the products of coupling reactions with chlorides is further established by the results obtained with allyl chloride and *n*-butyl chloromethyl ether. With the allyl halide the product was almost exclusively 3-methylhexadiene-1,5, while the α-chloro ether gave *s*-butenylcarbinyl *n*-butyl ether in 70% yield.

The significance of the present results lies in the fact that the products of coupling reactions of butenylmagnesium bromide like those obtained in carbonyl addition reactions[6,7] result in the introduction of a secondary butenyl group by the Grignard reagent. Additional evidence regarding the nature of the butenyl Grignard reagent will be presented in future papers.

Experimental

Butenyl halides and butenylmagnesium bromide were prepared as previously described.[5,6] The allyl halides were redistilled commercial products. The compositions of the diolefin mixtures were determined by fractionation through efficient columns.[8a,b] The physical properties of the products checked values reported previously.[2,4]

A. Reaction of Butylmagnesium Bromide with Allylic Bromides.—The allylic bromide (10–15% excess) was added dropwise to a stirred solution of 0.6 mole of butenylmagnesium bromide in 500 ml. of ether over a period of an hour while cooling to 15-20°. The mixture was then heated under reflux with stirring for three hours. Saturated ammonium chloride (200 ml.) was added slowly with cooling and the ether layer separated and dried. After removal of the bulk of the ether the residue was refluxed with dry pyridine (0.5 mole) for three to four hours to convert any excess halide to a quaternary ammonium salt. The liquid was cooled, decanted from the solids present and washed with water, dilute hydrochloric acid, water and dried over calcium chloride The ether was then distilled and the residue fractionated. The results are given in Table I.

B. Reaction of Butenylmagnesium Bromide with Allylic Chlorides.—The following procedure employed in the reaction of butenylmagnesium bromide with methylvinylcarbinyl chloride is typical. Details for the removal of excess halide by treatment with sodium in liquid ammonia[9] were kindly supplied by Dr. A. L. Henne of The Ohio State University.

To a solution of 0.38 mole of butenylmagnesium bromide was added slowly a solution of 35 g. (0.38 mole) of methylvinylcarbinyl chloride ($n^{20}D$ 1.4150) in 100 ml. of ether. The mixture was stirred at room temperature for two days, then poured into iced ammonium chloride solution. The ethereal layer was washed with water and dried over magnesium sulfate. The bulk of the ether was removed and the residue added to a solution of 1 g. of sodium metal in 200 ml. of liquid ammonia. On shaking, the blue color disappeared and small slices of sodium were added until a permanent color persisted. Sufficient alcohol was added to destroy the excess sodium and the ammonia was allowed to evaporate. The organic material was taken up in ether, washed with water, dilute hydrochloric acid, sodium bicarbonate solution, water, saturated calcium chloride solution and dried over calcium chloride. The ether was distilled and the residue fractionated. Table I gives the yield and composition of the reaction products.

C. Reaction of Allylmagnesium Chloride with Butenyl Chlorides.—The procedure was similar to that described in part B. The results are tabulated in Table II.

D. Reaction of Butenylmagnesium Bromide with *n*-Butyl Chloromethyl Ether.—*n*-Butyl chloromethyl ether (b. p. 72.0–73.0° (100 mm.)) was prepared by the method of Hill and Keach.[10] To an ethereal solution of butenylmagnesium bromide (360 ml., 0.29 mole) cooled in an ice-bath was added *n*-butyl chloromethyl ether (34.9 g., 0.29 mole) dissolved in an equal volume of ether. After four hours of stirring the mixture was poured onto iced ammonium chloride solution and worked up in the usual way. Fractionation gave, other than octadienes, 29.3 g. (70%) of *s*-butenylcarbinyl *n*-butyl ether; b. p. 89.7–90.3° (100 mm.), $n^{20}D$ 1.4130.

Anal. Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.75. Found: C, 75.63; H, 12.80.

The column holdup was distilled from a small Claisen flask, giving 3.4 g. of material; b. p. 85.0–93.0° (50 mm.), $n^{20}D$ 1.4188-1.4198. This boiling point appears to be higher than would be anticipated for pure pentenyl *n*-butyl ether and the material may have been seriously contaminated with ethylene glycol di-*n*-butyl ether formed by the coupling of two molecules of *n*-butyl chloromethyl ether. The combustion analysis shows the pentenyl butyl ether to be contaminated with material lowering the carbon content as would be expected for the above mentioned possibility as the impurity (calcd. for $C_{10}H_{22}O_2$: C, 68.91; H, 12.72). If any of the isomeric 3-pentenyl *n*-butyl ether was present this substance could not have accounted for more than 10% of the total product.

Anal. Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.75. Found: C, 72.67; H, 12.8.

The structure of the principal product was established as *s*-butenylcarbinyl *n*-butyl ether by hydrogenation in ethyl alcohol over platinum oxide to the saturated ether and comparison of physical properties with those of *n*-amyl *n*-butyl ether and *s*-butylcarbinyl *n*-butyl ether (Table III).

TABLE III

PHYSICAL PROPERTIES OF AMYL *n*-BUTYL ETHERS

Ether	B. p. (50 mm.), °C.	$n^{20}D$	d^{20}_4
n-Amyl *n*-butyl[a]	83.7–84.7	1.4069	0.772
s-Butylcarbinyl *n*-butyl	73.4–74.3	1.4045	.774
Hydrogenation product[b]	74.6–76.0	1.4045	.774

[a] Vaughan, Vogt and Nieuwland (This Journal, 57, 510 (1935)) report b. p. 163°. [b] *Anal.* Calcd. for $C_9H_{20}O$: C, 74.93; H, 13.97. Found: C, 75.62; H, 14.3.

n-Amyl *n*-butyl ether was prepared by the Williamson synthesis from *n*-butyl bromide and *n*-amyl alcohol. To 6 g. (0.26 gram atom) of sodium slices was added 100 ml. of *n*-amyl alcohol (b. p. 136°) and the mixture was heated and stirred until all of the sodium had dissolved. To the hot solution was added 40 g. (0.29 mole) of *n*-butyl bromide and the mixture was refluxed overnight. After filtration of the solids the products were diluted with ether, washed with water, dried over magnesium sulfate and distilled. The yield of ether was 28.9 g. (79%).

Anal. Calcd. for $C_9H_{20}O$: C, 74.93; H, 13.97. Found: C, 75.25; H, 14.0.

s-Butylcarbinyl *n*-butyl ether was prepared similarly in 65% yield from 6 g. (0.26 mole) of sodium metal, 50 ml. of

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[6] Lane, Roberts and Young, This Journal, **66**, 543 (1944).

[7] Roberts and Young, *ibid.*, **66**, 2131 (1944); **67**, 148, 319 (1945).

[8] (a) Goldwasser and Taylor, *ibid.*, **61**, 1751 (1939); *cf.* also Whitmore, *et al.*, **62**, 785 (1940); (b) Podbielniak, *Ind. Eng. Chem.*, **13**, 639 (1941).

[9] Henne and Chanan, This Journal, **66**, 392 (1944).

[10] Hill and Keach, *ibid.*, **48**, 257 (1926).

s-butylcarbinol (Eastman Kodak Co. "Synthetic") and 40 g. (0.29 mole) of *n*-butyl bromide.

Summary

1. Butenylmagnesium bromide couples with allylic bromides to give mixtures of diolefins, whereas with allylic chlorides individual products tend to predominate.

2. The principal products of the coupling reactions of allylic chlorides with butenylmagnesium bromide, like the products from carbonyl-addition reactions, may be considered to be derived from the secondary form of the Grignard reagent.

3. The reaction of butenylmagnesium bromide with *n*-butyl chloromethyl ether gives *s*-butenylcarbinyl *n*-butyl ether.

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The Isoelectric Nature of Sulfanilamide and *p*-Aminobenzoic Acid

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It has been assumed generally[1] in correlating the acid–base properties of sulfonamides with their mode of action that these substances, as well as their inhibitor, *p*-aminobenzoic acid, exist in neutral and not in zwitterionic form in their isoelectric state in aqueous solution. Conflicting evidence[17,18] is available for *p*-aminobenzoic acid but none is known for a sulfonamide. One possible approach to the question is the comparison of the ionization constants of the amino group in the acid and in its corresponding esters for the case of *p*-aminobenzoic acid, and in the amide and the corresponding N^1-alkyl-substituted amides for the case of sulfanilamide. The basis of this procedure was developed by Adams[2] and by Ebert[3] and has been applied widely to the amino acids by Edsall.[4] Data are presented in this paper which allow the necessary comparisons to be made for sulfanilamide and *p*-aminobenzoic acid. The results together with the ultraviolet absorption spectra from which they are derived substantiate the assumption that these substances are primarily neutral in their isoelectric state.

Experimental

The compounds examined were prepared as follows.

Sulfanilamide.—A commercial sample was recrystallized from water; m. p. 165°.

N^1,N^1-Dimethylsulfanilamide.—*p*-Acetaminobenzenesulfonyl chloride was treated with dimethylamine, the resultant acetyl compound hydrolyzed with 15% hydrochloric acid and the free amine obtained by neutralization with sodium bicarbonate. The solid was recrystallized first from acetone and then from ethyl alcohol; m. p. 170–171°.

N^1,N^1-Diethylsulfanilamide.—The same procedure was used as for the corresponding methyl compound, except that diethylamine replaced dimethylamine; m. p. 103–104°.

***p*-Aminobenzoic Acid.**—A commercial sample was decolorized twice with charcoal and then recrystallized from water; m. p. 187°.

Methyl *p*-Aminobenzoate.—A solution of *p*-aminobenzoic acid in methyl alcohol was saturated with hydrochloric acid and refluxed for six hours. The free base was liberated and then recrystallized three times from methyl alcohol; m. p. 110–111°.

Ethyl *p*-Aminobenzoate.—This compound was prepared in a manner analogous to that of the corresponding methyl ester; m. p. 86–87°.

Ultraviolet absorption spectra in the region of 2200–3200 Å. were obtained with a Beckman quartz spectrophotometer. Aqueous solutions approximately 5×10^{-5} molar in concentration were made by quantitative dilution of a more concentrated solution prepared from a weighed quantity of solute dissolved in the solvent in a volumetric flask. Two matched, silica absorption cells were used, one being filled with solvent and the second with solution. The cells were each 1 cm. in length. The temperatures of the *p*-aminobenzoic acid and ester solutions were between 25–27°, those of the sulfonamides between 23–25°.

For each of the six compounds investigated, three spectra were collected, one in pure distilled water, the second in an aqueous solution of approximately 0.005 *N* hydrochloric acid (exact concentration known) and the third in an aqueous solution of approximately 0.50 *N* hydrochloric acid.

Results and Calculations

If two isoelectric forms of sulfanilamide are in equilibrium with each other, the equilibrium constant

$$K_Z = \frac{{}^+H_3NC_6H_4SO_2NH^-}{H_2NC_6H_4SO_2NH_2} \qquad (1)$$

should be evaluated from an equation analogous to that used by Edsall,[4] that is

$$K_Z = \frac{K_S}{K_M} - 1 \qquad (2)$$

where K_S is the acid ionization constant of ${}^+H_3NC_6H_4SO_2NH_2$ and K_M is the acid ionization constant of the corresponding N^1,N^1-dimethyl or diethyl-substituted compound. Either of these constants may be represented by the equation

$$K = (H^+)(S)/({}^+HS) \qquad (3)$$

where (S) represents the total concentration of isoelectric sulfonamide.

The equations for *p*-aminobenzoic acid are identical in form but K_S represents the acid ionization constant of ${}^+H_3NC_6H_4CO_2H$ and K_M the corresponding constant for the methyl or ethyl ester.

Since most of the sulfonamides, especially the

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[1] Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942); Klotz, *ibid.*, **66**, 459 (1944).

[2] Adams, *ibid.*, **38**, 1503 (1916).

[3] Ebert, *Z. physik. Chem.*, **121**, 385 (1926).

[4] Cohn and Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943, pp. 96–99.