The Reaction of Methyl Vinyl Ketone with Alkyl Grignard Reagents

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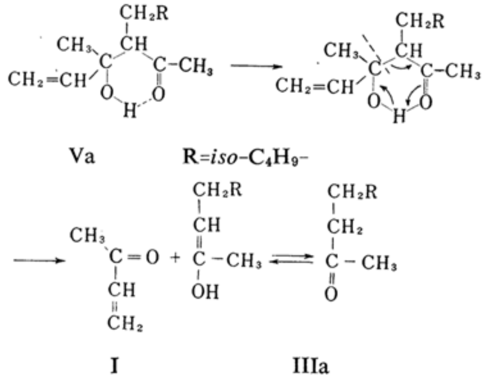
The reaction of methyl vinyl ketone (I) with acetylenic Grignard reagents has been reported[1,2] to afford almost exclusively the 1,2-addition product, ethynylcarbinol. However, Smith and Sprung[3] could not obtain a simple product in the reaction between laurylmagnesium bromide and the ketone I because of the polymerization of I. Sarycheva et al.[4] obtained the 1, 2-addition product in the reaction between the Grignard reagent from 5-bromo-2, 3-dimethylpentene-2 and I, but its infrared spectrum seems to indicate that the product is a mixture of the 1, 4- and 1, 2-addition products.

In a previous study,[5] isophytol was synthesized from pseudoionone and propargyl alcohol, and it was found that the ketone I reacted with laurylmagnesium bromide to yield the 1, 4-addition product rather than the 1, 2-addition product. The reactions of I with isobutylmagnesium bromide IIa or ethylmagnesium bromide IIb will be studied in the present paper to see whether or not the previous findings concerning 1, 4-addition indicate a general tendency in the reaction between methyl vinyl ketone and alkyl Grignard reagents.

The reactions were carried out at low concentrations of the reactants and at low temperatures in order to suppress the polymerization of I. The reaction between I and IIa at −50°C gave two products as colorless liquids. The lower boiling substance was found to be the 1, 4-addition product, methylheptanone (IIIa), and 3-isoamyl-2-vinyl-2-pentanol-4-one (Va) was assigned to the higher boiling product. The spectrum of Va indicated the presence of tertiary hydroxyl, non-conjugated carbonyl, and vinyl groups. When Va was treated with semicarbazide by an ordinary method,[6] no precipitate was formed. When the mixture with semicarbazide was warmed for thirty minutes or allowed to stand at room temperature for a long time, the semicarbazone of IIIa was obtained. In this reaction, IIIa was supposed to be derived by the decomposition of Va. Actually the compound, Va, decomposed readily when heated at 150°C to afford IIIa and I quatitatively. Such a decomposition supported the assignment of structure Va for the higher-boiling product, and the decomposition probably proceeds through a cyclic transitional state, as is illustrated below. This decomposition occurred also in the presence of sulfuric acid to give IIIa in a high yield.



Va R=*iso*-C_4H_9-

I IIIa

Thus, the reaction of I with IIa has been shown to yield a mixture of IIIa and Va. The formation of IIIa and Va can reasonably be explained by assuming the following reaction mechanism (Fig. 1). The Grignard reagent, IIa, condenses with I by the 1, 4-addition process to form an enolate III′a of methylheptanone in the first step. The enolate is converted into IIIa by hydrolysis. On the other hand, when the enolate is added to the carbon atom of the carbonyl group of another molecule of I, compound V′a is formed; this is finally hydrolyzed to Va. These courses of the reaction are shown by pathways A and B in Fig. 1 respectively.

The reaction mechanism of the Grignard

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[1] J. Cymerman, I. M. Heilbron and E. R. H. Jones, *J. Chem. Soc.*, **1944**, 144.

[2] N. A. Milas, F. X. Grossi, S. E. Penner and S. Kahn, *J. Am. Chem. Soc.*, **70**, 1292 (1948).

[3] L. I. Smith and J. A. Sprung, ibid., **65**, 1276 (1943).

[4] I. K. Sarycheva, G. A. Vorobyeva, L. G. Kucheryavenko and N. A. Preobrazhensky, *Zh. Obshch. Khim.*, **27**, 2994 (1957).

[5] K. Sato, Y. Kurihara and S. Abe, *J. Org. Chem.*, **28**, 45 (1963).

[6] R. L. Shriner and R. G. Fuson, "The Systematic Identification of Organic Compounds," John Wiley & Sons, New York, N. Y. (1948), p. 170.

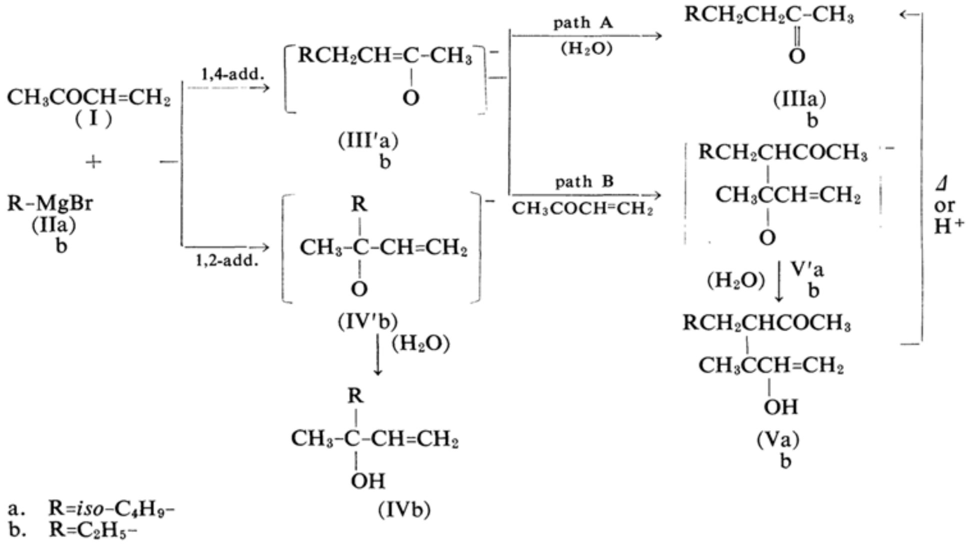

Fig. 1.

enolate ion with methyl vinyl ketone (pathway B) is supported by a number of investigations[7] of the condensation of ketones during the Grignard reaction. For example, Mosher and Lux[8] demonstrated that the interaction of methyl isopropyl ketone and *t*-butylmagnesium chloride led to the formation of not only the secondary alcohol to be expected from the reduction of the ketone but also of the ketol, 2, 3, 6-trimethyl-3-heptanol-5-one, which is a self-condensation product of methyl isopropyl ketone. According to the commonly accepted view,[7] the formation of this ketol may be explained as follows; the Grignard reagent causes the enolization of the ketone, as is already known, and the enolate thus formed is added to the carbon atom of the carbonyl group in a molecule of the corresponding keto form (Fig. 2).

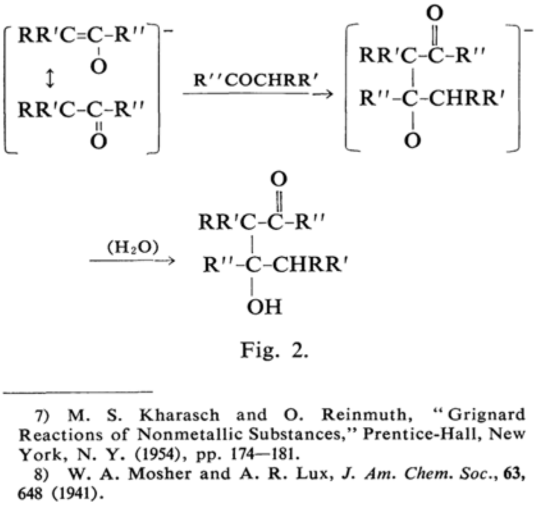

Fig. 2.

The yields of compound IIIa and compound Va were strongly influenced by the experimental conditions. The effect of varying the molar ratio of the reactants at −50°C was examined. When two moles of I per mole of IIa were used, the main product was Va, and only a trace of IIIa was obtained. When approximately equimolar amounts of I and IIa were used, both IIIa and Va were obtained in, respectively, 7.5% and 38% yields based on I. When half a mole of I was used, Va was again preferably obtained. Judging from these results, it seems likely that the reaction of the enolate, III'a, with I is faster than that of IIa with I. When the reaction temperature was raised to −15°C, only Va was obtained, even with equivalent moles of the reactants.

On the other hand, the reaction between equimolar amounts of I and ethylmagnesium bromide, IIb, at −50°C afforded 3-methyl-1-penten-3-ol (IVb, the 1, 2-addition product) contaminated with methyl *n*-butyl ketone (IIIa) and 3-propyl-2-vinyl-2-pentanol-4-one (Vb, the addition product between I and the 1, 4-addition product). The yields of IVb and Vb were, respectively, 6.6% and 17% based on I. The structure of IVb was established by infrared spectrum and by conversion into its 3, 5-dinitrobenzoate. The purification of IVb was unsuccessful, even by means of careful fractionation. Methyl *n*-butyl ketone as a contaminant was identified by gas chromatography using an authentic sample. The structure of Vb was established by means of elemental analysis and its infrared spectrum. Compound Vb may have been formed from III'b by a mechanism similar to that found in the formation of Va. It was decomposed into IIIb in

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[7] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y. (1954), pp. 174—181.

[8] W. A. Mosher and A. R. Lux, *J. Am. Chem. Soc.*, **63**, 648 (1941).

the presence of sulfuric acid. Although the ratios of the reaction products were not studied under a variety of reaction conditions, it might be concluded from the above results that the reaction of I with IIb proceeds by both 1, 2- and 1,4-addition, and that the 1, 4-addition product III'b subsquently condenses with I to afford Vb. As has been described above, IIa gives only the 1, 4-addition product. The reason for this difference in the reaction products has not been clariffied in the present study. It may, however, be worth noticing that, in the cases of both IIa and IIb, methyl vinyl ketone is added to their 1, 4-addition products, whereas no further addition was previously observed in the case of laurylmagnesium bromide.

Experimental⁽⁹⁾

Materials.—Methy vinyl ketone was prepared from γ-ketobutanol (78—80°C/18 mmHg, prepared from acetone and formalin) by dehydration with oxalic acid according to the method of Murata⁽¹⁰⁾; b. p. 80—82°C. Commercially available isobutyl bromide and ethyl bromide were used after purification (isobutyl bromide, b. p. 90—90.8°C; ethyl bromide, b. p. 38—39°C).

The Reaction of Methyl Vinyl Ketone (I) with Isobutylmagnesium Bromide (IIa).—**(a) At −50°C.** —*i) The Equimolar Ratio of I to IIa.*—The Grignard reagent was prepared from 54.8 g. of isobutyl bromide and 9.8 g. of magnesium in 300 ml. of anhydrous ether. To the solution, 22.4 g. of freshly-distilled methyl vinyl ketone in 150 ml. of anhydrous ether was added drop by drop at such a rate as to maintain the temperature at −50°C. After the reaction mixture had been continuously stirred for a further hour, it was decomposed with an ice-cooled saturated ammonium chloride solution and extracted with ether. The ether extract was washed with water and with a saturated sodium bicarbonate solution, dried, and evaporated. The residue was distilled fractionally; fraction I (5.5 g.) (b. p. 25—37.5°C/18 mmHg), fraction II (5 g.) (b. p. 27—50°C/4 mmHg), fraction III (14.5 g.) (b. p. 80—103°C/5 mmHg), and a residue (2.1 g.). By gas chromatographic analysis (column temp. 151°C; injection temp. 185°C; N_2 flow 12.8 ml./min.; silicon oil DC550, 2 m.), fraction I was found to be composed mostly of isobutyl alcohol (retention time 1.2 min.) contaminated with a small amount of methylheptanone (retention time 6 min.). These retention times were in good agreement with those for authentic samples. Fractions II and III were redistilled. Fraction II gave 3.0 g. (7.5% based on I) of methylheptanone, boiling at 30—31°C/4 mmHg, 166—167°C/760 mmHg, n_D^{20} 1.4230 (lit.⁽¹¹⁾ n_D^{19} 1.4144, b. p. 164—165°C/760 mmHg). The infrared spectrum indicated a band at 1715 cm⁻¹ ($\rangle$C=O).

Found: C, 74.13; H, 12.71. Calcd. for $C_8H_{16}O$: C, 74.96; H, 12.58%.

The semicarbazone was recrystallized from C_2H_5OH and H_2O (1 : 1); m. p. 150.5—151°C (lit. m. p. 157°C,⁽¹¹⁾ m. p. 146°C⁽¹²⁾).

Found: C, 58.12; H, 10.45; N, 22.65. Calcd. for $C_9H_{19}ON_3$: C, 58.34; H, 10.34; N, 22.68%.

Fraction III gave 12.0 g. (38% based on I) of Va, boiling at 88—90°C/3 mmHg, n_D^{20} 1.4602, d_4^{20} 0.9223. The infrared spectrum of this substance showed bands at 1640, 1415, 990, 920 (-CH=CH$_2$), 3450, 1165 (tert. OH), and 1705 cm⁻¹ (C=O).

Found: C, 72.33; H, 10.97. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18%.

ii) The Molar Ratio of I to IIa (2 : 1).—To the Grignard reagent (prepared from 54.8 g. of isobutyl bromide, 9.8 g. of magnesium and 300 ml. of anhydrous ether), 44.8 g. of I in 400 ml. of anhydrous ether was added at −50—−55°C. The reaction mixture was then treated by the same procedure as that described in part i. Methylheptanone (1.8 g.), b. p. 31—33°C/3 mmHg, the ketol (22.3 g.), b. p. 88—90°C/3 mmHg, and the residue (9.0 g.) were obtained. These materials were proved to be identical with the samples described in the preceding paragraph by gas chromatography or the refractive index.

iii) The Molar Ratio of I to IIa (1 : 2).—The same procedure as that described in the part i was employed. 3.4 g. of Va, b. p. 81—85°C/4 mmHg, and 0.2 g. of IIIa, b. p. 38—40°C/4 mmHg were obtained from 25.5 g. of isobutyl bromide, 4.8 g. of magnesium and 5.6 g. of I.

(b) At −15°C.—To the Grignard solution prepared from 27.4 g. of isobutyl bromide, 5.0 g. of magnesium in 150 ml. of anhydrous ether, 12.6 g. of I in 160 ml. of anhydrous ether was added. The oily product isolated was 5.8 g. of Va (b. p. 87—92°C/3 mmHg, redistilled, b. p. 97—100°C/5 mmHg). The refractive index of this substance agreed with that of the preceding sample.

The Decomposition of 3-Isoamyl-2-vinyl-2-pentanol-4-one (Va). — *a) By Sulfuric Acid.* — Three grams of Va, 2 ml. of ethyl alcohol and ten drops of diluted sulfuric acid (1 : 1) were placed in a flask; then the mixture was heated to 100°C while being stirred for half an hour. After cooling, the reaction mixture was neutralized with a sodium bicarbonate solution and extracted with ether. After the ether had been removed, the residual liquid was distilled under atmospheric pressure; b. p. 165—169°C (1.6 g.). The product gave the semicarbazone with a m. p. of 152°C, which did not depress the melting point of an authentic sample of IIIa.

b) By Heating.—The pyrolysis was carried out with a gas chromatograph apparatus (column temp. 150°C; injection temp. 181°C; N_2 flow 10.7 ml./min.; silicon oil DC 550, 2 m.). The two peaks

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9) The boiling points and melting points are uncorrected. The infrared spectra and gas chromatograms were recorded with a Hitachi Model EPI-S2 spectrophotometer and a Hitachi Model KGL-2 gas chromatograph.

10) J. Murata, "Synthetic Methods of Monomers," Vol. 9, Kyoritsu Shuppan Co., Tokyo (1957) p. 183.

11) O. Wallach, *Ann.*, **381**, 86 (1911).

12) M. Guerbert, *J. Pharm. Chim.*, **(7)**, **6**, 49 (1912); *Chem. Zentr.*, **83**, 1099 (1912 II).

in the chromatogram were found by the use of authentic samples to be methyl vinyl ketone (retention time 4.5 min.) and methylheptanone (retention time 9.8 min.) respectively.

The Reaction of I with Ethylmagnesium Bromide (IIb).—A procedure similar to that described for the reaction of I and IIa was adopted. To a Grignard reagent solution (prepared from 43.6 g. of ethyl bromide, 9.7 g. of magnesium and 150 ml. of anhydrous ether), freshly-distilled methyl vinyl ketone (39.6 g.) in 500 ml. of anhydrous ether was added in such a manner as to maintain the reaction temperature at -50—-55°C. The products were fractionated. Fraction I (3.7 g.) boiled at 33—35°C/17 mmHg. On redistillation, the sample was obtained at 117—119°C/760 mmHg; n_D^{20} 1.4310 (lit.[13] b. p. 116°C/760 mmHg). The infrared spectrum showed bands at 3400 and 1160 (tert. OH), 1850, 1650, 1415, 995 and 920 ($CH=CH_2$), and 1715 cm^{-1} (C=O, very weak). Two peaks appeared in the gas chromatogram (column temp. 96°C; injection temp. 120°C; N_2 flow 2.4 ml./min.; silicon oil DC 550, 2 m.). The peak corresponding to the ketone was increased when methyl *n*-butyl ketone was added (retention time 2.5 min.). The ratio of 3-methyl-1-penten-3-ol to methyl *n*-butyl ketone was estimated to be about 5 to 1. The 3, 5-dinitrobenzoate obtained from fraction I was recrystallized from ethyl alcohol, m. p. 91—92°C.

Found: N, 9.68. Calcd. for $C_{13}H_{14}N_2O_6$: N, 9.52%.

Fraction II (13.7 g.) boiled at 50—77°C/5 mmHg, and the residue amounted to 1.8 g. The redistillation of fraction II afforded 8.5 g. (17% based on I) of Vb, b. p. 73.5—75°C/3.5 mmHg, n_D^{20} 1.4589. The infrared spectrum showed bands at 1650, 1420, 995, 920 ($CH=CH_2$), 3500, 1170 (tert. OH), and 1705 cm^{-1} (C=O).

Found: C, 70.57; H, 10.84. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.

The semicarbazone, m. p. 124°C (lit.[14] m. p. 122°C), obtained from Vb by the action of sulfuric acid as described in the case of Va, did not depress the melting point of methyl *n*-butyl ketone semicarbazone. No attempt was made to determine the structure of the residue.

Summary

The reactions of methyl vinyl ketone with isobutylmagnesium bromide and ethylmagnesium bromide have been studied. Methyl vinyl ketone reacts with isobutylmagnesium bromide to give methylheptanone and 3-isoamyl-2-vinyl-2-pentanol-4-one as a result of 1, 4-addition; the latter compound is formed from 2 mol. of ketone and one mole of the Grignard reagent. On the other hand, in the reaction of ethylmagnesium bromide with methyl vinyl ketone, both 1, 2- and 1, 4-addition take place, and 3-methyl-1-penten-3-ol and 3-propyl-2-vinyl-2-pentanol-4-one are obtained. These keto-alcohols have been decomposed to the corresponding ketones and methyl vinyl ketone by heating or by treatment with sulfuric acid.

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[13] *Chem. Zentr.*, **86**, 1223 (1915 II).

[14] See Ref. 6, p. 262.