[Contribution from the Chemical Laboratories of Northwestern University]

THE REACTION OF A SUBSTITUTED ALLYLIC GRIGNARD REAGENT WITH CARBON DIOXIDE

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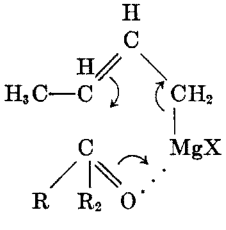
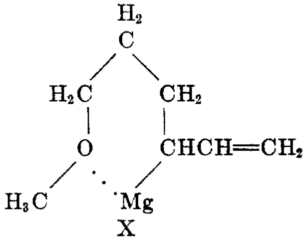
Received November 27, 1950

It has been established by the extensive work of Young and coworkers that butenylmagnesium chloride, prepared by the reaction of magnesium with either 1-chloro-2-butene or 3-chloro-1-butene, reacts with a variety of carbonyl reagents to give 3-substituted derivatives of 1-butene. Thus, the reaction with carbon dioxide leads to 2-methyl-3-butenoic acid (1). On the basis of numerous similar reactions it was suggested (2) that the carbonyl reagents may react by way of a cyclic intermediate (I). If the reaction does proceed in this manner, one might expect to obtain a primary rather than a secondary derivative if the magnesium atom could be made to reside on carbon three instead of carbon one. We describe in this paper an investigation of the reaction of carbon dioxide with the Grignard reagent from ω-methoxyhexenyl chloride (6-methoxy-3-chloro-1-hexene and/or 6-methoxy-1-chloro-2-hexene). In this system, the tendency of the oxygen to coordinate with the magnesium might cause the magnesium to take the three position by formation of a six membered ring (II) and thereby lead to a primary acid on carbonation. We found in fact, however, that here as in the case with butenylmagnesium chloride the principal acid which was formed was the secondary or branched chain one, 2-vinyl-5-methoxypentanoic acid.



I



II

ω-Methoxyhexenyl chloride was prepared from the alcohol made by the addition of 3-methoxypropylmagnesium chloride to acrolein. It was converted to the Grignard reagent in an ether solution and carbonated on Dry Ice. For identification purposes the unsaturated acid which was isolated was reduced with hydrogen. Two products were possible at this point, 2-ethyl-5-methoxypentanoic acid (III) and 7-methoxyheptanoic acid (IV). The former, which was unknown, was prepared by the addition of 3-methoxypropylmagnesium chloride to propionaldehyde, conversion of the alcohol thus obtained to the chloride, and carbonation of the magnesium derivative of this halide. The other possible product, 7-methoxyheptanoic acid, was synthesized for comparison purposes by the procedure of Harrower (3). In Table I are listed the refractive indices of these acids and the corresponding ethyl esters. On the basis of this evidence it is apparent that the branched chain acid was the principal product from the carbonation of 6-methoxyhexenyl chloride.

In order to minimize the effect of the ether solvent, another reaction was carried out in which, after the preparation of ω-methoxyhexenylmagnesium chloride, the ether was replaced by benzene. Considerable loss of the Grignard reagent occurred in this process, but a small amount of an acid was isolated and it corresponded as in the other case to the secondary product.

EXPERIMENTAL

1-Methoxy-3-chloropropane. Freshly distilled 1-methoxy-3-propanol (360 g., 4.00 moles)[1] and anhydrous pyridine (316 g., 4.00 moles) were cooled to 10° in the usual apparatus. With efficient stirring, there was added 714 g. (6.00 moles) of distilled technical thionyl chloride over a period of two hours, during which the temperature was maintained at 10–30°. The mixture was heated on the steam-bath to 65–70° with stirring for three hours, and then poured onto 1 kg. of crushed ice and 200 ml. of concentrated hydrochloric acid. The lower layer was extracted once with 100 ml. of ether and discarded. The combined organic layers were neutralized with potassium carbonate solution and dried over potassium carbonate. Distillation yielded 344 g. (79%) of 1-methoxy-3-chloropropane at 110–111°; $n_D^{24.5}$ 1.4120.

TABLE I

COMPARISON OF REACTION PRODUCT WITH SYNTHETIC ISOMERS

COMPOUND COMPARED	FREE ACID n_D^{20}	ETHYL ESTER n_D^{25}	ETHYL ESTER B.P., °C.	ETHYL ESTER mm.	Analyses[a] C	Analyses[a] H
Reaction A product	1.4358	1.4194	97–104	13	64.12	10.93
Branched chain series (III)	1.4352	1.4191	100–102.5	13	63.84	10.12
Straight chain series (IV)	1.4380	1.4216	104–105	14	63.75	10.63

[a] Calc'd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71.

6-Methoxy-3-hydroxy-1-hexene. A Grignard reagent was prepared in the usual manner from magnesium turnings (24 g., 1.0 g.-atom) and 1-methoxy-3-chloropropane (108.6 g., 1.00 mole) in 400 ml. of dry ether under a nitrogen atmosphere. The solution was cooled to 0–5°, and 56 g. (1.0 mole) of freshly distilled acrolein was added. The mixture was stirred until it reached room temperature and was decanted onto ice. Magnesium hydroxide was dissolved by the careful addition of hydrochloric acid until almost *p*H 8. The ether layer was dried and distilled; 60.0 g. (46%) of 6-methoxy-3-hydroxy-1-hexene was collected, b.p. 52° (0.6–0.7 mm.), $n_D^{24.5}$ 1.4412; d_4^{25} 0.9195.

Anal.[2] Calc'd for $C_7H_{14}O_2$: C, 64.58; H, 10.84.

Found: C, 64.18; H, 9.98.

ω-Methoxyhexenyl chloride. Concentrated hydrochloric acid (100 ml., 0.8 mole) was added to 30 g. (0.23 mole) of 6-methoxy-3-hydroxy-1-hexene with sufficient cooling to maintain the mixture below 25°. Over a period of 40 hours, during which the mixture was shaken occasionally, an oily layer separated. This was removed and the aqueous layer

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[1] A sample of 1-methoxy-3-propanol was kindly supplied us by the Shell Development Company.

[2] The analyses reported in this paper were made by J. Sorenson, C. Brauer and M. Hines.

extracted with petroleum ether (b.p. 29–35°). The combined organic layers were shaken briefly with a dilute potassium carbonate solution to remove hydrochloric acid, and dried over calcium chloride. On distillation 26.6 g. (78%) of ω-methoxyhexenyl chloride was obtained; b.p. 64–70° (11 mm.), n_D^{25} 1.4502, d_4^{25} 0.9871 (MR, 40.47; Calc'd, 40.57).

Anal. Calc'd for $C_7H_{13}ClO$: C, 56.56; H, 8.82.
Found: C, 56.55; H, 9.06.

Carbonation of the Grignard reagent from ω-methoxyhexenyl chloride. A. Magnesium filings (24 g., 1.0 g.-atom) were placed with a crystal of iodine in a flame-dried apparatus in which air was replaced with dry nitrogen. The reaction was initiated by the addition of 50 ml. of dry ether and 1 ml. of methyl iodide; then another 100 ml. of ether was added and a solution of 22.3 g. (0.15 mole) of 6-methoxyhexenyl chloride in 150 ml. of ether was dropped in over a period of five hours. The reaction mixture was refluxed for an additional 30 minutes, and then siphoned onto 200 g. of powdered Dry Ice mixed with ether. When the mixture had warmed to room temperature, water and dilute hydrochloric acid were added. The aqueous layer was extracted with ether and the combined ether layers extracted with sodium hydroxide solution. After acidification of this solution, the organic acids were removed with ether, dried, and distilled. A 38% yield (8.92 g.) of an acid boiling at 91–94° (0.15 mm.) was obtained; n_D^{25} 1.4470, d_4^{25} 1.006. The neutral fraction contained 9.0 g. of halogen-free liquid which was probably coupling product.

Hydrogenation of this acid (7.95 g., 0.05 mole) in methanol with 5% palladium-on-charcoal catalyst gave after distillation 6.88 g. (86%) of acid; b.p. 87–89° (0.15 mm.), n_D^{20} 1.4358, d_4^{25} 0.9921.

Anal. Calc'd for $C_8H_{16}O_3$: C, 59.95; H, 10.07.
Found: C, 59.93; H, 9.95.

B. By a similar procedure, a Grignard reagent was prepared from 14.9 g. (0.10 mole) of halide and 14.4 g. (0.6 g.-atom) of magnesium filings. This solution was filtered and by titration the 300 ml. of solution was found to contain 0.048 mole (48%) of Grignard reagent. The ether was removed and replaced with 190 ml. of benzene and 50 ml. of toluene. Distillation was continued until a total (including the ether portion) of 420 ml. of distillate had been collected. Carbonation and work up as in the previous case yielded 1.30 g. (8%) of acid; b.p. 94.5° (0.18 mm.), n_D^{25} 1.4471. Hydrogenation by the same procedure used in the previous case gave 0.70 g. of an acid, b.p. 89–90° (0.17 mm.), n_D^{20} 1.4346.

6-Methoxy-3-hexanol (4). Propionaldehyde (26.4 g., 0.454 mole) was added at 0–5° to the Grignard reagent formed from 55.6 g. (0.511 mole) of 3-methoxy-1-chloropropane and 12.3 g. (0.511 g.-atom) of magnesium turnings. Decomposition on ice, neutralization of magnesium hydroxide with hydrochloric acid, ether extraction, drying over potassium carbonate, and distillation gave 42.2 g. (70%) of 6-methoxy-3-hexanol; b.p. 58° (1.1 mm.), n_D^{25} 1.4268 d_4^{25} 0.9047.

Anal. Calc'd for $C_7H_{16}O_2$: C, 63.59; H, 12.20.
Found: C, 63.98; H, 12.33.

1-Methoxy-4-chlorohexane (4). To a cooled, stirred solution of 42 g. (0.32 mole) of 6-methoxy-3-hexanol and 50 g. (0.64 mole) of dry pyridine was added 100 g. (0.83 mole) of thionyl chloride. After addition was complete, the mixture was stirred on the steam-bath at 70–80° for three hours, poured onto ice and hydrochloric acid, and worked up by conventional procedures. A 43% yield (20.4 g.) of 1-methoxy-4-chlorohexane was obtained; b.p. 66–67° (15 mm.) n_D^{25} 1.4290, d_4^{25} 0.9444.

Anal. Calc'd for $C_7H_{15}ClO$: C, 55.81; H, 10.04.
Found: C, 55.97; H, 9.82.

2-Ethyl-5-methoxypentanoic acid (III). The Grignard reagent was prepared in the usual manner from 20.2 g. (0.134 mole) of 1-methoxy-4-chlorohexane and 3.2 g. (0.13 g.-atom) of magnesium turnings in dry ether under a nitrogen atmosphere. Carbonation was carried out by decantation onto 200 g. of Dry Ice. Acidification, extraction with ether, drying over sodium sulfate, and distillation gave 13.70 g. (64%) of 2-ethyl-5-methoxypentanoic acid; b.p. 104.0–104.5° (0.4–0.5 mm.), n_D^{20} 1.4352, d_4^{25} 0.9926.

Anal. Calc'd for $C_8H_{16}O_3$: C, 59.97; H, 10.07.
Found: C, 59.92; H, 9.87.

7-Methoxyheptanoic acid (IV). Pentamethylene bromide (b.p. 108–110°/20 mm.) was prepared by the cleavage of tetrahydropyran with hydrobromic acid. It was converted to 7-methoxyheptanoic acid by the method of Harrower (3). The dibromide was first converted to 1-methoxy-5-bromopentane (34% yield, b.p. 70–75° at 12 mm.) with sodium methoxide in methyl alcohol. This material with sodiomalonic ester gave a 62% yield of ethyl ϵ-methoxypentylmalonate; b.p. 158–161° (12 mm.), n_D^{25} 1.4312, d_4^{25} 1.000. Finally, this ester was saponified and decarboxylated to give 7-methoxyheptanoic acid (71%); b.p. 104.5–105.0° (0.3 mm.), n_D^{20} 1.4380; d_4^{25} 0.9927. Reported values (5) are n_D^{20} 1.4377; d_4^{20} 0.9922.

Anal. Calc'd for $C_8H_{16}O_3$: C, 59.97; H, 10.07.
Found: C, 59.60; H, 9.85.

Preparation of the ethyl esters. The ethyl esters were each prepared in a similar manner. One example will be sufficient to illustrate the method. 7-Methoxyheptanoic acid (8.0 g., 0.05 mole) was placed in a 30-ml. flask with 10 ml. of absolute ethanol, 7 ml. of benzene, and 0.5 g. of *p*-toluenesulfonic acid. The flask was attached to a 30-cm. Vigreux column fitted with a phase separation head. After 16 hours of reflux, 1.5 ml. of water had separated. The excess solvents were removed and the residue distilled in a small modified Claisen flask to give a quantitative yield of the ester.

SUMMARY

The Grignard reagent prepared from ω-methoxyhexenyl chloride was found to react with carbon dioxide to give primarily 2-ethyl-5-methoxypentanoic acid.

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