Grignard Reactions. XVI[1]

BY FRANK C. WHITMORE AND C. E. LEWIS[2]

The effect of an accumulation of substituents adjacent to the functional group of a carbonyl compound on its reaction with a Grignard reagent was first shown by Conant and Blatt.[3]

The present study is a continuation of the work started in this Laboratory on the enolization of aliphatic hindered carbonyl compounds by Grignard reagents.[1,4] Many of the compounds studied exhibit sufficient steric hindrance to prevent the addition reaction entirely. The results of the enolization studies are given in Table I.

The Grignard machine used in this work is essentially the same as the one originally designed by Kohler[5] and has been in use in this Laboratory.[1] The usual procedure was followed except for a few modifications. The reaction flask was always heated to ensure optimum reaction conditions. Aniline was used instead of water for decomposition of the excess Grignard reagent in order to eliminate the variation due to the vapor pressure of water. This allowed the elimination of a drying tower from the system. All calculations were based on the assumption that the

TABLE I

Compound	Enolization, %	Addition, %
Et₃CCOCH₃	94	0
Et₂MeCCOCH₃	84	0
EtMe₂CCOCH₃	14	74
Me₃CCOCH₃[a]	5	86
Me₃CCH₂COCH₃	0	100
Et₃CCOCH₂CHMe₂	85	0
Et₃CCOCH=CH₂	0	58
Et₃CCO₂Et	0	0
Et₃CCO₂Me	0	0
Et₂MeCCO₂Et	25[b]	45
Et₂MeCCO₂Bu	22[b]	60
EtMe₂CCO₂Et	0	100
Et₃CCOCH₂CH₂OH	58[c]	27
(Et₃CCO)₂CH₂	91/2	55/2
(Et₃CCO)₂CHCH₃	79/2	19/2

[a] Ref. 1. [b] The apparent enolization of these compounds is due to that of the ketones formed from the methylmagnesium bromide and the esters. [c] Corrected for the CH₄ liberated by the alcohol group.

amount of condensation of these carbonyl compounds is negligible.

The reactions in the series, methyl triethylcarbinyl ketone, methyl methyldiethylcarbinyl ketone, methyl dimethylethylcarbinyl ketone and pinacolone, illustrate the effect of an accumulation of substituents on the carbon adjacent to the carbonyl, the percentage enolization being 94, 84, 14 and 5, respectively. The difference in the amount of steric hindrance exerted by the methyl and ethyl groups is again clearly demonstrated. That substituents on the beta carbon have less effect on the carbonyl reaction than those on the adjacent carbon is shown by the fact that methyl neopentyl ketone gave 100% addition and no enolization while pinacolone gave 5% enolization. The effect of ethyl groups on the addition reaction is also shown in the action of the Grignard reagent with the esters of triethylacetic, methyldiethylacetic and dimethylethylacetic acids. These esters gave per cent. additions of 0, 45 and 100, respectively.

Vinyl triethylcarbinyl ketone gave only the addition reaction. This is to be expected since enolization would necessitate the formation of an allene system. The effect of introducing a substituent into the active methylene of beta-diketones is shown by the action of the Grignard reagent with bis-triethylacetylmethane and with 1,1-bis-triethylacetylethane. This introduction of a methyl group decreased both the enolization and addition reactions. The greater effect is shown on the addition reaction.

None of the monoketones investigated gave a positive test for the enol form by the usual ferric chloride and peroxide tests. Thus the "enolization reaction" between the carbonyl compound and the Grignard reagent starts with the carbonyl group. It is a competitive reaction, the extent of which is determined by the nature of the groups adjacent to the carbonyl.

We thank R. S. George of this Laboratory for his help.

Preparations

The Grignard reagents used in this work were prepared in the usual way. All fractionations were done with the

(1) XV, Whitmore and Block, THIS JOURNAL, 64, 1619 (1942).
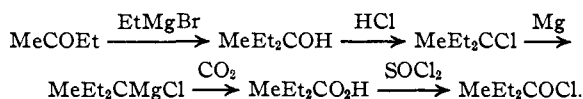(2) Present address: Calco Chem. Div., American Cyanamid Co., Bound Brook, New Jersey.
(3) Conant and Blatt, THIS JOURNAL, 51, 1227 (1929).
(4) Whitmore and George, ibid., 64, 1239 (1942).
(5) Kohler, Stone and Fuson, ibid., 49, 3181 (1927).

usual type of column[6] having 12–18 theoretical plates. The procedure used in making the enolization measurements was the same as that described by Whitmore and Block.[1] Methylmagnesium bromide in dibutyl ether was used. For the monoketones the reaction mixture was heated for two to five minutes at reflux temperature. Comparable results were obtained for several different periods of heating. Methyl methyldiethylcarbinyl ketone gave the same results when heated at reflux temperature for two minutes as when it was heated at 90° for one hour. In no case did prolonged heating have a noticeable effect. The diketones required longer heating at the reflux temperature, maximum reaction being obtained in ten minutes. The esters were heated by immersing the reaction flask in a water-bath at 75–80° upon addition of the methylmagnesium bromide, heating to 95–100° in ten minutes and holding at that temperature for thirty minutes. In all cases refluxing provided the necessary agitation.

The preparations of triethylacetyl chloride, methyl triethylcarbinyl ketone, bis-triethylacetylmethane and 3-keto-4,4-diethylhexan-1-ol have been described.[7] The methyldiethylacetyl chloride was prepared by standard reactions as follows

$$\text{MeCOEt} \xrightarrow{\text{EtMgBr}} \text{MeEt}_2\text{COH} \xrightarrow{\text{HCl}} \text{MeEt}_2\text{CCl} \xrightarrow{\text{Mg}}$$
$$\text{MeEt}_2\text{CMgCl} \xrightarrow{\text{CO}_2} \text{MeEt}_2\text{CO}_2\text{H} \xrightarrow{\text{SOCl}_2} \text{MeEt}_2\text{COCl}.$$

The acid chloride had b. p. 157° at 734 mm.

Vinyl Triethylcarbinyl Ketone.—Dehydration of 3-keto-4,4-diethylhexan-1-ol[7] by refluxing over anhydrous cupric sulfate gave vinyl triethylcarbinyl ketone, b. p. 97° at 36 mm., n^{20}D 1.4495–8. The ketone polymerized to a transparent resin on standing.

Isobutyl Triethylcarbinyl Ketone.—To one mole of isobutylmagnesium bromide was added 49 g., 0.3 mole, of triethylacetyl chloride. Decomposition and fractionation gave 16 g., 0.12 mole, or 40% of 2,2-diethylbutan-1-ol, b. p. 96–100° at 40 mm., n^{20}D 1.4392–1.4412, α-naphthylurethan m. p. 131–132° and 24.4 g., 0.13 mole, or 43% of isobutyl triethylcarbinyl ketone, b. p. 86–87° at 12 mm., n^{20}D 1.4381–2. No derivative of the ketone could be made.

Methyl Methyldiethylcarbinyl Ketone.—To an excess of methylmagnesium bromide was added 37.1 g., 0.25 mole, of methyldiethylacetyl chloride. Decomposition and fractionation as usual gave 15.3 g., 0.12 mole, or 48% of methyl methyldiethylcarbinyl ketone, b. p. 77–79° at 20 mm., n^{20}D 1.4489–98, 2,4-dinitrophenylhydrazone, m. p. 73–74°.

Methyl Dimethylethylcarbinyl Ketone.—Methyl-t-amylcarbinol was prepared by the action of t-amylmagnesium chloride with acetaldehyde. A solution of 33 g. of chromic oxide in 60 cc. of 65% aqueous acetic acid was added slowly to 56 g. of the carbinol in 25 cc. of glacial acetic acid. The reaction mixture was kept below 30°. About 150 cc. of water was then added, the oil layer was steam distilled and dried. Fractionation gave about 20 g. of methyl dimethylethylcarbinyl ketone, b. p. 130° at 733 mm., n^{20}D 1.4100, 2,4-dinitrophenylhydrazone m. p. and mixed m. p. 112°.

(6) Whitmore and Lux, THIS JOURNAL, **54**, 3451 (1932).

(7) Whitmore and Lewis, *ibid.*, **64**, 1618 (1942).

Preparation of the Ethyl Esters.—The ethyl esters were all prepared according to the same procedure. The addition of triethylacetyl chloride to sodium ethylate illustrates the procedure used.

To 50 cc. of absolute ethanol was added 6 g. of metallic sodium. After the reaction was completed, 24 g., 0.15 mole, of triethylacetyl chloride was added slowly. The excess sodium ethylate was decomposed by pouring on ice. The oil layer was separated, dried and fractionated.

Ester	B. p. °C.	Mm.	n^{20}D	Yield %
Ethyl triethylacetate	85–7	30	1.4218–9	57
Ethyl methyldiethylacetate	73	35	1.4129–32	64
Ethyl dimethylethylacetate	140–141	744	1.4025	63

Methyl Triethylacetate.—The procedure described above was used except that absolute methanol was substituted for ethanol, and the oil layer was distilled from a Claisen flask. The ester had b. p. 164–5° at 734 mm., n^{20}D 1.4240–1.

n-Butyl Methyldiethylacetate.—To 250 cc. of n-butyl alcohol was added 12 g. of metallic sodium. When the reaction was completed, 26 g., 0.17 mole, of ethyl methyldiethylacetate was added. The reaction mixture was heated for twelve hours at 125° under a reflux condenser held at 100°. The ethyl alcohol was thus removed as it was formed. The solution was acidified with 20% hydrochloric acid with cooling in an ice-bath. The alcoholic solution of ester was separated and dried. Fractionation gave 14.6 g., 0.08 mole, or 46% of n-butyl methyldiethylacetate, b. p. 104–5° at 38 mm., n^{20}D 1.4212–8.

Alkylation of Bis-triethylacetylmethane.—Metallic sodium, 1.5 g., and 25 cc. of anhydrous ether were added to 17.2 g., 0.064 mole, of bis-triethylacetylmethane.[7] The reaction mixture was refluxed on a steam-bath for forty-eight hours. The ether was removed by evaporation, and 25 cc. of dioxane and 21 g., 0.15 mole, of methyl iodide were added. This reaction mixture was heated on a steam-bath for twenty-four hours. The dioxane and the excess methyl iodide were distilled off. The residue was cooled, and just enough water to dissolve the sodium iodide was added. The oil layer was separated and dried. Fractionation gave 7.4 g., 0.026 mole, or 41% of 1,1-bis-triethylacetylethane, b. p. 164° at 6 mm., n^{20}D 1.4718–22. The beta-diketone did not give a positive test with ferric chloride or a derivative with ammoniacal cupric acetate.

Methyl Neopentyl Ketone.—This ketone was prepared by the dichromate oxidation of diisobutylene. It had b. p. 125.5° at 727 mm., n^{20}D 1.4038.

Summary

1.   The study of sterically hindered aliphatic carbonyl compounds, especially in relation to their enolization, has been continued.

2.   Fifteen such compounds have been analyzed in the Grignard machine with methylmagnesium bromide.

3.   The degree of enolization of the carbonyl compounds was shown to be dependent upon the character of the substituents on the carbon ad-

jacent to the carbonyl. Substitution on the beta carbon had no noticeable effect on the reactions of the carbonyl.

4. Vinyl triethylcarbinyl ketone gave only the addition reaction.

5. Substitution in the active methylene of a beta-diketone decreased the extent of both enolization and addition.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Grignard Reactions. XVII.[1] The Reactions of Esters and Acid Chlorides with Grignard Reagents

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In the course of the preparation of large amounts of diethyl-t-butylcarbinol, it was found that while ethylmagnesium bromide reacted with trimethylacetyl chloride to give 26% of this tertiary alcohol and 60% of the secondary alcohol, ethyl-t-butylcarbinol, the same reagent reacted with methyl trimethylacetate to give 78.5% of the tertiary alcohol and only 8.6% of the secondary alcohol.

TABLE I

TRIMETHYLACETYL CHLORIDE–METHYL TRIMETHYLACETATE

Grignard reagent	Products[a]	Acid chloride	Ester
Ethyl	Ethyl-t-butylcarbinol	60	8.6
	Diethyl-t-butylcarbinol	26.1	76.5
n-Propyl	Neopentyl alcohol	20[3]	0[4]
	n-Propyl-t-butylcarbinol	76[3]	48[4]
	Di-n-propyl-t-butylcarbinol	0[3]	40[4]
Isopropyl	Neopentyl alcohol	23[3]	0
	Isopropyl-t-butylcarbinol	53[3]	44.8
n-Butyl	Neopentyl alcohol	28[3]	0
	n-Butyl-t-butylcarbinol	71[3]	40[4]
	Di-n-butyl-t-butylcarbinol	0[3]	50[5]
Isobutyl	Neopentyl alcohol	61[3]	0
	Isobutyl-t-butylcarbinol	26[3]	25.7
	Isobutyl-t-butyl ketone	0	29.4

t-BUTYLACETYL CHLORIDE–METHYL t-BUTYLACETATE

Grignard reagent	Products	Acid chloride	Ester
Ethyl	Diethylneopentylcarbinol	57.6[5]	68.5
	Ethyl neopentyl ketone	0[5]	5
n-Propyl	n-Propylneopentylcarbinol	24.4[5]	20.4
	Di-n-propylneopentylcarbinol	57[5]	61.8
	n-Propyl neopentyl ketone		7
Isopropyl	Isopropylneopentylcarbinol	26.7	16.1
	Isopropyl neopentyl ketone	32.7	55.3
n-Butyl	n-Butylneopentylcarbinol	20.5	0
	Di-n-butylneopentylcarbinol	9.9	71.4
	n-Butyl neopentyl ketone		trace
Isobutyl	Isobutylneopentylcarbinol	48.9	9.2
	Diisobutylneopentylcarbinol	13.8	34.2
	Isobutyl neopentyl ketone	20.1	32

[a] The percentage yields of products given by the acid chloride and the ester are listed under the respective headings.

(1) XVI, Whitmore and Lewis, THIS JOURNAL, **64**, 2964 (1942).

(2) Present address: Calco Chemical Div., American Cyanamid Co., Bound Brook, New Jersey.

(3) Whitmore and co-workers, THIS JOURNAL, **60**, 2788 (1938).

(4) Leroide, Ann. chim., **16**, 354–410 (1921).

(5) Whitmore and co-workers, THIS JOURNAL, **60**, 2462 (1938).

These results made desirable a comparison of the reactions of Grignard reagents with esters and with the chlorides of the corresponding acids. The results in Table I include those of this investigation as well as some from other work which completes the comparison.

Although use of the ester in place of the acid chloride decreased the amount of reduction product, it will be seen that structure is also a factor. When a normal Grignard reagent was used, the yield of tertiary alcohol from the ester was greater than from the acid chloride. However, methyl Grignard reagent with the methyl ester of methyl-t-butylneopentylacetic acid,[6] beta-Butlerow's acid,[6] gave no reaction at 34° in diethyl ether or at 142° in di-n-butyl ether. This is in contrast to the reaction of the corresponding acid chloride which has been shown by Whitmore and Randall[7] to give a 90% yield of methyl methyl-t-butylneopentylcarbinyl ketone when treated with the methyl Grignard reagent. With trimethylacetyl chloride only methyl and ethyl Grignard reagents gave tertiary alcohols. With t-butylacetyl chloride only the primary reagents gave tertiary alcohols. Reduction to the primary alcohol fails with the primary t-butylacetyl chloride as compared with the tertiary trimethylacetyl chloride. It is significant that in no case was any primary alcohol found from the reaction of an ester with a Grignard reagent. This would indicate that aldehydes are not intermediates in the formation of secondary alcohols from esters.[8] This is in sharp contrast to the fact that trimethylacetyl chloride is reduced to neopentyl alcohol even by primary Grignard reagents in yields as high as 60%.[3] t-Butylacetyl chloride, however, gave no primary alcohol with the Grignard reagent.[5]

(6) Whitmore and Laughlin, ibid., **56**, 1128 (1934).

(7) Whitmore and Randall, ibid., **64**, 1242 (1942).

(8) Compare Whitmore and co-workers, ibid., **63**, 643 (1941).