

2. The relation of acidity of the dehydrating catalyst to the equilibrium in the resulting olefin mixture is considered.

3. Two closely related tertiary alcohols have been dehydrated under mild but definitely acidic

conditions. In *t*-amyl alcohol and dimethylneopentylcarbinol, under similar conditions, the ethyl group yields a proton in dehydration about thirty times as readily as does the neopentyl group.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Factors Determining the Course and Mechanism of Grignard Reactions. V. The Effect of Metallic Halides on the Reaction of Grignard Reagents with Benzalacetophenone and with Benzophenone

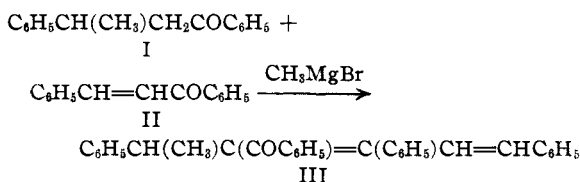
BY M. S. KHARASCH AND D. C. SAYLES

It has been shown that small amounts of some metallic halides exert a profound effect on the reactions of Grignard reagents with many compounds.¹ The present paper describes the results obtained when methyl- and ethylmagnesium bromides react with benzalacetophenone (chalcone) and benzophenone in the presence of ferric chloride, cuprous chloride, manganous chloride or cobaltous chloride.

The structures of the products formed by the addition of Grignard reagents to some α,β -unsaturated aldehydes and ketones have been determined by Kohler and his co-workers.² They report that, with chalcone, phenyl- and ethylmagnesium bromides give, respectively, 94 and 99% of the 1,4-addition product.^{2c} The reaction between ethylmagnesium bromide and chalcone has not been investigated, but Kohler reports that ethylmagnesium bromide reacts with benzalacetophenone to give 70% of the 1,4-addition product. Smith and Hanson,³ on the other hand, record only the 1,2-addition product of benzalacetophenone and ethylmagnesium iodide.

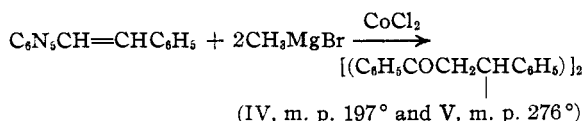
It is desirable to elucidate the conditions under which an optimum yield of β -phenylbutyrophenone (the 1,4-addition product) is obtained by condensation of ethylmagnesium bromide with chalcone. Kohler and Peterson^{2d} state explicitly that an excess of Grignard reagent is necessary to prevent the formation of "secondary" products, but they do not mention the exact

proportion of the reagents employed. In the experiments here reported in detail, a 40% excess of Grignard reagents was used, and (Table I) large quantities of 1,3,5-triphenyl-4-benzoylhexadiene-1,3 (m. p. 176°) (III) were produced, probably according to the equation



The structure of III was confirmed by independent syntheses from I and II where pyridine, trimethylamine or sodium ethylate was used as condensing agent. Other experiments showed that in order to avoid completely the formation of III, a very large excess of the Grignard reagent (200%) was required.

Although (Table I) no one of the metallic halides (2 to 5 mole per cent.) has any effect on the ratio of the 1,2 and 1,4 addition of ethylmagnesium bromide to chalcone, yet they profoundly influence the nature of the products formed in the reaction. This effect is most marked with cobaltous chloride. In the presence of this metallic halide the Grignard reagent does not add to the chalcone, but acts as a reducing agent leading to the formation of two products which melt at 197 and 276°, respectively.



These two substances (IV and V) were shown by analyses, molecular weight determinations and the melting points of mixtures to be identical

(1) (a) Kharasch, Kleiger, Martin and Mayo, *THIS JOURNAL*, **63**, 2305 (1941); (b) Kharasch and Lambert, *ibid.*, **63**, 2315 (1941); (c) Kharasch and Tawney, *ibid.*, **63**, 2308 (1941); (d) Kharasch and Fields, *ibid.*, **63**, 2316 (1941).

(2) (a) Kohler, *Am. Chem. J.*, **31**, 642 (1904); (b) *ibid.*, **37**, 369 (1907); (c) *ibid.*, **38**, 511 (1907); (d) Kohler and Peterson, *THIS JOURNAL*, **55**, 1073 (1933).

(3) Smith and Hanson, *ibid.*, **57**, 1376 (1935).

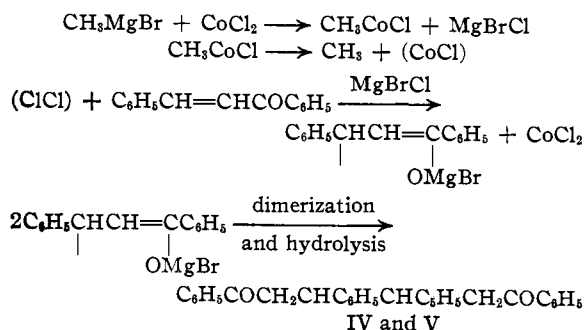
TABLE I
EFFECT OF METALLIC HALIDES ON THE ADDITION OF
METHYLMAGNESIUM BROMIDE^a TO CHALCONE

Product	Con- trol	Yield, % ^b of metallic halide			
		1 mole FeCl ₃	Cu ₂ Cl ₂	MnCl ₂	CoCl ₂ ^c
β -Phenylbutyrophenone	59	66	69	73	..
1,3,5-Triphenyl-4-benzoyl-hexadiene-1,3, m. p. 176° (III)	41	9	24	27	..
Dibenzylidiacetophenone, m. p. 197° (IV)	..	21	7	..	82
Stereoisomer of (II), m. p. 276° (V)	..	4	18

^a A 40% excess of Grignard reagent was used in all experiments. ^b Total yield of products was between 93 and 95% of the amount calculated on the basis of chalcone used. ^c One mole per cent. was added at the beginning of the reaction, and another mole per cent. midway in the addition of the chalcone.

with products previously obtained by reducing chalcone with zinc dust and glacial acetic acid,⁴ or with vanadous sulfate.⁵ Substance IV is considered to be 1,4-dibenzoyl-2,3-diphenylbutane because it readily undergoes intramolecular condensation to form a cyclopentene derivative.⁴ Substance V is regarded as a stereoisomer of IV, since distillation partly converts it into that substance.

Compounds IV and V have not hitherto been observed as products in the reaction of any Grignard reagent on chalcone. They are, however, formed whenever chalcone is treated with a powerful reducing agent or with methylmagnesium chloride in the presence of small amounts of cobaltous chloride. The latter reaction is readily explained by the chain mechanism proposed by Kharasch and Fields^{1d} to account for the catalytic effects of cobaltous, nickelous and ferrous chlorides on certain Grignard reactions.



In all such catalytic reactions the rate of the reaction and the stability of the compound

RCOCl at the temperature used are highly important. Their influence is illustrated in the reaction of ethylmagnesium bromide and benzophenone. At ordinary temperatures (20–25°) ethylmagnesium bromide adds to benzophenone either in the presence or in the absence of cobaltous chloride to give diphenylethylcarbinol; no reduction to benzopinacol or benzohydrol occurs.⁶ However, at –12°, a 50% yield of benzopinacol is readily obtained even though only 2 mole per cent. of cobaltous chloride is used. This large temperature effect is explained by the fact that at higher temperatures C₂H₅CoCl decomposes almost instantaneously with the liberation of metallic cobalt. Thus no chain reaction of the kind indicated is initiated.

Phenylmagnesium bromide, when added to chalcone, yields by 1,4 addition a saturated ketone, the product isolated by Kohler. The presence of small amounts of metallic halides has little effect on the course of this reaction; it is, however, significant that in the presence of ferric or cobaltous chloride (2–5 mole per cent.) even this Grignard reagent yields 2–5% of V.

The results here reported for the addition of ethylmagnesium bromide to chalcone differ considerably from the 94% of 1,4 addition reported by Kohler. In a number of experiments a 60% yield of the saturated ketone (β -phenylvalerophenone VI) was obtained. The remaining 40% was an oil which could not be crystallized. This oil readily absorbed bromine and decolorized potassium permanganate solution; it gave no ketonic reactions, and could not be acetylated by acetic anhydride in pyridine. It decomposed when distilled *in vacuo*. The only feasible method for purifying this oil was first to free it of ketonic materials by shaking it with a water solution of acetylhydrazide pyridinium chloride,⁷ and then to decolorize an ethyl alcohol solution of the water insoluble residue with norite. Evaporation of the alcohol again yielded an oil. Analysis of this oil indicated that it is probably styrylphenylethylcarbinol (VII). The additions of ethyl- and methylmagnesium bromide to chalcone thus differ significantly in the proportion of 1,2- and 1,4-addition products formed.

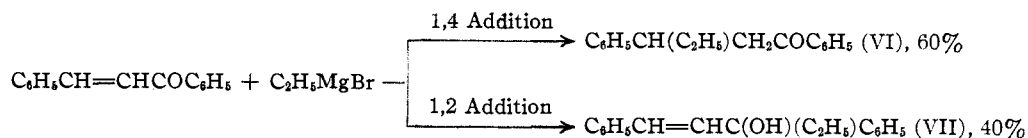
The discrepancy between the results here reported and those obtained by Kohler is not to be explained by the order in which the reagents are

(4) Harries and Hübner, *Ann.*, **296**, 326 (1897).

(5) Conant and Cutler, *This Journal*, **48**, 1016 (1926).

(6) Blicke and Powers, *ibid.*, **54**, 2503 (1932); Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 210 (1936).

(7) Girard and Sandulesco, *Org. Syntheses*, **18**, 10 (1938).



added to the reaction mixture. For the present no explanation can be offered.

The effect of temperature on the direction of addition of ethylmagnesium bromide to chalcone is slight. The amount of 1,2 addition is about 20–30% less at low temperatures (-25°) than at 25° .

Experimental Part

The organic compounds used were first purified by distillation or crystallization. Methyl bromide was obtained from the Dow Chemical Company. Benzalacetophenone was prepared according to "Organic Syntheses."⁸ The cuprous chloride was the commercial anhydrous reagent; anhydrous manganous chloride was prepared by heating the hydrated chloride in an oven for eight hours at 120° ; anhydrous ferric chloride was prepared from analytical grade iron wire and chlorine; anhydrous cobalt chloride was prepared by heating the hydrated dihalide at 150° in a stream of hydrogen chloride.

Preparation of Grignard Reagent.—Each Grignard reagent (prepared from sublimed magnesium) was siphoned from the reaction vessel through a glass tube filled with a glass wool plug into a dark storage bottle. Two milliliter aliquots were removed for standardization by the acid titration method.

General Procedure.—Aliquot parts of the Grignard reagent were transferred to three-necked flasks, each fitted with reflux condenser, mercury seal stirrer, dropping funnel and calcium chloride tubes. One flask was used as a control. Weighed quantities of anhydrous metal halides were added to the other flasks. The Grignard solution upon the addition of the metal salts changed color. Cobalt chloride produced a black solution; cuprous chloride, a blue-green solution; manganous chloride, a yellow solution.

Reaction of Ethylmagnesium Bromide and Chalcone.—Benzalacetophenone (0.19 mole) dissolved in anhydrous ether was added drop by drop to an excess of Grignard reagent (0.26 mole). During the addition, the temperature of the reaction mixture was maintained at $0-5^\circ$. After addition was complete, the reaction mixture was stirred for an additional thirty minutes; then the temperature was allowed to rise; finally, the mixture was refluxed for one hour and allowed to stand.

The reaction mixture was decomposed by pouring it onto 200 g. of cracked ice mixed with excess glacial acetic acid (25 cc.). The solution was filtered. The ethereal layer was separated, and the aqueous layer was extracted with ether. The combined ethereal layers after being washed with aqueous bicarbonate and water, were dried over anhydrous sodium sulfate. The ether was finally evaporated. The ethyl alcoholic extract of the residue (when ethylmagnesium bromide was used) yielded a substance melting

at 72° . The material insoluble in alcohol after crystallization from an ethanol–dioxane mixture yielded a compound melting at 176° .

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{O}$: C, 89.83; H, 6.28; mol. wt., 414. Found: C, 89.20; H, 6.90; mol. wt., 400.

The structure of this latter compound was proved by its synthesis. To an anhydrous ether solution of 0.5 g. of chalcone and 0.5 g. of β -phenylbutyrophenone was added a condensing agent (either pyridine or ethylmagnesium bromide), the whole mixture was refluxed for one hour. The solvent was evaporated, and the residue crystallized from a mixture of ethanol and dioxane. A quantitative yield of a solid melting at 176° was obtained. This melting point was not lowered by addition of the compound (m. p. 176°) obtained from the reaction of ethylmagnesium bromide with chalcone.

Dibenzylidiacetophenone.—In the experiments in which ferric, cuprous or cobalt chloride was used as a catalyst, a solid separated at the ether–water interface, when the reaction mixture was decomposed. This solid, when crystallized from an ethanol–dioxane mixture, melted at $197-198^\circ$. The material insoluble in the ethanol–dioxane, after crystallization from pyridine, melted at 276° .

Determination of β -Phenylvalerophenone (VI).—In the reactions between ethylmagnesium bromide and chalcone, the dried ethereal solution obtained as described above was transferred to a 100-cc. volumetric flask and made up to volume. A 5-cc. aliquot was removed to a weighed 50-cc. Erlenmeyer flask, the solvent evaporated and the flask reweighed. The total weight of product was thus obtained.

The ketonic material in this oil was determined by precipitation with 2,4-dinitrophenylhydrazine.⁹ The validity of this method of analysis was checked by control precipitations on chalcone and β -phenylvalerophenone.

Separation of the β -Phenylvalerophenone from Styrylphenylethylcarbinol (VII).—An aliquot of the ethereal solution was taken, and the solvent evaporated. The residue was dissolved in absolute alcohol containing 10% acetic acid and acetylhydrazide pyridinium chloride.⁸ The reaction mixture was then refluxed for an hour, and finally decomposed by being poured into ice-water containing sodium carbonate. The aqueous solution was extracted several times with ether, and the combined ethereal extracts were washed with water. When the solvent was evaporated, the unsaturated alcohol, styrylphenylethylcarbinol, was obtained.

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{O}$: C, 85.71; H, 7.56; mol. wt., 238. Found: C, 84.68; H, 7.84; mol. wt., 269.

Estimation of Styrylphenylethylcarbinol (VII) by Oxidation.—The solvent was evaporated from an aliquot of the original solution, and the residue was dissolved in purified acetone. Finely powdered potassium permanganate was added to the solution, and the whole was vigorously stirred. The temperature was kept below 20° . The unused potas-

(8) "Org. Syn." Coll. Vol. I, p. 71.

(9) Cooper, Ph.D. Thesis, University of Chicago.

sium permanganate was finally titrated. The accuracy of this oxidation method was checked by oxidation of chalcone.²

An unusual compound was isolated in one determination where manganous chloride was used as a catalyst. The ethereal solution was evaporated, and the residue crystallized from alcohol. A solid which melted at 136° was obtained.

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_2$: C, 85.71; H, 7.14; mol. wt., 448. Found: C, 85.82; H, 7.14; mol. wt., 470.

This compound could possibly be formed by the condensation of β -phenylvalerophenone and chalcone in a manner similar to the substance obtained from β -phenylbutyrophenone and chalcone. This compound yielded a 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $\text{C}_{28}\text{H}_{26}\text{O}_6\text{N}_4$: N, 8.92. Found: N, 9.11.

The compound could not be synthesized by condensing β -phenylvalerophenone with chalcone when either pyridine or ethylmagnesium bromide was used as a condensing agent.

Addition of Benzophenone to Ethylmagnesium Bromide.—Benzophenone (0.5 mole) in 40 cc. of anhydrous benzene was added slowly to a 100% excess of ethylmagnesium bromide containing 6 mole per cent. of cobaltous chloride. The temperature of the reaction was kept below 20° . A mixture of diphenylethylcarbinol and diphenylpropylene was obtained. The reaction product was dehydrated to diphenylpropylene by distillation with a trace of iodine. The yield was quantitative.

Benzophenone, 0.05 mole, in 40 cc. of anhydrous benzene containing 6 mole per cent. of cobaltous chloride was slowly added to 100% excess of ethylmagnesium bromide; the

reaction temperature was kept at -12° . The reaction mixture was then stirred for two hours at -12° , and allowed to stand overnight at room temperature. By the usual methods of isolation, benzopinacol (45%) and diphenylethylcarbinol (55%) were obtained from this mixture.

Summary

1. The effect of some metallic chlorides on the reaction of Grignard reagents with benzalacetophenone has been studied.

2. It has been shown that manganous chloride has little catalytic effect on the reaction between ethylmagnesium bromide or iodide and chalcone. Cobalt chloride is a powerful catalyst for the formation of reduction dimers. Cuprous and ferric chlorides are intermediate in their catalytic effect.

3. Metallic halides do not markedly affect the reaction between ethylmagnesium bromide and chalcone; they slightly favor 1,2 addition. Variations in temperature and in the order of addition of the reagents also produce only a slight effect.

4. Benzophenone at 25° reacts with ethylmagnesium bromide containing cobalt chloride to give only the addition product. Benzophenone at -12° reacts with ethylmagnesium bromide containing cobalt chloride to give both benzopinacol and diphenylethylcarbinol.

CHICAGO, ILLINOIS

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Carboxylation. IV. Direct Introduction of the Chloroformyl ($-\text{COCl}$) Group into Alicyclic and Aliphatic Acid Chlorides

BY M. S. KHARASCH, KENNETH EBERLY AND MORTON KLEIMAN

In the course of work on the introduction of the chloroformyl ($-\text{COCl}$) group¹ into cyclohexane by the use of trichloromethyl chloroformate, there was obtained under optimum conditions (six hours of heating at 225°) a 3% yield of a disubstitution product, identified as 1,1-dichloroformylcyclohexane by hydrolysis to cyclohexane-1,1-dicarboxylic acid. Despite careful search, no hexahydrobenzoyl chloride could be detected.

This rather striking result suggested that diphosgene reacts more readily with hexahydrobenzoyl chloride than with cyclohexane. Upon further investigation, it was found that ten hours

(1) For previous references, see Kharasch, Kane and Brown, *THIS JOURNAL*, **64**, 1621 (1942).

of heating of hexahydrobenzoyl chloride with diphosgene in a sealed tube at 225° , subsequent hydrolysis of the reaction product, and crystallization of the hydrolyzate from an ether-ligroin mixture, gave an 81% yield of cyclohexane-1,1-dicarboxylic acid.

In a like manner, diphosgene reacts with isobutyryl chloride to give a 70% yield of dimethylmalonyl chloride; with α -ethylbutyryl chloride to give a 90% yield of diethylmalonyl chloride; and with α -ethylhexoyl chloride to give a 30% (or possibly higher) yield of ethylbutylmalonyl chloride. In many experiments with propionyl chloride and diphosgene, however, the maximum yield of methylmalonic acid was only 15%. No