[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO, AND THE SAYLES CHEMICAL CONSULTANTS LABORATORY]

The Synthesis of Symmetrically Substituted Ethane Derivatives

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The interaction of a Grignard reagent with benzyl chloride, benzhydryl chloride, 2-chloro-2-phenylpropane, 1-chloro-1-phenylethane, and 1-chloro-2-phenylethane in the presence of catalytic amounts of the halides of cobalt, chromium, iron, copper, and manganese has resulted in the formation of excellent yields of the corresponding dimers—symmetrically substituted ethane derivatives. Similarly, polyhalogenated compounds, such as benzal chloride and benzophenone dichloride, formed stilbene dichloride and tetraphenylethylene respectively.

The interesting effects obtained as a result of the interaction of metallic halides and Grignard reagents with benzophenone,[2a,2b] isophorone,[3] benzalacetophenone,[4] aromatic halides,[5] vinyl halides,[6] alicyclic chlorides,[7] sterically hindered acid halides,[8] organic halides,[9] 1-phenyl-3-chloropropane, cinnamyl chloride, and phenylethynyl bromide,[10] alkylbenzenes,[11] ethers,[12] haloalkyl phenyl ethers,[13,14] and alkyl halides and ketones,[15] promoted an extension of these studies. This paper describes the results which were obtained when various Grignard reagents reacted with such organic halides as aryl, alkyl, and halogen-substituted benzyl halides, in the presence of catalytic quantities of the halides of cobalt, copper, iron, chromium, and manganese.

Many compounds having the skeletal grouping ArRR'CX, where R and R' may be alkyl or aryl groups and X a halogen, have been reported to undergo coupling reactions under the influence of Grignard reagents. Thus, for example, the benzyl halides,[16] methoxybenzyl halides,[17] bis(1-naphthyl)-chloromethane,[18] biphenylbromomethane,[19] 1-bromo-2-phenylpropane,[20] 2-chlorophenylacetic acid,[21] and the cyanobenzyl halides,[22] all undergo this coupling reaction, and all possess the structural grouping in question.

Comments on the reaction of phenylmagnesium bromide with organic halides in the presence of metallic halides. (1) Arylmagnesium halides usually do not react with substituted benzyl halides to any significant amount. (2) Arylmagnesium halides react with molar or greater quantities of metallic halides, such as cobalt chloride, ferric chloride, etc., to form biaryl compounds. (3) Excellent yields of biaryl compounds can be obtained when an aryl Grignard reagent is treated with an organic halide in the presence of 3 to 10 mole per cent of the halides of either iron, cobalt, chromium, etc.

However, in this particular series of reactions, as illustrated by the reaction involving benzhydryl chloride with a slight molar excess of phenylmagnesium bromide and five mole per cent of cobaltous chloride, a vigorous exothermic reaction ensured, and 1,1,2,2-tetraphenylethane was formed in excellent yield. By contrast, the normal reaction product would be triphenylmethane.

The original mechanism of these Kharasch-Grignard reactions recently has been reinterpreted by Slaugh,[23] and Wang and Yang.[24]

The postulated mechanism apparently involves the formation of free radicals by the removal of an halogen atom from the organic halide. It has been

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TABLE I

REACTION OF PHENYLMAGNESIUM BROMIDE WITH BENZHYDRYL CHLORIDE IN THE PRESENCE OF METALLIC SALTS

C_6H_5MgBr, Moles	$(C_6H_5)_2CHCl$, Moles	Metallic Salt, Moles	$(C_6H_5)_3CH$, Yield, %	$(C_6H_5)_2CHCH(C_6H_5)_2$, Yield, %
0.135	0.1	0.00	90	0
0.135	0.1	0.05 $CoCl_2$	6	82
0.135	0.1	0.05 $FeCl_3$	17	63
0.135	0.1	0.05 Cu_2Cl_2	47	30
0.135	0.1	0.05 $MnCl_2$	82	0

TABLE II

REACTION OF 1-BUTYLMAGNESIUM BROMIDE WITH 2-CHLORO-2-PHENYLPROPANE IN THE PRESENCE OF METALLIC SALTS

C_4H_9MgBr, Moles	$C_6H_5(CH_3)_2CCl$, Moles	Metallic Salt, Moles	Per Cent Reaction	2,3-Dimethyl-2,3-diphenyl-butane %	1-Phenyl-1-propene %
0.135	0.1	0.00	45	17	40[a]
0.135	0.1	0.00	49[b]	17	27[c]
0.135	0.1	0.05 $CoCl_2$	70	70	27
0.135	0.1	0.05 $FeCl_3$	65	63	10
0.135	0.1	0.05 $CrCl_3$	63	63	19
0.135	0.1	0.05 $CuCl_2$	54	52	20
0.135	0.1	0.05 $MnCl_2$	40	38	40

[a] The normal reaction product, 2-methyl-2-phenylhexane, was also obtained in this reaction. [b] This reaction was allowed to stand at room temperature for seven days to determine how time of reaction would influence the ratio of products and the yield. [c] 33% of 2-methyl-2-phenylhexane was also obtained.

further postulated that the interchange reactions between the Grignard reagent and the organic halide are competing reactions and may determine the product.

2,3-Diphenyl-2,3-dimethylbutane. Wallach[25] has reported the synthesis of a hydrocarbon $C_{18}H_{22}$ by the action of phosphoric anhydride on 2-methyl-2-phenylpropanamide (phenylisobutyramide). The hydrocarbon was reported to have the following physical constants: m.p. 55°–56°; b.p. 138–140° at 15 mm., and was assumed to be the 2,3-dimethyl-2,3-diphenylbutane. Klages,[26] on the other hand reported a hydrocarbon, m.p. 119–120°, which was produced by the action of zinc dust on the 2-iodo-2-phenylpropane (phenylisopropyl iodide). The reaction product was considered to be the 1,2-dimethyl-1,2-diphenylcyclobutane.

Investigations which involved the reactions of either phenylmagnesium bromide or 1-butylmagnesium bromide with 2-iodo-2-phenylpropane in a typical Kharasch-Grignard reaction, resulted in the formation of a hydrocarbon which proved to be identical with that reported by Klages.[26] This was further verified by duplication of Klages' work for a more thorough comparison of the two compounds. From a consideration of the series of analogous reactions which were investigated in these Laboratories and which involved the successful conversion of substituted benzyl halides into symmetrically substituted ethane derivatives, it is suggested that the hydrocarbon obtained by Klages was the 2,3-dimethyl-2,3-diphenylbutane instead of the 1,2-dimethyl-1,2-diphenylcyclobutane.

Catalyzed reactions of substituted benzyl halides with Grignard reagents. The observed catalytic effect of the transition metal halides on the amount of dimerization which occurred with the substituted benzyl halides: benzhydryl chloride, 2-chloro-2-phenylpropane, benzyl chloride, 1-chloro-1-phenylethane, 1-chloro-2-phenylethane, 1-chloro-1,1-diphenylethane, and triphenylmethyl chloride varied considerably depending upon the substituents appearing in the benzyl halide. The most marked effect was observed with benzyhydryl chloride and the least with 1-chloro-1,1-diphenylethane and triphenylmethane chloride.

Reaction of benzal chloride with organomagnesium compounds. The experimental investigation conducted within these Laboratories demonstrated that the uncatalyzed reaction of benzal chloride and phenylmagnesium bromide produced none or little 1,2-dichloro-1,2-diphenylethane or 1,2-diphenylethylene. A similar reaction using methylmagnesium bromide, as conducted by Fuson and Ross,[27] formed 1,2-dichloro-1,2-diphenylethane in 20–25% yield. When this manner of catalysis was investigated using the former reactants, the yield of the 1,2-dichloro-1,2-diphenylethane was increased to 20–30%. Therefore, it would appear that, here too, this type of catalysis favor dimerization.

Reaction of benzotrichloride with organomagnesium compounds. Fuson and Ross[27] have also reported experiments involving benzotrichloride and methyl-

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TABLE III

EFFECT OF COBALTOUS CHLORIDE CATALYSIS ON THE REACTIONS OF PHENYLMAGNESIUM BROMIDE WITH ORGANIC MONOHALIDES

C_6H_5MgBr, Moles	Organic Halide, Moles	$CoCl_2$, Moles	Per Cent Reaction	Ethane Derivative, Yield, %
0.135	0.1 Benzhydryl	0.00	87	0
	chloride	0.05	99	82
0.135	0.1 2-Chloro-2-	0.00	64	0
	phenylpropane	0.05	97	68
0.1	0.1 Benzyl chloride	0.00	22	0
		0.05	97	65
0.1	0.1 1-Chloro-1-	0.00	10	0
	phenylethane	0.05	80	55
0.1	0.1 1-Chloro-2-	0.00	7	0
	phenylethane	0.05	70	34
0.1	0.1 1-Chloro-1,1-	0.00		0
	diphenylethane	0.05		0
0.1	0.1 Triphenylmethyl	0.00		50
	chloride	0.05		54

TABLE IV

REACTION OF BENZOPHENONE DICHLORIDE WITH PHENYLMAGNESIUM BROMIDE IN THE PRESENCE OF METALLIC HALIDES

C_6H_5MgBr, Moles	Benzophenone Dichloride, Moles	Metallic Halides, Moles	Tetraphenylethylene, Yield, %
0.1	0.1	0.00	5
0.1	0.1	0.05 $CoCl_2$	48
0.2	0.1	0.05 $CoCl_2$	67
0.1	0.1	0.05 $FeCl_3$	41
0.1	0.1	0.05 Cu_2Cl_2	26

magnesium chloride in dilute and concentrated solution. In dilute solution, benzotrichloride underwent coupling to yield 1,1,2,2-tetrachloro-1,2-diphenylethane, as represented by the following equation:

$$2\ C_6H_5CCl_3 + CH_3MgCl \longrightarrow C_6H_5CCl_2\cdot CCl_2C_6H_5 + 2\ MgCl_2 + C_2H_6$$

In concentrated solution, no 1,1,2,2-tetrachloro-1,2-diphenylethane (tolane tetrachloride) was obtained, but the *cis* and *trans* forms of 1,2-dichloro-1,2-diphenylethene (tolane dichloride) resulted. Diphenylethyne (tolane) was demonstrated to be the initial compound formed which was then converted into the two geometrically isomeric 1,2-dichloro-1,2-diphenylethenes in the concentrated solution. In our experimental work, both 1,1,2,2-tetrachloro-1,2-diphenylethane and 1,2-dichloro-1,2-diphenylethenes were obtained in the catalytic and control experiments but in appreciably higher yields in the catalyzed reactions.

Reaction of dichlorodiphenylmethane with organomagnesium compounds. The reaction of phenylmagnesium bromide with dichlorodiphenylmethane (benzophenone dichloride) resulted in the formation of only 5% of tetraphenylethene. The yield of

TABLE V

REACTION OF TRIPHENYLMETHYL CHLORIDE WITH GRIGNARD REAGENTS IN THE PRESENCE OF COBALTOUS CHLORIDE

Grignard Reagents	Grignard Reagents, Moles	Triphenylmethyl Chloride, Moles	Cobalt Chloride, Moles	Triphenylmethyl Oxide, Yield, %
CH_3MgBr	0.135	0.1	0.00	0
CH_3MgBr	0.135	0.1	0.05	45
C_4H_9MgBr (*n*-)	0.135	0.1	0.05	70
C_6H_5MgBr	0.135	0.1	0.00	50
C_6H_5MgBr	0.135	0.1	0.05	54

TABLE VI

REACTION OF BENZHYDRYL CHLORIDE WITH VARIOUS GRIGNARD REAGENTS IN THE PRESENCE OF COBALTOUS CHLORIDE

Grignard Reagents	Grignard Reagents, Moles	Benzhydryl Chloride, Moles	Cobaltous Chloride, Moles	1,1,2,2-Tetraphenylethane, Yield, %
CH_3MgBr	0.135	0.1	0.05	77
C_2H_5MgBr	0.135	0.1	0.05	65
C_4H_9MgBr (*n*-)	0.135	0.1	0.05	61
C_4H_9MgBr (*i*-)	0.135	0.1	0.05	38
$C_6H_{11}MgBr$	0.135	0.1	0.05	60
C_6H_5MgBr	0.135	0.1	0.05	82

tetraphenylethene was increased to 26–48% as a result this type of metal halide catalysis.

EXPERIMENTAL

Preparation of the Grignard reagent. The preparation of each of the Grignard reagents was carried out in a 2-l. three-neck flask which was fitted with a mercury-seal stirrer, dropping funnel, and reflux condenser. An excess of magnesium turnings was placed in the flask, covered with anhydrous ether, and the reagent was formed by the addition over a period of one 1–2 hr. of the halide dissolved in an equal volume of anhydrous ether. After adding the halide the reaction mixture was heated at gentle reflux for 1 hr. The reagent was cooled by immersing the reaction flask in cold water, and then the reaction mixture was siphoned through a porous sintered glass funnel into a dark storage bottle. Two-milliliter aliquots were withdrawn for titrimetric standardization by both the acid and halogen methods.

Preparation of metallic halide. Cuprous chloride was the usual anhydrous reagent; anhydrous ferric chloride was prepared from analytical grade iron wire and chlorine gas; the anhydrous cobaltous chloride, manganous chloride, and chromic chloride were prepared by heating the hydrated form at 150° under diminished pressure.

Preparation of 2-chloro-2-phenylpropane. The preparation of 2-chloro-2-phenylpropane involved the reaction of an excess of phenylmagnesium bromide with anhydrous propanone. The purified carbinol was then treated with hydrogen chloride gas at 0° according to the method recommended by Klages,[24] and converted to the 2-chloro-2-phenylpropane.

Preparation of 1,1-diphenyl-1-chloroethane. The experimental method for the preparation of 1,1-diphenyl-1-chloroethane was similar to the procedure required in the preparation of 2-chloro-2-phenylpropane, and involved the reaction of methylmagnesium bromide with benzophenone, and sub-

TABLE VII

EFFECT OF COBALTOUS CHLORIDE CATALYSIS ON THE REACTIONS OF GRIGNARD REAGENTS WITH ORGANIC POLYHALIDES

Grignard Reagent, Moles	Polyhalogenated Compound, Moles	Cobaltous Chloride, Moles	Per Cent Reaction	Dimerization Product	Dimerization Product, Yield, %
0.1 n-C_4H_9MgBr	0.1 $C_6H_5CHCl_2$	0.00	10	1,2-Dichloro-1,2-diphenylethane	7
0.1 n-C_4H_9MgBr	0.1 $C_6H_5CHCl_2$	0.05	75	1,2-Dichloro-1,2-diphenylethane	30
0.1 C_6H_5MgBr	0.1 $C_6H_5CHCl_2$	0.00	4	1,2-Dichloro-1,2-diphenylethane	0
0.1 C_6H_5MgBr	0.1 $C_6H_5CHCl_2$	0.05	65	1,2-Dichloro-1,2-diphenylethane	24
0.1 n-C_4H_9MgBr	0.1 $C_6H_5CCl_3$	0.00	81	Tolane tetrachloride	18
0.1 n-C_4H_9MgBr	0.1 $C_6H_5CCl_3$	0.05	82	Tolane tetrachloride	18
0.1 n-C_4H_9MgBr	0.1 CCl_4	0.00	86	Hexachloroethane	0
0.1 n-C_4H_9MgBr	0.1 CCl_4	0.05	86	Hexachloroethane	0

sequent conversion of the carbinol to the corresponding chloro compound.

Preparation of benzophenone dichloride. Benzophenone dichloride was prepared by a Friedel-Crafts reaction involving benzene and carbon tetrachloride according to the method of Gomberg and Jekling,[28] b.p. 170–172° at 16 mm.

Preparation of 1-chloro-1-phenylethane. An excess of hydrogen chloride gas was passed into pure styrene which was contained in a Fischer-Hepp wash bottle for 48 hr. at room temperature. The reaction mixture was then poured into ice water and extracted with ether. The ethereal solution was washed with water, and then dried over anhydrous sodium sulfate. The ethereal solvent was evaporated, and the residue was distilled under diminished pressure, yield 60 to 65%.

Reaction of Grignard reagents with substituted benzyl halides in the presence of metallic halides. The anhydrous metallic salt (0.05 mole) was added to the Grignard reagent (0.135 mole) in anhydrous ether (100 ml.) which was contained in a 500 ml. three-neck flask which has been fitted with a mercury-seal stirrer, reflux condenser, dropping funnel, and drying tubes. The reaction mixture was stirred for 0.5 hr. at room temperature. Then the substituted benzyl halide (0.1 mole) dissolved in anhydrous ether (50 ml.) was added dropwise while the reaction mixture was stirred throughout. After complete addition, the reaction mixture was refluxed for 2–3 hr. to insure complete reaction. The reaction flask was then surrounded by an ice-salt freezing mixture, and a 10% solution of acetic acid (100 ml.) was slowly added to decompose the reaction mixture. Stirring was continued for 0.5 hr. to insure complete hydrolysis of the product and solution of all soluble materials. The solution was then filtered, and any insoluble material was washed first with water and then with ether. In one instance where the product, 1,1,2,2-tetraphenylethane was obtained (from the reaction of benzhydryl chloride and a Grignard reagent in the presence of a metallic halide) an ether-insoluble compound was produced, and it was collected and recrystallized from 95% ethanol (m.p. 209–210°).

The water-ether layers were separated, and the aqueous solution was extracted with ether. The combined ethereal extracts were washed with aqueous dilute sodium bicarbonate, and then washed twice with water. The combined aqueous solution was filtered into a 250 ml. volumetric flask, and diluted to volume. A 5-ml. aliquot of the aqueous solution was withdrawn for halogen estimation by a Volhard titration.

Whenever the Grignard reagent was phenylmagnesium bromide, the operational procedure was to transfer the ethereal solution to a steam distillation apparatus. Here the ether solvent was removed by evaporation and the residue was subjected to steam distillation. The steam distillate consisted of biphenyl which was collected, dried, and weighed.

The nonsteam distillable material was taken up in ether, and the ethereal solution was washed with water and dried over anhydrous sodium sulfate. The ether was then evaporated, and the residue was usually recrystallized from ethanol.

In the investigations involving the following substituted benzyl halides: 2-chloro-2-phenylpropane, benzyl chloride, 1-chloro-1-phenylethane, 1-bromo-2-phenylethane, the ethereal solution was dried over anhydrous sodium sulfate; the ether was removed by distillation; and the residue was fractioned at atmospheric pressure through an 18-in. distillation column which was packed with steel helices. The residue which remained in the still pot was then transferred to a modified Claisen flask, and fractionated under reduced pressure.

Reaction of 1-butylmagnesium bromide with benzal chloride. Cobaltous chloride (0.34 g., 0.025 mole) was added to 1-butylmagnesium bromide (0.1 mole) in anhydrous ether (100 ml.), and the mixture was stirred at room temperature for 15 min. The mixture was then transferred to a dropping funnel and added dropwise to a well stirred solution which consisted of benzal chloride (16.1 g., 0.1 mole) and cobaltous chloride (0.34 g., 0.025 mole) in anhydrous ether (100 ml.). After complete addition, the reaction mixture was refluxed for 2 hr. to insure complete reaction. The reaction product was decomposed in the usual manner, and the reaction products were fractionated.

Reaction of 1-butylmagnesium bromide with benzotrichloride. Benzotrichloride (19.4 g., 0.1 mole) was dissolved in anhydrous ether (100 ml.), and cobaltous chloride (0.68 g., 0.05 mole) was added, and the mixture was stirred for 15 min. 1-Butylmagnesium bromide (0.1 mole) in anhydrous ether (100 ml.) was slowly added, and the reaction mixture was allowed to remain at room temperature overnight before the mixture was decomposed. The ether-water insoluble material was collected by filtration and recrystallized from glacial acetic acid yielding tolane tetrachloride, m.p. 160–161°.

The ethereal solution was separated and washed with water. The ether was evaporated, and the residue was steam distilled. The solid which separated from the steam distillate was collected by filtration, and proved to be *cis*-tolane dichloride (m.p. 138–140°, yield 40–45%). The nonsteam distillable material was collected by filtration, recrystallized from methanol, and proved to be the *trans*-tolane dichloride (m.p. 62–63°, yield 2–5%).

Reaction of benzophenone dichloride with phenylmagnesium bromide in the presence of metallic halides. Phenylmagnesium bromide (0.1 mole) in anhydrous ether (100 ml.) was slowly added to a mixture containing benzophenone dichloride

(28) M. Gomberg and R. L. Jekling, *J. Am. Chem. Soc.*, **37**, 2577 (1915).

(22.7 g., 0.1 mole), cobaltous chloride (0.68 g., 0.05 mole), and anhydrous ether (100 ml.) during the course of 1 hr. The reaction mixture was refluxed for 2 hr. and was then decomposed in the usual manner. The ether-water insoluble material was collected by filtration, and the tetraphenylethylene thus obtained was recrystallized from 95% ethanol (m.p. 222–223°).

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Studies of the Grignard Reaction. I. Kinetics of the Normal Grignard Addition Reactions on Benzophenone and Pinacolone

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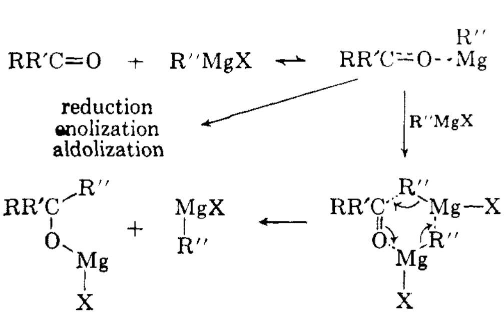
The kinetics of the reaction of methylmagnesium bromide with benzophenone and pinacolone have been studied. A third-order reaction law was found: V = k_3 (ketone) (Grignard).[2] The dependence of the velocity constant k_3 on the initial concentration of Grignard reagent is believed to be caused by complexation.

Several mechanisms for the Grignard addition reaction are proposed in the literature.[1–5] With the exception of Petit,[5] most authors agree that the participation of *two* molecules of Grignard reagent is necessary. This conclusion is based on the results of Pfeiffer and Blank[6] who isolated insoluble ketone-Grignard complexes and who found in this case that only the addition of a *second* molecule of the Grignard reagent yielded the expected carbinols.[7]

The most generally accepted scheme is the Swain mechanism.[1]



Solvation is here neglected although this factor can play an important role.[2] In any case, the structure of the intermediate[2] can be put into another form, or the occurrence of a hexagram[3] can be discussed, but all the proposed schemes appear to follow a kinetic equation of the form;

$$V = \frac{d(P)}{dT} = \frac{k_1k_2(G)^2(K)}{k_{-1} + k_2(G)},$$

where it is supposed that $K + G \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C; C + G \xrightarrow{k_2} P$ and where K_2 = ketone, G = Grignard reagent, C = complex, and P = product.[2] Therefore the reaction will be of second or third order, depending on whether k_{-1} is much smaller or much greater than k_2 (G).

Direct kinetic investigations of the Grignard reaction with nitriles have been carried out[9,10] but the corresponding investigation of the reaction with ketones is much more difficult because the velocity of the reaction is very high. Only one such study has apparently been reported.[11] According to this and in contradiction to the generally accepted Swain scheme,[1] the reaction with acetone and ethyl acetate was only first order with respect to the Grignard reagent.

We have studied the kinetics of the reaction of methyl Grignard reagents (bromide and iodide) with benzophenone and pinacolone. These ketones and Grignard reagents were chosen because side-reactions (reduction, enolization etc.) are impossible or negligible and because the reaction could be conveniently followed at low temperatures.[12] We found that the reaction was in all cases of third order. With a twenty-fold excess of Grignard reagent and after (graphically) correcting the reaction rate, the reaction reduced to (pseudo) first order. The whole process can thus be fitted to

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(12) With acetone and methylmagnesium bromide the reaction was almost complete within ten seconds even at −15°.