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Factors Determining the Course and Mechanisms of Grignard Reactions. XIII. The Effect of Metallic Halides on the Reaction of Sterically Hindered Acid Halides with Methylmagnesium Iodide

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Introduction

The usual products of the reaction between acid halides and Grignard reagents are ketones and tertiary alcohols. However, highly significant observations on the reaction of tri-substituted benzoyl halides and Grignard reagents show that the reaction may take a different course. Thus, Fuson and Corse[1] found that, when 2,4,6-trimethyl- or triethylbenzoyl chloride was added to an ether solution of methylmagnesium iodide, only the monoketone (1) was formed. However, when the order of addition was reversed, the reaction product was a mixture consisting of 35% of the expected ketone (I) and 38% of the substituted benzil (II). Fuson and Corse[1] represent the mechanism of these reactions as follows

$$R_3C_6H_2COCl + CH_3MgI \longrightarrow \underset{\text{(I)}}{R_3C_6H_2COCH_3} + MgICl \quad \text{(A)}$$

$$2R_3C_6H_2COCl + 2CH_3MgI \longrightarrow \underset{\text{(II)}}{(R_3C_6H_2CO-)_2} + C_2H_6{}^{2} + 2MgICl \quad \text{(B)}$$

Because of the uniqueness of the reaction (B), and because of our finding that methylmagnesium bromide does not undergo this reaction, a thorough investigation of the reaction of 2,4,6-trimethylbenzoyl (mesitoyl (β-isodurylyl)) chloride with Grignard reagents was undertaken.

Factors Influencing the Reaction of Mesitoyl Chloride with Grignard Reagents.—The effects of the following experimental conditions on the products formed in the reaction of mesitoyl chloride with Grignard reagents were thoroughly investigated: (a) the order of addition of the reagents; (b) the purity of the magnesium, and the age of the Grignard reagent; (c) the effect of the halides of iron, copper and manganese; (d) the effect of the halogen atom in CH_3MgX; (e) the effect of cobaltous chloride.

(a) As already demonstrated by Fuson and Corse,[1] the order of addition of the reagents plays an extremely important part in the reaction between methylmagnesium iodide and mesitoyl chloride. Our results (K, M and U), as well as those of Fuson and Corse (F and C) are given in Table I. The somewhat larger yield of the substituted benzil (II) obtained by us is readily accounted for by the findings presented under headings (c) and (d) (*q. v.*). The 50% yield of the substituted benzil (II) is a mean of sixteen experiments carried out in the dark and in the light; in the presence and in the absence of air. The average deviation in these experiments was about ±2%.

TABLE I

EFFECT OF THE ORDER OF ADDITION OF REAGENTS ON THE REACTION OF MESITOYL CHLORIDE AND METHYLMAGNESIUM IODIDE

	% Yield based on acid chloride used			
	Ketone		Substituted benzil	
Conditions	F and C	K, M and U	F and C	K, M and U
Grignard added to acid chloride	35	25	39	50
Acid chloride added to Grignard	86	83	0	0

(b) Because of the known effects of traces of metallic halides on the course of Grignard reactions,[3] the reaction of mesitoyl chloride with methylmagnesium iodide prepared both from Dow sublimed magnesium and from Mallinckrodt magnesium was investigated. Considerable variations in the yield of the substituted benzil (II) were at once apparent; it also became equally clear that the difference tended to disappear when the Grignard reagent prepared from the Mallinckrodt magnesium was aged by allowing it to stand before use. No such aging effect was noted with Grignard reagent prepared from Dow magnesium. It is significant that the highest yield of (II) prepared from Mallinckrodt magnesium is about equal to the yield of this substance obtained from Grignard reagent of any age prepared from Dow magnesium. The observations are summarized in Table II.

TABLE II

EFFECT OF AGE OF GRIGNARD REAGENT AND PURITY OF MAGNESIUM ON THE REACTION BETWEEN MESITOYL CHLORIDE AND METHYLMAGNESIUM IODIDE

Magnesium used	Age of Grignard	% Yield based on acid chloride Ketone	Benzil
Mallinckrodt	1 hour	40	31
Mallinckrodt	1 day	35	38
Mallinckrodt	30 days	18	54
Dow	1 hour	25	50
Dow	14 days	26	52

(c) It was suspected that the differences observed with the various magnesiums might be due to metallic impurities. It has been shown[4] that

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[1] Fuson and Corse, THIS JOURNAL, **60**, 2063 (1938).

[2] The formation of ethane in reaction (B) was not demonstrated experimentally by Fuson and Corse. This product was probably assumed because of the similarity of the reaction with that of the benzyl halides on methylmagnesium iodide; in this latter reaction, bibenzyl and ethane are formed in equivalent amounts (Fuson, THIS JOURNAL, **48**, 2681 (1926)).

[3] For previous references, see Kharasch and Fuchs, THIS JOURNAL, **65**, 504 (1943).

[4] Kharasch, Kleiger, Martin and Mayo, *ibid.*, **63**, 2305 (1941).

Dow sublimed magnesium is practically free of all heavy metals, except for 0.01% of lead; Mallinckrodt magnesium, on the other hand, contains 0.05–0.10% Mn, 0.01% Cu, 0.01% Sn and 0.01% Fe. In support of this hypothesis, we find that the addition of a little copper, manganese or iron halide to the Grignard reagent tends to increase the amount of the ketone (I) at the expense of the substituted benzil (II). The observations are summarized in Table III.

TABLE III

EFFECT OF METALLIC HALIDES ON THE REACTION BETWEEN MESITOYL CHLORIDE AND METHYLMAGNESIUM IODIDE

Metallic halide 1 mole %	% Yield based on acid chloride Ketone	Benzil
None	26	52
$MnCl_2$	88	1
$MnCl_2$ (0.1 mole %)	75	5
$FeCl_3$	85	7
Cu_2Cl_2	85	2
Cu[a]	45	30

[a] Grignard reagent prepared from a mixture of Dow magnesium and copper–magnesium alloy.

(d) and (e): in an attempt to find an explanation for the observations recorded in (a), (b) and (c), we examined the reaction of methylmagnesium bromide with mesitoyl chloride. Here, even under the optimum conditions (use of Dow magnesium, etc.), only traces of the substituted benzil (II) were obtained. Methylmagnesium chloride would doubtless act like the bromide. The formation of substituted benzil (II) from mesitoyl chloride is, therefore, specific for the iodide Grignard reagent. However, in the presence of a little cobaltous chloride, methylmagnesium bromide gives a fair (but probably not the optimum) yield of (II). These results are given in Table IV.

TABLE IV

EFFECT OF THE HALIDE OF THE GRIGNARD IN THE REACTION WITH MESITOYL CHLORIDE

Grignard reagent[a]	% Yield based on acid chloride Ketone	Substituted benzil
CH_3MgI	25	50
CH_3MgBr	87	1
$CH_3MgBr + CoCl_2$	35	31[b]
$CH_3MgI + CoCl_2$	17	63

[a] In each of these reactions, the Grignard was added to the acid chloride. [b] The lower total yield of known products is accounted for by the formation of an unidentified tarry material.

The fact that mesitoyl chloride forms a substituted benzil (II) when treated with (1) methylmagnesium iodide or with (2) methylmagnesium bromide and cobaltous chloride[5] but does not form such a benzil when treated with (3) methylmagnesium bromide alone suggests a common mechanism for the reactions with (1) and (2). In the reaction with (2), there is abundant evidence that the Grignard reagent exercises its reducing action on the acid chloride by first forming the cobalt subhalide (CoCl), which acts as a chain carrier. The essential features of the postulated mechanism are as follows

(1) $CH_3MgBr + CoCl_2 \longrightarrow CH_3CoCl + MgBrCl$
(2) $CH_3CoCl \longrightarrow CH_3\cdot + \cdot COCl$
(3) $RCOCl + CoCl\cdot \longrightarrow RCO\cdot + COCl_2$
(4) $2RCO\cdot \longrightarrow RCOCOR$

$$(5)\quad CH_3\cdot + C_2H_5O\text{-}C_2H_5 \xrightarrow{\text{gas}} CH_4\ (80\%) + C_2H_6\ (10\%) + C_2H_4\ (10\%)$$

It seems probable, therefore, that, where methylmagnesium iodide is used, a similar free radical must operate, although no chain reaction is required to account for the result. It is assumed that methylmagnesium iodide can react in two ways

(6) $CH_3MgI \longrightarrow CH_3^- + (MgI)^+$
(7) $CH_3MgI \longrightarrow CH_3\cdot + MgI\cdot$

The active reagents, insofar as the reaction with mesitoyl chloride is concerned, are, therefore, similar; where methylmagnesium bromide and cobaltous chloride are used, cobaltous subhalide is the reducing agent; where methylmagnesium iodide is used, the reducer is magnesious iodide.[6] This assumption, however, requires similarity in gaseous products of the reaction. Here there appeared at first to be a disagreement with experiment, for Fuson and Corse[1] (see Introduction) in writing the over-all reaction indicated that ethane is the exclusive gaseous product of the reaction (B). However, our experience has shown that whenever methyl radicals are formed in ether solution, the gas evolved consists, within ±5%, of about 80% methane,[7] 10% ethane and 10% ethylene. The latter gases are presumably formed in the cleavage of the ether molecule by the free methyl radicals. The gas evolved during the addition of the mixture of methylmagnesium bromide plus cobaltous chloride (5 mole per cent.) to the mesitoyl chloride is a mixture of methane (74%), ethane (16%) and ethylene (10%).[8] The molecular weight of the gas resulting from the interaction of methylmagnesium iodide with mesitoyl chloride is 18.0. This figure corresponds to a mixture containing 85% of methane and 15% of the heavier gases (ethane and ethylene).

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(5) Phenylmagnesium bromide reacts with mesitoyl chloride in the presence of cobaltous chloride to give 4% of the substituted benzil (II), 41% of phenyl mesityl ketone and 21% of *sym*-diphenyldimesitylpinacol.

(6) The observation of Fuson and Corse (THIS JOURNAL, **61**, 975 (1939)) that a mixture of magnesium and magnesium iodide reduces diortho-substituted acid halides as well as diortho-substituted diketones to enediols may be looked upon as further support of this hypothesis.

(7) The somewhat lower figure given for methane (62%) and higher figures for ethane (18%) and ethylene (20%) given by Kharasch, Lewis and Reynolds (THIS JOURNAL, **65**, 493 (1943)) were probably due to small losses of methane during the evacuation of the vessel. Our recent improved technique eliminates this slight error in the analyses.

(8) The gas evolved, when addition of the Grignard reagent has been completed and the reaction vessel is allowed to warm to room temperature, is almost pure methane. This gas is probably formed in the reaction between the ketone (I) and the Grignard reagent, a reaction known to take place slowly in the cold (Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927)).

Evidently, if the reaction proceeds as outlined by Fuson and Corse[1]

$$2\text{RCOCl} + 2\text{CH}_3\text{MgI} \longrightarrow \text{RCOCOR} + \text{C}_2\text{H}_6 + 2\text{MgClI}$$

the amount of ethane is too small and the amount of methane is too large to be strictly accounted for by enolization of the ketone. The amount of methane, however, is compatible with the hypothesis that free methyl radicals are formed (*cf.* equations (1) to (5)). On the other hand, another difficulty presents itself. The 15% of the heavier gas is not a mixture of equal parts of ethane and ethylene, but is almost pure ethane. Two explanations for this fact suggest themselves. In the first place, if 12% of the reaction proceeds according to the mechanism of Fuson and Corse[1] and 88% according to the mechanism suggested in reaction (7) and reactions (1) to (5), then the gas should contain only about 3% of ethylene, a quantity which we may have overlooked because of difficulties in the analytical procedure. Secondly, free methyl radicals in the presence of such reactive molecules as methylmagnesium iodide may react in a manner different from that indicated in equation (5). Thus, although removal of the hydrogen atom from the ether molecule may still be the dominant reaction (80–85%), the secondary cleavage of the ether molecule (15%), because of the stability of the magnesious iodide, may be outstripped by the faster reaction with the Grignard reagent.

$$\text{CH}_3\cdot + \text{CH}_3\text{:MgI} \longrightarrow \text{C}_2\text{H}_6 + \text{MgI}\cdot$$

Of the two alternative explanations, we prefer the latter, since it not only reconciles the facts recorded in this paper, but also explains observations which we hope to report in the near future.

Methylmagnesium iodide thus can react by either an ionic or a free-radical mechanism. The former is apparently much the faster of the two. The free-radical mechanism comes into play only where substances which can be reduced by magnesious iodide are present, and where the normal reaction of the Grignard reagent with the organic molecule is comparatively slow. High dilution of both components, and particularly of the Grignard reagent should, therefore, favor the free-radical reactions of the alkyl magnesium iodides.[9]

Experimental Details

Materials.—Mallinckrodt magnesium turnings or Dow sublimed magnesium was used. Methyl bromide was obtained from the Dow Chemical Company; bromobenzene from the Eastman Kodak Company. The bromobenzene was carefully fractionated before use. The methyl iodide was Mallinckrodt reagent grade. It was carefully distilled before use and was free from traces of iodine. The cuprous chloride was the usual anhydrous reagent. Anhydrous cobaltous and manganous chlorides were prepared from the hydrates by heating *in vacuo:* the former was heated to 150°, and the latter to 200°. Anhydrous ferric chloride was prepared from pure iron wire and chlorine.

Preparation of Grignard Reagents.—The Grignard reagents were prepared in a three-neck flask equipped with a mercury-sealed stirrer, reflux condenser, dropping funnel, and (in the case of the methylmagnesium bromide) an inlet tube extending nearly to the bottom of the flask. The apparatus was flushed with dry nitrogen and flamed before use.

Bromobenzene, diluted with enough dry ether to give a two-molar solution, was added to an excess of magnesium covered with a small amount of ether; the rate of addition was such that refluxing was maintained. After all the halide had been added, the mixture was refluxed for about an hour to insure completion of the reaction, and then filtered under nitrogen pressure through a coarse sintered glass filter. The reagent was stored under nitrogen in a brown bottle, and was titrated just before use.

Methylmagnesium iodide was prepared in a similar manner. The filtered Grignard reagent was always clear; where Dow magnesium was used, the liquid was water white.

The methyl bromide gas was bubbled into the flask containing excess magnesium and part of the ether at such a rate as to maintain refluxing. Portions of ether were added from time to time so that the final concentration was about two-molar. The Grignard reagent was refluxed, filtered, and stored as indicated previously.

Reaction of Phenylmagnesium Bromide with Mesitoyl Chloride.—The mesitoyl chloride (b. p. 86–88° at 4 mm.) was prepared from mesitoic acid according to the directions of Fuson, Corse and McKeever.[10]

Cobaltous chloride (0.01 mole) was added to phenylmagnesium bromide (0.28 mole in 330 ml. of ether) contained in a three-neck flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping funnel. The flask was cooled in an ice-bath. The resulting black mixture was siphoned under nitrogen pressure into the dropping funnel and added slowly to a second three-neck flask equipped like the first, and containing 0.10 mole of mesitoyl chloride and 0.01 mole of CoCl_2 in 330 ml. of dry ether; the second flask was kept cool in an ice-bath. The addition was complete in ninety minutes. The mixture was stirred for thirty minutes longer at room temperature, and then allowed to stand overnight.

The product was decomposed with ice and hydrochloric acid, the ether layer separated, and the water layer extracted twice with ether. The combined ether layers were washed first with sodium bicarbonate, then with water, and finally dried over sodium sulfate. The ether was removed and the residue was steam distilled. From the distillate there was obtained a solid (4.3 g.) which, after crystallization from alcohol, melted at 66–68°. This substance was identified as biphenyl by its melting point and by the fact that it did not depress the melting point of an authentic sample of biphenyl.

After the steam distillation, the residue remaining in the flask was poured into ethyl alcohol; a light yellow solid separated (wt. 4.7 g., m. p. 228-232°). This substance, After several crystallizations from benzene and sublimation under high vacuum, yielded a white solid (m. p. 237-238°).

Anal. Calcd. for $\text{C}_{32}\text{H}_{34}\text{O}_2$: C, 85.33; H, 7.55. Found: C, 84 97; H, 7.37.

This material did not depress the melting point of *sym* diphenyldimesitylpinacol prepared by another method The yield of pure material was 21% based on the acid chloride used.

The alcohol was removed from the filtrate and the residue distilled at 1 mm. pressure. A colorless liquid which boiled at 130–140° was collected. This substance was identified as 2,4,6-trimethylbenzophenone; the yield was 41% based on the acid chloride used.

The residue remaining in the flask was a black tar. From this tar, a yellow solid (0.5 g., m. p. 119–120°) was obtained by sublimation in high vacuum. This substance was identical with the hexamethylbenzil obtained by re-

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[9] The tendency of the Grignard reagent to dissociate into magnesious iodide and an organic free radical should increase with the decreasing electronegativity of the organic radical (*cf.* Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936)).

[10] Fuson, Corse and McKeever, THIS JOURNAL, **61**, 2010 (1939).

action of methylmagnesium iodide with mesitoyl chloride. The yield of this material was 4% based on the acid chloride used. The material which could not be sublimed weighed 3 g.

When phenylmagnesium bromide was added to mesitoyl chloride (in the absence of cobaltous chloride), only 2,4,6-trimethylbenzophenone was isolated. The yield was 90%, based on the acid chloride used.

Reactions of Methylmagnesium Bromide and Mesitoyl Chloride in the Presence of Cobaltous Chloride.—The procedure was similar to that previously described, except that the Grignard reagent was mixed with the catalyst in a flask cooled in an ice-salt bath, and the dropping funnel into which the mixture was siphoned was equipped with a cold-finger filled with a mixture of ice and salt. Mesitoyl chloride (0.06 mole), methylmagnesium bromide (0.15 mole) and cobaltous chloride (0.0075 mole) were used. The reaction mixture was worked up in the usual manner. The quantities of the products formed are recorded in Table IV.

A total of 1700 cc. (corrected to standard) of gas was collected. The first 500 cc. of this gas was rejected. The molecular weight of the gas contained in the second 500 cc. was 19.4, and the unsaturation amounted to 10%. The gas analyses were made by the method of Kharasch, Lewis and Reynolds.[7]

When methylmagnesium bromide was added to mesitoyl chloride in the absence of cobaltous chloride, an 87% yield of 2,4,6-methylmesityl ketone was obtained; there was only a trace of the substituted benzil.

Reaction of Methylmagnesium Iodide and Mesitoyl Chloride.—In all experiments with these reagents, the concentrations and proportions of reactants, as well as the rate of addition and the manner of working up the products, were the same as previously described. The isolation procedure was similar to that of Fuson and Corse. The results of the experiments are given in Tables I, II, III and IV.

In the experiments in which metallic halides were used, the metal halide was usually added to the Grignard reagent; the resulting mixture was added to the mesitoyl chloride dissolved in ether. In the cobaltous, copper and iron chloride experiments, the Grignard reagent turned almost black; when manganous chloride was used, the solution remained clear and colorless.

Summary

1. In the reaction between mesitoyl chloride and methylmagnesium iodide it has been shown that: (a) the order of addition of the reactants is important; (b) light and small amounts of oxygen have no effect upon the reaction; (c) the use of pure magnesium in making the Grignard reagent and aging of the reagent made from ordinary magnesium give higher yields of 2,4,6,2′,4′,6′-hexamethylbenzil; (d) traces of the halides of iron, copper, and manganese limit the reaction to the normal addition; (e) small amounts of cobaltous chloride increase the yield of the substituted benzil, as is also the case when methylmagnesium bromide is used.

2. A mechanism has been proposed to account for the products of the reaction of mesitoyl chloride with Grignard reagents.

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[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES OF THE MONSANTO CHEMICAL COMPANY]

Unsaturated Esters of Glycolonitrile

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In aqueous solution a mixture of formaldehyde and sodium cyanide reacts like glycolonitrile and sodium hydroxide.

$$CH_2O + NaCN + H_2O \rightleftharpoons HOCH_2CN + NaOH$$

With benzoyl chloride a typical Schotten–Baumann reaction occurs to give cyanomethyl benzoate[1] in 45% yields.

$$C_6H_5COCl + HOCH_2CN + NaOH \longrightarrow C_6H_5COOCH_2CN + NaCl + H_2O$$

In extending this reaction we have found that good yields (53–73%) of cyanomethyl esters of α,β-unsaturated acids can be obtained from the corresponding acid chlorides. Acrylyl chloride, however, gives poor yields because of a side reaction leading to the formation of an ester, $C_6H_9O_3N$, the structure of which has not yet been established. Furthermore, dibasic acid chlorides, such as fumaryl chloride, give only insignificant yields of diesters by the aqueous method. These esters are satisfactorily prepared by the method of Hechenbleikner[2] in which the acid chloride is treated with glycolonitrile in anhydrous ether in the presence of a tertiary amine.

Inasmuch as it has been observed[3] that acetyl chloride gives low yields in the Schotten–Baumann reaction, it is not surprising that the method is of little value for the preparation of cyanomethyl esters of saturated aliphatic acids. A better procedure appears to be the reaction of the sodium salt of the acid with chloroacetonitrile.[4] The properties of the unsaturated esters are reported in Table I.

Experimental

Reagents.—The methacrylyl, crotonyl, cinnamoyl and α-methylcinnamoyl chlorides were prepared by the action of thionyl chloride on the acids. Acrylyl chloride was prepared in 27% yields by the action of phosphorus oxychloride on sodium acrylate[5] and in 35% yield by dehydrohalogenation[6] of β-chloropropionyl chloride over alumina at 250°. β-Chlorocrotonyl chloride was obtained from ethyl acetoacetate and phosphorus pentachloride.[7] Fu-

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[1] Aloy and Rabaut, *Bull. soc. chim.*, [4] **13**, 457 (1913).

[2] Hechenbleikner, U. S. Patents 2,266,199 (1941), 2,307,649 (1943).

[3] Menalda, *Rec. trav. chim.*, **49**, 967 (1930).

[4] Henry, *Bull. soc. chim.*, [2] **46**, 42 (1886); *Rec. trav. chim.*, **24**, 170 (1905).

[5] Moureu, *Ann. chim.*, [7] **2**, 145 (1894).

[6] Fikentsher, U. S. Patent 2,050,752 (1936).

[7] Shriner and Keyser, This Journal, **60**, 286 (1938).