

A STUDY OF THE STERIC EFFECTS IN THE REACTION OF ARYL ESTERS WITH AN ARYL GRIGNARD REAGENT

> Thesis for the Degree of M. S. MICHIGAN STATE UNIVERSITY Robert Eugene McComb 1957

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Robert Eugene McComb

A THESIS

Submitted to the College of Science and Arts of Michigan State University of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

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Department of Chemistry

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ABSTRACT

A study of the steric effects of ortho substitution on aryl esters in the reaction of these esters with mesitylmagnesium bromide has been made. Mesitylmagnesium bromide was caused to react with the phenyl and <u>o</u>-oresyl esters of benzoic acid, and <u>o</u>-methyl-, <u>p</u>-methyl-, <u>o</u>-ethyl-, and <u>o</u>-isopropylbenzoic acids. The reaction mixtures were analyzed quantitatively by infrared absorption spectroscopy for the diaryl ketone and triaryl tertiary alcohols formed and for the unreacted aryl esters remaining after the reaction. Verification of the infrared method was done by determining the percent ketone formed as an oxime using hydroxylamine hydrochloride in pyridine and percent unreacted ester by hydrolyzing the ester with excess base and back titrating the excess base.

Results of this study indicate that ortho substitution of alkyl groups on either the aroyl or aryloxy portion of the ester hinder the reaction of these esters with the highly hindered Grignard reagent. On the other hand, para substitution of the methyl group enhanced the reactivity of the esters with the Grignard reagent. The reactivity of ester with mesitylmagnesium bromide was virtually independent of the size of o-alkyl substituent on the aroyl group.

The greatest decrease in reactivity was found for ortho substitution on the aryloxy portion of the ester.

The reactivity of the complex formed was the reverse of the reactivity of the esters. The ortho substitution on the aryloxy portion of the ester increased the reactivity of the complex when compared to unsubstituted esters. The ortho substitution on the aroyl portion likewise increased the reactivity of the complex when compared to unsubstituted esters but this increase was not as large as for substitution on the aryloxy portion of the ester. The size of the ortho substituent on the aroyl portion did not greatly effect this reactivity.

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INTRODUCTION

Statement of Problem

The effects of steric hindrance of alkyl groups in the reaction between Grignard reagents and esters or ketones have been widely studied (1-15). But until recently (16) no systematic study of the interplay of steric factors in the reaction of Grignard reagents with esters has been reported. There are three steric areas involved in this reaction. These areas are the acyl portion of the ester, the alcohol portion of the ester and the Grignard reagent.

This investigation is specifically a study of the effects of steric hindrance on the reaction of mesitylmagnesium bromide with the phenyl and <u>o</u>-cresyl esters of benzoic acid and <u>o</u>-methyl-, <u>p</u>-methyl-, <u>o</u>-ethyl- and <u>o</u>-isopropylbenzoic acid. The <u>p</u>-methylbenzoates were used to measure the electron donating effect of the alkyl group.

The purpose of this investigation was to determine the nature of the interplay of the steric factors of the esters when the steric hindrance in the Grignard reagent was extremely high. It was also desired to determine how sensitive the reaction of the formation of alcohol was to steric factors. Finally, from this investigation it was hoped that more information would be obtained on the mechanism of this reaction.

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The study was carried out by causing a 1:1 mole ratio of Grignard reagent to ester to react in refluxing toluene for one hour. Due to the difficulty in initiating the formation of Grignard reagent of bromomesitylene one drop of ethyl bromide was employed to start the reaction. The Grignard reagent was added to the ester which is the reverse of the normal addition so as not to favor the formation of tertiary alcohol. The Grignard reagent was filtered before use to remove any excess magnesium so as to stop any undesirable side reactions. The products, ketones and tertiary alcohol and the unreacted ester were determined by quantitative infrared absorption methods. The infrared method was checked by a volumetric determination of the oxime derivative of the ketone and by saponification of the unreacted ester.

Historical

The reaction between Grignard reagents and esters and the effects of steric hindrance in both the Grignard and the ester have been studied by many investigators. Normal addition, formation of tertiary alcohol, reactions which lead to formation of hydrocarbons, reduction, enolization and other reactions have been included in these studies.

Boyd and Hatt (1) studied the reaction between <u>o-methyl-</u> phenylmagnesium bromide with ethyl <u>o-toluate</u> and found that no tri-<u>o-tolyl</u> carbinol was formed. They isolated a diaryl

ketone and the pinacol of the diaryl ketone and postulated that this formation was due to the excess magnesium present.

Kohler and Baltzly (2) studied the reaction of acetomesitylene, dimesityl ketone and dimesityl diketone with ethylmagnesium bromide. They found that the steric hindrance due to the methyl substitution in the ortho position stopped the normal reaction of addition to the carbonyl and caused enclization in the case of the acetomesitylene, but for the other two compounds no reaction could be detected. They expressed the thought that the decreased velocity of the reaction, because of steric factors, allowed other slower reactions to take place. Complete blocking of the functional group stopped any reaction from taking place.

Smith and Guss (3) in studies similar to those of Kohler and Baltzly verified their results. The alkyl ketones hindered near the functional group gave methans when reacted with methylmagnesium iodide. This was apparently due to enclization of the ketone. This enclization was a function of the hindrance in the ketone, and the greatest effect was found when the alpha position was hindered by methyl groups.

Arnold and co-workers (4) investigated reactions between phenylmagnesium bromide and allyl benzoates, toluates and isodurylates which were substituted in the ortho position. They found upon reacting phenylmagnesium bromide with allyl benzoate and allyl o-toluate yields of 86% and

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68% respectively, were found of the triphenyl carbinol. They felt that one <u>o</u>-methyl group did not greatly hinder the normal addition of the Grignard reagent. When they reacted phenylmagnesium bromide with allyl β -isodurylate, they obtained allylbensene, a magnesium halocarboxylate and no alcohol. This was interpreted as steric hindrance stopping the normal addition. They investigated also the reaction between allyl trimethylacetate and phenylmagnesium bromide and found the normal addition to take place which gave <u>tert</u>butyldiphenyl carbinol.

Fuson and co-workers (5) studied the reactions of certain alkyl and aryl esters of mesitoic acid with alkyl and aryl Grignard reagents. The expected products were not found even though a reaction was in evidence. With the alkyl mesitoates and alkylmagnesium halide, they found mesitoic acid and an alkyl halide which came from the alkyl group of the ester and no alkylation was observed in any of these reactions. With the aryl mesitoates and alkylmagnesium halides they obtained alkyl mesityl ketone and phenol. When both reactants were aryl compounds, they found arylation or substitution in the ortho position of the ketone produced.

Whitmore and George (6) reacted different Grignard reagents with di-isopropyl ketone and found that enolisation increased from 0 to 90% going from methylmagnesium bromide, ethylmagnesium bromide, <u>sec</u>-butylmagnesium bromide, <u>tert</u>-butyl

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magnesium bromide to neopentylmagnesium bromide. This enolization was due in part to the steric hindrance and caused a decrease in the reactivity of normal addition. Whitmore postulates a cyclic intermediate to account for this.

Hauser and co-workers (7) studied the reactions of carboxylic esters with different Grignard reagents. They found that as the Grignard reagent became more complex (from methyl, ethyl, isopropyl, <u>tert</u>-butyl to mesitylmagnesium bromide) the normal addition dropped off. Under these conditions condensation reactions and some enolization occurred.

Trieb (8) studied the effects of substituents in esters on the reaction rates with methylmagnesium iodide and he postulated the following rules for the ester RCOOR':

- Increase in the size of normal R' up to propyl causes decrease in reactivity, negligible thereafter (steric).
- Benzyl esters are the most reactive, but further separation of the phenyl by a normal carbon chain decreases the activity (polar).
- Branching in R⁴ inhibits when adjacent to COObut accelerates when removed by at least one carbon atom (polar and steric).
- 4. Diastereomeric esters react at different rates

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(isomenthyl) neoisomenthyl) menthyl) neomenthyl acetates) (steric).

- Phenyl groups in R cause acceleration, but the effect is diminished by separation from -COO (polar).
- Branching in R causes retardation in rate (steric).

Whitmore and Lewis (9) and other co-workers (10-14) studied the effects of substitutions on the seyl part of alkyl esters, alkyl acid chlorides and ketones. When substitution was on the alpha carbon, they found that an ethyl group produces a more profound effect than a methyl group and that as the size of the alkyl substituent increased the normal addition reaction decreased in importance. This verified Trieb's sixth rule.

In discussing steric hindrance in the reaction of Grignard reagents with esters, Kharasch and Reinmuth (15) commented that Trieb's (8) studies showed that substitution on both the acidic and alcoholic constituents influence the addition rates. It was established that these influences were more steric than energetic and that the abnormalities in the reactions observed were due solely to these steric factors. Therefore, branching in the acid chain of an alkyl acid near the functional group retarded addition of the Grignard reagent. Branching in the alcoholic portion of the

ester had less influence sterically on addition but the effects were still noticeable. They suggested that the alcoholic portions influence was more of an energetic effect than steric. These postulates and suggestions were based on a wide variety of experimental results conducted under many different conditions.

Kharasch and Reinmuth also pointed out that if the intermediate first formed was ether soluble, the ability to form ketones was a function of the Grignard reagent and not the ester. In this view it was shown that branched alkylmagnesium halides and diortho substituted arylmagnesium halides form a ketone preferentially. This would suggest that the effect is steric rather than energetic. If the intermediate was ether insoluble, the formation of the ketone found was primarily due to the ester and not the Grignard reagent.

The literature referred to no systematic study of the effects of ortho substitution of methyl, ethyl or isopropyl groups on the aroyl portion or of <u>o</u>-methyl substitution on the aryloxy portion of the ester. Until recently (18) this study seemed to have been ignored, though it apparently has been done partially for ketones.

EXFERIMENTAL

The following esters were caused to react with mesitylmagnesium bromide: phenyl benzoate, phenyl <u>o</u>-methylbenzoate, phenyl <u>p</u>-methylbenzoate, <u>p</u>-oresyl <u>o</u>-methyl-<u>o</u>-isopropylbenzoate; <u>o</u>-oresyl <u>benzoate</u>, <u>o</u>-oresyl <u>o</u>-methylbenzoate, <u>o</u>-oresyl <u>p</u>-methylbenzoate. The resulting reaction mixture was analyzed by infrared analysis for the amounts of ketone and tertiary alcohol produced and for the amount of ester that remained unreacted. Further analyses were performed by determining the ketones in certain of the reaction mixtures using hydroxylamine hydrochloride in pyridine, and the unreacted esters by hydrolysis, with an excess of standard base in alcohol and back titrating the excess base with standard acid.

SOURCES AND FREPARATION OF STARTING MATERIALS

The chemicals used in this study were: phenol, <u>o</u>-cresol, benzoyl chloride, <u>o</u>-toluic acid, <u>p</u>-toluic acid, thionyl chloride, <u>o</u>-bromoethylbenzene, <u>o</u>-bromoisopropylbenzene, and mesitylene. Compounds prepared from the above were phenyl and <u>o</u>-cresyl benzoate, <u>o</u>-methylbenzoyl chloride, phenyl and <u>o</u>-cresyl <u>o</u>-methylbenzozl chloride, phenyl and <u>o</u>-cresyl <u>o</u>-methylbenzozl chloride, phenyl and <u>o</u>-cresyl <u>p</u>-methylbenzozte, <u>o</u>-ethylbenzoic acid, <u>o</u>-ethylbenzoyl chloride, phenyl and <u>o</u>-cresyl <u>o</u>-ethylbenzozte,

o-isopropylbensoio acid, o-isopropylbensoyl chloride, phenyl and o-cresyl o-isopropylbenzoate, and bromomesitylene.

Materials Purchased

Fhenol, Kerck and Company, Analytical Reagent Grade.

o-Bromosthylbenzens, The Dow Chemical Company, redistilled by Arthur J. Pastor and fraction boiling 98°C at 30 mm. Hg. was used, np²⁵ 1.5462.

<u>o</u>-Bromoisopropylbensene, The Dow Chemical Company, redistilled by Arthur J. Pastor and fraction boiling 107° C at 30 mm. Hg. was used, np^{25} 1.5385.

<u>o-Toluic acid, Eastman Kodak Company, white label No.</u> 1646, m.p. 179-180°C.

Mesitylene, Matheson Coleman and Bell Division, white label, b.p. 163-165°C, n_D^{25} 1.4987.

Benzoyl chloride, J. T. Baker Chemical Company, b.p. 193.1-197.1°C, 99.9% purity.

Thionyl chloride, Eastman Kodak Company, white label.

<u>o</u>-Gresol, Eastman Kodak Company, yellow label (Technical), it was distilled twice through a wrapped 40 cm. Vigreux column and fraction boiling at 93-94°C at 25 mm. Hg. was used.

Magnesium metal turnings, Merck and Company, specific for Grignard resctions, 99.5% purity.

Pyridine, Werck and Company, Analytical Resgent Grade.

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Chloroform, Merck and Company, U.S.P.

Ethyl alcohol, Union Carbide and Carbon Co., U.S.P. 95%.

Preparation of Bromomesitylene

Bromomesitylene was prepared from bromine and mesitylene by the method described in Organic Synthesis (17).

In a one liter three neck round-bottom flask equipped with a true bore stirrer, a 500 ml. dropping funnel and a parallel side arm holding a thermometer and reflux condenser, were placed 321.2 g. (2.675 moles) of mesitylene and 150 ml. of carbon tetrachloride.

A rubber tube from the top of the condenser to the water drain was used to remove the hydrogen bromide vapors formed. The flask was cooled to 2°C and 483 g. (161 ml., 3 moles) of bromine in 190 ml. of carbon tetrachloride were added over a period of two and one-half hours while the temperature was maintained at 6°C by means of an ice bath. After all the bromine was added, the mixture was refluxed for one hour. The reaction mixture was washed with two 200 ml. portions of distilled water and two 250 ml. portions of a 5% sodium hydroxide solution. The reaction mixture was dried over anhydrous calcium chloride and the carbon tetrachloride distilled at atmospheric pressure through a 40 cm. Fenske column. The residue of the distillation was then added to one liter of 95% ethyl alcohol which hed previously
reacted with 30 g. of sodium metal. The reaction mixture was then refluxed for two hours and allowed to stand over night: It was then diluted with three liters of distilled water and separated. The water layer was washed with three 100 ml. portions of carbon tetrachloride. The extracts were combined with the orude product and this mixture dried over anhydrous calcium chloride. After drying, the carbon tetrachloride was removed by distilling through a 40 cm. Fenske column. The product was then distilled through the same column at reduced pressure. The fraction boiling at 97-101°C at 15 mm. of Hg. was used. The yield was 396.5 g. (1.983 moles) 74% of theoretical based on mesitylene, n_D^{25} 1.5488-1.5500.

Preparation of o-Ethylbenzoic Acid and o-Isopropylbenzoic Acid

These two acids were prepared by causing the Grignard reagents of <u>o</u>-bromosthylbenzene and <u>o</u>-bromoisopropylbenzene to react with solid carbon dioxide (18).

In a 1000 ml. three neck round-bottom flask, equipped with a true bore stirrer, a 500 ml. dropping funnel and a reflux condenser, both funnel and condenser guarded by a drying tube containing anhydrous calcium chloride, was placed 14.4 g. (0.594 g.-atoms) or 11.8 g. (0.485 g.-atoms) of magnesium turnings and 75 ml. of sodium dried diethyl ether. Six grams of o-bromoethylbensene or o-bromoisopropylbensene

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were added directly to the flask. The reaction was initiated by crushing the magnesium with the stirrer. After the reaction had started the remaining dried diethyl ether (325 ml.) and o-bromoethylbenzene (68.7 g. total 74.7 g., 0.404 moles) or o-bromoisopropylbenzene (72.4 g., total 78.4 g., 0.393 moles) were mixed and added dropwise over a period of one hour. The system was refluxed for another hour. The reaction mixture was cooled to room temperature and transferred slowly with dried nitrogen onto 1000 g. of finely divided solid carbon dioxide. The mixture was stirred continuously during the addition of the Grignard reagent and was allowed to stand until all of the unreacted solid carbon dioxide had sublimed. Three hundred fifty milliliters of a 10% hydrochloric acid solution and 100 g. of ice were added and the mixture was stirred vigorously until all cloudiness had disappeared. It was then transferred to a one liter separatory funnel and the water layer discarded. The organic layer was extracted twice with 200 ml. of a 10% sodium hydroxide solution and the other layer discarded.

The basic solution was returned to the separatory funnel and acidified with 100 ml. of a 36% hydrochloric acid solution. The acidified solution was extracted twice with 250 ml. of chloroform. The chloroform extract was washed with 200 ml. of a 1.5% hydrochloric acid solution and transferred to a tared container from which the chloroform was evaporated.

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The yield of the crude <u>o</u>-ethylbenzoic acid melting at 62-64^oC (literature value, 65^oC) (19) was 50 g., (0.333 moles), 82.6% of theoretical; or <u>o</u>-isopropylbensoic acid (it was a dark amber liquid initially but crystalized on standing) melting at 53-55^oC (16) was 48.4 g., (0.294 moles) 75.0% of theoretical.

Preparation of Acid Chlorides

The acyl halides of <u>o-methyl</u>, <u>p-methyl-</u>, <u>o-ethyl-</u> and <u>o-isopropylbenzoic acid were prepared by causing each of the</u> acids to react with thionyl chloride (20).

In a 500 ml. one neck round-bottom flask, equipped with a Claisen distillation head which was fitted with a thermometer, cork and reflux condenser guarded by a drying tube containing anhydrous calcium chloride, was placed 51.7 g. (0.381 moles) of o-toluic acid and 63.6 g. (0.534 moles) of thionyl chloride, or 58.0 g. (0.426 moles) of p-toluic acid and 71.4 g. (0.605 moles) of thionyl chloride, or 45.3 g. (0.301 moles) of o-ethylbenzoic acid and 57.2 g. (0.480 moles) of thionyl chloride, or 47.2 g. (0.286 moles) of o-isopropylbenzoic acid and 54.6 g. (0.460 moles) of thionyl chloride. The apparatus was tilted until the side arm of the Claisen head was almost upright and the reaction mixture refluxed gently for 6.5 hours, after which it was allowed to stand overnight. The condenser was then removed and the apparatus rearranged to permit normal distillation. The

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unreacted thionyl chloride was distilled at atmospheric pressure, over the temperature range 75-85°C. The system was then subjected to 30 mm. Hg pressure and a second fraction was collected and discarded.

The third fraction, which was the product, gave 52.9 g. (0.342 moles) of <u>o</u>-tolyl chloride, b.p. 96-100°C at 16 mm., yield 90% of theoretical; 60.8 g. (0.394 moles) of <u>p</u>-tolyl chloride, b.p. 106-108°C at 20 mm., yield 92% of theoretical; 50.1 g. (0.296 moles) of <u>o</u>-ethylbenzoyl chloride, b.p. 120- 121° C at 30 mm., yield 98% of theoretical or 48.0 g. (0.263 moles) of <u>o</u>-isopropylbenzoyl chloride, b.p. 128°C at 30 mm., yield 92% of theoretical.

Freparation of Phenyl and o-Greeyl Esters

Phenyl and <u>o</u>-cresyl esters were prepared from benzoyl chloride, and from <u>o</u>-methyl-, <u>p</u>-methyl-, <u>o</u>-ethyl-, and <u>o</u>-iso propylbenzoyl chlorides by mixing phenol and <u>o</u>-cresol dissolved in pyridine with each of the soyl halides (21).

A detailed account of the preparation of phenyl <u>o-methyl-</u> benzoate is presented below:

In a 500 ml. three neck round-bottom flask equipped with true bore stirrer and reflux condenser guarded by a drying tube containing anhydrous calcium chloride was placed 24.3 g. (0.258 moles) phenol dissolved in 100 ml. of pyridine. The flask cooled to 5°C in an ice bath. After cooling, 23.8 g. (0.186 moles) o-tolyl chloride was added with vigorous

agitation, the reaction mixture was stirred for three hours and allowed to stand.

After approximately 16 hours, 200 ml. of chloroform was added and the mixture extracted six times with equivalent volume of 35 sodium carbonate solution and two times with equivalent volume of distilled water. The chloroform-ester mixture was dried by pouring it through three batches of anhydrous sodium sulfate. The chloroform was evaporated. The yield of phenyl <u>o</u>-methylbenzoate was 33.8 g. (0.159 moles) 85.7% of theoretical, refractive index of light yellow liquid n_D^{25} 1.5715.

All other esters were prepared using nearly identical conditions. Solid esters were recrystallized from ethyl alcohol. Yields and physical constants of these esters are given in Table I.

Preparation of Mesitylmagnesium Bromide

Mesitylmagnesium bromide was prepared by causing the bromomesitylene to react with the magnesium turnings in sodium dried other. The reaction was initiated with othyl bromide.

In a 500 ml. three neck flask, equipped with true bore stirrer, 250 ml. dropping funnel and reflux condenser, both funnel and condenser guarded by drying tube of anhydrous celcium chloride, was placed 2.68 g. (0.11 g.-atoms) of magnesium turnings and 10 ml. of sodium dried diethyl ether,

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YIELDS AND PHYSICAL CONSTANTS OF ESTERS PREPARED

Refractive Index nD25	estion was in A santle was 1	1.5631	1.5545	1.5680	1.5644		1.5586	1.5500
the ether ylone (16 76 aluttod 100 point 100 p	at gentle rofl 91 g., total 1 ed other and a over a period bromomositylen hours with con	142-142.5/lam.	183-186/16mm.				149-152/law.	163.5-166/Smm.
Point of	e ther was add N 9 400ml. The 91 9 9 00 filtered 69 92				ė	46.2-48.5		i.
The read	the Grighard to 10 ml. of 6 5 hydrochlor as titrated to hydroxide sol	68.5%	62.5%	\$0.66	91.1%	71.0%	89.0%	71.0%
llioquiva ard reage The method libr and silli <u>2.46-</u>	Phenyl benzoate Phenyl 2-methylbenzoate Phenyl 2-methylbenzoate	Phenyl <u>o</u> -ethylbenzoate	Phenyl 0-1sopropylbenzoate	Q-Cresyl benzoate	o-Cresyl o-methylbenzoate	o-Gresyl D-methylbenzoate	o-Gresyl o-ethylbenzoate	o-Gresyl o-isopropylbenzoste

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3 g. of bromomesitylene was added and one drop of ethylbromide. The reaction was initiated by heating flask with a micro burner. A mantle was then used to heat the flask to keep the ether at gentle reflux. The remainder of the bromomesitylene (16.91 g., total 19.91 g., 0.1 mole) was mixed with 75 ml. dried ether and added dropwise by means of the dropping funnel over a period of one-half hour.

After the bromomesitylene was added, the mixture was refluxed for 4 hours with constant stirring. Fifty milliliters of dried ether was added to bring the volume to approximately 140 ml. The mixture was allowed to cool to room temperature and filtered through glass wool into a dried bottle.

To analyze the Grignard reagent, two milliliters of it was pipetted into 10 ml. of distilled water and a known excess of 0.6163 N hydrochloric acid was added. The excess standard acid was titrated to a Methyl Red endpoint with 0.6163 N sodium hydroxide solution to determine the number of milliequivalence per milliliter and rough yield of Grignard reagent.

The method of calculating the milliequivalents per milliliter and percent Grignard reagent is given below:

millieq./ml. =
$$\frac{ml. \text{ of ecid x N acid}}{2}$$
 =
2.46 ml. x Q6163 N = Q758 millieq./ml.

% Grignard reagent = millieq./ml. x ml. of Grignard x 100 = 100 millieq.

0.758 x 120 = 91%.

The remaining portion of the Grignard reagent was used in the reactions with the esters.

Reactions of mesitylmagnesium Bromide With the Esters

Approximately 0.02 moles of mesitylmagnesium bromide was mixed with approximately 0.02 moles of each of the esters and allowed to reflux for one hour in 100 ml, of toluene. The reaction mixture was then quenched with aqueous hydrochloric acid and worked up for analysis. An example of a typical reaction is given below:

In a 250 ml. three neck round-bottom flask equipped with a true bore stirrer, Dean-Stark take-off tube fitted with a reflux condenser guarded by a drying tube containing anhydrous calcium chloride, and a parallel side arm adapter fitted with a 250 ml. dropping funnel guarded by a tube containing anhydrous calcium chloride and a thermometer, was placed 4.2562 g. (0.02005 moles) of <u>p</u>-cresyl benzoate in 75 ml. of modium dried toluene.

To this ester mixture is added by means of the dropping funnel 30 ml. of the Grignard containing 0.758 millieq./ml. or total of 22.7 millieq. or 0.0227 moles. The Grignard was added with agitation over a 10 minute period. The ether Was removed, without concentrating the solution by adding

30 ml. of sodium dried toluene to the reaction mixture and collecting the ether in a Dean-Stark trap. After the ether was removed, the system was refluxed for one hour at 110°C and the reaction quenched with 60 ml. of a 10% hydrochloric acid solution. After vigorously agitating the reaction mixture for 15 minutes it was transferred to a 250 ml. separatory funnel and the water layer discarded. The organic layer was washed twice with 100 ml. portions of distilled water, twice with 100 ml. portions of a 5% potassium hydroxide solution and three times with 100 ml. of distilled water. The reaction mixture was returned to the original reaction flask and the water remaining was azeotropically removed by the Dean-Stark trap. The reaction mixture was allowed to cool and transferred to a 250 ml. volumetric flask, made to volume with sodium dried toluene and then transferred to a glass stoppered bottle.

All the other esters were caused to react using identical conditions. The concentrations of the esters and Grignard used in these reactions are given in Table II.

The yields of ketone and alcohol and the amount of unreacted ester obtained in each reaction will be given under Analysis of Products.

Analysis of Products

The principal products in the reactions of mesitylmagnesium bromide with the aryl esters prepared are diaryl

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Reaction	Concentr	ations Foles/Liter
	Ester	Grignard Reagent
Fhenyl benzoate	0.2000	0.2625
Phenyl o-methylbenzoate	0.2005	0.2079
Fhenyl p-methylbenzoate	0.2000	0.2625
Phenyl <u>o</u> -ethylbenzoate	0.2000	0.2052
Phenyl o-isopropylbenzoate	0.2010	0.2181
o-Cresyl benzoate	0.2005	0.2274
<u>o-Cresyl o-methylbenzoate</u>	0.2004	0.2274
o-Cresyl p-methylbenzoate	0.2004	0.2052
o-Cresyl o-ethylbenzoate	0.2001	0.2079
o-Cresyl o-isopropylbenzoate	0.2000	0.2181

INITIAL CONCENTRATIONS OF REAGENTS IN REACTIONS OF RESITYLNAGNESIUM BROWIDE WITH ARYL ESTERS

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ketones and triaryl tertiary sloohols. In all cases unreacted ester remained at the end of the reaction. These three organic compounds were determined by infrared analysis using a Perkin-Elmer Nodel 21 Double Besu Infrared Spectrophotomater. The three standards used to determine these compounds were phenyl benzoate absorbing at 5.75 microns, benzophenone absorbing at 6.00 microns, and triphenyl carbinol absorbing at 2.80 microns. Standard solutions of these substances dissolved in toluene were prepared and run on the Perkin-Elmer Infrared Spectrophotometer. Calibration curves were then prepared by plotting transmittancy versus concentration. These calibration curves were used for all of the other ketones, alcohols and esters prepared during this investigation. The justification for using one member of the series as the infrared analytical standard in determining the other members of the series has been discussed by Bellamy (22).

To determine if there was any interference between ester, ketone and alcohol in the infrared absorption, a known colution was made up containing 0.033 moles of phenyl benzoate, triphenyl carbinol and benzophenone. This solution was run on the Perkin-Elmer Infrared Spectrophotometer. The results found were 0.034 moles of the alcohol, 0.034 moles of the ketone and 0.033 moles of the ester. These results indicate that there was no interaction among the three compounds.

The infrared analysis of the ketone and ester were checked by volumetric methods using hydroxylamine hydroohloride in pyridine for the ketone and hydrolysis with standard base in ethylene glycol for the ester. The results of the analysis of the reaction mixtures are given in Tables III and IV.

INFRARED METHOD

Determination of Ketones

A calibration curve for ketones was made using the absorption at 6.00 microns. Benzophenone was used as the standard on the Perkin-Elmer Model 21 Infrared Spectrophotometer using 0.495 mm. sodium chloride solution cells. The eight solutions used for calibration were made up in sodium dried toluene. They were 0.0500, QD250, 0.0200, 0.0125, 0.0100, 0.0050, 0.0025 and 0.0010 moles per liter.

The method of calibration was as follows: Both the reference and sample cells were filled with sodium dried toluene and the zero percent and hundred percent curves were made from 2 to 7 microns.

Each of the eight solutions were then run scanning from 2 to 7 microns and the peak height was found at 6.00 microns. To find the transmittancy, the peak height in cms. was divided by the distance between zero and hundred percent lines in cms. at 6.00 microns and these values plotted on graph paper to give concentration in moles per liter versus transmittancy.

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TABLE III

INFRARED DETERMINATION OF DIARYL KETONES, TRIARYL TERTIARY ALCOHOLS AND UNREACTED AFYL ESTERS IN REACTIONS OF MESITYLWAGNESIUM BROWIDE WITH ESTERS

Reaction	Ketone (Moles)	Tertiary Alcohol (Moles)	Unreacted Ester (Noles)
Phenyl benzoate	0.00570	0.00206	0.00765
Fhenyl <u>o-methylbenzoate</u>	0.00450	0.00177	0.00940
Phenyl o-ethylbenzoate	0.00428	0.00220	0.01080
Phenyl <u>o-isopropylbenzoate</u>	0.00460	0.00220	0.01130
Phenyl <u>p</u> -methylbenzoate	0.00698	0.00230	0.00680
o-Cresyl benzoate	0.00420	0.00170	0.01040
<u>o-Cresyl</u> <u>o-methylbenzoate</u>	0.00270	0.00230	0.01140
<u>o-Cresyl</u> <u>o</u> -ethylbenzoate	0.00370	0.00152	0.01360
<u>o-Cresyl</u> <u>o-isopropylbenzoate</u>	0.00360	0.00156	0.01450
<u>o-Cresyl</u> <u>p-methylbenzoate</u>	0.00500	0.00193	0.00880

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TABLE IV

DETERMINATION OF DIARYL KETONES BY HYDROXYLAMINE HYDRO-CHLORIDE IN PYRIDINE AND OF UNREACTED ARYL ESTERS BY HYDROLYSIS OF ESTER WITH STANDARD BASE IN ETHYLENE GLYCOL FOR THE FOLLOWING REACTION MIXTURE

Reaction	Ketone (Woles)	Unreacted Ester (Moles)
Phenyl o-methylbenzoate	0.00461	0.00957
Phenyl <u>o-isopropylbenzoate</u>	0.00470	0.01130
o-Cresyl benzoate	0.00437	0.01030
<u>o-Cresyl o-ethylbenzoate</u>	0.00381	0.01300

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Table V gives the measured transmittancy for each of the standard solutions used. Figure 1 is the calibration curve obtained from the data of Table V.

Analysis of the ketones in the reaction mixture was made at two concentrations in each case. The first concentration was identical to that of the reaction mixture diluted to 250 ml. with toluene, the second concentration, half that of the first, was obtained by diluting a 5 ml. sample of the first concentration to 10 ml. using toluene as the diluent. The solution cells and general procedure used were the same as those employed in the calibration studies.

The results of the infrared analysis for ketones in each of the reaction mixtures are given in Table VI.

Determination of Alcohols

A calibration curve for alcohols was made using the absorption at 2.80 microns. Triphenyl carbinol was used as the standard. The procedure was the same for the ketones except the solutions used were 0.1000, 0.0500, 0.0250, 0.0200, 0.0125, 0.0100, 0.0050 and 0.0025 moles per liter. Table VII gives the measured transmittancy for each of the standard alcohol solutions and Figure 2 is the calibration curve obtained from the data of Table VII.

Since the yield of alcohol was very small in all reactions studied, it was necessary to concentrate the reaction mixture for alcohol analysis. This was done as

TABLE V

Concentration of Solution in Moles/liter	Transmittancy"
0.0500	0.182
0.0250	0.366
0.0200	0.428
0.0125	0.587
0.0100	0.661
0.0050	0.814
0.0025	0.916
0.0010	0.978

INFRARED TRANSMITTANCY FOR STANDARD SOLUTIONS OF BENZOPHENCNE IN TOLUENE

*Obtained from Perkin-Elmer Model 21 Infrared Spectrophotometer at 6.00 microns using 0.495 mm. sodium chloride solution cells.



TABLE VI

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RESULTS OF INFRAREI IN REAC	DETERMINATIONS TION MIXTURES	OP	KETONES
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Reaction Lixture of	Concent Ketone (a Method 18	tration of oles/liter) wethod 20	Yield of Ketone ≴ Theoretical
Phenyl benzoate	0.0057	0.0056	28.5
Phenyl <u>o-methylbenzoate</u>	0.0046	0. 004 4	23.0
Ph enyl <u>p-methylbenzoate</u>	0.0069	0.0065	34.5
Phenyl <u>o</u> -ethylbenzoate	0.0043	0.0041	21.5
Phenyl <u>o</u> -isopropylbenzoate	0.0046	0.0045	23.0
<u>o-Cresyl benzoate</u>	0.0043	0.0041	21.5
<u>o-Cresyl</u> <u>o-methylbenzoate</u>	0.0027	0.0027	13.5
<u>o-Cresyl</u> <u>p-methylbenzoate</u>	0.0050	0.0044	25.0
<u>o-Cresyl</u> <u>o-ethylbenzoate</u>	0.0037	0.0035	13.5
<u>o-Cresyl</u> <u>o-1sopropylbenzoate</u>	0.0036	0.0036	17.7

- a) Method 1 concentration obtained from original 250 ml. of reaction mixture.
- b) Method 2 concentration obtained from diluting 5 ml. of original to 10 ml. with toluene as diluent.

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TABLE VII

INFRARED	TRANSLITTA	NCY FOR	STANDARD	SOLUTIONS
OF	TRIPHENYL	CARBINOL	IN TOLIN	

Concentration of Solution in Moles/liter	Transaittanoy"
0.1000	0.540
0.0500	0.734
0.0250	0.861
0.0200	0.883
0.0125	0.924
0.0100	0.939
0.0050	0.980
0.0025	0.994

*Obtained from Perkin-Elmer Model 21 Infrared Spectrophotometer at 2.80 microns using 0.495 mm. sodium chloride solution cells.
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follows: One hundred milliliters of the original 250 ml. reaction mixture was pipetted into a 250 ml. distillation flask and approximately 70 ml. of the toluene was distilled and discarded. The residue in the flask was diluted to 50 ml. in a volumetric flask with toluene, thus increasing the concentration by a factor of 2. After concentrating the solution, the infrared determinations were made by exactly the same procedure used for the ketones.

The results of the alcohol determinations are given in Table VIII.

Determination of Unreacted Ester

A calibration curve for the esters was made using the absorption at 5.75 microns. Fhenyl benzoate was used as the standard. The concentration of the solutions and the procedure used were identical to that used for the ketones.

Table IX gives the measured transmittancy for each of the standard solutions and Figure 3 is the calibration curve obtained from the data of Table IX.

Two analyses for unreacted ester in each of the reaction mixtures were made exactly as for the ketone. The reason for this was that some of the esters were too concentrated in the original 250 ml. of the reaction mixtures to run undiluted. The analyses were made and the results for the ester determination are given in Table X.

TABLE VIII

RESULTS OF INFRAPED DETERMINATIONS OF ALCOHOLS IN REACTION MIXTURES

Reaction Mixture of	Concentration of Alcohol (Moles/liter)	Yield of Ketone % Theoretical
Phenyl bensoate	0.0021	10.5
Phenyl o-methylbenzoate	0.0018	9.0
Phenyl <u>p-methylbenzoate</u>	0.0023	11.5
Phenyl <u>o-ethylbenzoate</u>	0.0022	11.0
Phenyl <u>0-1sopropylbenzoate</u>	0.0022	11.0
o-Cresyl benzoate	0.0017	8.5
<u>o-methylbenzoate</u>	0.0023	11.5
<u>p-Cresyl</u> <u>p-methylbenzoate</u>	0.0019	9.5
<u>o-ethylbenzoate</u>	0.0015	7.5
-Cresyl <u>0</u> -isopropylbenzoate	0.0016	8.0

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TABLE IX

INFRARED TRANSMITTANCY FOR STANDARD SOLUTIONS OF PHENYL BUNLOATE IN TOLUENE

Concentration of Solution in Moles/liter	Transmittancy*
0.0500	0.194
0.0250	0.328
0.0200	0.418
0.0125	0.549
0.0100	0.617
0.0050	0.783
0.0025	0.889
0.0010	0.951

*Obtained from Perkin-Elmer Model 21 Infrared Spectrophotometer at 5.75 microns using 0.495 mm. sodium chloride solution cells.

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TABLE X

RESULTS	OP INFRARED ESTERS IN	DETERMINATIONS OF THE THE FRACTION MINTURE	UNREACTED
		TUT PERCITON MIXIONES	

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Reaction Mixture of	Concent: Ester (M Lethod 1	ration of oles/liter) wethod 25	Tield of Unreacted Ester & Theoretical
Phenyl benzoate	0.0077	0.0074	38,5
Phenyl <u>o-methylbenzoate</u>	0.0093	0.0094	47.0
Phenyl <u>p-methylbenzoate</u>	0.0063	0.0057	34.0
Ph enyl <u>o</u> -ethylbenzoate	0.0108	0.0094	54.0
Phenyl <u>o-isopropylbenzoate</u>	0.0113	0.0098	56.5
<u>o-Cresyl bensoate</u>	0.0104	0.0099	5 2.0
<u>o-Gresyl</u> <u>o-methylbenzoate</u>	0.0114	0.0109	57.0
<u>o-Cresyl</u> <u>p-methylbensoate</u>	0.0087	0.0093	43.5
<u>o-Cresyl</u> <u>o-ethylbenzoate</u>	0.0136	0.0124	68.0
<u>o-Cresyl</u> <u>o-isopropylbenzoate</u>	0.0145	0.0130	72.5

- a) Method 1 concentration obtained from original 250 ml. of reaction mixture.
- b) Method 2 concentration obtained from diluting 5 ml. of original to 10 ml. with toluene as diluent.

DETERMINATION OF DIABYL KETCHES BY HYDROXYLAMINE HYDROCHLORIDE PETHOD

For the purpose of checking the results obtained by infrared analysis, the oximes of the diaryl ketones were prepared by the method of Byrant and Smith (23) for the reaction mixtures of mesitylmagnesium bromide with phenyl <u>o-methyl-</u> benzoate, phenyl <u>o-isopropylbenzoate</u>, <u>o-cresyl benzoate</u> and o-cresyl o-ethylbenzoate.

A 50 ml. aliquot of the reaction mixture in 250 ml. toluene was pipetted into a Citrate of Magnesia bottle containing 25 ml. of 0.5 N hydroxyl amine hydrochloride in 80% ethanol and 100 ml. of a 20% pyridine in ethanol solution containing 0.02% bromophenol blue indicator. The samples and two blanks containing only toluene with the reagents were heated in a steam bath at 95°C for 4 hours. After heating, the samples and blanks were allowed to cool to room temperature and the samples were titrated to the color of the blank with 0.222 N potassium hydroxids in ethanol. Along with the unknown samples, two knowns were analyzed containing 0.00350 moles and 0.00249 moles of benzophenone. An example of the method of calculating the amount of ketone in the samples is given below for the <u>0</u>-cresyl benzoate reaction mixture:

moles of ketone = $\frac{\text{milliliters of base x normality}}{50/250 \times 1000}$ moles of ketone = $\frac{3.94 \text{ ml. x } 0.992}{0.2 \times 1000} = 0.00437 \text{ moles}$

For the two known samples, results obtained were 0.00350 moles ketone for the known of 0.00350 moles and 0.00249 moles for the known of 0.00249 moles. The results obtained for the ketones in the reaction mixtures by the hydroxylamine hydrochloride method are given in Table IV and agree within experimental error with those obtained by infrared analysis which are given in Table III.

DETERMINATION OF THE UNREACTED AFYL ESTERS BY HYDROLYSIS

The moles of unreacted ester were determined by hydrolysis in four of the reaction mixtures for the purpose of checking the results obtained by infrared analysis. The reaction mixtures used were phenyl o-methylbenzoate and phenyl O-isopropylbensoate and o-cresyl benzoate and o-cresyl o-ethylbenzoate. Hydrolysis was accomplished by pipetting a 50 ml. aliquot of the reaction mixture which has been diluted to 250 ml. into a 250 ml. reflux flask containing 25 ml. of a 0.318 N potassium hydroxide in 90% ethylene glycol 10% water solution. A reflux condenser was attached and the mixture was caused to reflux for 24 hours. The mixture was then allowed to cool to room temperature and was transferred to a 250 ml. beaker using 50 ml. of ethanol as a washing agent. Two blanks containing toluene and two known solutions containing 0.00350 and 0.00248 moles of phenyl bensoate in toluone were hydrolysed along with the reaction mixtures.

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The mixtures were titrated with 0.253 N hydrochloric acid in ethanol employing a Beckman Model G pH meter equipped with a glass and a calomel electrode. The equivalence point of the blank, known and unknown mixture was found by plotting pH versus milliliters of hydrochloric acid added. The difference in the titration between the blank and known or unknown mixture was the measure of the milliequivalents of the aryl acid and hence equal to the milliequivalents of the unreacted aryl ester. An example of the method of calculating the moles of unreacted ester is given below for the <u>o</u>-cresyl benzoate reaction mixture.

moles of unreacted ester =

moles of o-cresyl benzoate =

$$\frac{(30.95 \text{ ml. } x \text{ 0.253}) - (22.73 \text{ ml. } x \text{ 0.253})}{0.2 \text{ x 1000}} =$$

0.01030 moles

For the two known samples, results obtained were 0.00349 moles ester for the known of 0.00350 moles and 0.00247 moles ester for the known of 0.00248 moles. The results obtained for the unreacted esters in the reaction mixtures by hydrolysis are given in Table IV and agree within experimental error with those obtained by infrared analysis which are given in Table III.

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RESULTS

The results of this study will be presented under four headings: 1) the percent of ester reacting; 2) the percent of ketone complex* formed, calculated from the yield of ketone formed plus the yield of alcohol formed; 3) the percent of this ketone complex reacting to form alcohol; and 4) the percent of Grignard reagent reacting, calculated from the yield of ketone formed plus twice the yield of alcohol formed. (It takes two molecules of Grignard reagent to form one molecule of alcohol.) In general, the results may be summarized as follows:

The percent of ester reacting appears to decrease with increasing steric hindrance in the esters, while the other factors, (percent of ketone complex formed, percent of ketone complex reacting to form the tertiary alcohol and percent of Grignard reagent reacting) are relatively insensitive to the steric changes in the aroyl portion of the ester. Significant changes in these factors appear with substitution in the ortho position of the aryloxy portion of

[&]quot;The ketone complex is defined as the intermediate resulting when one molecule of Grignard reagent reacts with one molecule of ester. This complex may decompose to give the ketone, it may react with more Grignard reagent to give the tertiary alcohol or it may remain intact until hydrolysis at which time it will decompose to give the ketone.

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the ester. The results are summarized in Table XI and will be discussed in more detail in the paragraphs which follow.

Percent Ester Reacting

A marked decrease in the percent of ester reacting is observed when sterio hindrance in either the aroyl or aryloxy portion of the ester is increased. The magnitude of this decrease can be seen by comparing the values obtained from the phenyl benzoate reaction with that from the phenyl <u>o</u>-isopropylbenzoate reaction, 61.7% in the former against 43.6% in the latter and by comparing the values obtained from the phenyl <u>o</u>-ethylbenzoate reaction with that from the <u>o</u>-cresyl <u>o</u>-ethylbenzoate reaction, 46% on the former compared to 32% in the latter. Both phenyl and <u>o</u>-cresyl <u>p</u>-methylbenzoate reacted more rapidly with the Grignard reagent than their corresponding phenyl and <u>o</u>-cresyl benzoate analogues.

Percent Ketone Complex Formed

The results are discussed under the heading Percent Ketone Complex Formed rather than under Percent Ketone Formed because presumably each molecule of alcohol produced consumes one molecule of the ketone or ketone complex. The total moles of ketone or ketone complex produced is measured by adding the number of moles of alcohol and ketone. The values for the percent ketone complex formed were obtained by dividing the total moles of ketone or ketone complex produced

TABLE XI

PERCENT ESTER REACTING, PERCENT KETONE COMPLEX FORMED, I-LECENT KETONE COMPLEX CONVERTED TO ALCOMOL AND PERCENT GRIGNARD REACTING IN THE REACTIONS OF MESITYL-MAGNESIUM BROMIDE WITH THE ARYL ESTERS

Ester	X Ester Reacting	<pre>% Ketone Complex Formed</pre>	<pre>% Ketone Complex Converted To Alcohol</pre>	% Grignard Reacting
Phenyl benzoate	61.7	38.8	26.5	49.1
Phenyl <u>o-methylbenzozte</u>	53.0	31.4	28.2	40.2
Phenyl o-ethylbenzoate	46.0	32.4	33.9	43.4
Phenyl <u>o-isopropylbenzoate</u>	43.5	34.0	32.3	45.0
Phenyl <u>p-methylbenzoate</u>	65.0	46.4	24.7	57.9
o-Cresyl benzoate	48.0	29.5	28.8	38.0
<u>o-Cresyl</u> <u>o-methylbenzoate</u>	43.0	25.0	46.0	36.5
<u>o-Cresyl</u> <u>o-ethylbenzoate</u>	32.0	26.1	29.1	33.7
<u>o-Cresyl</u> <u>o-isopropylbenzoate</u>	27.5	25.8	30.2	33,6
<u>o-Cresyl</u> <u>p-methylbenzoate</u>	56.0	34.7	27.9	44.3

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by the maximum number of moles of ketone which could potentially be formed.

Table XI indicates that the percent of ketone complex formed is virtually independent of the size of the ortho aroyl substituent provided this substituent is not a hydrogen atom. Comparing the values obtained for the phenyl with those for the <u>o</u>-cresyl ester, it can be seen that there is a significant decrease in reactivity of the <u>o</u>-cresyl compounds over their phenyl analogues. The magnitude of this decrease can be visualized by comparing the values obtained for the phenyl <u>o</u>-isopropylbenzoate reaction with that for the <u>o</u>-cresyl <u>o</u>-isopropylbenzoate reaction, 34% in the former against 25.8% in the latter. Here, as in the case of percent esters reacting, the results indicate that the <u>p</u>-methylbenzoates are more reactive than the other esters in the formation of the ketone complex.

Percent Ketone Complex Reacting to Form the Alcohol

To form a molecule of alcohol, one molecule of ketone or ketone complex must be consumed. The percent of ketone complex reacting to form alcohol is found by dividing the number of moles of alcohol produced by the total number of moles of ketone complex formed.

Table XI indicates that the percent of ketone complex reacting to form alcohol is not appreciably effected by the ortho aroyl substituent, provided the substituent is not a

hydrogen atom. There is a slight increase in the percent of ketone complex reacting when comparing ortho hydrogen to ortho alkyl substituents. This may be interpreted as a loosening of the bonds of the complex by the ortho alkyl substituent, or the electron density at the reacting center is increased by the ortho alkyl substituent. The magnitude of this increase can be seen when comparing the values obtained from the phenyl benzoate reaction to that from the phenyl o-ethylbenzoate reaction, 25.6% in former against 33.9% in the latter. The same trends are noted in comparing the orthosubstituents in the o-cresyl esters to o-cresyl benzoate. But upon comparing the phenyl and o-cresyl esters as to the percent ketone complex reacting, it is found that the ortho aryloxy substituent does not appreciably effect the reactivity, except in the case of the o-cresyl o-methylbensoate which is unexplainable. The results indicate that the complex formed from the phenyl and o-cresyl p-methylbenzoates are less reactive than their corresponding phenyl and o-cresyl banzoate analogues and less complex is converted to alcohol.

Percent Grignard Reagent Reacting

The percent of Grignard reagent reacting is found by adding the moles of ketone formed to twice the moles of alcohol formed and dividing this sum by total moles of Grignard that could react. The Grignard is the limiting factor because it is in equal moler proportion to the esters

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and it has two methods of reacting. It reacts with the ester to form the complex and can then react with the complex to form the alcohol.

The results in Table XI indicate that the percent Grignard reacting is virtually independent of the size of the ortho aroyl substituent in both the phenyl and <u>o</u>-oresyl esters. There is a decrease in the percent Grignard reacting when comparing or the hydrogen to or the alkyl substitution. The magnitude of this decrease can be seen by comparing the values obtained from the phenyl benzoate reaction with that from phenyl <u>o</u>-methylbenzoate reaction, 49.1% in former against 40.2% in latter. There is also a decrease in reactivity when comparing phenyl esters to <u>o</u>-cresyl esters. This can be seen by comparing the values obtained from phenyl <u>o</u>-isopropylbenzoate reaction, 45.0% in former against 33.6% in latter.

The results indicate that the Grignard reagent is more reactive toward the <u>p</u>-methylbenzoates than their corresponding <u>o</u>-alkyl benzoate analogues.

4) Toluene was used as a reaction medium for two reasons: a) to avoid the complex formation which occurs between the Grignard reagent and ethers. This complex would introduce an uncontrolled steric factor; b) to acquire the higher reaction temperatures obtainable by using toluene as the solvent.

II. Table XII summarizes the results as relative reactivities compared to phenyl benzoate. The table shows that the relative reactivities of the Grignard reagent, the ester, and the ketone complex are remarkably constant for the ortho substituted phenyl esters. Comparing the results obtained for the phenyl esters with those of the o-cresyl esters indicates that the o-cresyl esters are less reactive by about 20%. But the ketone complex formed from the o-cresyl esters apparently reacts more readily with the Grignard reagent than the complex formed from the phenyl esters. This may be due to the loosening of the ketone complex by a steric effect or an electrical effect of the o-methyl substituent of the cresyl group. The electron donating effect of this o-methyl group would increase the basicity of the aryloxy oxygen atom of the ester. This should favor a greater reactivity of this oxygen atom toward the magnesium atom of the Grignard reagent. The steric effect due to the o-methyl group in the aryloxy portion of the ester causes the bonds of the complex to be lengthened thereby making it easier for the second

4) Toluene was used as a reaction medium for two reasons: a) to avoid the complex formation which occurs between the Grignard reagent and others. This complex would introduce an uncontrolled sterio factor; b) to acquire the higher reaction temperatures obtainable by using toluene as the solvent.

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TABLE XII

	است بر ۱۹۹۰ کار منظوم می می می از میگرد. مربوع به کرده کار میزون مورد و معمد اس	الاستان، مید کارد می بنداند. ۲۰۰ میرود مید مالاد دان میزود شدهد .				ر)» د خطیباری بران براند. این اطراف براند ، در وال سالی مارید مارید.
	React of F	tivity Ister*	Feactivity of Ketone Complex**		Reactivity of Grignard	
Reproste	1		1		1	
Denzoate		0.759		1.086		0.774
o-Hethyl-	0.808		1.065		0.819	
benzoate		0.644		1.734		0.744
a 1946-13	0.834		1.280		0.885	
bensoate		0.672		1.100		0.685
	0.875		1.220		0.916	
<u>o-Isopropyl-</u> benzoate		0.685		1.140		0.684
n-Hethyl.	1.191		0.934		1.179	
<u>p-Methyl-</u> bensoate		0.691		1.052		0.902

THE REACTIVITIES OF ECTER, KETCHE COMPLEX AND GRIGNARD, RELATIVE TO PHENYL BENZOATE



*Measured by the amount of ketone complex formed.

**Measured by the amount of alcohol formed.

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molecule of the Grignard reagent to attack the aryl carbon. This would then cause the bond between the aryl carbon and the aryloxy oxygen atoms to be broken and would remove this steric factor.

Some interesting comparisons can be made in the relative reactivities of the esters in these reactions.

One interesting comparison is that of phenyl benzoate, phenyl <u>o</u>-methylbenzoate and <u>o</u>-oresyl benzoate. From Table XII, it is observed that an <u>o</u>-methyl substituent on the aroyl portion of the ester decreases the reactivity of the ester by about 20%. When an <u>o</u>-methyl group is substituted on the aryloxy portion of the ester, the reactivity is decreased by about 25% as compared with the unsubstituted ester and 50% as compared with phenyl <u>o</u>-methylbenzoate. This would indicate that substitution on the aryloxy portion of the ester has a greater steric effect than substitution on the aroyl portion. Exactly the same trend is found for the reactivity of Grignard reagent.

Considering the ketone complex, it is found that the relative reactivities are approximately equal and that an <u>O-methyl</u> substitution on either aroyl or aryloxy portion of the ester has the same effect.

The comparison of the relative reactivities of the phenyl <u>o-methyl-</u> and <u>p-methylbenzoates</u> with phenyl and <u>O-eresyl benzoates is also of interest. From Table XII, it</u>
(a) a second state of the s

is seen that <u>o</u>-methyl substitution on the aroyl portion deereases the reactivity of the ester. On the other hand, <u>p</u>-methyl substitution shows an increase in reactivity of about 20% compared to the unsubstituted benzoates and an inerease of 40% compared with the <u>o</u>-methylbenzoates. Likewise, a 45% increase in reactivity is observed when comparing phenyl <u>p</u>-methylbenzoate to <u>o</u>-cresyl benzoate.

These increases in reactivity could be due to the electron donating effect of the p-methyl group, which makes the aroyl oxygen atom of the ester more basic and more reactive toward the magnesium atom of the Grignard reagent. Determinations of the amount of Grignard reagent reacting support these observations. Considering now the reactivity of the ketone complex, a decrease in reactivity is observed for the phenyl p-methylbenzoate compared to phenyl benzoate and phenyl <u>o</u>-methylbenzoate by about 10%. It was observed that the p-methyl group enhances the formation of the complex by its electron donating effects. But this same effect seems to be a detriment to the reactivity of the complex. This would suggest that the reactivity of the complex is governed more by sterie factors than by electrical factors.

Another interesting comparison is of phenyl and <u>g</u>-cresyl <u>g</u>-methylbenseates with phenyl and <u>g</u>-cresyl <u>p</u>-methylbenseates. It was observed that the phenyl <u>p</u>-methylbenseate was more reactive toward the Grignard reagent than phenyl

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o-methylbenzoate. On the other hand, the reactivities of the respective ketone complex was reversed. Considering the reactivities of the phenyl esters compared to the o-cresyl esters, it is observed that the reactivity of the ester and of the Grignard reagent de crease going from phenyl to o-cresyl. The largest decrease is observed for the transition from phenyl p-methylbenzoate to o-cresyl p-methylbenzoate. The magnitude of this decrease is about 30%. The reactivities for the transition from phenyl o-methyl- to o-cresyl o-methylbenzoate is decreased about 15%. On the other hand, the reverse of these transitions is observed for the reactivity of the ketone complex. The transition of phenyl o-methyl- to o-cresyl o-methylbenzoate has an increase of reactivity by about 70%, whereas, the transition of phenyl p-methyl- to o-cresyl p-methylbenzoate has an increase of only 10%. This would further indicate that the o-methyl group of the aryloxy portion of the ester has the greatest effect upon reactivity and that this effect is more steric than electrical in nature.

Also, there must be some electrical effects of the <u>p-methyl</u> substituent because the reactivity of the ketone complex, while it increases from phenyl to <u>o</u>-cresyl, is not as large an increase as for the <u>o</u>-methyl substituted esters. This electrical effect which increases the formation of the complex must also form a more stable complex by forming a

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charge cloud around the functional group of the complex which repels the second molecule of attacking Grignard reagent. Likewise, if the effect caused by <u>o</u>-methyl substitutent of aryloxy group (<u>o</u>-cresyl) was electrical rather than steric, the electron donating effects of the methyl group should make the reactivity of the <u>o</u>-cresyl <u>p</u>-methylbenzoate at least as reactive as the <u>o</u>-cresyl <u>o</u>-methylbenzoate, but this is not observed. The reactivity of the complex of the <u>o</u>-cresyl <u>p</u>-methylbenzoate is comparable to that of <u>o</u>-cresyl benzoate and, therefore, suggests that the increased reactivity of the <u>o</u>-cresyl <u>o</u>-methylbenzoate to the <u>o</u>-cresyl <u>p</u>-methylbenzoate is due only to steric rather than electrical factors.

The effects of further increasing the size of the <u>o</u>-alkyl substituent (on aroyl portion) does not appreciably change the reactivity of the ester compared to the <u>o</u>-methyl substituent, except in the case of the reactivity of the complex formed. This difference in reactivity of the complex is interpreted as due to the larger alkyl group causing more loosening of the complex as compared to the <u>o</u>-methyl group and thereby making it easier for the second molecule of Grignard reagent to attack the complex formed from the phenyl esters. In the case of the <u>o</u>-cresyl esters, this increased steric factor of alkyl groups on both the aryl and aryloxy portions hinder further attack by the highly hindered

Grignard, even though the complex may be loosened, the alkyl groups shield the acyl carbon from any further attack.

CONCLUSIONS

- Results of this study indicate that bulky groups in the two sterio areas studied, i.e. the aroyl portion of the ester and the aryloxy portion of the ester, hinder the reaction of a highly hindered Grignard reagent with esters.
- 2. The degree of hindrance has been shown to be virtually independent of the size of the ortho substituent due to the large degree of steric hindrance in the Grignard reagent.
- 3. Formation of the initial complex of the Grignard and ester has been shown to be virtually independent of steric factors of the order of magnitude employed in this study.
- 4. The formation of alcohol has been shown to be greatly influenced by steric factors in the aryloxy portion of the ester.

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