

A STUDY OF THE REFORMATSKY REACTION
WITH SOME
ORTHO AND PARA SUBSTITUTED BENZOPHENONES

by
Peter Charleson

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the degree of
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To
Dode and Len Charleson
My inifinitely patient parents

"And so I penned
It down, until at last it came to be,
For length and breadth, the bigness which you see."
(Bunyan - Pilgrim's Progress. Apology for his book.)

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation for the kind and patient guidance given by Dr. E.H. Charlesworth during the course of this research project; and to the National Research Council of Canada for a Summer Research Assistantship which facilitated this investigation.

ABSTRACT

In this study, fifteen β, β -diarylhydracrylic acids were synthesized from the condensation of a series of monosubstituted benzophenones with ethyl bromoacetate. Nine of these hydroxyacids are new compounds, viz.,

β -(2-aminophenyl)- , β -(4-aminophenyl)- ,
 β -(2-hydroxyphenyl)- , β -(4-hydroxyphenyl)- ,
 β -(2-bromophenyl)- , β -(4-bromophenyl)- ,
 β -(2-chlorophenyl)- , β -(4-fluorophenyl)- , and
 β -(4-nitrophenyl)- β -phenylhydracrylic acids.

The reaction of 2-chlorobenzophenone in benzene-toluene afforded a new unsaturated acid, β -(2-chlorophenyl)- β -phenylacrylic acid.

The failure of 2-nitrobenzophenone to react, was attributed to a steric effect.

It was demonstrated that the use of a low boiling, polar reaction solvent, improved the yields and purity of hydroxyacids over those from higher boiling, non-polar solvents.

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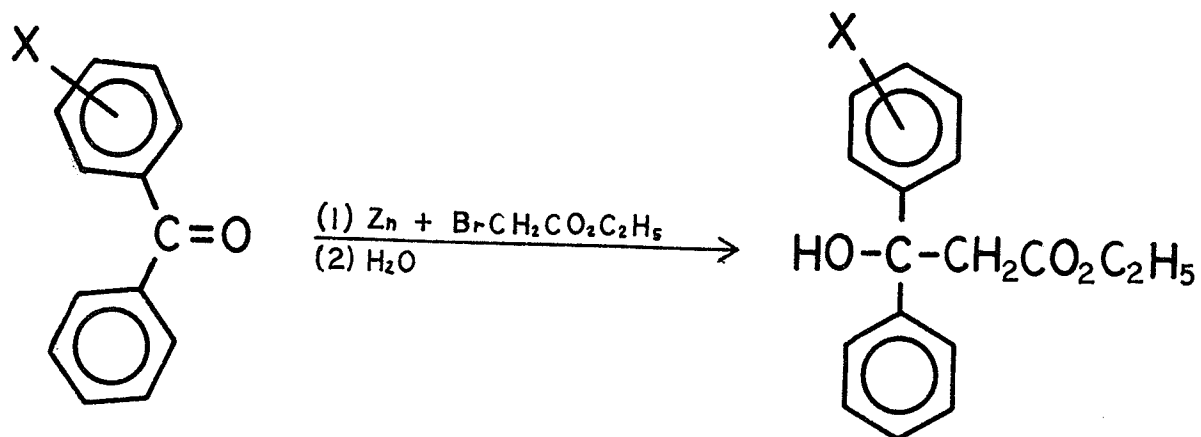
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INTRODUCTION

In 1958, Klemm and Bower (61) commented that "there has been very little investigation of the Reformatsky reaction employing diaryl ketones".

Inspired by this remark, the present research was undertaken. This entailed the condensation of a series of monosubstituted benzophenones with ethyl bromoacetate, in the presence of metallic zinc:



The three major objectives of this investigation have been:

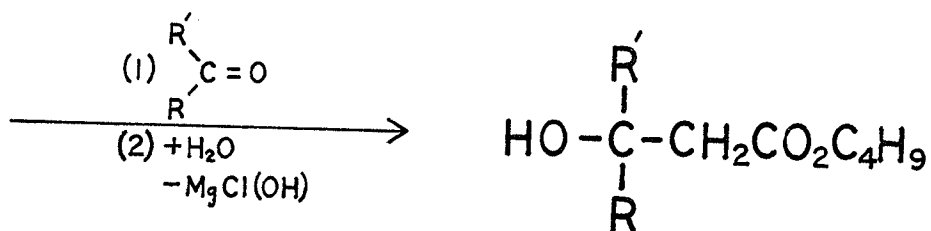
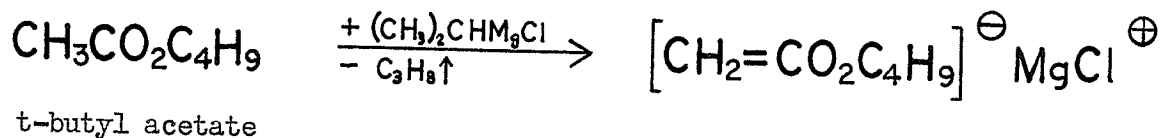
- 1) A study of the influences of substituents (attached to the 2- and 4- positions of the benzophenone nucleus) on the yields of products.
- 2) The comparison of the relative effectiveness of two dissimilar reaction solvents, viz., diethyl ether and benzene-toluene.
- 3) The isolation and characterization of the β, β -diarylhydraacrylic acids produced in this series of reactions.

Three minor objectives, arising out of problems encountered during the course of this research, were:

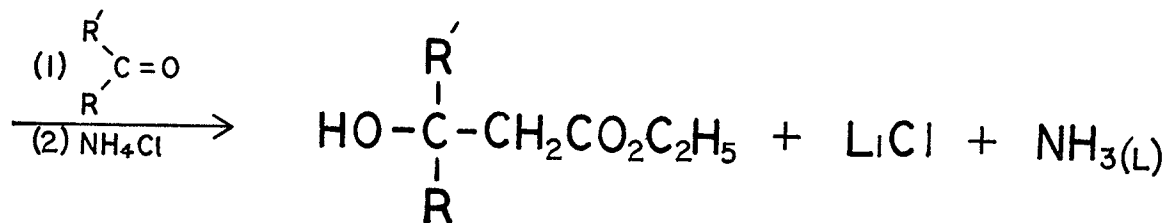
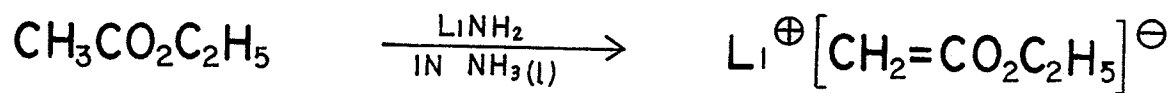
- 1) The attempt to react nitrobenzophenones in a two-stage Reformatsky reaction.
- 2) The attempt to employ anisole as a reaction solvent through the use of a reduced pressure technique.
- 3) A study of two zinc complexes in an endeavor to learn something of their solubilities in benzene and benzene-toluene.

From the beginning of this century, particularly within the last fifteen years, there have been new methods developed for the preparation of β -hydroxyesters. Two of these methods are now seriously challenging the Reformatsky reaction in this field of synthesis. They are analogous to the latter method in that they both involve the condensation of ester and carbonyl moieties in the presence of organo-metallic intermediates:

- 1) Condensation in the presence of Grignard reagents, (6, 54, 94, 95):



2) Condensation by means of lithium amide (36, 48):



Included in this thesis is information pertaining not only to the above Reformatsky analogs, but also to many earlier references that were not included in Shriner's review (89). The latter's compilation is almost twenty-five years old, and it is anticipated that the supplementary material in this thesis will become part of, or at least demonstrate the need for a new review.

LITERATURE SURVEY

THE REFORMATSKY REACTION

1. HISTORY

The introduction of organozinc compounds antedated that of the Reformatsky reagents by some thirty-six years. A brief chronology, giving the historical development of the Reformatsky reaction and its relation to the Grignard reaction, is given in the appendix (pages 93 - 94).

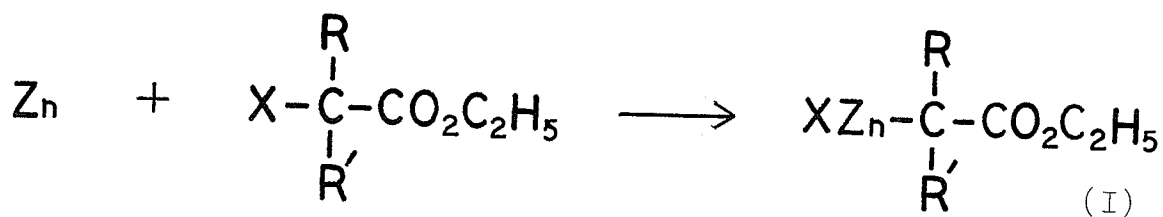
With the advent of the Grignard reaction in the early 1900's, all the other syntheses involving the use of the troublesome zinc dialkyls lost their importance. However, the Reformatsky reaction retained its significance because it was known that the use of haloester in the Grignard reaction did not lead to the formation of a β -hydroxyester (108).

At present, the only comprehensive review of the Reformatsky reaction is that by R.L. Shriner (89) which gives a fair coverage of the literature up to 1942. This review contains tables of results from some 157 condensations involving carbonyl compounds and haloesters. In the following survey, only those parts of the above review that are relevant to the present study are considered in any detail.

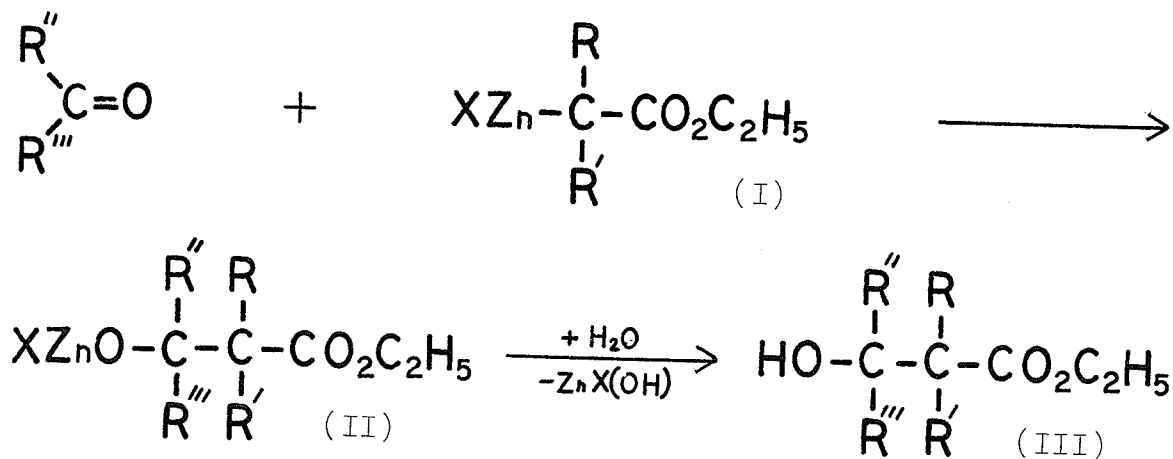
2. MECHANISM

The Reformatsky reaction is an organometallic modification of the aldol condensation. The oldest and most commonly accepted mechanism proposed (33, 80) for this reaction is as follows:

1) An α -haloester reacts with zinc to produce a halozinc ester (Reformatsky reagent):



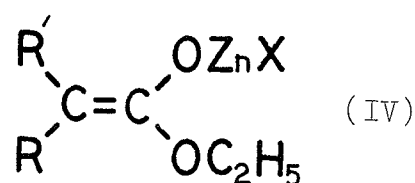
2) This halozinc ester (I) subsequently reacts with a carbonyl compound to form a halozinc enolate (zinc complex) which can be readily hydrolyzed to the β -hydroxyester:



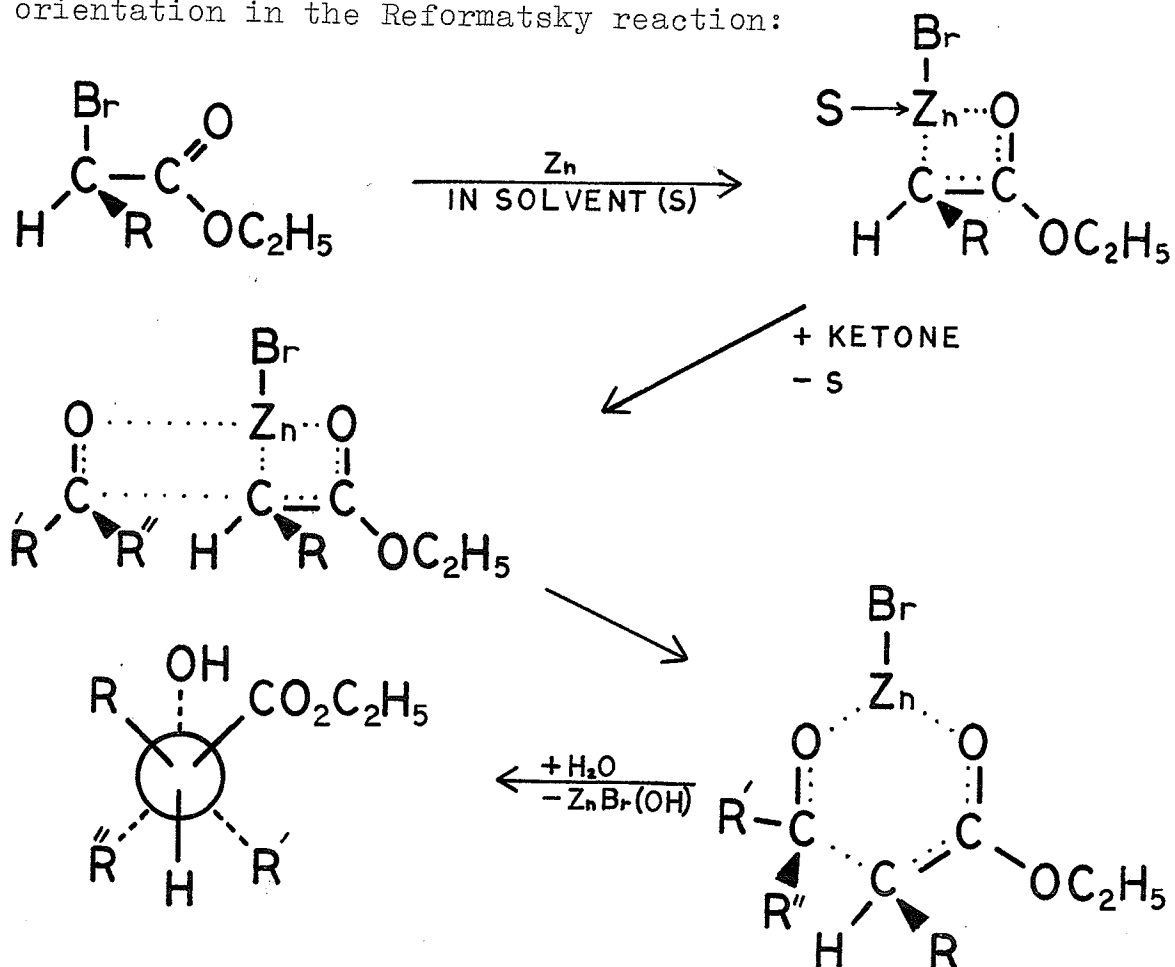
Evidence for the existence of the zinc complex (II)

has been provided by Dain (25) and by Dippy and Parkins (33). These investigators isolated and analyzed zinc complexes from Reformatsky reactions involving a variety of carbonyl compounds.

However, more recent studies (70, 103, 109) on the nature of the Reformatsky reagent strongly suggest that this reagent is in the form of an isomeric halozinc enol (IV) rather than that of the classical halozinc ester (I).



Using a similar enol formulation, Mousseron et al. (70) have proposed a cyclic mechanism to explain steric orientation in the Reformatsky reaction:

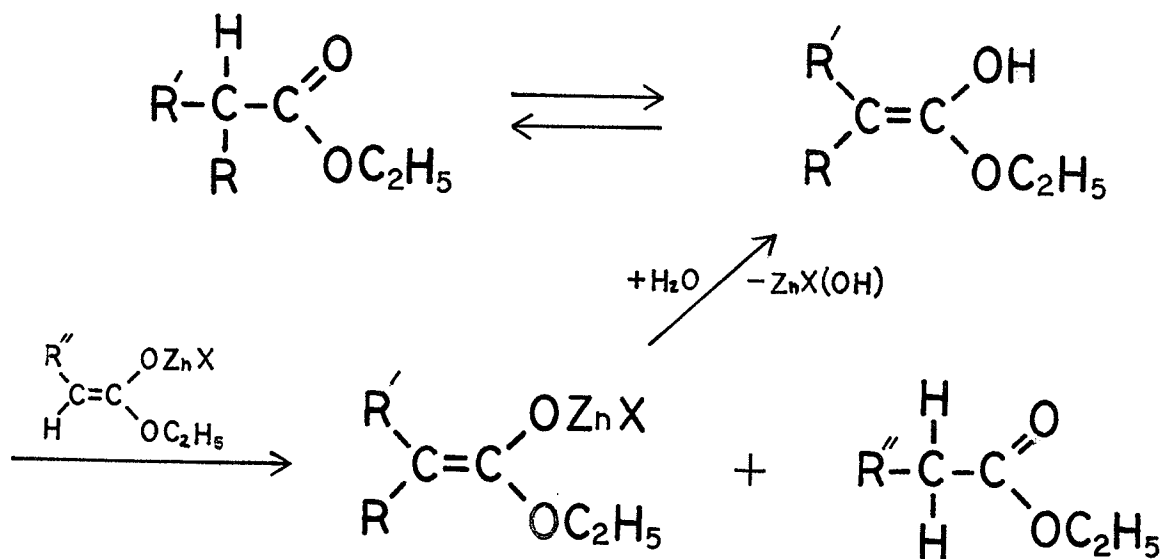


3. SIDE REACTIONS

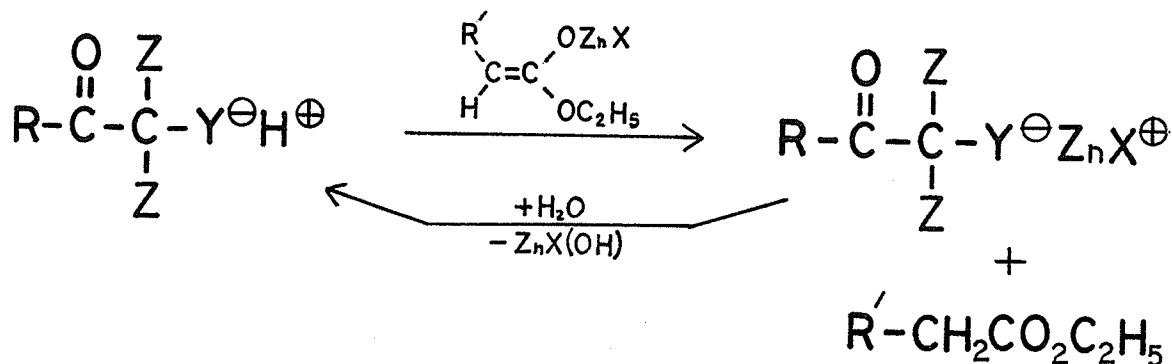
There are a number of side reactions attendant to the Reformatsky reaction which lower the yields of product by destroying the Reformatsky reagent (72, 89, 103). Only three of these side reactions are important enough to merit comment in this survey:

1) Dimerization of Reformatsky reagent (see pages 18-19).

2) Enolization of a carbonyl compound with an acidic hydrogen:



3) Proton transfer from a carbonyl compound containing a functional group with an acidic hydrogen:



4. REAGENTS

a) Activated Zinc

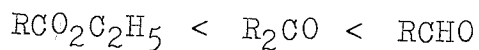
Many forms of metallic zinc have been used in the Reformatsky reaction. The literature abounds with an even greater number of procedures for cleaning the zinc prior to its addition to a reaction mixture, and for activating it in situ prior to initiation of the reaction proper. The following references are recommended for specific examples on this topic: (77, 89, 103).

b) Haloester

An examination of Shriner's review (89) revealed that the most commonly used haloester was ethyl bromoacetate. It has been demonstrated to be more reactive than the corresponding chloroester (67) and more stable and accessible than ethyl iodoacetate (16).

c) Carbonyl Compound

The reactivity of carbonyl compounds in the Reformatsky reaction is of the order:



As stated in the introduction, there have been many reports of Reformatsky reactions involving aldehydes, cyclic ketones, dialkyl ketones and alkyl aryl ketones, but very little work involving diaryl ketones has been reported (61). A chronology on the use of benzophenones in the Reformatsky reaction is to be found on pages 28 - 31.

The effect of substituents attached to the carbonyl substrate on the reactivity of the latter in the Reformatsky reaction, is yet another area of study which has received little attention. In 1957, Bohlmann (17) carried out Reformatsky syntheses with methyl γ -bromocrotonate and a series of substituted benzaldehydes. He concluded that inductive and mesomeric effects appeared to be without great influence, and that the unreactivity of 3-nitrobenzaldehyde was due to steric hindrance by the nitro group. A year later, Vinograd and Vul'fson (104) reported that 2-, 3-, and 4-nitrobenzaldehydes reacted with ethyl bromoacetate and zinc to give yields of 41.9, 48.9 and 50.3% respectively, of the expected hydroxyesters.

Klemm and Bower (61) have carried out Reformatsky reactions with methoxy-substituted benzophenones. They accounted for the superior yields from benzophenone and 3-methoxybenzophenone in terms of electronic effects (see page 31).

5. SOLVENT AND TEMPERATURE EFFECTS.

1887

The first Reformatsky reaction (page 95) was performed by heating the reactants in the absence of an inert solvent. Later workers used inert solvents such as benzene or benzene-toluene as an aid to regulating the temperature of the reaction mixture and to facilitate stirring.

1931

Nieuwland and Daly (74) carried out reactions between α -chloroesters and aldehydes, esters, and ketones in the presence of zinc and copper powder. They employed three different solvent conditions, viz., benzene, xylene and no solvent. Some of their results are as follows:

CARBONYL COMPOUND	PRODUCT ISOLATED	% YIELD IN		
		BENZENE	XYLENE	NO SOLVENT
Benzaldehyde	Cinnamic acid	35	10	22
Acetophenone	Ethyl β -methyl- cinnamate	40	10.5	0
p-Methyl- acetophenone	Ethyl β -(p-tolyl)- β -methylacrylate	13	--	0

They effected a study of reaction times (varying from one to eight hours) and solvent and temperature effects by carrying out reactions between acetophenone and ethyl chloroacetate under different solvent conditions:

REACTION TIME	% YIELD IN		
	BENZENE	XYLENE	NO SOLVENT
1 hour	42	28	14
8 hours	38	10.5	0

They observed that in xylene, the reaction product was insoluble and coated the zinc in the bottom of the flask. On the other hand, the reaction products were completely soluble in benzene.

A reaction involving 4-methoxyacetophenone with ethyl phenylchloroacetate in benzene failed to yield any hydroxy-ester. However, when sufficient benzene was added to regulate the temperature at 98-100°C, synthesis was effected.

1939

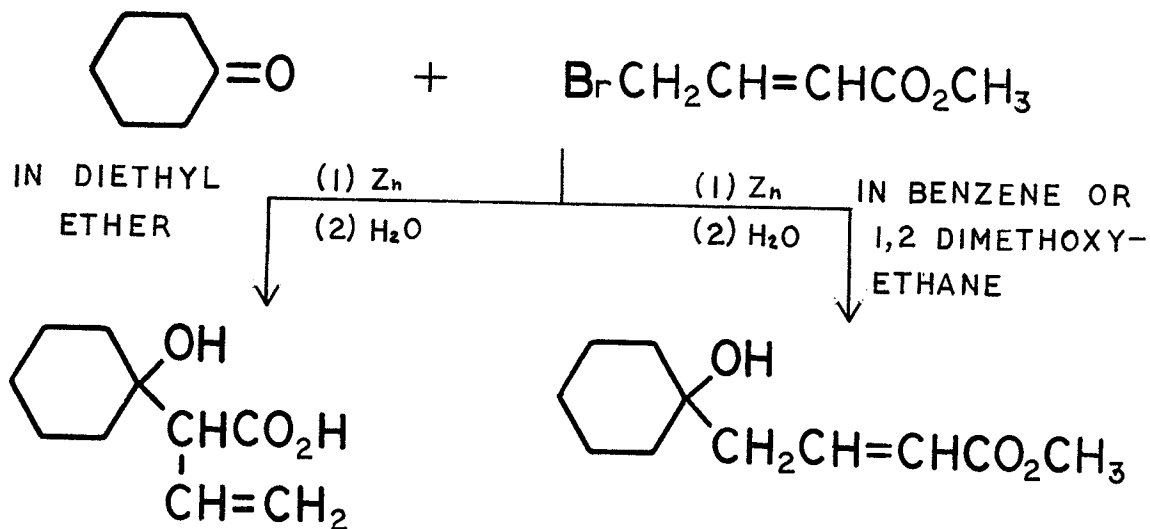
Natelson and Gottfried (71), after examining the literature, concluded that the best yields were obtained when the concentration of the reactants in the Reformatsky reaction was such as to give a reaction temperature in the range 95-105°C. They suggested that the use of benzene-toluene (ca. 1:1) as a solvent was a convenient way of achieving and maintaining the reflux temperature of the reaction mixture within this optimum range.

1951

Miller and Nord (67) observed that their Reformatsky reactions had to be carried out at the reflux temperature of the solvent to insure adequate reaction.

1953

Dreiding and Pratt (35) obtained moderate yields from γ -bromocrotonic esters in the Reformatsky reaction. However they observed that when the reaction solvent was changed from benzene or 1, 2-dimethoxyethane to diethyl ether, they obtained different products:



It was not determined whether the change in product structure was due to the temperature differential at which the reaction occurred, or whether other properties of the solvents were responsible. The fact that 1, 2-dimethoxyethane and benzene gave the same product, implied that the former possibility appeared to be favored.

1957

Cason and Fessenden (22) found that with sterically hindered ketones, Reformatsky reactions in benzene-ether solvent gave better yields than the conventional benzene or benzene-toluene solvents. The following results supported their observation:

CARBONYL COMPOUND	AVERAGE YIELDS (%) IN	
	BENZENE	BENZENE-ETHER
$\text{CH}_3-(\text{CH}_2)_5-\text{CHO}$	64	73
$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{C}_6\text{H}_{13}$	79	76
$\text{C}_3\text{H}_7-\overset{\text{O}}{\parallel}{\text{C}}-\text{C}_3\text{H}_7$	66	80
$\text{CH}_3-\underset{\text{CH}_3}{\text{CH}}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{CH}_3$	25	68

1958

Jacques and Weidmann (54) offered an explanation to account for the above results of Cason and Fessenden. They pointed out that organometallic compounds, such as Reformatsky reagents or Grignard reagents, are definitely known to be solvated by ether and that this solvation decreases the reactivity of the organometallic reagents. Thus, a non-polar solvent such as benzene would exert little or no indirect steric effect on the Reformatsky reagent. They suggested that ether would have a relatively greater influence on any side reaction involving the carbonyl group of the haloester than on the normal reaction involving the carbonyl group of the carbonyl compound (ketone or aldehyde). As a result there would be less side reaction(s) in benzene-ether solvent as compared to benzene alone. This solvent effect would thus account for the greater yields of normal products in the former solvent.

1958

Evans, (38) carried out a reaction between ethyl α -bromopropionate and 5, 8-dimethyl-1-tetralone in benzene-ether and obtained a yield of 73%. An identical reaction carried out in benzene by Hussey and Newman (53), ten years earlier, gave only a 17% yield.

1960

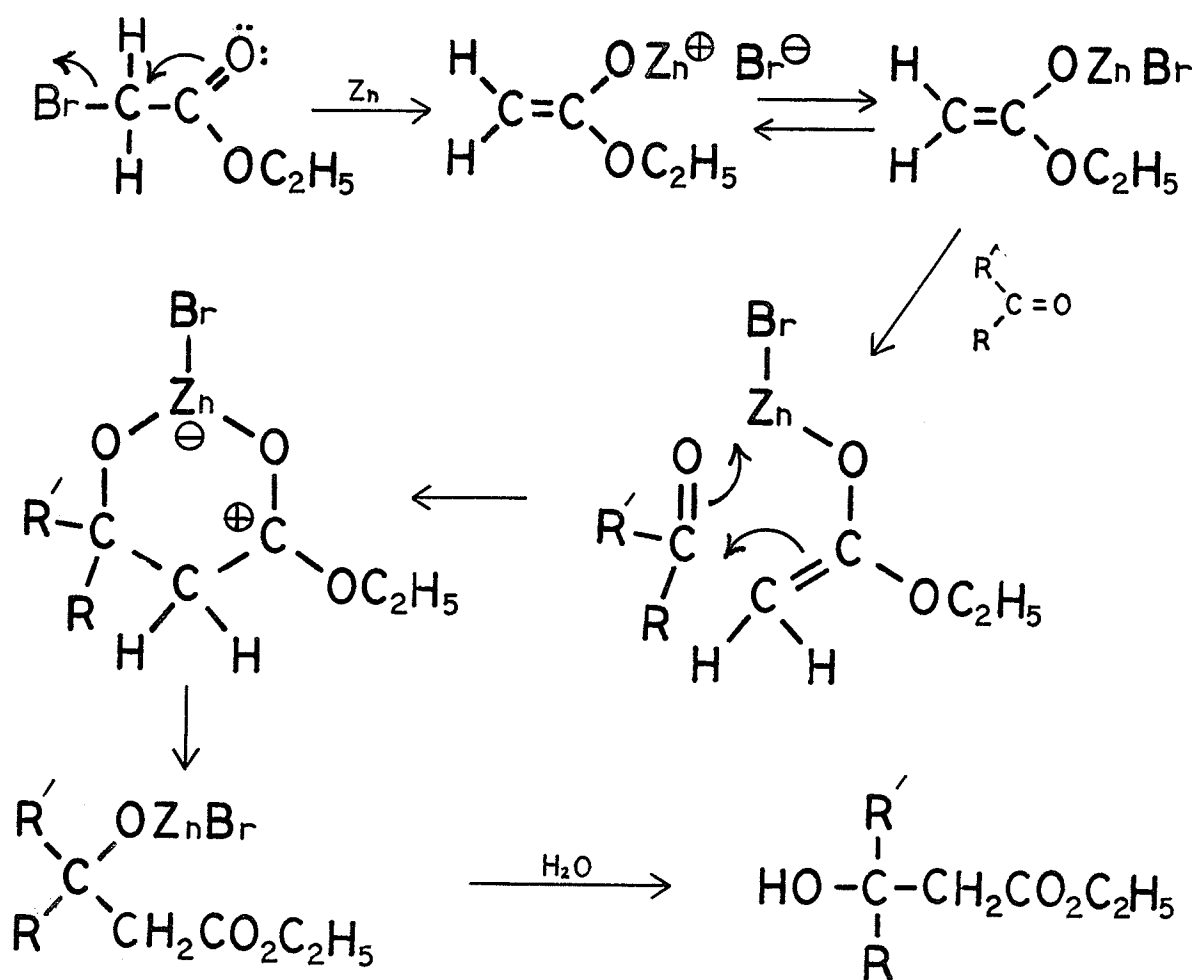
Palmer and Reid (77) carried out the syntheses of diastereoisomeric (-)-menthyl β -hydroxy- β -phenylbutyrates from (-)-menthyl bromoacetate and acetophenone. They noted that the degree of asymmetric synthesis in different solvents increased in the order: toluene < benzene < benzene-ether < ether. Attempts to carry out reactions in benzene or in toluene below their boiling points were unsuccessful, and as a result it was not possible to show whether the degree of asymmetric synthesis depended solely on the temperature or also on the solvent. The reaction of acetophenone and (-)-menthyl bromoacetate in different solvents and for varying reaction times, gave the following results:

SOLVENT	REACTION TIME (hours)	% YIELD OF HYDROXY ACID
Benzene	4	64
Benzene-ether	4	64
Toluene	4	58
Benzene	1	64
Benzene	10	60
Benzene	20	55

1963

Mousseron et al. (70) stated that a basic solvent was indispensable in the preparation of the Reformatsky reagent. In discussing one of their reaction mechanisms, involving a

cyclic intermediate (page 6), they emphasized the importance of the carbonyl groups of the bromoester and of the carbonyl compound (ketone or aldehyde) as well as the presence of a nucleophilic centre in the solvent, all of which would aid the zinc in participating efficiently in the enolization process with concurrent formation of a cyclic complex:



6. EXPERIMENTAL PROCEDURES

a) The Classical Reformatsky Reaction

Shriner's review (89) is one of a very few references which deals with the topic of selecting experimental procedures, and is the only source to date which deals with this topic in a comprehensive manner.

The following is an itemized summary of factors which have had some bearing on the choice of procedures as reported in the literature, and a direct or indirect influence on the yields of products from the Reformatsky reaction:

- 1) An induction period often precedes the reaction. This is attributed to traces of water in the reactants or the solvent, as well as to impurities on the surface of the zinc. Shortening or elimination of this induction period has been effected by the use of anhydrous reagents and a preliminary cleaning and activation of the zinc.
- 2) The initial reaction can be markedly exothermic and may be moderated by:
 - i) external cooling of the reaction vessel,
 - ii) use of a solvent,
 - iii) addition of the zinc in small portions,
 - iv) addition of the haloester to the other reactants at such a rate as to maintain an even reflux action.
- 3) To effect condensation, the reaction has always been carried out at reflux temperature. This temperature can

be varied by the choice of solvent and the concentration of reactants therein. There have been no reports to date on the use of reduced pressure in the Reformatsky reaction.

4) As the reaction proceeds, the zinc complex (II) which forms, may precipitate (often as an oil) and hinder the reaction by coating the unreacted zinc (43). In some cases this can be prevented or alleviated by:

i) choosing a solvent in which the complex is soluble, or from which the complex is precipitated in a crystalline form which can be easily shaken from the surface of the zinc.

ii) stirring the reaction mixture.

iii) addition of excess zinc in small portions over the course of the reaction (4).

5) To illustrate the choice of reactant proportions for the Reformatsky reaction, six references were consulted: (17, 22, 33, 61, 67, 77). From these was calculated the average ratio of gm.-atoms of zinc : moles of haloester : moles of carbonyl compound : mls. of solvent. This was found to be 1.8 : 1.4 : 1.0 : 1000 .

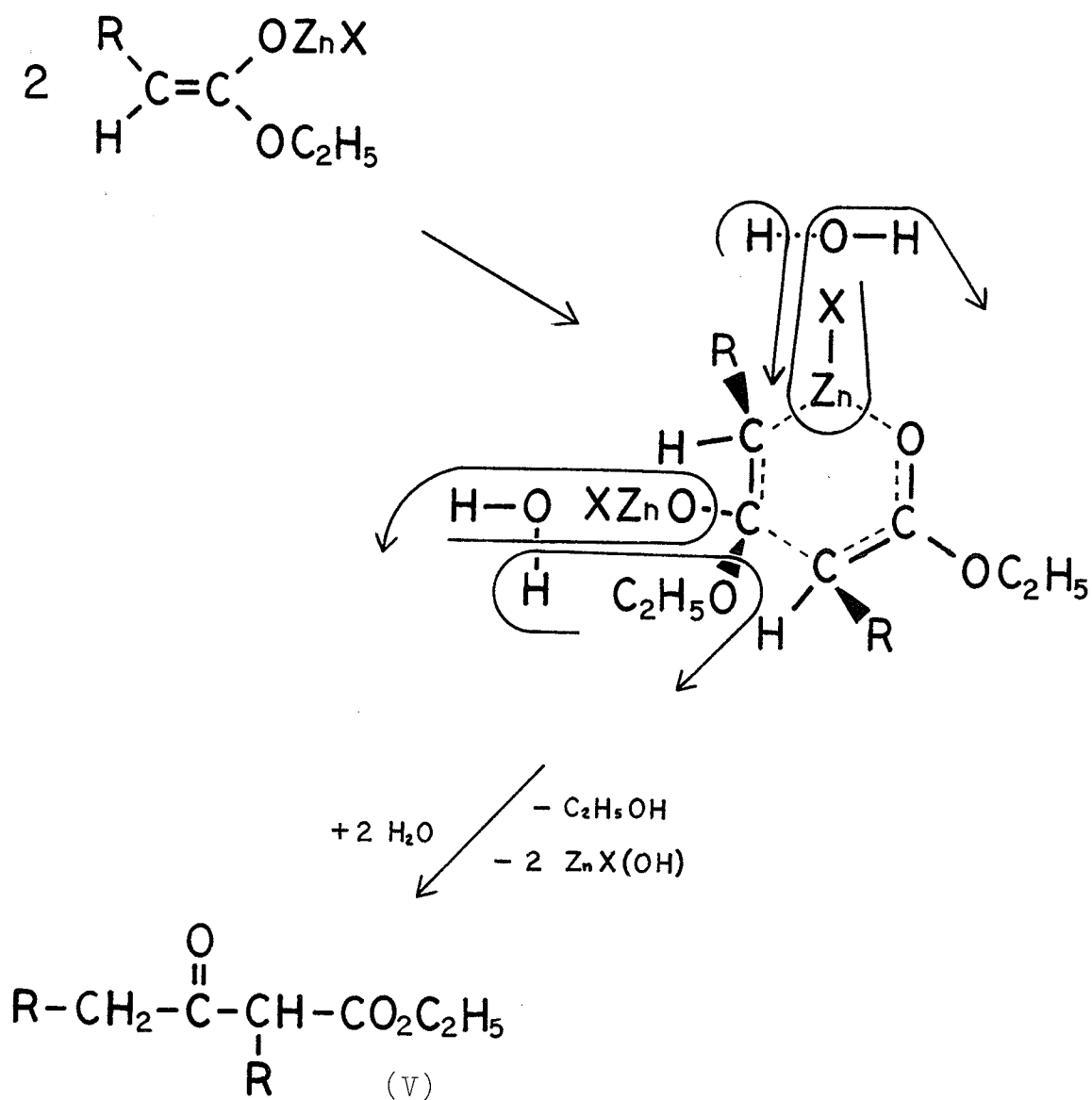
Thus the carbonyl compound is generally made to be the limiting factor with the zinc and haloester in slight excess. There are of course many exceptions to this pattern to be found in the literature. One of the most common modifications is the use of a large excess of zinc and haloester, recommended for carbonyl compounds available only in small amounts (29, 76).

6) The use of catalysts in the Reformatsky reaction has been investigated to some extent (67, 77, 89) but will not be discussed in this survey (see Recommendations for Future Work, page 113).

7) The manner in which the reaction mixture is hydrolyzed at the end of the reaction and worked up to the final product, is another topic which will not be dealt with in this survey.

b) The Two-Stage Reformatsky Reaction

On closer examination of the chart on page 93, it will be noted that the reaction of Siegel and Keckeis (modified Reformatsky reaction) and the Grignard reaction (modified Barbier reaction) are analogous in that they both involve a two step or two-stage procedure. Vaughan et al. (103) have offered an explanation to account for the considerable delay in the development of the former reaction. They suggested that the reluctance to use the Grignard-like procedure stems from early reports (89, 108) on the formation of β -ketoester and reduced ester from the reaction of zinc or magnesium with haloester in the absence of carbonyl compound. Dimerization of the Reformatsky reagent appeared to be the most likely explanation for the formation of β -ketoester (V). Using a cyclic intermediate similar to that used on page 6, the following dimerization mechanism is possible:

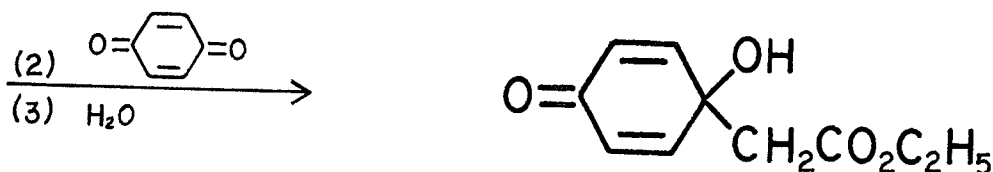
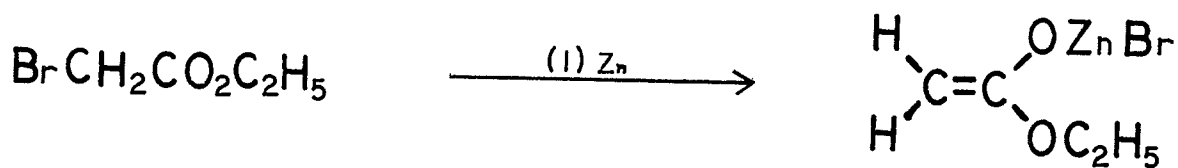


At the present time there are only five reports on the use of the two-stage Reformatsky reaction in the literature:

1953

Seigel and Keckeis (92) were the first to develop the two-stage procedure. They observed that the reaction of benzoquinone with a previously prepared Reformatsky reagent (from ethyl bromoacetate and zinc in ether) gave a 26% yield

of expected hydroxyester:



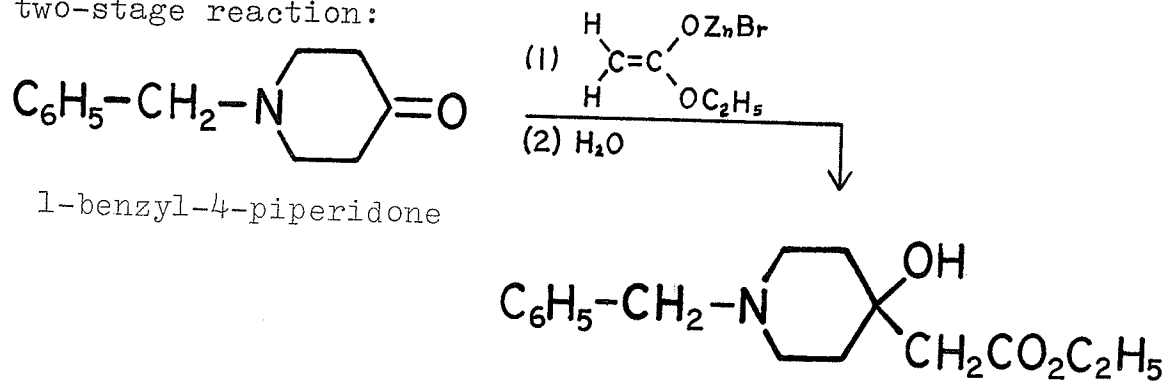
A normal one-stage reaction with the quinol-acetate failed to yield any hydroxyester.

1958

Vinograd and Vul'fson (104) obtained yields of 41.9, 48.9 and 50.3%, respectively, when they used 2-, 3-, and 4-nitrobenzaldehydes in the two-stage reaction with ethyl bromoacetate. A classical one-stage reaction performed by Bohlmann (17) between 2-nitrobenzaldehyde and methyl γ -bromocrotonate gave no reaction.

1958

Grob and Brenneisen (47) carried out the following two-stage reaction:



1-benzyl-4-piperidone

83%

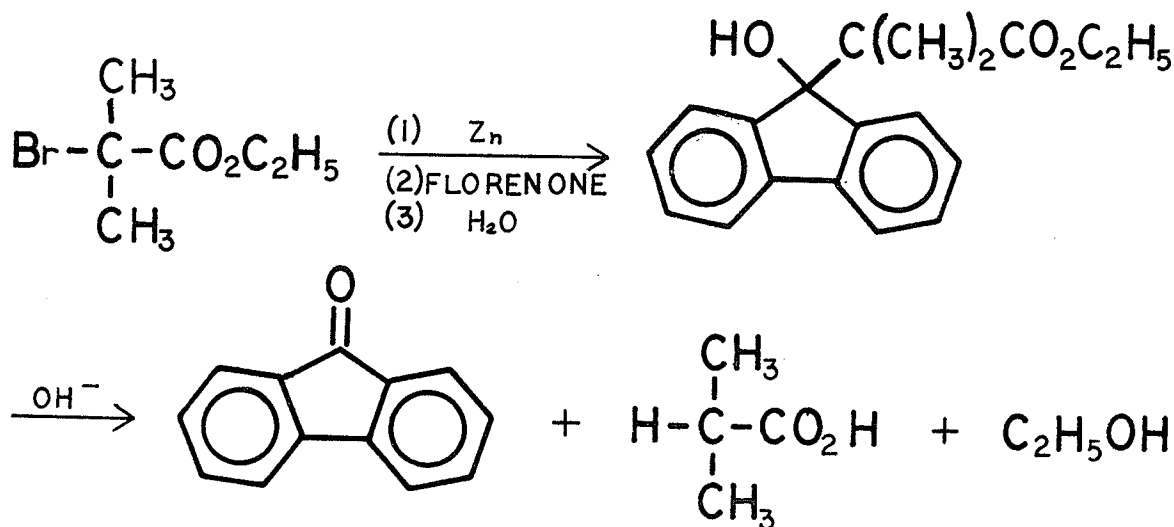
A conventional one-stage reaction, with a similar ketone, 1-benzoyl-4-piperidone, gave a 47% yield of expected hydroxyester.

1960

Palmer and Reid (77), while carrying out partial asymmetric syntheses of β -hydroxyacids, employed the two-stage technique with zinc, (-)-menthyl bromoacetate and acetophenone in ether, and obtained a 37% yield of expected hydroxyester. A one-stage reaction with the same reagents (in different proportions) in benzene gave a 64% yield.

1965

Vaughan et al. (103) used the two-stage Reformatsky reaction to synthesize ethyl α -(9-hydroxy-9-fluorenyl) isobutyrate in 93.4% yield from ethyl α -bromoisobutyrate and fluorene. They observed that the reaction of the Reformatsky reagent with ketone was virtually instantaneous but that all attempts at hydrolysis of the resultant hydroxyester led to recovery of 9-fluorenone:



There are indications that conventional (one-stage) Reformatsky reactions involving fluorenone and the ethyl α -bromoesters corresponding to the following acids: acetic, propionic, valeric, and isovaleric, give little or no reaction (55).

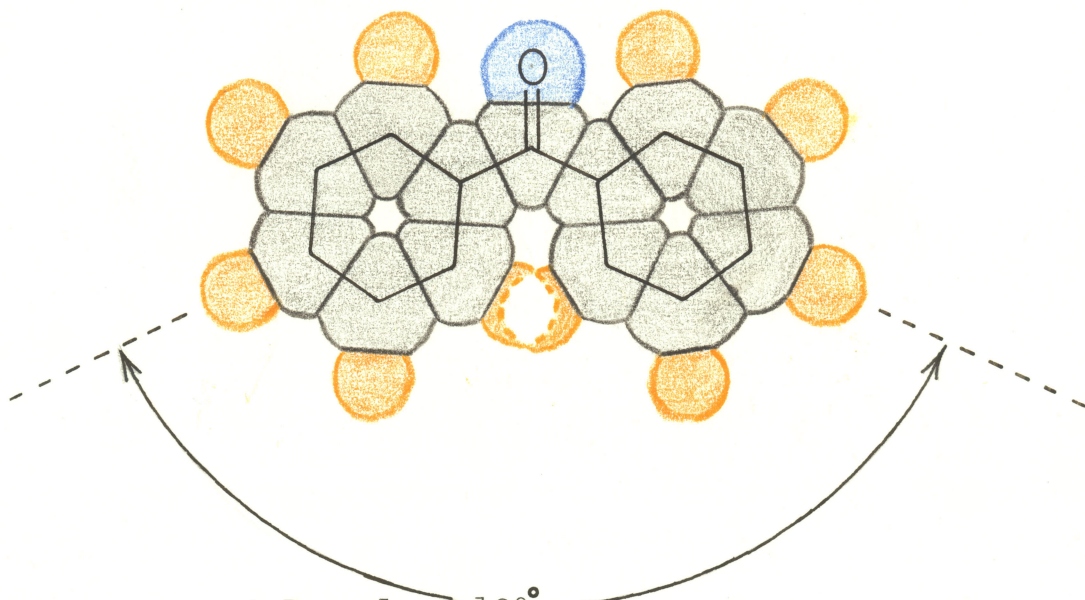
SUBSTITUTED BENZOPHENONES

1. STRUCTURE

The electric dipole moment measurements reported by Bergmann et al. (9) indicated that the angle between the 1,4-axes of the phenyl groups in benzophenone is 130° . Coates and Sutton (24) using this interaxial angle and other data for atomic dimensions, calculated that the minimum angle between the planes of the phenyl groups is approximately 30° .

A spectral study by Jones (56) indicated that the 30° rotation of one of the phenyl groups out of the plane of the benzoyl group definitely reduced resonance across the ring systems.

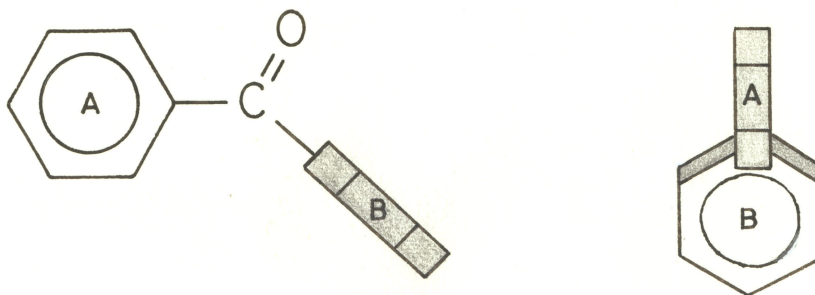
The following diagram of a Fisher-Hirschfelder model of a benzophenone molecule, drawn in the plane of the page, will give some idea of how interference between the 2- and 2'-hydrogen atoms prevent both the phenyl rings from being simultaneously coplanar with the carbonyl group in an actual three-dimensional model:



Interaxial angle: 130° .

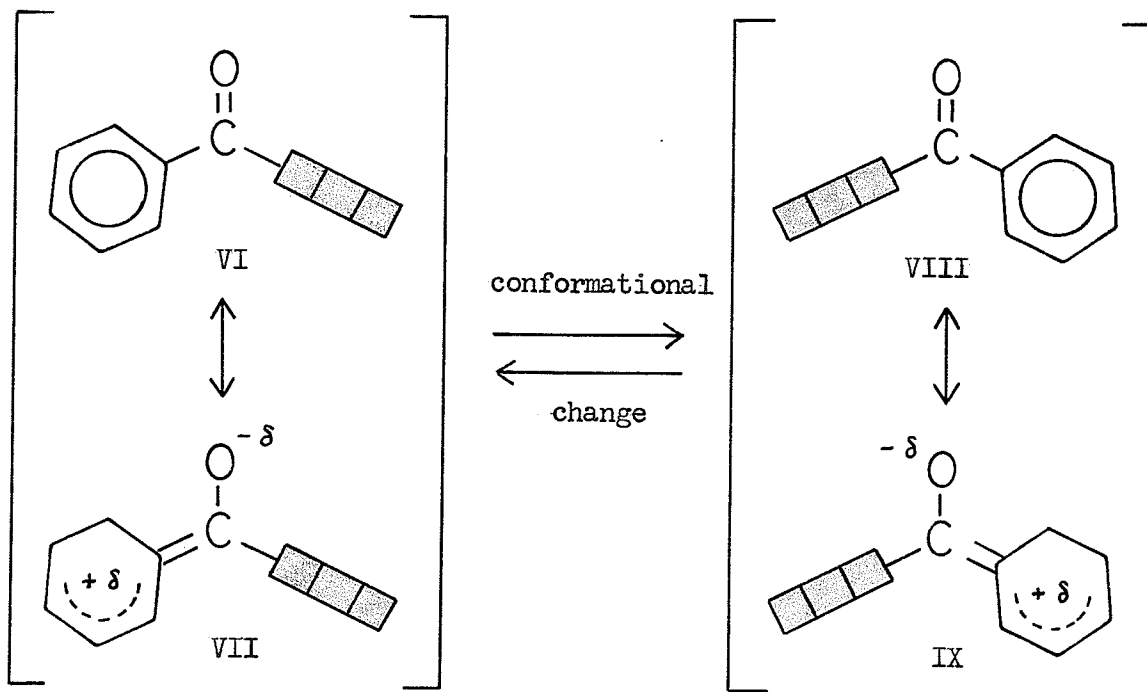
Interplanar angle: 0° (as shown here).

Interference by the two ortho hydrogen atoms is indicated by the area bounded by dotted lines.

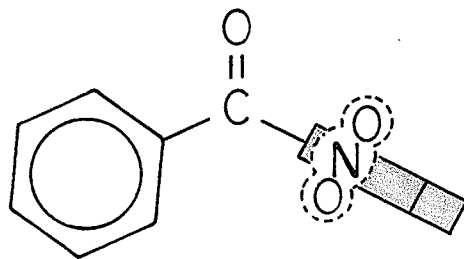


Side and end view of a benzophenone model with an interplanar angle of 90° .

Thus, canonical structures such as VII and IX, below, are possible but resonance involving cross-conjugation is not favored since both phenyl groups cannot be coplanar at the same time.

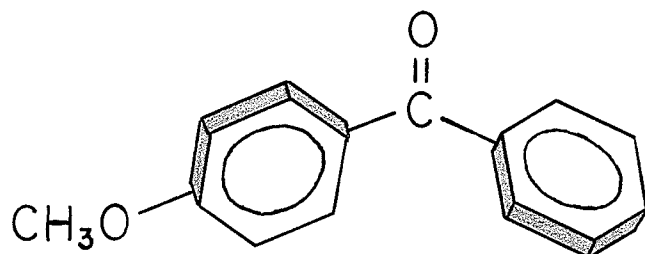


Similar spectral studies with monosubstituted benzophenones such as 2-nitrobenzophenone (69, 99) have provided evidence for the following conformation:

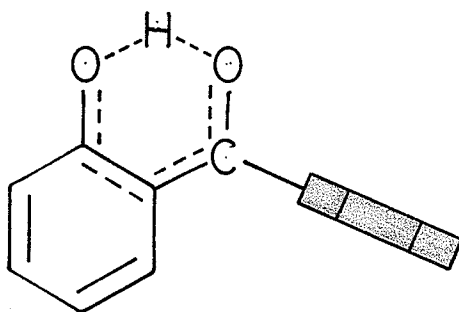


This conformation is favored because it permits conjugation between the carbonyl group and the more electron-donating of the two aryl groups.

In the case of 4-methoxybenzophenone, the two aryl rings are believed to occupy planes which are at a similar angle to the plane of the carbonyl group (68):



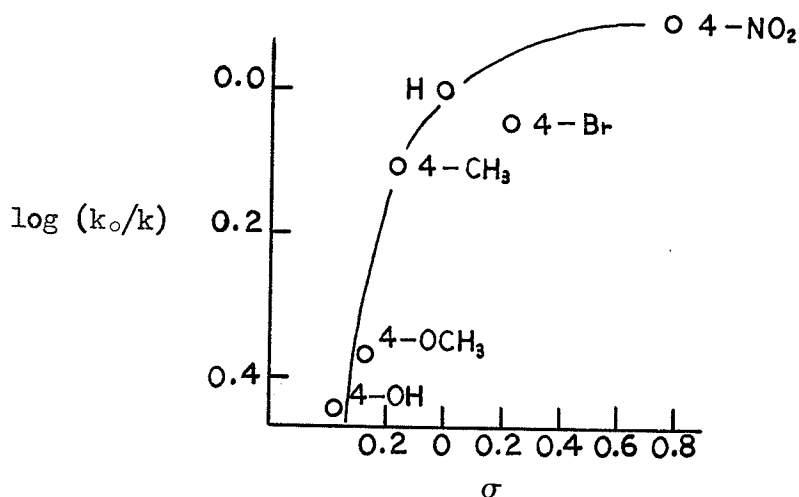
The spectrum of 2-hydroxybenzophenone indicated that it has a single non-planar conformation with the hydroxy group, linked by means of an intramolecular hydrogen bond to the carbonyl group (68):



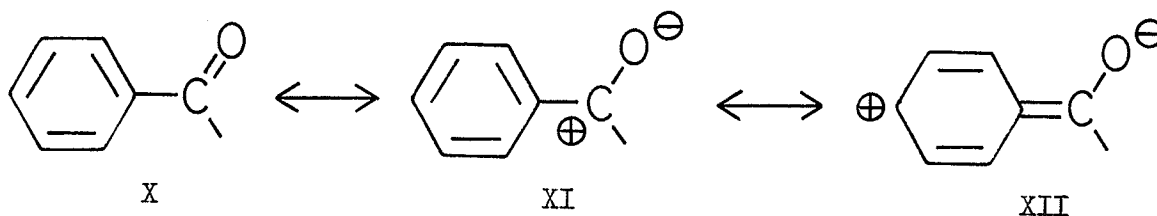
2. REACTIVITY

Spectral, polarographic, and kinetic studies (31,44,57) involving carbonyl band frequency shifts, oxidation-reduction potentials and rate constants, respectively, associated with meta and para substituted benzophenones, have indicated that these parameters are all affected by the same factors that control chemical reactivity, insofar as these are identified with Hammett sigma constants.

In a kinetic study on the formation of benzophenone oximes, performed by Dickinson and Eaborn (31), it was noted that for reactions involving addition to carbonyl groups in aryl carbonyl compounds, the graph of $\log(k_o/k)$ versus σ generally appears curved as shown:



They attributed this to the fact that ordinary σ_p constants do not indicate the effect of substituents on canonical structures (XI) and (XII) below:

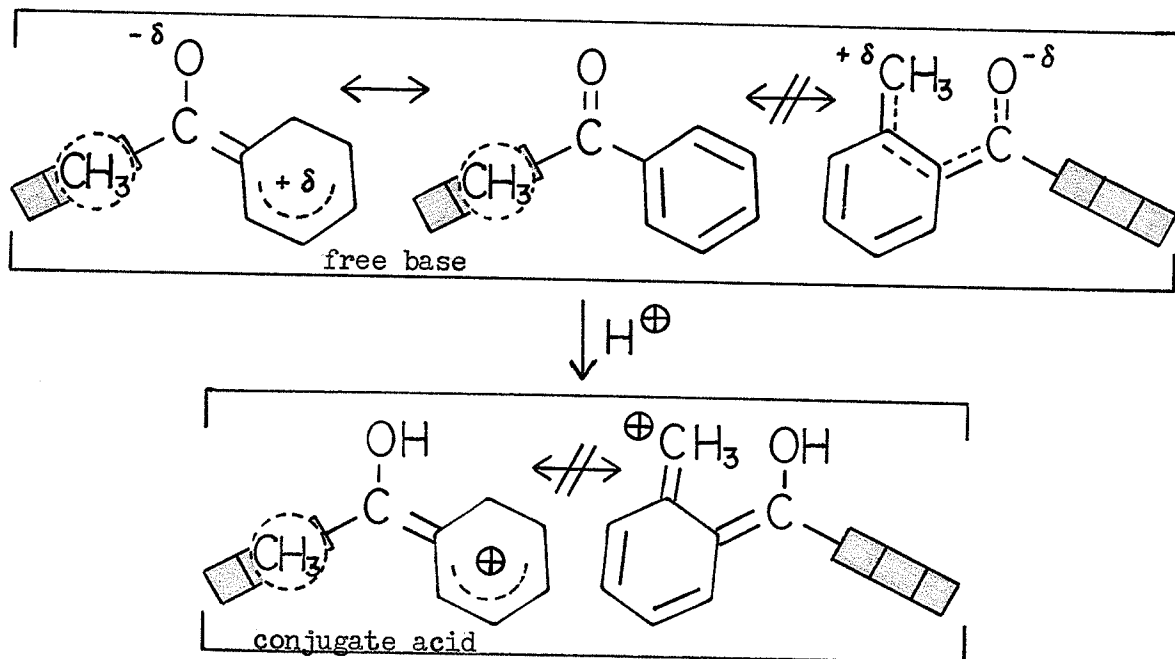


Steric interactions between reacting carbonyl groups and ortho substituents in benzophenones are responsible for the failure of the Hammett equation to correlate the reactivities of these ketones.

Yates and Scott (106) noted that in addition to steric

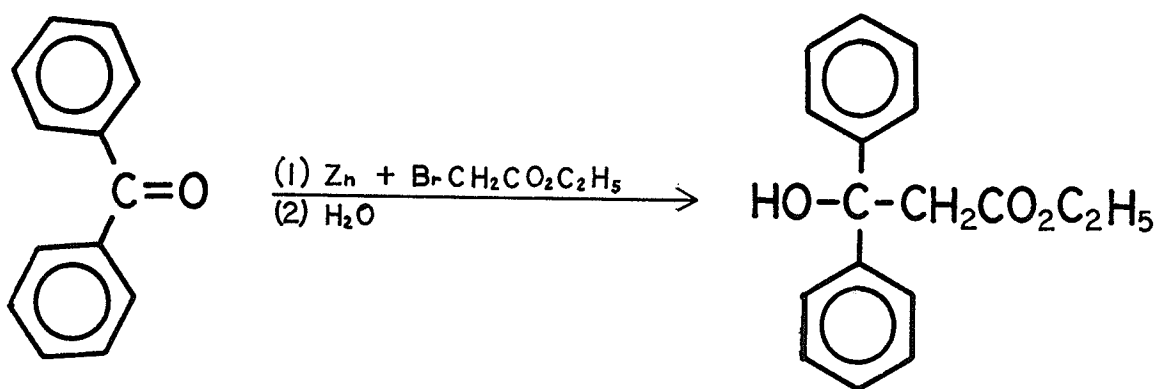
effects, other factors to be considered were steric inhibition of solvation, the electronic effect of substituents, and possible specific interactions such as hydrogen bonding.

One of the ketones these workers chose to study was 2-methylbenzophenone because the interactions of the methyl group approximated closely to bulk steric effects, the specific interactions being small, and the electronic effects determinable from the effects of the methyl substituent in 4-methylbenzophenone. It was found that 2-methylbenzophenone was a weaker base than benzophenone. They reasoned that a methyl group (normally having a base-strengthening electronic effect) in the 2-position of benzophenone, caused steric inhibition of coplanarity between the carbonyl group and the phenyl ring bearing the methyl group. The resulting loss in resonance stabilization energy, was more serious in the conjugate acid than in the free base.



3. SUBSTITUTED BENZOPHENONES IN THE REFORMATSKY REACTION1907

Rupe and Busolt (82) were the first to carry out a Reformatsky reaction with a diarylketone. They produced ethyl β, β -diphenylhydracrylate in 95% yield by condensing benzophenone with ethyl bromoacetate in the presence of zinc:



The ester was saponified to the corresponding acid in 70% yield (after recrystallization).

1908

Stoermer and Friderici (98) reported that they had prepared ethyl β -(2-methoxyphenyl)- β -phenylhydracrylate in 60 - 70% yield in a similar procedure using 2-methoxybenzophenone. This ester was converted into the corresponding hydroxyacid (yield and analysis of this acid were not given).

1929

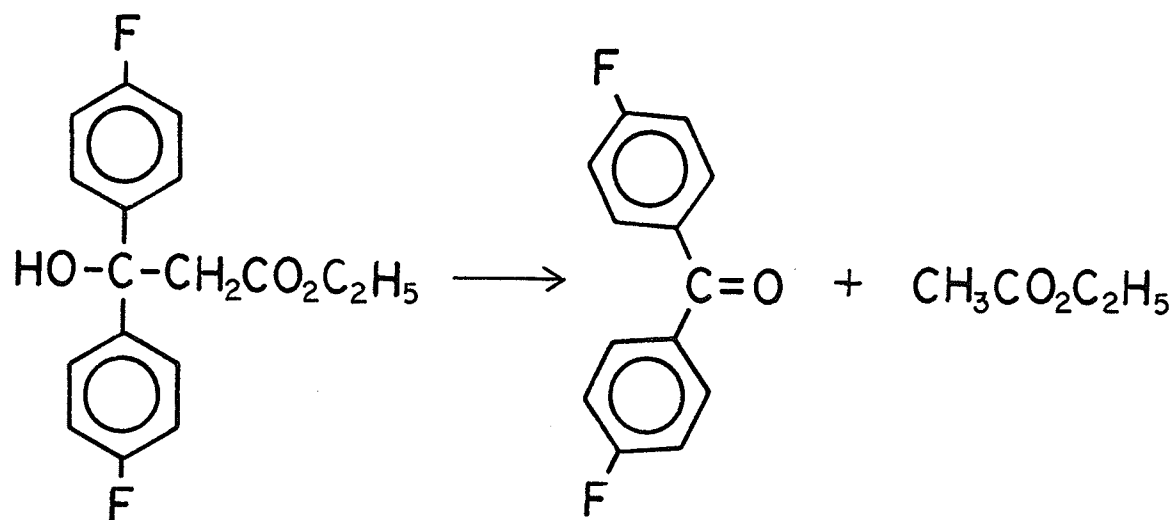
von Braun et al. (18) reported Reformatsky syntheses of three isomeric ethyl β -(methylphenyl)- β -phenylhydracrylates

from the 2-, 3-, and 4-methylbenzophenones. In the reaction between 2-methylbenzophenone and ethyl bromoacetate they recovered up to 35% of the unreacted ketone. 4-Methylbenzophenone appeared to react to a greater extent than either 2- or 3-methylbenzophenones.

1932

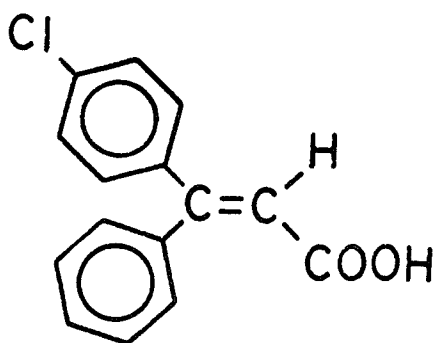
Bergmann et al. (10) carried out reactions between ethyl bromoacetate and the following monosubstituted benzophenones: 4-F, 4-Cl, 4-Br, and 4-I and obtained 48%, 67%, 47%, and 56% yields of hydroxyesters, respectively (after recrystallization).

They also carried out reactions with four disubstituted benzophenones, viz., 4,4'-difluoro-, 4,4'-dichloro-, 4,4'-dibromo-, and 4,4'-dimethylbenzophenones. The isolation of the resultant esters from the latter two ketones was difficult, and that from the difluoro compound, impossible due to a disproportionation reaction:



1935

Alexander et al. (2) reacted 4-chlorobenzophenone with ethyl bromoacetate in benzene and obtained a 79% yield of hydroxyester (after recrystallization). Subsequent saponification and dehydration yielded the unsaturated acid which Bergmann et al. (8) later showed to have the following trans configuration:

1951

Dippy and Parkins (33) carried out the synthesis of ethyl β, β -diphenylhydracrylate (97% yield) from benzophenone and ethyl bromoacetate in benzene-toluene (40:35 v/v).

1955

Heilmann and Glenat (51) repeated the above reaction with benzene as solvent, and a mls. of solvent : moles of benzophenone ratio only 1/6 that employed by Dippy and Parkins. The yield of hydroxyester was only 57%.

1958

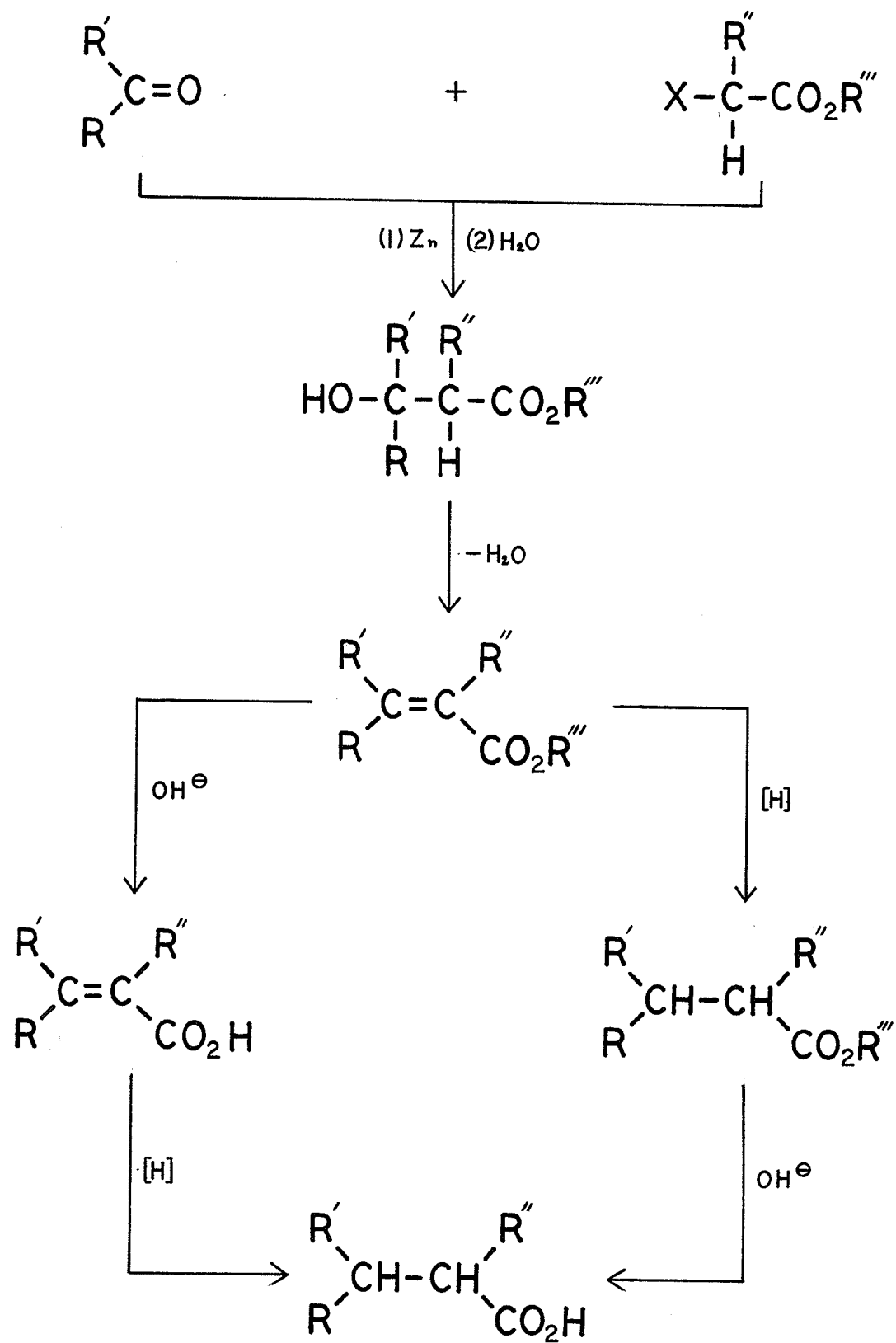
Klemm and Bower (61) reported the Reformatsky reactions

of 3- and 4-methoxybenzophenones with ethyl bromoacetate in benzene. The yields of hydroxyesters were 95-100% (estimated) and 78%, respectively. These investigators noted the high yields from benzophenone and 3-methoxybenzophenone relative to those of the other benzophenones in their work. They stated that these results agreed with, "the point of view that the Reformatsky reaction, like the addition of a Grignard reagent to a carbon-oxygen double bond, occurs via nucleophilic attack of the halogen-bearing carbon on to the carbonyl carbon". Thus a 2- or 4-methoxy group hinders this nucleophilic attack whereas the addition is possibly aided by the electron-withdrawing methoxy group in the 3-position.

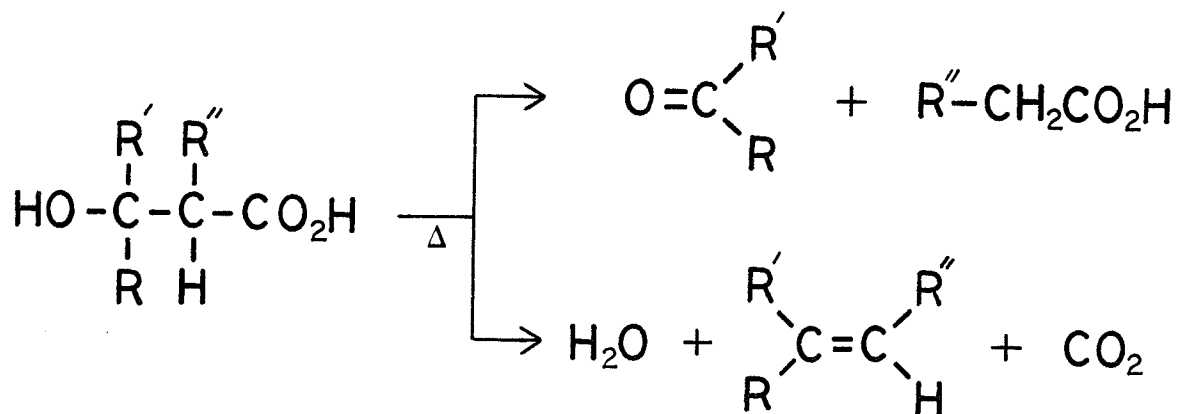
β, β -DIARYLHYDRACRYLIC ACIDS

In 1907, Rupe and Busolt (82) employed a Reformatsky procedure to synthesize the first, and parent acid of this kind, viz., β, β -diphenylhydracrylic acid (page 28). Later additions to this series of compounds have been prepared not only by Reformatsky reactions, but also by other methods which have continually challenged the former reaction in this area of synthesis. A chronological list of these alternate methods is given in the Appendix (pages 99 - 105).

It is important to note that the Reformatsky reaction has been used primarily to prepare hydroxyesters, unsaturated esters and acids, and the corresponding saturated compounds, according to the general scheme shown on the next page.



The unsaturated and saturated acids are not usually prepared via the β -hydroxyacids. Decomposition and cleavage of β -hydroxyesters during saponification, or of β -hydroxyacids during dehydration, can occur:



Thus, it has generally been considered essential to dehydrate the β -hydroxyester first, and then to saponify, as indicated in the reaction scheme on the previous page.

As a result, there are relatively few β, β -diaryl-hydracrylic acids and even fewer of their derivatives reported in the literature.

DISCUSSION OF EXPERIMENTAL RESULTS

PREPARATION OF MONOSUBSTITUTED BENZOPHENONES

The sixteen benzophenones employed in this study were all known compounds. However, the syntheses of four of these merit some comment:

2-Hydroxybenzophenone (page 61).

There have been no reports to date on Friedel-Crafts syntheses involving 2-hydroxybenzoyl chloride. The reaction of this acid chloride with benzene was successfully carried out in this investigation. In the past, 2-hydroxybenzophenone was usually prepared from the reaction of 2-methoxybenzoyl chloride and benzene; excess aluminum chloride being used to ensure arylation as well as demethylation (15).

2-Aminobenzophenone (pages 64 -65).

The modified procedure employed in the latter part of the present synthesis was developed as a result of a chance observation. The intermediate, 2-toluenesulfonylamidobenzophenone was found to be readily hydrolyzed to the parent amine by hot 10% hydrochloric acid. This was surprising, since the hydrolysis of a sulfonamide of a primary amine normally requires 24 to 36 hours refluxing with 25% hydrochloric acid (90). In the present synthesis, hot concentrated sulfuric acid served to hydrolyze and remove traces of the amine from the sulfone by-product.

4-Nitrobenzophenone (pages 65 - 66).

This synthesis was carried out as an experiment to determine the effect of reaction temperature on the yield of product. The yield (95%) and purity of the product from the reaction carried out entirely at room temperature, were notably better than those from a reaction performed at 50° (61% yield).

The high yields in the preparation of this ketone, and its conversion into the corresponding amino compound (88%), would make 4-nitrobenzophenone a valuable precursor in the synthesis of a number of para substituted benzophenones.

2-Nitrobenzophenone (pages 68 and 70 -71).

Of all the ketones in this investigation, this proved to be the most troublesome to prepare. The attempt to effect its synthesis via the organocadmium method was inspired by Cason's (21) observation that, "There seems to be no report concerning the reactivity of cadmium reagents toward the aromatic nitro grouping", and a later comment by Shirley (88), "The organocadmium compounds do not react with the nitrogroup in an aromatic nucleus. Advantage does not seem to have been taken of this in the synthesis of ketones from acid chlorides". In addition to the method used in this investigation, there have been a number of different syntheses reported but none of these presented a simple method giving a good yield of 2-nitrophenone.

REFORMATSKY REACTIONS

One of the primary objectives of this study has been to demonstrate that the modification of certain traditionally accepted Reformatsky reaction conditions, would result in improved yields of products.*

The following modifications were attempted in this investigation:

- 1) the use of ether, in contrast to benzene-toluene, as a reaction solvent,
- 2) the use of a novel "reduced-pressure" technique, and
- 3) the use of the recently developed two-stage procedure.

The new techniques, mentioned in 2) and 3), are both modifications of the classical Reformatsky reaction (one-stage procedure at atmospheric pressure).

1. SOLVENT AND TEMPERATURE EFFECTS

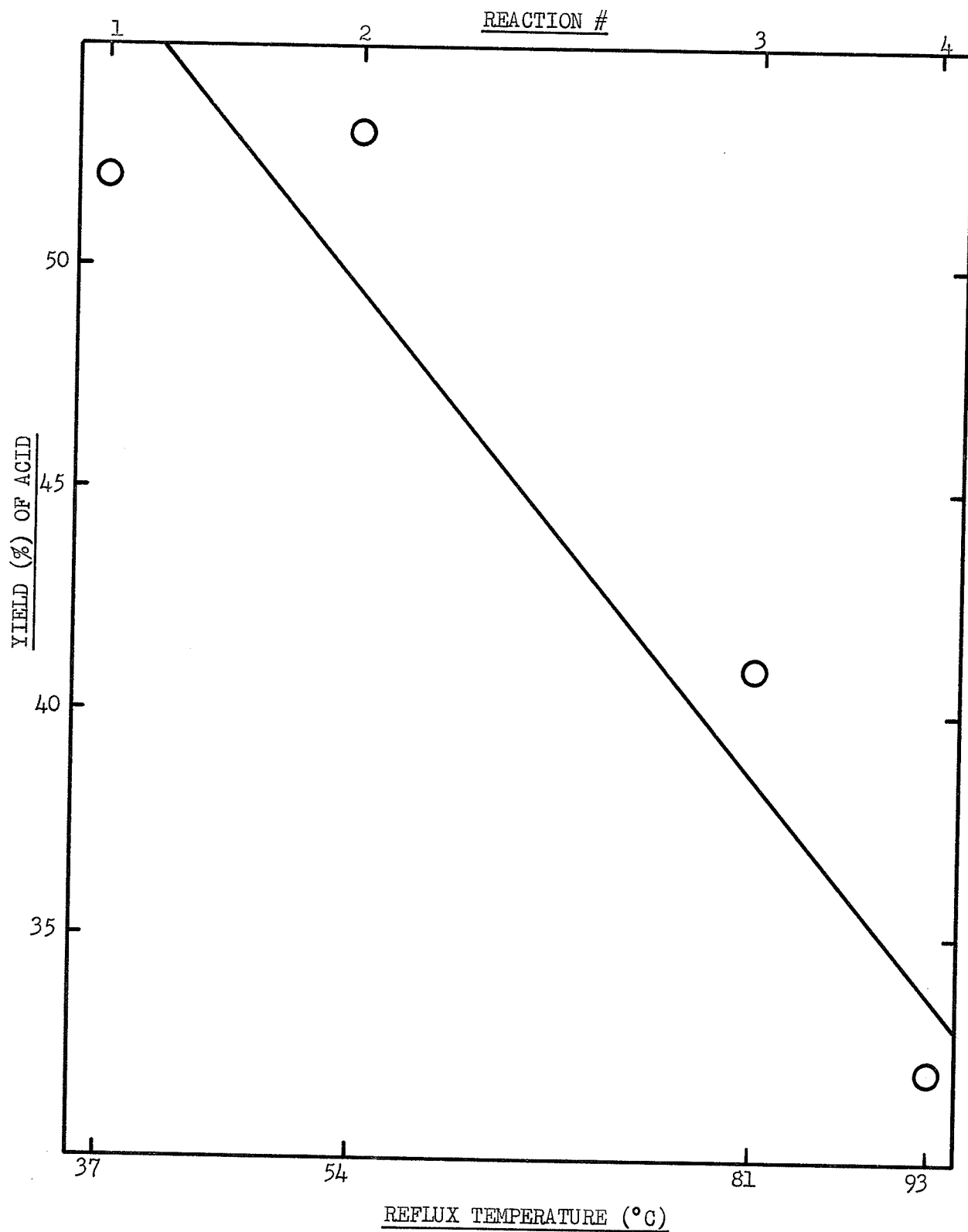
a) Variation of Solvents

Graphs 1 and 2 below, illustrate the results from the preliminary experiments with 2- and 4-methylbenzophenones, respectively (see Table 2, page 78). Each graph displays a plot of yield (%) of impure product versus the reflux temperatures, corresponding to the four reaction solvents employed, viz., ether (37°), benzene-ether (54°), benzene (81°), and benzene-toluene (93°).

* All reactions in this investigation were refluxed for two hours beyond initiation (see page 73).

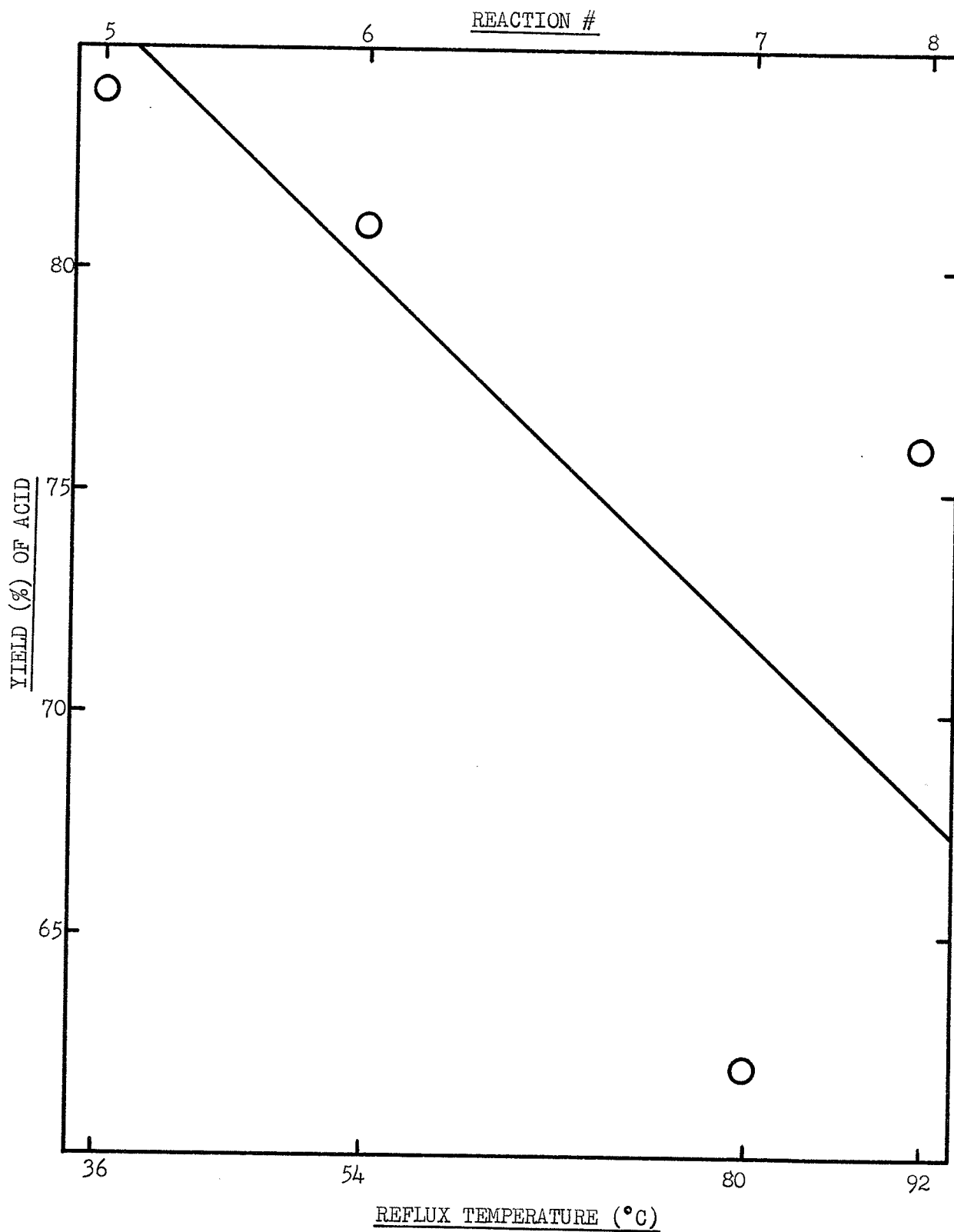
GRAPH 1

Reformatsky Reactions with 2-Methylbenzophenone in Different Solvents



GRAPH 2

Reformatsky Reactions with 4-Methylbenzophenone in Different Solvents



The data on these graphs revealed that yield tended to be approximately inversely proportional to reaction temperature.

In conclusion, these preliminary experiments indicated that ether was superior to the higher boiling solvents, in regards to the yield and purity of products.

At this point, it was felt that the study of a larger series of monosubstituted benzophenones, in ether and in benzene-toluene, would demonstrate, beyond question, the advantages offered by the former solvent. The data from this extended study, involving sixteen ortho and para substituted benzophenones (see Table 3, page 80) is recorded on Graph 3, on the following page.

This data shows at a glance that ether was, with few exceptions, superior to benzene-toluene as a reaction solvent.

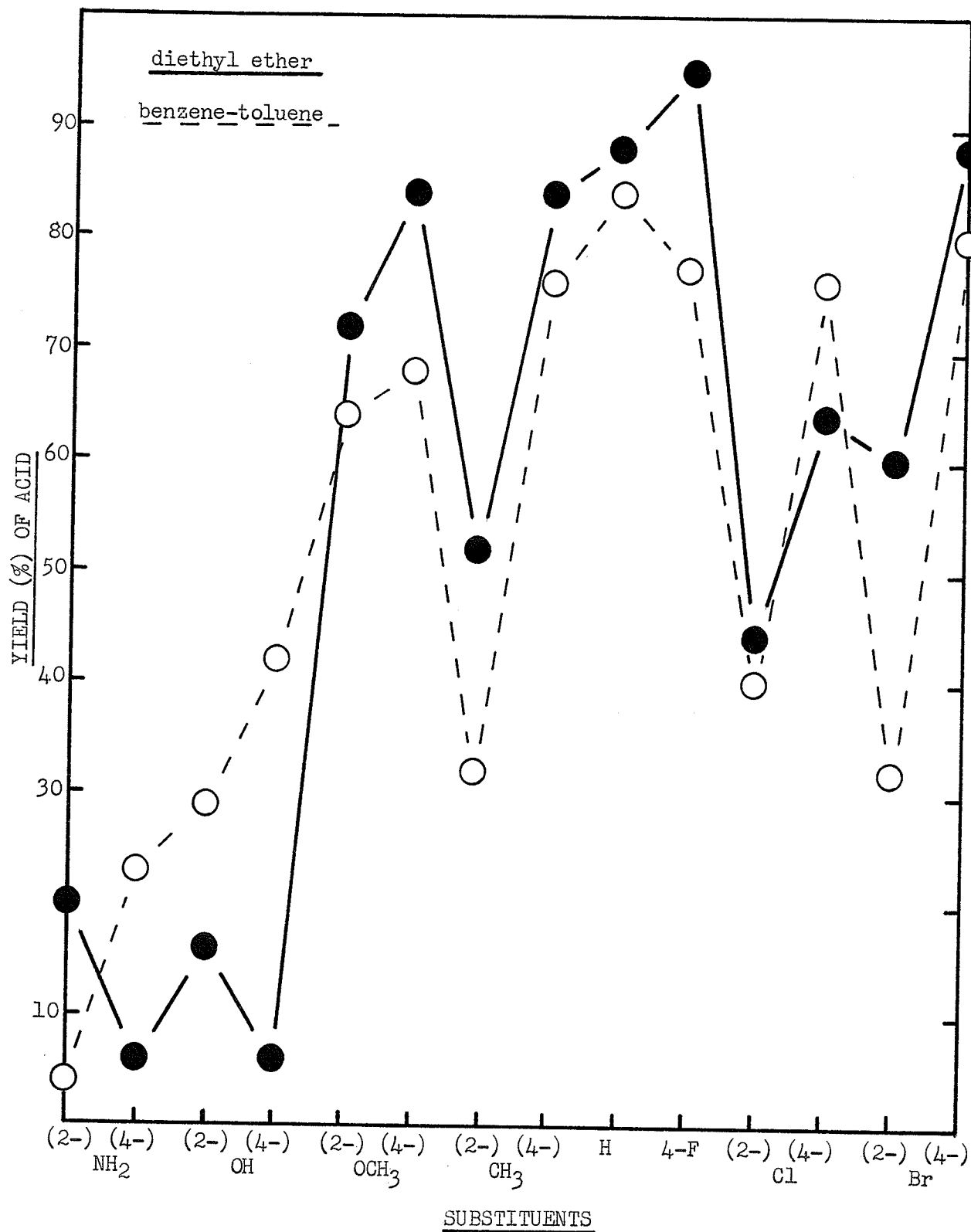
b) Variation of Ambient Pressure

Lewis and Wright (64) in their report on solvent effects in the Grignard reaction, reported that anisole was superior to ether in the reaction of ethylmagnesium bromide with benzophenone. They assumed that the better yields and purer products resulted from faster and hence more complete reactions in the former solvent.

In the present study a Reformatsky reaction was attempted with ethyl bromoacetate and benzophenone in anisole at atmospheric pressure. However, due to the relatively high reflux temperature (ca. 170°) considerable decomposition occurred and no attempt was made to work up the reaction mixture.

GRAPH 3

Yields of Hydroxyacids from Reactions of Monosubstituted
Benzophenones in Diethyl Ether and in Benzene-Toluene



Palmer and Reid (77) have reported that Reformatsky reactions must be performed at the reflux temperature of the solvent in order to ensure adequate condensation.

It was this observation that inspired the use of a reduced pressure procedure in the present study. This technique was anticipated to prevent the decomposition that had occurred in the anisole reaction at atmospheric pressure. The data from the reactions with 2- and 4-methylbenzophenones in anisole under reduced pressure (reactions #37 and #38) and in ether at atmospheric pressure (reactions #8 and #4) is given below (from Table 4, page 84):

SUBSTITUTED BENZOPHENONE	YIELD (%) IN	
	ANISOLE (63 / 26mm.)	ETHER (38 /atm.)
2-CH ₃	58	52
4-CH ₃	76	84

These results indicate that anisole may be equivalent to ether as a solvent in the Reformatsky reaction. However, no lucid comparison can be drawn until further studies are carried out with a wider variety of carbonyl compounds.

After the initial success of this novel technique, a second series of experiments was undertaken. Its aim was to determine how a change in reaction temperature, and a change in reaction solvent, would affect the yields of products in Reformatsky reactions with 2-methyl-, 2-methoxy-, and 2-bromo-

benzophenones. The results from this study are as follows:

SUBSTITUTED BENZOPHENONE	YIELD (%) IN		
	BENZENE-TOLUENE (91-93°/atm.)	BENZENE-TOLUENE (37-38°/82-85mm.)	ETHER (38°/atm.)
2-CH ₃	32	16	52
2-OCH ₃	64	52	72
2-Br	32	24	60

It is apparent from these results that a drop of 54° in reaction temperature for the reactions in benzene-toluene, caused decreases in yields ranging from 8 to 16%. Similarly, changing the reaction solvent from benzene-toluene to ether (at 38°) caused yields to increase by 20 to 36%.

2. THE TWO-STAGE REFORMATSKY REACTION

a) Preliminary Experiments

The 2- and 4-nitrobenzophenones failed to react in the classical Reformatsky reaction (see Table 3, page 80). A cursory examination of the unreacted zinc from the 4-nitrobenzophenone experiments revealed that the metallic granules possessed a greenish tint. Apparently the zinc had been rendered passive by some manner of reaction with the ketone. This difficulty was by-passed by the use of a two-stage reaction procedure which involved the addition of the ketone in benzene-toluene solution, to the previously prepared

Reformatsky reagent in ether (see Experimental, page 75).

Hauser and Puterbaugh (49) stated, "Since the zinc-halo intermediate (Reformatsky reagent)* in the Reformatsky reaction has been prepared in the presence of the ketone, the inverse addition procedure which appears to be required with nitro ketones has not been feasible." These workers were the first to express the need for a two-stage method ("inverse addition procedure"). Their phrase, "has not been feasible" alludes to the absence of any references to nitro carbonyl compounds in Shriner's review (89) and to a universal reluctance to develop a two-stage procedure for the Reformatsky reaction (see Literature Survey, page 18).

The application of the two-stage technique to 4-nitrobenzophenone (reaction #47, page 85) marks the first time a nitro ketone has successfully undergone a Reformatsky reaction. 2-Nitrobenzophenone failed to react under identical conditions (reaction #46). The dissimilar reactivities of these two nitro ketones are discussed further on in this section (see page 52).

These preliminary experiments substantiated what other workers have discovered, viz., that the preparation of the Reformatsky reagent is best affected in ether, or a solvent containing ether (e.g., benzene-ether). It seems that a low boiling, polar solvent helps to minimize those side reactions which the Reformatsky reagent is capable of undergoing prior to its reaction with the carbonyl compound.

* Author's insertion

b) Experiments with Monosubstituted Benzophenones

Following the successful application of the two-stage technique to 4-nitrobenzophenone, this method was employed with four other ketones, viz., 2-amino-, 4-amino-, 4-methoxy-, and 2-methylbenzophenones. The objective of this series of experiments was to effect a comparison between the two-stage, and one-stage reactions. The results from these reactions (reactions #42 to #45 inclusive) are recorded below, along with those from the corresponding one-stage reactions in ether and in benzene-toluene:

SUBSTITUTED BENZOPHENONE	YIELD (%) IN		
	TWO-STAGE	ONE-STAGE ETHER	ONE-STAGE BENZENE-TOLUENE
2-NH ₂	16	20	4
4-NH ₂	31	6	23
4-OCH ₃	82	84	68
2-CH ₃	56	52	32

The two-stage procedure, as used in this study, was anticipated to have three factors in its favor:

1) The yield of Reformatsky reagent should be improved by the use of ether in the first stage of the procedure (see preceding page).

2) The solubility of the ketone should be increased by the use of benzene-toluene in the second stage. It was feared that certain benzophenones, having somewhat limited solubilities in ether alone, would coat the zinc and thereby hinder the reactions.

3) In the first stage, the reacting zinc could not possibly be contaminated by the ketone or any insoluble zinc complex.

The following deductions have been drawn from the experimental results listed on the previous page, with respect to these three factors:

1) The first factor appears to be the most influential. The yields from the reactions employing ether were, almost without exception, superior to those from the classical reactions in benzene-toluene. On the average, the two-stage reactions did not appear to possess any definite advantage over the classical reactions in ether.

2) The slight insolubility of 4-aminobenzophenone in ether, might account for the low yield from the one-stage reaction employing that solvent.

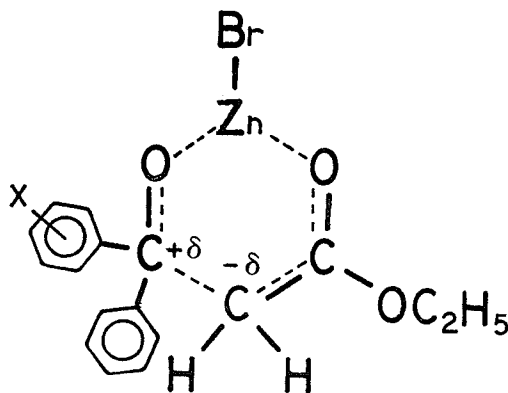
3) On the other hand, the difference in yields from 4-aminobenzophenone in the two-stage reaction and the classical reaction employing benzene-toluene, might have something to do with the third factor.

To better demonstrate the advantage(s) to be gained from the use of the two-stage technique, a more extensive study encompassing a wider variety of solvents and carbonyl compounds is needed.

3. THE CLASSICAL REFORMATSKY REACTION

a) Substituent Effects

The sequence of substituents in Table 3 and Graph 3 is in the order of increasing Hammett sigma constants for para substituents. This arrangement demonstrated that the yields of hydroxyacids from the para substituted benzophenones were, in general, affected by the same factors that control chemical reactivity, insofar as these are identified with Hammett σ_p constants. Such a relationship can be called upon to account for the increase in yields observed in passing from amino to nitro substituents. Taking one example: the low yields from the amino- and hydroxybenzophenones can be explained in terms of electronic effects. The two mechanisms proposed for the Reformatsky reaction (see Mechanism, pages 5 - 6) both involve a nucleophilic attack of the Reformatsky reagent on the carbonyl carbon of the ketone:



Such an attack is facilitated by electron-withdrawing ortho or para groups but is hindered by electron-donating

groups such as amino or hydroxy (see Literature Survey, page 31).

Due to the fact that both the hydroxybenzophenones were aromatic phenols possessing acidic character, the separation of the final saponification mixtures into ketonic and acidic fractions was difficult to perform. Consequently, the results from reactions #13 to #16 inclusive, are somewhat inaccurate insofar as they express the extent to which these reactions occurred.

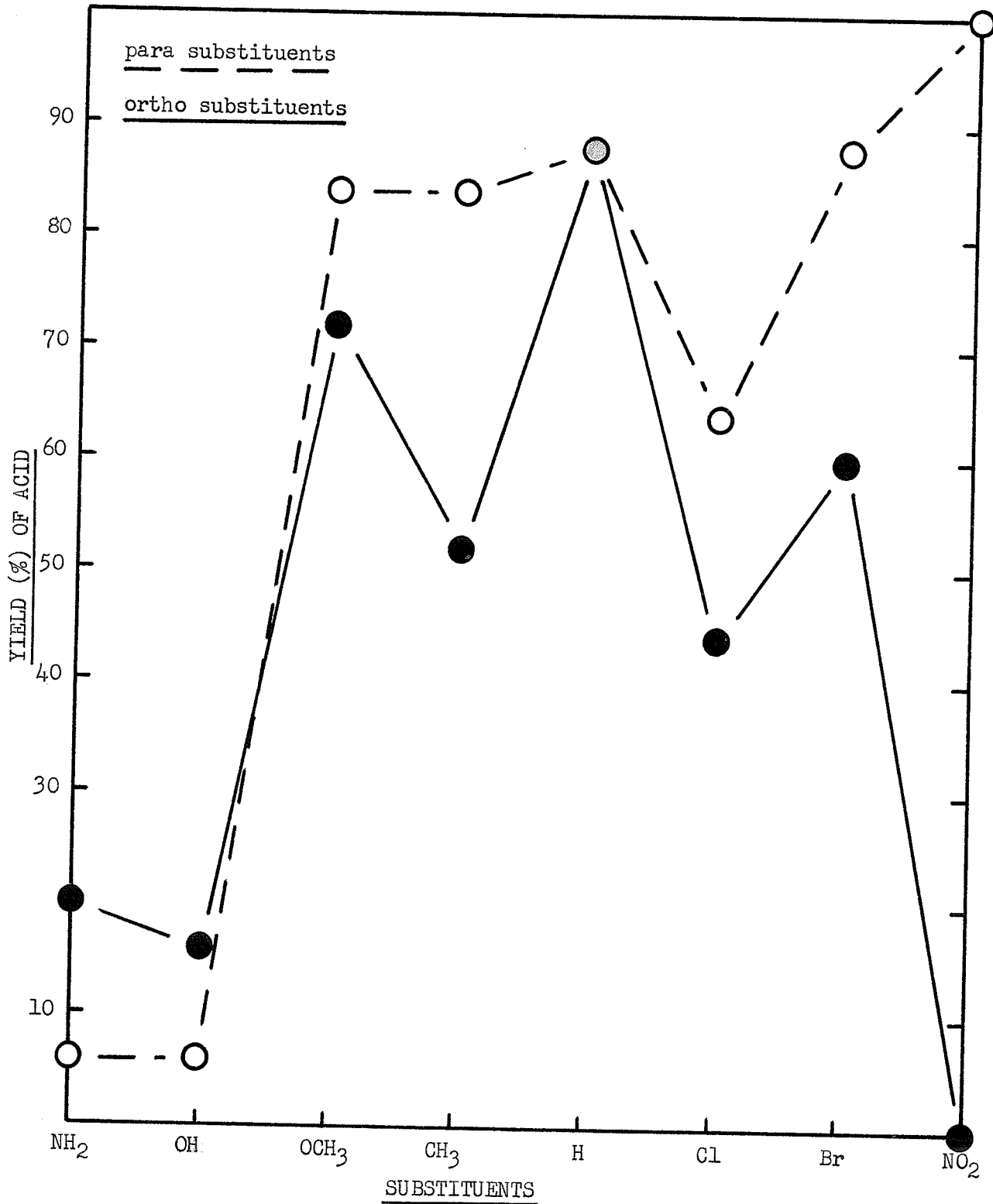
The ortho substituted benzophenones exhibit steric effects not present in the corresponding para isomers. It is for this reason that Hammett sigma constants cannot be used to correlate the reactivities of these hindered benzophenones.

Graphs 4 and 5 below, contrast the yields of hydroxyacids from the ortho substituted ketones (points joined by solid lines) with those from the para isomers (circles joined by dotted lines) under identical solvent conditions. Included with this data are the results from the two-stage reactions with the nitrobenzophenones.

As anticipated, the lowest yields were those from the ortho substituted ketones. However, two exceptions to this rule are to be seen on Graph 4 (ie., the reactions of 2-amino- and 2-hydroxybenzophenones in ether). Three possible explanations to account for these deviations are as follows:

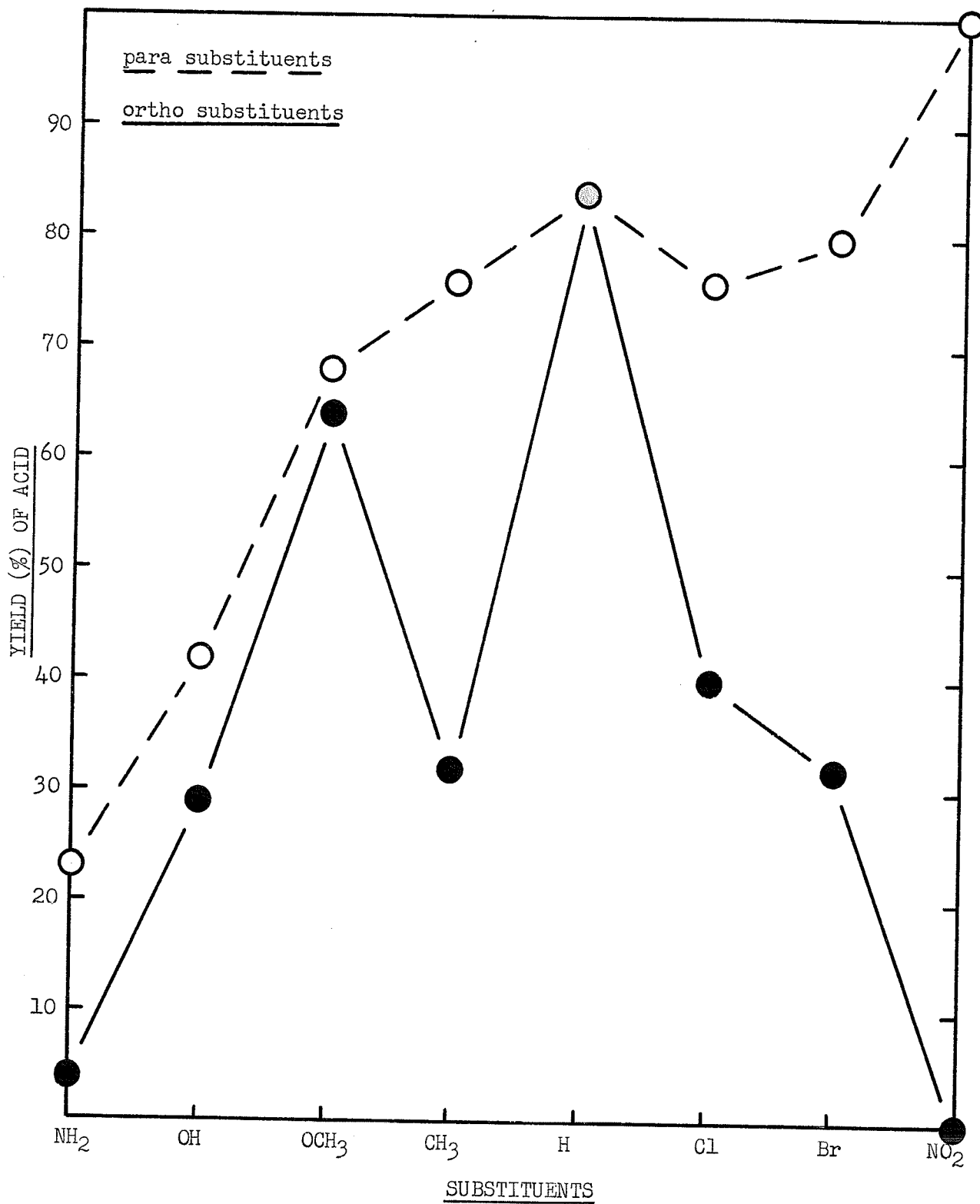
GRAPH 4

Yields of Hydroxyacids from Reactions of Ortho and
Para Substituted Benzophenones in Diethyl Ether



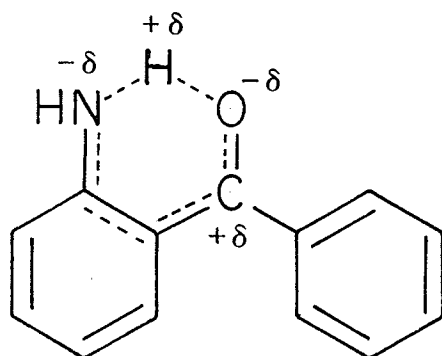
GRAPH 5

Yields of Hydroxyacids from Reactions of Ortho and
Para Substituted Benzophenones in Benzene-Toluene



1) Steric inhibition of coplanarity in the ortho substituted benzophenones, which decreases resonance stabilization of the carbonyl group by an electron-donating 2-amino-phenyl or 2-hydroxyphenyl group, might be greater in ether than in benzene-toluene. Thus, in the former solvent, the reactivities of these two ketones would be slightly greater than the corresponding para isomers.

2) Intramolecular hydrogen bonding such as that which is known to occur in 2-hydroxybenzophenone (see page 25), would tend to destabilize the carbonyl group (as shown), thus making it more susceptible to nucleophilic attack.



Such a partially ionic structure would be stabilized by ether.

3) Experimental error, while the most likely explanation for these deviations, is also the most difficult to define. It would be easier to deal with this subject in a wider context, by very briefly discussing the accuracy and precision of the data in Table 3.

Calculation of possible experimental errors for the lowest, median, and highest yields in this table gave the following values:

REACTION #	% YIELD	% ERROR
10	4	75
4	52	8
23	94	6

As expected, the lower yields were subject to the largest experimental errors.

The close correspondence between the % yield, and the % reaction with respect to recovered ketone, demonstrated that the method employed for separating the saponification mixtures into ketonic and acidic fractions, was both accurate and precise. The anomalous results from the hydroxy-benzophenone reactions are due to difficulties encountered in this separation procedure.

Deviation from 100% in the column headed % REACTION with respect to recovered zinc, simply served to indicate incomplete reaction (see page 17).

The close agreement of the results from the present research with those reported in the literature (see Table 1, page 56) indicated that the Reformatsky reaction per se, is capable of a certain degree of precision notwithstanding the heterogeneous reaction conditions employed.

Of all the pairs of positional isomers on Graphs 4 and 5, none give a more striking contrast in yields than the

nitrobenzophenones. The conformation of the 2-nitro ketone molecule shown on page 24, must succeed completely in preventing the electron-withdrawing nitro group from destabilizing the carbonyl group. Conversely, 4-nitrobenzophenone must possess a conformation in which the p-nitrophenyl group is coplanar with the carbonyl group, thus permitting resonance destabilization of the latter group by the former.

In comparing results from different substituents in the same solvent, or from a single substituent in different solvents, one must consider the possibility that solvent-substituent interaction, and steric inhibition of solvation, may work for or against the bulk steric and electronic effects mentioned above. In the preliminary trials with the methylbenzophenones, such solvent effects might account for the deviations observed on Graphs 1 and 2. However, until further evidence is forthcoming, such solvent effects must remain as merely interesting topics for speculation (see Recommendations for Future Work, page 113).

b) Zinc Complexes

Dippy and Parkins (33), in their study on "the solid deposits which separate in Reformatsky reactions", made the following statement: "it is true that some of these complexes have been isolated by precipitation from apparent solution in benzene, but it is thought that these are very fine suspensions rather than true solutions".

It was this comment which inspired the experiments reported in the Supplementary Notes to Table 2, page 79. The present study has demonstrated that although a few of the reactions did not produce visible solids, their translucent appearances indicated that they did contain colloidal solids. However, the formation of distinctly crystalline solids from these reaction mixtures on cooling, suggests that these complexes may indeed be soluble. Unfortunately, no further solubility tests were attempted with these solids. Nevertheless a somewhat similar check was effected with the insoluble complex from a reaction of 4-chlorobenzophenone in ether (similar to reaction #27). A portion of the white complex, isolated by suction filtration, was found to be almost completely soluble in benzene-toluene. A residual suspension of what may have been zinc hydroxide was all that remained undissolved.

Dippy and Parkins (33) synthesized a number of zinc complexes which gave anomalous analyses. They attributed this to contamination by β -ketonic ester complexes formed in side reactions (see page 6). It was perhaps these, and other high molecular weight by-products, as well as small amounts of zinc hydroxide (formed from the hydrolyses of the Reformatsky reagents and the zinc complexes by traces of moisture) that were responsible for the appearance of the colloidal material mentioned above.

These same workers reacted benzophenone with ethyl

bromoacetate in benzene-toluene and obtained an insoluble, pale yellow complex. In the present investigation, a similar reaction under almost identical conditions confirmed this observation. However, the corresponding reaction in ether gave the same complex as a pure white solid. A number of trials involving ether versus benzene-toluene in this study, gave complexes (and/or reaction mixtures) which displayed the same contrast in colors. This observation is in keeping with the conclusion, previously reached, viz., that the use of a low boiling, polar solvent, such as ether, minimizes the formation of by-products in the Reformatsky reaction.

The following is a summary of zinc complex solubility data, compiled from Table 3.

Of the fourteen ketones that reacted under classical Reformatsky conditions:

10 gave complexes insoluble in ether,

6	"	"	"	"	benzene-toluene,
4	"	"	"	"	ether only,
0	"	"	"	"	benzene-toluene only,
6	"	"	"	"	both ether and benzene-toluene,
4	"	"	soluble	"	"

The higher solubilities in benzene-toluene can most easily be explained by the principle of 'like dissolves like' since the zinc complexes do possess some aromatic character. Also, ether would tend to promote and stabilize complexes in partially ionic or highly polar configurations of limited solubility.

In three of the six reactions in which the complexes were insoluble in both solvents, those in benzene-toluene (reactions #12, #14 and #16) gave the highest yields. However, in the corresponding reactions in ether (reactions #11, #13 and #15) there were some indications that the zinc complexes coated the zinc and hindered the reaction. This was substantiated by the recovery of relatively large amounts of unreacted zinc from these three reactions.

4. THE PREPARATION AND CHARACTERIZATION OF

β, β -DIARYLHYDRACRYLIC ACIDS

a) β, β -Diarylhydracrylic Acids

The hydroxyacids referred to in this section are all derivatives of β, β -diphenylhydracrylic acid, and will be designated by the name of the substituent, preceded by the position on the parent nucleus to which it is attached. This designation is the same as that employed in all other tables and graphs in this thesis.

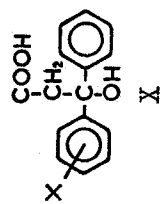
Six of the fifteen acids synthesized in this study have previously been reported in the literature (see pages 28 - 31 and 99 - 105). Table 1 below, compares the data obtained on these six hydroxyacids in this study with that reported in the literature.

Concerning the nine acids which were synthesized for the first time in this study, only two of these require comment:

TABLE 1

β, β -Diarylhydraacrylic Acids.

A Comparison of Literature and Experimental Results



	LITERATURE		PRESENT STUDY	
	% YIELD (as ester)	MELTING POINT * OF ACID (°C)	% YIELD (as acid)	MELTING POINT * OF ACID (°C)
2-OCH ₃	60 - 70	139	64 - 72	139 - 140.5
4-OCH ₃	78	-----	64 - 84	154 - 155
" **	63 - 72	160 - 160.5	(94)	
2-CH ₃	65	-----	32 - 52	147 - 148
" **	64 - 79	152.5 - 153	(94)	
4-CH ₃ **	65 - 76	187.5 - 188	76 - 84	180 - 182
"	88	-----	(36)	
H	95	212	84 - 88	210 - 211
"	97	-----	(33)	
4-Cl	67	188.5 - 190	64 - 76	187 - 190
"	79	-----	(2)	
" **	41 - 75	188.5	(94)	

* Melted with decomposition (frothing).

** Prepared by a method analogous to the Reformatsky reaction (see page 102).

4-Hydroxy acid

As reported on pages 81 - 82, this acid was accompanied by an appreciable amount of unreacted ketone. From the point of view of synthesis, this acid, as well as the 4-amino acid, might be more economically prepared from the corresponding 4-nitro compound.

2-Chloro acid

Whenever 2-chlorobenzophenone was reacted in benzene-toluene (reaction #26), the end product was always the unsaturated acid, β -(2-chlorophenyl)- β -phenylacrylic acid. It was not determined at what stage, or for what reason, the dehydration occurred.

Matzurevich (65) obtained β -methyl- β -(4-methylphenyl)-acrylic acid from the saponification of the corresponding ethyl hydroxyester. On the other hand, Blicke and Cox (14) found that β, β -diphenylhydracrylic acid was stable in refluxing alkali solution (16 hours) and could be recovered in essentially quantitative yield.

b) p-Nitrobenzyl Esters

The choice of this particular type of derivative was prompted, in part, by the work of Holmberg (52). This author reported that the p-nitrobenzyl esters of β, β -diarylpropionic acids could be readily synthesized, and their melting points were sufficiently different for identification purposes.

The present research has shown that the differences in melting points for several of the p-nitrobenzyl esters, are not sufficiently large to warrant the use of this type of derivative for the identification of β, β -diarylhydraacrylic acids.

EXPERIMENTAL

PREPARATION OF MONOSUBSTITUTED BENZOPHENONES

1. FRIEDEL-CRAFTS SYNTHESSES

a) 2-METHYLBENZOPHENONE

2-Methylbenzoyl Chloride. A mixture of o-toluic acid (124 gm., 0.91 mole) was refluxed with thionyl chloride (129 gm., 1.08 mole) until the evolution of hydrogen chloride and sulfur dioxide ceased. The excess thionyl chloride was distilled off at atmospheric pressure by heating to 130°. Vacuum distillation of the residue at 52.5 - 56°/ 1 mm. yielded 112.8 gm. (80%) of 2-methylbenzoyl chloride.

Norris and Young (75) reported a boiling point of 75 - 75.5°/ 2 mm.

2-Methylbenzophenone. This ketone was prepared by the condensation of 2-methylbenzoyl chloride (62 gm., 0.40 mole) with benzene in the presence of aluminum chloride, according to Reddelien's method (78). The yield of 2-methylbenzophenone was 94.6 gm. (74%) which boiled at 112 - 116°/ 1 mm.

Eastham et al. (37) reported a boiling point of 121.5 - 122.5°/ 1.25 mm.

b) 4-METHYLBENZOPHENONE

This compound was synthesized by a Friedel-Crafts reaction between benzoyl chloride (100 gm., 0.71 mole) and toluene, according to a method reported by Shirley (87).

The present synthesis differed from the latter in that the crude product was subjected to two successive vacuum distillations (132 - 137°/ 1 mm. and 125 - 130°/ 1 mm.) prior to recrystallization from petroleum ether. The yield of 4-methylbenzophenone was 37.1 gm. (27% with respect to benzoyl chloride) which melted at 56 - 57°.

Shirley (87) reported a melting point of 56°.

c) 4-METHOXYBENZOPHENONE

This ketone was prepared by the general method of Dorofeenko, Dulenko and Dulenko (34).

A mixture of 60% perchloric acid (3.4 gm., 0.02 mole), anisole (43.2 gm., 0.40 mole) and benzoyl chloride (84.4 gm., 0.60 mole) was refluxed for three hours. The reaction mixture was poured onto a mixture of ice and dilute sulfuric acid. The aqueous mixture was extracted with ether, and the combined ethereal extracts were washed with water and 5% sodium carbonate solution, and dried over magnesium sulfate. Removal of the ether by distillation yielded the ketone and a large amount of tar. It was only with great difficulty that the ketone was isolated by repeated extractions with petroleum

ether (in which the tar was only slightly soluble) followed by recrystallization from petroleum ether-diethyl ether (1:1). The ketone melted at 60 - 62°.

Dorfeenko et al. (34) reported a melting point of 60 - 61°.

d) 2-HYDROXYBENZOPHENONE

2-Hydroxybenzoyl Chloride. This acid chloride was prepared by Kirpal's method (60) using salicylic acid (50 gm., 0.36 mole). The reaction mixture was not worked up, but instead was diluted with benzene (200 ml.) and used immediately in the preparation of the hydroxy ketone.

2-Hydroxybenzophenone. A suspension of anhydrous aluminum chloride (77 gm., 0.58 mole) in benzene (450 ml.) was heated in a one liter three-necked flask equipped with a reflux condenser, stirrer and dropping funnel. The previously prepared benzene solution of 2-hydroxybenzoyl chloride was added slowly with stirring to the refluxing suspension. After the addition was completed, refluxing and stirring were continued until the evolution of hydrogen chloride ceased. On cooling, the reaction mixture was observed to separate into two immiscible layers. Hydrolysis of the reaction mixture was carried out by pouring it cautiously onto a mixture of ice and dilute acid. The aqueous layer was separated and extracted once with benzene. The combined organic layers were washed successively with

dilute hydrochloric acid, water, 5% sodium carbonate solution and water. After drying over magnesium sulfate and removing the benzene by distillation, the residue was subjected to vacuum distillation. 46.5 gm. of the crude product was collected at 119 - 138°/ 1 mm. as a yellow oil. Recrystallization from aqueous-acetone yielded 37.2 gm. (52%) which melted at 39 - 41°.

DeTar (30) reported a melting point of 38.5 - 39.0°.

e) 2-CHLOROBENZOPHENONE

2-Chlorobenzoyl Chloride. Following the same general procedure as that employed in the preparation of 2-methylbenzoyl chloride, a mixture of 2-chlorobenzoic acid (36 gm., 0.23 mole) and thionyl chloride (80 gm., 0.67 mole) yielded 33.8 gm. (77%) of 2-chlorobenzoyl chloride, collected at 75 - 76°/ 1 mm.

Thompson and Norris (102) reported a boiling point of 78.9 - 79.2°/ 2 mm.

2-Chlorobenzophenone. This ketone was prepared following the same procedure as that reported by Reddelien (78) for the synthesis of 2-methylbenzophenone.

2-Chlorobenzoyl chloride (53.7 gm., 0.31 mole) was reacted with benzene in the presence of aluminum chloride to yield 41.5 gm. of 2-chlorobenzophenone which boiled at 176 - 182°/ 9.5 mm. and melted at 42 - 48°. Recrystallization

of this impure product gave 34.5 gm. (57%) with a melting point of 44.5 - 46.5°.

von Auwers et al. (3) reported a boiling point of 185 - 188°/ 13 mm. ; Newton and Groggins (73) reported a melting point of 45.5 - 46°.

f) 2-BROMOBENZOPHENONE

2-Bromobenzoic Acid. This acid was prepared by repeating Bigelow's method (12). 2-Bromotoluene (50 gm., 0.29 mole) was oxidized by potassium permanganate (102 gm.) in a solution of sodium hydroxide (8 gm.) in water (3000 ml.). The yield of 2-bromobenzoic acid was 29.5 gm. (50%).

2-Bromobenzoyl Chloride. This acid chloride was prepared from thionyl chloride and 2-bromobenzoic acid following the same procedure as that described by Shirley (85) for the preparation of 4-bromobenzoyl chloride.

2-Bromobenzoic acid (29.5 gm., 0.147 mole) yielded 28.4 gm. (88%) of 2-bromobenzoyl chloride collected at 102 - 104°/ 3 mm.

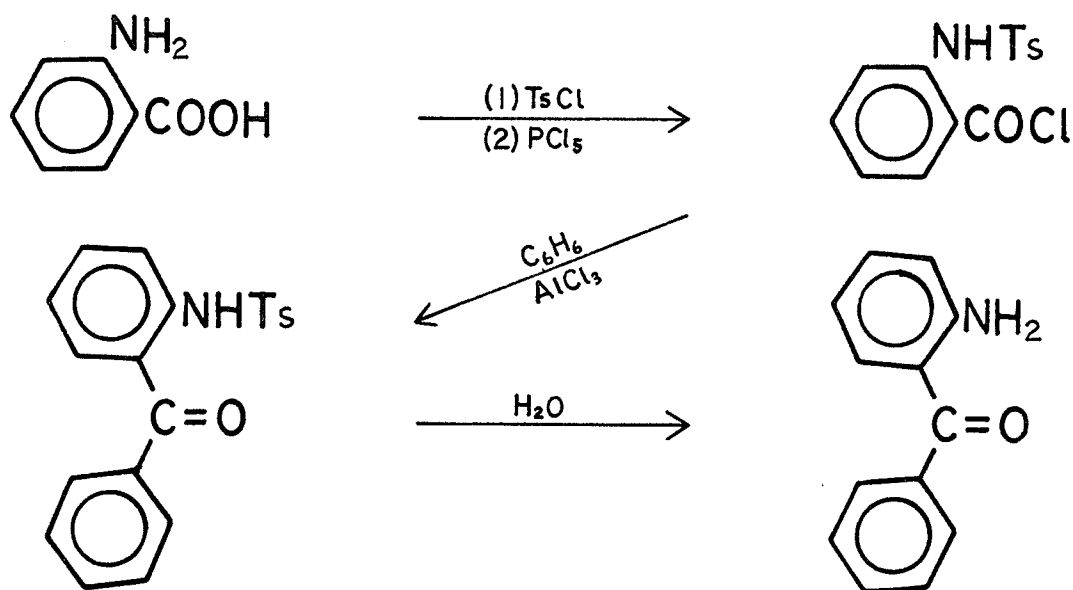
Norris and Young (75) reported a boiling point of 100 - 101°/ 1 mm.

2-Bromobenzophenone. This compound was prepared by Shirley's method (86) for the synthesis of 2-chlorobenzophenone.

The Friedel-Crafts reaction between benzene and 2-bromobenzoyl chloride (28.4 gm., 0.130 mole) yielded 28.6 gm. (84%) which melted at 39 - 42.5°. Two successive vacuum distillations were required to purify the product. The first distillation gave 30.2 gm. at 140 - 160°/ 1 mm., and the second yielded 28.6 gm. at 139 - 144°/ 1 mm.

Meldola and Hollely (66) reported a melting point of 42°.

g) 2-AMINO BENZOPHENONE



This ketone was prepared by the method of Scheifele and DeTar (83), with the following modification:

The Friedel-Crafts reaction mixture was cooled to room temperature and poured onto a mixture of ice and concentrated hydrochloric acid. This hydrolyzed mixture was filtered free of a considerable quantity of light olive-green solid. This substance, which was apparently impure 2-toluenesulfonylamido-

benzophenone, was readily hydrolyzed by 10% hydrochloric acid to 2-aminobenzophenone. The benzene layer from the filtrate was separated from the aqueous phase, washed with water and dried. Removal of the benzene by distillation under reduced pressure afforded 120 gm. of a brown solid. This substance was heated with concentrated sulfuric acid (200 ml.) on a steam bath for 15 minutes. The resultant solution was cooled, poured into water (500 ml.) and filtered free of a solid (which was apparently phenyl-p-tolyl sulfone) and the filtrate was neutralized with 6N sodium hydroxide solution. The precipitate of impure 2-aminobenzophenone was collected by suction filtration, combined with the main portion of ketone and recrystallized from aqueous-ethanol. The yield of 2-aminobenzophenone was 40.8 gm. (41% based on p-toluene-sulfonylanthranilic acid used) which melted at 105 - 107°.

Scheifele and DeTar (83) reported a yield of 54% and a melting point of 105 - 106°.

h) 4-NITROBENZOPHENONE

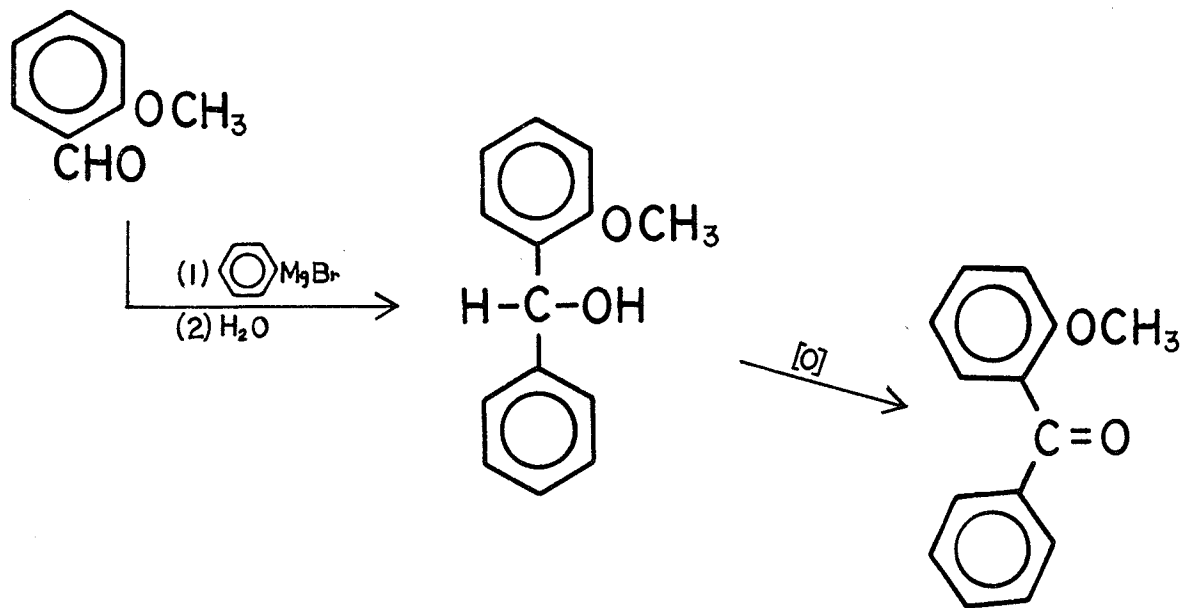
4-Nitrobenzoyl chloride (66.8 gm., 0.36 mole) was dissolved in anhydrous benzene (250 ml.) and the solution was filtered (6.8 gm. of insoluble material was recovered, thus leaving 60.0 gm., 0.32 mole of acid chloride in the filtrate). This benzene solution was added dropwise (over a period of two hours) to a well-stirred suspension of anhydrous aluminum chloride (96 gm., 0.72 mole) in benzene

(700 ml.) at room temperature. Three hours after the addition was completed, a solid complex was observed to have settled out. The reaction mixture was allowed to stand overnight at room temperature and then hydrolyzed with ice and dilute hydrochloric acid. The resultant two phase system (additional benzene may be required to dissolve any solid present) was separated and the organic layer was washed and dried in the usual manner. Removal of the benzene by vacuum distillation yielded 70 gm. (95%) of almost pure ketone which melted at 135 - 137°.

Schroeter (84) has reported a melting point of 138°.

2. OXIDATION OF SUBSTITUTED BENZHYDROLS

a) 2-METHOXYBENZOPHENONE



2-Methoxybenzhydrol. This intermediate was prepared according

to the method of Kohler and Patch (62) but using quantities of reagents equivalent to those described by Stoermer and Friderici (98).

A solution of 2-methoxybenzaldehyde (35.5 gm., 0.26 mole) in an equal volume of anhydrous ether was added dropwise with stirring to an ice-cold solution of phenylmagnesium bromide prepared in the usual manner from magnesium (6.5 gm., 0.27 mole), bromobenzene (41.4 gm., 0.27 mole) and absolute ether (120 ml.) . The reaction mixture was stored in an air-tight flask and left overnight in a refrigerator (0°) for approximately 24 hours prior to hydrolysis with cold dilute sulfuric acid. The organic layer was separated and washed successively with dilute acid, water, 5% sodium carbonate solution, and water. After drying over magnesium sulfate, the ether was removed by vacuum distillation.

The yield of crude alcohol was approximately 52 gm. (93%), and was pure enough for use in the next step.

2-Methoxybenzophenone. This compound was prepared by the oxidation of the above benzhydrol (0.24 mole) according to the method of Stoermer and Friderici (98).

The product collected at 134 - 144°/ 1 mm. weighed 25 gm. (49%) and melted at 35 - 37°.

Stoermer and Friderici (98) reported a melting point of 39°.

b) 2-NITROBENZOPHENONE

2-Nitrobenzhydrol. This alcohol was prepared by a Grignard synthesis involving phenylmagnesium bromide and 2-nitrobenzaldehyde as reported by Hey and Mulley (50).

The yield of 2-nitrobenzhydrol from 2-nitrobenzaldehyde (36 gm., 0.24 mole) was 30.9 gm. (57%) collected at 172 - 179° / 1 mm.

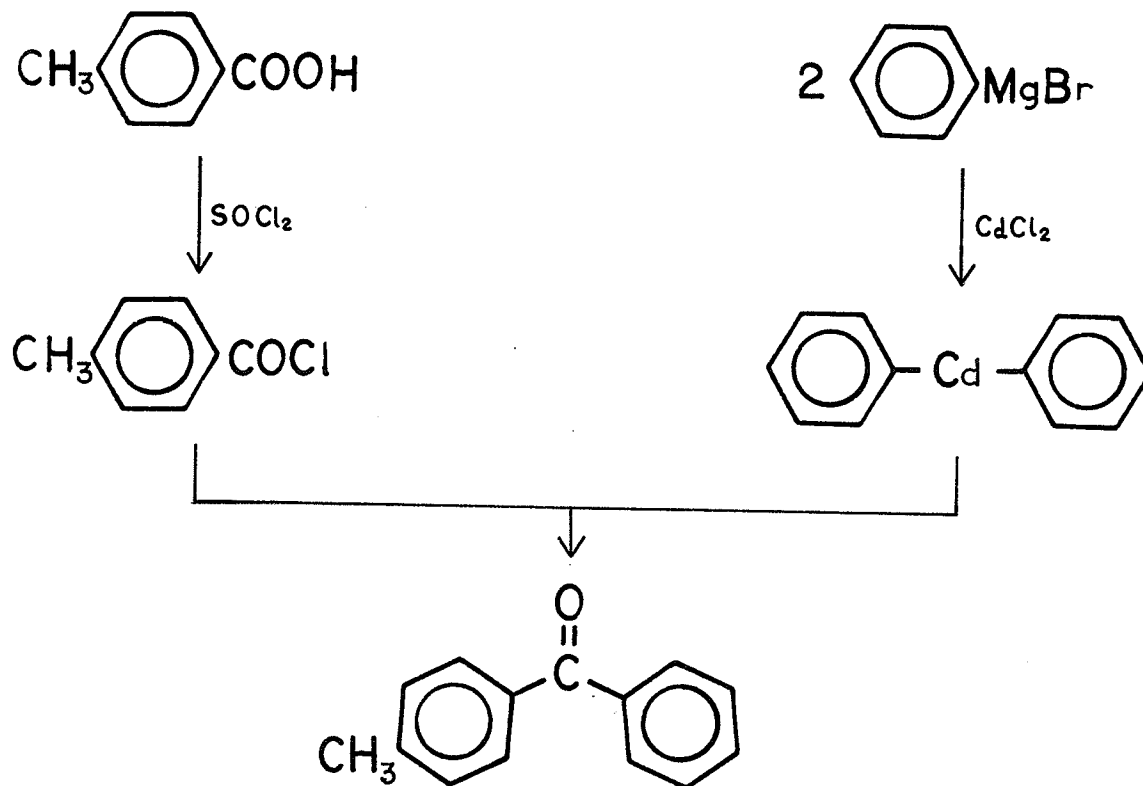
2-Nitrobenzophenone. This ketone was synthesized by a method similar to that described by Stoermer and Frederici (98) for the oxidation of 2-methoxybenzhydrol to 2-methoxybenzophenone.

A solution of potassium dichromate (55.6 gm., 0.29 mole), concentrated sulfuric acid (46 ml.) and water (256 ml.) was added in one portion, with stirring, to 2-nitrobenzhydrol (30.9 gm., 0.13 mole) in a 500 ml. flask. The temperature of the mixture was observed to rise quickly to 45°, and then slowly drop back to room temperature. The dark colored liquid was poured into water (500 ml.) and the crude product was isolated by filtration, washed with water, and air-dried. The yield of crude ketone was 30.8 gm. (100%). Recrystallization from methanol afforded a product which melted at 103.5 - 106°.

Hay and Mulley (50) reported a melting point of 103 - 104°.

3. SYNTHESES WITH DIPHENYLCADMIUM

a) 4-METHYLBENZOPHENONE



4-Methylbenzoyl Chloride. This compound was synthesized by exactly the same method as that for 2-methylbenzoyl chloride (page 59). p.Toluic acid (124 gm., 0.91 mole) yielded 116.2 gm. (83%) of acid chloride boiling at 67 - 69°/ 1 mm.

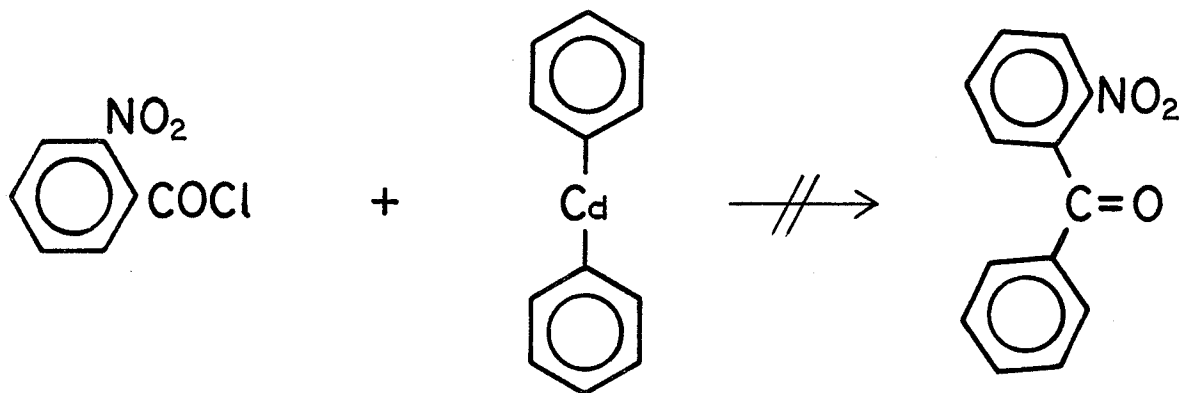
Norris and Young (75) reported the boiling point as 90 - 90.5°/ 3 mm.

4-Methylbenzophenone. This ketone was prepared by essentially the same method as that described by Cason and Prout (23) for the synthesis of methyl 4-keto-7-methyloctanoate.

In this instance, 4-methylbenzoyl chloride (50 gm., 0.323 mole) was the limiting factor. The present method involved a slight modification in regards to the isolation of the final product: the benzene was not removed in a flash evaporator; instead, the organic layer was simply vacuum distilled. The yield of 4-methylbenzophenone, boiling at 127 - 130°/ 1 mm., was 36.2 gm. (57%). Recrystallization from alcohol afforded a product which melted at 55 - 59.5°.

Muraoka et al. (70a) reported a boiling point of 153 - 155°/ 5 mm. Blakey and Scarborough (13) have reported a melting point of 56°.

b) ATTEMPTED PREPARATION OF 2-NITROBENZOPHENONE



2-Nitrobenzoic Acid. This acid was obtained in 68% yield by the oxidation of o-nitrotoluene (50 gm., 0.37 mole) with potassium permanganate (128 gm.) in dilute basic solution (64 gm. sodium hydroxide and 3150 ml. water) according to the method of Bigelow (11).

2-Nitrobenzoyl Chloride. A mixture of 2-nitrobenzoic acid (20 gm., 0.12 mole), thionyl chloride (15.7 gm., 0.10 mole) and benzene (33 ml.) was refluxed for a few minutes until the initial evolution of sulfur dioxide and hydrogen chloride began to subside. Then a stream of dry natural gas was bubbled through the refluxing solution until the presence of the two acidic gases could no longer be detected in the elutant. The reaction mixture was cooled and stored in a stoppered flask.

2-Nitrobenzophenone. This synthesis was attempted by following the same procedure as that for the preparation of 4-methylbenzophenone (page 69). The limiting factor was 2-nitrobenzoyl chloride (see above) and all other reagents were scaled to bromobenzene (78.5 gm., 0.5 mole).

On working up the reaction mixture, an impure brown solid was obtained. Sublimation of a portion of this material yielded a crystalline solid, which was found to be biphenyl (by a mixed melting point with a known sample).

4. PREPARATION OF 4-AMINOBENZOPHENONE

This ketone was prepared by the reduction of 4-nitrobenzophenone (effected with iron and acetic acid) according to the procedure of Simpson et al. (93) for the reduction of 2-nitrobenzophenone.

The yield of crude product was 23 gm. (88%) which

melted at 113 - 118°. Repeated recrystallizations from ether eventually gave a product melting at 122 - 124°.

Theilacker and von Blumercrom (101) reported a melting point of 124°.

REFORMATSKY REACTIONS

1. SYNTHESES OF β, β -DIARYLHYDRACRYLIC ACIDS

GENERAL PROCEDURES

a) CLASSICAL (ONE-STAGE) REACTION

Preparation of Activated Zinc. The zinc used in this investigation was in the form of 20 mesh granules (Fisher Scientific Corporation) activated by the procedure of Palmer and Reid (77).

A quantity of zinc was given a brief preliminary cleaning by washing it with a small portion of dilute hydrochloric acid, followed by rinsing with water and acetone, and then dried in air. The metal granules were heated in a test tube with a side arm, under vacuum (ca. 1 mm.) with a few crystals of iodine. Heating was discontinued when the zinc began to sublime (as evidenced by the appearance of a metallic mirror on the sides of the containing vessel) and before the zinc granules could melt and fuse together.

Synthesis of a β, β -Diarylhydraacrylic Acid. Activated zinc granules (3.8 gm., 0.058 gram atom) were added to a solution of diaryketone (0.058 mole) and ethyl bromoacetate (4.5 gm., 0.027 mole) in an anhydrous solvent (30 ml.). The reaction mixture was contained within a 100 ml. three-necked flask equipped with a magnetic stirrer, electric heating mantle, thermometer, and an efficient reflux condenser protected by a calcium chloride tube.

The mixture was stirred and cautiously heated to the reflux temperature. If, after several minutes of refluxing, the reaction showed no signs of having initiated (viz., a distinct change in clarity and/or color of the solution), one or two small crystals of iodine and/or mercuric chloride were added to reactivate the zinc in situ. In the event that the initial exothermic reaction threatened to "froth over", the heating mantle was removed and the flask was cooled as long as it was necessary to keep the reaction under control, but not enough to stop the reaction. Once under control, the reaction was refluxed and stirred for an additional two hours.

At the end of this period the reaction mixture was decanted from the unreacted zinc, and both the zinc and the flask were rinsed with additional solvent. The zinc was dried and its weight recorded. The decanted mixture was combined with the solvent and hydrolyzed with 10% sulfuric acid (20 ml.).

The resultant two phase system was separated; the aqueous layer was extracted with ether (2 x 25 ml.) and then discarded. The combined organic layers were evaporated under reduced pressure. The residue was saponified according to the method of Palmer and Reid (77) by refluxing it with a 2.5N solution of potassium hydroxide (13 ml.) in ethyl alcohol (25 ml.) for 4 hours. The saponification mixture was diluted with water (25 ml.) and most of the alcohol was removed at 60° under reduced pressure.

The residue was extracted with ether (2 x 25 ml., 2 x 10 ml.) and the combined ethereal extracts were washed with 5% sodium carbonate solution (these washings were combined with the main aqueous layer). Then the ether layer was dried over magnesium sulfate and carefully filtered into a tared distillation flask. Removal of the ether under reduced pressure left a neutral residue (mainly unreacted ketone) whose weight was recorded. The combined aqueous layers (above), containing the potassium salt of the hydroxy acid and excess base were heated on a steam bath to drive off traces of ether, cooled, and acidified with dilute hydrochloric acid. In most instances, the precipitated acid was isolated by suction filtration, washed, and dried. In a few cases it was necessary to extract the acid with ether, with subsequent washing, drying, and removal of ether. The weight and melting point of the impure acid were recorded.

b) REACTION UNDER REDUCED PRESSURE

This procedure was exactly the same as the above except that the apparatus was connected (via the top of the condenser) to a vacuum pump, manometer and bleeder valve (for adjusting and maintaining a constant low pressure). This set-up permitted the reaction mixture to be refluxed at a temperature considerably lower than that at atmospheric pressure. The low pressure was maintained throughout the initiation, and the two hour reflux period.

c) TWO-STAGE REACTION

As the name implies, this reaction was carried out in two steps:

First; a reaction of activated zinc granules (3.8 gm., 0.058 mole) with ethyl bromoacetate (4.5 gm., 0.027 mole) in anhydrous ether (30 ml.) was initiated as in the one-stage procedure (page 73), and refluxed one hour beyond initiation. At the end of this period the ethereal solution was cooled and quickly decanted into another dry reaction flask.

Second; a solution of the diarylketone (0.0063 mole) in 30 ml. of benzene-toluene (40:35 v/v) was added in one portion to the above ether solution. The total reaction mixture was refluxed for two hours, and worked up as in the one-stage procedure.

2. KEY TO THE TABLES OF EXPERIMENTAL RESULTS

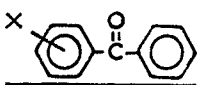
Data obtained from the reactions of monosubstituted benzophenones in the classical (one-stage) procedure is collected together in Tables 2 and 3 (pages 78 and 80).

Table 4 (page 84) gives data on reactions utilizing the reduced pressure technique (page 75). This table also includes, for the sake of comparison, the results from certain reactions carried out at atmospheric pressure (repeated from table 3).

Table 5 (page 85) lists the results from the two-stage reactions carried out according to the general procedure on page 75.

All the tables employ essentially the same format with the following column headings:

REACTION # : each experiment in this investigation has been given a number for reference purposes.

 : general formula for a monosubstituted benzophenone with a substituent X in either the 2- or 4- position of the aromatic nucleus.

SOLVENT : note the following abbreviations: Et₂O for diethyl ether and B-T for benzene-toluene (40:35 v/v).

Table 4, in addition to the solvent, lists the boiling point and pressure of the reaction mixture.

Table 5 omits this solvent heading altogether, since each reaction employed the same solvent system (see general procedure, page 75).

% REACTION : (with respect to recovered starting materials)

% YIELD : (or % reaction with respect to the isolated product, i.e., the impure hydroxyacid).

All of these calculations were based on the ketone as the limiting factor.

Thus % reaction on the basis of recovered ketone =

$$\left(1 - \frac{\text{weight of recovered ketone}}{\text{weight of original ketone}}\right) \times 100$$

and % reaction on the basis of unreacted zinc =

$$\frac{(\text{weight of original zinc} - \text{weight of recovered zinc})}{65.4 \times \text{moles of original ketone}} \times 100$$

Similarly, % yield of acid = $\frac{\text{moles of acid}}{\text{limiting factor}} \times 100$

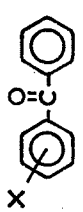
MELTING POINT : both the yield (above), and the melting point are those of the impure acid which was isolated according to the directions in the general procedure (page 74).

ZINC COMPLEX : Table 3 gives a brief description of the halozinc complex as it appeared in situ, prior to hydrolysis.

Supplementary notes are to be found on the pages immediately following Tables 2 and 3.

TABLE 2

Preliminary Reactions with 2- and 4-Methylbenzophenones

REACTION #	 <chem>Xc1ccc(cc1)C(=O)c2ccccc2</chem>	SOLVENT	% REACTION with respect to recovered		% YIELD OF ACID	MELTING POINT * (°C)
			Zn	KETONE		
1 **	2-CH ₃	B-T ***	96	36	32	112 - 128
2 **	"	B ***	100	43	41	126 - 132
3	"	B-Et ₂ O ***	100	53	53	136 - 140.5
4	"	Et ₂ O	96	48	52	130 - 137
5 **	4-CH ₃	B-T	100	68	76	172.5 - 174.5
6 **	"	B	100	61	62	114 - 123
7	"	B-Et ₂ O	100	80	81	104 - 115
8	"	Et ₂ O	100	80	84	166 - 169

* Melted with decomposition (frothing).

** See supplementary notes on next page.

*** B-T, benzene-toluene (40:35 v/v) ; B, benzene ; B-Et₂O, benzene-ether (1:1 v/v).

SUPPLEMENTARY NOTES TO TABLE 2

Reaction #1 (2-methylbenzophenone in benzene-toluene)

The decanted reaction mixture, on cooling overnight in a glass-stoppered flask, prior to hydrolysis, separated into three apparent phases, viz., top: clear brown solution; middle: translucent suspension; bottom: dark brown viscous oil.

Reaction #2 (2-methylbenzophenone in benzene)

Prior to hydrolysis, the filtered reaction mixture was stored at 0° in an air tight flask for a few hours and then allowed to stand at room temperature for two days. The mixture, at the end of that time, consisted of a clear tan colored solution over a finely divided yellow solid (with a green colored impurity).

Reaction #5 (4-methylbenzophenone in benzene-toluene)

Cooling the mixture overnight at 0° (in a glass-stoppered flask) caused it to separate into two layers; viz., top: a clear yellow solution, and bottom: an opaque suspension.

Reaction #6 (4-methylbenzophenone in benzene)

Cooling at 0° for a few hours caused the filtered reaction mixture to separate into a clear yellow solution and a greenish-white solid.

TABLE 3

Reactions of Monosubstituted Benzophenones
in Diethyl Ether and Benzene-Toluene

SUPPLEMENTARY NOTES TO TABLE 3

Reaction #9 (2-aminobenzophenone in ether)

The ketone was not completely soluble in the refluxing reaction mixture prior to initiation. The dark red zinc complex, which formed shortly after initiation, coated the zinc granules and hindered the stirring action somewhat.

Reaction #11 (4-aminobenzophenone in ether)

Only 0.017 mole ketone was used in this reaction with all other quantities of reagents identical to those in the general procedure (page 73). This ketone was only partially soluble in the refluxing solvent, and as a result, it was difficult to tell whether or not an insoluble zinc complex formed during the course of the reaction.

Reaction #12 (4-aminobenzophenone in benzene-toluene)

Only 0.017 mole of ketone was used in this experiment with all other quantities of reagents identical to those in general procedure (a) (page 73). This ketone was completely soluble in the refluxing reaction mixture.

Reactions #14 and #16

(2- and 4-hydroxybenzophenones in benzene-toluene)

These reactions could not be completely separated into ketonic and acidic fractions after the saponification step, due to the acidic natures of the phenolic ketones. Therefore, the results from these experiments were considered to be only approximate.

Reactions #13 and #15

(2- and 4-hydroxybenzophenones in ether)

In an attempt to obtain a better separation of ketonic and acidic fractions from the saponification mixtures, the following modification to the general procedure was employed for these two reactions: the acid (containing ketone impurity) from the general procedure, was dissolved in a small amount of 10% sodium bicarbonate solution. This solution was worked up, in the same way as the saponification mixture in the general procedure, giving weakly acidic (ketone) and acid fractions. The ketone fractions from the general procedure and the above modification were combined and % reaction and % yield were calculated in the usual manner. As in reactions #14 and #16, these results are considered to be in error.

It should be noted that the saponification mixtures for reactions #15 and #16 (4-hydroxybenzophenone reactions) yielded small quantities of the potassium salt of 4-hydroxybenzophenone. This material was taken into account in the calculations of % reaction (with respect to recovered ketone).

Reactions #23 and #24

(4-fluorobenzophenone in ether and in benzene-toluene)

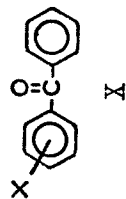
All quantities of reagents were scaled down by a factor of 7/8.

Reaction #26 (2-chlorobenzophenone in benzene-toluene)

The final product was isolated as the unsaturated acid, β -(2-chlorophenyl)- β -phenylacrylic acid (see Discussion of Experimental Results, page 57).

TABLE 4

Reactions Under Various Pressures



REACTION

#

% REACTION
with respect
to recovered
Zn
KETONE

% YIELD
OF ACID

MELTING POINT *
(°C)

SOLVENT

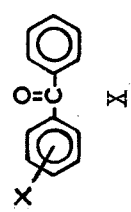
37	4-CH ₃	anisole Bp. 64°/26mm.	100	--	76	126 - 140
38	2-CH ₃	anisole Bp. 62°/26mm.	100	--	58	135 - 139.5
39	2-CH ₃	B-T ** Bp. 37°/82mm.	44	16	16	-----
1	"	B-T Bp. 93°/atm.	96	36	32	112 - 128
40	2-OCH ₃	B-T Bp. 38°/84mm.	92	48	52	101 - 116
18	"	B-T Bp. 91°/atm.	100	56	64	123 - 128
41	2-Br	B-T Bp. 38°/85mm.	80	32	24	151 - 153
30	"	B-T Bp. 92°/atm.	92	28	32	142.5 - 145

* Melted with decomposition (frothing).

** Benzene-Toluene (40:35 v/v).

TABLE 5

Two-Stage Reactions

REACTION #		% REACTION with respect to recovered		% YIELD OF ACID	MELTING POINT * (°C)
		Zn	KETONE		
42	2-NH ₂	100	11	16	ca. 130
43	4-NH ₂	100	27	31	ca. 110
44	4-OCH ₃	100	91	82	70 - 131
45	2-CH ₃	100	51	56	127 - 137
46	2-NO ₂	100	8	0	-----
47 **	4-NO ₂	100	93	100	148 - 151

* Melted with decomposition (frothing).

** The zinc complex formed in this reaction was soluble.

PURIFICATION AND CHARACTERIZATION OF THE
 β, β -DIARYLHYDRACRYLIC ACIDS

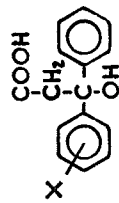
The melting points and analyses for the purified β -hydroxyacids and the corresponding p-nitrobenzyl esters are given in tables 6 and 7, respectively. Additional information pertaining to the acids is to be found in the supplementary notes immediately following table 6.

1. THE β, β -DIARYLHYDRACRYLIC ACIDS

Analyses were not carried out on those compounds whose existence has been reported in the literature. However, the literature melting points for these acids are compared with those from the present study in table 1, page 56.

All of the hydroxyacids, with the exception of the 2-amino, 2-hydroxy, and 4-nitro compounds, were recrystallized from aqueous-alcohol (ethanol or methanol) as white, crystalline solids.

TABLE 6 β, β -Diarylhydracrylic Acids



MELTING POINT *

ANALYSIS

	MELTING POINT * (°C)	CALCULATED	FOUND
2-NH ₂	186 - 189	C ₁₅ H ₁₅ NO ₃ , C, 70.0 ; H, 5.9 ; N, 5.4 .	C, 70.1 ; H, 5.2 ; N, 5.6
4-NH ₂	ca. 171		
2-OH	109 - 111	C ₁₅ H ₁₄ O ₄ , C, 69.8 ; H, 5.4	C, 71.3 ; H, 5.0
4-OH	154 - 156	" "	C, 69.7 ; H, 4.9
2-OCH ₃	139 - 140.5 **		
4-OCH ₃	154 - 155 **		
2-CH ₃	147 - 148 **		
4-CH ₃	180 - 182 **		
H	210 - 211 **		
4-F	174 - 175.5	C ₁₅ H ₁₃ FO ₃ , C, 69.2 ; H, 5.0 ; F, 7.3 .	C, 69.4 ; H, 5.2 ; F, 8.3
2-Cl	153 - 157	C ₁₅ H ₁₃ ClO ₃ , C, 65.1 ; H, 4.7 ; Cl, 12.8 .	C, 65.4 ; H, 4.7 ; Cl, 12.8
4-Cl	187 - 190 **		
2-Br	154 - 155	C ₁₅ H ₁₃ BrO ₃ , C, 56.1 ; H, 4.1 ; Br, 24.9 .	C, 56.7 ; H, 4.3 ; Br, 24.8
4-Br	186 - 188	" "	C, 55.8 ; H, 4.2 ; Br, 25.0
4-NO ₂	142 - 143	C ₁₅ H ₁₃ NO ₅ ,	N, 4.9 .

* Melted with decomposition (frothing).

** These melting points are compared with literature values in Table 1 (page 56).

SUPPLEMENTARY NOTES TO TABLE 6

2-NH₂: Recrystallized from aqueous-methanol as bright yellow needles.

Neutralization equivalent, Calculated: 257.3; Found: 258 ± 3.

4-NH₂: After attempting several recrystallizations from a variety of solvents, this acid was isolated, still impure, and in too small a quantity for further purification.

2-OH : Recrystallized from benzene as a white crystalline powder. A second analysis for this acid gave the following results:

Calculated for C₁₅H₁₄O₄ : C, 69.8; H, 5.4 .

Found : C, 70.8; H, 4.2 .

4-OH : The crude acid was contaminated by a considerable quantity of the ketone, 4-hydroxybenzophenone, and what appeared to be the potassium salt of the latter (which melted at 317 - 322°dec.) .

4-CH₃: The melting point of the silver salt of this acid was 233 - 234°dec. (with frothing).

H: The zinc complex, prior to hydrolysis and saponification to the acid, was found to decompose (with apparent formation of zinc hydroxide) at ca. 118 - 120°.

4-F :

Neutralization equivalent, Calculated: 260.3; Found: 262 ± 3.

2-Cl : The unsaturated acid, formed in reaction #26, melted at 140 - 141.5° and gave the following analysis:

Calculated for $C_{15}H_{11}ClO_2$: C, 70.0 ; H, 4.25 ; Cl, 13.7

Found : C, 69.7 ; H, 4.28 ; Cl, 13.9

Neutralization equivalent, Calculated: 258.5 ; Found: 260 ± 3.

4-Cl : The zinc complex, prior to hydrolysis and saponification to the acid, melted at ca. 78 - 83° dec. (with frothing) and then decomposed further at ca. 123° (with apparent formation of zinc hydroxide).

2-Br :

Neutralization equivalent, Calculated: 321.2 ; Found: 321 ± 3.

4-Br :

Neutralization equivalent, Calculated: 321.2 ; Found: 320 ± 3.

4-NO₂: Recrystallized from benzene as small transparent crystals having a slight tan color. After several days in a vacuum desiccator, these crystals decomposed into a white powder (which melted at 142 - 143°) due to apparent loss of benzene of crystallization.

2. THE p-NITROBENZYL β, β -DIARYLHYDRACRYLATES

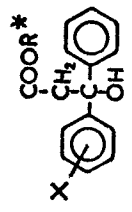
These esters were prepared by a method similar to that recommended by Shriner, Fuson, and Curtin (91).

The acid (1.0 gm.) was mixed with a small quantity of water (5 ml.) and neutralized with a dilute solution of sodium hydroxide. A drop of very dilute hydrochloric acid was added to make the solution just acid to litmus. p-Nitrobenzyl bromide (1.0 gm.) and alcohol (10 ml.) were added and the reaction mixture was refluxed for one hour. Additional alcohol was added from time to time as was necessary to keep the mixture clear. The solution was cooled and extracted with ether (1 x 30 ml.) . The organic phase was washed successively with 5% sodium bicarbonate solution (2 x 5 ml.) and water (2 x 10 ml.) . After drying and evaporating off the ether, the resultant ester was recrystallized from aqueous-alcohol (methanol or ethanol).

Acids bearing the following substituents were not prepared: 2-NH₂, 4-NH₂, 4-CH₃O, and H (unsubstituted).

TABLE 7

p-Nitrobenzyl β, β -Diarylhydracrylates



MELTING POINT ANALYSIS

X	MELTING POINT (°C)	ANALYSIS	
		CALCULATED	FOUND
2-NH ₂	-----		
4-NH ₂	-----		
2-OH	86 - 89	C ₂₂ H ₁₉ NO ₆ , N, 3.6	. N, 3.9
4-OH	106 - 108	" "	. N, 3.3
2-OCH ₃	106.5 - 108	C ₂₃ H ₂₁ NO ₆ , N, 3.4	. N, 3.9
4-OCH ₃	-----		
2-CH ₃	130 - 132	C ₂₃ H ₂₁ NO ₅ , N, 3.6	. N, 3.8
4-CH ₃	101 - 102.5	" "	. N, 3.7
H	-----		
4-F	105 - 106	C ₂₂ H ₁₈ NFO ₅ , N, 4.8 ; F, 3.5	. N, 4.2 ; F, 3.3
2-Cl	108 - 110	C ₂₂ H ₁₈ NCLO ₅ , N, 3.4 ; Cl, 8.6	. N, 3.6 ; Cl, 8.7
4-Cl	111.5 - 112.5	" "	. N, 3.6 ; Cl, 8.9
2-Br	120.5 - 122	C ₂₂ H ₁₈ NBrO ₅ , N, 3.1 ; Br, 17.5	. N, 2.3 ; Br, 19.6
4-Br	125.5 - 127	" "	. N, 2.7 ; Br, 19.9
4-NO ₂	139 - 140.5	C ₂₂ H ₁₈ N ₂ O ₇ , N, 6.6 ;	. N, 6.4

* R : -CH₂-C₆H₄-NO₂

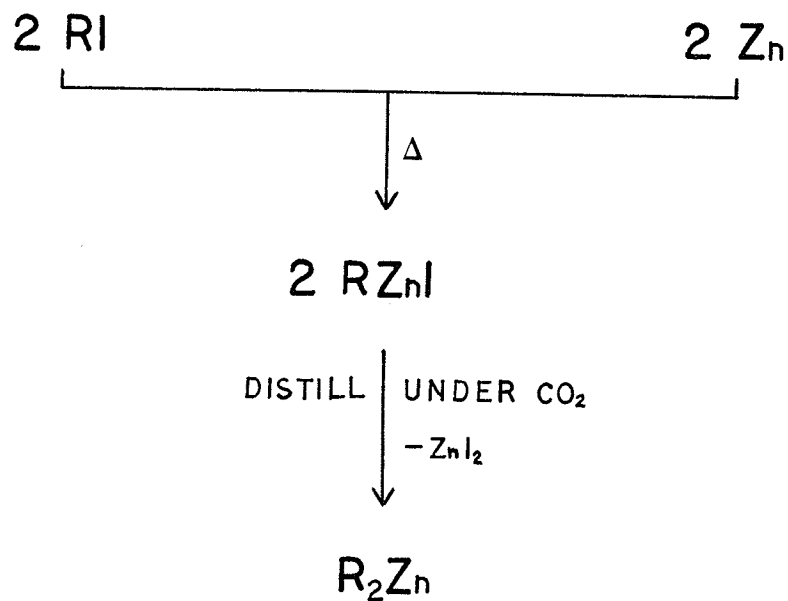
APPENDIX A

HISTORY OF THE REFORMATSKY REACTION

The introduction of organozinc compounds antedated that of the Reformatsky reagents (halozinc enolates) by some thirty-six years. The chart on the next page and the accompanying chronology, give the historical development of the Reformatsky reaction and its relation to the Grignard reaction.

1849

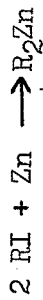
E. Frankland discovered the dialkylzinc compounds (the first organometallic compounds). The synthesis involved the heating of an alkyl iodide with zinc metal in an inert atmosphere:



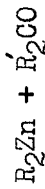
CHART

Historical Development of the Reformatsky Reaction.

E. Frankland (1849)

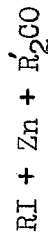


Butlerov (1863)

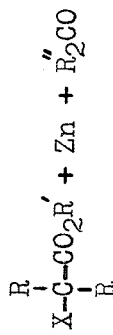


Wagner - Saytzeff

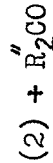
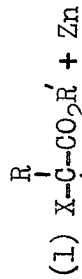
Reaction (1875)



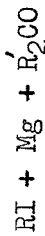
Reformatsky Reaction (1887)



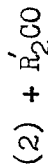
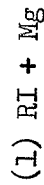
Siegel and Keckeis (1953)



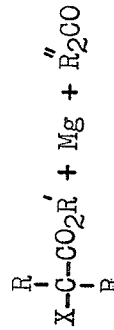
Barbier Reaction (1898)



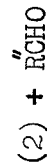
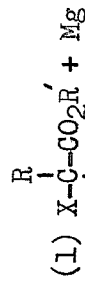
Grignard Reaction (1900)



Zelinsky and Gutt (1902)

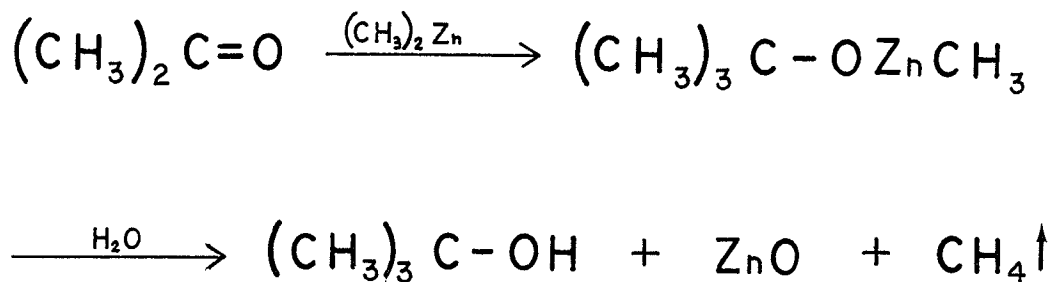


Zeltner (1908) [attempted reaction]

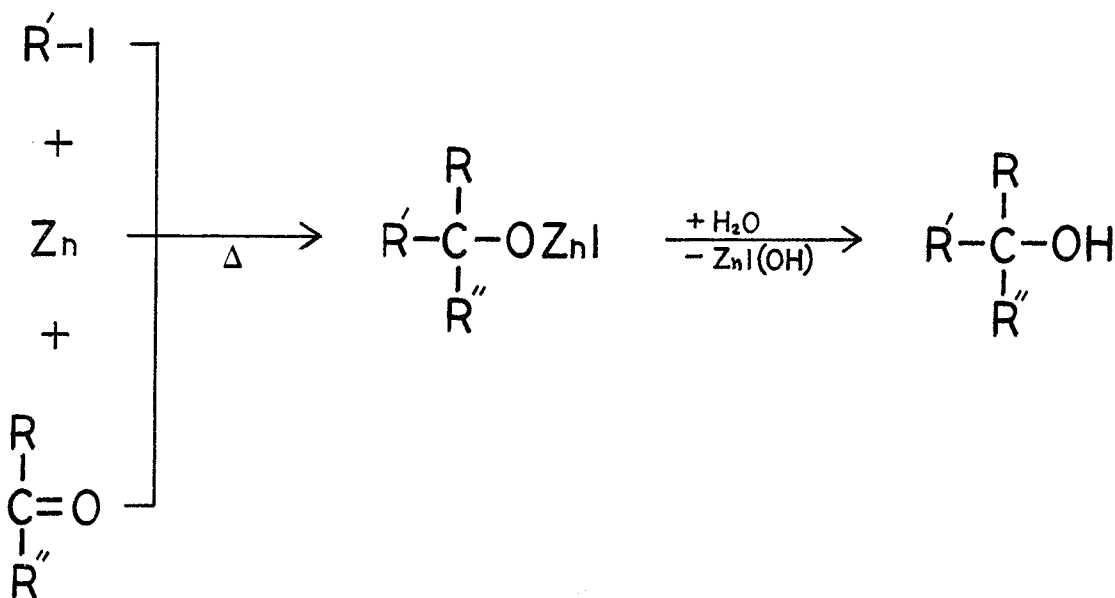


1863

A. M. Butlerov (20) prepared trimethyl carbinol by reacting dimethylzinc with acetone followed by hydrolysis of the resultant complex:

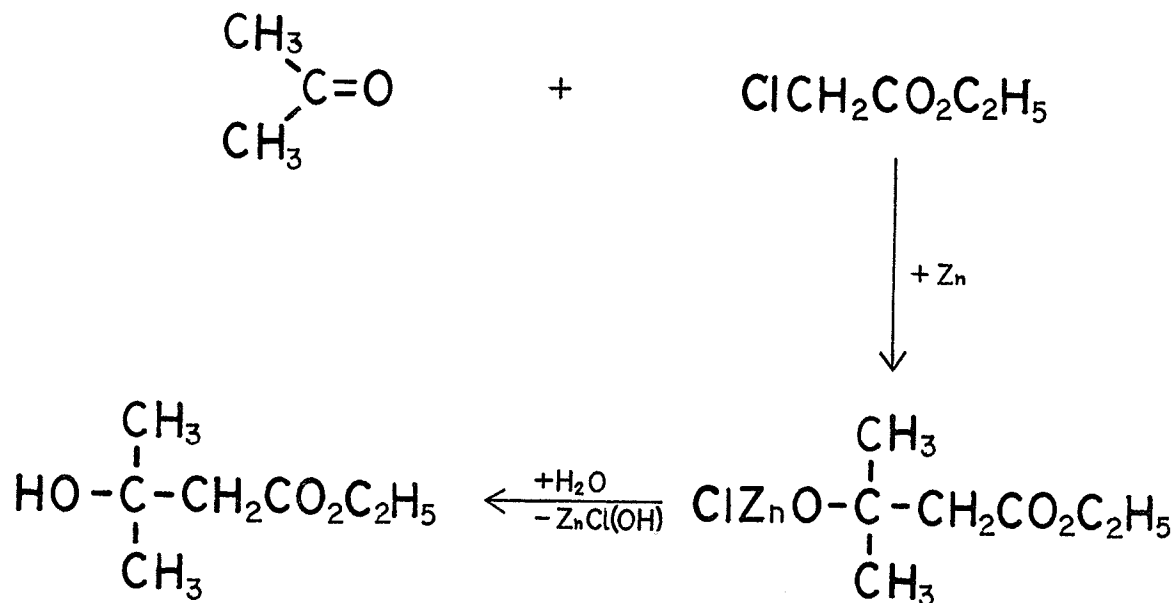
1875

Saytzeff (a former student of Butlerov) and Wagner (105) avoided the use of the spontaneously flammable dialkylzinc reagent by generating the alkylzinc iodide in the presence of the carbonyl compound. Hydrolysis of the resultant halo-zinc enolate gave the expected tertiary alcohol:

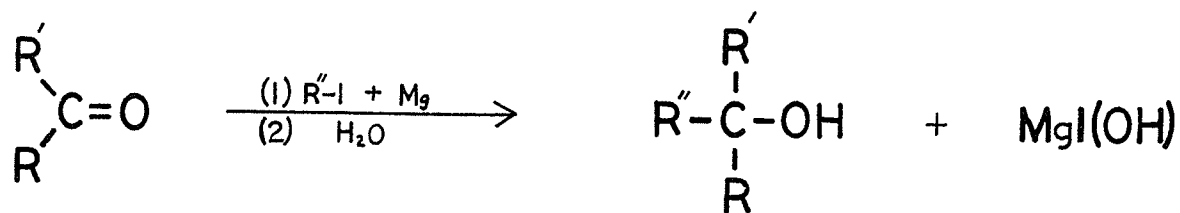


1887

Sergei Nikolayevich Reformatsky (79), a former student of Saytzeff, extended the Wagner-Saytzeff reaction by replacing the alkyl iodides with α -halogen esters:

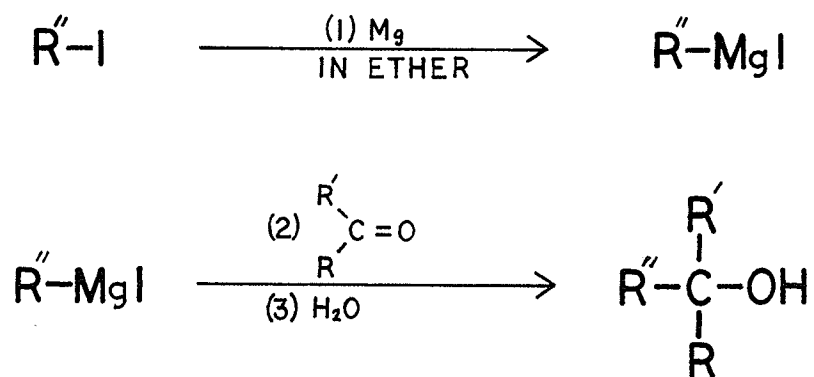
1898

P. Barbier (5) attempted to improve the Wagner - Saytzeff reaction by substituting magnesium for zinc:

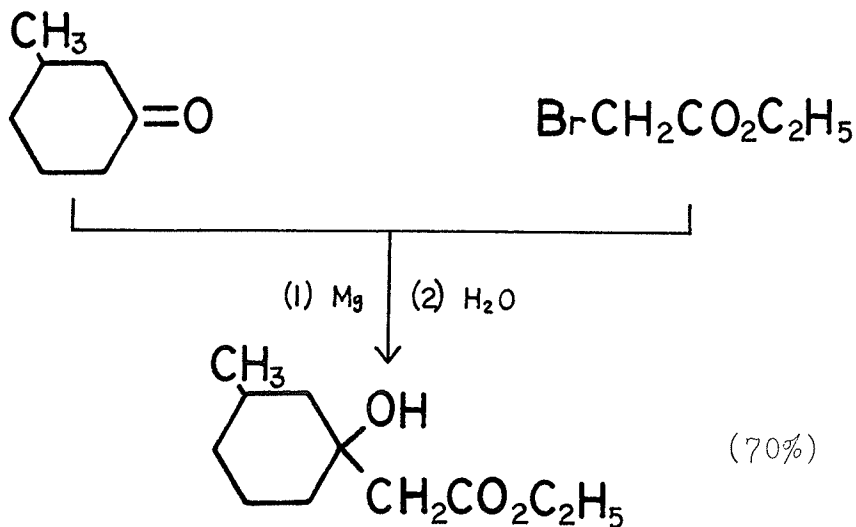


1900

Victor Grignard (45), one of Barbier's students, discovered that the intermediate RMgX could be generated in diethyl ether prior to reaction with the carbonyl compound. Thus the Grignard reaction was essentially a two-stage Barbier reaction:

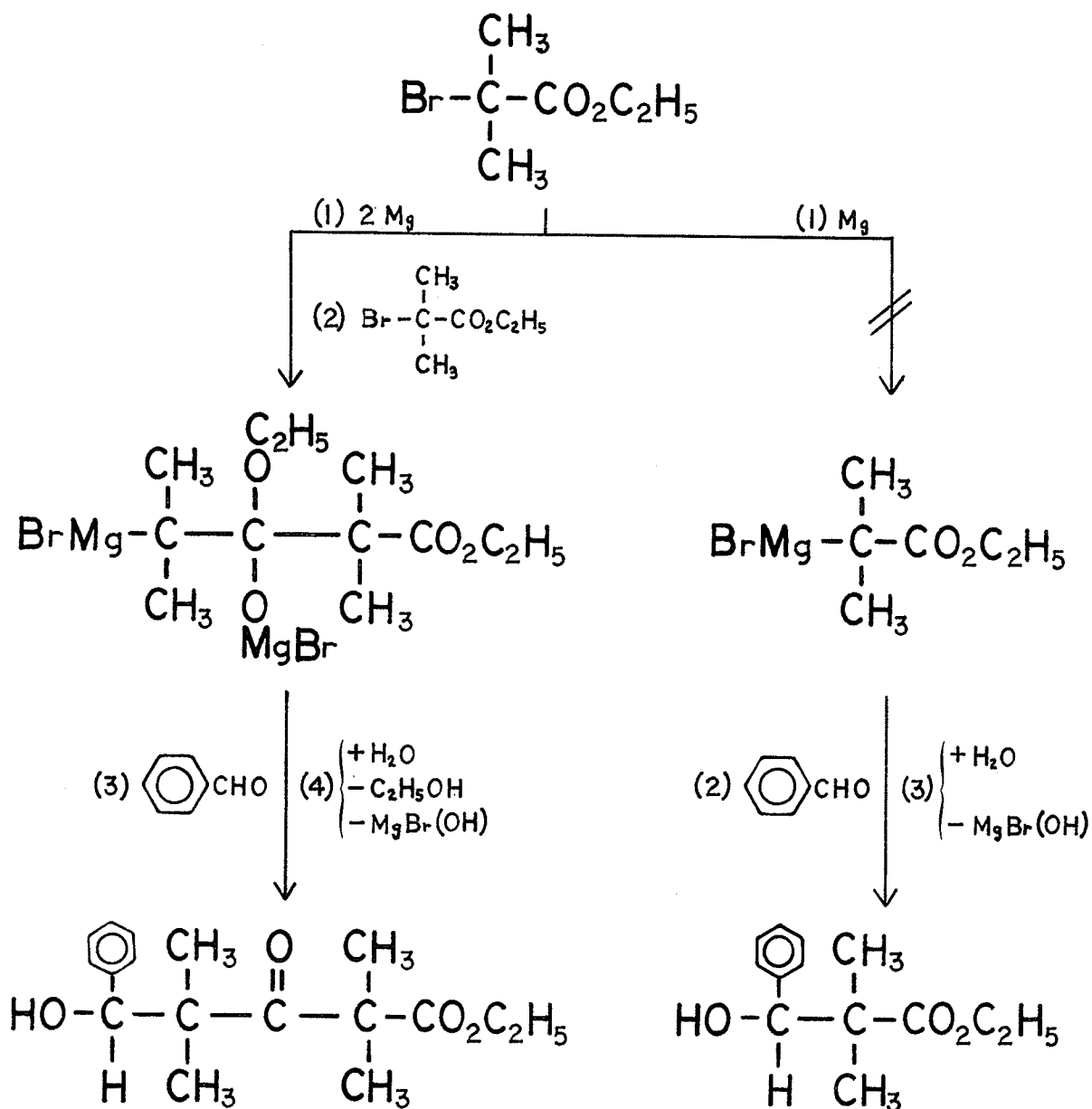
1902

Zelinsky and Gutt (107) replaced zinc with magnesium in the Reformatsky reaction. One of their reactions involved the condensation of 3-methylcyclohexanone with ethyl bromoacetate:



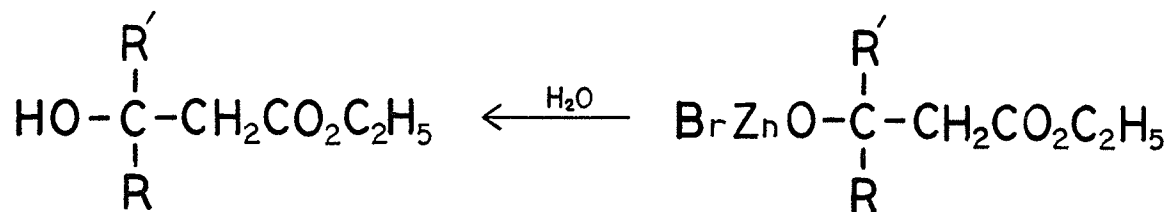
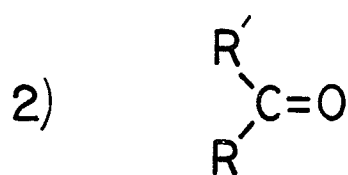
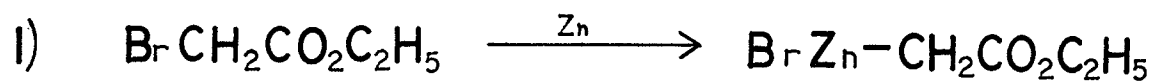
1908

Zeltner (108), under the guidance of Reformatsky, reacted magnesium in an ethereal solution of a tertiary bromoester and then introduced benzaldehyde into the reaction mixture obtained. Zeltner did not obtain the expected hydroxyester due to self condensation of the Grignard reagent:



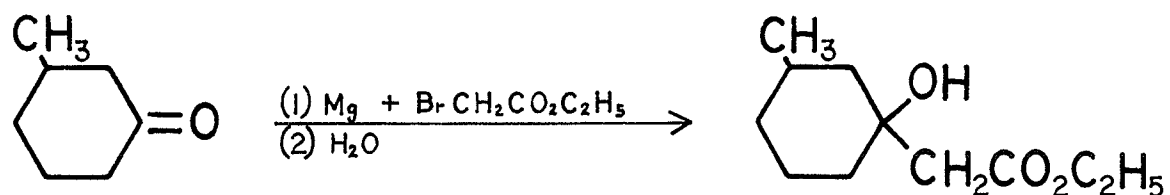
1953

Siegel and Keckeis (92) demonstrated that the Reformatsky reaction could be carried out in a two-stage procedure similar to the Grignard reaction, i.e., the haloester was brought into reaction with zinc in an inert solvent and the resulting solution of the organozinc compound (Reformatsky reagent), then treated with a carbonyl compound:

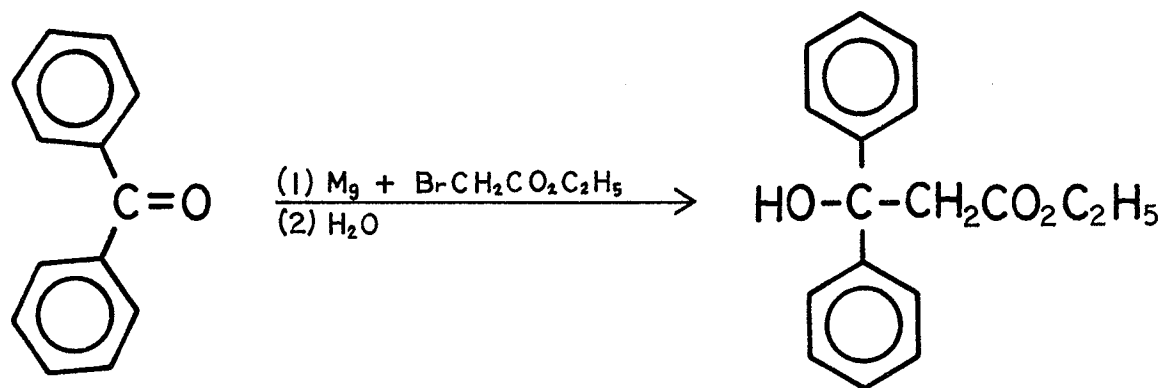


APPENDIX BSYNTHESES OF β -HYDROXY ESTERS AND ACIDS BY METHODS OTHER THAN THE REFORMATSKY REACTION1902

Zelinsky and Gutt (107)

1908

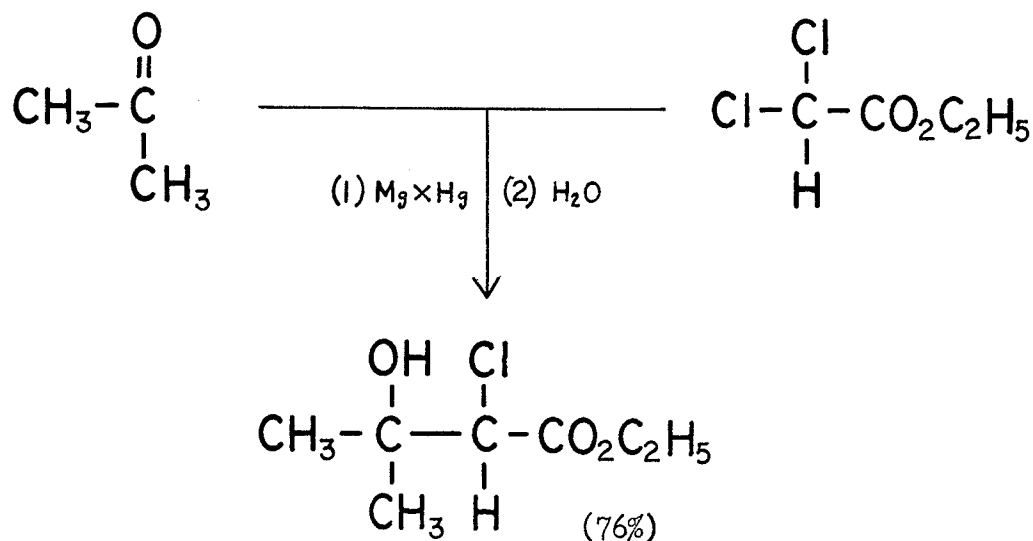
Ferrario and Vinay (42)



These workers claimed that the hydroxyester obtained from this reaction was purer, and in higher yield than that from the Reformatsky reaction.

1910

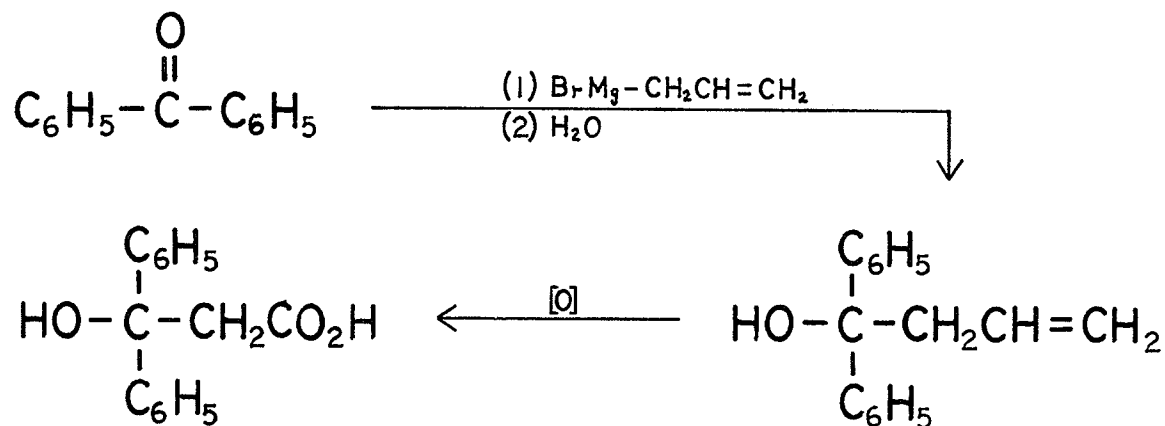
Darzens (26)



Approximately a quarter of a century later, Darzens repeated this procedure with acetophenone (27) and cyclohexanone (28) and obtained the expected β -hydroxy- α -chloroesters in yields of 90% and 97% respectively.

1910

Tarassov (100)



This reaction was repeated by Kharasch and Weinhouse (59)

in 1934, and by Favorskaya and Fridman (39) in 1948.

1910

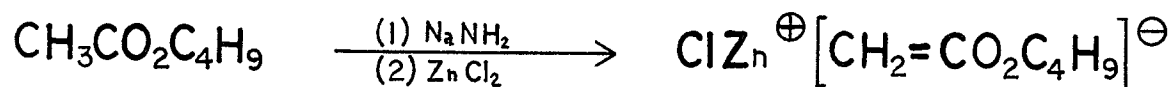
Kusjimin (63) repeated the above procedure with 4-methylbenzophenone and obtained β -(4-methylphenyl)- β -phenylhydracrylic acid.

1915

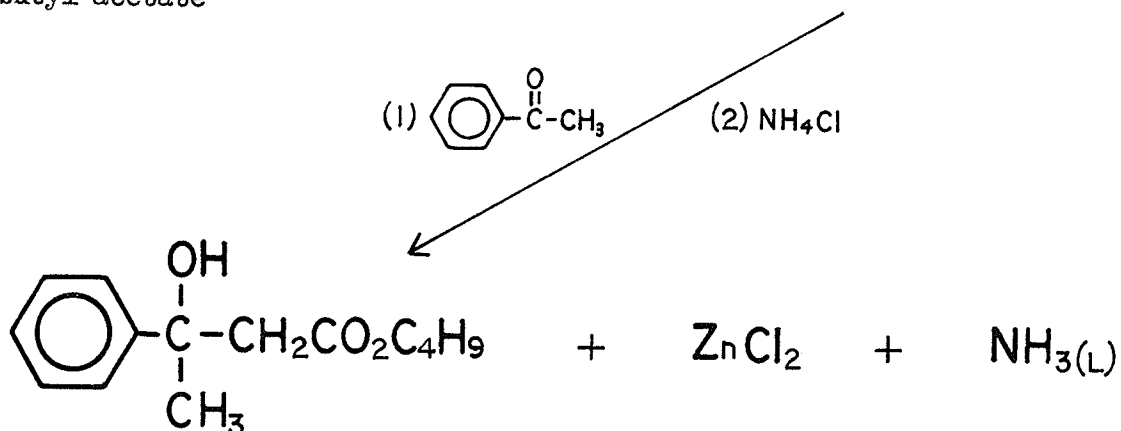
Berberianu (7) carried out condensations between benzophenone and a number of bromoesters in the presence of magnesium in benzene. A reaction between 4-methoxybenzophenone and methyl α -bromopropionate was also reported.

1951

Hauser and Puterbaugh (48)



t-butyl acetate



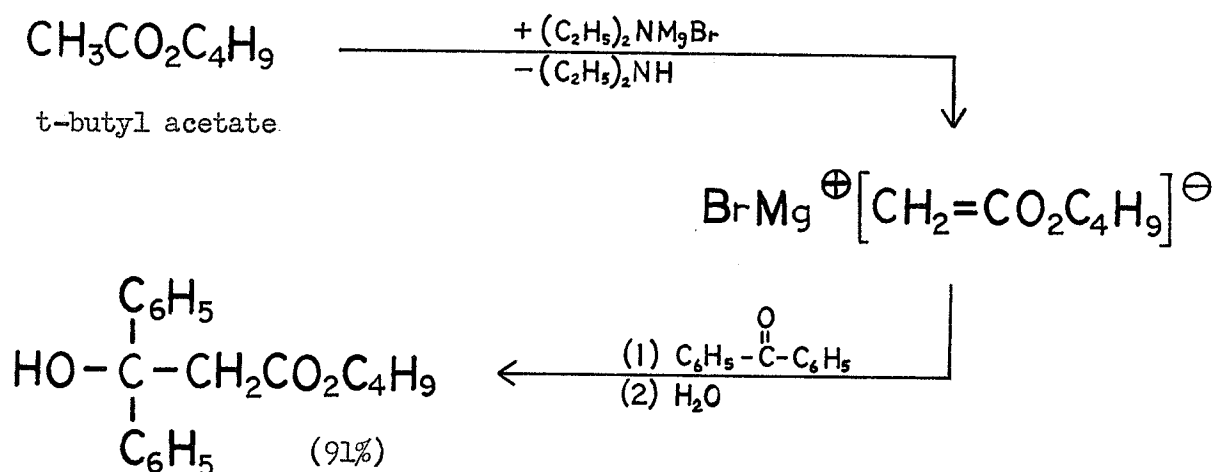
The entire reaction was performed in liquid ammonia. It was found that the use of lithium amide in place of sodium

amide, without zinc chloride, and with ether as a solvent, gave higher yields.

Two years later, they extended this organolithium procedure to the preparation of t-butyl β -hydroxyesters from 4-chloro and 4-nitroacetophenones (49). The yields from this method were either comparable with, or significantly better than, those from the analogous Reformatsky reactions.

1952

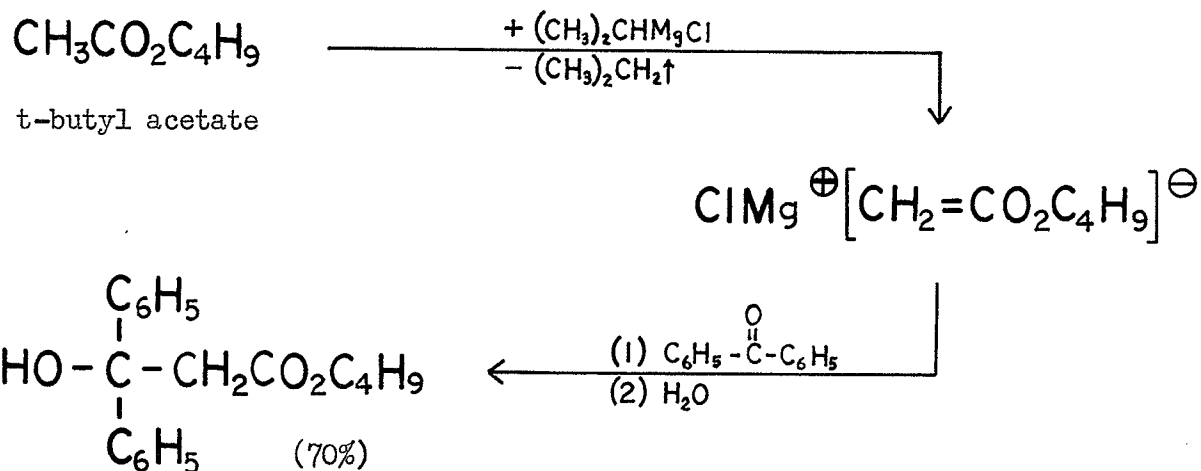
Sisido et al. (95)



Several years later, Sisido et al. (94) used this method to condense (-)-menthyl and (-)-bornyl acetates with several substituted benzophenones, including 4-methoxy-, 2-methyl-, 4-methyl-, and 4-chlorobenzophenones. The yields of diastereoisomeric hydroxyesters from these ketones were 72, 73, 70 and 74%, respectively. The lack of self-condensation of the esters was attributed to the bulkiness of the menthyl and bornyl groups.

1955

Barnaud and Dubois (6)



They claimed that other ketones gave yields that were greater than, or at least comparable to, those from the Reformatsky reaction.

1957

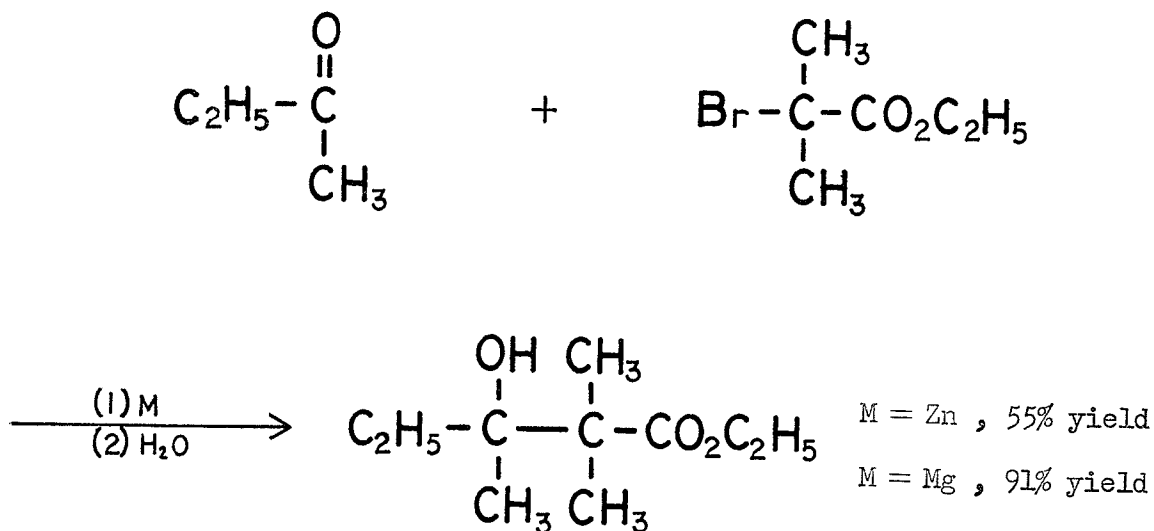
Cason and Fessenden (22) studied the use of di-n-propyl cadmium and zinc as condensing agents in reactions between the following ketones and bromoesters:

KETONE	α -BROMOESTER	AVERAGE YIELDS (%) FROM	
		DI-n-PROPYL CADMIUM	REFORMATSKY REACTION
2-Octanone	Ethyl α -bromopropionate	75	79
2-Octanone	Ethyl α -bromoisobutyrate	83	78
Diisobutyl ketone	Ethyl α -bromopropionate	47	68

1958

Jacques and Weidmann (54) demonstrated that when tertiary α -bromoesters were condensed with ketones, it was advantageous to replace zinc with magnesium in the Reformatsky reaction.

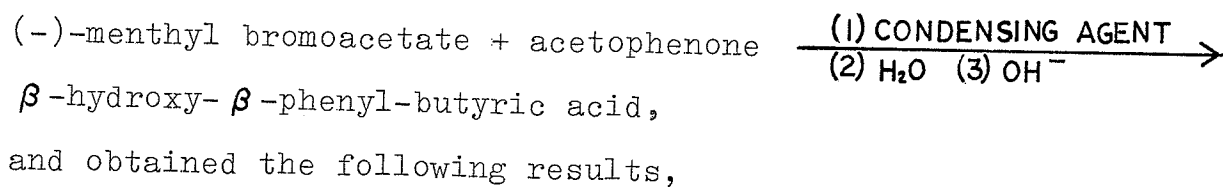
For example,



They attributed the success of this type of reaction to the relatively large steric effect in the tertiary bromoester which diminished the attack of the Grignard reagent on the carbonyl group of the bromoester, relative to the attack on the carbonyl group of the ketone.

1960

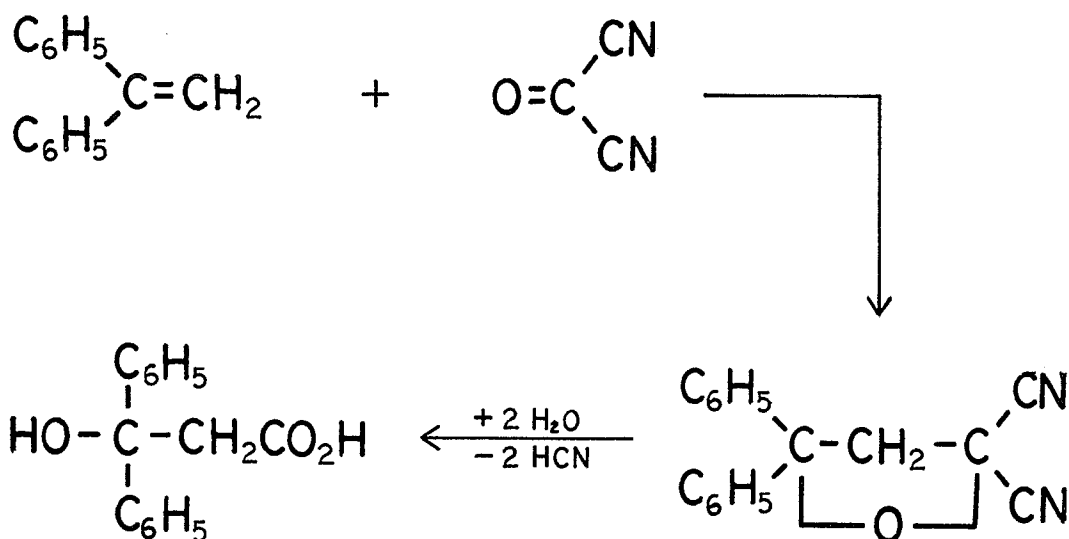
Palmer and Reid (77) carried out the reaction:



CONDENSING AGENT	PROCEDURE	% YIELD OF ACID
zinc	classical Reformatsky	64
zinc	two-stage Reformatsky	37
di-n-propyl zinc	Grignard	66
di-n-propyl cadmium	Grignard	63

1960

Achmatowicz and Leplawy (1)

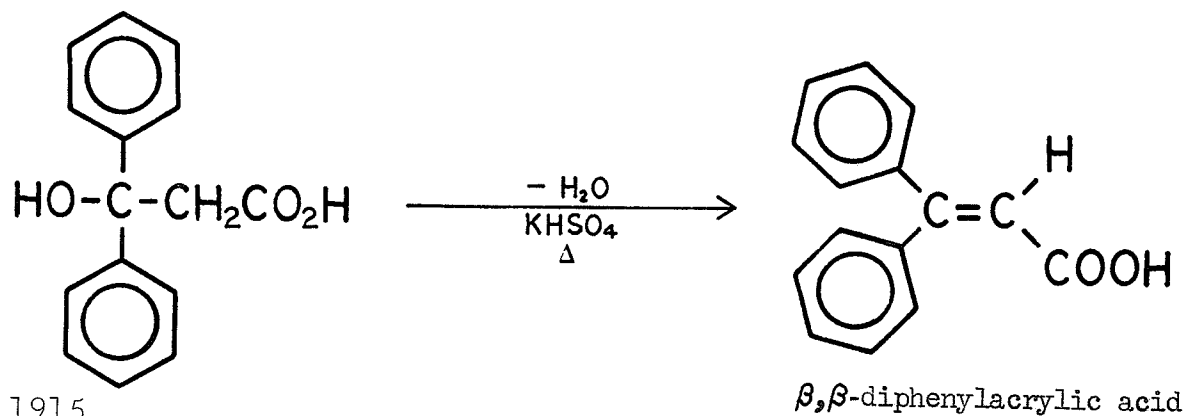


1960

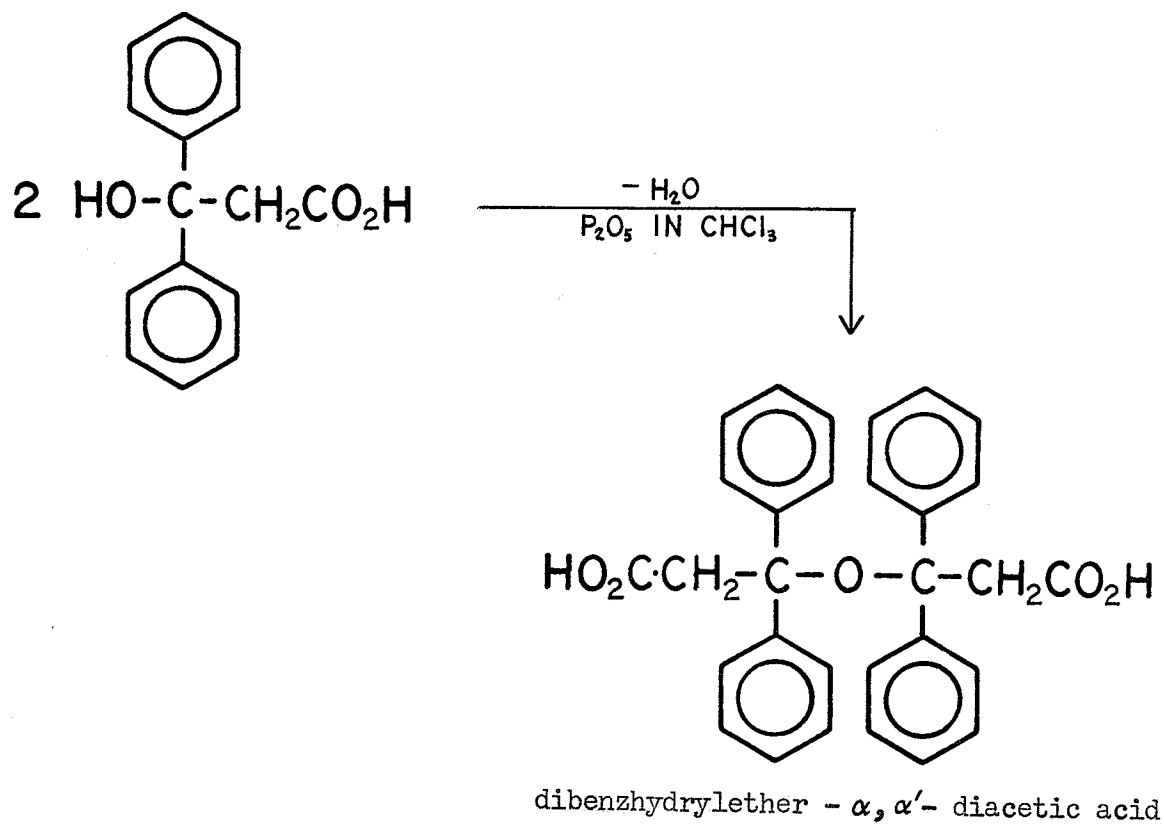
Dunnavant and Hauser (36) synthesized β -hydroxyesters from ethyl acetate and carbonyl compounds, using lithium amide as a condensing agent. They considered their procedure to be more convenient than the Reformatsky reaction. Benzophenone and 4-methylbenzophenone gave yields of 84 and 88% respectively, of the expected hydroxyesters in this organolithium reaction.

APPENDIX CDERIVATIVES PREPARED FROM β, β -DIARYLHYDRACRYLIC ACIDS1907

Rupe and Busolt (82)

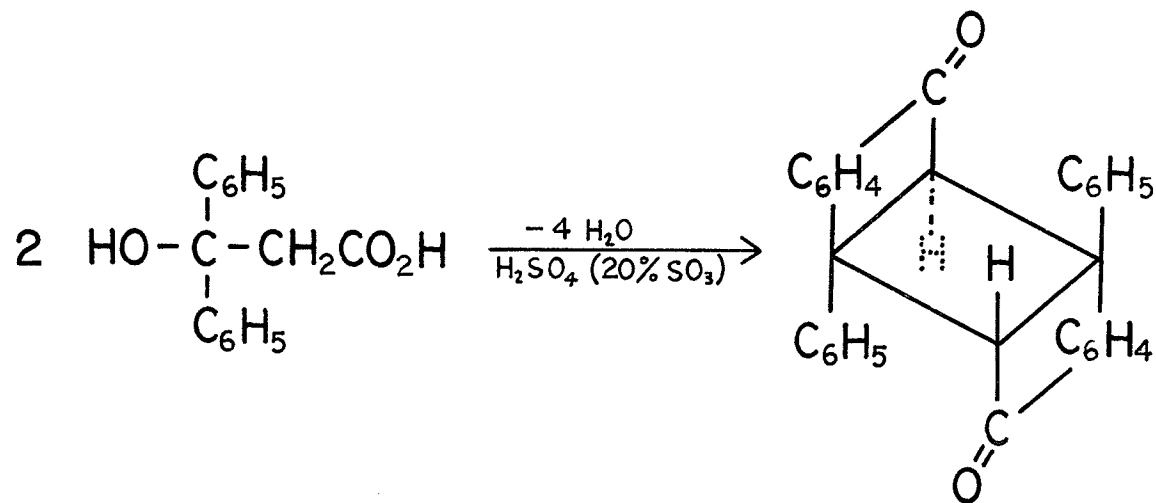
1915

de Fazi (40)



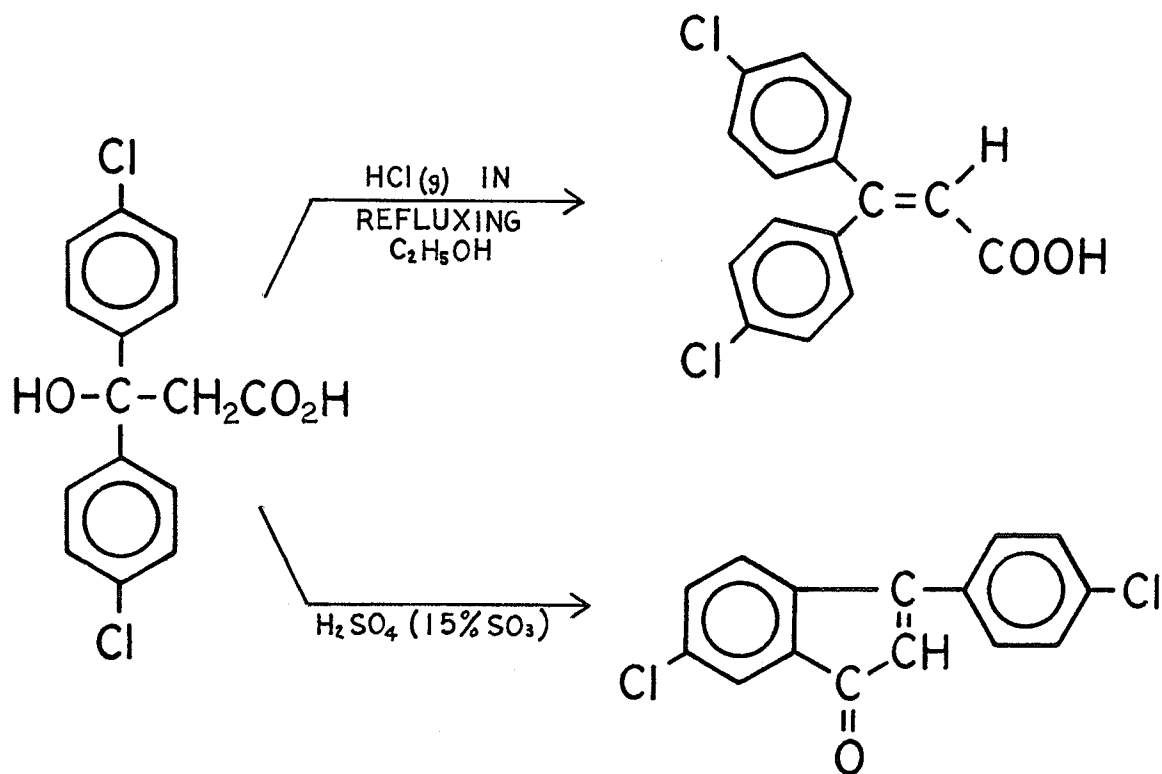
1919

Stoermer and Foerster (97)

 α -diphenyltruxone

1950

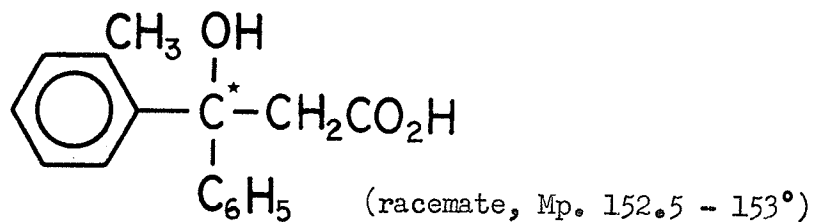
Feeman and Amstutz (41)



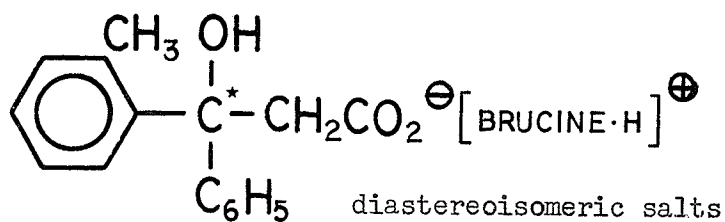
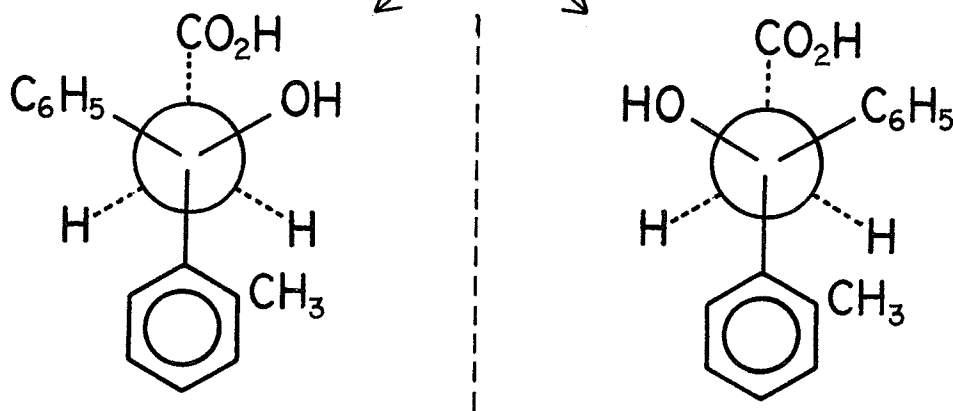
6-chloro-3-(4-chlorophenyl)-1-indenone

1960

Sisido et al. (94)



+ BRUCINE

(1) SEPARATION
OF SALTS(2) + HCl ; REMOVAL OF
BRUCINE · HCl

d- and l- acids

Mp.'s 154 - 154.5° and 153.5 - 154°, respectively

(absolute configurations unknown)

SUMMARY

1. A study has been made on the preparation of β, β -diaryl-hydracrylic acids from the condensation of a series of monosubstituted benzophenones with ethyl bromoacetate in the Reformatsky reaction.

Resonance and steric effects, associated with the substituent groups attached to the benzophenone nucleus, were found to have predictable influences on the yields of hydroxyacids.

Nine of the fifteen acids synthesized in this study were new compounds, viz.,

β -(2-aminophenyl)- , β -(4-aminophenyl)- ,
 β -(2-hydroxyphenyl)- , β -(4-hydroxyphenyl)- ,
 β -(2-bromophenyl)- , β -(4-bromophenyl)- ,
 β -(2-chlorophenyl)- , β -(4-fluorophenyl)- , and
 β -(4-nitrophenyl)- β -phenylhydracrylic acids.

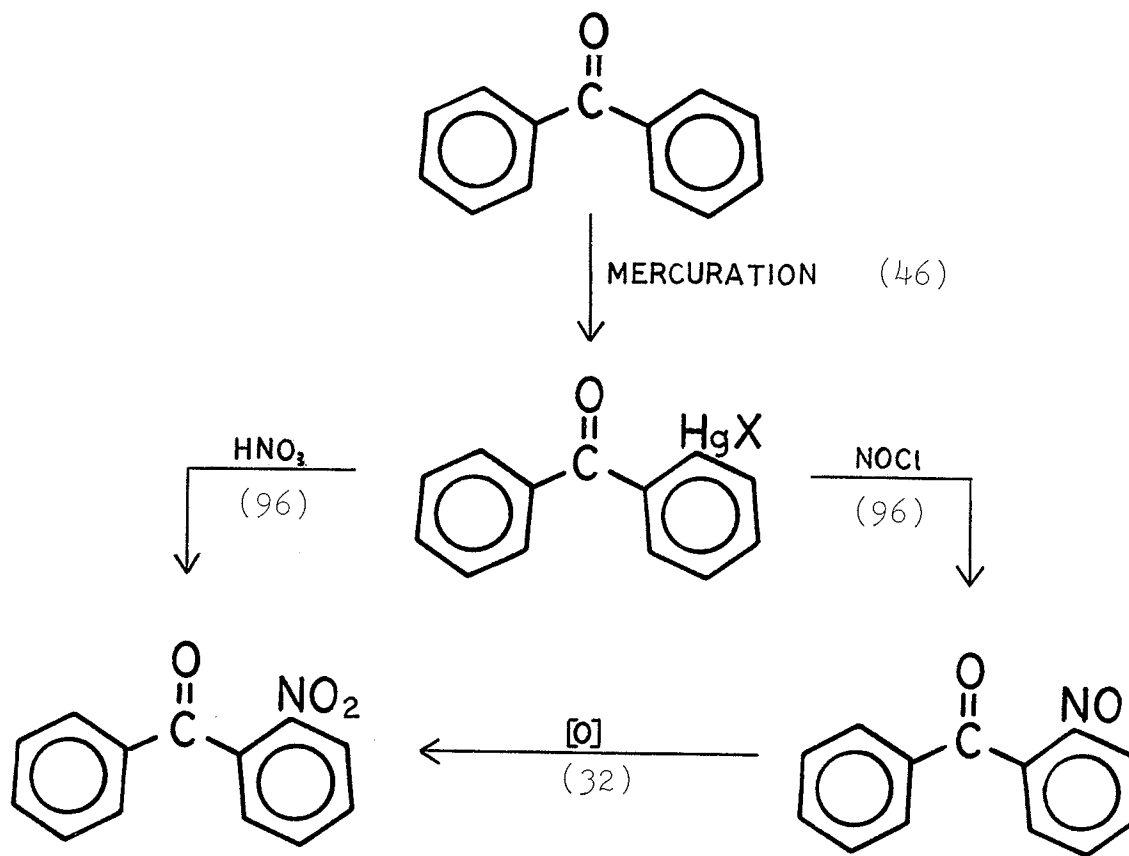
Twelve of the fifteen acids were successfully converted into the corresponding p-nitrobenzyl esters bearing the following substituent groups: 2-amino, 2-hydroxy, 4-hydroxy, 2-methoxy, 2-methyl, 4-methyl, 4-fluoro, 2-chloro, 4-chloro, 2-bromo, 4-bromo, and 4-nitro.

2. The reaction of 2-chlorobenzophenone in benzene-toluene resulted in the formation of a new unsaturated acid, β -(2-chlorophenyl)- β -phenylacrylic acid.

3. The reaction of 4-nitrobenzophenone, which would not occur under classical reaction conditions, was effected by means of a two-stage procedure similar to that developed by Seigel and Keckeis. This is the first time that a nitro ketone has undergone a Reformatsky reaction.
4. The reaction of 2-nitrobenzophenone could not be brought about under any circumstances. This result was attributed to a steric effect.
5. Diethyl ether proved to be, on the average, superior to benzene-toluene as a reaction solvent.
6. By means of a reduced pressure technique, anisole was successfully employed as a reaction solvent. This marks the first time that such a procedure has been applied to the Reformatsky reaction.
7. Evidence was found to support the view that certain zinc complexes are soluble in benzene.

RECOMMENDATIONS FOR FUTURE WORK

1. Considerable difficulty was encountered in the preparation of 2-nitrobenzophenone in this work. This ketone might be more readily prepared according to the following scheme:



2. A study of the following ketones in the Reformatsky reaction would be of interest:
- meta-substituted benzophenones,
 - substituted 9-fluorenones,
 - substituted thiobenzophenones.

3. In reference to the reaction of ortho and para substituted benzophenones in the present study, it might be instructive to employ the following substituent groups: 2-F, -I, -COOR, -CONH₂, -C₆H₅ and -OC₆H₅ .
4. Vaughan et al. (103) have recently developed a titrimetric method for determining the concentration of active Reformatsky reagent in the two-stage reaction. The use of such a technique, in conjunction with the homogeneous conditions offered by the two-stage reaction, would permit one to conduct a series of investigations with a wide range of carbonyl compounds, haloesters, and solvents. In regards to the use of this procedure in the present investigation, it would have been advisable to have employed the following modification: the initial reaction (first stage) is carried out on a large scale, and the active reagent concentration carefully measured (see above) at the end of the reaction. Aliquots of this solution are then reacted with the carbonyl compounds (second stage).

Vaughan et al. (op. cit.) reported that the amount of active Reformatsky reagent in the initial reaction was lowered appreciably by a dimerization reaction. In a two-stage reaction where the molar ratio of ketone : haloester is 1 : 1, the above titrimetric method would offer a convenient and precise way of establishing the limiting factor (moles of active Reformatsky reagent).

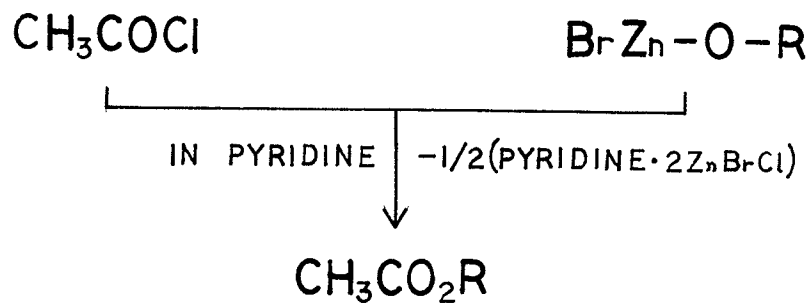
5. Employing the two-stage reaction, it would be informative to perform a kinetic study of the Reformatsky reaction with emphasis on one or more of the following parameters:
- a) solvent basicity,
 - b) reaction temperature and ambient pressure,
 - c) solvent-substituent interaction, and steric inhibition of solvation,
 - d) side reactions,
 - e) catalysts.

Such a study could also take into account other reaction conditions (see Literature Survey, pages 16 - 18).

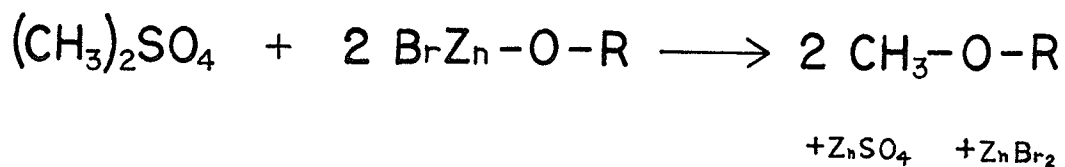
6. Renaud (81) has successfully used ultrasonic waves to facilitate the preparation of Grignard reagents. This technique even permitted these reactions to proceed in the presence of oily complexes and traces of water. Such a cleansing agent could serve a similar role in the Reformatsky reaction.

7. Further studies ought to be carried out on the zinc complexes. The following problems might be considered:
- a) the elucidation of structures by spectroscopic methods
 - b) the determination of solubilities, and the detection of solvent-complex interaction with a variety of solvents
 - c) the preparation of derivatives from zinc complexes, for example:

i)



ii)



8. The present study has indicated that p-nitrobenzyl esters are not the most suitable derivatives for the identification of β, β -diarylhydracrylic acids. One or more of the following derivatives might better serve this purpose:
- β -hydroxyacid hydrazides (19),
 - ethyl esters (from unsaponified Reformatsky reaction mixtures),
 - unsaturated acids (see pages 31 - 33 and 106 - 107),
 - unsaturated esters (41).

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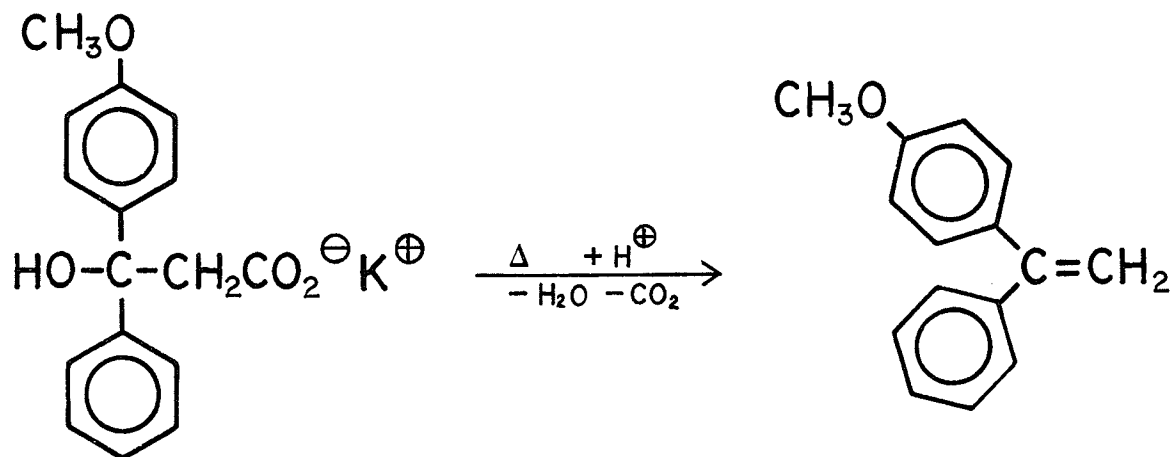
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ADDENDUM

Page 89

β -(4-Methoxyphenyl)- β -phenylhydracrylic Acid

When a hot alkaline solution of this acid was acidified with dilute hydrochloric acid, the following decomposition reaction occurred:



The α -(4-methoxyphenyl)- α -phenylethylene isolated from this reaction, melted at 74 - 76° (aq. alcohol) and gave the following analysis:

Calculated for: $C_{15}H_{14}O$; C, 85.7 ; H, 6.7 .

Found : C, 85.5 ; H, 6.5 .

Hurd and Webb* have reported a melting point of 75° for this compound.

* Hurd, C. D. and Webb, C. N., J. Am. Chem. Soc. 49, 549 (1927).