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Studies in the Preparation of Metal Enolates of 3,3,5,5-Tetramethylcyclohexanone and Their Reactions with Lead(IV) and Mercury(II) Acetates

Donald Robert Paveska

Eastern Illinois University

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STUDIES IN THE PREPARATION OF METAL
ENOLATES OF 3,3,5,5-TETRAMETHYLCYCLOHEXANONE
AND THEIR REACTIONS WITH LEAD(IV) AND MERCURY(II) ACETATES
(TITLE)

BY

Donald Robert Paveska
Bachelor of Science
University of Illinois, Urbana
January, 1964

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

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IN THE GRADUATE SCHOOL, EASTERN ILLINOIS UNIVERSITY
CHARLESTON, ILLINOIS

1971

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STUDIES IN THE PREPARATION OF METAL
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School of the Eastern Illinois University
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CHAPTER I

INTRODUCTION

An extensive number of α -acetoxy derivatives of numerous ketones have been prepared including steroids and other physiologically important compounds.^{1,2,3}

The α -acetoxyketones may be hydrolyzed or derivatives made thus making it possible to utilize them as precursors for additional syntheses.⁴

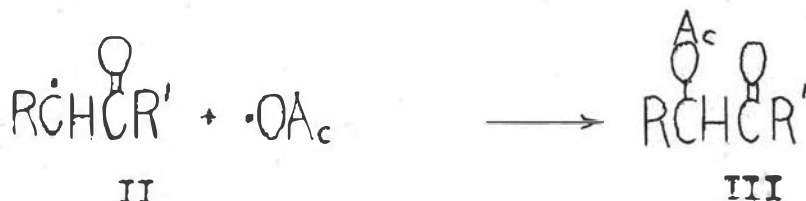
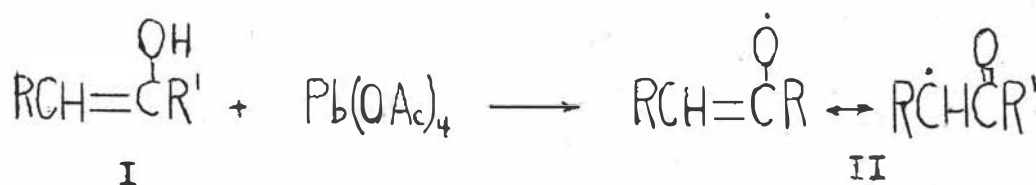
Recent developments in the formation of α -acetoxyketones using either ketoxime derivatives⁵ or thallium triacetate⁶ exhibit disadvantages of only moderate yields, relatively long periods of reaction time, the necessity of isolation of intermediates, and use of expensive reagents. The general purpose of this study was to discover or study new ways to accomplish acetoxylation.

Historical Review

It has long been known⁷ that lead tetraacetate (LTA) will react with ketones to produce the α -acetoxy compounds. However, under the usual conditions the process was rather time consuming and the yields of the desired α -acetoxyketones were not high. Some improvements in the process have been made by Henbst⁸ using catalysts such as BF_3 etherate. A prudent selection of solvent in at least one example near-

ly doubled the yield of the acetoxylation product.⁹

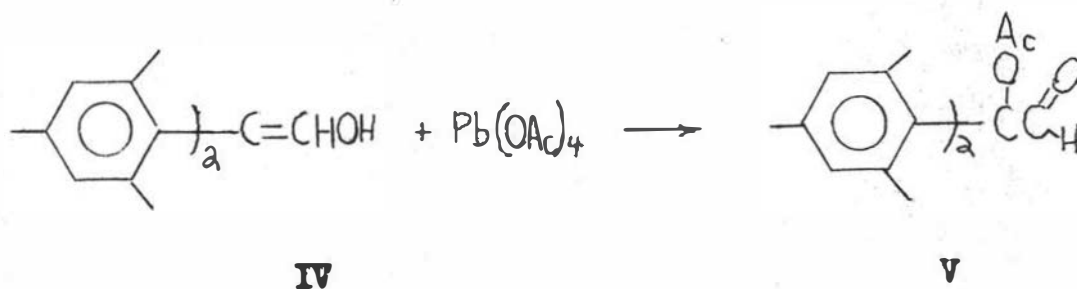
By-products due to dehydrogenative coupling led Cavill and Solomon to conclude a radical mechanism was operative as shown below.¹⁰



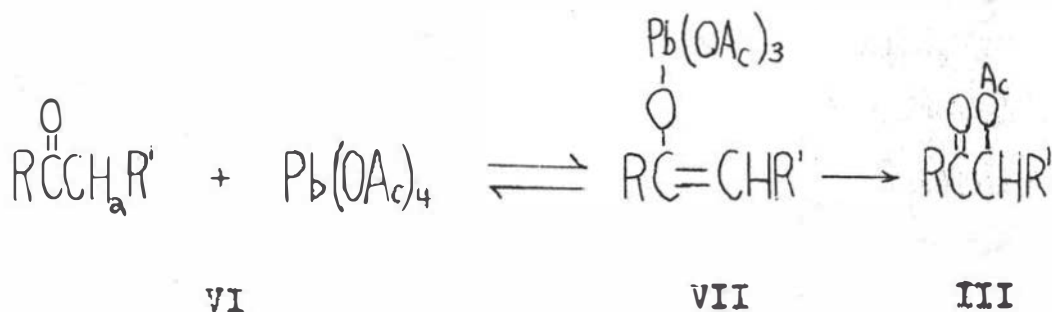
However, other workers reported that air oxidation was probably responsible for the observed radicals.¹¹

Criegee¹ has listed evidence by Ichikawa and Yanaguchi claiming the rate of acetoxylation is dependent only on the concentration of the ketone, not LTA. This indicates that enolization of the ketone is the rate determining step of acetoxylation. This argument was supported by Littler.¹²

Fuson¹³ reacted compounds which exist only as enols, such as IV, with LTA to give the corresponding acetoxyaldehydes, as V, in quantitative yields.



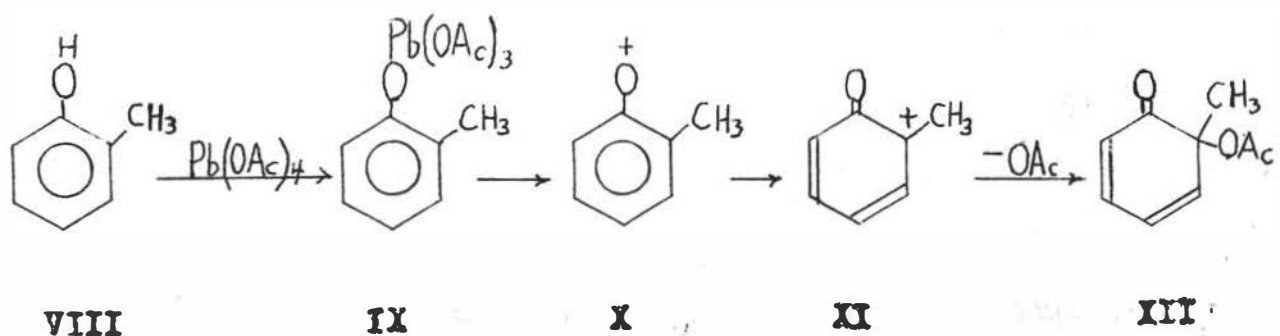
Corey¹⁴ proposed that acetoxylation of ketones may proceed via an enol-lead triacetate derivative, such as VII, formed directly from the ketone followed by internal rearrangement and elimination.



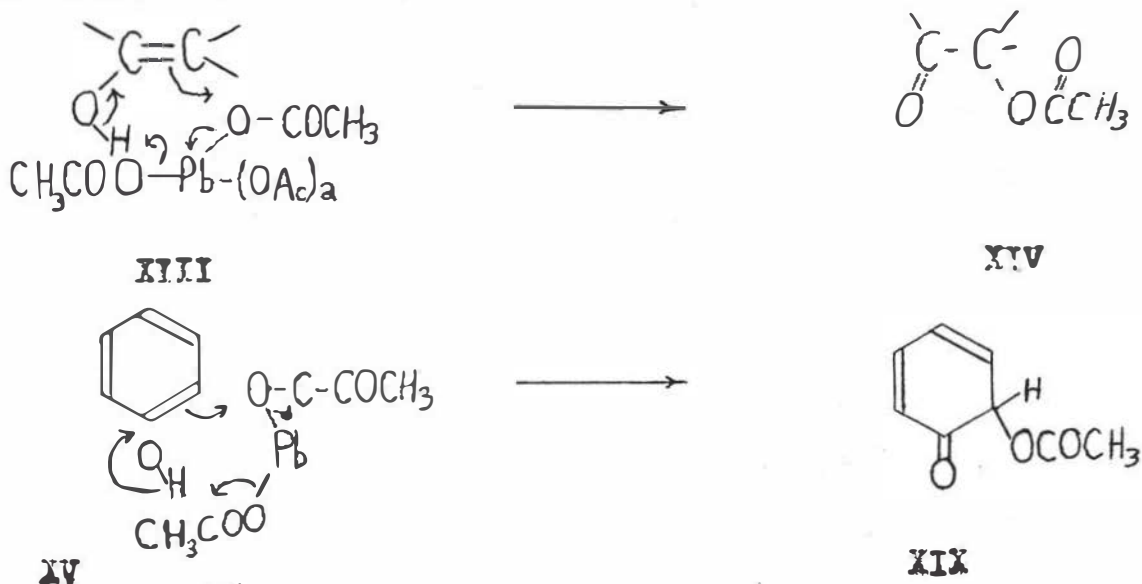
Henbest⁸ and later Criegee¹ concluded that acceleration of the reaction with BF_3 etherate is probably due to its power to increase the rate of the enolization step.

Phenols can be considered dienones which are entirely in the enol form. Criegee¹ proposed from his work on

phenols, that the acetoxylation resulted from the formation of a lead(IV) triacetoxy phenol derivative, such as IX, followed by rearrangement of the lead ester to the product XII.

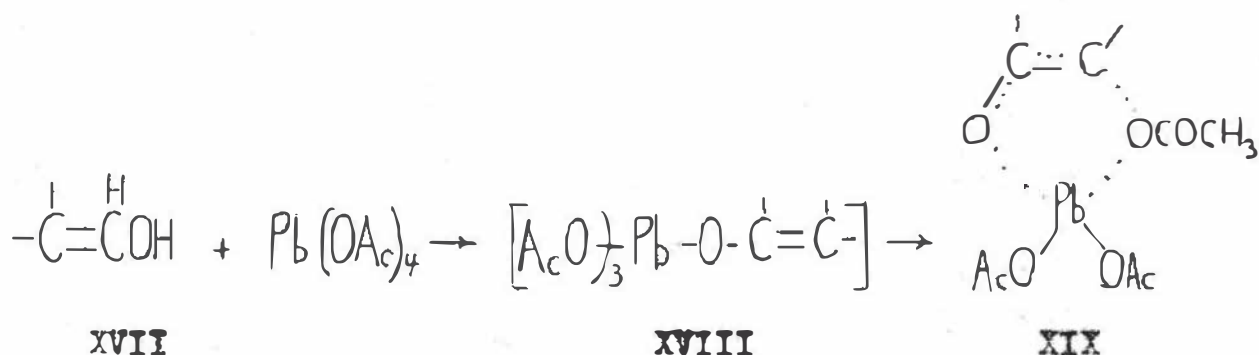


Waters¹⁵ has suggested a concerted mechanism for both the enol form of ketones, such as XIII, and phenols, for example XV.

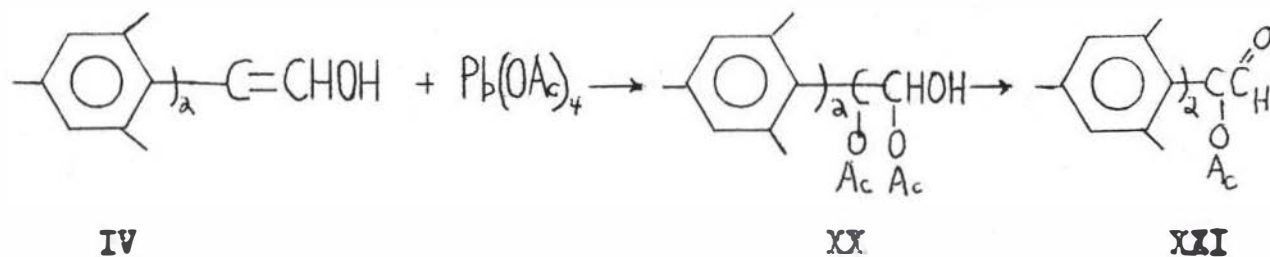


Fieser¹⁶ theorized a quasi cyclic, delocalized trans-

ition state with the enol of the ketone and the triacetoxycation of lead.



However, Pleser¹⁶ has presumed Fuson's reaction of LTA with dimesityl vinyl alcohol proceeded via diacetoxycation, followed by elimination of acetic acid. This mechanism is analogous to that proposed for LTA addition to olefins.

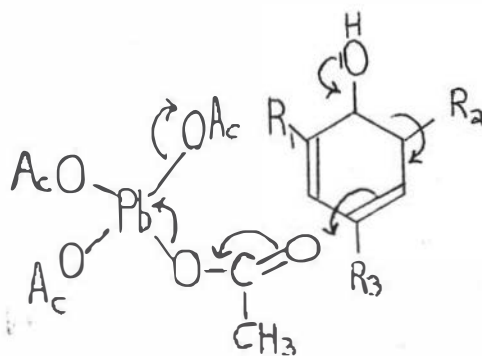


Norman¹⁷ recently has explained the mechanism of oxidation of 2,4,6-tri-*t*-butylphenol with LTA using the triacetoxycation lead ester XXII intermediate followed by a

2 electron transfer to the product XXIII.



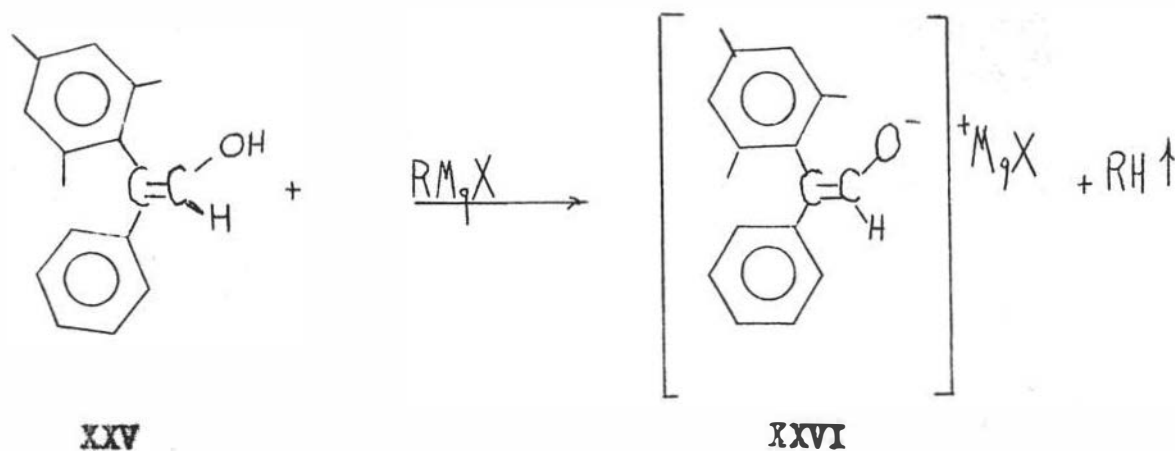
However, current studies indicate that LTA may be considered acting as an electrophile with addition in the 4 position, as in the phenolic compound XXIV. Electron-donating substituents accelerate and electron-withdrawing groups retard the reaction.¹⁸



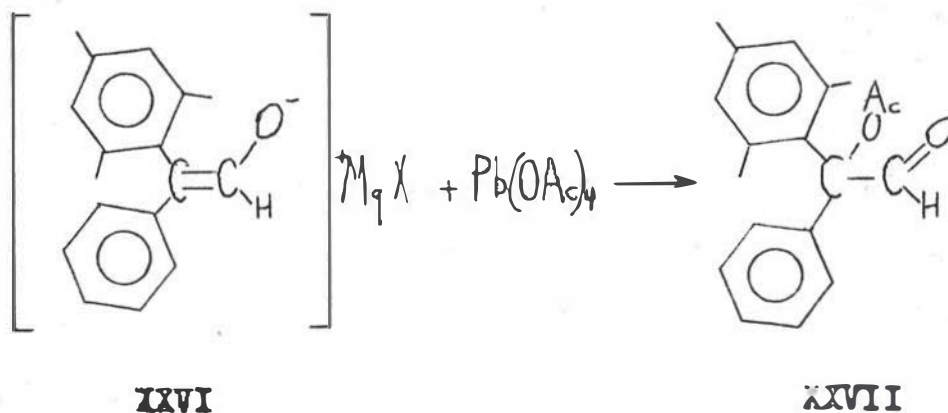
XXIV

While the mechanism of the acetoxylation may not be fully understood, it was of interest that Fuson¹³ also reacted the vinyl alcohol XXV with a Grignard reagent to

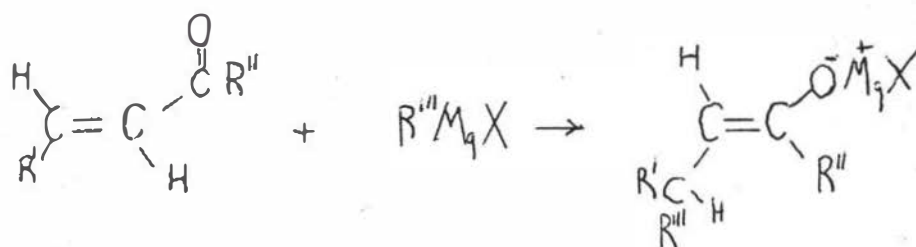
form the corresponding enolate XXVI.



The enolate was then refluxed in benzene with LTA to obtain the α -acetoxyaldehyde.

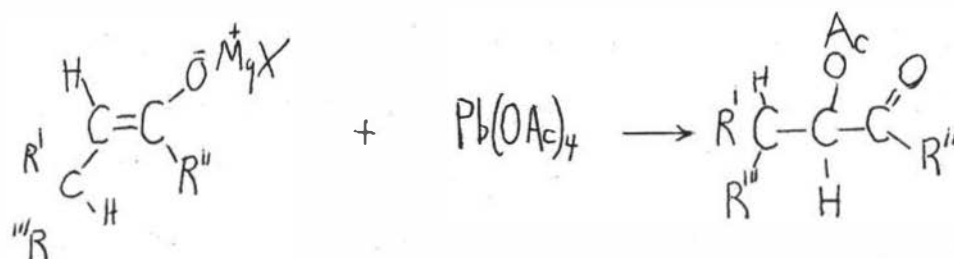


If an α,β -unsaturated ketone XXVIII could be made to undergo 1,4 addition, the resulting enolate XXIX should also react with LTA to form the acetoxy compound XXX in a manner analogous to XXVI.



XXVIII

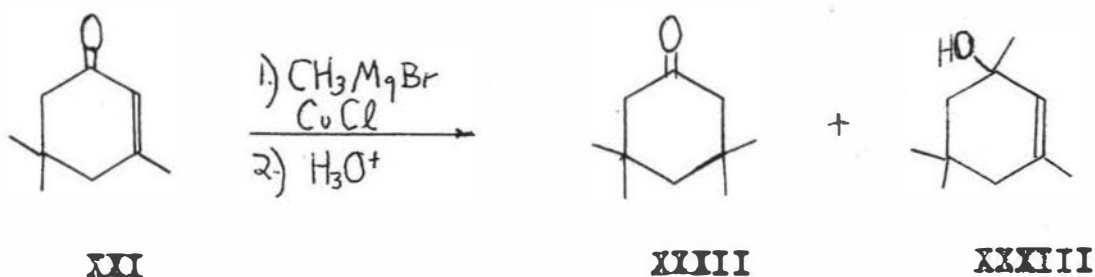
XXIX



XXIX

XXI

While certain compounds are known to yield only 1,4 addition products, usually a combination of 1,2 and 1,4 addition products is obtained. However, it is generally known that copper(I) salts tend to promote 1,4 over 1,2 addition to α -unsaturated ketones. Isophorone **XXI** has been treated with copper(I)chloride and methylmagnesium bromide to yield the 3,3,5,5-tetramethylcyclohexanone **XXII** in 80% yield.¹⁹



XXI

XXII

XXIII

More recently other copper salts have been used to selectively obtain high yields of 1,4 addition products.²⁰

In 1966 House²¹ was able to form methylcopper, considered to be a polymeric substance, which provided excellent yields of the corresponding enolate. Thus, cyclohexanones were found to react with methylcopper to give the 1,4 addition products in very high yields, (92-97%).²² In addition, the trimethylphosphite-methylcopper complex, $\text{MeO}(\text{P})_3\text{CuMe}$, was used in catalytic amounts to increase the yields of 1,4 addition.²³ This complex has also been used because of the ligand's volatility and ease of separation from the crude reaction mixture. The nmr shift indicates that the ligands increase electron density in the methylcopper complex.

The exact mechanism of Cu(I) 1,4 catalyzed Grignard addition has not been established. Originally it had been suggested that the probable mechanism of 1,4 addition involves a transition state containing a six membered ring.²⁴

Initially, evidence against a cyclic intermolecular route process came from Alexander and Corcor.²⁵ They found that 2-cyclohexene-1-one undergoes conjugate addition with Grignard reagents but the distance between the

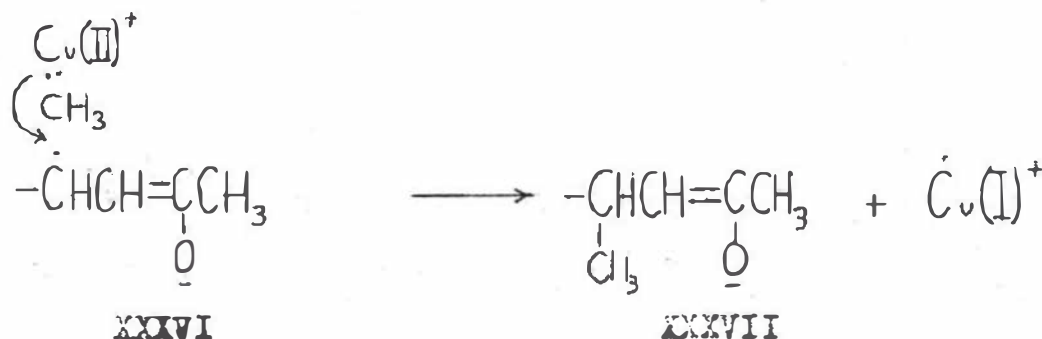
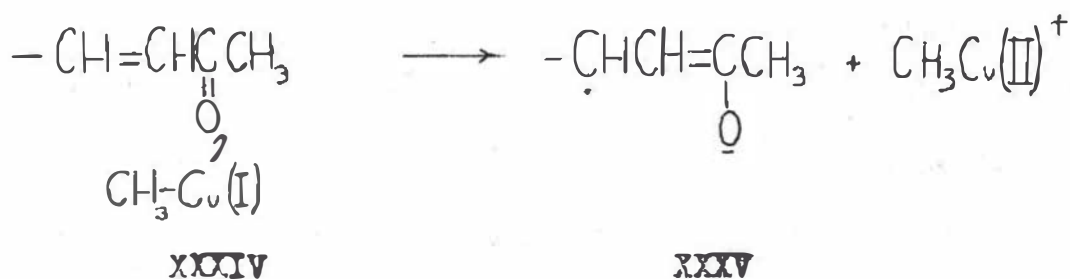
carbonyl oxygen and the carbon is too great to have a cyclic transition state operative. In support of this, they observed no difference in the proportion of 1,4 and 1,2 addition products when comparing a cyclic compound with an open chain analogue.

Kharasch,²⁴ however, questioned whether such a system would be so rigid, expressing the thought that the double bond of the ketone might be changed by a complex with magnesium, allowing the bond to increase its angular flexibility. The copper halide was thought to labilize the carbon-carbon double bond complex, and hence add to the flexibility of the system. Kharasch also cites 1,6 Grignard addition by Fuson without copper salts. Such an addition, he admitted would have to exclude a cyclooid system and he suggested a two carbonyl complex involving intermolecular bonding.

House²⁶ more recently has indicated that dialkyl Grignard reagent (R_2Mg) may be responsible for 1,4 addition to unsaturated ketone. He suggested that a 4 centered mechanism might be possible.

House²¹ further found that methylcopper added 1,4 to α,β -unsaturated ketones and did not add 1,2 with saturated ketones. In an effort to test the stereo-

chemistry of addition, he acetylated the enolate anion produced from 4-methyl-2-pentanone. He concluded that a cyclic addition for at least 69% of the reagent was impossible and could find no direct evidence for a cyclic mechanism. In addition, complexing agents added with organocopper compounds showed no effect on the yield, nor could any spectral evidence be found for a copper-carbonyl complex. House suggests that a partial or complete electron transfer to form a charge-transfer complex or ion radical might occur. A radical transfer or collapse of the charge-transfer complex would provide a route to the product. This is shown with formulae XXXIV through XXXVII.



House²² has indicated that additions of methylmagnesium bromide and methylcopper to α,β -unsaturated ketones differ in their stereochemistry.

It should be pointed out that a recent investigation of the decomposition of the tri-n-butyl phosphorous complex of CuI indicates that a radical is not present.²⁷

Broadly speaking, the transition state energy of the non-catalyzed Grignard addition to isophorone XXXI is much lower for 1,2 than 1,4 addition, since only 1,2 product is formed.²⁸ Possibly the methyl groups on the 5 and 3 positions prevent by steric hindrance, a cyclic 1,4 transition state with isophorone. Since methylcopper does not add 1,2 even to saturated carbonyls, it cannot be considered a strong nucleophile.

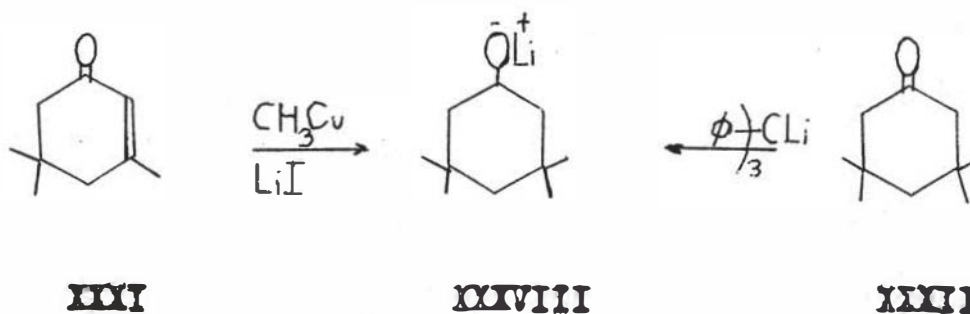
A Tentative Route of Synthesis

The specific purpose of this study was to determine the optimum conditions for the best yield of 1,4 Grignard enolates of α,β -unsaturated ketones and investigate the reaction of the enolate with Pb(IV) and Hg(II) acetates. Such a process could be extended by variations of the Grignard reagent employed, using different carboxylates of lead(IV), and various α,β -unsaturated ketones.

A variety of enolates may be prepared by either treating a saturated ketone with a strong base, as trityllithium,

or by reacting an α,β -unsaturated ketone with a metallic reducing agent, such as lithium in liquid ammonia.

Application of the methylcopper reagent would provide a lithium enolate, such as XIXVIII. An equivalent enolate could be made using trityllithium as a base with the saturated ketone analogue 3,3,5,5-tetramethylcyclohexanone (XXII).

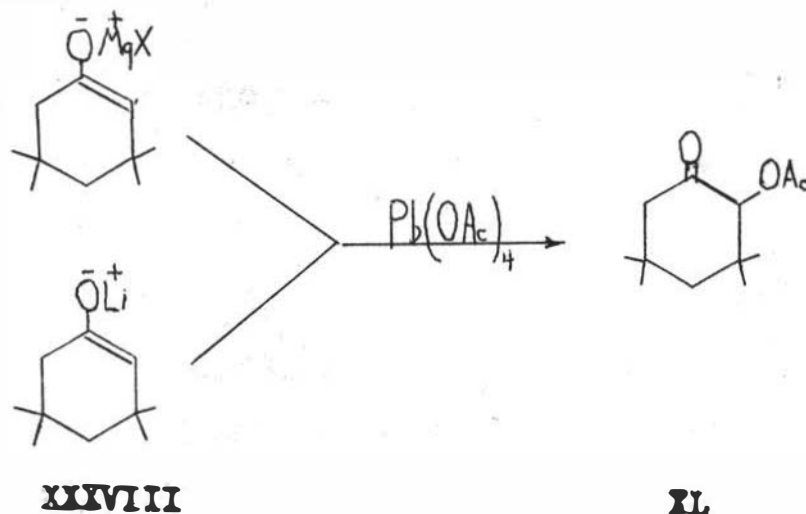


The use of Kharasch's catalytic method yields the magnesium enolate XXIX.

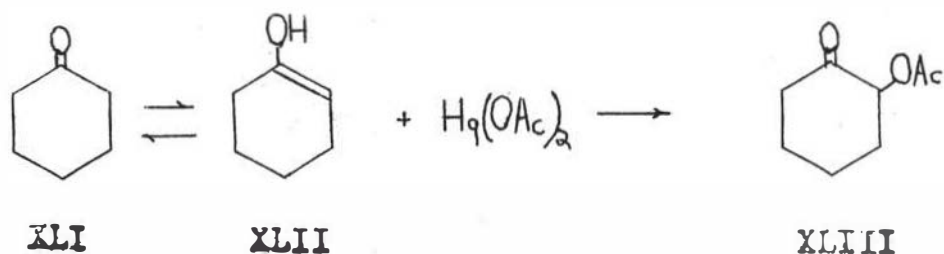


The enolate thus prepared would be expected to react

with LTA in a manner similar to that postulated by previous workers.^{13,28}



In addition, it has been reported that the α -acetoxy derivative of cyclohexanone XLIII has been prepared by the reaction of cyclohexanone with mercury(II) acetate, though in low yield.³⁰ If the mechanism is similar to that proposed by Corey for LTA, then the enol XLII, or an enolate anion, ought to react faster and in a yield higher than the unenolized ketone.



CHAPTER II

RESULTS AND DISCUSSION

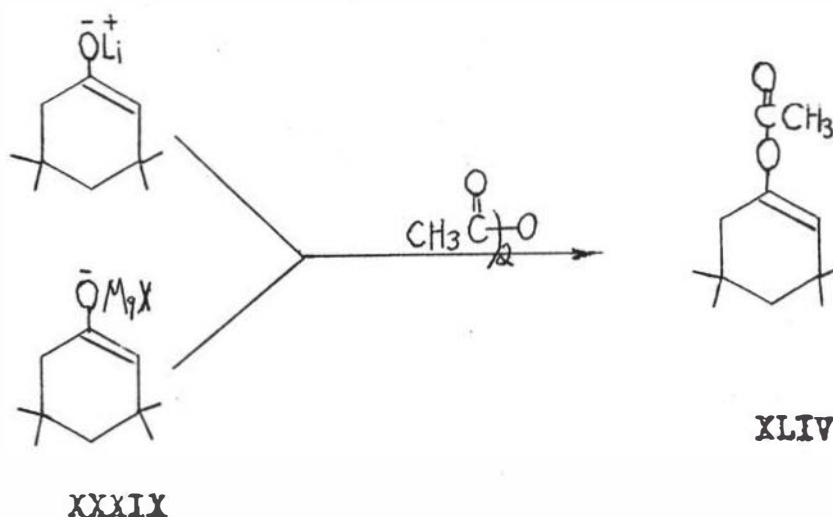
Two routes to the desired 1,4 addition product enolate of isophorone are the reaction of methylcopper with isophorone or alternatively the Cu(I) catalyzed reaction of a Grignard reagent with isophorone. The disadvantage of the former method lies in that it uses a 4 to 1 ratio of reagent to ketone. The latter method has a tendency to give lower yields compared to the methylcopper reagent.

Normally excess organometallic reagent is used to provide maximum yields. However, excess organometallic reacts with LTA.³¹ In order to prevent this undesirable side reaction with LTA, it was necessary to use a minimum amount of organometallic reagent above the stoichiometric equivalent of ketone.

Numerous experiments were therefore needed to determine the optimum conditions to afford high yields of enolate and yet be compatible with LTA. If these conditions could be determined, previous analogous reactions would indicate that an excellent synthesis of α -acetoxyketones would be achieved.

The Enolate Preparation

The method used by House²¹ was followed using a 4 to 1 ratio of standardised methyllithium and CuI to ketone. The key to the preparation appeared to be the use of an optimum concentration of organocopper reagent. Addition of isophorone to the yellow reagent at 0 to -5° required only a few minutes and the total reaction about an hour. The workup avoided the dialkylation with excess reagent by addition of the enolate to aqueous ammonium chloride solution. Analysis by vpc using (-)-carvone as an internal standard, indicated a 94% yield of the conjugate addition product 3,3,5,5-tetramethylcyclohexanone. House²² has reported this reaction in "good yield" but gave no specific details. The presence of the enolate XXVIII was shown by its reaction with acetic anhydride to form the enol acetate XLIV, identified by vpc and ir.



An investigation of the amount of 1,4 addition product formed by the addition of equimolar amounts of isophorone and reagent indicated that under these conditions only one-fourth of the isophorone was converted to 3,3,5,5-tetramethylcyclohexanone. This experiment tended to confirm the fact that a large excess of methylcopper is needed to obtain high yields of enolate.

In one experiment, while using methylmagnesium bromide and copper(I)iodide, the reaction mixture was transferred with ether and the residue in the flask was briefly warmed by steam. The flask containing solid methylcopper residue was set aside and after a few minutes violently exploded. The procedures thereafter excluded any warming and all residues were quickly destroyed by addition of water.

The catalytic effect of a number of copper salts was examined. The salts included anhydrous $\text{Cu}(\text{OAc})_2$, CuCl , CuI , and the copper complex $\text{A-Bu}_3\text{PCuI}$. CuCl appeared to be the best catalyst as estimated by comparisons of the areas of chromatograms recorded by vpc of 3,3,5,5-tetramethylcyclohexanone.

Various temperatures were examined including room temperature, 0, -15, -35, and approximately -50°. Since methylcopper decomposes above 0°, lower temperature seems

more favorable. However, vpc comparisons of product yields indicated that there was no apparent advantage to using temperatures below -15° . Examination of the temperatures listed indicated that -15° tended to give the highest amount of 1,4 addition product.

Dimethyl ether was used as solvent for the Grignard reagent since it was considered by House²¹ to give higher yields of 1,4 addition product than other solvents. The relative proportions of ether solvent was varied to obtain best results. Originally it was thought a dilute solution would provide a better yield. Several experiments were conducted in high dilution using ether solvent. Results indicated a reduction of yield using high dilutions.

The normal order of addition was that of ketone to the organometallic reagent. When copper catalyst was added to the ketone instead of the Grignard reagent, a loss of catalytic effect was noted. It was found that when using anhydrous $\text{Cu}(\text{OAc})_2$ as a catalyst, the simultaneous addition of ketone and Grignard reagent appeared to enhance the quantity of the 1,4 addition product found. However, simultaneous addition had no apparent effect when used with CuCl catalyst.

The concentration of isophorone was also changed.

Since the concentration may affect enolization of the ketone which might protonate the enolate,³² it was desirable to find the optimum concentration for the ketone. The findings indicated that variation in concentrations of the ketone had no effect upon protonation of the enolate.

The temperature of the ketone was reduced to determine its effect on protonation of the enolate. A lower temperature ought to reduce the amount of enolization of the ketone,³² and if the enol form of the ketone is the proton donating source, the amount of protonation of the enolate should be reduced. It was found that cooling an ether solution of the ketone with liquid nitrogen tended to lower the amount of protonation by 50%.

Since the enolate **XUVIII** or **XXIX**, not the ketone, should react with LTA, it was necessary to determine the enolate's presence in the reaction mixture prior to its addition to LTA. This was accomplished by adding the enolate **XUVIII** to acetic anhydride. Enolates will react with acetic anhydride to form enol acetates, but ketones such as **XXI** will not. Hence, any enolate that is protonated prior to workup will be recovered as **XXI**, while the enolate will be converted to the enol acetate.

The enolate was reacted with acetic anhydride and worked up with sodium bicarbonate until free of acid and

then analysed by vpc. The structure of the enol acetate was confirmed by ir and nmr analysis.

It was necessary to add concentrated methylmagnesium bromide to cold CuCl and mix the components at 0°. The ratio of methylmagnesium bromide to isophorone was 1.2 to 1.0. Since it was known that excess Grignard reagent reacted with LTA, it was necessary to keep the ratio of methylmagnesium bromide to ketone as close to unity as possible. There was a tendency for the 1,2 addition product formed to be constant in yield whether the ketone was added rapidly or slowly to the Grignard reagent.

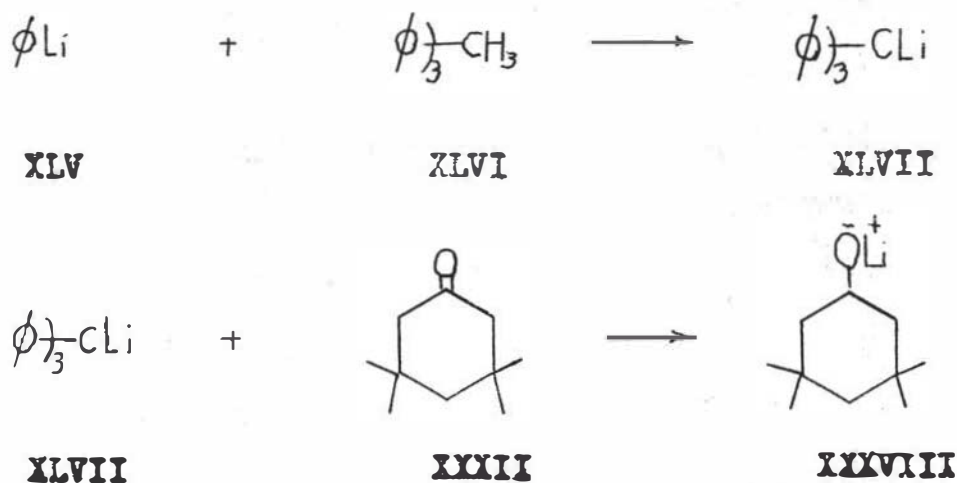
After the optimum reaction conditions were combined, the best results were obtained using 10 mole percent CuCl, at -15°, using a high concentration of methylmagnesium bromide. It is of interest that Munch-Peterson³³ working with α,β -unsaturated esters, arrived at similar conditions for optimum 1,4 addition yields. The ketone was cooled in an ether solution with liquid nitrogen. The relative areas obtained from the vpc analysis, indicated approximately a 92% yield of 3,3,5,5-methylcyclohexanone (XXXII) or a 86% yield of enol acetate XLIV with no trace of starting material XXI.

Reactions using no copper catalyst yielded only 1,2 Product XXXIII while another experiment at -30° using CH_3Li

and catalytic copper showed only a trace of 1,4 addition. Simultaneous addition of isophorone and the methylmagnesium bromide offered no apparent advantage.

While the experiments were conducted on a small scale (0.02 moles of ketone), on a larger scale an isolated yield of 78% by distillation approximately matches the yield of (82%) obtained by Kharasch. However, more work may improve this procedure.

Trityllithium can be synthesized by preparing phenyllithium from lithium and bromobenzene, then reacting the phenyllithium with triphenylmethane.



The reaction of the saturated ketone 3,3,5,5-tetramethylcyclohexanone with trityllithium using the method outlined by Huff³⁴ provided another route to XXXVIII. The

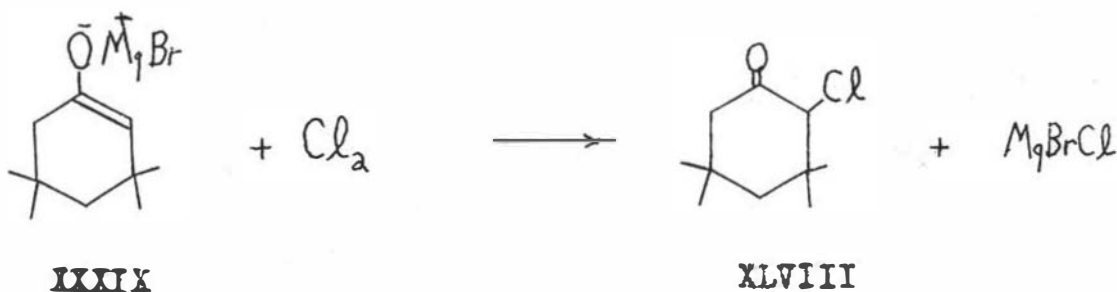
phenyllithium was prepared in a 30% ether-70% benzene solution and added to triphenylmethane dissolved in 1,2-dimethoxyethane. The reaction was carried out at room temperature and completed in 45 minutes. The enolate XXVIII was treated with acetic anhydride, worked up in the usual manner, and analysed by vpc. It was estimated by comparisons of areas of chromatograms recorded by vpc that 75% of the ketone was converted to the enolate as measured by the amount of enol acetate produced. The ir spectrum and vpc retention values of the product were identical with those of previously prepared enol acetate.

The Reaction of the Enolate of 3,3,5,5-Tetramethylcyclohexanone with Lead(IV) Acetate and Mercury(II) Acetate

The enolate of 3,3,5,5-tetramethylcyclohexanone previously stated using a 4 to 1 ratio of methylcopper reagent to isophorone was directly added to a slurry of 1.5 equivalents LTA in benzene. An immediate color change was observed, and after several hours the thick mixture was worked up and subjected to vpc analysis. No additional product besides 3,3,5,5-tetramethylcyclohexanone was detected by vpc. Inverse addition of LTA to the enolate XXVIII gave similar results. It is believed that the excess alkyl copper reagent reacted with the LTA.

An examination by vpc was made of the crude product of the reaction of methylcopper reagent with LTA. The only product detected was an orange solid, but the isolation was not attempted. The literature³¹ would indicate the expected product to be tetramethyllead.

The enolate **XXXIX** from the CuCl catalysed addition of methylmagnesium bromide to isophorone using a 1.0 to 1.2 ratio of isophorone to methylmagnesium bromide, was added to 1.55 equivalents of LTA in benzene. The flask became quite warm and the color became light brown to light green. After several hours the mixture was worked up and vpc results indicated a product whose retention time differed from that of the authentic 2-acetoxy-3,3,5,5-tetramethylcyclohexanone (**XL**) prepared by a known method.³⁵ Distillation of the reaction residue and recrystallization provided a white compound which was found by sodium fusion to contain chlorine.

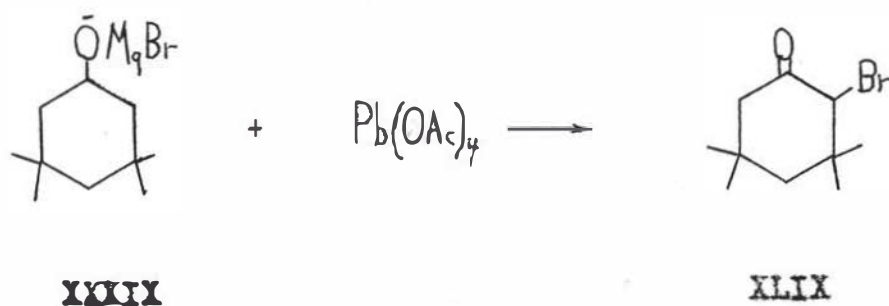


Verification of the product as 2-chloro-3,3,5,5-tetramethylcyclohexanone (XLVIII) was made by examination of the purified compound. The assignments of the ir and nmr spectra, measurements of retention times on different vpc columns, and a melting point corresponding to the reported literature values³⁶ were all consistent with structure XLVIII. Originally XLVIII was isolated due to selective precipitation, however a corresponding compound XLIX had to be present since the total quantity of product exceeded the stoichiometry of the chloride present.

Thus the one step synthesis of an α -bromo, β -alkyl ketone from α,β -unsaturated ketone can be quickly made without the inconvenience of direct halogenation. Hence, the reaction provides addition of an alkyl halide across the double bond of an α,β -unsaturated ketone.

When anhydrous $\text{Cu}(\text{OAc})_2$ was used in place of CuCl in a 1.0 to 1.2 ratio of isophorone methylmagnesium bromide to LTA, a compound with similar properties was isolated but contained bromine in place of chlorine. Again verification by means previously employed indicated the compound was 2-bromo-3,3,5,5-tetramethylcyclohexanone. The melting point of the purified compound was exactly as stated in literature,³⁷ and the ir spectrum was identical with that of an authentic

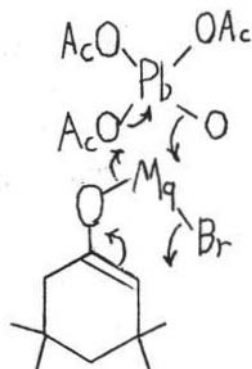
sample prepared by bromination of pure 3,3,5,5-tetramethylcyclohexanone.



The yield of 2-bromo-3,3,5,5-tetramethylcyclohexanone was 48% as determined by vpc using an internal standard, while a 40% yield was afforded by distillation.

Modified reaction conditions also produced the same product. Fuson¹³ originally refluxed the mixture of the enolate and LTA for 12 hours. If an α -bromo compound was initially formed, an acetate ion may have displaced the bromide ion during reflux. The reaction was repeated, refluxing the reaction mixture for 12 hours. As before, the only product was 2-bromo-3,3,5,5-tetramethylcyclohexanone.

Compound XLVIII could have been formed by the oxidation of CuCl or an exchange of halogens from CuCl to magnesium bromide enolate followed by electrophilic attack by LTA. However, the α -bromo compound XLIX may have resulted from an electrophilic attack by LTA.



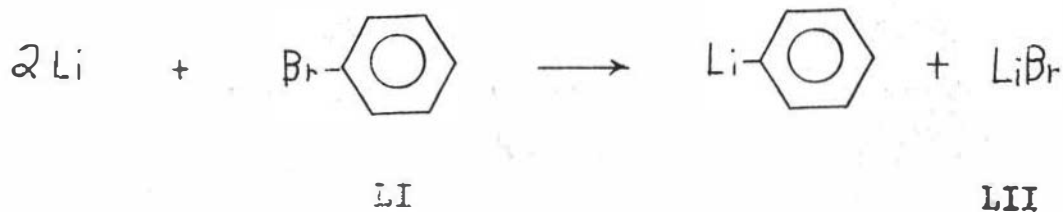
L

Oxidation of bromide ion to form free bromine as previously indicated for chlorine cannot be ruled out. Bromination of the enolate would produce more free magnesium bromide as a by-product. The magnesium bromide formed could then be oxidized by LTA to bromine which could further react with more enolate.

An attempt to prove that free bromine was present in the reaction mixture by adding excess cyclohexane to the LTA-benzene slurry prior to the addition of the enolate was inconclusive. A trace of a compound which had the same retention time as authentic 1,2-dibromocyclohexane was detected by vpc. The ir spectrum of the crude product indicated no evidence for the presence of 1,2-dibromocyclohexane when comparison was made with an authentic sample.

Another mechanism is possible. Kochi³⁷ was able to react LTA with a carboxylic acid in the presence of lithium halides to obtain an alkylhalide and carbon dioxide. A refluxed benzene solvent was used under a nitrogen atmosphere. It was found that the absence of a nitrogen atmosphere curtailed the reaction. A complicated radical mechanism was proposed. Since the reaction conditions were similar to those used to react 3,3,5,5-tetramethylcyclohexanone with LTA, perhaps an analogous mechanism produced the α -bromo compound.

The lithium enolate XLVIII of compound XXII formed by its reaction with trityllithium was added to LTA at room temperature in a 1.0 to 1.2 ratio. Isolation and identification showed the product to be XLIX. The halogen source presumably came from the lithium bromide, formed in the preparation of phenyllithium. The bromide could then be oxidized by LTA to free bromine which could then react with the enolate XLVIII to form the product XLIX.

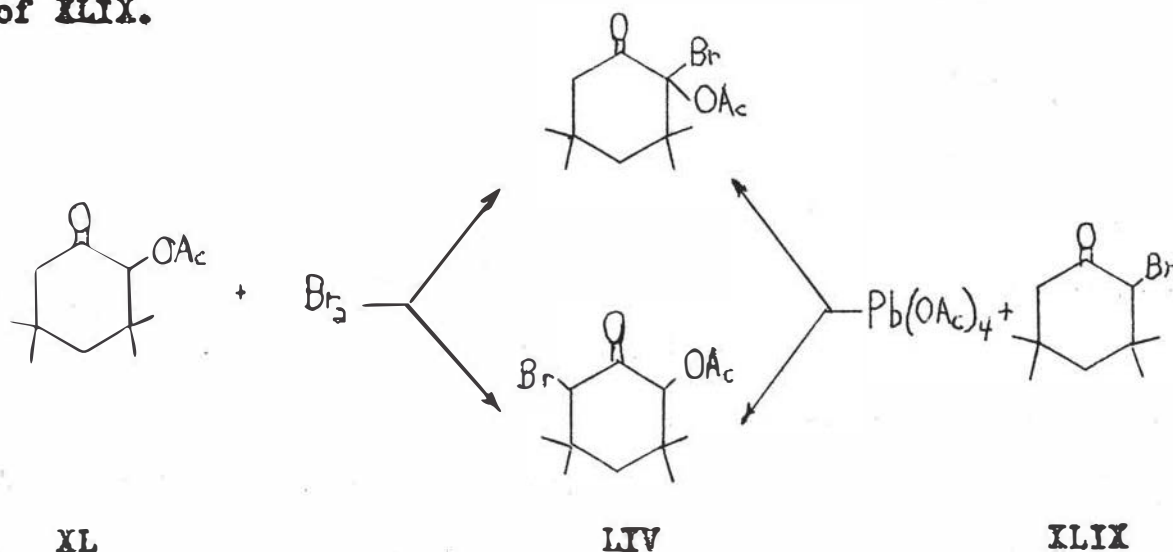


The enolate prepared by using a 10 mole percent anhydrous $\text{Cu}(\text{OAc})_2$ catalyst under conditions identical to those used for CuCl was added to $\text{Hg}(\text{OAc})_2$ in benzene in a ratio of 1.0, 1.2, to 1.0 isophorone, methylmagnesium bromide, $\text{Hg}(\text{OAc})_2$. After one hour at room temperature, the mixture was refluxed for 6 hours. The reaction mixture was worked up as usual and analysis of the crude reaction mixture indicated that only 2-bromo-3,3,5,5-tetramethylcyclohexanone was present; no 2-acetoxy-3,3,5,5-tetramethylcyclohexanone was detected. The yield was found by comparisons of areas of chromatograms recorded by vpc to be approximately 30%.

Evidence for a Possible Bromoacetate Compound

In reactions involving the methylmagnesium bromide or trityllithium enolate with LTA, the crude residue prior to distillation had properties which could not be attributed to XLVIII or XLIX or XL. The nmr spectrum of the reaction mixture prior to distillation has a strong proton signal at δ 2.0, indicating a possible acetoxy group. The reaction mixture gave a positive silver nitrate test which the isolated compounds XLVIII and XLIX did not exhibit. Thin layer chromatography of the reaction mixture prior to distillation indicated a major product, XLIX, and a trace of a minor product with a slightly higher R_f value.

Such a compound or compounds could arise from either or both of two ways, bromination of XL or acetoxylation of XLIX.



Attempts to isolate LIII or LIV were unsuccessful. Similar compounds are known to be unstable.³⁸

Although the mechanism of the reaction is not clear, the results indicate that only the α -bromo compound was formed in contrast to the previously prepared α -acetoxy compounds. Since C_6H_5ONa is approximately 3 times as strong an electron transferring agent as C_6H_5OH ,³⁹ enolates should also be considered as much stronger electron transferring agents than the corresponding enols. It would therefore seem that the enolate anions are not reacting in an analogous manner to phenols or ketones. Perhaps Fieser's mechanism to explain the α -acetoxy aldehyde obtained by Fuson may be correct.¹⁶ In addition, Fuson did not report

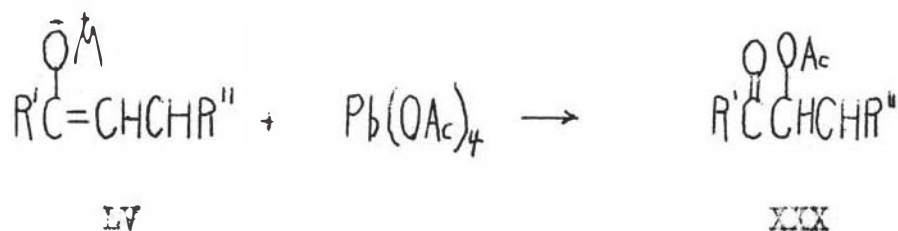
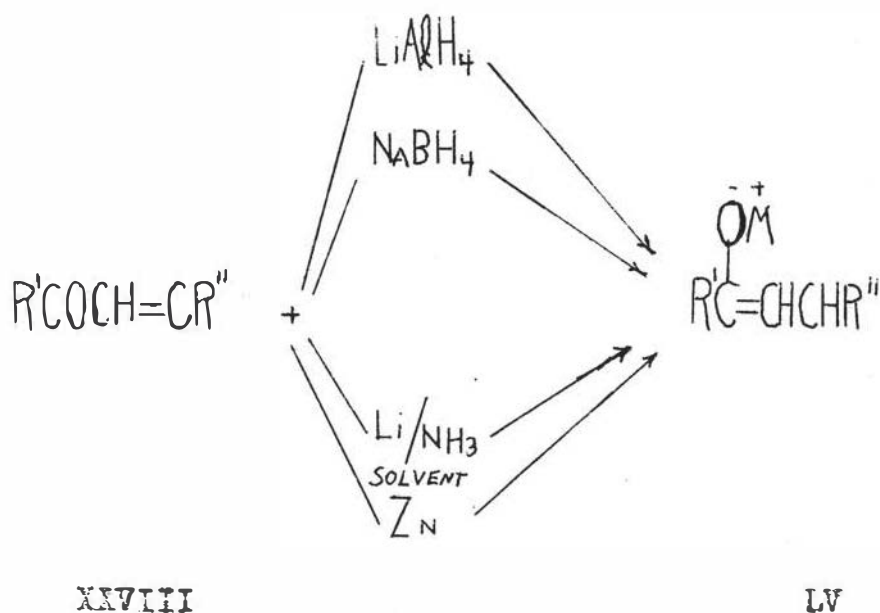
using a nitrogen atmosphere. Thus, the possibility arises that the presence of air or moisture contaminated the reaction mixture causing regeneration of the vinyl alcohol from the enolate or repression of a radical reaction.

Reported acetoxylation²⁸ of 3,3,5,5-tetramethylcyclohexanone enolate may have proceeded via another mechanism since tetrahydrofuran solvent was used and the reaction was run in air. Also, a possible misidentification of the product may have resulted, since both the 2-acetoxy-3,3,5,5-tetramethylcyclohexanone have identical retention times on the 10 ft. column of 43 neopentylglycol sebacate at 170°.

Suggested Research

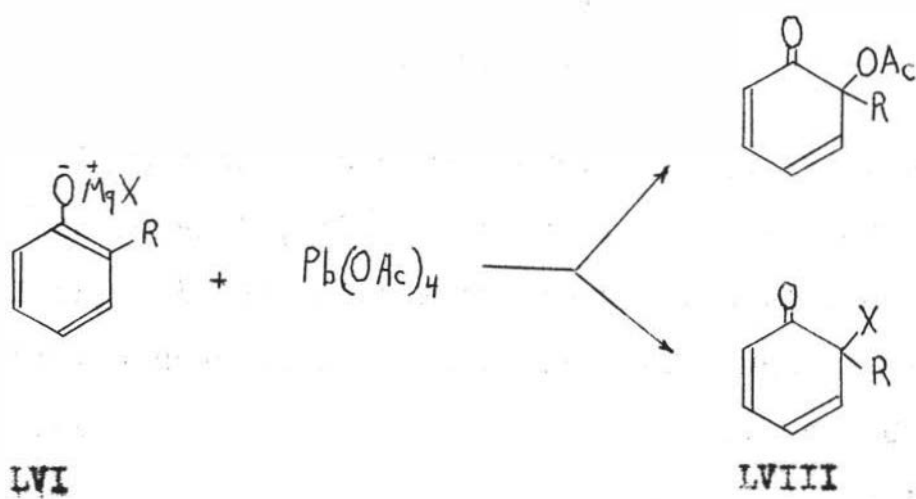
It would appear that Criegee's mechanism is not operative in the reaction of enolates and LTA. The problem may be clarified by using other enolates as previously mentioned. Thus stable enolates generated from other sources may react with LTA to form α -acetoxyketones.

Strong metal reducing agents such as lithium aluminum hydride,⁴⁰ sodium borohydride,⁴¹ lithium in liquid ammonia⁴² (Birch reduction), and zinc⁴³ form stable enolates. The reaction of these enolates with LTA should proceed in a manner analogous to Fuson's reaction of LTA with Grignard enolates.



NaOCH_3 may also exchange with LTA to form $\text{Pb}(\text{OAc})_2-(\text{OCH}_3)_2$. This compound would act as a strong methoxylating agent and form methoxy compounds via addition to olefins.

Likewise, it would be of interest to determine the product of the reaction of LTA with phenols treated with Grignard reagent to form enolates. Either the α -halo or α -acetoxydienone should be formed.



CHAPTER III

EXPERIMENTAL

All reactions were run under nitrogen in oven dried, and when possible, flame heated flasks. A Thomas-Hoover capillary melting point instrument was used and melting points were uncorrected. A Varian T-60 Nuclear Magnetic Resonance Spectrometer, with CCl_4 as solvent and tetramethylsilane as an internal standard, and a Perkins-Elmer 337 Infrared Spectrometer were used for all spectra. Gas phase chromatographic analyses were made using a Sargent SR recorder and a Perkin-Elmer Model 154 L gas chromatograph with a $\frac{1}{8}$ inch x 5 ft. column of dinonyl phtalate (dnp) on 60-90 mesh non-acid washed Chromosorb P and a $\frac{1}{8}$ inch x 10 ft. column of 4% neopentylglycol sebacate (npgs) on 60 to 90 mesh non-acid washed Chromosorb W. Both columns were run using a helium flow rate of 60/ml/min. Silica Gel G with CHCl_3 solvent and iodine vapor detection served for thin layer chromatography use. Organometallic reagents were standardized by hydrolyzing in standardized acid and back titrating with a standard base. Anhydrous $\text{Cu}(\text{OAc})_2$ ⁴⁴ and CuCl ⁴⁵ were prepared by standard means. The molar percentages of catalyst were based on the moles

of ketone used. Diethyl ether, dried by distillation over lithium aluminum hydride, was the only ether used unless otherwise indicated. Lead tetraacetate (LTA) was dried over KOH under reduced pressure, just prior to use.

The Preparation of 3,3,5,5,-Tetramethylcyclohexanone (XXXII)
Using Methylcopper Reagent with Isophorone (XXXI).

CuI (5.54 g, 0.03 mol) was slurried in 25 ml of ether at 0 to -5° , using a salt-ice bath, and 25 ml of 1.2 M CH_3Li (0.03 mol) in ether was added. The thick mixture appeared gray on completion of addition of CH_3Li . Isophorone (1.00 g, 0.0075 mol) in 20 ml of ether was added over a period of 5 to 10 minutes and after 45 minutes a deep yellow color developed. The mixture was then washed into 100 ml of saturated NH_4Cl solution, four ether extracts of the water layer were added to the organic layer, and dried (MgSO_4). Analysis was made using (-)-carvone as an internal standard on the npgs column, at 170° . A 94% yield of the product was observed with a retention time of 6.0 minutes at 170° . Distillation gave a colorless product; bp 78° (3.0 mm Hg); ir (film) 1700 cm^{-1} (C=O); nmr δ 2.1 (s, 2, $\text{CH}_2\text{C=O}$), 1.6 (s, 2, CH_2), and 1.0 (s, 3, CH_3).

An Investigation of the Amount of 3,3,5,5-Tetramethylcyclohexanone Formed by Variation of the Ratio of Isophorone to Methylcopper Reagent.

To a slurry of CuI (5.6 g, 0.03 mol) in 15 ml of ether was added 23 ml of 1.3 M CH_3Li (0.03 mol) in ether. Isophorone (1.0 g, 0.0072 mol) in 5 ml of ether was added and after 15 minutes, two 1 ml aliquots were taken and added separately to saturated NH_4Cl and acetic anhydride. Isophorone (1.0 g, 0.0072 mol) in 5 ml of ether was again added to the reaction mixture. After 15 minutes, 1 ml aliquots were again taken and treated as above. This process was repeated twice more, so that at the end of the final addition the amount of isophorone and methylcopper reagent were equivalent. The samples placed in saturated NH_4Cl were extracted with ether, dried (MgSO_4), and then concentrated under reduced pressure. The samples placed in acetic anhydride were mixed and after 15 minutes, ether was added and saturated NaHCO_3 was used to destroy the excess acetic anhydride and acetic acid. The ether layer was dried (MgSO_4) and concentrated under reduced pressure. Both fractions were examined by vpc using the npgs column at 170° . Measurement of the areas of the chromatogram of the products relative to the areas of the chromatogram of the unreacted isophorone indicated that 25% of the total

recovery was the 1,4 addition product (XXXII) and 67% of this amount came from the first fraction. Investigation of the enol acetate XLIV formed from the acetic anhydride treatment of the first and fourth fractions indicated a loss of enolate XXVIII possibly due to protonation by the unreacted isophorone.

The Preparation of the Enol Acetate XLIV Using 10 Mole Percent CuCl and Methylmagnesium Bromide on Isophorone.

To CuCl (0.15g, 0.0015 mol) at 0° was added 15 ml of 1.22 M methylmagnesium bromide (0.018 mol) in ether. The contents were concentrated to near dryness by mechanical stirring and a stream of nitrogen, then cooled to -15°. Isophorone (2.07 g, 0.015 mol) in 10 ml of ether, cooled with liquid nitrogen for 5 minutes, was then added over a period of approximately 5 minutes to the reaction flask. About 30% of the mixture was added to 5 ml of acetic anhydride, which resulted in the formation of a white precipitate. After stirring for 30 minutes, it was diluted with ether and saturated NaHCO₃ was added until the acetic acid was completely neutralized. The ether layer was dried (MgSO₄) and concentrated under reduced pressure. Comparisons of relative areas of the chromatogram indicated an 86% yield of the enol acetate XLIV, an 8% yield of the 1,2 addition product XXXIII, and a

6% yield of ketone **XXXI**.

The crude products from a number of similar experiments were collected and distilled; bp 65° (1.5 mm Hg). The colorless liquid exhibited a retention time of 4.4 minutes at 170° while the retention time for isophorone was 6.0 minutes at 170° on the same npgs column; ir (film) 1760 (ester $C=O$) 1690 ($C=C$) 1240 cm^{-1} ($C-O$); nmr δ 5.05 (s, 1, CH), 2.0 (s, 2, $C=OCH_2$), 1.35 (s, 2, CH_2) and 1.00 (s, 3, CH_3).

Preparation of 3,3,5,5-Tetramethylcyclohexanone Using 10 Mole Percent CuCl Catalyst.

To CuCl (0.75 g, 0.0075 mol) at 0° was added 33.8 ml of 2.45 M methylmagnesium bromide (0.083 mol) in ether. The light gray colored mixture was stirred under nitrogen flow for 10 minutes and cooled to -15° . Isophorone (10.35 g, 0.075 mol) in 25 ml of ether was added over a period of 15 minutes and after 5 minutes of stirring, the reaction mixture was added to 100 ml of saturated NH_4Cl . Three 50 ml ether extracts of the water layer were combined with the ether layer, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The yield by vpc using (-)-carvone as internal standard on the npgs column was 79%. Distillation afforded a 76% yield of the product 3,3,5,5-tetramethylcyclohexanone.

The Attempted Synthesis of the Enol Acetate of 3,3,5,5-Tetramethylcyclohexanone (XLIV) Using 5 Mole Percent CuCl and Methyllithium.

To CuCl (0.075 g, 0.00075 mol) at room temperature was added 13 ml of 1.2 M CH_3Li (0.016 mol) in ether. The mixture was then stirred under a stream of nitrogen for 10 minutes to concentrate the mixture to near dryness and cooled to -13° . Isophorone (2.07 g, 0.15 mol) in 10 ml of ether was added over a period of approximately 10 minutes. An aliquot of the mixture was added to acetic anhydride and worked up in the usual way. The organic layer was dried (MgSO_4) and concentrated under reduced pressure. The chromatogram from the npgs column at 170° indicated that only 1,2 addition had occurred forming ~~XXXX~~ which exhibited a retention of 2.2 minutes. The chromatogram also indicated that only a trace of possible enol acetate XLIV was present with a retention time of 4.4 minutes. Similar results were obtained when the reaction was carried out at -35° using 10 mole percent CuCl.

The Reaction of the Methylmagnesium Bromide Conjugate Addition Enolate with Lead Tetraacetate (LTA).

(a) To anhydrous $\text{Cu}(\text{OAc})_2$ (1.40 g, 0.0077 mol) at 0° was added 33.8 ml of 2.45 M methylmagnesium bromide (0.083-mol) in ether. The mixture was concentrated to near dryness

by evaporation of solvent with a gentle flow of nitrogen. Isophorone (10.35 g, 0.075 mol) in 25 ml of ether was cooled with liquid nitrogen and then added over a period of approximately 15 minutes. This mixture was then quickly added to LTA (36 g, 0.081 mol) in 200 ml of benzene at room temperature. The flask became warm and turned a light green. The potassium iodide-starch test was negative after the contents were stirred for 12 hours. The thick reaction mixture was added to ether and water, stirred for 1 hour, and the insoluble inorganic salts were removed by filtration. Three ether extracts of the aqueous filtrate were added to the organic layer and the entire organic extract was then washed with Na_2SO_3 . The ether extract was dried (MgSO_4), and concentrated under reduced pressure, leaving a yellow oil. Inspection of the chromatogram on the dnp column at 170° indicated no acetoxylation of the enolate, since authentic α -acetoxyketone XL was clearly distinguished when it was added to a small portion of the reaction mixture. The sodium fusion of the crystals gave a positive bromide test. Recrystallization by seeding from 95% methanol afforded soft, white crystals, mp 51° (lit.³⁷ mp 51°). Distillation gave XLIX (40%); bp $54\text{--}58^\circ$ (0.065 mm); ir (as a melt) $1725, 1740\text{ cm}^{-1}$ (cyclic α -bromo ketone);⁴⁶ nmr δ 4.1 (s, 1, CHBr), 2.5 (m, 2, CH_2O), 1.7 (m, 2, CH_2), and 1.1 (m, 3, CH_3).

The multiple splitting was complicated, and assignments were incomplete. The calculated yield by vpc using dibromobenzene as internal standard was 48%.

(b) Experiments similar to that in part (a) where CuCl was used in place of anhydrous $\text{Cu}(\text{OAc})_2$ were collected. Distillation gave soft, white crystals whose structure were assigned as XLVIII. Sodium fusion of the crystals gave a positive chloride test. The distillate was recrystallized from 95% methanol, mp 50° (lit. ³⁶ 50°). XLVIII had ir and nmr spectra and retention times with both npcs and dnp columns identical with those of compound XLIX.

(c) In an experiment similar to that in part (a), 6.3 ml of an ether solution of 2.5 M methylmagnesium bromide (0.0157 mol) was added to anhydrous $\text{Cu}(\text{OAc})_2$ (0.27 g, 0.0016-mol) at 0° . The mixture was cooled at -14° and allowed to concentrate under a slow stream of nitrogen. Isophorone (2.07 g, 0.015 mol) which had been previously cooled with liquid nitrogen, was added over a period of approximately 15 minutes. The reaction mixture was then added to a flask containing LTA (6.7 g, 0.015 mol) in a 100 ml of benzene. The color of the thick mixture was a light green and after 20 hours, the potassium iodide-starch test for LTA was negative. The crude reaction mixture was added to ether and water and the aqueous layer extracted with ether, the

organic layers combined, dried (MgSO_4), and concentrated under reduced pressure, leaving a yellow oil. The sodium fusion of the residue gave a positive bromide test. The chromatogram on the dnp column at 170° indicated no acetoxylation product but a compound with a retention time (10.6 minutes) identical with that of the α -bromoketone, XXIX. The ir of the crude product was identical with that of the crude product in part (a) which provided XXIX.

Attempted Trapping of Free Bromine with Cyclohexene.

Anhydrous $\text{Cu}(\text{OAc})_2$ (0.27 g, 0.0016 mol) at 0° was treated with 6.3 ml of 2.5 M methylmagnesium bromide (0.0157 mol) in ether. The mixture was stirred under a slow stream of nitrogen until concentrated to a thick consistency and cooled to -14° . Isophorone (2.07 g, 0.015 mol) which had been previously cooled with liquid nitrogen, was then added during a period of approximately 15 minutes. The contents of the flask were quickly added to a mixture of LTA (12 g, 0.027 mol) and 15 ml of cyclohexane (0.17 mol) in 100 ml of benzene. The potassium iodide-starch test for LTA was negative after 1.5 hours. The reaction mixture was then added to ether and water, and the aqueous layer was extracted with three portions of ether. The organic layer was washed with Na_2SO_3 , dried (MgSO_4), and concentrated under reduced pressure. The vpc analysis of the

crude product indicated only a possible trace of 1,2-dibromocyclohexane when compared to the chromatogram of authentic 1,2-dibromocyclohexane under identical conditions. The ir spectrum of the crude product did not indicate the presence of 1,2-dibromocyclohexane when compared to the ir of the authentic sample.

Reaction of the Lithium Enolate XXVI, Prepared from 3,3,5,5-Tetramethylcyclohexanone (XXXII) and Trityllithium (XLVII), with Lead Tetraacetate (LTA).

A solution of trityllithium was prepared from triphenylmethane (4.89 g, 0.02 mol) in 50 ml of 1,2-dimethoxyethane (DME) and 0.21 mol of phenyllithium (1.9 M in 70:30 benzene-ether). A deep red color resulted and the mixture was allowed to stir at room temperature for 45 minutes. A solution of 3,3,5,5-tetramethylcyclohexanone (3.08 g, 0.02 mol) in 25 ml of DME was added over a period of 10 minutes and the solution became tan colored. An aliquot of 25 ml was added to 5 ml of acetic anhydride, and after stirring for 45 minutes, a precipitate formed. After a total of 3 hours of stirring, 50 ml of ether and 50 ml of saturated NaHCO_3 was added and the mixture stirred until the acetic acid was neutralized. The organic layer was dried (MgSO_4), and concentrated under reduced pressure. Using the npgs column at 170° , the enol acetate XLIV exhibited a retention time of 4.8 minutes, and

a comparison of relative areas indicated that a 67% yield of enol acetate XLIV had been produced. The ir of the crude product was identical with that of previously prepared enol acetate.

Having established the presence of the enolate XXXVIII, approximately one half of the reaction mixture was added to LTA (12 g, 0.027 mol) in 100 ml of benzene at room temperature. The mixture was stirred for 3 hours and then poured into ether and water. The organic layer was washed with Na_2SO_3 solution, dried (MgSO_4), and concentrated under reduced pressure. Analysis of the crude yellow product by sodium fusion indicated that bromine was present. The ir spectrum and retention times using both npgs and dnp columns of the crude product were identical with those of other crude products which eventually yielded only compound XLIX.

Reaction of the Methylmagnesium Bromide Enolate of Isophorone (XXXIX) with Mercury(II) Acetate.

Anhydrous $\text{Cu}(\text{OAc})_2$ (0.27 g, 0.0016 mol) at 0° was treated with 6.3 ml of an ether solution of 2.5 M methylmagnesium bromide (0.0157 mol). The mixture was then concentrated to near dryness by evaporation of the ether solvent by use of nitrogen, then cooled to -14° . Isophorone (2.07 g, 0.015 mol) was cooled with liquid nitrogen and added to the mixture during a period of 5 minutes. The resulting enolate was

added to mercury(II) acetate (4.9 g, 0.015 mol) in 100 ml benzene. The color was light green at room temperature but turned a light yellow after refluxing 6 hours. No free mercury was observed. The contents were poured into ether and water, the organic layer washed with saturated Na_2SO_3 solution, dried (MgSO_4), and concentrated under reduced pressure. Analysis of the crude product by sodium fusion indicated that bromine was present. The ir spectrum and the retention times using both npgs and dnp columns of the crude product were identical with those of crude products which eventually yielded only compound XLIX. A comparison of relative areas of the chromatogram indicated that an approximate yield of 30% was present in the residue liquid.

CHAPTER IV

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