REACTIONS OF ENOLATE ANIONS

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ABSTRACT

REACTIONS OF ENOLATE ANIONS

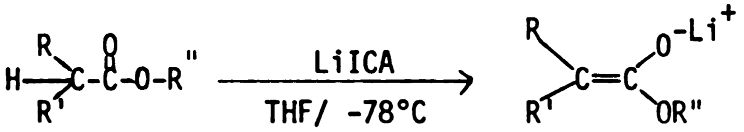
By

Andreas Lindert

The formation of polyalkylated products is a major source of diffulty in the alkylation of ketone enolates. In order to reduce this side reaction, trialkylborates and boranes were added to ketone enolates prior to alkylation. Both triethanolamineborate and triethylborane were effective additives for controlling polyalkylation. The organic borons function by coordinating with the ketone enolates to furnish a new anion which possesses greater selectivity for alkylation. Thus cyclohexanone, 2-methylcyclohexanone, cyclopentanone, and 3-pentanone were monomethylated in 80-95% yield (0.0% to 1.0% dimethylation), and cyclohexanone was monobutylated with n-butyl iodide in 64% yield (1% to 7% dibutylation). Especially noteworthy were the results obtained in the methylation of 2-methylcyclohexanone. The thermodynamically controlled enolate distribution gave predominately 2,2-dimethylcyclohexanone upon methylation; while the kinetically controlled distribution of enolates yielded mainly the 2,6-dimethylated product.

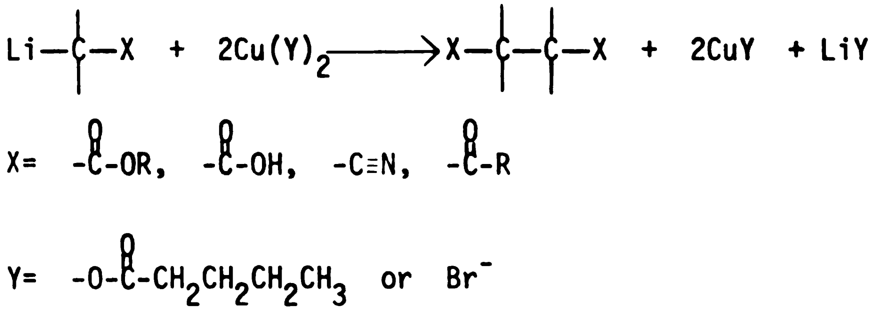
In part II, stable lithium ester enolates were prepared by the reaction of lithium N-isopropylcyclohexylamide (LiICA) with the ethyl or tert-butyl esters of acetic acid and mono- or di-alkyl acetic acids.

Andreas Lindert



These ester enolates were alkylated at 0°C with methyl, n-butyl, n-octyl, isobutyl, isoamyl, and isopropyl iodide and allyl and benzyl bromide by the addition of the ester enolate to a DMSO solution of the organic halide. The best yields of the desired alkylated products were obtained when the less sterically hindered and the more reactive organic halides were employed.

In part III, the lithium anions of esters, dialkyl amide, carboxylic acids, nitriles and ketones were dimerized with either copper (II) bromide or copper (II) valerate.



$$\mathrm{Li-\overset{|}{\underset{|}{C}}-X \;+\; 2Cu(Y)_2 \longrightarrow X-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-X \;+\; 2CuY \;+\; LiY}$$

$$\mathrm{X = \;-\overset{O}{\overset{\|}{C}}-OR,\;\; -\overset{O}{\overset{\|}{C}}-OH,\;\; -C{\equiv}N,\;\; -\overset{O}{\overset{\|}{C}}-R}$$

$$\mathrm{Y = \;-O-\overset{O}{\overset{\|}{C}}-CH_2CH_2CH_2CH_3 \;\; or \;\; Br^-}$$

The ester enolates and their derivatives rapidly dimerized and either the $CuBr_2$ or $Cu(V)_2$ oxidant could be successfully used in dimerization. In the coupling of ketone enolates, only copper (II) valerate gave satisfactory yields of the 1,4-diketone. With all compounds studied, the best yields were afforded when sterically unhindered enolate anions were coupled (63-100%). Bulky substituted carbanions gave lower yields of the desired dimer (20-50%) and greater yields of side products.

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Zu meiner Familie und meiner lieber Frau, Gudrun

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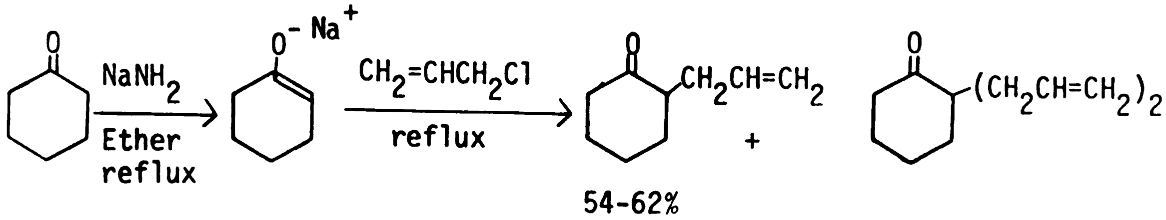
PART I

THE ALKYLATION OF KETONE ENOLATES

HISTORICAL INTRODUCTION

The base-promoted alkylation of ketones provides the chemist with a useful method for the formation of a new carbon to carbon bond. Generation of intermediate ketone enolate anions has been accomplished both quantitatively by the action of strong bases or in equilibrium amounts by using weaker bases such as the sodium alkoxides. The subsequent alkylation of the enolates provides a useful method of synthesizing substituted ketones (1).



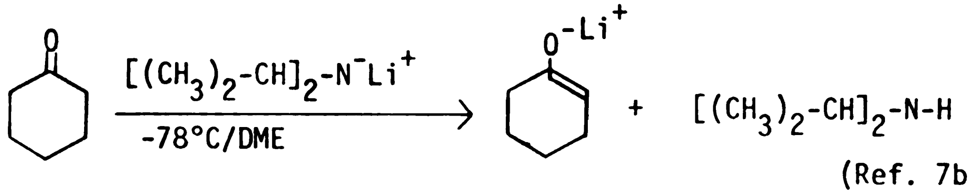
(Ref. 2)

Alpha-alkylation of ketones is often beset with undesirable side reactions which decrease its usefulness in synthesis, and ingeneous methods have been developed to overcome or circumvent these difficulties (1). Normal monoalkylation of ketones has always been plagued by di- and polyalkylation (3), self-condensation (4) to aldol-type side products and, to a much lesser extent, O-alkylation (1). The importance of these side reactions is largely dependent on the nature of the ketone, and the reaction conditions employed.

In performing the alpha alkylation of ketones, it is always important to choose conditions that will minimize side reactions. In the past, the chemist has often effected the alkylations of ketones under unfavorable conditions. This is particularly true when heterogeneous bases (NaH) or weak bases such as metal alkoxides (1) are used to generate the ketone enolates, since these bases generate the enolates slowly or in equilibrium concentrations. In order to reduce self-condensation, it is therefore necessary to generate the enolate in the presence of excess alkylating agent. This method of running the reaction leads to increased yields of dialkylation, and the degree to which self-condensation under these conditions takes place varies greatly from ketone to ketone. With cyclohexanone self-condensation is relatively unimportant, while with cyclobutanone and especially cyclopentanone, self-condensation is of major importance (3).

Self-condensation of the enolate with starting material can be largely eliminated by employing strong, homogenous bases. A wide variety of strong bases has been used in the quantitative generation of ketone enolates and a comprehensive list is presented on page 547 of ref. one.

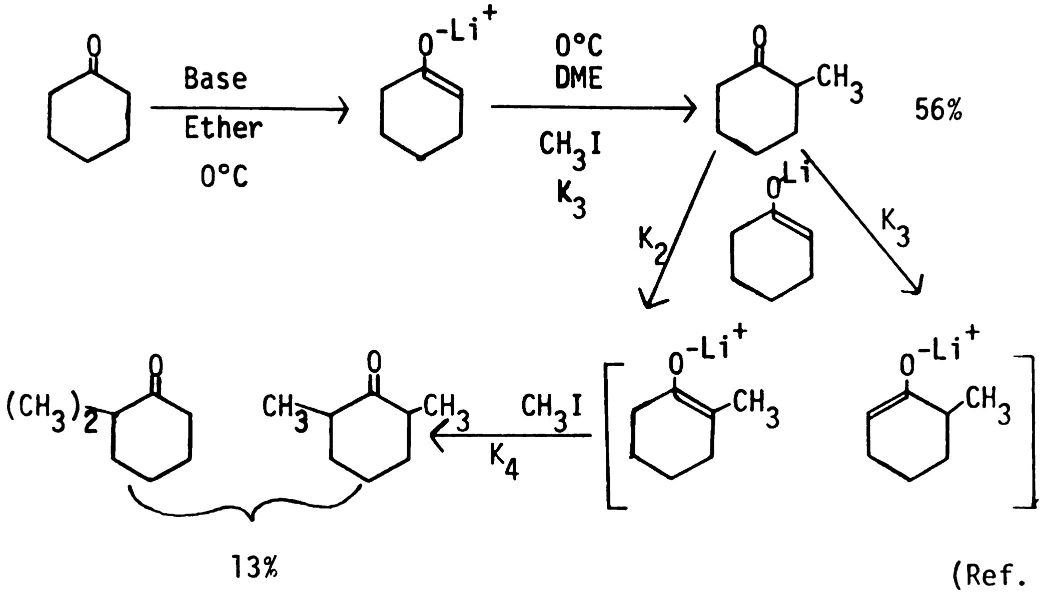
Of the bases listed, the sodium and lithium dialkylamides are the most useful since they can be easily prepared and are of sufficient strength to generate the enolates quantitatively (5). It is desirable to employ metal dialkylamides such as the sodium or lithium salts of diisopropylamine (6,7), hexamethyldisilazane (8), or N-isopropylcyclohexylamine (9), since these amines possess bulky alkyl groups. The sterically hindered bases therefore preferentially abstract an alpha proton from a ketone and no side-products resulting from attack upon the carbonyl are observed:



(Ref. 7b)

A further advantage achieved by the use of bulky alkyl substituents is the increased solubility of the basic reagent. Most metal dialkylamides have been shown to be soluble in a wide range of solvents from non-polar hydrocarbons, and benzene derivatives to the polar ethers, THF, DMSO, HMPA and DMF. These soluble, homogeneous bases react rapidly with ketones to generate ketone enolates with little self-condensation being observed. Furthermore, the bases are easily separated from the final reaction products by either simple distillation or extraction with an acid solution.

If an equivalent amount of a strong base is employed in the monoalkylation of ketones, the amount of di- and polyalkylation can be reduced but not eliminated. This polyalkylation is due to a proton exchange of alkylated products with the starting enolate (reaction K_2 and K_3) illustrated in the following reaction with cyclohexanone:



(Ref. 7b)

If reactions K_2, K_3, and K_4 can compete with the initial alkylation reaction K_1 considerable dialkylation will be observed (2).

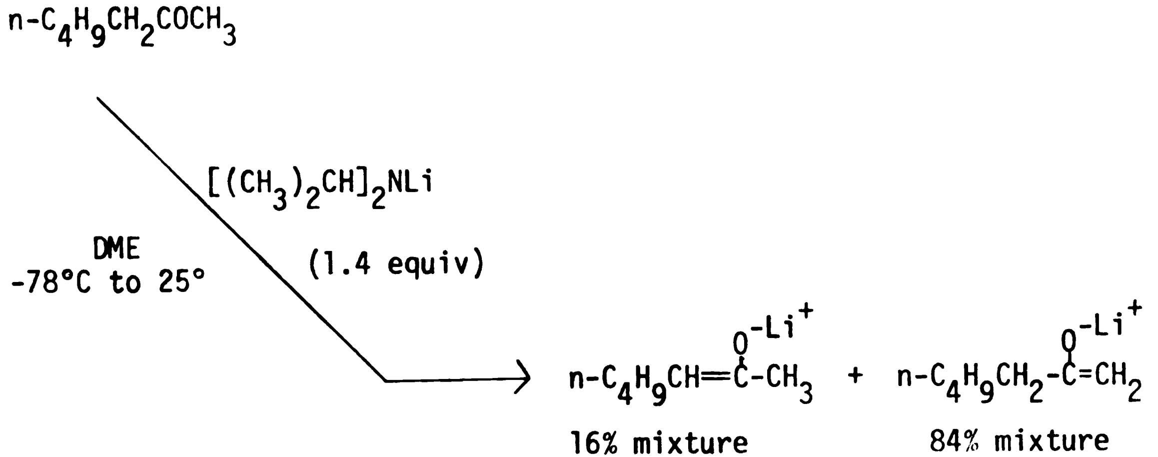
Generation of a Specific Ketone Enolate.

Often in the course of a synthesis the need arises to introduce an alkyl group selectively at one of the two alpha positions of an symmetrical ketone. Many imaginative methods have been developed to accomplish specific alkylation. Among the most common and useful procedures for the formation of the desired alkylated ketone has been the reaction of the ketone with activating or blocking groups or the preparation of enamine derivatives of the ketone prior to alkylation (1).

In recent years, the alkylation of a specific enolate anion under conditions where equilibrium among the possible structural isomers cannot occur has been increasingly used (1). The reduction of α, β-unsaturated ketones (10) or α-halo-ketones (11), the reaction of enol esters (1) and enol silyl ethers with organometallic (1,6,7a) reagents, and the direct reaction of ketones with bases under suitable conditions have proven to be the most useful methods for the generation of specific ketone enolates.

The reaction of a ketone with base provides the only direct method of generating a specific ketone enolate from the corresponding ketone. Two differing procedures can be used to generate enolates. When weak bases are used, or the reaction is run under conditions which allow the formation of an equilibrium mixture (i.e. with an excess of ketone), the more highly substituted enolate usually predominates (1).

In the second method, the enolate anion is generated under kinetically controlled condition. For this purpose strong hindered bases, such as the metal dialkylamides are most satisfactory and yield the less highly substituted ketone enolate as the predominant conjugate base.

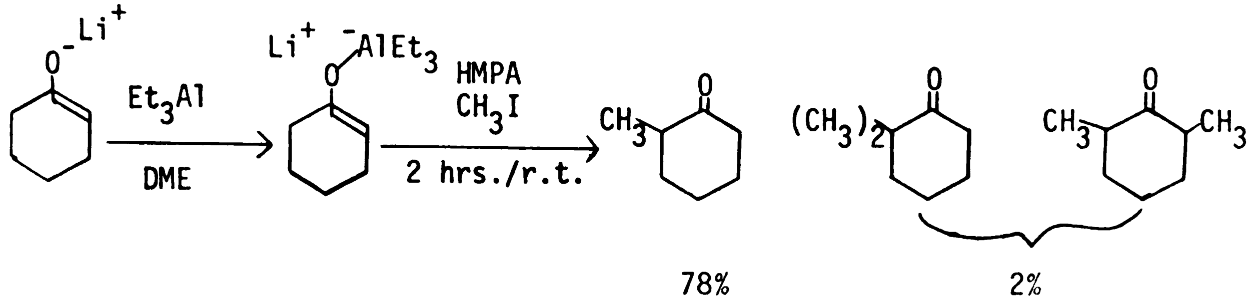


(Ref. 7b)

Subsequent alkylation of the enolates produces the desired product along with some di- and polyalkylation.

Reduction of Side-Reactions in Alkylation.

To limit self-condensation, O-alkylation and di- and polyalkylation in the alkylating of ketone enolates a variety of cations and complexing agents have been utilized. For example, by increasing the covalent character of the oxygen to metal bond, it has been possible to decrease side reactions in some instances (1). Also complexation of the ketone enolate with tributyl tin chloride or triethylaluminum prior to alkylation has proved useful in reducing side reactions (12).



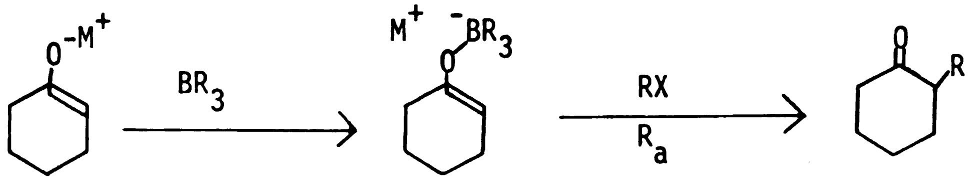
In the latter case a lower rate of alkylation necessitated the addition of hexamethylphosphoramide in order to achieve reaction in a reasonable time. Triethylaluminum is much more useful as an additive with lithium enolates than tributyl tin chloride, however it possesses the disadvantage of being extremely flammable and is therefore inconvenient to use.

A more tractable reagent that would complex with ketone enolates and reduce the side reactions that normally accompany monoalkylation would be useful to the organic chemist. In order to find such a convenient complexing reagent for ketone alkylation, a study to determine the effectiveness of employing trisubstituted boron compounds in reducing the reactivity of ketone enolates was undertaken.

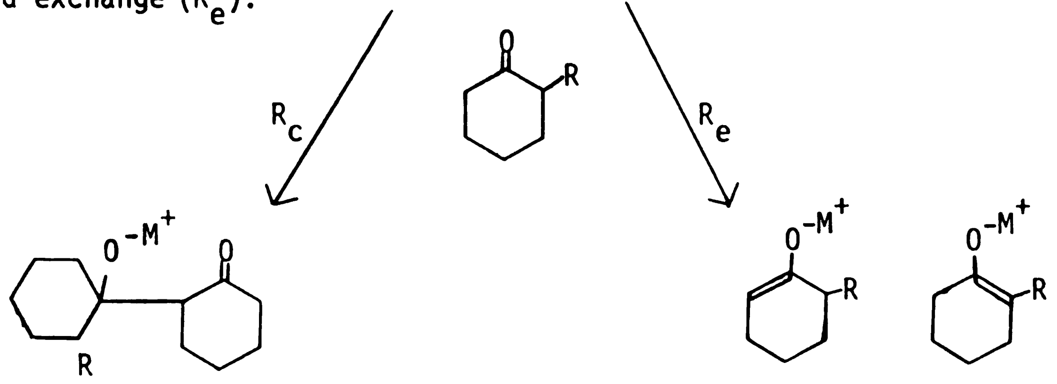
INTRODUCTION

A systematic study of the effect of borane and borate compounds on ketone enolates in α-alkylation reactions has been made. In most reactions, cyclohexanones were employed since condensation is seldom encountered with cyclohexanone derivatives. Consequently the effect of boron compounds on di- and polyalkylation could be determined with less regard to other side reactions. The boron compounds that were used in these alkylation reactions were tri-t-butyl borate, triisopropyl borate, trimethyl borate, triethanolamine borate, triethyl borane, and tricyclopentyl borane.

It was hoped that a boron compound could be found that would form a ketone enolate complex (I):



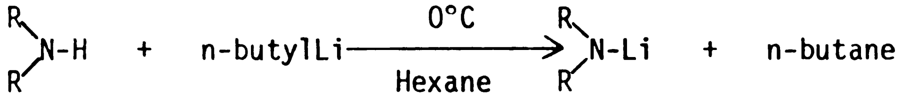
which would alkylate (R_a) much faster than undergoing condensation (R_c), and exchange (R_e).



The results presented in the following section demonstrate that some boron compounds are indeed useful in maximizing the alkylation reactions of ketones.

RESULTS

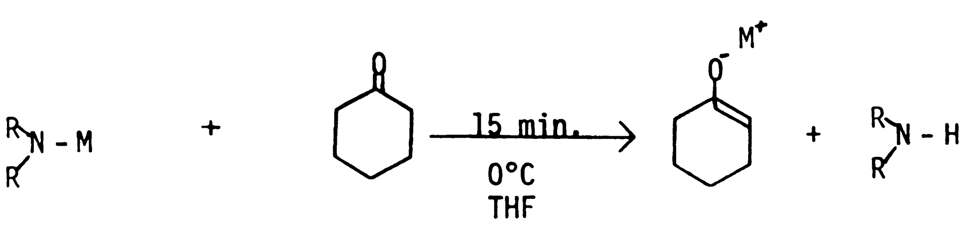
Two methods were employed to generate metal dialkylamides used in this study. In the first, lithium N-Isopropylcyclohexylamide (LiICA) and lithium bis(trimethylsilyl)amide (LiHMDS) were easily prepared by the reaction of the corresponding amine at 0°C with n-butyllithium in hexane.



$$\begin{matrix}R\\R\end{matrix}\!\!>\!N\text{-}H \;+\; \text{n-butylLi} \xrightarrow[\text{Hexane}]{0^\circ C} \begin{matrix}R\\R\end{matrix}\!\!>\!N\text{-}Li \;+\; \text{n-butane}$$

The sodium salts of the amines, on the other hand, are more difficult to generate and were prepared by refluxing a heterogeneous mixture of the amine with sodium amide in dry benzene (13). Sodium amide can be successfully used only in the preparation of sodium bis(trimethylsilyl)-amide, and is not of sufficient reactivity to generate the sodium salt of N-Isopropylcyclohexylamine.

The sodium or lithium ketone enolate employed in the alkylation reactions was generated by addition of the ketone to the corresponding metal dialkylamides in THF solution.

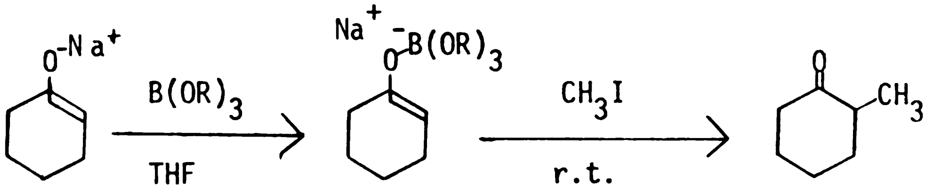


The ketone enolate thus produced is stable in THF over a prolonged period and the parent ketone can be recovered in 89-95% yield by quenching with diluted acid and analysis by GLC.

The metal cyclohexanone enolate thus generated was alkylated, and the extent of polyalkylation was determined as a function of both cation and solvent system. The results are shown in Table 1 and all future work concerned with preventing dialkylation was compared with the results of Table 1. All reactions were performed at 0°C and were complete within 15 minutes. As expected, the least amount of dialkylation was obtained with the more covalent lithium cation and the greatest dialkylation resulted when the THF/DMSO solvent system was utilized.

Trialkyl Borates.

In an attempt to prevent dialkylation, organic borates were used to reduce the reactivity of the enolate. The sodium cyclohexanone enolate was complexed with the borate prior to methylation.



Whereas the sodium and lithium enolates react instantly the trimethyl borate-enolate complex did not give products even after 2 hours at 0°C. Increasing the reaction to 3 1/2 days yielded 5.6% product while refluxing the reaction for 4 hrs. yielded 11% of the 2-methylcyclohexanone. The borate was changed from triisopropyl borate to tri-n-butyl borate, to

Table 1. Methylation of Cyclohexanone Enolate.

Cation	Solvent	Cyclohexanone	Methylcyclohexanone	Di-Methylcyclohexanones
Li	THF	9.0%	74.0%	5.5%
Na	THF	-------	50.0%	17.0%
Na	THF/DMSO	25.0%	43.0%	23.5%

Table 2. Methylation of Cyclohexanone Metal Enolate with TEAB in THF/DMSO (1:1 ratio).

Cation	Monomethylated Cyclohexanone	Di-Methylated Cyclohexanones	Cyclohexanone	TEAB	Order of Addition *
Li	71.5%	6.8%	1.0%	---	-
Na	73.1%	12.0%	15.0%	---	-
Li	79.0%	0.0%	1.7%	yes	+
Na	78.7%	3.5%	4.6%	yes	+
Na	66.8%	26.6%	10.0%	yes	-

* + means that DMSO is added before the alkyl halide.

- means that alkyl halide and DMSO are added to the enolate solution all at the same time.

tri-t-butyl borate but the yield of 2-methylcyclohexanone only increased from 15 to 25%. In all cases, large amounts of cyclohexanone were isolated and little or no dialkylation was observed.

Triethanolamine borate (TEAB) proved to be the only borate investigated which increased the yield of 2-methylcyclohexanone and at the same time reduced dialkylation. As shown in Table 2, the yield of 2-methylcyclohexanone is high, ranging from 71 to 79%. TEAB also proved useful in the methylation of 3—pentanone and cyclopentanone (see Table 3). It is necessary to use a THF/DMSO solvent system when employing TEAB due to the insolubility of TEAB in THF even in the presence of the enolate.

The aprotic solvent must be added prior to the addition of the alkylating agent with sufficient time being allowed (usually 5 minutes) for the reaction mixture to become homogeneous, otherwise the borate-enolate complex does not form and considerable dialkylation is observed (see Table 2).

Trialkyl Boranes.

Two trialkyl boranes were evaluated to determine their usefulness in reducing dialkylation in the methylation of ketone enolates. Tricyclopentylborane was useful in reducing dimethylation, however the yield of monoalkylated cyclohexanone was low (see Table 4). Increasing the reaction time improved this yield slightly, however the dialkylation side product also increased.

Triethylborane proved to be the most successful reagent employed in limiting the side reactions in ketone alkylations. Using a THF solvent system 76 to 80% of the monoalkylation product can be obtained with no corresponding dialkylation being detected. The reaction in THF is slow,

Table 3. Methylation of the Lithium Ketone Enolates Using TEAB in Monalkylation.

Ketone	TEAB	Monoalkylated Ketone	Dialkylated Ketones	Alkylating Agent
3-Pentanone	No	90%	10%	CH_3-I
3-Pentanone	Yes	92%	1%	CH_3-I
Cyclopentanone	No	85%	12%	CH_3-I
Cyclopentanone	Yes	95%	0%	CH_3-I

Table 4. Methylation of Cyclohexanone Metal Enolates Using Tricyclopentylborane.

Cation	RX'N Time	Solvent	Cyclohexanone	Methylcyclohexanone	Di-Methylcyclohexanones
Li	1 hrs.	THF	18.4%	55.5%	None
Li	2 hrs.	THF	19.5%	55.0%	3.3%
Li	18 hrs.	THF	13.0%	56.0%	6.0%
Na	2 hrs.	THF	17.0%	44.0%	None
Na	11 hrs.	THF	17.0%	45.0%	8.7%

requiring two hours for at least 97% of the reaction to go to completion. The reaction time can be shortened to 1/2 hours and the yield increased to 90% by using a THF/DMSO solvent system in 1:1 ratio (see Table 5).

Butylation of Cyclohexanone.

The reactivity of the alkylating agent is of utmost importance in α-alkylation reactions of ketones. When the alkylating agent is unreactive, as in the case of long chain alkyl halides, self-condensation and exchange can compete favorably with the alkylation reaction. Thus the butylation of cyclohexanone proceeds slowly, and considerable dialkylation is observed. Changing the cation from lithium to sodium or using DMSO/THF solvent has little effect in reducing dialkylation (see Table 6).

Both triethanolamine borate and triethylborane were used to decrease dialkylation. The butylation of the triethylborane-enolate complex is extremely slow at room temperature (see Table 7) and refluxing the reaction only results in greater yields of dialkylation products. The highest yield of monoalkylation and smallest yield of dialkylation products are obtained by using a 1:1 ratio of DMSO/THF solvent in conjunction with triethylborane. The use of DMSO or HMPA proved superior to DMF as a solvent.

An attempt to run the reaction in 100% DMSO proved futile since it was impossible to generate the enolate from lithium N-isoproplycyclohexylamide in a DMSO solvent.

TEAB also proved useful in the butylation of cyclohexanone and yielded as much as 60-69% of the monoalkylated product (Table 8). The amount of dialkylation was reduced, but not to the extent observed with triethylborane.

Table 5. Methylation of Cyclohexanone Metal Enolate Using Triethylborane.

Cation	Reaction Time	Solvent System	Cyclo- hexanone	Methylcyclo- hexanone	Di-Methylcyclo- hexanone
Li	2 hrs.	THF	12.6%	77.8%	None
Na	2 hrs.	THF	10.3%	80.8%	None
Na	1 hrs.	DMSO/ THF (1:1)	.5%	90.5%	None

Table 6. n-Butylation of Cyclohexanone Metal Enolates

Cation	Reaction Time	Temp.	Solvent System	Cyclo- hexanone	Butylcyclo- hexanone	Di-Butylcyclo- hexanone
Na	1 hrs.	r.t.	THF	82.0%	18.6%	None
Na	2 hrs.	r.t.	THF	47.7%	51.5%	10.0%
Na	8 hrs.	r.t.	THF	15.8%	66.0%	25.0%
Na	12 hrs.	reflux	THF	3.7%	39.5%	23.7%
Li	20 hrs.	r.t.	THF	14.3%	55.6%	18.6%
Li	1 hrs.	r.t.	DMSO/ THF (1:1)	----	56.5%	23.2%
Na	1 hrs.	r.t.	DMSO/ THF (1:1)	20.6%	63.3%	21.0%

Table 7. Butylation of Sodium Cyclohexanone Enolate Using Triethylborane.

Solvent Ratio	Reaction Time	Solvent System	Cyclo-hexanone	Butylcyclo-hexanone	Di-Butylcyclo-hexanone
---	2.5 hrs.	THF	89.0%	8.9%	None
---	8.0 hrs.	THF	64.0%	22.3%	6.1%
1:1	.5 hrs.	DMSO/THF	19.7%	70.0%	.5%
1:1	2.0 hrs.	DMSO/THF	10.9%	76.3%	1.4%
1:5	20.0 hrs.	DMSO/THF	22.0%	50.5%	11.8%
1:5	20.0 hrs.	DMSO/THF	28.0%	56.3%	17.0%
1:5	20.0 hrs.	DMSO/THF	25.4%	46.3%	25.3%

Table 8. Butylation of Metal Enolates of Cyclohexanone with TEAB in THF/DMSO (1:1 ratio).

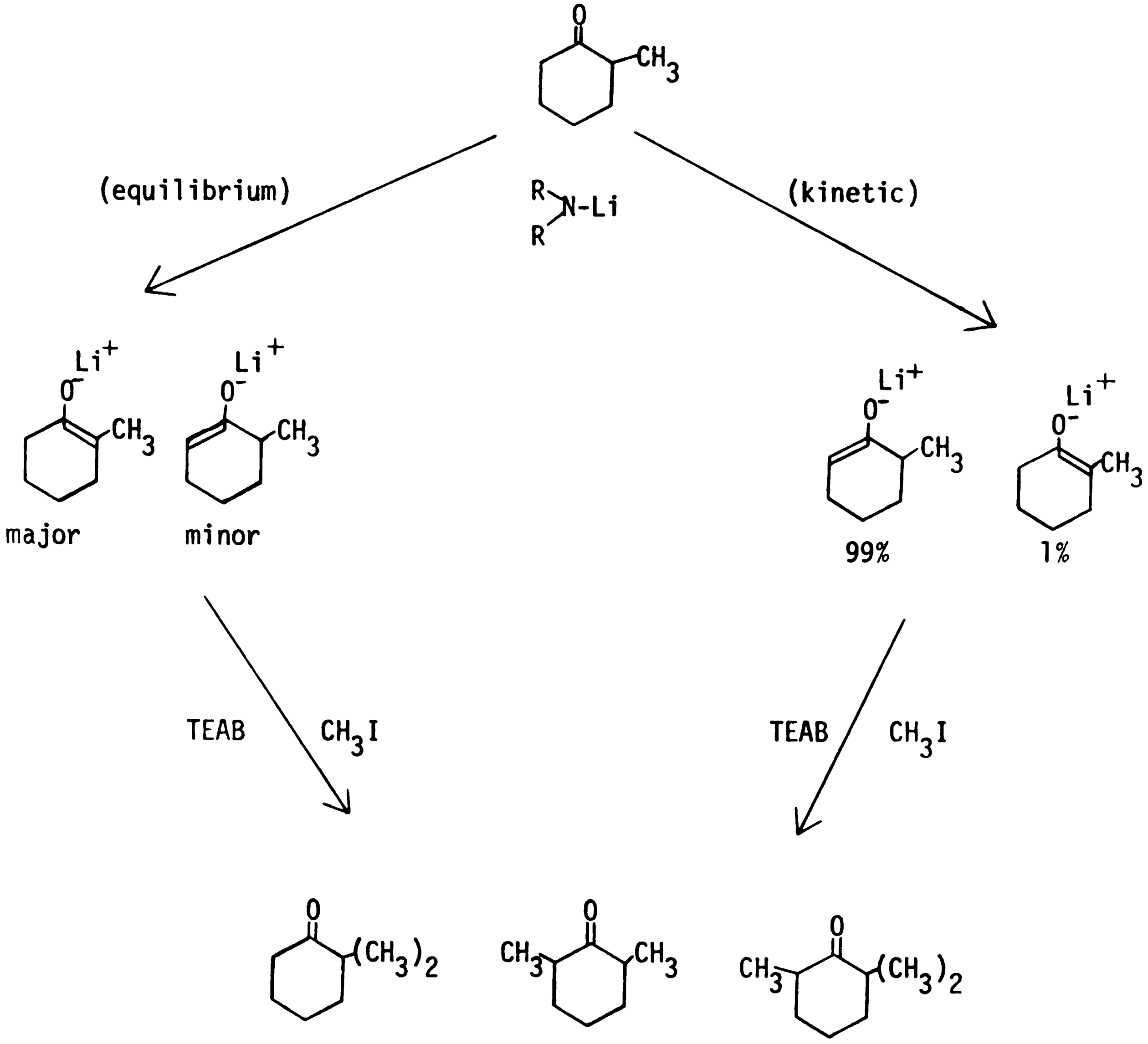
Cation	Monobutylated Cyclohexanone	Di-Butylated Cyclohexanones	Cyclo-hexanone	TEAB	Order of Addition*
Li	56.5%	23.2%	----	----	+
Na	63.3%	21.0%	20.6%	----	+
Na	60.8%	24.9%	13.8%	----	-
Li	63.5%	7.3%	----	yes	+
Na	58.5%	15.6%	16.0%	yes	+
Na	69.0%	15.6%	12.7%	yes	-

* + means that DMSO is added before the alkyl halide.

- means that alkyl halide and DMSO are added to the enolate solution all at the same time.

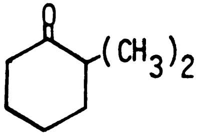
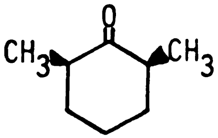
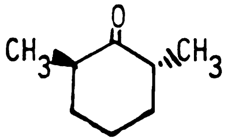
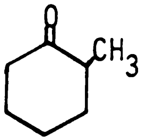
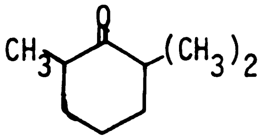
Methylation of 2-Methylcyclohexanone.

By reacting 2-Methylcyclohexanone with NaHMDS under both equilibrium and kinetically controlled conditions, it was possible to produce the enolate predominately at either the two or six position in the ketone.



(see Table 9)

Table 9. Methylation of 2-Methylcyclohexanone with TEAB in a THF/DMSO solvent (1:1 ratio)

Enolate		TEAB					
Preparation & reaction temp.	Equilibration time						
0°C/r.t.	-----	---	3.3%	40.5%	35.8%	4.0%	2.5%
0°C/r.t.	-----	yes	6.7%	40.0%	34.6%	7.0%	.2%
50°C/r.t.	-----	yes	9.9%	33.3%	29.7%	5.5%	.3%
-78°C/r.t.	-----	yes	11.3%	27.1%	25.0%	17.4%	.4%
0°C/r.t.	35 min.	yes	58.0%	7.3%	5.0%	13.4%	.56%
0°C/r.t.	90 min.	yes	62.5%	5.1%	4.1%	18.9%	.5%

Methylation of the kinetically controlled enolate yielded a cis-trans mixture of 2,6-dimethylcyclohexanone isomer.

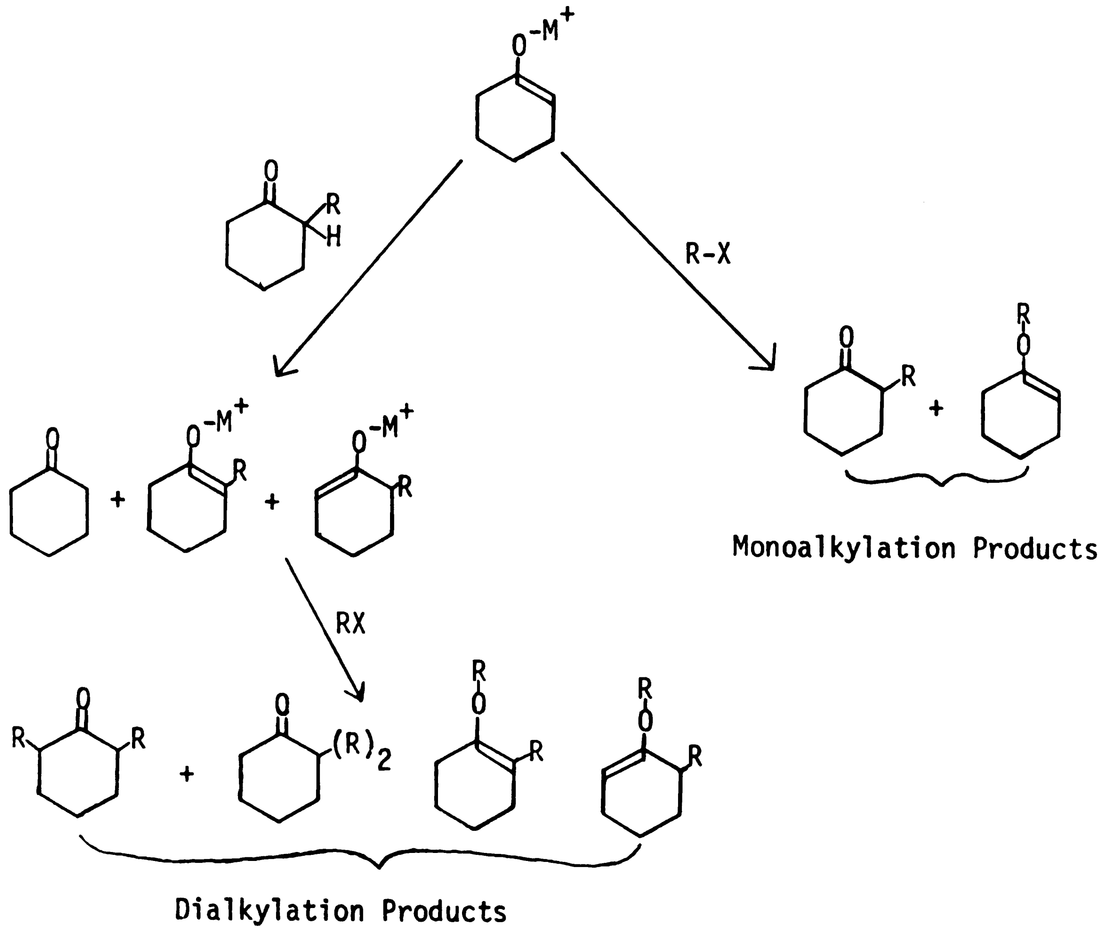
Alkylation of the equilibrium mixture of enolates yielded 2,2-dimethylcyclohexanone in 58-62% and only 9-12% of the 2,6-dimethylated isomer. Dialkylation of methylcyclohexanone is less of a problem and amounts to only 2.5%. This side reaction can be reduced to from 0.2 to 0.56% by the use of TEAB (see Table 9) in a THF/DMSO solvent.

Summary.

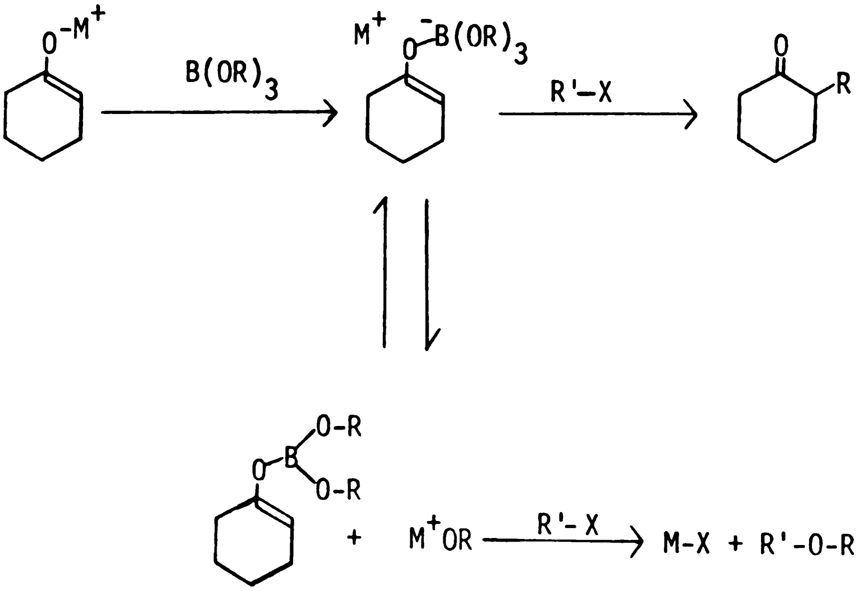
The dialkylations normally encountered in the alkylation of ketones can be considerably reduced by the use of either TEAB or triethylborane. Triethylborane is the most successful reagent in eliminating dialkylation. This is not particularly noticeable in the methylation of cyclohexanone since with both reagents little or no dimethylation is obtained. However, in the butylation of cyclohexanone, triethylborane is much more effective at reducing dialkylation. In the use of both reagents, best results are obtained when considerable amounts of polar aprotic solvents are used in conjunction with THF. This is a particularily striking result, since aprotic solvents normally increase dialkylation.

DISCUSSION SECTION

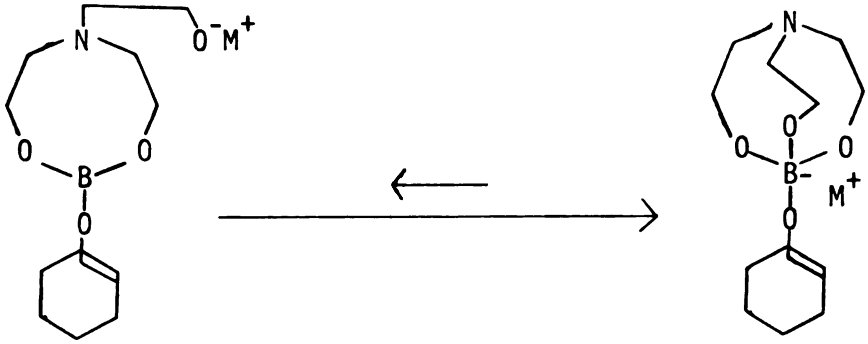
In an alkylation reaction, a ketone enolate can react by two competing pathways. The ambident nature of the conjugate base permits C- or O-alkylation, and the course of the reaction depends on the alkylating agent and reaction conditions employed. Equilibration of the initially formed enolate anion with the mono-C-alkylated product will compete with monoalkylation and result in dialkylated product as shown in the following scheme.



Reducing the reactivity of a ketone enolate either by the use of a more covalent cation or by complexation with borate or borane compounds, decreases the rate of all the above mentioned reactions. Fortunately, in most instances, the rate of proton transfer from the monoalkylated product was retarded by an even larger factor; consequently, the reduction of reactivity of the enolate is a useful method for promoting the monoalkylation of ketones. The use of trialkyl boranes and borates for this porpose has been most successful with the compounds triethylborane and triethanolamine borate. The trialkylborates gave unsatisfactory yields of monalkylated products, since the enolate alkylation reaction must compete with the dissociation of the enolate-borate complex, as shown in the following scheme.



With TEAB, this side reaction is minimized, since the leaving alkoxide cannot migrate from the reaction site and intramolecular return is favored kinetically.



By changing to trialkyl boranes this side reaction can be completely eliminated; however, triethylborane proved to be the only useful borane in alkylation reactions, possibly because it exhibits less steric bulk than many of the other compounds studied.

The reactivity of the alkylating agent made a dramatic difference in the amount of dialkylation products obtained in the alkylation of a ketone enolate. When a reactive alkylating agent such as methyl iodide was used, the alkylation reaction could compete successfully with dialkylation and good yields of monoalkylation product were obtained. However, when less reactive alkylating agents such as n-butyl iodide were used, the alkylation reaction was slow and the ketone had sufficient time to equalibrate with the small amount of monoalkylated product formed. Considerable dialkylation was therefore obtained with higher alkyl halides.

Enolate-borane or borate complex were almost totally unreactive to alkylation with n-butyl iodide. Polar aprotic solvents, however, increased their reactivities toward this alkylating agent, and the borane or borate compounds once again proved useful in limiting side reactions. This decrease in dialkylation observed with a DMSO/THF solvent system is unusual, since polar aprotic solvents normally increase the yield of the dialkylated product. It seems unlikely that the DMSO solvent increases the reactivity by solvation of the cation as is normally postulated with metal enolates (14). The increased reactivity may be due either to a lowering of the transition state energy by solvation of the reactants, or by a reaction of the boron-enolate complex with the solvent which provides a low steady state concentration of the enolate.

EXPERIMENTAL SECTION

I. General

Spectra.

Infrared spectra were obtained with a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra were measured using either a Varian A-60 or Varian Model T-60 spectrometer. All NMR spectra were recorded using tetramethyl silane as an internal standard. The mass spectra were determined by Mrs. Lorraine Guile of this department with a Hitachi-Perkin-Elmer model RMU-6 spectrometer.

Gas Chromatography.

Vapor phase chromatographic analysis were performed with a Varian Aerograph 1400 flame ionization chromatograph, or a Varian Aerograph A-90P-3 thermal conductivity chromatograph. Preparative work was carried out on the Varian Aerograph A-90 chromatograph. Relative peak areas were determined by the triangulation method.

Melting Points.

All melting points were determined with a Hoover "Uni-Melt" capillary melting point apparatus and are uncorrected.

Refractive Index.

A Bausch and Lomb "Abbe" refractometer was used to determine all refractive indexes.

II. Materials

Tri-t-butylborate.

A solution of 18.9 gms(.50 moles) of sodium borohydride in 500 ml (5.3 moles) of t-butyl alcohol was placed in a dry 1000 ml three-necked flask equipped with a nitrogen bubbler, reflux condenser, and addition funnel. After 31.5 ml (.55 moles) of glacial acetic acid was added over a 20 minute period, the reaction was refluxed for 3 hours in the absence of oxygen and water. The excess t-butyl alcohol was then removed by distillation at atmospheric pressure, giving 38 ml(26%) of the desired product, b.p. 59.3°C, density .7900 gm/ml at 25°C.

Triisopropylborate.

This borate was prepared on a one-half mole scale using the above procedure. During the reaction, sodium acetate precipitated and was filtered off before the excess isopropyl alcohol was distilled at atmospheric pressure using a vigreux column. The remaining tri-isopropylborate was purified by vacuum distillation; 12 ml(10%) of pure product was obtained, b.p. 52-53°C/15mm.

Tri-n-butylborate.

A solution of 18.9 gms(.5 moles) of sodium borohydride and 178.5 ml (20 moles) of n-butyl alcohol in 550 ml of dry ether was placed in a 1000 ml three-necked flask equipped with an addition funnel, condenser and overhead stirrer. Acetic acid (31.5 ml, .5 moles) was added over 30 minutes and the reaction refluxed for 12 hours. The solvent was evaporated and the crude product vacuum distilled to yield 90 ml (62.5%) of very pure product, b.p. 101°C/6.2mm, density .8562 gm/ml at 25°C.

Trimethylborate.

This borate was obtained from Aldrich Chemical Co. and used without further purification, n_D^{20} 1.3570.

Triethanolamineborate.

Trimethylborate (57 ml, .5 moles) and 66.5 ml (.5 moles) of triethanolamine were simultaneously added, with stirring, to 200 ml of dry ether over a one hour period at room temperature while the reaction mixture was kept under a nitrogen blanket. The insoluble white solid precipitate was filtered and washed repeatedly with dry ether and dried by vacuum over-night. 74.5 gms(95%) of pure product were obtained (15).

Triethylborane.

This borane compound was obtained from Callery Chemical Co. and was used without further purification.

Tricyclopentylborane.

A 1.54 M solution in tetrahydrofuran was prepared by the addition of a THF solution of diborane to cyclopentene.

Ketones.

Both cyclohexanone and cyclopentanone were obtained from Eastman Organic Chemicals and were distilled before use. 2,6-Dimethylcyclohexanone (cis and trans isomers) was obtained from Chemical Samples Company (n_D^{20} = 1.4466). 3-Pentanone was obtained from Eastman Organic Chemicals, n_D^{20} = 1.3899 [Lit. n_D^{20} = 1.3924] (16) and was used without further purification.

Alkyl Halides.

Methyl iodide was obtained from Baker Chemical Company and used without further purification. N-butyl iodide, obtained from an unknown source, was shaken repeatedly with a dilute solution of sodium thiosulfate, dried over anhydrous calcium chloride and distilled at 30°C/ 14 mm (17).

III. Bases

Preparation of Lithium bis (trimethylsilyl)amide (LiHMDS).

A 250 ml round-bottomed flask equipped as in Figure 1, was attached to a gas connection tube and mercury bubbler. The apparatus was flame dried under nitrogen and allowed to cool to room temperature, at which point 33.3 ml (.16 moles) of hexamethyldisilazane was injected into the flask and then cooled by an ice bath. After a few minutes, butyl lithium (100 ml of a 1.6M solution in hexane) was injected dropwise over a period of 10 minutes. As the reaction proceeded, butane was evolved and the temperature of the reaction mixture increased. The reaction was complete in 15 minutes and was allowed to come to room temperature under a nitrogen blanket. A 1 ml aliquot of the solution was injected into 25 ml of glacial acetic acid and titrated with standard perchloric acid solution using a methyl violet indicator. The concentration of the base ranged between 1.0M and 1.25M for a number of preparations.

Preparation of Lithium N-Isopropylcyclohexaylamide (LiICA).

This base was prepared from 107 ml(0.63 moles) of isopropylcyclohexylamine and 395 ml of a 1.6M solution of butyl lithium in hexane

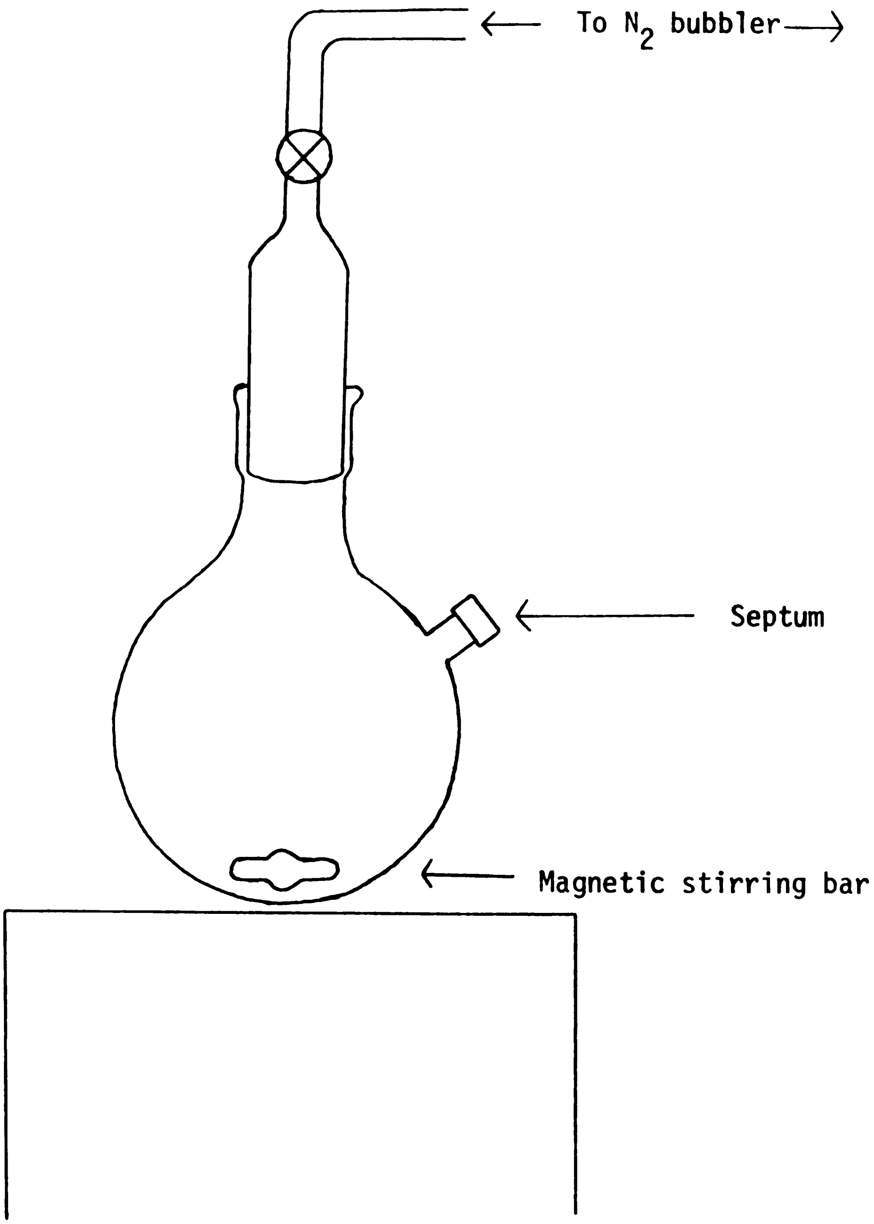


Figure 1. Reaction Apparatus.

by a procedure similar to that used for the preparation of LiHMDS.

A 1 ml aliquot of the LiICA base was injected into 20 ml of water and the free amine was extracted with ether. The water layer containing LiOH was titrated with standard (.0905N) hydrochloric acid. Solutions of base made in this manner were approximately one molar in hexane.

Preparation of Sodium bis (trimethylsilyl)amide (NaHMDS).

In a modified procedure of Wannagat and Niederprüm (13), NaHMDS was synthesized by reacting 105 ml (.5 moles) of hexamethyldisilazane with 24.92 gms(.65 moles) of $NaNH_2$ in refluxing benzene. The evolution of ammonia stopped in 4-5 hours and the reaction was cooled to room temperature, and filtered under a nitrogen atmosphere to remove a gray precipitate.

A 1 ml aliquot of the benzene solution was injected into 25 ml of glacial acetic acid and titrated with standard perchloric acid solution using a methyl violet indicator. The concentration of the base was between .60 to 79 M for a number of preparations.

IV. The Preparation and Reactions of Ketone Enolates

The ketone enolates were prepared and treated in a manner similar to that illustrated below for cyclohexanone. Either p-Cymene or p-diisopropylbenzene was used as an internal standard and all analyses were performed on a 1/4 inch by 6 ft. SE-30 column. All liquids were accurately measured and transfered by the use of syringes.

Preparation of Cyclohexanone Enolate.

A 50 ml flask equipped as in Figure 1 was flame dried under a nitrogen stream and then cooled in an ice-bath. To the flask was then added 5 mmoles of either sodium or lithium bis(trimethylsilyl)amide solution and 5 ml of tetrahydrofuran. Cyclohexanone (0.52 ml, 5mmoles) was slowly added from a syringe, and after 30 minutes of stirring, the reaction mixture became cloudy but no precipitate formed.

Recovery of Cyclohexanone.

The stability of the enolate in THF was tested by stirring the enolate for one hour at 0°C and then quenching the reaction mixture with 5 ml of dilute hydrochloric acid and extracting the products with 30 ml of pentane. The organic layer was dried over anhydrous potassium carbonate, an internal standard was added (p-diisopropylbenzene) and the reaction mixture then analyzed by GLC which revealed 89-95% recovery of cyclohexanone.

Reaction of Ketone Enolates with Alkyl Halides.

If polar aprotic solvents were employed, then from 1 to 2.5 ml of DMSO, HMPA or DMF was added to the sodium or lithium enolate at 0°C before the rapid addition of 5.5 mmoles of methyl iodide or n-butyl iodide. The reaction was then brought to room temperature and stirred for one hour. It was noted that the reaction mixture was cloudy and more viscous immediately after the addition of the alkyl halide, particularly when the DMSO/THF solvent system was used. The reaction was quenched with dilute hydrochloric acid, extracted by 30 ml of pentane and the organic layer dried over anhydrous potassium carbonate. The results were analyzed by GLC.

The Use of Alkyl Borates and Boranes.

The enolate was prepared as above and 5 mmoles of the alkyl borate or tricyclopentylborane added. If DMSO was used, it was added before the addition of 5.5 mmoles of methyl iodide or n-butyl iodide. The reaction was quenched with dilute hydrochloric acid, extracted by 30 ml of pentane and the organic layer was dried before analysis by GLC.

The Use of Triethanolamine Borate (TEAB).

Because of the insolubility of TEAB, a different procedure was employed. To the enolate (5 mmoles) was added 0.864 gms(5.5 mmoles) of TEAB and 3.0 ml of DMSO which promoted solution of TEAB. The alkyl halide was then added to this solution, and the reaction was quenched as usual and analyzed by GLC.

The Use of Triethylborane.

The borane-enolate complex was prepared by the addition of 0.52 ml (5 mmoles) of cyclohexanone to a 5 ml solution of THF containing 5 m-moles of metal dialkylamide and 0.71 ml(5 mmoles) of triethylborane. The enolate-borane complex was alkylated by the rapid addition of the alkyl halide followed by warming to room temperature. Reaction times varied from 1 to 2 hours and, after the usual work-up, the organic layer was analyzed by GLC.

Methylation of 2-Methylcyclohexanone.

Two methods were used to obtain either the kinetic or thermodynamically controlled ketone enolate. In all cases p-diisopropylbenzene was used as the internal standard and the analyses were performed utilizing a 150 ft. Perkin-Elmer DC-550 silicone capillary column.

(A). The kinetically controlled enolate was prepared by the slow addition of .607 ml (5 mmoles) of 2-methylcyclohexanone to a 2.5 ml THF solution of lithium N-isopropylcyclohexylamide (5 mmoles) at -78°C. After a 15 minute period, TEAB was added, the reaction mixture was warmed to room temperature and 2.5 ml of DMSO was added. The reaction mixture was stirred for 15 minutes before the rapid addition of .373 ml (6 mmoles) of methyl iodide. The reaction was stirred for one hour before the addition of 5 ml of dilute hydrochloric acid and 30 ml of pentane. After drying the organic layer over sodium sulfate, the pentane was filtered twice to remove all solids before being analyzed. The product consisted largely of a mixture of cis- and trans- 2,6-dimethylcyclohexanone.

(B). The thermodynamically controlled enolate was produced by the addition of .607 ml(5 mmoles) of 2-methylcyclohexanone to a 2.5 ml THF solution of lithium N-isopropylcyclohexylamide (5 mmoles) at 0°C. The reaction was warmed to room temperature, 2.5 ml of DMSO added and allowed to equilibrate for 1.5 hours before the addition of .864 gms(5.5 mmoles) of TEAB. After the solution again became clear (3 minutes), .373 ml (6 mmoles) of methyl iodide was added, and the reaction mixture was stirred for one hour. The reaction was then quenched with dilute hydrochloric acid and 30 ml of pentane was added. The organic layer was dried over anhydrous sodium sulfate and filtered twice before analysis. The major product was 2,2-dimethylcyclohexanone.

PART II

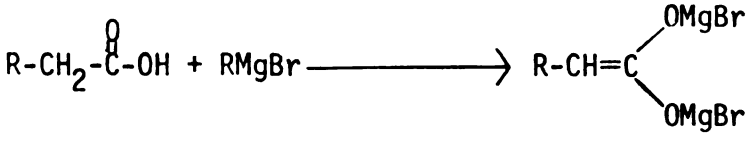
THE ALKYLATION OF ESTER ENOLATES

ACID and ESTER ENOLATES in ALKYLATION REACTIONS

Ester enolates occur as reactive intermediates in a number of well known organic reactions. In the Stobbe and Perkin reactions as well as the Dieckman and Claisen condensations, an ester enolate is produced in equilibrium concentration by weak alkoxide bases (1). The production of the zinc ester enolate from zinc metal and α-haloesters provided the first stable ester enolate (18). Although this Reformatsky reagent has proved useful in organic synthesis, the low reactivity of the zinc enolates has limited their use in direct alkylation reactions.

Since the introduction of the zinc ester enolate in 1887 (19), the acid and ester enolates of magnesium, lithium and sodium have been produced and have proved useful in organic synthesis.

The acid enolate has been extensively studied. The first of these reagents discovered was the Ivanov reagent, generated by the reaction of an organic acid with the t-butyl (20), isopropyl (21), or mesityl magnesium halides (22).



$$R\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}OH + RMgBr \longrightarrow R\text{-}CH{=}C\begin{matrix}\diagup OMgBr\\ \diagdown OMgBr\end{matrix}$$

Although magnesium acid and ester enolates have not been successfully alkylated (23), probably due to their low reactivity, the acid magnesium enolate has been employed in condensation reactions with esters (24), acid chlorides (25), ketones (21b, 26), aldehydes (27) and isocyanates (28) producing the corresponding β-keto acids, hydroxy acids and α-carbanyl-acetic acid derivatives in fair to good yields.

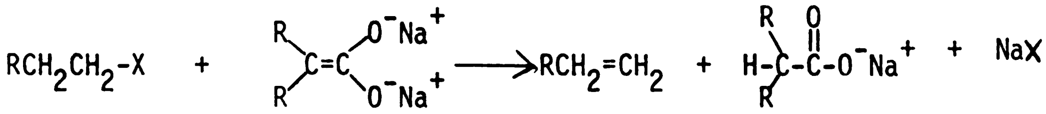
The lithium and sodium acid and ester enolates have also been formed and can be successfully alkylated. The acid enolate has given the highest yields of alkylation product (50-90%) (29) depending on the method used to generate the enolate, the acid involved, and the reaction conditions.

The acid enolates have been generated by a variety of methods:

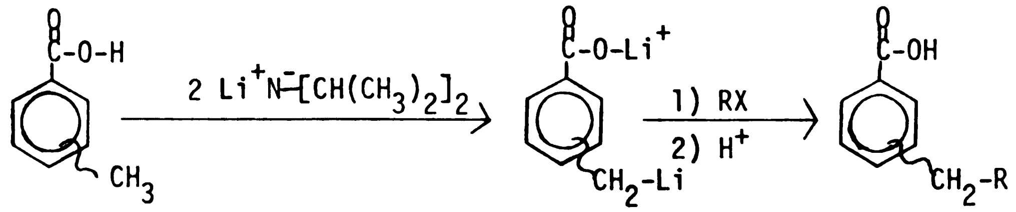
1) Alkylation of the sodium acid enolate, generated by sodium amide in liquid ammonia gives good yield of alkylated product (50-70%) (30).

2) An extraordinary method of generating an acid enolate has been developed by DePree (14). Using liquid sodium amide at 200°C he has prepared the acid enolates of acetic and methylacrylic acid (31). These unusually stable enolates were then carboxylated in good yield (60-70%). Alkylation of these acid enolates, however, gave very low yields of alkylated products (32).

3) The use of lithium diisopropyl amide (6,29) to generate the acid enolate and subsequent alkylation in THF or THF/HMPA has proved to be the most useful method of producing substituted acids. The THF/HMPA solvent system is most useful with straight chain acids, giving yields of 87-93%. With hindered acid enolates, THF is the solvent of choice, giving yields of 45-80%. The use of THF/HMPA with hindered acid enolates gives increased elimination reactions of the alkyl halides resulting in olefin by-products.



4) P.L. Creger (6) has successfully extended the usefulness of acid enolates to aromatic systems by producing and alkylating the acid enolates of toluic acids and dimethylbenzoic acids.



90%

5) M.M. Larcheveque (33) has obtained lithio acid enolates by the reduction of α, β-unsaturated acids with lithium metal in HMPA. Methylation of the lithuim acid enolate resulted in moderate yields of methylated products.

Ester Enolates.

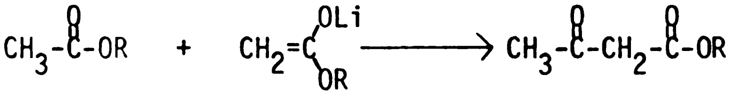
The increased solubility of ester enolates in organic solvents as well as the ease of handling and purification of the ester products, make the ester enolates desirable intermediates in organic synthesis. In some instances, as in the carboxylation of ester enolates to produce mixed malonic acid derivatives (34), the ester enolates provide the most direct method of synthesis.

The generation and alkylation of ester enolates has proved less successful than the acid enolates due to side reactions.

The following bases have been employed in generating and alkylating ester enolates.

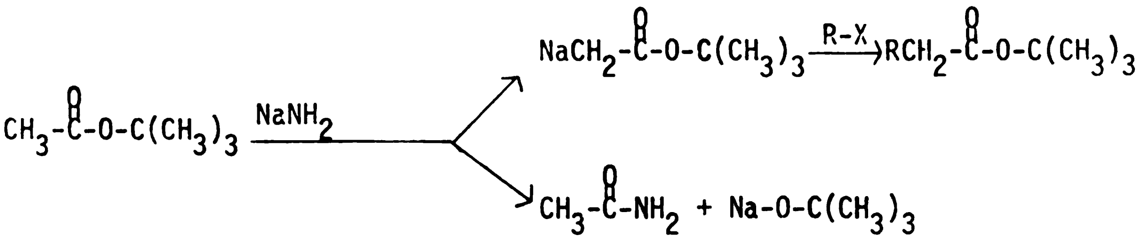
NaH	(35)
Na or $LiCO_3$	(36)
Li or $Na[Si(CH_3)_3]_2$	(8a,c)
$Na,Li-N-R_2$	(5)
$K,Na-NH_2$	(37)

With the weaker bases or in poor alkylation solvents, self-condensation of the ester seriously reduces the yield of expected product, producing instead a β-keto ester.



$$CH_3-\overset{\overset{O}{\|}}{C}-OR + CH_2=C\begin{smallmatrix}OLi\\OR\end{smallmatrix} \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OR$$

When strong metal amide bases are used, self-condensation can be reduced; however, the formation of amides becomes a competing side-reaction as illustrated below with sodium amide (39).



$$CH_3-\overset{\overset{O}{\|}}{C}-O-C(CH_3)_3 \xrightarrow{NaNH_2} NaCH_2-\overset{\overset{O}{\|}}{C}-O-C(CH_3)_3 \xrightarrow{R-X} RCH_2-\overset{\overset{O}{\|}}{C}-O-C(CH_3)_3$$

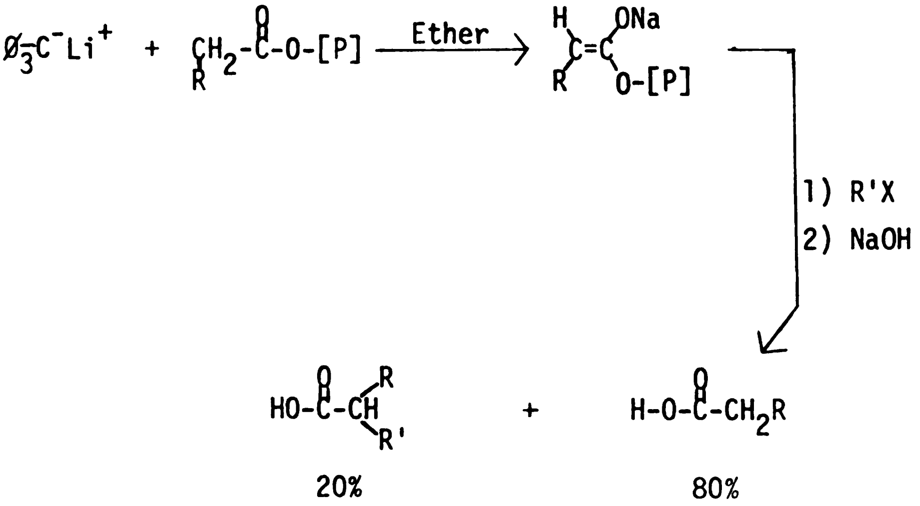
$$CH_3-\overset{\overset{O}{\|}}{C}-O-C(CH_3)_3 \xrightarrow{NaNH_2} CH_3-\overset{\overset{O}{\|}}{C}-NH_2 + Na-O-C(CH_3)_3$$

When the t-butyl or t-amyl esters were alkylated from 30% to 87% of the desired product was isolated (37). The increased steric hindrance afforded by the use of the triethylcarbinyl ester of dialkylacetic acids enabled Hauser to increase the yield of the alkylated product to 70-80% (38). The alkylation reaction is most successful with the esters of acetic acid or dialkylacetic acids and least successful with the esters of straight-chain acids giving only poor to fair yields of the desired product.

The use of sterically hindered metal dialkyl amides greatly reduces both amide formation and self-condensation. The first attempts by Hauser to use a solution of lithium diisopropylamide in ether to generate the lithium ester enolate of ethyl isobutyrate proved unsuccessful (37). Kruger and Rochow, however, were able to produce the sodium ester enolate in ether by employing the more reactive sodium salt of hexamethyldisilazane. Since the sodium enolates are less stable than their lithium counterparts, they pose difficulties as synthetic reagents.

Both our work (40) and that of others (5,34) has shown that the lithium dialkyl amides are very useful reagents for the generation of ester enolates when the polar aprotic solvents THF, DMSO, or HMPA are employed. The reaction conditions for alkylation using these bases will be discussed in the following experimental section.

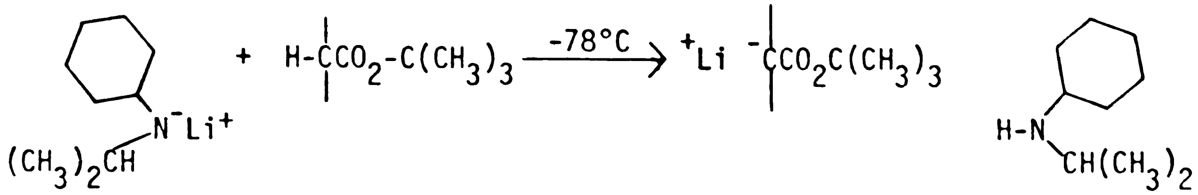
To decrease self-condensation, the sodium ester enolate has also been generated on the surface of a polystyrene polymer (41).



The alkylated acid was isolated in only 20% after hydrolysis of the ester. The low yield obtained is most likely a result of the unfavorable solvent system employed in the alkylation reaction. This method of generating ester enolates on a polymer surface has however proved useful for the synthesis of ketones by acylation and decarboxylation of an ester enolate (36b) as well as for specific Dieckman ring formation (42).

RESULTS AND DISCUSSION

The lithium ester enolates were prepared by the slow addition of an ester to lithium bis(trimethylsilyl)amide (LiHMDS) or lithium N-isopropylcyclohexylamide (LiICA) in a THF solution.



The LiHMDS base is useful in the preparation of the less hindered and more reactive acetate esters. Unfortunately, attempts to generate the lithium conjugate base of ethyl hexanoate at -78°C resulted in slow condensation of the ester over a one hour period. The use of the more sterically hindered t-butyl hexanoate gave similar results; however, the rate of self-condensation was much reduced.

The LiICA base proved to be useful for the preparation of all the lithio ester enolates studied. The generation of the lithium ester enolates by LiICA was studied by reacting the base with the ester at either -78°C or 0°C. The reaction was quenched with deuterium oxide and the product examined by GLC for recovered starting material and by NMR for deuterium incorporation (see Table 10).

Table 10. Results of Deuterium Oxide Quenching Experiments of Ester Enolate Solutions Generated with LiLCA.

Ester	Recovered Ester, %	Deuterium Incorp., %	Temp.
Ethyl propionate	90	50	-78°C
	60	50	0°C
Ethyl hexanoate	100	55	-78°C
	70	50	0°C
tert-Butyl hexanoate	97	45	-78°C
Ethyl nonanoate	100	50	-78°C
Ethyl isobutyrate	97	75	-78°C
	92	70	0°C
Ethyl isovalerate	97	60	-78°C
Ethyl cyclohexanecarboxylate	95	70	-78°C
Ethyl phenylacetate	98	60	-78°C

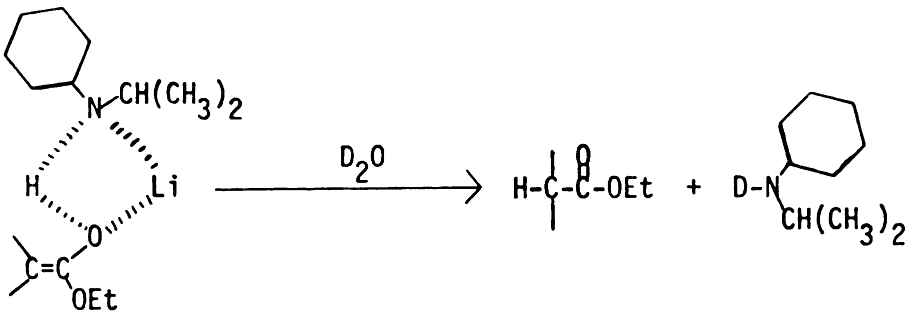
Table 11. n-Butylation of Lithium tert-Butyl Acetate with n-Butyl Iodide.

Temp.	Solvent	Alkylated Product*	Order of Addition
-78°C	THF	.2%	Halide to Enolate
-45°	THF	3.9%	" " "
-22°C	THF	4.9%	" " "
0°C	THF	53.0%	" " "
r.t.	THF	55.0%	" " "
r.t.	DMSO/THF	71.0%	" " "
r.t.	DMSO/THF	85.0%	Enolate to Halide
-45°C	HMPA/THF	64.0%	Halide to Enolate

* All reaction times 1 hour.

When the LiICA base was used to generate lithium ester enolates at -78°C, the ester was 90-100% recovered on quenching, demonstrating that self-condensation does not occur. When the lithium ester enolate was prepared at 0°C, 60-92% of the ester was recovered indicating that some side reaction is taking place at the higher temperature.

The deuterium incorporation was never quantitative and varied from 50 to 75%. The low deuterium incorporation cannot represent incomplete formation of the ester enolate (as in an equilibrium), since extensive condensation would have resulted. This was demonstrated by the addition of a slight excess of ethyl hexanoate to the enolate at -78°C. Quenching of this reaction after 5 minutes showed almost complete disappearance of ester. These results are consistant only with quantitative and irreversible formation of the ester enolate, consequently, the incomplete deuterium incorporation must be a result of an unusual protonation mechanism involving the N-isopropylcyclohexylamine.



Although the ester enolates are more stable at low temperatures; alkylation in THF does not occur readily at temperatures below 0°C (see Table 11). The alkylation reaction can be enhanced either by raising the temperature or by using HMPA or DMSO as co-solvents.

Thus in THF lithium tert-butyl acetate reactions at -45°C with excess butyl iodide to yield only 3.9% of alkylated products, while addition of either DMSO or HMPA co-solvent at the same temperature yields 71% of the desired product. The yield of this reaction can be further improved to 85% by adding the ester enolate to a solution of butyl iodide in DMSO at room temperature.

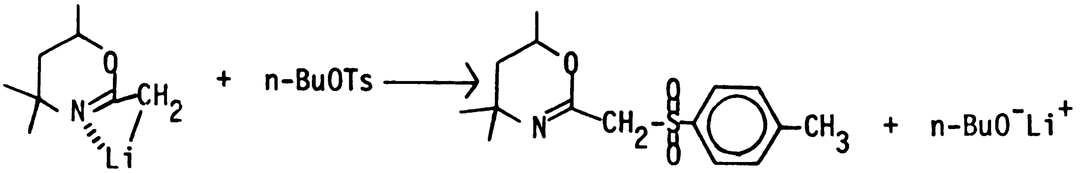
The steric hindrance and reactivity of the alkylating agent plays an important role in these alkylation reactions. The use of more reactive alkyl iodides gives superior yields, as demonstrated by the alkylation of t-butyl acetate with BuCl, BuBr and BuI, which gives respectively 5%, 75%, or 85% yields of t-butyl hexanoate (see Table 12).

It has also been demonstrated that increasing steric hindrance in the alkyl halide reduces the yield of alkylated product. Thus when lithium t-butyl acetate was alkylated with the following alkylating agents the yield of product decreased in the designated order: isoamyl iodide > isobutyl iodide > isopropyl iodide.

Since the alkyl iodides, of all the halides gave the best yields of alkylated product, an attempt was made to use alkyl tosylates as the alkylating agents. n-Butyl, n-benzyl, alkyl, octyl and n-propyl tosylate were synthesized and reacted with lithium t-butyl acetate under a wide variety of reaction conditions. No alkylated products or side products were ever obtained. In some cases, the starting ester was isolated but never in quantitative amounts. A.I. Meyers observed that the reaction of the lithium dihydro-1,3-oxazine anion with n-butyl tosylate resulted in the formation of the sulfone (43).

Table 12. Alkylation of Lithium Ester Enolates with Organic Halides.

Ester	Alkylating Agent	Products	DMSO/ THF	THF
tert-Butyl acetate	n-Butyl iodide	$CH_3(CH_2)_4CO_2C(CH_3)_3$	85%	55%
tert-Butyl acetate	n-Butyl bromide	$CH_3(CH_2)_4CO_2C(CH_3)_3$	75%	7%
tert-Butyl acetate	n-Butyl chloride	$CH_3(CH_2)_4CO_2C(CH_3)_3$	5%	0%
tert-Butyl acetate	n-Octyl iodide	$CH_3(CH_2)_8CO_2C(CH_3)_3$	100%	64%
tert-Butyl acetate	Isobutyl iodide	$(CH_3)_2\text{-}CH(CH_2)_2\text{-}CO_2C(CH_3)_3$	42%	17%
tert-Butyl acetate	Isoamyl iodide	$(CH_3)_2CH(CH_2)_3CO_2C(CH_3)_3$	75%	26%
tert-Butyl acetate	Allyl bromide	$CH_2{=}CH(CH_2)_2CO_2C(CH_3)_3$	100%	81%
tert-Butyl acetate	Benzyl bromide	$C_6H_5(CH_2)_2CO_2C(CH_3)_3$	96%	34%
tert-Butyl acetate	Isopropyl iodide	$(CH_3)_2CHCH_2CO_2C(CH_3)_3$	50%	3%
tert-Butyl isobutyrate	Methyl iodide	$(CH_3)_3CO_2C(CH_3)_3$	98%	---
tert-Butyl hexanoate	Methyl iodide	$CH_3(CH_2)_3CHCH_3CO_2C(CH_3)_3$	94%	---
Ethyl hexanoate	Methyl iodide	$CH_3(CH_2)_3CHCH_2CO_2CH_2CH_3$	92%	---
Ethyl hexanoate	Isopropyl iodide	$CH_3(CH_2)_3CHCH(CH_3)_2CO_2CH_2CH_3$	53%	18%
Ethyl isobutyrate	Methyl iodide	$(CH_3)_3CO_2CH_2CH_3$	87%	---

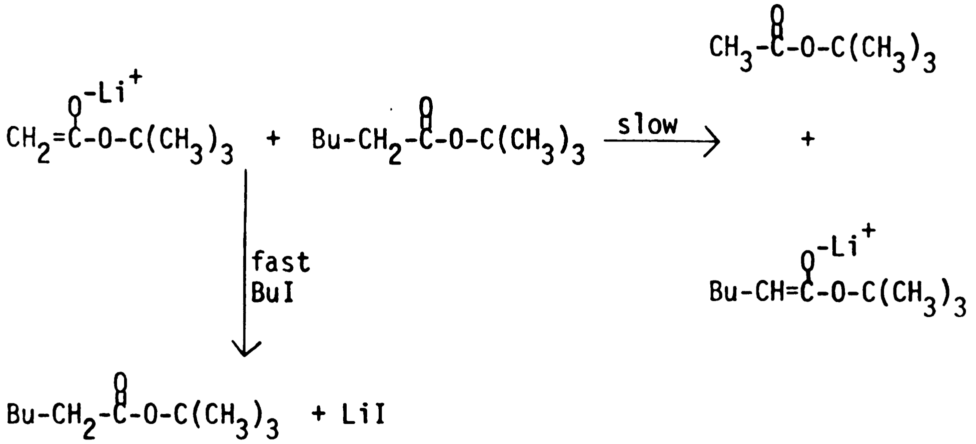


It is possible that the lithium ester enolate reacts in a similar fashion with tosylates, attacking the sulfur atom, however, this product was not isolated from the reaction mixture.

The lithium enolates of acetate esters are particularly prone to self-condensation, and it is advantageous to employ the more hindered t-butyl ester in synthesis in order to reduce this unfavorable side reaction.

The substituted ester acetates are less susceptible to the condensation reaction; consequently, they give better yields of alkylated products, and even the ethyl ester can be satisfactorily alkylated with only a minimum of side reaction. The main by-product is unreacted starting material, with only a little β-keto ester being formed.

Polyalkylation, which is so troublesome in the alkylation of ketones, was not observed in the alkylation of lithium ester enolates. Thus the equilibrium reaction of the lithium ester enolate with alkylated product must be slow in relation to the rate of alkylation.



In general, alkylation of lithium ester enolates is most successful when unbranched alkyl iodides are used as the alkylating agent and a THF/DMSO solvent system is employed. The alkylation of lithio ester enolates provides a convenient method of synthesizing a large variety of alkylated esters from readily available starting materials.

EXPERIMENTAL SECTION

I. Materials

Alkyl Halides.

Commercial n-butyl bromide, n-butyl chloride and n-octyl iodide were used without further purification. Isobutyl iodide (31-32°C/38mm), isoamyl iodide (62°C/55mm) and isopropyl iodide (88-89°C) were shaken repeatedly with a dilute solution of sodium thiosulfate dried over anhydrous calcium chloride and distilled prior to use. Allyl bromide (70°C) and benzyl bromide (110°C/13mm) were purified by distillation and stored over a few drops of mercury in an amber bottle.

Tosylates.

The tosylates were prepared either by the method of Schleyer (44) from the alcohol and p-toluenesulfonyl chloride in a pyridine solution or by the method of Drahowzal and Klamann (45) from the alcohol and tosyl chloride in a 25% sodium hydroxide solution. The following tosylates were synthesized. n-Butyl tosylate 32-34°C/10mm; n_D^{20} 1.5004, [lit. n_D^{20} 1.5046] (45); n-propyl tosylate n_D^{20} 1.5042 [lit. n_D^{20} 1.5080] (45); n-octyl tosylate n_D^{20} 1.4931 [lit. n_D^{20} 1.4946] (45); benzyl tosylate m.p. 54-56°C [lit. 56°C] (45); and allyl tosylate b.p. 137-140°C/2mm, n_D^{20} 1.5174 [lit. n_D^{20} 1.5209] (45).

Esters.

All esters were commercially available except tert-butyl hexanoate and ethyl cyclohexanecarboxylate which were synthesized from readily available starting materials. All esters were dried over molecular sieves prior to use.

II. Preparation and Reactions of Ester Enolates

The ester enolates were prepared and treated in a manner similar to that illustrated for tert-butyl acetate. All analyses were performed using a 1/4 inch by 6 ft. SE-30 column. All liquids were accurately measured and transferred with syringes.

Preparation of Lithium tert-Butyl Acetate.

A 50 ml flask equipped as in Figure 1 was flame dried under a nitrogen steam and then cooled to -78°C in a dry-ice acetone bath. To this flask was added 5 mmoles of lithium N-isopropylcyclohexylamide in 5 ml of tetrahydrofuran, followed by .67 ml (5 mmoles) of tert-butyl acetate. After 30 minutes of stirring at -78°C, the formation of the lithio ester enolate was considered complete.

Recovery and Deuteration of the Esters.

The ester enolate (10 mmoles), prepared as above either at -78°C or 0°C, was quenched with deuterium oxide. Extraction by 25 ml of pentane, gave after drying over anhydrous magnesium sulfate a solution of the ester which was analyzed by GLC, using an inert internal standard. The amount of deuterium incorporation was determined by NMR examination of the recovered ester isolated by preparative GLC from the pentane solution. In some cases the ester was examined in a crude state by simple evaporation of the solvent with identical results.

Reaction of the Ester Enolate with Alkyl Halide.

Two methods were used to react the enolate with an alkylating agent, as demonstrated below for the butylation of lithium tert-butyl acetate.

(A). The ester enolate was prepared on a 5 mmole scale as described above. When desired, 2 ml of DMSO was added before rapid addition of .855 ml (7.5 mmoles) of butyl iodide. The reaction mixture was warmed to room temperature, stirred for one hour and then quenched with 6N hydrochloric acid. Following the addition of 30 ml of pentane, and an internal standard, the organic layer was dried over anhydrous potassium carbonate and analyzed by GLC.

(B). The ester enolate prepared at -78°C as previously described was added to a solution of .855 ml (7.5 mmoles) of butyl iodide in 5 ml of DMSO/THF solvent (3:2 ratio) at either 0°C or room temperature. The reaction was stirred for one hour and quenched with 6N hydrochloric acid, followed by the addition of 30 ml of pentane and an internal standard. The organic layer was then dried and analyzed by GLC.

Product Analysis.

The physical constants of five esters synthesized are compared with published values for these compounds in Table 13. All compounds in this Table were also analyzed by NMR and IR spectra and were in agreement with the proposed structure. The spectral data and physical constants for the remaining esters synthesized are also presented in this section.

Table 13. Product Constants Compared with Literature Values.

Products	Experimental b.p.	 Refractive index	Literature b.p.	 Refractive index	Ref.
tert-Butyl decanoate	76-77°C/.3mm	n_D^{20} 1.4274	123°C/12mm	n_D^{12} 1.4234	(37b)
tert-Butyl 5-methyl-hexanoate	74-76°C/10mm	----------	81-84°C/13mm	----------	(37b)
tert-Butyl 4-pentenoate	56-58°C/20mm	n_D^{20} 1.4140	68-69°C/26mm	n_D^{12} 1.4142	(37b)
tert-Butyl 3-phenyl-propanoate	87-89°C/1mm	n_D^{20} 1.4798	144°C/8mm	n_D^{25} 1.4801	(46,47)
Ethyl 2,2-dimethyl-propanoate	118-120°C	n_D^{20} 1.3892	118-118.2°C	n_D^{20} 1.3912	(16)

tert-Butyl Hexanoate.

This compound was compared with authentic material. I.r. 1750 cm^{-1}, 1165 cm^{-1}. Mass spectrum m/e 172. Refractive index n_D^{20} 1.4073. B.p. 56-58°C/20mm.

tert-Butyl 4-Methylpentanoate.

NMR (CCl_4): 7.86τ(t, 2H), J=6.5cps; 8.43τ(m, 1H), one $-CH_2-$ from 8.50τ to 8.70τ; 8.59τ(s, 9H); 9.12τ(d, 6H), J=5.5cps. I.r. 1730 cm^{-1}, 1155 cm^{-1}.

tert-Butyl 3-Methylbutanoate.

NMR (CCl_4): 7.97τ(d, 2H), J=1.75cps; -CH- 8.55τ(s, 9H); 9.07τ (d, 6H), J=3.5cps.

tert-Butyl 2-Methylhexanoate.

NMR (neat): 7.78τ(m, 1H), J=3.5cps; $-CH_2CH_2CH_2-$ from 8.30τ to 8.93τ; 8.58τ(s, 9H); 8.95τ(d, 3H). I.r. 1725 cm^{-1}, 1160 cm^{-1}. B.p. 84-86°C/20mm. Refractive index n_D^{20} 1.4078.

tert-Butyl 2,2-Dimethylpropanoate.

NMR (neat): 7.10τ(s, 9H); 7.70τ(s, 9H); I.r. 1735 cm^{-1}. B.p. 130°C. Refractive index n_D^{20} 1.3921.

Ethyl 2-Isopropylhexanoate.

NMR (CCl_4): 5.93τ(q, 2H); 1.97τ(m, 1H); 8.70τ(t, 3H); -CH- and $-CH_2CH_2CH_2-$ from 8.33τ to 9.00τ; three methyl groups from: 9.00τ to 9.33τ. I.r. 1730 cm^{-1}, 1165 cm^{-1}. B.p. 89-95°C/9mm.

Ethyl 2-Methylhexanoate.

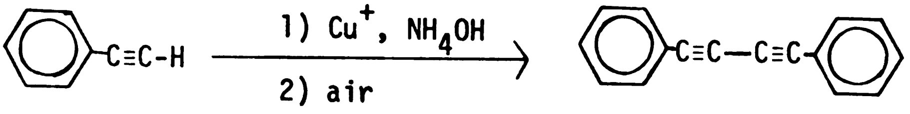
NMR (neat): 5.92τ(q, 2H), J=3.5cps; 7.68τ(m, 1H), J=3.5cps; $-CH_2CH_2CH_2-$ from 8.30τ to 8.94τ; 8.80τ(t, 3H); 8.91τ(d, 3H); 9.12τ (t, 3H), J=3.0cps. I.r. 1750 cm^{-1}, 1185 cm^{-1}, 1150 cm^{-1}. B.p. 73-74°C/18mm. Refractive Index n_D^{20} 1.4078.

PART III

THE COUPLING OF ENOLATE ANIONS
with
COPPER COMPOUNDS

INTRODUCTION AND HISTORY

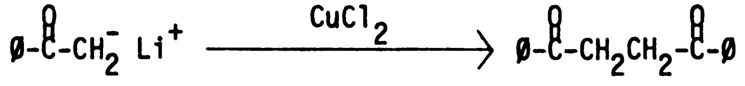
Over a hundred years ago, oxidative coupling became a useful synthetic reaction with the discovery of the copper coupling of phenylacetylene by C. Glaser (48).



The oxidative coupling of acetylenes had been extensively studied in the last 30 years and is widely used in the synthesis of symmetrical and unsymmetrical di- and polyacetylenes (49).

The oxidative coupling reaction has by no means been restricted to acetylene derivatives, and a search of the literature reveals a wealth of organic anions that yield useful dimerization products with cupric salts, as exemplified by the list in Figure 2.

The last of these reactions, the oxidative coupling of the phenyl methyl ketone enolate by cupric halides gives only a low yield of dimeric product.



$$\emptyset\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2^-\ Li^+ \xrightarrow{CuCl_2} \emptyset\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}\emptyset$$

15%

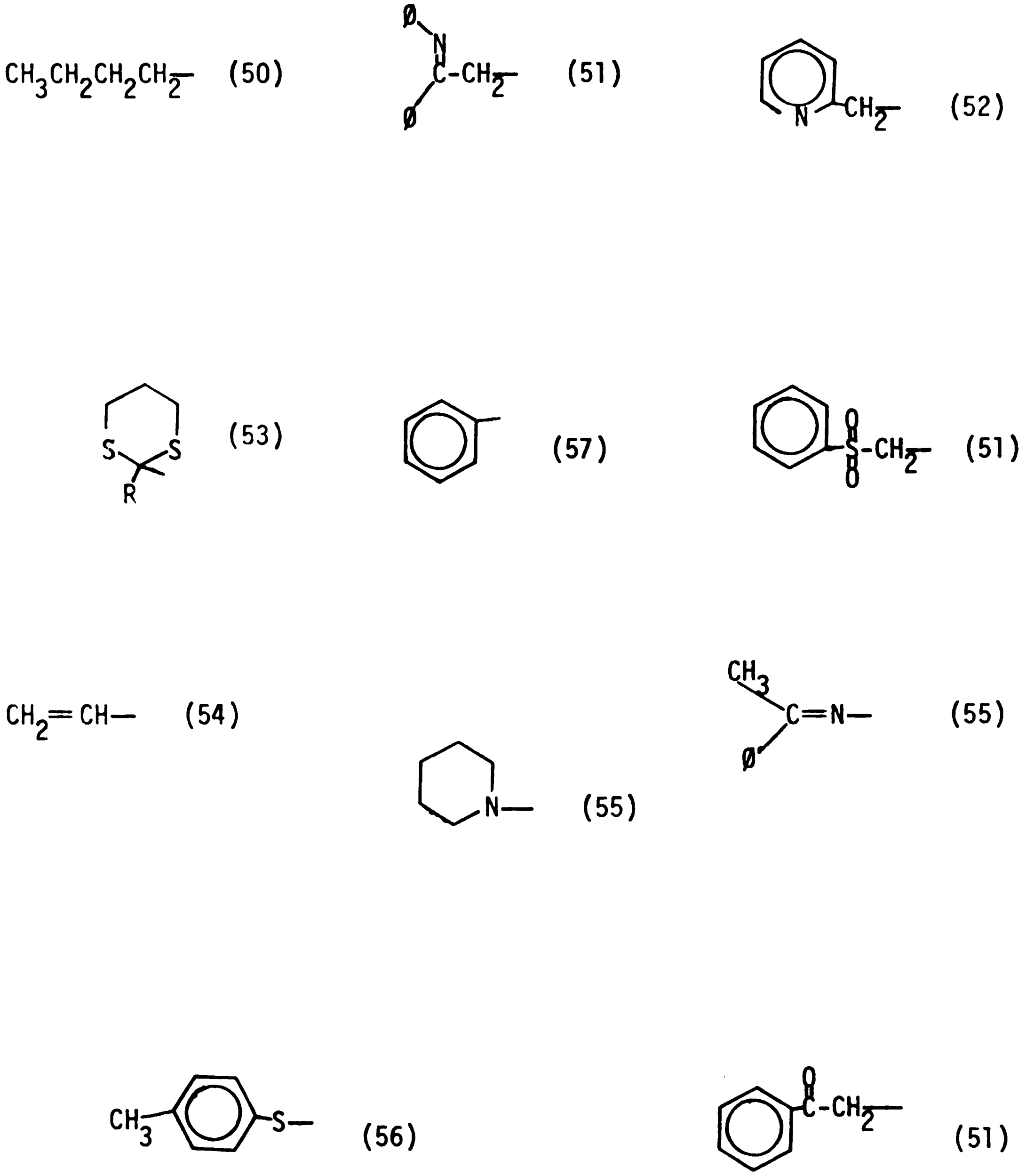
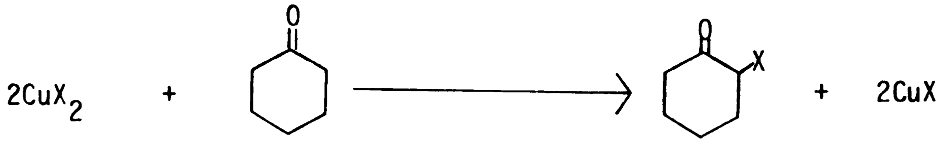
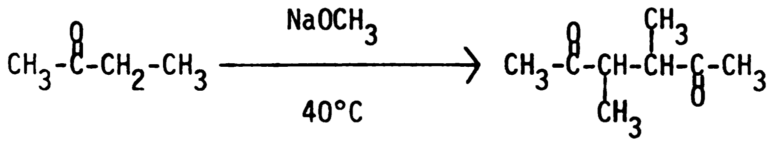


Figure 2. The Coupling of Anions with Copper Compounds.

The coupling of enolate anions has apparently been sparsely investigated. The lack of suitable methods for the quantitative generation of ketone enolates as well as the knowledge that ketones give α-halo products with the cupric halides normally used in coupling reactions (58), has limited the interest in such reactions.



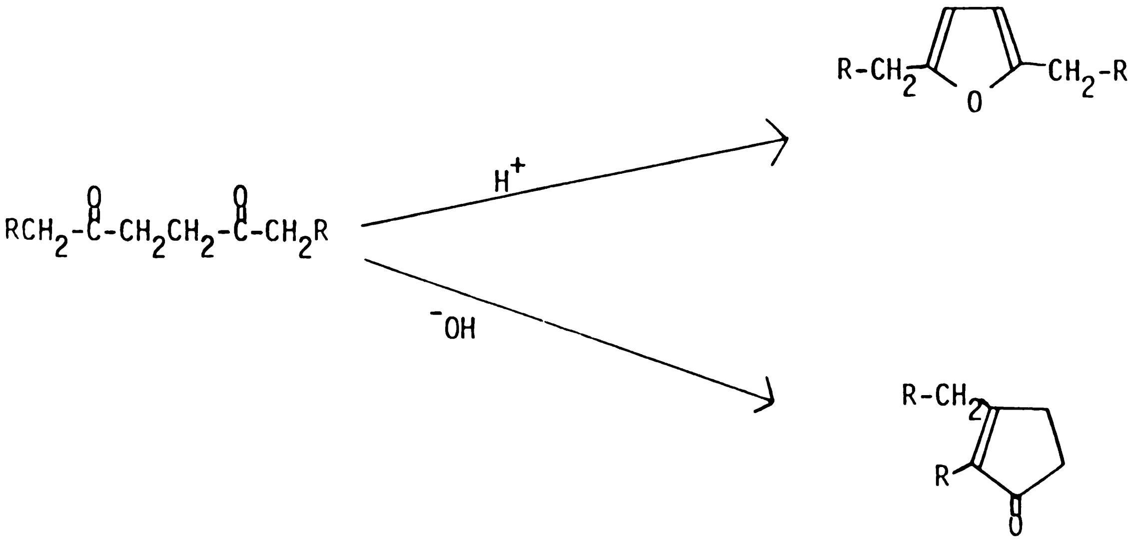
Nevertheless, W. Brackman and H.C. Volger discovered that ketone enolates could be oxidatively coupled by a solution of cupric nitrate in methanol, pyridine and triphenylphosphine (59).



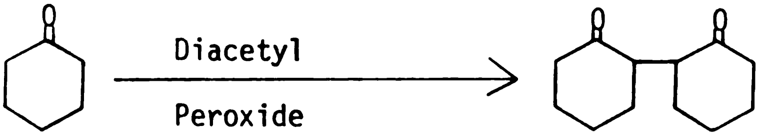
$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}CH_3 \xrightarrow[40°C]{NaOCH_3} CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_3}{\underset{|}{C}}H\text{-}\overset{CH_3}{\overset{|}{C}}H\text{-}\underset{O}{\underset{\|}{C}}\text{-}CH_3$$

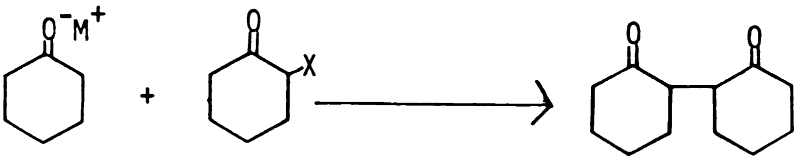
The coupled products of the above reaction were isolated in low yield based on starting ketone and since sodium methoxide generates an equilibrium mixture of conjugate bases, this reaction is generally restricted to the production of 1,4-diketone products resulting from the more stable ketone enolates.

These 1,4-diketone products are useful intermediates in the synthesis of symmetrical furans (60) and in the preparation of cyclopentenone derivatives (61).



The chemical literature abounds with unique synthetic methods for the preparation of 1,4-dicarbonyl compounds. Only two methods exist that effect such a synthesis by direct α-coupling of carbonyl compounds:





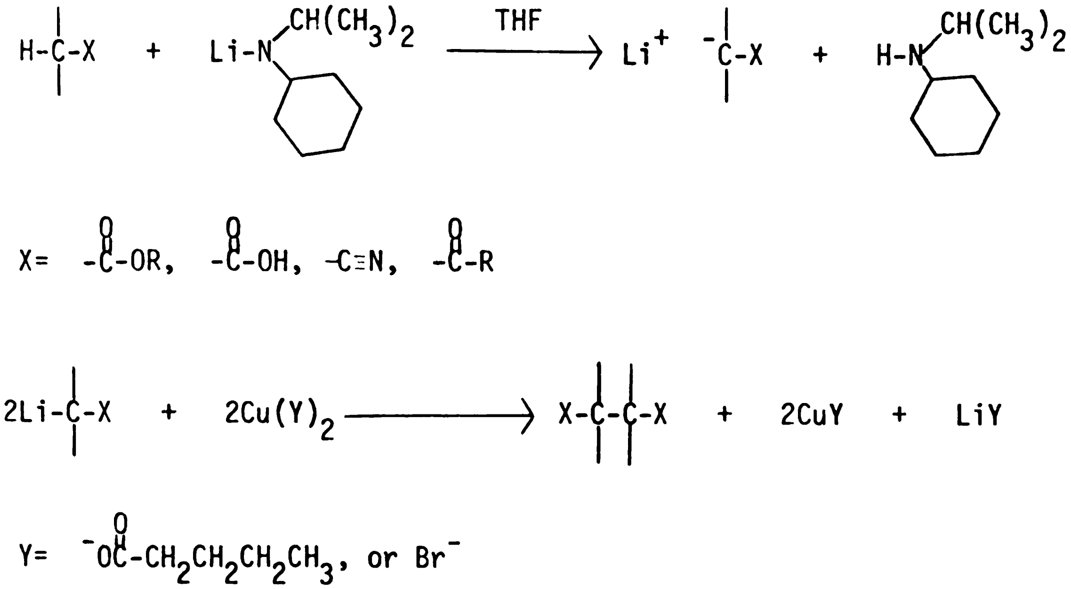
However, the yield in these reactions usually is very low (62, 63).

A general coupling reaction of enolate anions would provide the chemist with a useful synthetic method for the preparation of 1,4-dicarbonyl compounds. Since the ketone, acid, ester and amide enolates were readily available to us by the use of hindered lithium dialkylamide bases, an investigation of the feasibility of oxidative coupling of these intermediates was undertaken.

Although metal ions other than cupric salts are capable of one-electron oxidative coupling, the great success in the use of cupric salts in coupling reactions and the unique properties of cupric salts (49b) prompted an initial study of this metal salt in enolate coupling reactions.

RESULTS

A study of the cupric salt promoted oxidative coupling reactions of ester, acid, amide, ketone and nitrile anions has been conducted. All anions were prepared by the slow addition of the substrate to a THF solution of lithium N-isopropylcyclohexylamide at -78°C. Addition of cupric salts and subsequent warming of the reaction to room temperature resulted in a facile reaction with the copper (II) compounds, which in most cases, provide a satisfactory yield of the corresponding dimer.



$$\text{H-}\overset{|}{\underset{|}{\text{C}}}\text{-X} + \text{Li-N(CH(CH}_3)_2)(\text{C}_6\text{H}_{11}) \xrightarrow{\text{THF}} \text{Li}^+ \; {}^-\overset{|}{\underset{|}{\text{C}}}\text{-X} + \text{H-N(CH(CH}_3)_2)(\text{C}_6\text{H}_{11})$$

$$\text{X} = \; -\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-OR}, \quad -\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-OH}, \quad -\text{C}\equiv\text{N}, \quad -\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-R}$$

$$2\text{Li-}\overset{|}{\underset{|}{\text{C}}}\text{-X} + 2\text{Cu(Y)}_2 \longrightarrow \text{X-}\overset{|}{\underset{|}{\text{C}}}\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-X} + 2\text{CuY} + \text{LiY}$$

$$\text{Y} = \; {}^-\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_3, \text{ or Br}^-$$

Esters.

The results obtained in the dimerization of ester enolates with both copper (II) bromide and copper (II) valerate are illustrated in

Table 14. Dimerization of Esters Using Copper (II) Salts.

Ester	Product[a]	Yield %[b] $CuBr_2$	Yield %[b] $Cu(O_2C_5H_9)_2$
t-Butyl acetate	Di-*t*-butyl succinate	85	95
Ethyl propionate	Diethyl 2,3-dimethylsuccinate	81	50
Ethyl hexanoate	Diethyl 2,3-di-*n*-butylsuccinate	63	--
Ethyl isobutyrate	Diethyl tetramethylsuccinate	25	20
Ethyl isovalerate	Diethyl 2,3-di-isopropylsuccinate	20	20
Ethyl phenylacetate	Diethyl 2,3-diphenylsuccinate	75	60

[a] Usually obtained as a mixture of sterioisomers

[b] Reaction time was one hour at r.t. and all yields were determined by GLC using an internal standard.

Table 14. With the exception of di-t-butyl succinate, the succinic esters were obtained as a mixture of racemic and meso isomers.

The most favorable experimental conditions for the ester enolate dimerization reaction were determined by varying the reaction conditions and reagent concentrations in the coupling of lithium t-butyl acetate. The addition of only one-half molar equivalent of copper (II) valerate resulted in reduced (50%) yield of the di-t-butyl succinate. Execution of the reaction entirely at -78°C or room temperature gave a 45% yield of succinate product. An inverse addition of lithium t-butyl acetate to a THF solution of copper (II) valerate was also detrimental to the dimerization reaction (44% yield). Best results (95%) were obtained when one molar equivalent of the copper compound was added at -78°C to the enolate and the reaction subsequently warmed to room temperature.

Increased amounts of unreacted starting material and α-bromoester were obtained from the copper (II) bromide coupling reactions as the steric bulk of the enolate increased. When copper (II) valerate was employed as the oxidant, the yield of coupled product decreased in most cases; however, no side products could be isolated which would account for this decrease in yield.

Acids.

The feasibility of preparing succinic acids by the coupling of the lithium acid enolates was investigated with octanoic and isobutyric acid substrates. Difficulties in separating the racemic and meso products from each other as well as from the starting acid and cuprous and cupric salts, reduced the usefulness of this coupling reaction. Thus, from octanoic acid only 40% of crude product was isolated and after repeated recrystalizations small quantities of the racemic and meso isomers were separated. The more hindered isobutyric acid enolate did not dimerize with $CuBr_2$, and the starting material was isolated in 91% yield.

Amides.

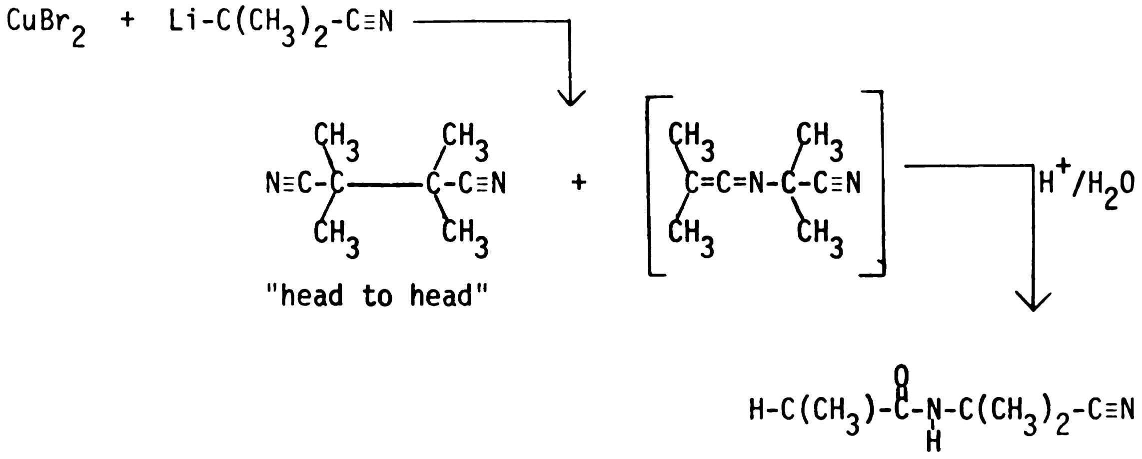
Since primary and secondary amides couple at the nitrogen (52), only N,N-dialkyl amides are capable of successful dimerization to succinamide products. Moreover, the increased solubility of amides and succinamides in water hampers their isolation from the reaction mixture. In an attempt to synthesize the succinamide dimer of N,N-dimethylacetamide by the coupling of the enolate with copper (II) bromide, for example, neither starting material nor product could be isolated. It is clear then that facile isolation of the coupled products necessitates the use of N,N-dialkylamides with sufficient solubility in non-polar solvents to facilitate their isolation. Thus N,N-di-n-butylacetamide readily coupled to yield dimerization products which were isolated in 75% yield by extraction of the aquous solution with ether. Recovered starting material (19%) was also obtained.

These sterically hindered N,N-dialkylamides gave slightly lower yields than their corresponding esters. This was amply demonstrated in the coupling of N,N-diethylisobutyramide which gave no succinamide product; only starting material (86%) and N,N-diethyl methylacrylamide were isolated (12%) from the reaction mixture.

In general, amides can be successfully coupled. However, the yields are slightly lower than those obtained with esters, and non-polar N,N-dialkylamides must be employed in order to facilitate separation of the products from the reaction mixture.

Nitriles.

In the copper (II) promoted coupling of ester, acid and amide enolates, the yield of dimerized product significantly decreases with increased steric bulk in the lithium enolate. Since the nitrile functional group is smaller than the previously noted carboxylic acid derivatives, coupling reactions of isobutyronitrile anion were investigated in order to determine whether nitrile coupling might offer an alternative means of preparing highly substituted succinic acid derivatives. Two products were obtained, as shown in the following equation:

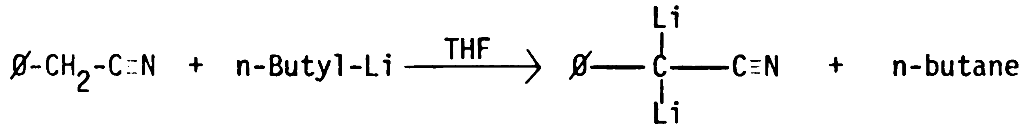


"head to tail"

These products were difficult to separate, both from the copper salts and from the solvent. The "head-to-head" dimer was isolated in 21% yield and the "head-to-tail" dimer was isolated in 10% yield. Due to the low yields and difficulties in separating the products, nitrile coupling does not provide a useful synthesis of succinic acid derivatives.

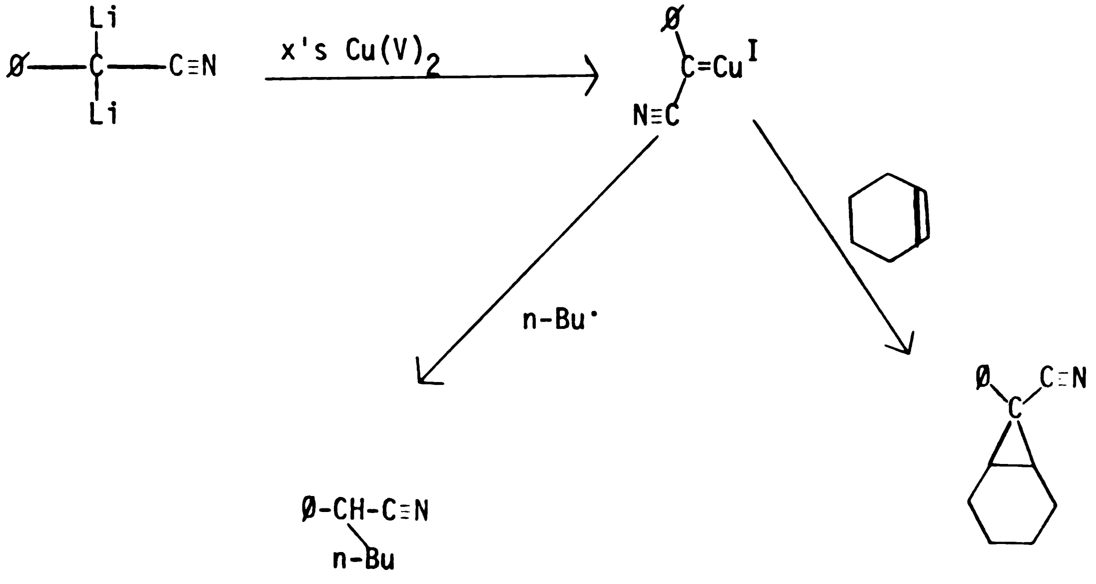
Benzylonitrile.

The dilithium dianion of benzylonitrile was prepared from butyl lithium in hexane (64).



$$\text{Ø-CH}_2\text{-C}\equiv\text{N} + \text{n-Butyl-Li} \xrightarrow{\text{THF}} \text{Ø}-\overset{\text{Li}}{\underset{\text{Li}}{\text{C}}}-\text{C}\equiv\text{N} + \text{n-butane}$$

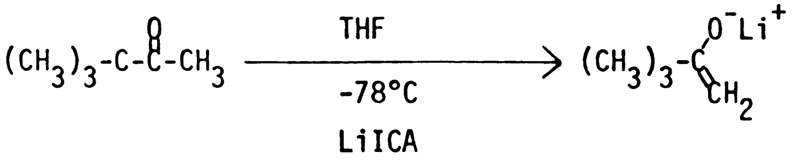
This dianion was subsequently oxidized by the addition of copper (II) valerate in the presence of cyclohexene. It was hoped that reduction of the dianion which, in the presence of cyclohexene, would result in the formation of a cyclopropyl derivative.



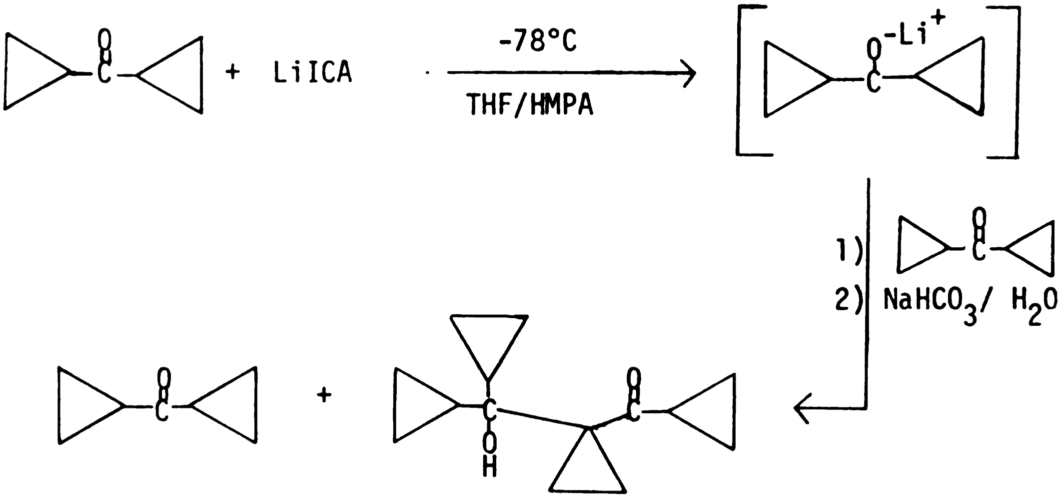
However, only starting materials and 1-cyano-1-phenyl-n-pentane (33%) were isolated from the reaction mixture.

Ketones.

Ketone enolates were quantitatively prepared by slow addition of the ketone to a THF solution of lithium N-isopropylcyclohexylamide at -78°.



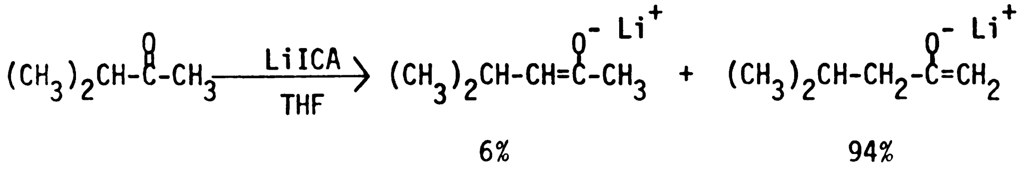
This method did not work well with dicyclopropyl ketone. An aldol condensation product was the major component of the reaction mixture. A THF/HMPA solvent system resulted in even greater yields of the aldol condensation side-product.



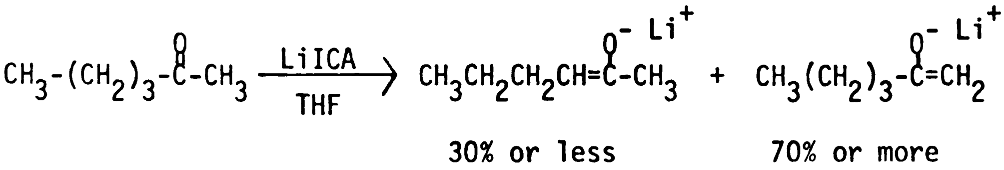
THF:	10.8%	44.0%
HMPA/THF	10.5%	64.0%

A slow rate of enolization of dicyclopropyl ketone is probably responsible for the formation of the aldol product. This repression of enolization in the ketone has been attributed to angle strain in the delocalization of the anion in the transition state (65).

All other ketones studied were successfully enolized and were coupled with either $CuBr_2$ or $Cu(V)_2$. In the case of 3-methyl-2-butanone and 2-hexanone, a kinetically controlled mixture of enolates was obtained (3).



$$(CH_3)_2CH-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[THF]{LiICA} \underset{6\%}{(CH_3)_2CH-CH=\overset{O^-\,Li^+}{\overset{|}{C}}-CH_3} + \underset{94\%}{(CH_3)_2CH-CH_2-\overset{O^-\,Li^+}{\overset{|}{C}}=CH_2}$$



$$CH_3-(CH_2)_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[THF]{LiICA} \underset{30\%\text{ or less}}{CH_3CH_2CH_2CH=\overset{O^-\,Li^+}{\overset{|}{C}}-CH_3} + \underset{70\%\text{ or more}}{CH_3(CH_2)_3-\overset{O^-\,Li^+}{\overset{|}{C}}=CH_2}$$

Reaction of these enolate mixtures with $Cu(V)_2$ resulted in formation of the 1,4-diketone from coupling of the most abundant enolate and from cross coupling of the enolates. No product was isolated which would have required coupling of the least abundant enolate (see Table 15).

From Table 15 it can be seen that the highest yields of 1,4-diketone were obtained from dimerization of sterically unhindered ketone enolates. A decrease in enolate reactivity and/or an increase in the steric bulk of the enolate resulted in lower yields of dimers, increased recovery of starting material and small amounts of unsaturated 1,4-diketones and α,β-unsaturated ketones.

The results obtained in the coupling of cyclohexanone and 3,3-dimethyl-2-butanone enolates with copper (II) bromide are presented in Table 16. When 3,3-dimethyl-2-butanone, was coupled considerable amounts of α-bromoketone and unsaturated 1,4-diketone were obtained. The dimerization of the more hindered cyclohexanone enolate resulted in none of the desired 1,4-diketone and even the side-products were obtained in lower yields. However, the coupling of the above ketone

Table 15. The Dimerization of Ketones with Copper (II) Valerate[a]

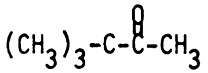
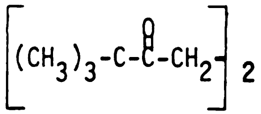
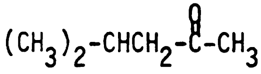
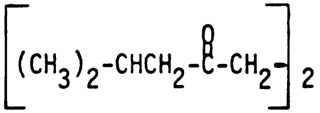
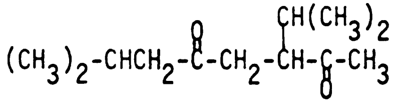
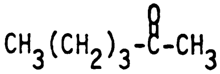
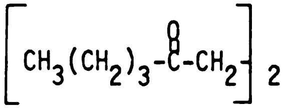
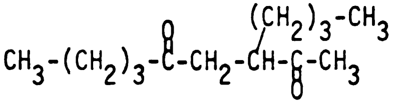
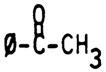
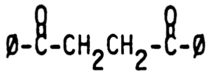
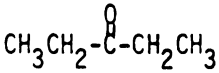
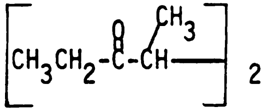
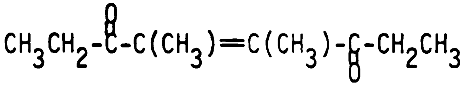
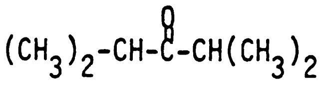
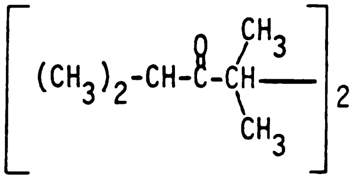
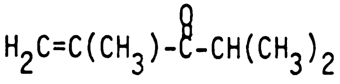
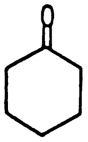
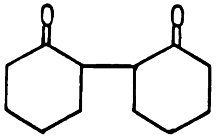
Starting Ketone		Dimer Product		Other Products	
 $(CH_3)_3-C-\overset{O}{\overset{\|}{C}}-CH_3$	0.0%	 $\left[(CH_3)_3-C-\overset{O}{\overset{\|}{C}}-CH_2-\right]_2$	100%	--------------	
 $(CH_3)_2-CHCH_2-\overset{O}{\overset{\|}{C}}-CH_3$	7.0%	 $\left[(CH_3)_2-CHCH_2-\overset{O}{\overset{\|}{C}}-CH_2-\right]_2$	66.0%	 $(CH_3)_2-CHCH_2-\overset{O}{\overset{\|}{C}}-CH_2-\overset{CH(CH_3)_2}{\overset{\|}{C}H}-\underset{\underset{O}{\|}}{C}-CH_3$	8.0%
 $CH_3(CH_2)_3-\overset{O}{\overset{\|}{C}}-CH_3$	4.0%	 $\left[CH_3(CH_2)_3-\overset{O}{\overset{\|}{C}}-CH_2-\right]_2$	40.6%	 $CH_3-(CH_2)_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{(CH_2)_3-CH_3}{\overset{/}{C}H}-\underset{\underset{O}{\|}}{C}-CH_3$	17.5%
 $\emptyset-\overset{O}{\overset{\|}{C}}-CH_3$	(24.3%)[b]	 $\emptyset-\overset{O}{\overset{\|}{C}}-CH_2CH_2-\overset{O}{\overset{\|}{C}}-\emptyset$	27.3%	--------------	
 $CH_3CH_2-\overset{O}{\overset{\|}{C}}-CH_2CH_3$	-----	 $\left[CH_3CH_2-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{/}{C}H}-\right]_2$	22.6%	 $CH_3CH_2-\overset{O}{\overset{\|}{C}}-C(CH_3)=C(CH_3)-\underset{\underset{O}{\|}}{C}-CH_2CH_3$	29.4%

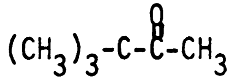
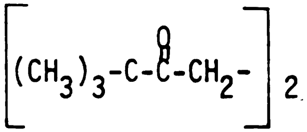
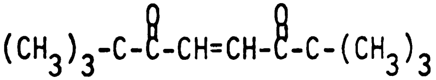
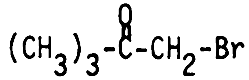
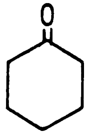
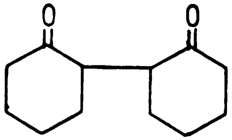
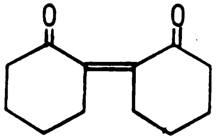
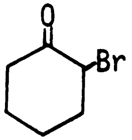
Table 15 (cont'd.).

Starting Ketone		Dimer Product		Other Products	
 $(CH_3)_2\text{-}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH(CH_3)_2$	65.0%	 $\left[(CH_3)_2\text{-}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{CH_3}{\underset{CH_3}{CH}}\text{—}\right]_2$	17.0%	 $H_2C{=}C(CH_3)\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH(CH_3)_2$	10.0%
	10.0%		(70.0%)[b]	--------------	

[a] The $Cu(V)_2$ was added to the enolate at -78°C, reaction raised to r.t. and stirred for 1 hour. The percent yield was determined by GLC using an internal standard unless otherwise mentioned.

[b] These yields were determined by isolution of the compounds.

Table 16. The Dimerization of Ketones with Copper (II) Bromide.*

Ketone	Dimer	Unsaturated 1,4-Diketone	α-Bromo-Ketone
 $(CH_3)_3\text{-C-}\overset{\overset{O}{\|}}{C}\text{-}CH_3$ 9%	 $\left[(CH_3)_3\text{-C-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-}\right]_2$ 52%	 $(CH_3)_3\text{-C-}\overset{\overset{O}{\|}}{C}\text{-CH=CH-}\overset{\overset{O}{\|}}{C}\text{-C-}(CH_3)_3$ 10%	 $(CH_3)_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\text{-Br}$ 29%
 6%	 None	 5%	 18%

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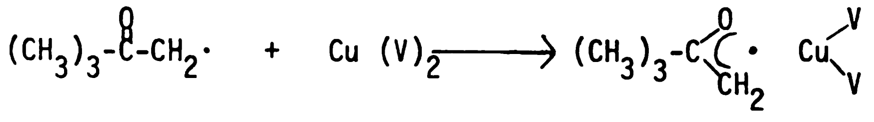
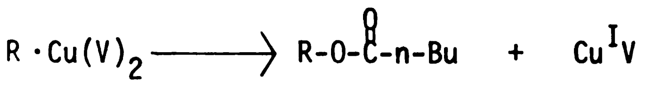
* The $CuBr_2$ was added to the enolate at -78°C, reaction raised to r.t. and stirred for 1 hour. All yields were determined by GLC using an internal standard.

enolates with copper (II) valerate was more successful in obtaining the desired 1,4-diketone product. When the 3,3-dimethyl-2-butanone enolate was coupled a 100% yield of the 1,4-diketone was obtained and when the cyclohexanone enolate was coupled 70% of the desired product was isolated.

Table 17 shows the results from the coupling of the lithium 3,3-dimethyl-2-butanone enolate with copper (II) valerate under varying reaction conditions. It is of particular interest to note that 100% excess copper (II) valerate was not detrimental to the dimerization reaction. Since $Cu(V)_2$ is a good radical scavanger, considerable quantities of a radical-copper (II) complex are probably formed when excess copper (II) valerate is employed as the oxidant (66).



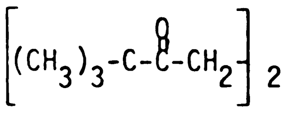
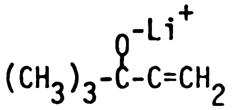
However, the high yield of 1,4-diketone (98%) obtained indicates that radical coupling in this reaction is much faster than ligand or electron transfer, although the former reaction (shown below) has been observed in other systems (67).



$$R\cdot Cu(V)_2 \longrightarrow R\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}n\text{-}Bu \quad + \quad Cu^{I}V$$

Not unexpectedly, the ketone enolates did not couple at -78°C and therefore are less reactive than ester enolates to dimerization.

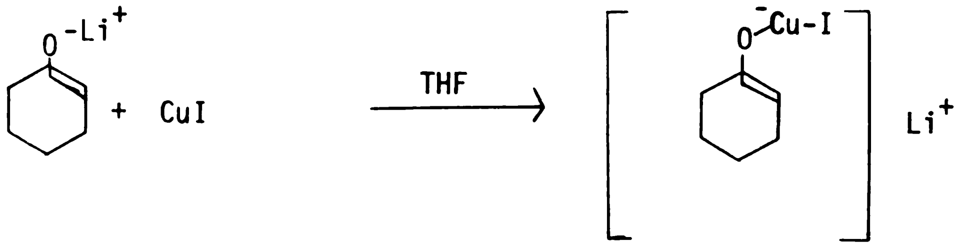
Table 17. Coupling of 3,3-Dimethyl-2-Butanone.*

 $\left[(CH_3)_3\text{-C-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\right]_2$	$Cu(V)_2$ moles	 $(CH_3)_3\text{-}\overset{O^{-}Li^{+}}{\overset{\vert}{C}}\text{-C=}CH_2$ moles	Temp.
100%	.0050	.005	-78°C to r.t.
98.0%	.0100	.005	-78°C to r.t.
49.0%	.0025	.005	-78°C to r.t.
2.3%	.0050	.005	-78°C

* Reaction run for one hour.

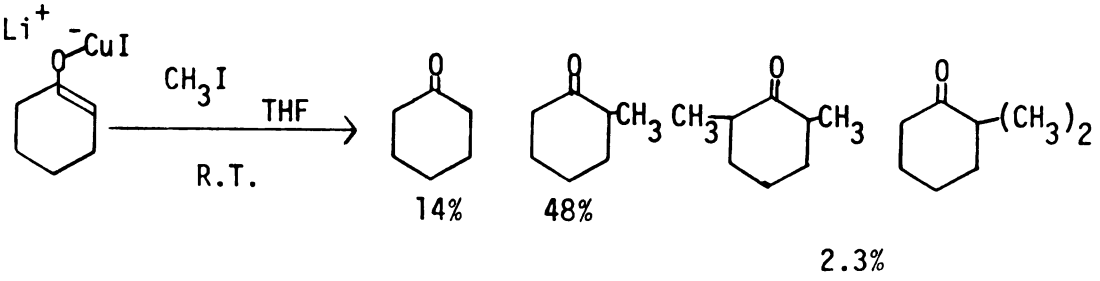
Copper (I) Enolate Complexes.

Cyclohexanone and 3,3-dimethyl-2-butanone enolate-copper (I) complexes were prepared by the reaction of the enolate with copper (I) iodide.

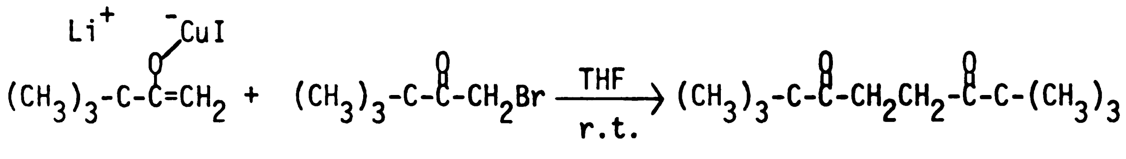


red solution

It is known that alkyl copper (I) compounds will react with iodobenzenes to yield phenyl alkanes (68). However, an attempt to prepare 2-phenylcyclohexanone by the reaction of the enolate-copper (I) complex with iodobenzene proved fruitless and only starting material was isolated. The enolate-copper (I) complex did react with methyl iodide and gave results similiar to those obtained with the alkali metal enolates, although the yields were lower.



The reaction of dialkyl cuprates with α-bromoketones has been shown to be useful in the preparation of alkyl ketone products (69). However, the reaction of enolate-copper (I) complexes with α-bromoketones gave only low yields of 1,4-diketone products.



$$\overset{\text{Li}^{+}\quad {}^{-}\text{CuI}}{(CH_3)_3\text{-C-}\overset{\text{O}}{\text{C}}\text{=CH}_2} + (CH_3)_3\text{-C-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-CH}_2\text{Br} \xrightarrow[\text{r.t.}]{\text{THF}} (CH_3)_3\text{-C-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-CH}_2\text{CH}_2\text{-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-C-}(CH_3)_3$$

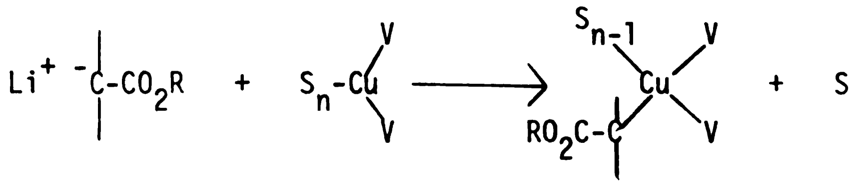
15%

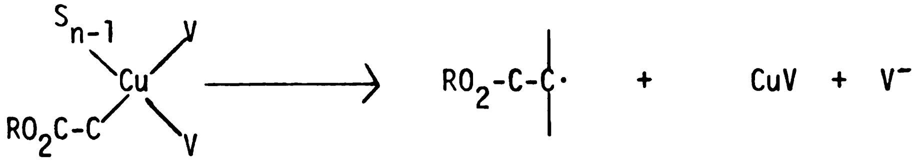
The same reaction carried out in the absence of copper (I) iodide gave 11% yield of 1,4-diketone product, indicating that neither method is useful in the preparation of 1,4-diketones.

DISCUSSION

Although the dimerization of carbanions has become a familiar reaction in organic synthesis, no great effort has been exerted in determining the detailed reaction mechanism. Nevertheless, sufficient examples can be found in the literature to give an insight into the reaction mechanism. A rationale based on available knowledge and experimental results is presented in this section.

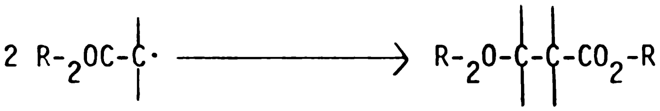
The initial step in the dimerization of enolate anions and carbanions is probably the substitution of a solvent ligand by the anion.





Carbanions are exceedingly soft (highly polarizable) ligands and the metal-ligand complex produced is expected to be very short lived and extremely unstable. A rapid one-electron redox reaction should take place resulting in the formation of a radical species and a copper (I) compound.

Subsequent dimerization of the radical will then give the desired dimeric product.

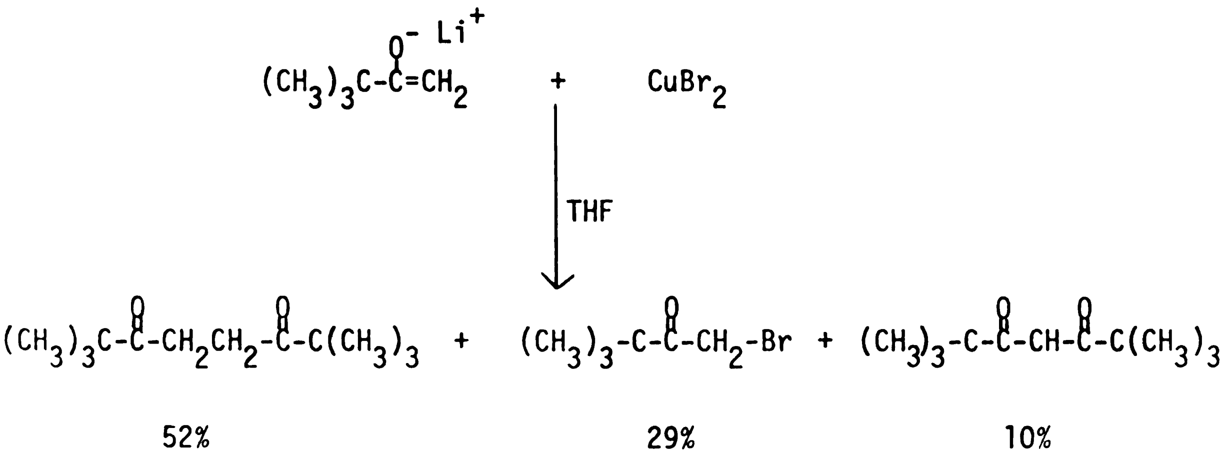


$$2\ R\text{-}_2OC\text{-}C\cdot \longrightarrow R\text{-}_2O\text{-}C\text{-}C\text{-}CO_2\text{-}R$$

The side products normally obtained are the result of radical reactions with various reagents present in the reaction mixture before dimerization can take place. The experimental results suggest that in order to obtain a high yield of the desired dimer, the redox reaction must be of sufficient rapidity to produce high concentrations of the radical. The factors which effect the redox reaction and which would subsequently influence the yield of the reaction are: 1) The reactivity and nature of the copper compound. 2) The reactivity of the enolate. 3) Steric hindrance.

Copper (II) Salts.

The polarizability of a ligand should greatly affect the reactivity of the metal ion in a redox reaction. It is expected that polarizable or "soft" ligands would reduce the reactivity of copper (II) ions while "hard" ligands would increase the reactivity of the metal ion in the redox reaction. Consequently, of the copper compounds employed in this work, copper (II) valerate was the most reactive and effective. The practicability of copper (II) bromide in enolate coupling was limited to acids and their derivatives, since its use in the coupling of ketones led to considerable side product formation. This failure is particularly stricking in the case of 3,3-dimethyl-2-butanone.

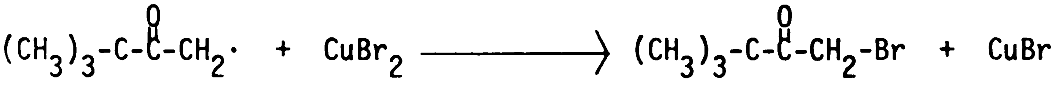


$$(CH_3)_3C\text{-}\overset{O^-\,Li^+}{C}{=}CH_2 \quad + \quad CuBr_2 \xrightarrow{THF}$$

$$(CH_3)_3C\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}C(CH_3)_3 \; + \; (CH_3)_3\text{-}C\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}Br \; + \; (CH_3)_3\text{-}C\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}C(CH_3)_3$$

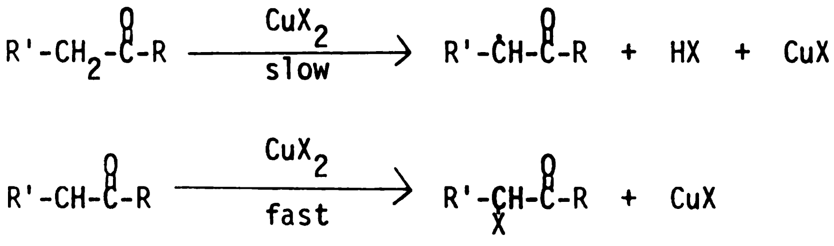
52% 29% 10%

The formation of α-bromoketone results from the reaction of the radical produced in the redox step with copper (II) bromide by a ligand transfer reaction (66,70).



$$(CH_3)_3\text{-}C\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\cdot \; + \; CuBr_2 \longrightarrow (CH_3)_3\text{-}C\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}Br \; + \; CuBr$$

The formation of both 1,4-diketone and α-bromoketone in the above reaction gives support to the following radical mechanism for the α-halogenation of ketones and aldehydes.

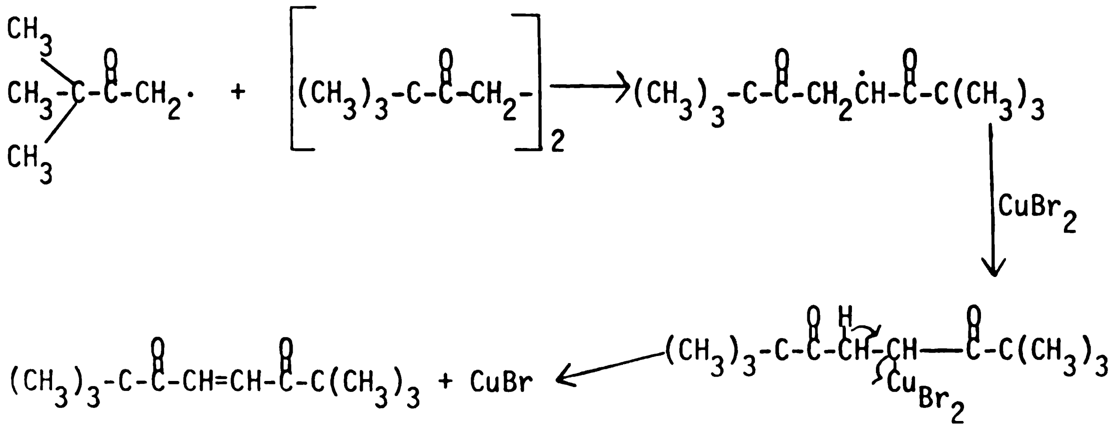


$$R'\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \xrightarrow[slow]{CuX_2} R'\text{-}\dot{C}H\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \; + \; HX \; + \; CuX$$

$$R'\text{-}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \xrightarrow[fast]{CuX_2} R'\text{-}\underset{X}{C}H\text{-}\overset{O}{\overset{\|}{C}}\text{-}R \; + \; CuX$$

This mechanism has recently been supported by Walling (71), however alternate mechanisms for this reaction have been proposed by Kosower (72) and Kochi (70).

The formation of the unsaturated 1,4-diketone can be most satisfactorily explained by a radical process.



The above reaction has precedent in the work of Kochi who has demonstrated that alkyl radicals can be readily converted to alkenes by an electron-transfer oxidation with a carboxylatocopper (II) species (66).

$$C_4H_9^{\cdot} + Cu^{II}({}^{-}{}_2OC\text{-}C_4H_9)_2 \longrightarrow CH_3CH_2CH{=}CH_2 + C_4H_9CO_2H + Cu^{I}({}^{-}{}_2OC\text{-}C_4H_9)$$

The formation of unsaturated 1,4-diketone in the coupling of ketones with $CuBr_2$ indicates that the reduction with $CuBr_2$ is slow and that both $CuBr_2$ and product are present in solution while the radical is still being generated.

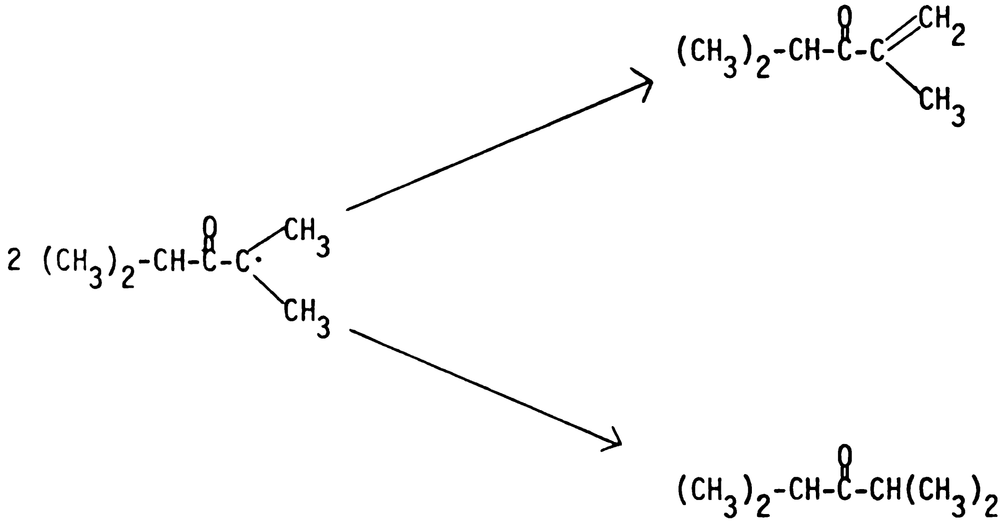
The Reactivity and Nature of the Anion.

The more reactive ester enolates and their derivatives are reduced at a faster rate, consequently, the less reactive copper (II) bromide oxidant can be used in this coupling reaction. With ketone enolates only copper (II) valerate gives adequate results, since the slowness of the redox reaction with $CuBr_2$ leads to considerable side-product formation. The use of copper (II) valerate in the dimerization of ester enolates gives lower yields of dimer, however, the side-products from the use of this reagent have not been elucidated.

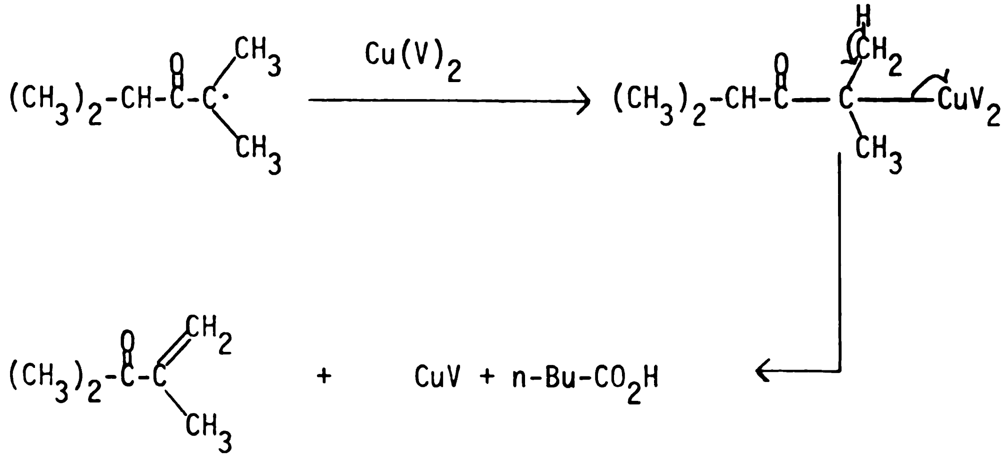
Steric Hindrance in the Anion.

In all the coupling reactions studied, the yield of coupled product decreases as the steric hindrance in the carbanion increases. This decrease in dimerized product is accompanied by a corresponding increase in recovered starting material, plus small amounts of α,β-unsaturated ketone or acid derivatives, and in the cases where copper bromide was employed, an increase in the α-bromo-derivative.

The α,β-unsatured product formed in the dimerization reaction of hindered reactants is most likely the result of a radical disproportionation reaction.



The alternative formation of α,β-unsaturated products from the reaction of a radical intermediate with copper (II) salts seems unlikely due to the high activation energy expected for this reaction (59b).

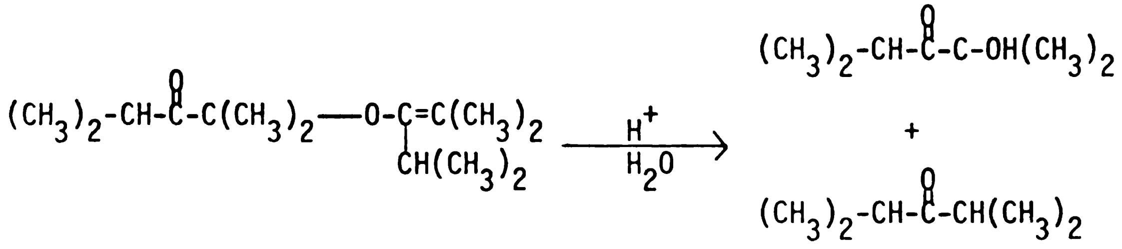


This disporportionation reaction, however, cannot account for the large quantities of starting material isolated from the reaction mixture.

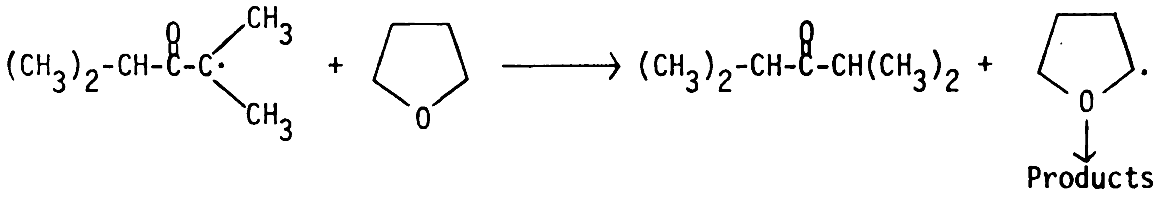
Three explanations that can account for the recovery of starting material are:

1) The recovered starting material may be the result of incomplete reaction.

2) The recovery of starting material could result from carbon-oxygen coupling of the ketone enolate as proposed by Brackman (59b). If carbon to oxygen radical coupling occurs, the subsequent hydrolysis of this unstable intermediate would result in the formation of starting material and a α-hydroxy product. The fact that α-hydroxy ketones were never isolated from the reaction mixture argues against this explanation, however.



3) Due to the slower reduction of hindered carbanions, the radicals formed should have sufficient time to react with solvent resulting in the formation of starting material.



The THF radical formed by this solvent reaction would also consume cupric reagents and result in the depletion of the cupric compound and in unreacted enolate.

In summary, cupric compounds are useful reagents for the formation of new carbon-carbon bonds. Highest yields are obtained when reactive and unhindered enolates are employed. The more reactive the enolate, the less side products are generated in the coupling reaction. The nature of the cupric reagent is also vital.

EXPERIMENTAL SECTION

I. Materials

1-Bromo-3,3-Dimethyl-2-Butanone.

3,3-Dimethyl-2-butanone (50 ml or 40 mmoles) was dissolved in 100 ml of ether and placed in a three necked flask equipped with a reflux condenser, addition funnel and magnetic stirring apparatus. To this solution, 21 ml (40 mmoles) of bromine was added over a 30 minute period. The reaction was quenched with ice-water, the ether washed twice with 50 ml of water and dried over anhydrous calcium sulfate. The solvent was evaporated and the product distilled at b.p. 69-71°C/13mm yielding 51% of the desired product (73) GLC analysis revealed only a trace of dibromination.

Cuprous Iodide.

Impure cuprous iodide (8.77 gms or .138 moles) was dissolved in a solution of 130 gms of potassium iodide in 100 ml of water. The solution was diluted with distilled water to precipitate the pure cuprous iodide; the product was collected on a sintered glass filtering funnel and was washed successively with ethyl alcohol, acetone and dry ether. The purified white cuprous iodide was dried in vacuum over night and stored in an amber bottle (74).

Ketones.

All ketones were readily available commercially and were dried over molecular sieves and used without further purification. Dicyclopropyl ketone was impure and distilled (b.p. 66-67°C/18mm) prior to use.

Preparation of Copper (II) Valerate.

This compound was prepared by the method of Lieben and Rossi (75). In a typical preparation, a solution of 23 ml (200 mmoles) of valeric acid in 100 ml of water was slowly added to a solution of 8.0 gms(200 mmoles) of sodium dydroxide in 100 ml of water. The sodium valerate solution thus prepared was added to a water solution of copper (II) sulfate over a fifteen minute period. An insoluble green precipitate was rapidly formed. The product was collected on a sintered filtering funnel, washed repeatedly with distilled water and dried under vacuum in a desiccator until no further weight loss was observed (24 hours). The turquoise product weighed 23.9 gms (86.5%), and yields as high as 98% were occasionally obtained.

Preparation of N,N-Dibutyl Acetamide.

The amide was prepared by the slow addition of 35.5 ml (.5 moles) of acetyl chloride to an ether solution of 168 ml (1 mole) of dibutylamine kept at 0°C. The reaction mixture was warmed to 50-55°C for 30 minutes to complete the reaction. The amine hydrochloride which had precipitated was then filtered off, the ether layer washed with hydrochloric acid, and sodium bicarbonate and the organic layer was

dried over anhydrous potassium carbonate. After the evaporation of the ether solvent, the product was distilled at 66°C/2mm to yield 65.2 gms (76.2%) of very pure product. NMR (neat): 6.70τ(t, 4H), J=3.5cps; 8.03τ(s, 3H); 8.60τ(m, 8H); 9.08τ(t, 6H).

Preparation of N,N-Diethyl Isobutrate.

The product was prepared by an identical procedure employed in the synthesis of N,N-dibutylacetamide. The reaction was run on a one-half mole scale and 33.417 gms (63%) of the desired product was isolated in pure form after distillation at 46.5-48°C/1mm. NMR (neat): 6.63τ (q, 4H), J=4.0cps; 7.20τ(m, 1H), J=3.25cps; 8.83τ(t, 6H); 8.95τ(d, 6H), J=2.5cps.

II. Coupling of Enolate Anions

Esters.

The ester enolates were coupled in a manner analogous to the dimerization of ethyl propionate presented below.

Dimerization of Ethyl Propionate.

A dry flask was equipped with a magnetic stirrer, septum inlet and mercury bubbler. The flask was flushed with nitrogen and 25 ml of a 1.0M solution of lithium N-isopropylcyclohexylamide in tetrahydrofuran was injected with a syringe. The flask was immersed in a dry-ice acetone bath and 2.6 gms(25 mmoles) of ethyl propionate was added dropwise. After 15 minutes, $CuBr_2$ (6.7 gms, 36 mmoles) was added all at once through a powder funnel. The solution was stirred for 15 minutes and then allowed to reach room temperature and stirred for an additional hour. Hydrochloric acid (15 ml or a 10% solution) was added together with 30 ml of pentane. The separated organic layer was dried over anhydrous magnesium sulfate and subjected to vacuum distillation to obtain 2.1 gms (75%) of a racemic and meso mixture of diethyl-2,3-dimethylsuccinate. B.p. 106-109°C/15mm [lit. b.p. 108°C/15mm] (76), n_D^{20}= 1.4262, NMR (CCl_4): 5.90τ(q, 4H), J=3.5cps; 7.70τ and 7.73τ(v, 2H), 8.77τ(t, 6H), 8.91τ(d, 6H), J=3.5cps.

Dimerization of Ethyl Isovalerate.

Diethyl-2,3-isopropylsuccinate was isolated in 20% yield and NMR showed a mixture of racemic and meso isomers. B.p. 79-83°C/.15mm; n_D^{20}= 1.4371; i.r. 1725 cm^{-1}, 1158 cm^{-1}, 1185 cm^{-1}.

Dimerization of Ethyl Hexanoate.

Diethyl-2,3-di-n-butylsuccinate was obtained as a racemic and meso mixture as indicated by NMR (CCl_4): 5.90τ and 5.95τ(q, 4H); 7.49τ(m, 2H); and 8.77τ and 8.80τ(t, 6H), J=3.0cps; and 12H under triplet peak ($-CH_2CH_2CH_2-$), 9.13τ(t, 6H), J=3.5cps. I.r. $\nu_{C=O}$ 1740 cm^{-1}, 1178 cm^{-1}; b.p. 90-95°C/.1mm [lit. 149°C/7mm] (77).

Dimerization of Ethyl Isobutyrate.

Diethyl tetramethylsuccinate was isolated in 25% yield. B.p. 115-117°C/12mm [lit. 122°C/15mm] (36a). n_D^{20}= 1.4357 [lit. n_D^{20} = 1.439] (78). NMR (CCl_4): 5.92τ(q, 4H), J=3.5cps; 8.76τ(t, 6H); 8.81τ(s, 12H). Ethyl 2-bromo-2-methylpropionate was isolated from the above reaction mixture and purified by GLC. NMR (CCl_4): 5.77τ(q, 2H), J=3.5cps; 8.10τ(s, 6H); 8.68τ(t, 3H).

Dimerization of Ethyl Phenylacetate.

Diethyl-2,3-diphenylsuccinate was isolated as a mixture of racemic and meso isomers. Repeated recrystallization from ethanol (95%) yielded the meso form M.P. 139-141°C [lit. 141°C] (79). NMR (CCl_4): 2.62τ(m, 10H); 5.75τ(s, 2H); 6.18τ(q, 4H), J=3.5cps; 9.13τ(t, 6H).

Dimerization of T-Butyl Acetate.

Di-t-butyl succinate was obtained in yields as high as 95%. B.p. 100°C/10mm [lit. 115°C/14mm] (80). M.P. 34-35°C [lit. 36°C] (36a). NMR (CCl_4): 7.61τ(s, 4H); 8.58τ(s, 18H). I.r. 1730 cm^{-1}, 1115 cm^{-1}.

Amides.

The following lithium amide enolates were coupled with copper (II) bromide.

Dimerization of N,N-Di-n-Butylacetamide.

The enolate was prepared from 1.713 gms(10 mmoles) of acetamide in the usual manner, then brought to room temperature for 15 minutes before again being cooled to -78°C and 2.234 gms(10 mmoles) of copper (II) bromide added. The reaction was brought to room temperature, stirred 30 minutes, quenched with an ammonium chloride saturated ammonia solution and 25 ml of pentane added. The pentane was dried over anhydrous potassium carbonate, treated with Dowex A-1, and evaporated under vacuum yielding 1.5991 gms (94%) of product. Analysis by NMR showed that the reaction mixture contained 79% of the desired coupled product and 14% starting material. NMR ($CDCl_3$): 6.67τ(t, 8H), J=3.5cps; 7.35τ(s,4H); 8.57τ(m, 6H); 9.03τ(t, 12H), J=3.0cps.

Dimerization of N, N-Diethylisobutyramide.

This reaction was run as above on a 10 mmole scale and yielded 1.4122 gms (98.5%) of recovered material which consisted of 86% starting material identified by NMR and 12% N, N-di-n-butyl methylacrylamide as indicated by vinyl peaks at 4.97τ and 5.15τ in the NMR.

Carboxylic Acids.

Two carboxylic acid enolates were coupled with copper (II) bromide and the results are presented below.

Dimerization of Octanoic Acid.

To a 150 ml flask equipped as in Figure 1 was added a solution of 55 mmoles of LICA in 50 ml of THF and cooled to 0°C. The dilithium dianion of octanoic acid was then prepared by the slow addition of 3.96 ml (25 mmoles) of octanoic acid to the above solution of base and subsequently heated at 50-55°C for 1.5 hrs. A white jelly solution was formed when the reaction mixture was cooled to -78°C. Addition of copper (II) bromide (5.5843 gms or 25 mmoles) decomposed this white gel and resulted in the formation of a dark green solution. The reaction was then warmed to room temperature and stirred for .5 hrs. during which time a brown precipitate formed. The reaction was then quenched with 6N hydrochloric acid and the aquous layer extracted three times with 100 ml of ether. The cuprous and cupric salts were difficult to separate from the products, however, best results were obtained by reduction of the cupric salts with sodium thiosulfate. Subsequent addition of a dilute solution of sodium thiocyanate resulted in the formation of a cuprous thiocyanate precipitate which was filtered off. The ether layer was dried over anhydrous sodium sulfate, and the solvent evaporated yielding 1.45 gms (40%) of crude product. Repeated recrystallization from pentane resulted in the formation of .6047 gms (17%) of the diacid M.P. 144.5-145°C [lit. 144-144.5°C] (81). The pentane mother liquid was evaporated and the residue recrystallized from chloroform yielding .3110 gms (8.6%) of the lower melting isomer M.P. 91-96°C [lit. 95-96°C] (81). Examination of the reaction mixture by GLC gave three peaks. The first peak was octanoic acid identified by the retention time of an authentic sample and the second peak was 2-bromooctanoic acid. NMR ($CDCl_3$): $-.53\tau$(s, 1H); 5.83τ(t, 1H), J=3.5 cps; 7.83τ(m, 2H); $-CH_2CH_2CH_2CH_2-$ from 8.33τ to 9.00τ; 9.10τ(t, 3H), J=3.0cps. I.r. 3300 cm^{-1} to 2500 cm^{-1}(s), 1710 cm^{-1}(s), 1425 cm^{-1}(m), and 1280 cm^{-1}(m). The third peak was identified as 2,3-di-n-hexylsuccinic anhydride from the i.r. 1860 cm^{-1}(m), 1780 cm^{-1}, 1225 cm^{-1}(m), and resulted from the dehydration of the diacid on the SE-30 chromatography column.

Dimerization of 3-Methylpropionoic Acid.

The above procedure was repeated using 2.2035 gms(25 mmoles) of isobutyric acid. All other reagents and conditions were kept the same. After evaporation of the solvent and filtration of .0346 gms of an unidentified copper compound, only starting material (1.9582 gms or 91%) was isolated, NMR ($CDCl_3$): $.73\tau$(s, 1H); 7.50τ(m, 1H), J=3.5cps; 8.90τ(d, 6H).

Dimerization of Isobutyronitrile.

In a 50 ml flask equipped as in Figure 1, 15 mmoles of lithium N-isopropylcyclohexylamide in THF (15 ml) was prepared in the usual manner. The reaction was cooled to -78°C and 1.34 ml (15 mmoles) of isobutyronitrile was slowly added. The reaction was brought to room temperature for 15 minutes and then cooled to -78°C before the rapid addition of 3.56 gms (16 mmoles) of copper (II) bromide. The reaction mixture was again brought to room temperature, stirred for one hour, quenched with 6N hydrochloric acid and 30 ml of ether was added. The organic layer was washed with an ammonium chloride saturated ammonia solution and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded .3689 gms (35%) of a mixture of products. Addition of pentane resulted in the formation of a precipitate identified as (2-cyanoisopropyl)-isobutryamide. M.P. 101-103°C NMR ($CDCl_3$): 4.60τ (s, 1H); 7.63τ(m, 1H); 8.30τ(s, 6H); 8.87τ(d, 6H), J=3.25cps. I.r. 3280 cm^{-1}(m), 2220 cm^{-1}(w), 1640 cm^{-1}(m), 1530 cm^{-1}(m).

Evaporation of the pentane solvent resulted in the slow precipitation of 2,3-dicyano-2,3-dimethylbutane (.220 gms or 21%). M.P. 166-167°C [lit. 167-167.5°C] (82). NMR ($CDCl_3$): 8.47τ singlet. Mass spectrum m/e = 136, 121, 69, 68.

Benzylnitrile.

The lithium dianion of this nitrile was prepared by the addition of 6.75 ml (11.25 mmoles) of butyl lithium to a solution of .577 ml (5 mmoles) of benzylonitrile and .51 ml (5 mmoles) of cyclohexene in 7 ml of THF at -78°C (64). The reaction was stirred for one hour at -78°C. When copper valerate (7.5 mmoles) was added, the reaction mixture turned black. The reaction was warmed to room temperature, stirred for one hour, quenched with 6N hydrochloric acid, and 30 ml of pentane was added. The pentane layer was washed with an ammonium chloride saturated ammonia solution and dried over anhydrous calcium sulfate. Evaporation of the solvent yielded .550 gms of product. NMR analysis of the product mixture showed 66% of starting material and a 33% yield of 1-cyano-1phenyl-n-pentane. Mass spectra m/e = 173. NMR (CCl_4): 2.67τ(s, 5H); 6.33τ(t, 1H), J=3.5cps; 2H multiplet from 7.92τ to 8.38τ, 4H multiplet from 8.38τ to 8.87τ; 9.10τ(t, 3H), J=3.0cps.

Ketones.

The following ketones were coupled with either $Cu(V)_2$ or $Cu(Br)_2$ in a manner similar to the coupling of ester enolates. All yields were obtained by GLC using an internal standard.

Dimerization of 3,3-Dimethyl-2-Butanone.

2,2,7,7-Tetramethyl-3,6-octandione was obtained in 100% yield by enolate coupling with copper (II) valerate and in 52% yield by enolate coupling with copper (II) bromide. B.p. 58-64°C/.5mm. n_D^{20}= 1.4396 [lit. n_D^{20}= 1.4400] (62). M.P. 23-25°C [lit. 22-25.5°C] (62). NMR (CCl_4) 8.87τ(s, 18H); 7.32τ(s, 4H). I.r. 1701 cm^{-1}.

Dimerization of Cyclohexanone.

2.2'-Dicyclohexan-1,1'-dione was obtained in 70% yield from $Cu(V)_2$ dimerization of the ketone enolate. M.P. 71.5-73°C [lit. 70-71°C] (62). NMR (CCl_4): the spectra consists of three broad peaks: from 6.90τ to 7.50τ(2H); from 7.50τ to 7.93τ(4H); and from 7.93τ to 9.10τ(12H).

From the coupling reaction of the ketone enolate with $CuBr_2$ two products were obtained: 2-bromocyclohexanone (18%) NMR (CCl_4):

6.30τ(m, 1H); two broad peaks from 6.87τ to 7.93τ(4H) and from 7.93τ to 9.00τ(4H). 2,2'-dicyclo-2-hexen-1,1'-dione (6%) NMR (CCl_4): broad peaks from 7.33τ to 8.00τ(4H) and at 8.20τ(4H). I.r. 1810 cm^{-1}, 1601 cm^{-1}.

Dimerization of 4-Methyl-2-Pentanone.

The ketone enolate was dimerized with Cu(V)$_2$ and the following product was obtained: 2,9-dimethyl-4,7-decadione in 66% yield (isolated 60%). B.p. 85-87°C/.5mm. NMR (CCl_4): 7.45τ(s, 4H); 7.73τ(4H), 7.90τ (m, 2H); 9.10τ(d, 12H), J=3.5cps. I.r. 1705 cm^{-1}.

Dimerization of 2,4-Dimethyl-3-Pentanone.

2,4,4,5,5,7-Hexamethyl-3,6-octandione was obtained in 17% yield from ketone enolate coupling with Cu(V)$_2$. B.p. 93-98°C/1mm. NMR (CCl_4): 6.90τ(m, 2H), J=3.5cps; 8.80τ(s, 12H); 9.00τ(d, 12H). I.r. 1690 cm^{-1}.

2,4-Dimethyl-1-penten-3-one was identified in the above reaction mixture. NMR showed $H_2C=C<$ protons at 4.07τ(s) and 4.23τ(s) and $>C=C-CH_3$ methyl group at 8.13τ.

Dimerization of 3-Pentanone.

Two products were isolated from the enolate coupling reaction with Cu(V)$_2$; 4,5-dimethyl-3,6-dione NMR (CCl_4): 7.13τ and 9.17τ(q, 2H); 7.54τ(q, 4H); 9.05τ(t, 6H), J=3.75cps; 9,98τ(d, 6H), J=2.75cps. I.r. 1705 cm^{-1}. This product was isolated as a mixture of racemic and meso isomers. 4,5-Dimethyl-4-octendi-3,6-one NMR (CCl_4): 7.48τ(q, 4H), J=3.8cps; 8.18τ(t, 6H); 8.85τ(t, 6H). I.r. 1700 cm^{-1}, 1640 cm^{-1}.

Dimerization of 2-Hexanone.

Two compounds were obtained from the Cu(V)$_2$ketone enolate coupling reaction: 5,8-dodecandione (40.6%) M.P. 48-49°C. NMR (CCl_4): 7.43τ (s, 4H); 7.62τ(t, 8H), J=3.5cps; $-CH_2CH_2-$ from 8.17τ to 8.93τ; 9.10τ (t, 6H), J=3.0cps. Mass spectrum m/e = 198.

3-Propyl-2,5-octandione (17.5%). GLC retention time and NMR were consistent with structure. Mass spectrum m/e = 198.

Dimerization of Acetophenone.

The following compound was obtained by Cu(V)$_2$ coupling of the ketone enolate: diphenyl-1,4-butandione (27%) M.P. 146-7°C [lit. 145-147°C] (83). NMR ($CDCl_3$): aromatic protons (10H) from 1.73τ to 2.73τ, 6.53τ(s, 4H).

Aldol Condensation Reaction of Dicyclopropyl Ketone.

In an attempt to prepare the lithium enolate of dicyclopropyl ketone the following reactions were performed. Dicyclopropyl ketone (.57 ml or 5 mmoles) was added to 5 mmoles of N-isopropylcyclohexylamide at -78°C in either 5 ml of THF or in 10 ml of a HMPA/THF (ratio 1:5) solution. The reaction was quenched with a saturated sodium bicarbonate solution, then 30 ml of pentane and .473 ml (2.5 mmoles) of diisopropylbenzene were added. The organic layer was dried and the solutions analyzed by GLC. When THF was used as the reaction solvent 10.8% of the starting ketone and 44.0% of the aldol product were obtained while when HMPA/THF solvent system was used 10.5% of the starting ketone and 64.0% of the aldol product were obtained. NMR (CCl_4): 6.02τ(s, 1H), and multiple peaks from 8.05τ to 9.97τ(19H). I.r. 3410 cm^{-1}, 3080 cm^{-1}, 3000 cm^{-1}, 1650 cm^{-1}, Mass spectra m/e = 220, 179, 111, 110, 109, 69, 41.

III. Reactions of Ketone Enolate-Copper (I) Complexes

Cyclohexanone Enolate.

The lithium cyclohexanone enolate was prepared by the addition of .52 ml (5 mmoles) of cyclohexanone to a THF solution of LiICA (5 mmoles). Copper (I) iodide (.9600 gms or 5 mmoles) was added and the reaction brought to room temperature for 15 minutes during which time the copper (I) iodide dissolved producing a deep red solution. Three reactions were performed using the enolate-copper (I) complex:

1) To the reaction mixture was added 5 ml of dilute hydrochloric acid and 30 ml of pentane. The organic layer was then separated and dried over anhydrous calcium chloride. Analysis by GLC showed 61% recovery of the starting ketone.

2) Addition of .34 ml of methyl iodide to the enolate-copper (I) complex and reaction of the solution at room temperature for 1 hour resulted in the formation of 48% 2-methylcyclohexanone and 2.3% dialkylated product.

3) The copper (I)-enolate complex was reacted with 1.02 gms(5 mmoles) of iodobenzene at room temperature for 6 hours. No 2-phenylcyclohexanone formation was observed and only starting materials were isolated from the reaction mixture.

3,3-Dimethyl-2-Butanone Enolate.

The lithium 3,3-dimethyl-2-butanone enolate was prepared as above for cyclohexanone from .623 ml (5 mmoles) of the ketone at -78°C.and

Copper (I) iodide (.96 gms or 5 mmoles) was added to the THF solution of the ketone enolate and the reaction was brought to room temperature. 1-Bromo-3,3-dimethyl-2-butanone (68 ml or 5 mmoles) was added to this solution all at once and the solution changed color from red to light green over a one hour period. Examination of the reaction mixture by GLC after the usual work-up, showed 15% yield of 2,2,7,7-tetramethyl-3,6-octandione. The above reaction was repeated except the copper (I) iodide was excluded from the reaction mixture. The yield of 1,4-diketone by GLC revealed a 10% yield of the desired product.

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