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COUPLING REACTIONS OF ENOLATE ANIONS

By

Robert S. Nygren

A DISSERTATION

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Department of Chemistry

ABSTRACT

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By

Robert S. Nygren

Lithium ester enclates are dimerized by titanium tetrachloride to give symmetrical succinates. Yields are excellent for ethyl isobutyrate and ethyl phenylacetate but decrease as substitution at the <u>alpha</u> carbon of the ester decreases. The reaction is thus a complementary procedure to the copper(II) bromide-promoted coupling of unsubstituted ester enclates. Where stereoisomerism in the product is possible, a mixture of <u>dl</u> and <u>meso</u> diastereomers is obtained.

Lithium ketone enolates are dimerized by iron(III) chloride to give symmetrical 1,4-diketones. The yield is excellent for diisopropyl ketone and decreases as substitution at the <u>alpha</u> carbon decreases. The reaction is thus a complementary procedure to the copper(II) chloride-promoted coupling of unsubstituted ketone enolates. Where stereoisomerism in the product is possible, a mixture of diastereomers is obtained. Cyclohexanone behaves anomalously as its enolate is dimerized in only thirty percent yield by iron(III) chloride but in sixty eight percent yield by silver acetate. With all other enolates examined iron(III) chloride gave higher yields of 1,4-diketone than did silver acetate.

Lithium ester enolates react with α -iodoesters generated <u>in situ</u> from ester enolate and elemental iodine to give unsymmetrical succinates. The reaction is thus a one-pot procedure for the cross-coupling of ester enolates. Lithium ketone enolates react with <u>tert</u>-butyl haloacetates to give γ -ketoesters. Once again, the highest yield was obtained with diisopropyl ketone. Yields decreased as substitution at the <u>alpha</u> carbon of the enolate decreased. то

Pamela

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CHAPTER I

INTRODUCTION

1,4-dicarbonyl compounds have long been important intermediates in organic synthesis. The 1,4-diketones may be converted into furans,¹ pyrroles,² and cyclopentenones^{3,6} (Eq. 1). α -Ketoesters may be converted to cyclopentane-1,3-diones¹ (Eq. 2). Both cyclopentenones⁴ and cyclopentane-1,3-diones⁵ are precursors to prostaglandins.



Dicarbonyl compounds are usually formed by condensation reactions. However, the 1,4 disposition of two carbonyl groups cannot be brought about by simple condensation of two carbonyl fragments.

1,4-Dicarbonyl compounds have been synthesized by conjugate addition of acyl anion equivalents, such as nitro-stabilized carbanions,^{2,6} lithium di[bis(phenyl-thio)methyl]copper,⁷ and acyl carbonylnickelate,⁸ to α,β -unsaturated carbonyls (Eq. 3).

$$\frac{-}{NO_2} + CH_2 = CHCOR' + R - CHCH_2CH_2COR' + CH_2^{T1Cl_3}$$
(3)

 ${\rm Ho}^9$ reported an interesting variation of this Michael condensation method, using an enamine followed by oxidation (Eq. 4).

$$\frac{\text{RCH=CHNR}_{2} + \text{CH}_{2} = \text{CHCO}_{2}\text{C}_{2}\text{H}_{5} + \frac{\text{RCCH}_{2}\text{CH}_{2}\text{CO}_{2}\text{C}_{2}\text{H}_{5}}{\text{CH}_{1}}$$

$$\overset{O_2}{\xrightarrow{}} \text{RCOCH}_2\text{CH}_2\text{CO}_2\text{C}_2^{H}_5$$
(4)
CuCl

Kuwajima¹⁰ used a ketal plus silylated cyclobutene diolate in a method which forms the bond between the γ and δ carbons of a γ -ketoester (Eq. 5).



Wehrli and Chu^{ll} reported the radical-initiated reaction of an aldehyde with diethyl maleate to form the bond between the β and γ carbons of a γ -ketoester (Eq. 6).



Pelter and coworkers¹² combined a trialkyl borane, a lithium acetylide, and an α -halocarbonyl compound to form both the bonds between the α and β carbons and the γ and δ carbons (Eq. 7). This technique may be used not only to make γ -ketoesters and 1,4-diketones, but also to synthesize β , γ -unsaturated ketones and esters.



Z = alkyl or alkoxide

While all of these methods are useful for the synthesis of particular compounds, they all have limitations. Some require multistep procedures; others require starting materials not readily available from the carbonyl compound itself. Several of the methods place limitations on the substitution at the α or β carbon.

From the standpoint of simplicity, one of the most attractive synthetic routes to 1,4-dicarbonyl compounds is oxidative dimerization of enolate anions. Lithium ester and ketone enolates are readily available from reaction of the corresponding esters¹³ and ketones¹⁴ with lithium diisopropylamide (LDA) (Eq. 8).

$$\begin{array}{c} 0 \\ -CH-C-Z + LDA + C=C \\ Z \end{array} + HN$$
(8)

Z = alkyl or alkoxide

Formation of a bond between the α carbons of two enolates, with concurrent removal of two electrons by an oxidizing agent, would lead to the desired product (Eq. 9).

$$2 = C = C \xrightarrow{OLi}_{Z} \xrightarrow{-2 e}_{Z} \xrightarrow{-C = C - C - Z}_{I = 0}$$
(9)
$$Z = alkyl \text{ or alkoxide}$$

Transition metal-promoted dimerization of carbanions has been a convenient method for the formation of carboncarbon bonds in organic synthesis. Copper-promoted dimerizations of carbanions stabilized by sulfonyl, phosphoryl, and imidoyl groups are known.¹⁵ Copper-promoted dimerizations of ester¹⁶ and ketone¹⁷ enolates have been reported, but suffer limitations. Iron (III) promoted cross-coupling of a ketone and an ester enolate has been effected in moderate yield.¹⁸ We proposed to explore the transition metal-promoted dimerization of ester and ketone enolates as synthetic routes to symmetrically substituted succinates and symmetric 1,4-diketones. Such a study should not only be synthetically useful because of the wide availability of enolates, but should also add to our knowledge of the reactions of ester and ketone enolates and especially the behavior of transition metal enolates.

CHAPTER II

DIMERIZATION OF α -SUBSTITUTED ESTER ENOLATES

Introduction

Although the dimerization of carbanions in the presence of copper salts is a well-established reaction in organic chemistry,¹⁵ until the 1970's there were relatively few examples of the copper-promoted dimerization of enolate anions. Vogler¹⁹ had reported the formation of dimers as a side product from the copper-catalyzed oxidation of α , β -unsaturated aldehydes and ketones and Kauffman had reported²⁰ the dimerization of sodioacetophenone by copper(II) chloride.

In 1971 it was reported¹⁶ that lithium ester enolates react with copper (II) salts to give the corresponding dimerized esters (Eq. 10). However, yields are reported to decrease drastically with increasing alkyl substitution at the <u>alpha</u> carbon of the enolate. For example, the enolate of <u>tert</u>-butyl acetate is dimerized in 85% yield by $CuBr_2$, while, under the same conditions, the enolate of ethyl isobutyrate is dimerized in only 25% yield.

$$2 CH_{2} = C \begin{pmatrix} OLi \\ 0 + 2 CuBr_{2} + 1 \\ CH_{2}CO_{2} + 1 \end{pmatrix}$$
(10)

We proposed to develop a transition metal-promoted reaction to dimerize <u>alpha</u>-substituted ester enolates in good yield, using ethyl isobutyrate as a model of a highly <u>alpha</u>-substituted ester. We chose anhydrous iron (III) chloride as our initial one-electron oxidizing agent because we had observed that it dimerized phenyllithium and lithium acetylides, suggesting that it might oxidize organolithium reagents to radicals (Eq. 11).

$$\phi \text{Li} + \text{FeCl}_{3} \neq [\phi \cdot] \neq \phi - \phi$$
(11)
$$\text{RC=CLi} + \text{FeCl}_{3} \neq [\text{RC=C} \cdot] \neq \text{RC=C} - \text{C=C} - \text{R}$$

If iron (III) chloride were to oxidize an ester enolate to a radical, one might expect that radical to react with another enolate to form a ketyl (Eq. 12). FeCl₃ has been

shown to oxidize simple ketyls to ketones¹⁸ so one might

expect a second FeCl₃ to oxidize the ketyl to product (Eq. 13).

$$-\dot{C}-CO_{2}R \qquad -\dot{C}-CO_{2}R \qquad (13)$$

$$-C-\dot{C}-O^{-} \qquad -C-CO_{2}R \qquad (13)$$

$$-C-\dot{C}-O^{-} \qquad -C-CO_{2}R \qquad (13)$$

The formation of the free radical in Equation 12 should be favored by increasing substitution on the <u>alpha</u> carbon of the enolate since that would lead to a more highly substituted radical. If this were true, we might be able to couple al<u>pha</u>-substituted ester enolates in good yield.

Results

1.0 molar solutions of lithio ethyl isobutyrate were prepared by adding one equivalent of ester to LDA in tetrahydrofuran (THF) at -78° C. FeCl₃ was added to these solutions, which were then allowed to reach room temperature over the period of approximately one hour. Analysis revealed the principal organic products to be ethyl isobutyrate and diethyl tetramethylsuccinate. Yields of coupled product <u>vs</u>. the ratio of enolate to iron are shown in Table I.

1.0 M solutions of lithic ethyl isobutyrate were reacted with one equivalent of $FeCl_3$ in various solvent

Table I. Reaction of Lithio Ethyl Isobutyrate with Iron (III) Chloride in THF.

$$\bigvee_{\text{OEt}}^{\text{OLi}} + \text{FeCl}_3 \xrightarrow{\text{THF 1.0M}} \xrightarrow{\text{CO}_2\text{Et}}_{\text{CO}_2\text{Et}}$$

Equivalents of Enolate	Equivalents of FeCl ₃	Yield (%) ^C
1	1/2	32 ^a
l	l	45 ^a
l	1 1/2	50 ^a
1	2	39 ^a
10	l	78 ^b

^aYield based on amount of starting ester.

^bYield based on amount of FeCl₃.

^CGLC yields.

systems. These results are shown in Table II. THF or THF/ pentane proved to give the best yields. Therefore all further reactions were done in THF.

Removal of the diisopropyl amine from the enolate solution prior to addition of the FeCl₃ reduced the yield from 45% to 34%. Use of the cobalt(II) enolate in place of the lithium enolate reduced the yield to 27%, with almost 43% recovered ethyl isobutyrate. Inverse addition, <u>i.e.</u>, adding a solution of the enolate to a solution of FeCl₃ in THF, reduced the yield of coupling to 25% with almost 40% recovered ethyl isobutyrate.

In an attempt to determine whether the recovered ester resulted from free radicals abstracting hydrogen from THF, the reaction was carried out in perdeuterated THF. Mass spectroscopic analysis of recovered ethyl isobutyrate showed no deuterium incorporation. At this point, we needed an ester with by-products more easily monitored on the gas chromatograph. Therefore, we changed our model from ethyl isobutyrate to ethyl cyclohexanecarboxylate. We were then able to separate and quantify coupled ester, original starting ester, and a third product; ethyl 1cyclohexenecarboxylate. The optimum yield of coupled product was obtained by direct addition of 1.1 equivalent of FeCl₃ to a 1.0 molar THF solution of lithio ethyl cyclohexanecarboxylate at -78° C. This resulted in 53% coupled ester, 33% ethyl cyclohexanecarboxylate (starting

Table II. Reaction of $LiC(CH_3)_2CO_2Et + FeCl_3$ in Various Solvent Systems.



		Yield (%) ^C		
Solvent	T (°C)	<u>1</u>	2	
THF	-78	45	28	
THF	-100	53	29	
Pentane/CH ₃ CN ^a	-38	35	^b	
Glyme	-38	0	100	
TMEDA	-78	34	24	
Pentane/DMSO ^a	-78	18	52	
Pentane/THF ^a	-78	49	8	
Pentane/pyridine ^a	-78	19	^b	
Pentane/DMF ^a	-78	0	^b	
Et ₂ 0	-78	32	45	
^{фСН} З	-78	17	^b	

^aRatio pentane:cosolvent=9:1.

^bCould not separate from solvent by GLC.

^CGLC yields.

ester) and 13% ethyl 1-cyclohexenecarboxylate (unsaturated ester).

We then surveyed various other anhydrous transition metal salts which could act as one-electron oxidizing agents. These results are shown in Table III. We found TiCl₄ to give the best yield of coupled ester. Highest yields were obtained when TiCl₄ was added dropwise to 1.0 molar solutions of ester enolate at 0°C. Reaction mixtures were allowed to reach room temperature over the period of about 45 minutes and then quenched with three equivalents of 5.0 <u>M</u> aqueous sodium hydroxide. Removal of diisopropyl amine from enolate solutions prior to addition of TiCl₄ gave no improvement in yield.

A tan precipitate forms upon addition of TiCl_4 to the ester enolate solution. With warming and time, the reaction mixture darkens and the viscosity increases markedly. Then, as the reaction nears completion, the reaction mixture thins down to a dark brown, almost homogeneous solution. Quenching by aqueous sodium hydroxide followed by addition of pentane gives a colorless organic phase over a thick, blue aqueous layer reminiscent of aqueous TiCl₃.

We discovered that the reaction was highly sensitive to benzophenone impurities in THF and to lithium butoxide in butyllithium. THF had to be distilled from lithium aluminum hydride and <u>n</u>-butyllithium had to be free from

Table III. Reaction of Lithio Ethyl Cyclohexanecarboxylate with Various Transition Metal Salts.



	Y	Yield (%)					
Metal Salt	A	В	С				
FeCl ₃	53	34	13				
Fe(acac) ^a	34	22	13				
Fe(0 ₂ CR) ₃ b	0	^d	0				
Co(acac) ₃ a	13	29	20				
CrCl ₃	12	39	20				
Cr(acac) ^a	18	80	l				
CuBr ₂	48	18	7				
CeSO ₄	0	^d	0				
MnBr ₂	0	^d	0				
HgI ₂	0	^d	0				
1/2 I ₂	0	^d	0				
TiCl4	64	8	5				
Ti(OEt) ₄	0	51	0				
T1(0-<)4	0	84	0				
ZrCl4	0	d	0				
Ti(Cp) ₂ Cl ₂	0	d	0				

 $b_{R=-CH-(CH_2)_3-CH_3}$ $a_{acac}=2,5-pentanedionate.$ ^CCp=cyclopentadienate. dYield of B not determined.

any turbidity in order to maximize the yield.

While TiCl₄ gave only a modest improvement in yield for ethyl cyclohexanecarboxylate (TiCl₄: 64%; FeCl₃: 53%), it raised the yield for the coupling of ethyl isobutyrate from 45% with FeCl₃ to 89%. A series of ester enolates were coupled with TiCl₄. The results are shown in Table IV. Clearly α -branched and α -phenyl enolates gave the highest yield. The yield plummets dramatically as <u>alpha</u> substitution decreases. A ketone enolate, lithio cyclohexanone, did not dimerize.

When the reaction was carried out in the presence of anisole to trap the intermediate free radical, no adduct was observed.

Several experiments were done in an attempt to determine the source of the recovered ethyl cyclohexanecarboxylate. The coupling reaction was carried out in perdeuterated THF both at 1.0 molar and 0.1 molar. Recovered ester was analyzed by mass spectrometry and no deuterium was found to be incorporated. The reaction was carried out as usual and quenched with D_2O . Recovered ester was again measured by mass spectrometry and found to contain no deuterium. The reaction was carried out as usual and then carefully analyzed for ethylene to check the possibility of removal of a hydrogen from the ethoxy group of the enclate (Eq. 14).

$C = C OLi \qquad TiC:$ OR $T^{\circ}C$	$\xrightarrow{1_{4}/\text{THF}} \xrightarrow{-C-CO_{2}} \xrightarrow{-C-CO_{2}}$	R R
Starting Carbonyl Compound	Т	Yield (%) ^e
$\frac{cyclo}{6} - C_{6}H_{11}CO_{2}Et$ $\frac{1}{2} - C_{3}H_{7}CO_{2}Et$ $C_{6}H_{5}CH_{2}CO_{2}Et$ $\frac{cyclo}{6} - C_{4}H_{7}CO_{2}Et$ $\frac{cyclo}{6} - C_{3}H_{5}CO_{2}Et$ $CH_{3}CH_{2}CO_{2}Et$ $CH_{3}(CH_{2})_{4}CO_{2}Et$ $CH_{3}CH=CHCO_{2}Et$ $CH_{3}CO_{2}C(CH_{3})_{2}$ $CH_{3}CO_{2}C(CH_{3})_{3}$	0^{a} 0^{a} 0^{a} -78^{b} -78^{b} -78^{c}	$ \begin{array}{c} 64\\ 89\\ 94^{f}\\ 67\\ 54\\ 0\\ 10-15^{f}\\ 0\\ 0\\ 0\\ 0\\ 0 \end{array} $
CH ₃ CO ₂ C(CH ₃) ₃ ^d cyclohexanone	-78 -78 [°]	16 0

Table IV. Direct Addition of TiCl₄ to Enolates.

^aYields 5-10% less if addition is carried out at -78°.

^bYields 5-10% less if addition is carried out at 0°.

^CYield 0 if addition is carried out at 0°.

^dAmine-free enolate used.

e_{Yields} based on GLC analysis.

^fObtained as a mixture of stereoisomers.

Less than one mole percent of ethylene was found. The same amount of ethylene was liberated by adding the ester to LDA in THF and allowing it to warm to room temperature with no transition metal present.

Further investigations were carried out to look for the intermediacy of α -chloroester. Lithio ethyl isobutyrate was added dropwise to two equivalents of TiCl₄ in THF. No chloroester was observed. Lithio ethyl isobutyrate was coupled in the presence of one equivalent of ethyl α -chloroisobutyrate, yielding 58% coupled product and 79% recovered chloroester. Lithio ethyl isobutyrate was added to one equivalent of ethyl α -chloroisobutyrate, giving no coupled product. Finally, ethyl β , β , β -trideuteroisobutyrate was reacted with TiCl₄ in the presence of one equivalent of ethyl α -chloroisobutyrate (Eq. 15).

(15)

Recovered chloroester showed no deuterium incorporation, though the coupled product showed some deuterium loss.

Less substituted ester enolates were found to give increased yields of coupled products when an inverse addition procedure, where the enolate solution is added to a solution/suspension of TiCl₄ in THF, was used. This procedure drastically reduced the yield with the highly substituted esters. Results of inverse addition of various enolates to TiCl₄ are shown in Table V.

In an attempt to draw comparisons among the various metal coupling agents, lithic ethyl cyclohexanecarboxylate was coupled with $CuCl_2$, $FeCl_3$, and $TiCl_4$ in THF at 1.0 molar, 0.1 molar, and 0.01 molar concentrations. All reactions were done by adding the metal salt to the enolate at $-78^{\circ}C$ and allowing the reaction to reach room temperature. No attempt was made to optimize the procedure for each metal. $CuCl_2$ was used instead of $CuBr_2$ in the interest of consistency.

The results are shown in Table VI. $CuCl_2$ does not couple the enolate of ethyl cyclohexanecarboxylate well at any concentration. The yields with FeCl₃ appear to be unchanged from 1.0 to 0.1 molar, then to decrease drastically while the yields with TiCl₄ seem to vary more or less smoothly with concentration.

Table V. Inverse Addition of Enolates to $TiCl_4$.

$$TiCl_{4}/THF + C=C \xrightarrow{OLi}_{OR} \xrightarrow{-78^{\circ}}_{THF} \xrightarrow{-C-CO_{2}Et}_{-C-CO_{2}Et}$$

Ester	Yield (%) ^C	
i-C ₃ H ₇ CO ₂ Et	41	
cyclo-C6 ^H 11 ^{CO} 2 ^{Et}	30	
CH ₃ CH ₂ CO ₂ Et ^d	28	
EtO ₂ C(CH ₂) ₆ CO ₂ Et ^a	32 ^a	
сн ₃ со ₂ с(сн ₃) ₃	27	
CH ₃ CO ₂ C(CH ₃) ₃ ^b	61	

^aProduct is 1,2-dicarboethoxycyclohexane.

^bAmine-free enolate used.

^CYield based on GLC analysis.

^dProduct is a mixture of stereoisomers.

Table VI. Effects of Dilution on Metal Coupling Agents.



Metal Salt	Molarity	Yield (%) ^a			
		A	В	С	
CuCl ₂	1.00	6	50	11	
	0.10	3	53	4	
	0.01	3	33	2	
FeCl ₃	1.00	30	32	18	
	0.10	34	31	18	
	0.01	9	71	7	
TiCl4	1.00	52	14	7	
	0.10	30	34	13	
	0.01	13	60	10	

^aYield based on GLC analysis.

Discussion

Direct addition of TiCl_4 couples <u>alpha</u>-substituted lithium ester enolates in THF solution. Yields decrease as substitution on the <u>alpha</u> carbon of the enolate decreases. Thus TiCl_4 -promoted coupling of substituted ester enolates is a complementary procedure to the CuBr_2 promoted coupling of unsubstituted ester enolates.

While inverse addition increases the yields obtained with less substituted enolates, it drastically decreases the yield for highly substituted enolates. This suggests that the less substituted ester enolates couple by a different mechanism than the highly substituted ester enolates.

This dependence upon order of addition also suggests that coordination of the enolate to the titanium is important to the coupling of substituted enolates. Direct addition of TiCl_4 to the enolate solution allows the enolate and the solvent to compete for coordination sites on the titanium. Inverse addition allows the titanium to completely coordinate with the solvent before the enolate is present and significantly lowers the yield. We observe that the addition of TiCl_4 to pure THF is qualitatively more violent than addition of TiCl_4 to one molar ester enolate in THF. We also observe that titanium (IV) alkoxides do not dimerize ester enolates. Addition of titanium tetraethoxide or titanium tetraisopropoxide to

ester enclates gives a red solution but no brown color or precipitate. Upon quenching, one finds titanium dioxide but no blue material in the aqueous layer. The organic phase contains only starting ester and condensation products.

The first three entries in Table IV, ethyl isobutyrate, ethyl cyclohexanecarboxylate and ethyl phenylacetate, show the highest yield when $TiCl_{\mu}$ is added at 0°C, while the next two entries, ethyl cyclopropanecarboxylate and ethyl cyclobutanecarboxylate, show the highest yield when TiCl_h is added at -78° C. This may be rationalized by considering that the three and four membered rings have considerable strain introduced into them by enolization. Addition of TiCl_{μ} at -78°C may slow down enolate decomposition caused by hot spots in the exothermic reaction. Sixmember ring and acyclic enolates may be stable enough to withstand addition of $TiCl_{ll}$ at 0°C. It is possible that lithium ester enclates do not compete with THF for coordination sites on titanium (IV) as well at -78° C as at 0°C, which would explain why addition of $TiCl_h$ at -78°C lowers the yield with the six member ring and acyclic enolates.

The major side products of the reaction are starting ester and the corresponding α , β -unsaturated ester. There is always more of the former than the latter, which is not surprising since the unsaturated ester is susceptible

to Michael condensation as well as metal-promoted polymerization. However, it is of both theoretical and practical interest to know whether all of the saturated ester comes from formation of unsaturated ester or whether some significant portion of it has another source. This is equivalent to asking where the <u>alpha</u> hydrogen on the recovered saturated ester comes from. Does it all come from the <u>beta</u> carbon of another molecule, or does part of it come from somewhere else?

We are able to rule out the solvent, the amine, the work-up, and the ethoxy group as sources of hydrogen. The reactions in deuterated THF show that, at least at 1.0 and 0.1 molar, no hydrogen is abstracted from THF. Removal of diisopropyl amine does not affect the yield of coupled product or unsaturated ester, suggesting that the amine is not a hydrogen or proton source. Quenching the reaction with D_2O shows that none of the saturated ester comes from unreacted enolate which is protonated during aqueous work-up. Abstraction of a hydrogen from the ethoxy group of the enolate should lead to the formation of ethylene (Eq. 14), yet we observe only less than 1% ethylene. Therefore, we must conclude that all of the saturated ester is formed by removal of a hydrogen from the beta carbon of another molecule, so that one molecule of unsaturated ester must be formed for every molecule of saturated ester.

We felt that it was necessary to consider whether the reaction might proceed <u>via</u> an α -chloroester intermediate (Eq. 16).

$$C = C \xrightarrow{OLi}_{OR} \xrightarrow{TiCl_4} Cl - C - CO_2 R \xrightarrow{C} = C \xrightarrow{OLi}_{OR} \xrightarrow{-C - CO_2 R} (16)$$

 α -Bromoester has been reported¹⁶ as a side product in the CuBr₂-promoted coupling of unsubstituted ester enolates. However, it was shown that the bromoester was not a necessary intermediate by using copper (II) valerate instead of copper (II) bromide to effect the coupling. We were unable to do this since our titanium (IV) alkoxides failed to couple ester enclates. Although it seemed unlikely that the enclate of ethyl isobutyrate would substitute the tertiary chlorine of ethyl α -chloroisobutyrate, Brock- som^{22} had reported an 85% yield for the corresponding reaction with the iodoester and we had observed a 40% yield with the bromoester. We were unable to observe any substitution when we reacted lithio ethyl isobutyrate with ethyl α -chloroisobutyrate. We also added the enolate dropwise to two equivalents of TiCl_{μ} and observed no chloroester. This was, in our estimation, the most likely procedure for maximizing the yield of any chloroester that might be formed. These results strongly
suggested that chloroester was neither formed nor consumed in the reaction, but did not prove that chloroester was not formed slowly and used up quickly under the reaction conditions. However, the TiCl_4 -promoted coupling of lithic ethyl β , β , β -trideuteroisobutyrate in the presence of non-deuterated ethyl α -chloroisobutyrate shows that while the enclate apparently does react with the chloroester in the presence of TiCl_4 (Eq. 17), no chloroester is formed from the enclate under the reaction



conditions (Eq. 18).



We had originally conceived the coupling of substituted enolates occurring through a ketyl mechanism (Eq. 12, 13), although we did not rule out the possible dimerization of two free radicals (Eq. 19). Either mechanism would explain the by-products, either by disproportionation of two free radicals (Eq. 19) or by abstraction



$$2 \rightarrow co_{2R} \rightarrow H \rightarrow co_{2R} + \rightarrow co_{2R}$$
 (19)

of a <u>beta-hydrogen</u> from an enolate (Eq. 20). In order to distinguish between dimerization of two free radicals



and a reaction involving some metal-containing species, lithic ethyl cyclohexanecarboxylate was coupled at three concentrations and with three different metals. If all of the reactions involved disproportionation and dimerization of free radicals, then the yields of coupled product and saturated ester should vary with concentration in a similar manner for each metal. If, on the other hand, the metal were involved in the coupling, the ratios of coupled and unsaturated ester should show a different variation with concentration for each metal. The results in Table VI show that $CuCl_2$ does not couple the hindered ester very well at any concentration. The yields with FeCl₃ are essentially unchanged going from 1.0 to 0.1 molar, then fall off sharply at 0.01 molar. The yields with TiCl₄, on the other hand, vary more or less regularly with concentration. This suggests that at the very most only one of the metals could promote coupling <u>via</u> dimerization of two free radicals.

The exact nature of the intermediate remains unknown. The failure of the intermediate to abstract hydrogen from THF and diisopropylamine or to form an adduct with anisole suggests something other than a free radical. On the other hand, yields are lowered by the presence of radical scavengers such as lithium butoxide and benzophenone. Because there is no clear evidence for free radicals, we considered mechanistic alternatives.

One such alternative involves an intermediate having two enolates on the same titanium atom. This could account for all of the products but would involve two-electron oxidations (Eq. 21) either from an unknown titanium (V) species (Eq. 21, n=5), or to an unknown titanium (II) species (Eq. 21, n=4). This difficulty could possibly

$$\frac{\text{reductive}}{\text{elim}} \text{Ti}^{n-2} + \frac{-\overset{-}{\text{C}} - \text{CO}_2 R}{-\overset{-}{\text{C}} - \text{CO}_2 R}$$
$$\frac{\text{Ti}^n (c = c \overset{-}{\text{OR}})_2 \frac{\beta}{\text{elim}} c = c \overset{-}{\text{OR}} + \text{H} - \text{Ti}^n (c = c \overset{-}{\text{OR}}) + \frac{\beta}{\text{elim}} c = c \overset{-}{\text{OR}} + \frac{\beta}{\text{elim}} + \frac{\beta}{\text{elim}} + \frac{\beta}{\text{elim}} c = c \overset{-}{\text{OR}} + \frac{\beta}{\text{elim}} + \frac{\beta}{\text{elim}} c = c \overset{-}{\text{OR}} + \frac{\beta}{\text{elim}} + \frac{\beta}{\text{elim}}$$

$$\xrightarrow{\text{reductive}} \text{Ti}^{n-2} + \text{H-CCO}_2 R \qquad (21)$$

be rationalized by postulating either a transient titanium (V) which immediately goes to titanium (III) or a transient titanium (II) which immediately reacts with another titanium (IV) to form two molecules of titanium (III).

It seems likely that, whatever the nature of the intermediate, the first step is transmetalation to form a titanium enolate²³ (Eq. 22). The titanium (IV) enolate may

$$C = C OLi + TiCl_4 \rightarrow C = C OTi^{IV} + LiCl$$
(22)

next be oxidized to a radical plus titanium (III) and then couple (stepwise reaction) (Eq. 23), or couple and oxidize

$$\sum_{OR}^{OTi} + \sum_{OR}^{V} + \sum_{C-CO_2R}^{V} + Ti^{III} + + \int_{-C-CO_2R}^{-C-CO_2R}$$
(23)

simultaneously (concerted reaction) (Eq. 24).



A similar concerted mechanism could account for the byproducts (Eq. 25). The concerted mechanism accommodates



the fact that the intermediate reacts to form a bond between <u>alpha</u> carbons or to abstract <u>beta</u> hydrogens but does not do other typical free radical reactions. It also accommodates the fact that titanium (IV) is a relatively weak oxidizing agent. In the concerted mechanism, the titanium (IV) is never required to generate a free radical or other high-energy species, but only to accept an electron while a stable molecule is being formed.

Finally, we should consider why TiCl_{h} dimerizes highly substituted enclates but fails with unsubstituted enclates. Titanium (IV) is a weak oxidizing agent and may therefore require substituents on the alpha carbon to stabilize any radical character that may develop there over the course of the reaction. We typically observe unreduced titanium (IV) in the aqueous work-up of attempted couplings of unsubstituted ester enclates, suggesting that the enclates have otherwise decomposed before oxidation could occur. It is tempting therefore to suggest that success of the reaction depends upon the stability of the enolate. One could argue that the more substituted enclates survive longer at the temperature and conditions at which coupling occurs. One must note, however, that the enolate on N,Ndimethylacetamide is undimerized by TiCl_{μ} even though it is considered to be exceptionally stable.²⁵

Since TiCl₄ is a potent Lewis acid and the data indicate that coordination is important, one might want to consider an oxygen-bridged intermediate, possibly polymeric, where titanium enolates complex each other. This could account for the observation that the reaction mixture first thickens considerably and then thins out again as the reaction proceeds. A bridged intermediate could nicely

accommodate the concerted reaction mechanism, holding together the <u>alpha</u> carbons, or <u>alpha</u> carbon and <u>beta</u> hydrogen, thus facilitating the reaction. One possibility for a bridged intermediate is shown in Equation 26. How



close together the <u>alpha</u> carbons could actually be in such a hypothetical intermediate would depend upon the number and nature of the other ligands (Cl, THF, diisopropylamine) on the titanium.

Experimental

I. Materials

<u>n</u>-Butyllithium, Aldrich, was obtained as a 1.6 <u>M</u> hexane solution and standardized by the method of Watson and Eastham.¹⁴ Diisopropylamine and dimethylformamide were distilled from calcium hydride and stored under argon. Tetrahydrofuran (THF) was distilled over lithium aluminum

hydride. Ethyl α -chloroisobutyrate was prepared from ethyl isobutyrate and carbon tetrachloride by the method of Arnold and Kulenovic.²⁹ Ethyl β , β , β -trideuteroisobutyrate was prepared from ethyl propanoate and trideuteromethyl iodide by the method of Schlessinger.³⁹ Other esters were obtained commercially and distilled from calcium hydride. Titanium tetrachloride, Alfa, was distilled prior to use. Anhydrous iron (III) chloride and chromium (III) chloride, Baker, were stored and handled in an argon atmosphere. Anhydrous copper (II) chloride, Matheson, Coleman and Bell, was stored in a drying oven at 130°C and handled briefly in the atmosphere. All other anhydrous transition metal salts were purchased from Alfa, stored in a desicator, and handled in an argon atmosphere.

II. <u>Reaction of Lithio Ethyl Isobutyrate with Iron</u> (III) Chloride

A. Preparation of Lithium Diisopropylamide (LDA) -

A 50 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon, immersed in an ice water bath and charged with 3.34ml (5.5 mmole) 1.6 <u>M</u> <u>n</u>-butyllithium solution and 2.5 ml <u>n</u>-pentane. Stirring was initiated and 0.775 ml (5.5 mmole) diisopropylamine was added dropwise. The cooling bath was replaced by a warm (approximately 40°C) water bath and the mixture stirred for five minutes. The solvent was removed

under vacuum to yield LDA as a white powder.

B. Reaction of Lithio Ethyl Isobutyrate with Iron

(III) Chloride in THF - The following procedure is representative of the preparation of lithium ester enolates and the dimerization of lithium ester enolates by FeCl₃ in THF: LDA (7.35 mmole), prepared as previously described, was dissolved in 7.35 ml THF and cooled to -78°C in a Dry Ice/acetone bath. Ethyl isobutyrate (0.98 ml: 7.35 mmole) was added dropwise and stirred for 15 minutes. FeCl₃ (1.19 g; 7.35 mmole) was added through a powder funnel under a stream of argon. The reaction was stirred for 15 minutes at -78°C, then allowed to reach 25°C over the period of 45 minutes. n-Pentadecane was added as an internal GLC standard. The reaction was cooled to 0°C and 3 ml saturated aqueous KH_2PO_4 and 10 ml n-pentane were added. The organic phase was dried over K₂CO₃ and analyzed by GLC (column temperature: 100°C for four minutes, then 175°C). Diethyl tetramethylsuccinate was observed in 45% yield.

C. <u>Reaction of Lithio Ethyl Isobutyrate with</u> <u>FeCl₃ in Ether, Toluene, Tetramethylethylene-</u>

<u>diamine, and Glyme</u> - The procedure previously described for THF was followed, except that the appropriate solvent is substituted for the THF. For example, 5.62 mmoles of LDA was dissolved in 5.62 ml diethyl ether and cooled to -78° C. Ethyl isobutyrate (0.75 ml; 5.62 mmole) was added dropwise. The reaction was stirred for 15 minutes at -78° C, then 0.912 g (5.62 mmole) FeCl₃ was added. The reaction was stirred for 15 minutes at -78° C then allowed to reach 25°C and analyzed as previously described. Diethyl tetramethylsuccinate was observed in 32% yield.

D. <u>Reaction of Lithio Ethyl Isobutyrate with</u>

FeCl₃ in Pentane With a Co-solvent - The following procedure is representative: a 50 ml round-bottomed flask equipped with septum inlet, magnetic stirrer and mercury bubbler was flushed with argon, immersed in an ice water bath, and charged with 2.79 ml (4.33 mmole) n-butyllithium and 2.0 ml n-pentane. Stirring was initiated and 0.61 ml (4.33 mmole) diisopropylamine was added dropwise. The reaction was stirred for 15 minutes at 0°C, the ice water bath replaced by a Dry Ice/acetone bath, and 0.58 ml (4.33 mmole) ethyl isobutyrate added dropwise. The reaction was stirred for 15 minutes at -78 °C, then 0.5 ml (10% of solvent) pyridine was added, followed by 0.70 g (4.33 mmole) FeCl₃. The reaction was stirred for 15 minutes at -78°C then allowed to warm to 25°C and analyzed as previously described. Diethyl tetramethylsuccinate was observed in 19% yield.

E. Reaction of Lithio Ethyl Isobutyrate with

FeCl₃, Amine-free - The following procedure is representative of the preparation of amine-free lithium ester enolate solutions: a 1.0 M pentane solution of lithic ethyl isobutyrate was prepared as described in the preceding procedure. The cooling bath was removed and the solvent and amine evaporated under vacuum. After most of the solvent had been evaporated, a warm (approximately 40°C) water bath was placed under the reaction flask and the remaining solvent and amine evaporated, leaving the lithium ester enolate as a white powder. The enolate was dissolved in 4.3 ml THF to make a 1.0 M solution and cooled to -78°C. FeCl₃ (0.70 g; 4.3 mmole) was added through a powder funnel. The reaction was stirred for 15 minutes at -78°C then allowed to warm to 25°C and analyzed as previously described. Diethyl tetramethylsuccinate was observed in 34% yield.

F. Reaction of the Cobalt (II) Enolate of Ethyl

<u>Isobutyrate with FeCl₃ in THF</u> - A 1.0 <u>M</u> THF solution (6.9 ml; 6.9 mmole) was prepared at -78° C as previously described. Cobalt (II) bromide (1.51 g; 6.9 mmole) was added through a powder funnel. The cooling bath was removed and the mixture warmed with stirring until the CoBr₂ dissolved and an intense blue solution was formed. The Dry Ice/acetone bath was then replaced and

the reaction allowed to reach -78° C. $CoBr_2$ did not precipitate. FeCl₃ (1.12 g; 6.9 mmole) was added through a powder funnel and the reaction carried out and analyzed as usual. Diethyl tetramethylsuccinate was observed in 22% yield.

III. <u>Reaction of Lithio Ethyl Cyclohexanecarboxylate</u> with Transition Metal Salts

A. <u>Reaction of Lithio Ethyl Cyclohexanecarboxylate</u>

with $Co(CH_3COCHCOCH_3)_3$ - The following procedure is representative of the reaction of lithio ethyl cyclohexanecarboxylate with transition metal salts: a 1.0 \underline{M} THF solution of lithic ethyl cyclohexanecarboxylate (4.8 mmole) was prepared by the method previously described for lithio ethyl isobutyrate. Co(CH₃COCHCOCH₃)₃ (1.88 g; 5.3 mmole) was added through a powder funnel. The reaction was stirred for 15 minutes at -78°C then allowed to warm to 25°C. <u>n</u>-Pentadecane (0.67 ml; 2.4 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C and 5 ml saturated aqueous KH_2PO_4 and 10 ml $\underline{n}\text{-pentane}$ were added. The organic phase was dried over K_2CO_3 and analyzed by GLC (column temperature 100°C for 2 minutes, 150°C for 3 minutes, 170°C for 3 minutes, then 240°C). 1,1'dicarboethoxybicyclohexyl was observed in 13% yield. Ethyl cyclohexanecarboxylate was observed in 29% yield. Ethyl 1-cyclohexenecarboxylate was observed in 20% yield.

B. <u>Product Analysis</u> - GLC analysis were performed on a Varian Model 920 gas chromatograph equipped with a 4 ft x 0.25 in stainless steel column packed with 2.5% SE-30 on Chromosorb G. The flow rate was maintained at 1 ml per second. NMR spectra were determined on a Varian T-60 using tetramethylsilane as internal standard. Mass spectra were taken with a Hitachi/Perkin-Elmer RMU-6.

1,1'-Carboethoxybicyclohexyl

¹H NMR (CCl₄): δ1.40 (t,6H); δ1.75 (m,12H); δ2.30 (m,8H); δ4.20 (q,4H) MS: m/e 262 (M⁺).

Ethyl 1-cyclohexenecarboxylate

¹H NMR (CCl₄): δ1.15 (t,3H); δ1.60 (m,4H); δ2.20 (m,4H); δ4.10 (q,2H); δ6.80 (m,1H).

IV. Reaction of Lithium Ester Enclates with TiCl4

A. Reaction of Lithio Ethyl Cyclohexanecarboxylate

with TiCl_{4} - The following procedure is representative of the dimerization of lithium ester enolates by direct addition of TiCl_{4} : A 1.0 <u>M</u> THF solution of lithio ethyl cyclohexanecarboxylate (5.0 mmole) was prepared at -78°C as previously described. The Dry Ice/acetone bath was replaced with an ice water bath and 0.605 ml (5.5 mmole) TiCl₄ was added dropwise with a syringe. The reaction was

stirred for 20 minutes at 0°C, then allowed to warm to 25°C. <u>n</u>-Pentadecane (0.69 ml; 2.5 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C and 3.3 ml 5.0 <u>N</u> aqueous NaOH and 10 ml <u>n</u>-pentane were added. The organic phase was dried over K_2CO_3 . GLC analysis showed 1,1'-dicarboethoxybicyclohexyl in 64% yield.

B. Reaction of Lithio Ethyl Isobutyrate with TiCl₄

via Inverse Addition - The following procedure is representative of the inverse addition of ester enolates to TiCl_{μ} : A 50 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon and immersed in a Dry Ice/acetone bath. Stirring was initiated and 0.605 ml (5.5 mmole) TiCl_{μ} added. When the TiCl_{\downarrow} was frozen, 5 ml THF was added at such a rate that the $TiCl_{\perp}$ was not warmed. The cooling bath was then removed and the mixture allowed to warm until a yellow precipitate formed and all visible reaction had ceased. The bath was replaced and the suspension cooled to -78° C. In a second flask a 1.0 M THF solution of lithic ethyl isobutyrate was prepared as previously described. This enolate solution was added dropwise through a Teflon tube to the $TiCl_{\mu}/THF$ suspension over the period of 15 minutes. The cooling bath was removed and the reaction allowed to reach 25°C over the period of 45 minutes. $\underline{n}-C_{15}H_{32}$ was added as an internal GLC standard. The reaction was cooled to 0°C and treated with 3.3 ml 5.0 N NaOH and 10 ml

<u>n</u>-pentane. The organic phase was dried over K_2CO_3 and analyzed by GLC as previously described. Diethyl tetramethylsuccinate was observed in 41% yield.

C. <u>Product Analysis</u> - Products were analyzed by GLC, NMR and MS as previously described. IR spectra were determined on a Perkin-Elmer 327-B grating spectrophotometer using polystyrene film as reference.

Diethyl tetramethylsuccinate

¹H NMR (CCl₄): δ1.35 (s,12H); δ1.43 (t,6H); δ4.25 (q,4H). MS: m/e 230 (M⁺)

Diethyl 2,3-diphenylsuccinate

¹H NMR (CDCl₃): δ1.0 (t,3H); δ1.3 (t,3H); δ3.6-4.4 (complex m,6H); δ6.8-7.4 (m,10H) MS: m/e 256 (M⁺)

1,1'-Dicarboethoxybicyclobutyl

¹H NMR (CCl₄): δ1.2 (t,6H); δ1.5-2.5 (m,12H); δ4.0 (q,4H) IR (CCl₄): 1730 cm⁻¹ (C=0) MS: m/e 208 (M⁺)

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1,1'-Dicarboethoxybicyclopropyl
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¹H NMR (CCl₄): δ0.0-1.1 (m,8H); δ1.2 (t,6H); δ4.0 (q,4H) IR (CCl₄): 1730 cm⁻¹ (C=0) MS: m/e 178 (M⁺)

1,2-Dicarboethoxycyclohexane

¹H NMR (CCl₄): δl.l (t,6H); δl.5 (m,4H); δl.8 (m,4H); δ2.6 (m,2H); δ4.l (q,4H) IR (CCl₄): 1730 cm⁻¹ (C=O) MS: m/e 228 (M⁺)

Di-tert-butyl succinate

¹H NMR (CCl_μ): δ1.4 (s,18H); δ2.3 (s,4H)

V. <u>Attempted Observation of Ethylene in the Reaction</u> of Lithio Ethyl Isobutyrate with TiCl_{ll}

A 1.0 <u>M</u> THF solution of lithio ethyl isobutyrate was treated with TiCl_4 as previously described. The reaction flask was sealed, 2 ml <u>n</u>-propane added as internal GLC standard, and the cooling bath removed. After the reaction had warmed to 25°C, a 1 ml aliquot of the gas above the reaction mixture was withdrawn and analyzed by GLC using a 20 ft x 0.125 in stainless steel column packed with Duropak (n-octane on Porasil) maintained at 60° C. Ethylene was identified by co-injection with an authentic sample, but less than 1% ethylene was found. As a control, an enolate solution containing no TiCl₄ was allowed to warm to 25°C in a sealed flask under the same conditions. The gas above the reaction mixture of this flask was observed to contain approximately the same (less than 1%) amount of ethylene.

- VI. <u>Investigation of Ethyl α-Chloroisobutyrate as an</u> <u>Intermediate in the Reaction of Lithio Ethyl</u> <u>Isobutyrate with TiCl</u>_μ
 - A. Attempt to Observe Ethyl α -Chloroisobutyrate in the Reaction of Lithio Ethyl Isobutyrate with TiCl_h - A 1.0 <u>M</u> THF solution of lithio

ethyl isobutyrate (5.0 mmole) was prepared as previously described and added dropwise through a Teflon tube to a suspension of 1.21 ml (11 mmole) TiCl₄ in 10 ml THF, prepared as described in the procedure for inverse addition of enolates to TiCl₄. The reaction was allowed to warm to 25° C over the period of 45 minutes. GLC analysis of aliquots of the reaction mixture showed no ethyl α -chloroisobutyrate. Authentic ethyl α -chloroisobutyrate (0.71 ml; 5.0 mmole) was added to the reaction. The amount of ethyl α -chloroisobutyrate observable by GLC did not diminish during one half hour of stirring at 25°C.

B. Reaction of Lithio Ethyl Isobutyrate with

TiCl₄ in the Presence of Ethyl a-Chloroiso-

<u>butyrate</u> - A 1.0 <u>M</u> THF solution of lithio ethyl isobutyrate (5.0 mmole) was prepared as previously described and treated at -78°C with 0.71 ml (5.0 mmole) ethyl α -chloroisobutyrate followed by 0.605 ml (5.5 mmole) TiCl₄. The reaction was allowed to warm to 25°C over 45 minutes. <u>n</u>-C₁₅H₃₂ was added as an internal GLC standard and the reaction quenched as usual with aqueous NaOH and extracted with <u>n</u>-pentane. The organic phase was analyzed by GLC (column temperature: 60°C for 3 minutes, 100°C for 3 minutes, then 170°C). Diethyl tetramethylsuccinate was observed in 59% yield and ethyl α -chloroisobutyrate was observed in 79% yield.

C. Reaction of Lithio Ethyl β , β , β -trideuteroisobutyrate with TiCl₄ in the Presence of Ethyl

<u>a-Chloroisobutyrate</u> - A 1.0 <u>M</u> THF solution of lithic ethyl β , β , β -trideuteroisobutyrate was prepared by the method previously described. Ethyl a-chloroisobutyrate (0.71 ml; 5.0 mmole) was added at -78°C, followed by 0.605 ml (5.5 mmole) TiCl₄. The reaction was allowed to warm to 25°C over 45 minutes, then worked up with aqueous NaOH and pentane as usual. Diethyl tetramethylsuccinate and ethyl a-chloroisobutyrate were isolated from the organic phase by preparative GLC and analyzed by mass

spectrometry. The mass spectra for ethyl α -chloroisobutyrate showed no deuterium incorporation. Mass spectra for diethyl tetramethylsuccinate showed some product containing six deuterium atoms and some containing three deuteriums, in a 2.5:1 ratio.

VII. <u>Attempts to Observe Ethyl α-Deuterocyclohexane-</u> <u>carboxylate</u>

A. Reaction of Lithio Ethyl Cyclohexanecarboxylate with TiCl₄ in Perdeuterated THF - A 1.0 M

THF solution of lithio ethyl cyclohexanecarboxylate (5.0 mmole) was prepared at $-78\,^{\circ}$ C as previously described, except that THF d₈ was used as solvent. This solution was treated with 0.605 ml (5.5 mmole) TiCl₄ and allowed to warm to 25°C. The reaction was then cooled to 0°C and treated with 5 ml H₂O, followed by pentane extraction. Ethyl cyclohexane-carboxylate was isolated from the organic phase by preparative GLC and analyzed by mass spectrometry. No deuterium incorporation was observed. The same results were obtained when the reaction is carried out at 0.1 <u>M</u> in THF d₈.

B. Reaction of Lithio Ethyl Cyclohexanecarboxylate

with TiCl_{μ} Quenching with D₂O - A 1.0 <u>M</u> THF solution of amine-free lithic ethyl cyclohexanecarboxylate (5.0 mmole) was treated with 0.605 ml (5.5 mmole) and allowed to warm to 25°C as previously described. The reaction was then cooled to 0°C, treated with 5 ml D_2O , and extracted with pentane. Ethyl cyclohexanecarboxylate was isolated from the organic phase by preparative GLC and analyzed by mass spectrometry. No deuterium incorporation was observed.

VIII. <u>Dilution Study of Transition Metal-Promoted</u> Coupling of Lithic Ethyl Cyclohexanecarboxylate

A 1.0 <u>M</u> THF solution of lithio ethyl cyclohexanecarboxylate was prepared as usual and maintained at $-78\,^{\circ}$ C while being diluted to the desired molarity (1.00, 0.10, or 0.01 <u>M</u>). The transition metal salt was added and the cooling bath removed. The reaction was then allowed to warm to 25°C (45 minutes for 1.00 <u>M</u> reactions, 2 hours for 0.10 <u>M</u> reactions, and 5 hours for 0.01 <u>M</u> reaction). <u>n</u>-C₁₅H₃₂ was added as internal GLC standard. The reaction was cooled to 0°C, quenched (5.0 <u>N</u> NaOH for TiCl₄; saturated KH₂PO₄ for FeCl₃; 5.0 <u>N</u> NH₄OH for CuCl₂) and extracted with pentane. The organic phase was dried over K₂CO₃ and analyzed by GLC for ethyl cyclohexanecarboxylate, ethyl 1-cyclohexenecarboxylate, and 1,1'-dicarboethoxybicyclohexyl.

CHAPTER III

DIMERIZATION OF α -SUBSTITUTED KETONE ENOLATES

Introduction

Since copper-promoted dimerizations of carbanions stabilized by sulfonyl,¹⁵ phosphoryl,¹⁵ imidoyl,¹⁵ and alkoxycarbonyl¹⁶ groups have been reported, it would seem that the oxidative dimerization of ketone enolates is the most straightforward approach to the synthesis of symmetric 1,4-diketones. However, prior to 1975 no successful dimerization of ketone enolates by metal salts had been reported. In 1975 Saegusa and co-workers reported¹⁷ that lithium ketone enolates, generated <u>in situ</u> from ketone and LDA in THF, are dimerized upon treatment with CuCl₂ in dimethylformamide (DMF) (Eq. 27). Methyl ketones were

$$2 \int_{R-C=CH_{2}}^{OLi} + 2 CuCl_{2}/DMF \xrightarrow{THF} RCOCH_{2}CH_{2}COR$$
(27)

dimerized to 1,4-diketones in excellent to moderate yields, but increasing alkyl substitution at the coupling site led to "a remarkable reduction in the yield."¹⁷ For example, acetophenone was dimerized in 95% yield

while propiophenone was dimerized under the same conditions in 28% yield. Isobutyrophenone was dimerized in only 2% yield. Saegusa and coworkers reported the same trend in yields with the oxidative dimerization of silyl enol ethers by $Ag_20.^{24}$

We aspired to develop a transition metal-promoted coupling reaction for <u>alpha</u> substituted ketone enolates which would serve as a complementary method to Saegusa's $CuCl_2/DMF$ procedure, just as $TiCl_4$ is a complementary method to $CuBr_2$ for the coupling of ester enolates. We chose 3-pentanone as our preliminary model of a substituted ketone. From the ketone itself we prepared the <u>tert</u>-butyl imine, the oxime, and the dimethyl hydrazone. We planned to attempt coupling of the anions of these four species (the dianion in the case of the oxime) with $CuCl_2$, $FeCl_3$, and $TiCl_4$; the transition metal salts which had proven most effective for coupling ester enolates.

Results

3-Pentanone was dimerized with a series of transition metal salts. The results are summarized in Table VII. TiCl₄ yielded no 1,4-diketone but gave about equal amounts of dehydrated Aldol product and a symmetric furan which could be formed by acid-promoted cyclization of the product diketone (Eq. 28).

Table VII. Dimerization of Lithio 3-Pentanone by Various Transition Metal Salts.

$$2 CH_3CH_2C=CHCH_3 + 2 MX_n \xrightarrow{\text{THF}} CH_3CH_2CH_2CH(CH_3)CH$$

Metal Salt	Yield (%) ^{a,c}	
CuCl ₂	49	
CuCl ₂ (amine free)	trace	
FeC1 ₃	73	
FeCl ₃ (amine free)	47	
TiCl ₄	٥b	
AgOCOCH ₃	33	
AgNO3	33	
-		

^aProduct obtained as a mixture of <u>dl</u> and <u>meso</u> diasteriomers.

^bProduct apparently cyclizes to symmetrical dimethyl diethylfuran.

^CYield based on GLC analysis.



(28)

CuCl₂ without DMF dimerized the enolate of 3-pentanone in 49% yield. The major by-product was an unsymmetrical furan which must somehow be produced from the aldol product (Eqs. 29, 30).

 $CH_3CH_2C=CHCH_3 \xrightarrow{CuCl_2} CH_3CH_2COCH(CH_3)CH(CH_3)COCH_2CH_3$





Anhydrous FeCl₃, however, dimerized the enolate of 3pentanone in 73% yield. The product is a mixture of <u>dl</u> and meso diasteriomers. The highest yield is obtained by dissolving the FeCl₃ in THF (0.5 \underline{M}) and adding this solution dropwise to the enclate solution at -78°C, then allowing the reaction to warm to room temperature. The reaction is then quenched with a saturated aqueous solution of monobasic potassium phosphate which, upon addition of pentane, produces a colorless organic phase over an aqueous layer containing a fine grey precipitate. Quenching with aqueous HCl does not appear to lower the yield but does not remove all of the dissolved iron from the organic phase. Removal of the diisopropylamine from the enolate prior to addition of the metal salt decreases the yield of coupled product from 73% to 47% in the case of FeCl $_3$ and from 49% to almost zero in the case of CuCl₂. When the FeCl₃-promoted dimerization of the enolate of 3-pentanone was carried out in the presence of anisole, the yield of 1,4-diketone fell to 65% but no adduct with anisole was observed.

The <u>tert</u>-butyl imine of 3-pentanone was treated first with <u>n</u>-butyllithium to form the anion then with TiCl₄ at -78°C. The reaction was allowed to reach 25°C and quenched with NaOH. Although a mixture of products was obtained, more than 50% of the starting imine was recovered. Treatment of the anion with FeCl₃ gave no recovered starting material but a complex mixture of products, none of which appeared to be formed in more than 20% yield. Since 3pentanone itself gave good yields of dimerized ketone, further work with its derivatives was abandoned.

We decided to try the dimerization of two other substituted ketones: cyclohexanone and 2,4-dimethyl-3-pentanone (diisopropyl ketone). FeCl₃ dimerized cyclohexanone enolate in only 31%. CuCl₂ and TiCl₄ dimerized cyclohexanone enolate in 30% yield each. Interestingly enough, Saegusa's method, CuCl₂/DMF, gave only a 15% yield. Quenching the TiCl₄ reaction with aqueous NaOH showed some reduced titanium (blue color) but considerable amounts of unreduced titanium (TiO₂ precipitate) remaining.

At this point, we began a general survey of the transition metal salts that were at hand. These results are shown in Table VIII. Anhydrous silver acetate proved to be the best coupling agent for cyclohexanone. The yield of 1,4-diketone was 68% when the enolate solution was added to a solution of silver acetate in THF at -78° C, kept at -78° C for thirty minutes, and then allowed to



Metal Salt	Yield (%) ^{a,c}	
FeCl ₃	31	
FeCl ₃ (amine-free)	30	
TiCl ₄	30	
$TiCl_4$ (amine-free)	7	
CuCl ₂	30	
CuCl ₂ /DMF	15	
ZrCl ₄	0	
MnBr ₂	0	
Co(acac) ^b 3	23	
$Cr(acac)_{3}^{b}$	0	
CrCl ₃	0	
AgOCOCH ₃	68	
AgNO3	43	
AgClO ₄	30	

^aProduct obtained as a mixture of stereoisomers.

^bacac=2,5-pentadionate.

^CYield based on GLC analysis.

warm to room temperature over the period of about one hour. Anhydrous silver nitrate and silver perchlorate gave lowered yields. We attempted to dimerize the enolate of 3-pentanone with silver salts but found them to be inferior to FeCl₃ (Table VII).

The enclate of diisopropyl ketone was dimerized with $CuCl_2$, $FeCl_3$, $TiCl_4$, and silver acetate. The results are summarized in Table IX. Once Again, $FeCl_3$ gives by far the best yield of 1,4-diketone. Also, once again $CuCl_2$ in THF gives as good or better yields than Saegusa's $CuCl_2/$ DMF method.

Discussion

With the exception of cyclohexanone, iron (III) chloride apparently dimerizes lithium enolates of <u>alpha</u>-substituted ketones in good to excellent yields. Comparison of 3pentanone to diisopropyl ketone indicates that the yield increases as <u>alpha</u> substitution increases.

Since we were able to couple ketone enolates generated <u>in situ</u> from ketones plus LDA in THF, we were able to dimerize ketones in one pot in approximately two hours. There was, therefore, no interest in pursuing the couplings of anions of the imines, oximes, and hydrazones. Preliminary studies showing that TiCl_4 did not dimerize ketone enolates were done by the optimal procedure for dimerizing

Table IX. Dimerization of Lithio 2,4-Dimethyl-3-Pentanone with Various Transition Metal Salts.



Metal Salt	Yield (%) ^a	
AgOCOCH ₃	35	
CuCl2	21	
CuCl ₂ /DMF	18	
FeCl ₃	91	
TiCl ₄	24	

^aYield based on GLC analysis.

ester enclates, <u>i.e.</u>, direct addition of TiCl_{4} to the enolate. We found that inverse addition of ketone enclate solutions to TiCl_{4} already complexed with THF gave some coupling, though the yields were poor. While the yield with CuCl_2/DMF did decrease dramatically with increasing <u>alpha</u> substitution, we found that CuCl_2 in THF gave better yields in our systems. Most importantly, we discovered that reports¹⁸ indicating that FeCl₃ would not appreciably dimerize ketone enclates were misleading because they were based upon results obtained with cyclohexanone.

Saegusa repeatedly makes the point that "the use of DMF as a cosolvent is crucial in the oxidative dimerization of ketone enclates."¹⁷ Our findings indicate the opposite. It is conceivable that CuCl₂ dimerizes substituted ketone enolates via a different mechanism than the one operating for nonsubstituted enolates and that the results cannot be meaningfully compared. However, an alternative explanation may be found in Saegusa's experimental technique. Saegusa generates LDA by adding nbutyllithium in hexane solution to diisopropylamine in THF, obtaining a THF solution of LDA containing considerable amounts of n-hexane. Our own procedure results in a THF solution of LDA containing no n-hexane. It is possible that Saegusa found it necessary to use DMF as a co-solvent only to offset the deleterious effects of hexane on both enolate and CuCl₂ solubility. It is not clear why DMF

lowers the yields with our substituted ketone enclates though it may compete for coordination sites on the copper.

It does seem clear, however, that molecules capable of complexing metals play a crucial role in the reaction. Saegusa found that, for whatever reason, DMF was essential in his system. We find that removal of the diisopropyl-amine from the enolate before reaction with the metal drastically lowers the yield for $CuCl_2$, $FeCl_3$, and $TiCl_4$. Though the exact role of the amine is unknown, it may be important either as a ligand for an intermediate metal species or as a complexing agent for Li^+ at some stage in the reaction.

While the mechanism is unknown, the following comments are offered. There seems to be no reason to consider oligomeric bridged intermediates. The optimum yield for all three metals is obtained by dissolving/suspending the metal in THF prior to contact with the enolate. The order of addition does not appear to be important. During the course of the reaction color changes are observed but no phase change or large change in viscosity is apparent.

The reaction is sensitive to the presence of benzophenone and lithium butoxide though no direct evidence of free radicals has been observed. The yield apparently increases with increasing alkyl substitution at the <u>alpha</u> carbon of the enolate. This may be rationalized by a radical-type mechanism which requires substituents on the <u>alpha</u> carbon

to stabilize radical character at that site. The byproducts of the reaction are starting ketone, aldol product, and intractable high-boiling material. The latter may result from polymerization of hypothetical unsaturated ketone, which is never directly observed, or from condensation of the enolate with the product 1,4-diketone.

The latter possibility, along with the fact that aldol product is observed, suggests that the more substituted ketone enolates may give higher yields simply because they are more sterically hindered and therefore undergo selfcondensation and condensation with the product at a much slower rate. There is some evidence suggesting that the factor which limits the yield is decomposition of the enolate. When the coupling agent is TiCl, one can see qualitatively how much unreduced titanium remains after the reaction is quenched. After coupling a ketone enolate and quenching with NaOH, one observes much more titanium dioxide than blue reduced titanium. When the coupling agent is FeCl₃, one can obtain high yields of coupling based on the amount of starting iron (III) if a 10-fold excess of ketone (or ester) enclate is used. This suggests that the product distribution is the result of a competition between oxidative coupling of the enolate and decomposition of the enclate, possibly via interaction with the metal as a Lewis acid but without reducing the metal.

All of the data are consistent with either the

dimerization of two free radicals, the original ketyl mechanism suggested in the Introduction of Chapter II (Scheme I), or a two-electron oxidation mechanism similar to the one suggested¹⁸ for the FeCl₃-promoted cross-coupling of pinacolone and <u>tert</u>-butyl acetate enolates (Scheme II).



SCHEME I



SCHEME II

There is, of course, no reason to rule out a concertedtype mechanism (Scheme III) similar to the one discussed in Chapter II.

As a final comment about the transition metal-promoted dimerization of enolates, we caution that the mechanism or mechanisms actually in operation may well be somewhere in between the models we have suggested. If one conceives the ketyl mechanism, for example, so that the enolate leading to the radical is an iron (III) enolate and the enolate capturing the radical to lead to ketyl is an iron (III) enolate, the ketyl mechanism begins to look very much like the concerted mechanism (Scheme IV). Similarly, if an iron (III) enolate is a precursor to free radicals, then the free radical dimerization mechanism also begins to look like the other two (Scheme V).



SCHEME III







SCHEME V

Experimental

I. Materials

<u>n</u>-Butyllithium, diisopropylamine, solvents, and transition metal compounds were obtained and handled as described in Chapter II. All ketones were obtained commercially and distilled prior to use. The <u>tert</u>-butyl imine of 3-pentanone was prepared from the ketone, <u>tert</u>-butylamine, and TiCl₄ by the method of Weingarten, Chupp, & White.²¹ The corresponding oxime was prepared by treatment of the ketone with hydroxylamine hydrochloride and Na_2CO_3 by the method of Bousquet.²⁸ The N,N-dimethylhydrazone was prepared by treatment of the ketone with unsymmetrical dimethylhydrazone in ethanol by the method of Newkome and Fishel.³⁵ Silver salts were purchased from Matheson, Coleman & Bell, and used without further refinement.
II. Preparation of Ketone Enolate Solutions

A. <u>Preparation of Lithio 3-Pentanone</u> - The following procedure is representative of the preparation of solutions of ketone enolate containing amine: A 1.0 <u>M</u> THF solution of LDA (5.5 mmole) was prepared as described in Chapter II and cooled to 0°C in an ice water bath. 3-Pentanone (0.53 ml; 5.0 mmole) was added dropwise. The reaction was then stirred for 15 minutes at 0°C, giving a 1.0 <u>M</u> THF solution of ketone enolate containing one equivalent of amine.

Β. Preparation of Amine-free Lithio cyclohexanone -The following procedure is representative of the preparation of amine-free ketone enolate solutions: A 50 ml roundbottomed flask equipped with septum inlet, magnetic stirrer and mercury bubbler was flushed with argon, immersed in an ice water bath and charged with 4.97 ml (8.18 mmole) nbutyllithium solution and 3.2 ml n-pentane. Stirring was initiated and 1.16 ml (8.18 mmole) diisopropylamine was added dropwise. After stirring for 15 minutes at 0°C, 0.52 ml (7.44mmole) cyclohexanone was added dropwise. The reaction was stirred for 15 additional minutes, then the solvent and amine were removed under vacuum. When most of the solvent had evaporated, the cooling bath was replaced by a warm (approximately 40°C) water bath to facilitate the evaporation of the remaining solvent and amine.

Lithio cyclohexanone was obtained as a white powder which was dissolved in 8.18 ml THF to provide a 1.0 \underline{M} THF solution of amine-free enolate.

III. <u>Dimerization of Lithium Ketone Enolates by Cu^{II}</u>, Fe^{III}, and Ti^{IV}

A. FeCl₃-Promoted Dimerization of Lithio 3-

Pentanone - The following procedure is representative of the iron (III) promoted dimerization of lithium ketone enclates: A 1.0 M THF solution of lithio 3-pentanone (4.5 mmole) was prepared as previously described and cooled to -78°C in a Dry Ice/acetone bath. A second roundbottomed flask equipped with septum inlet, mercury bubbler and magnetic stirrer was flushed with argon and charged with 0.66 g (4.6 mmole) FeCl₃ and 9.2 ml THF. Stirring was initiated. After all the FeCl₃ had dissolved, the $FeCl_3/$ THF solution was added dropwise to the enolate solution through a Teflon tube. The reaction was stirred for 30 minutes at -78°C then allowed to warm to 25°C over the period of 45 minutes. $\underline{n}-C_{15}H_{32}$ (0.635 ml, 2.3 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C, treated with 3 ml saturated aqueous $\rm KH_2PO_4$, and extracted with pentane. The organic phase was dried over K_2CO_3 and analyzed by GLC (column temperature: 100°C for 3 minutes, 150°C for 4 minutes, then 170°C). 4,5-Dimethyl-3,6-heptanedione was observed in 73% yield as a mixture

of two stereoisomers.

B. TiCl_h-Promoted Dimerization of Lithio cyclo-

hexanone - The following procedure is representative of the reactions of lithium ketone enolates with $TiCl_{li}$: A 1.0 M THF solution of lithic cyclohexanone (5.0 mmole) was prepared by the method previously described for lithio 3-pentanone and cooled to -78° C in a Dry Ice/acetone bath. A second 50 ml round-bottomed flask equipped with septum inlet, magnetic stirrer and mercury bubbler was flushed with argon, immersed in a Dry Ice/acetone bath and charged with 0.605 ml (5.5 mmole) TiCl_{μ}. When the TiCl_{μ} had frozen, 5 ml THF was added and stirring was initiated. The cooling bath was then removed and the reaction allowed to warm until a yellow precipitate had formed and all visible reaction had creased. The cooling bath was replaced and the suspension allowed to reach -78°C. The enolate solution was added to the suspension through a Teflon tube, stirred for 30 minutes at -78°C, then allowed to warm to 25°C over the period of 45 minutes. $\underline{n}-C_{15}H_{32}$ (0.69 ml; 2.5 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C, treated with 3.3 ml 5.0 \underline{N} aqueous NaOH, and extracted with pentane. The organic phase was dried over K_3CO_3 and analyzed by GLC (column temperature: 100°C for 4 minutes, 170°C for 5 minutes, 220°C for 3 minutes, then 240°C). Bicyclohexyl-2,2'-dione

was observed in 30% yield.

C. <u>CuCl₂-Promoted Dimerization of 2,4-Dimethyl-3-</u>

Pentanone - The following procedure is representative of the reactions of lithium ketone enolates with CuCl₂: A 1.0 <u>M</u> THF solution of lithio 2,4-dimethyl-3pentanone (5.0 mmole) was prepared as previously described and cooled to -78°C in a Dry Ice/acetone bath. A second 50 ml round-bottomed flask, equipped as described in the preceding procedure, was flushed with argon, charged with 0.74 g (5.5 mmole) CuCl₂ and 5.0 ml THF and cooled to -78°C in a Dry Ice/acetone bath. The enolate solution was added to the CuCl₂/THF mixture through a Teflon tube. The reaction was stirred at -78°C for 30 minutes then allowed to warm to 25°C over the period of 45 minutes. $\underline{n}-C_{16}H_{34}$ (0.773 ml; 2.5 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C, treated with 3.3 ml 3 \underline{N} HCl and extracted with pentane. The organic phase was dried over K_2CO_3 and analyzed by GLC (column temperature: 150°C for four minutes, then 200°C). 2,4,4,5,5,7-Hexamethy1-3,6-octanedione was observed in 22% yield.

D. <u>Product Analysis</u> - Products were analyzed by GLC, NMR, IR, and mass spectrometry as described in Chapter II.

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<u>4,5-Dimethyl-3,6-octanedione (obtained as a mixture</u>
of stereoisomers)
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¹H NMR (CCl₄): δ1.0 (m,12H); δ2.1-2.6 (m,4H); δ2.6-2.9 (m,2H) IR (CCl₄): 1710 cm⁻¹ (C=O) MS: m/e 170 (M⁺)

Bicyclohexyl-2,2'-dione³⁶

¹H NMR (CCl₄): δ1.2-2.1 (m,12H); δ2.2-2.6 (m,4H); δ2.6-3.1 (m,2H) IR (neat): 1704 cm⁻¹ (C=O) MS: m/e 194 (M⁺)

2,4,4,5,5,7-Hexamethy1-3,6-octanedione

¹H NMR (CCl₄): δ1.0 (d,12H); δ1.1 (s,12H); δ2.9 (septet,2H) IR (CCl₄): 1704 cm⁻¹ (C=0) MS: m/e 226 (M⁺)

3-Ethyl-4-methyl-3-heptene-5-one

¹H NMR (CCl₄): δ1.0 (t,9H); δ1.8 (s,3H); δ2.1 (q,4H); δ2.5 (q,2H) IR (CCl₄): 1690 cm⁻¹ (C=O); 1605 cm⁻¹ (C=C) MS: m/e 154 (M⁺)

2,5-Diethyl-3,4-dimethylfuran

¹H NMR (CCl₄): δ1.0 (t,6H); δ1.8 (s,6H); δ2.4 (q,4H) MS: m/e 152 (M⁺) IR shows no C=O

2,4-Diethyl,3,5-dimethylfuran

1_{H NMR} (CCl₄): δ1.1 (q,6H); δ1.8 (s,3H); δ2.1 (s,3H); δ2.3 (quintet, 4H) MS: m/e 152 (M⁺) IR shows no C=0

IV. <u>Reaction of Ketone Enclates with Other Metal</u> Compounds

The enolates of 3-pentanone, cyclohexanone, and 2,4dimethyl-3-pentanone were reacted with various silver salts. Lithio cyclohexanone was also reacted with chromium (III), cobalt (III), manganese (II) and zirconium (IV) compounds. The following procedure, for the reaction of lithio cyclohexanone with silver acetate, is representative of all of these reactions: A 50 ml round-bottomed flask, equipped with a septum inlet magnetic stirrer, and mercury bubbler was flushed with argon, immersed in a Dry Ice/ acetone bath, and charged with 0.637 g (3.82 mmole) AgOCOCH₃ and 3.9 ml THF. The mixture was stirred at -78° C for 10 minutes. A 1.0 <u>M</u> THF solution of lithio cyclohexanone (3.82 mmole) was prepared as previously described, cooled to -78° C, and added to the AgOCOCH₃/THF mixture through a Teflon tube. The reaction was stirred at -78° C for 30 minutes then allowed to warm to 25°C over 45 minutes. $\underline{n}-C_{15}H_{32}$ (0.998 ml; 3.6 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C, treated with 3.3 ml 3 N HCl, and extracted with pentane. The organic phase was dried over K_2CO_3 and analyzed by GLC as previously described. Bicyclohexyl-2,2'-dione was observed in 68% yield.

CHAPTER IV

REACTIONS OF ENOLATES WITH α -HALOESTERS

Introduction

In 1941, Hauser reported³¹ the iodine-promoted dimerization of sodio ethyl isobutyrate in very poor yield. Later he reported³² dimerizing the anions of either the ethyl ester or the nitrile of phenylacetic and diphenylacetic acids, using various vicinal alkyl dihalides or polyhalides.

More recently, Brocksom and Petragnani²² have dimerized lithium ester enolates using elemental iodine (Eq. 31). The iodine is added to a THF solution of the enolate at

$$2 c=c OLi - \frac{I_2 - C - CO_2 R}{OR}$$
(31)

-78°C. The reaction gave excellent yields for isobutyrate esters, and in cases where R equals <u>tert</u>-butyl, but poor yields with methyl or ethyl esters without <u>alpha</u>-branching. We have observed that the reaction fails with lithic ethyl cyclohexanecarboxylate. Lithium ester enclates have been shown²⁶ to react with iodine or bromine at -78°C in THF to form the corresponding α -iodo or α -bromoester (Eq. 32). Brocksom²² has identified α -iodoester as the initial

$$\begin{array}{c} \begin{array}{c} C = C \end{array} \xrightarrow{OL1} & \begin{array}{c} I_2 \\ \hline \\ OR \end{array} \xrightarrow{I - C - CO_2 R} \end{array}$$
(32)

product formed in his reaction (Eq. 31) and suggests that the reaction proceeds <u>via</u> a substitution of the iodine by another enolate anion (Eq. 33), citing successful alkylation of ester enolates by α -haloacetates³³ and successful intramolecular substitutions of secondary α -haloesters by ester enolates.³⁴ If this were true, there

$$I - C - CO_2R + C = C OLi OR + RO_2 CCCO_2R$$
(33)

would seem to be no reason why the iodoester, generated \underline{in} <u>situ</u> by reaction of iodine with an ester enolate, could not be reacted in the same pot with a different ester enolate.

We felt that this could be the basis for a simple preparation of unsymmetrical 1,4-dicarbonyl compounds and so proposed to react α -haloesters with both ester and ketone enolates to synthesize, respectively, unsymmetrical succinates and γ -ketoesters.

We proposed to first investigate whether unsymmetrical succinates could be made by adding one equivalent of enolate to one equivalent of elemental halogen, allowing the α -haloester to form, then adding a second equivalent of a different enolate. We chose as our model esters ethyl

isobutyrate and tert-butyl acetate.

Since we felt that γ -ketoesters were more useful synthetic intermediates than succinates, we decided to devote most of our efforts to studying the reaction between ketone enolates and α -haloesters. We chose to begin with the reaction of ketone enolates with iodoacetates to yield γ -ketoesters which would be precursors to cyclopentane-1,3-diones (Eq. 34).

We chose cyclohexanone as our initial ketone because of the importance of the six-member ring in naturally occurring ketones and because the product was available from the cross-coupling of the enolates with FeCl_3^{18} (Eq. 35). Thus not only was the product well characterized



but there was an alternative procedure of roughly equal expense and convenience with which to compare results.

Results

We began by comparing the bromine and chlorine-promoted dimerization of lithic ethyl isobutyrate with the results of Brocksom reported for iodine. We found that the yield dropped remarkably as the halogen changed, as shown in Table X. We also found that lithic <u>tert</u>-butyl acetate reacted with <u>tert</u>-butyl bromoacetate to yield di-<u>tert</u>-butyl succinate in only 44% yield (Eq. 36); considerably less than the 97% Brocksom had reported for the iodinepromoted dimerization (Eq. 37).

$$CH_2 = C OL1 + BrCH_2CO_2 + + + OCOCH_2CH_2CO_2 + 44\%$$
(36)

$$2 CH_2 = c_0 + I_2 + + OCOCH_2CH_2CO_2 + 97\%$$
 (37)

Lithio ethyl isobutyrate reacted with <u>tert</u>-butyl bromoacetate to give an unsummetrical succinate in 80% yield (Eq. 38).

Table X. Reaction of Lithio Ethyl Isobutyrate with Ethyl α -Haloisobutyrates.

$x-c^{CH_3}_{CH_3}CO_2Et +$	$CH_{3} C=C + CH_{3} - C - CO_{2}Et$ $CH_{3} - C - CO_{2}Et$
Halogen	Yield (%) ^d
I	85 ^a
Br	40 ^b
Cl	0 ^c

CH₂

^aReference 22, one equivalent I₂ added to 2 equivalents enolate.

^bOne equivalent Br_2 added to 2 equivalents enolate.

^CChloroester added dropwise to enolate solution.

$$\sum_{CH_3}^{CH_3} \bigvee_{OEt}^{OL1} + BrCH_2CO_2 + \rightarrow EtOCOC(CH_3)_2CH_2CO_2 + (38)$$

All attempts failed to form the same unsymmetrical succinate from addition of a <u>tert</u>-butyl acetate enolate to ethyl α -bromoisobutyrate formed <u>in situ</u> by addition of lithic ethyl isobutyrate to bromine in THF at -78°C (Eq. 39).



$$\longrightarrow \text{EtoCOC(CH_3)_2CH_2CO_2} + \text{M=Li, Co^{II}, Cu^{I}}$$
(39)

However, replacing the bromine in Equation 39 with iodine resulted in a 64% yield of the unsymmetrical succinate when the lithium enolate of <u>tert</u>-butyl acetate was used. Besides product, the reaction mixture contained <u>tert</u>-butyl acetate and a trace of iodoester. No symmetrical succinates were observed. Thus we are effectively able to cross-couple two different ester enolates without isolating any intermediates.

Alpha-iodoacetates are not readily available from ester enclates as addition of the enclate solution to iddine results in formation of succinate even at -100°C. Ethyl iodoacetate and tert-butyl iodoacetate were prepared by treatment of the corresponding chloroesters with sodium iodide in acetone.²⁷ Ethyl iodoacetate was found to be extremely sensitive to heating and air, decomposing with concurrent formation of elemental iodine. Ethyl iodoacetate were also found to be an extremely potent lachrymator, which proved especially inconvenient because it is also essentially odorless. tert-Butyl iodoacetate, on the other hand, seemed much less inclined to decompose and was much more pleasant to work with. We were able to prepare tert-butyl iodoacetate on a 300 millimole scale in 83% isolated yield, taking only routine precautions to degas solvents, washwater, and drying agents. The lithium enolate of cyclohexanone was added to one equivalent of tert-butyl iodoacetate to give the corresponding γ -ketoester in excellent yield (Eq. 40). Use of the potassium enolate of cyclohexanone lowered the yield to 34%.

$$\bigcup_{i=1}^{OL1} + \operatorname{ICH}_2\operatorname{CO}_2\operatorname{C(CH}_3)_3 \longrightarrow \bigcup_{i=1}^{O} \operatorname{CO}_2\operatorname{C(CH}_3)_3$$
(40)

Results of experiments to optimize reaction conditions

are shown in Table XI. While the reaction appears to proceed slowly to completion at -78°C, the most convenient procedure is to cool the solution of ketone enolate (prepared by addition of ketone to LDA in THF at 0°C) to -78°C, add the iodoester, and allow the reaction to warm to 25°C over the period of approximately one hour.

A survey was done of the reaction of various lithium ketone enolates with <u>tert</u>-butyl iodoacetate. The results are shown in Table XII. One notes that enolates with alkyl substitution at the <u>alpha</u> carbon give higher yields than the methyl ketone acetophenone. Also, we found that the reaction was somewhat sensitive to excess base. Use of ketone enolate containing ten percent excess LDA lowered the yield from 79% to 75% in the case of 3-pentanone and from 69% to 51% in the case of cyclopentanone. Removal of the diisopropylamine from the enolate prior to addition of the iodoester lowered the yield with 3-pentanone from 79% to 56%, while use of lithium diethylamide or lithium 2,2,6,6-tetramethylpiperidide in place of LDA had no effect upon the yield. Use of excess iodoester improved the yield somewhat, as shown in Table XIII for the case of 3-pentanone.

Finally, we contrasted <u>tert</u>-butyl iodoacetate with other α -haloacetates in the reaction with lithic cyclohexanone. The results, summarized in Table XIV, show that the reaction is not very sensitive to the nature of the halogen but is adversely affected by replacement of the tert-butyl group by an ethyl group.

Table XI. Reaction of Lithio Cyclohexanone with <u>tert</u>-Butyl Iodoacetate.

$$\overset{\text{OL1}}{\longrightarrow} + \text{ICH}_2\text{CO}_2\text{C(CH}_3)_3 \xrightarrow{1.M} \overset{\text{OL1}}{\longrightarrow} \text{CH}_2\text{CO}_2\text{C(CH}_3)_3$$

Conditions	Yield (%) ^a	
THF, $-78^{\circ}C \rightarrow 25^{\circ}C$	97	
THF, $0^{\circ}C \rightarrow 25^{\circ}C$	87	
DMF, 0°C → 25°C	28	
DMSO, 25°C	13	
THF, -78°C, 3 hours	100	

Table	XII.	Reaction	of	Ketone	Enolates	with	tert-Butyl
		Iodoaceta	te.	•			

$ \begin{array}{c} \text{OL1} \\ \text{R-C=C-+ ICH}_2\text{CO}_2\text{C(CH}_3)_3 \xrightarrow{\text{THF, 1.0 } \underline{M}} \\ \hline -78^{\circ}\text{C} \rightarrow 25^{\circ}\text{C} \xrightarrow{\text{R-C-C-CH}_2\text{CO}_2\text{C(CH}_3)_3} \end{array} $				
Ketone	Yield (%) ^a			
Cyclohexanone	97			
3-Pentanone	79			
Cyclopentanone	69			
2,4-Dimethy1-3-pentanone	100			
Acetophenone	40			

Table XIII. Reaction of Lithio 3-Pentanone with Various Ratios of <u>tert</u>-Butyl Iodoacetate.

$$\begin{array}{c} O \\ II \\ EtC=CHCH_3 + ICH_2CO_2C(CH_3)_3 \rightarrow CH_3CH_2CCH(CH_3)CH_2CO_2C(CH_3)_3 \end{array}$$

Ratio of Enolate: Iodoester	Yield (%) ^a
1:1	79
1:1-1/2	82
1:2	96

Table XIV. Reaction of Lithic Cyclohexanone with α -Halo-acetates.



Haloester	Yield (%) ^a	
ICH2CO2(CH3)3	97	
BrCH ₂ CO ₂ (CH ₃) ₃	91	
clcH ₂ co ₂ (CH ₃) ₃	87	
ICH2CO2C2H5	62	

Discussion

Tertiary α -iodoesters and tertiary α -bromoesters apparently do undergo substitution by ester enolates. The reaction appears to be extremely dependent on the nature of the halogen and seems to work best when the <u>alpha</u> carbon of the enolate has alkyl substituents. When lithio <u>tert</u>-butyl acetate is reacted with ethyl α -iodoisobutyrate, we observe <u>tert</u>-butyl acetate in the product mixture. The absence of ethyl isobutyrate suggests that the halogen does not exchange (Eq. 41), even though we cannot separate

$$CH_{2} = C \xrightarrow{OLi}_{O+} + I \xrightarrow{CH_{3}}_{CH_{3}} CO_{2}Et \xrightarrow{ICH_{2}CO_{2}+} + \sum_{CH_{3}}^{CH_{3}} OLi$$

$$(41)$$

and distinguish <u>tert</u>-butyl iodoacetate from ethyl α -iodoisobutyrate in the trace quantities in which it appears in the reaction. The absence of di-<u>tert</u>-butyl succinate and diethyl tetramethylsuccinate also suggests that the halogen does not exchange.

Brocksom states²² only that he "prefers to consider an SN_2 mechanism" and makes no further comment about the path of the reaction. While it is conceivable that the influence of the carbonyl group speeds up substitution relative to elimination, this does not explain why lithio

ethyl isobutyrate gives a higher yield than lithio <u>tert</u>butyl acetate when reacted with the same tertiary α -haloester. One would expect the more hindered enolate to be less nucleophilic and thus favor elimination over substitution. One could rationalize this problem by proposing that the more hindered enolate is less likely to lower the yield by condensation with the product.

Arnold²⁹ has recently observed that lithium ester enolates react with carbon tetrachloride and carbon tetrabromide to give the corresponding α -haloesters plus haloform (Eq. 42). Meyers had previously reported³⁰ that

$$\sum_{OR}^{OL1} + Cx_4 \xrightarrow{1)THF} x - C - CO_2R + HCX_3$$
(42)

ketones and sulfones react with CCl_4 -KOH-<u>tert</u>-BuOH to give α -chloro products or poly- α -chloro products or their derivatives. Meyers had also observed products derived from dichlorocarbene and thus proposed an electron-transfer mechanism shown in Scheme VI. A similar mechanism can be envisioned for the reaction of ester enolates with α -haloesters and is shown in Scheme VII.

$$c = c \operatorname{OLi}_{OR} + cx_{4} \rightarrow [c - co_{2}R + cx_{4}] \rightarrow$$

SCHEME VI

$$\sum_{OR} c = c \Big(\begin{array}{c} OLi \\ OR \end{array} + x - \begin{array}{c} -C - CO_2R \\ -C - CO_2R \end{array} + \left[x - \begin{array}{c} -C - CO_2R \\ -C - CO_2R \end{array} + \left[x - \begin{array}{c} -C - CO_2R \\ -C - CO_2R \end{array} + \left[x - \begin{array}{c} -C - CO_2R \\ -C - CO_2R \end{array} \right]^{-1} \Big)$$

SCHEME VII

Arnold observed substantial amounts of haloform but no products derived from dihalocarbene and thus proposes²⁹ that the trichloromethyl anion is stable under the reaction conditions: enolate, product, and diisopropylamine in THF solution at temperatures up to 25°C. We have observed that trichloromethyl anions decompose in THF solution even at -78°C. This suggests that we consider as an alternate possibility the formation of a different radical-radical anion pair (Scheme VIII).



SCHEME VIII

The equivalent pathway for enolate and α -haloester is shown in Scheme IX. While Scheme IX involves a more familiar radical anion, the ketyl; Scheme VI, involving electron transfer from the enolate, offers a more attractive explanation for the higher yields with <u>alpha</u>-branched enolates. Whatever the nature of the intermediate, an electron-transfer mechanism is attractive because of the marked difference in reactivity of the various halides and the fact that <u>alpha</u>-branched enolates give the best yield.



SCHEME IX

The reaction of ketone enolates with α -haloacetates shows relatively little dependence on the halogen, suggesting that perhaps a simple SN₂ mechanism is in operation. While Table XII shows that <u>alpha</u>-substituted enolates give better yields than acetophenone, one may rationalize that the more substituted enolates are more stable and thus reduce competing enolate decomposition. The more hindered enolate should also be less likely to reduce the yield by condensation with the product γ -ketoester.

Whatever the mechanism, the reaction is certainly sensitive to the nature of the alkoxy group on the iodoester. Brocksom suggests²² that the role of the <u>tert</u>butyl group is to stabilize the enolate and thus prevent competing enolate decomposition. In our case the <u>tert</u>-butyl iodoacetate is preformed and so no <u>tert</u>-butyl enolate is involved in the reaction. It seems reasonable to suggest that the <u>tert</u>-butyl group stabilizes the iodoester, however, and prevents its competing decomposition. It is evident from our preparation of iodoacetate that the <u>tert</u>-butyl group stabilizes the iodoester to heat and air and lessens its lachrymatory potency. Table XIII may be interpreted to suggest that decomposition of the iodoester independent of reaction with the enolate is a competing process.

On the other hand, the <u>tert</u>-butyl group may serve only to protect the ester function from attack by the enolate and Table XIII may only indicate that increasing the concentration of iodoester speeds up the desired reaction and thus reduces both competing enolate decomposition and competing condensation of enolate with the product.

In conclusion, we have demonstrated that, in principle, unsymmetrical succinates may be conveniently prepared from the corresponding esters without isolation of intermediates. We have shown that <u>tert</u>-butyl iodoacetate, unavailable from the corresponding ester enolate, may be prepared in good yield, and stored without apparent decomposition and that this iodoester reacts with ketone enolates to give the corresponding γ -ketoesters. Clearly, several directions for further research are indicated. The scope and limitation of the reactions of ester enolates with α -iodoesters

generated <u>in situ</u> have not been fully explored. The reactions of ketone enolates with α -haloesters other than acetate have not been studied. Finally, the most straight forward route to unsymmetrical 1,4-diketones would appear to be a substitution reaction between a ketone enolate and an α -haloketone, yet to our knowledge this has not been attempted with lithium ketone enolates prepared from ketones plus LDA.

Experimental

I. <u>Materials</u>

A. <u>General</u> - Diisopropylamine, <u>n</u>-butyllithium, solvents, and esters were prepared or obtained as described in Chapter II. Potassium hydride, Ventron Corp., was obtained as a 25-30% mineral oil dispersion and standardized by measuring H_2 evolved when a known volume was added to water. <u>tert</u>-Butyl bromoacetate and ethyl chloroacetate, Eastman, were stored over 5A molecular sieves and used without further purification. Ethyl iodoacetate was prepared by treating ethyl chloroacetate with NaI/ acetone by the method of Ashworth and Coller.²⁷ Monochloroacetic acid, Fisher, was converted to the acid chloride by treatment with two equivalents of benzoyl chloride by the method of H. C. Brown³⁷ and distilled at 105-107°C. <u>tert</u>-Butyl alcohol was stirred overnight

over CaO before use. Dimethylaniline was freshly distilled before use.

B. <u>Preparation of tert-Butyl Chloroacetate³⁸ -</u>

A 300 ml round-bottomed flask equipped with a magnetic stirrer and a dropping funnel protected by a drying tube was charged with 50.5 ml (400 mmole) N,N-dimethylaniline and 45.4 g (400 mmole) monochloroacetyl chloride and cooled to 0°C. <u>tert</u>-Butyl alcohol (37.5 ml, 400 mmole) was added dropwise over the period of one hour while the temperature was maintained between 10°C and 20°C. The reaction was then placed in an ice water bath and allowed to stir overnight while the bath warmed to 25°C. The reaction was treated with 100 ml H₂O. The layers are separated and the aqueous phase extracted with 3 x 40 ml diethyl ether. The combined organic phase was washed three times with 2 <u>N</u> HCl then with saturated NaHCO₃. The ether was evaporated and the residue distilled at 56-9°C at 13 mm to provide 23.6 g (63%) product.

C. <u>Preparation of tert-Butyl Iodoacetate²⁷</u> -A 500 ml round-bottomed flask equipped with septum inlet, magnetic and mercury bubbler was flushed with argon and charged with 300 ml acetone. Argon was bubbled through the acetone with a gas dispersion tube for 20 minutes to remove all traces of dissolved oxygen. Sodium iodide (45 g, 300 mmole) was added through a powder funnel and the mixture stirred until the NaI dissolved. <u>tert</u>-Butyl chloroacetate (32.5 g, 272 mmole) was added and the reaction stirred at 25°C under argon for 24 hours. 100 ml H₂O, degassed with argon in the same manner as the acetone, was added. The solution was extracted with degassed diethyl ether, washed with saturated $Na_2S_2O_3$ solution to remove any I₂, and dried with degassed MgSO₄. The ethereal solution was filtered through Celite under argon in a Schlenk funnel. Evaporation of the ether and distillation at 53°C at 2 mm provided 54.6 g (83%) product.

II. Preparation of Ester Enolate Solutions

Lithium ester enolates were prepared by the same procedure described in Chapter II. Cobalt (II) and copper (I) enolates were prepared by the reaction of $CoBr_2$ and Cu_2I_2 , respectively, with the lithium enolate.²³ The preparation of the copper (I) enolate of <u>tert</u>-butyl acetate is representative: A 1.0 <u>M</u> THF solution of lithio <u>tert</u>-butyl acetate (5.0 mmole) was prepared at -78°C as previously described. Cu_2I_2 (0.95 g, 2.5 mmole) was added through a powder funnel. The cooling bath was removed and the reaction allowed to warm until the Cu_2I_2 dissolved and an intense purple solution formed. The cooling bath was replaced and the reaction re-cooled to -78°C. The color remained and Cu_2I_2 did not precipitate, providing a 1.0 <u>M</u>

THF solution of the copper (I) enolate of <u>tert</u>-butyl acetate.

III. Reaction of Ester Enclates with α -Haloesters

A. Reaction of Lithio Ethyl Isobutyrate with tert-

Butyl Bromoacetate - The following procedure is representative of the reaction of ester enolates with preformed α -haloesters: A 1.0 <u>M</u> THF solution of lithio ethyl isobutyrate (5.0 mmole) was prepared at -78°C as previously described. <u>tert</u>-Butyl bromoacetate (0.73 ml, 5.0 mmole) was added. The reaction was stirred for 5 minutes at -78°C, then allowed to reach 25°C over the period of 1.25 hours. <u>n</u>-C₁₅H₃₂ (1.38 ml. 5.0 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C, treated with 3.3 ml 3 <u>N</u> HCl, and extracted with pentane. The organic phase was dried over K₂CO₃ and analyzed by GLC (column temperature: 100°C for 4 minutes, 150°C for 2 minutes, 175°C for 5 minutes, then 240°C). 2,2-Dimethylsuccinic acid 1-ethyl ester 2-<u>tert</u>-butyl ester was observed in 80% yield.

B. <u>Reaction of Lithio tert-Butyl Acetate with</u> <u>Ethyl α-Iodoisobutyrate Formed in situ from I</u>₂

and Lithio Ethyl Isobutyrate - The following procedure is representative of the reaction of an ester enolate with an α -haloester formed <u>in situ</u> from the

corresponding ester enclate and molecular halogen: A 50 ml round-bottomed flask equipped with septum inlet, magnetic stirrer and mercury bubbler was flushed with argon, charged with 1.27 g (5.0 mmole) I₂ dissolved in 5 ml THF, and cooled to -78° C in a Dry Ice/acetone bath. A 1.0 M THF solution of lithic ethyl isobutyrate (5.0 mmole), prepared as previously described, was added dropwise through a Teflon tube. The iodine color was observed to disappear as the enclate solution was added. The reaction was stirred for 15 minutes at -78° C, then a 1.0 <u>M</u> THF solution of lithio tert-butyl acetate, prepared as previously described, was added dropwise through a Teflon tube. The reaction was stirred for 5 minutes at -78°C then allowed to warm to 25°C over 1.25 hours. $\underline{n}-C_{15}H_{32}$ (1.32 ml, 5.0 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C and worked up as described in the preceding procedure. GLC analysis showed 64% 2,2-dimethylsuccinic acid 1-ethyl-2-tert-butyl ester.

C. <u>Product Analysis</u> - Products were analyzed by GLC, NMR, and MS as described in Chapter II.

2,2-Dimethylsuccinic acid 1-ethyl-2-tert-butyl ester ¹H NMR (CCl₄): δ1.20 (s,6H); δ1.21 (t,3H); δ1.37 (s,9H); δ2.35 (s,2H); δ4.00 (q,2H) MS: m/e 230 (M⁺)

IV. Reaction of Ketone Enclates with α -Haloketones

A. Reaction of Potassium Ketone Enolates with

a-Haloacetates - The procedure for cyclohexanone and tert-butyl iodoacetate is representative: A 50 ml round-bottomed flask equipped with a septum inlet, magnetic stirrer and mercury bubbler was flushed with argon, immersed in an ice water bath and charged with 5 ml THF and 1 ml (5.0 mmole) KH-mineral oil suspension. Stirring was initiated and 0.52 ml (5.0 mmole) cyclohexanone was added dropwise. The reaction was stirred for 15 minutes at 0°C, then 0.774 ml (5.0 mmole) tert-butyl iodoacetate was added. The reaction was stirred at 0°C for 10 additional minutes then allowed to warm to 25°C over the period of one hour. $\underline{n}-C_{16}H_{34}$ (1.46 ml, 5.0 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C, treated with 3.3 ml 3 N HCl and extracted with pentane. The organic phase was dried over K_2CO_3 and analyzed by GLC (column temperature: 100°C for 3 minutes, then 175°C). tert-Butyl 2-oxocyclohexylacetate was observed in 34% yield.

B. Reaction of Lithium Ketone Enolates with

 α -Haloacetates - The reaction of lithio 3pentanone with <u>tert</u>-butyl iodoacetate is representative: A 1.0 <u>M</u> THF solution of lithio 3-pentanone (5.0 mmole) was prepared as described in Chapter III and cooled to

-78°C. <u>tert</u>-Butyl iodoacetate (0.774 ml, 5.0 mmole) was added. The reaction was stirred at -78°C for 5 minutes then allowed to warm to 25°C over 1.25 hours. <u>n</u>-C₁₅H₃₂ (1.38 ml, 5.0 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C, treated with 3.3 ml 3 <u>N</u> HCl, and extracted with pentane. The organic layer was dried over K_2CO_3 and analyzed by GLC (column temperature: 100°C for 4 minutes, 150°C for 5 minutes, then 175°C). <u>tert</u>-Butyl 3-methyl-4-oxohexanoate was observed in 73% yield.

C. <u>Reaction of Lithium Ketone Enolates with</u>

 α -Haloacetates in Solvents Other Than THF -

The reaction of lithio cyclohexanone with <u>tert</u>-butyl iodoacetate in DMF is representative: Lithio cyclohexanone (5.0 mmole) was prepared from LDA in <u>n</u>-pentane and isolated as a white powder as described in Chapter III. The enolate was dissolved in 5 ml DMF. The reaction was cooled to 0°C and 0.774 ml (5.0 mmole) <u>tert</u>-butyl iodoacetate was added. The reaction was stirred at 0°C for 10 minutes then allowed to warm to 25°C. <u>n</u>-C₁₆H₃₄ (1.46 ml, 5.0 mmole) was added as an internal GLC standard. The reaction was cooled to 0°C and worked up and analyzed as previously described. <u>tert</u>-Butyl 2-oxocyclohexylacetate was observed in 29% yield.

D. <u>Product Analysis</u> - Products were analyzed by GLC, NMR, and MS as described in Chapter II.

tert-Butyl 2-oxocyclohexylacetate¹⁸

¹H NMR (CCl₄): δ1.4 (s,9H); δ1.6-2.8 (m,11H) MS: m/e 212 (M⁺)

tert-Butyl 3-methyl-4-oxohexanoate

¹H NMR (CCl₄): δ1.0 (t,3H); δ1.1 (d,3H); δ1.4 (s,9H); δ2.0-3.0 (m,4H) MS: m/e 200 (M⁺)

<u>tert-Butyl 2-oxocyclopentylacetate</u> (GLC column temp. 200°C) ¹H NMR (CCl₄): δ1.4 (s,9H); δ1.6-2.6 (m,9H) MS: m/e 198 (M⁺)

tert-Butyl 3,3,5-trimethyl-4-oxohexanoate (GLC column
temp. 165°C)

¹H NMR (CCl₄): δ1.05 (d,6H); δ1.20 (s,6H); δ1.40 (s,9H); δ2.35 (s,2H); δ3.0 (septet, 1H) MS: m/e 240 (M⁺) tert-Butyl 4-phenyl-4-oxobutanoate

GLC column temp: 100°C for 3 minutes, then 175°C ¹H NMR (CCl₄): δ1.4 (s,9H); δ2.5 (t,2H); δ3.1 (t,2H); δ7.3 (m,3H); δ7.8 (m,2H) MS: m/e 234 (M⁺) BIBLIOGRAPHY

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