THE REACTIONS OF ESTER ENOLATES

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
DONALD F. SULLIVAN
1974

This is to certify that the

thesis entitled

THE REACTIONS OF ESTER ENOLATES

presented by

Donald F. Sullivan

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Michael W. Rathke
Major professor

Date August 2, 1974

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ABSTRACT

THE REACTIONS OF ESTER ENOLATES

by

Donald F. Sullivan

Lithium dialkyl amide bases can be used to prepare stable solutions of lithium ester enolates in THF at -78°. The enolate solutions react at -78° with carbonyl compounds to produce, after hydrolysis, β-hydroxyesters in good yield. Only ethyl isovalerate failed to give high yields of β-hydroxyesters by this procedure.

This procedure for generating ester enolates was extended to α,β-unsaturated esters. Stable solutions of α,β-unsaturated ester enolates can be generated in THF-HMPA at -78°. Hydrolysis of these solutions produces the β,γ-unsaturated isomers of the starting esters. These ester enolates also react with alkylating reagents and carbonyl compounds exclusively at the α carbon.

Silylation of ester enolates produces α-silylated esters and/or trialkylsilyl ketene acetals. The course of the reaction is dependent on the structure of the enolate. The synthetic utility of these two products is investigated in a number of reactions.

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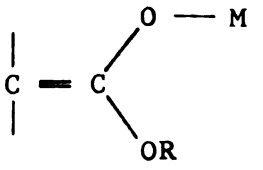
Spectral evidence in support of an oxygen-metalated enolate, $\underset{\sim}{I}$, as the preferred structure for an ester enolate, is presented. Kinetic and synthetic data are also given as evidence for the existence of ketene intermediates in the decomposition of ester enolates.



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THE REACTIONS OF ESTER ENOLATES

By

Donald F. Sullivan

A THESIS

Submitted to

Michigan State University

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To

Linda

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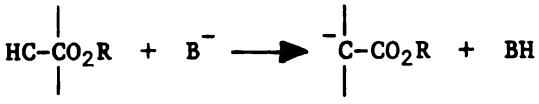
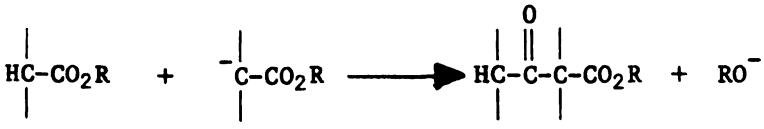
CHAPTER I

THE REACTIONS OF ESTER ENOLATES WITH CARBONYL COMPOUNDS

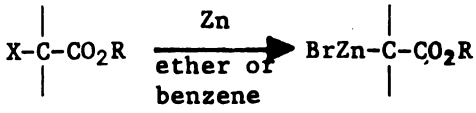
INTRODUCTION

Although ketone and aldehyde enolates have been used extensively in organic synthesis (1), the chemistry of ester enolates is a relatively new and little-studied field. While solutions containing equilibrium concentrations of aldehyde or ketone enolates are synthetically useful, equilibrium solutions of ester enolates undergo rapid, irreversable condensations to form β-keto esters (i.e. Claisen condensation) (2).



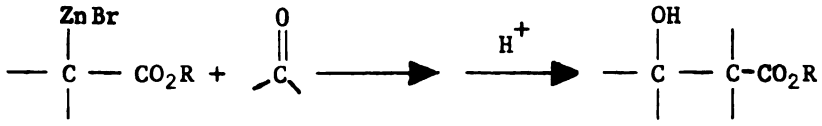


In the past, if ester enolates were to be used in other than Claisen reactions, they were generated from zinc metal and the corresponding α-haloester (Reformatsky reaction) (3).



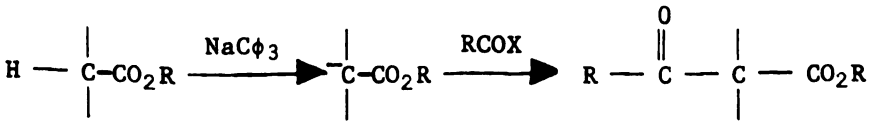
Due to the instability of zinc enolates at the temperatures required for their generation, further reactions using the ester enolates are limited to those reagents which can be present in the reaction mixture

from the beginning. The Reformatsky reaction, though widely used, is subject to a host of side reactions and the yields of β-hydroxyester formed from the reaction of the enolate with carbonyl compound are often low. Finally,



the generality of the reaction is limited by the availability of the appropriate α-haloester.

Direct proton removal from an ester provides a more convenient and general preparation of ester enolates. Such proton removal requires a strong (pKa of an ester ≅ 24) (4), organic-soluble base. Early attempts (5) to generate ester enolates utilized sodium triphenylmethane as base. The enolates were then reacted with acid halides to obtain β-keto esters.

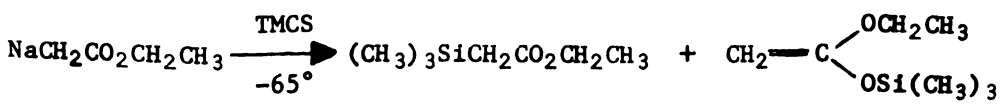


Hauser later developed (6) an alternative procedure by which enolates of t-butyl esters were generated in liquid ammonia using lithium amide as base. The enolates were relatively stable at the temperature employed (-37°); however, the sequence had to be completed as rapidly as possible to avoid appreciable self-condensation. A major disadvan-

tage of this method is the use of liquid ammonia as solvent, since this precludes the subsequent use of many reagents such as acid chlorides or the more reactive alkyl halides.

Dialkyl amide bases are strong (pKa of the amine > 34) (7), soluble, non-nucleophilic bases capable of generating ester enolates quantitatively at dry-ice temperatures. At -78°, the enolates are indefinitely stable.

Sodium bis(trimethylsilyl)amide was the first amide used to generate an ester enolate (8). Formed at -65° in ether, sodio ethyl acetate, upon reaction with trimethylchlorosilane (TMCS), produced a mixture of ethyl trimethylsilylacetate (22.3%) and O-trimethylsilyl-O-ethyl ketene acetal (13.7%).



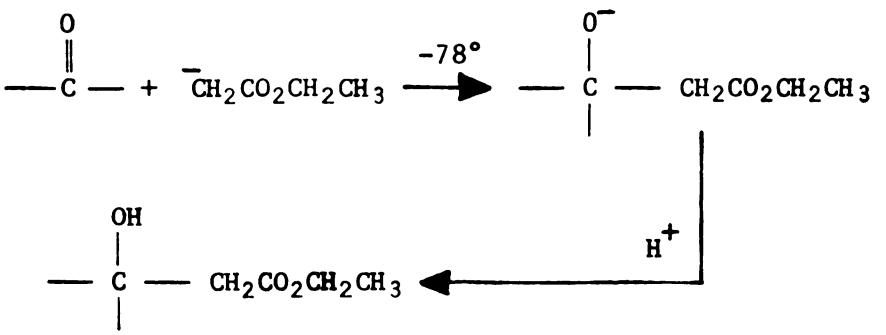
(22.3%) (13.7%)

Lithium bis(trimethylsilyl)amide, formed in hexane by reaction of the amine with a commercial butyllithium solution, generated the ester enolate of ethyl acetate quantitatively at -78° in THF (9).

$$[(CH_3)_3Si]_2NH \xrightarrow[\text{hexane}]{\text{BuLi}} [(CH_3)_3Si]_2NLi + \text{butane}$$

$$[(CH_3)_3Si]_2NLi + CH_3CO_2CH_2CH_3 \xrightarrow[\text{THF}]{-78^\circ} \overset{\text{Li}}{\underset{|}{C}}H_2CO_2CH_2CH_3 + [(CH_3)_3Si]_2NH$$

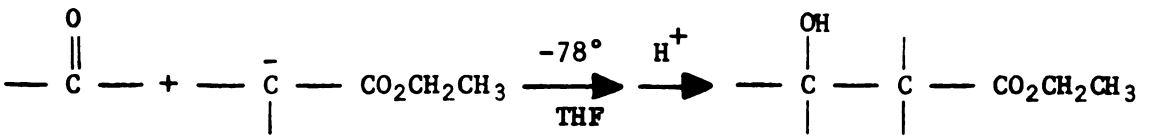
This lithium enolate reacted readily with aldehydes and ketones at -78° to produce, after addition of acid, β-hydroxyesters in excellent yield.



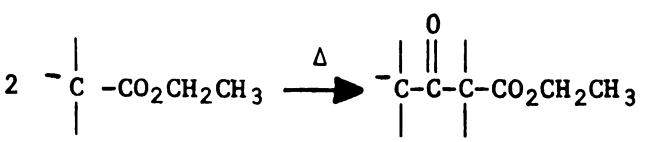
Attempts to extend this procedure to the preparation of other ester enolates proved unsuccessful. For example, addition of ethyl hexanoate to a solution of lithium bis(trimethylsilyl)amide at -78° resulted in a slow condensation of the ester, which was complete in one hour. Subsequently, it was discovered (10) that the base lithium isopropylcyclohexylamide (LiICA) was capable of generating a variety of stable ester enolates at -78°. No self-condensation products were observed at -78° and the lithium ester enolate solutions, thus produced, can be used as discrete synthetic intermediates. Consequently, a study of the addition reaction between these ester enolates and carbonyl-containing compounds was undertaken.

RESULTS

Reaction of the lithium enolates of ethyl acetate, ethyl butyrate, and ethyl isobutyrate with various carbonyl compounds proceeded smoothly at -78° in THF to produce the corresponding β-hydroxyesters in reasonably high yields. (Table I).



The enolates themselves were produced in quantitative yield at -78° by treatment of the corresponding ester with lithium isopropylcyclohexylamide in THF. These enolates were stable indefinitely at -78°, decomposing principally to β-keto esters on warming to room temperature.



The LiICA was generated by addition of N-isopropylcyclohexylamine to a butyllithium-hexane solution at 0°. The reaction was complete within 5 minutes.

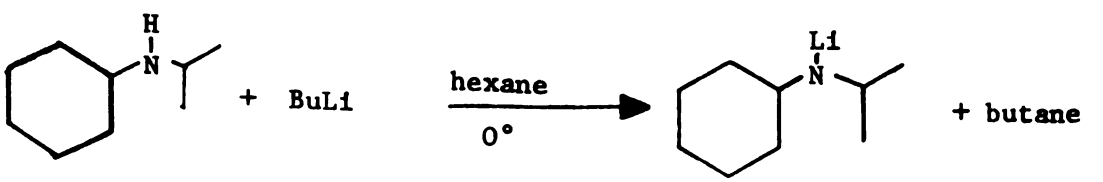
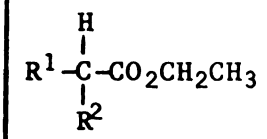
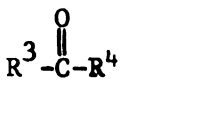
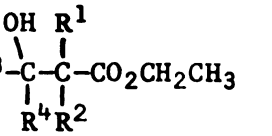


TABLE I

Yields of β-Hydroxyester Using Lithium Ester Enolates

Ester	Substrate	Yield of Hydroxy Ester[c]
		
$R^1=R^2=H$	$R^3,R^4=(CH_2)_4$	65%[a]
$R^1=R^2=CH_3$	$R^3,R^4=(CH_2)_5$	81%[b]
$R^1=R^2=CH_3$	$R^3=H,R^4=CH_2CH_3$	75%[a]
$R^1=R^2=CH_3$	$R^3,R^4=(CH_2)_4$	75%[b]
$R^1=H$ $R^2=CH_2CH_3$	$R^3,R^4=(CH_2)_5$	76%[a]
$R^1=H$ $R^2=CH_2CH_3$	$R^3,R^4=(CH_2)_4$	75%[a]
$R^1=R^2=CH_3$	$R^3=H,R^4=\phi$	66%[b]

a ≡ glpc yield

b ≡ isolated yield

c ≡ all compounds had spectral and physical data consistent with their assigned structures

Removal of the hexane and addition of THF gave a solution of the amide. This solution was cooled to -78° and the ester was added dropwise. Quenched samples of these solutions showed quantitative recovery of the starting esters. (Table II).

For the preparation of the β-hydroxyesters, an ester enolate was generated at -78° and after stirring for 15 minutes the carbonyl compound was added slowly over a period of one minute. After five more minutes the solution was quenched and worked-up with ether or pentane. Table I lists some representative yields for this procedure.

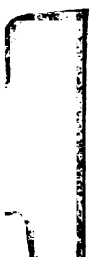
Under these conditions only ethyl isovalerate failed to yield pure products. Reaction of the lithium enolate of ethyl isovalerate with acetone, diethyl ketone, propionaldehyde, and cyclohexanone invariably yielded an additional product. In the case of diethyl ketone an extensive effort was made to ascertain the structure of this side product without success. It was found, however, that the unknown side product could be removed by allowing the reaction mixture (enolate plus ketone) to warm to room temperature for approximately one half hour prior to quenching. This modification, while improving the purity of the crude reaction mixture, drastically reduced the yield of the desired β-hydroxyester. In the case of diethyl ketone, only 41% of the ethyl 3-ethyl-3-hydroxy-2-isopropylpentanoate was obtained under these new conditions.

TABLE II

Results of Quenching Ester Enolate Solutions at -78°

Ester	Recovered ester, %[a]
Ethyl propionate	90
Ethyl hexanoate	100
tert-Butyl hexanoate	97
Ethyl nonanoate	100
Ethyl isobutyrate	97
Ethyl isovalerate	97
Ethyl cyclohexanecarboxylate	95
Ethyl phenylacetate	98

[a]Determined by glpc analysis of aliquots quenched with water.



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DISCUSSION

The use of ester enolates to make β-hydroxyesters from aldehydes and ketones provides a convenient alternative to the Reformatsky reaction. The reaction time was much shorter, the reaction conditions were less vigorous, the yields exceeded, or were comparable to, those obtained using the zinc enolates, (Table III), and the α-halo derivatives of the esters were not required. In most cases, the crude β-hydroxyester, after routine work-up, was pure enough to use in further synthetic applications.

As noted in Tables I and III, excellent yields of the β-hydroxyesters were obtained from a variety of esters and carbonyl substrates. Only ethyl isovalerate failed to react as expected.

The lithium enolate of ethyl isovalerate is formed at -78° and is stable indefinitely at this temperature. The enolate reacts with benzaldehyde to yield the corresponding β-hydroxyester quantitatively. However, reaction of the enolate with aldehydes or ketones having α protons invariably yields a side product.

Ethyl 2-bromoisovalerate behaves similarly when used in the Reformatsky reaction. With the exception of acetone, yields are reported in the literature only when the carbonyl compound has no enolizable protons (Table IV).

The increased steric requirements of the enolate of ethyl isovalerate apparently result in some side reaction, possibly involving enoliza-

TABLE III

Comparison of Yields of β-Hydroxyesters Obtained via Reformatsky Reaction and Using Lithium Ester Enolate

Ester	Carbonyl	β-Hydroxyester		Reference
		Yield via Reformatsky[a]	Yield via Lithium Enolate	
Ethyl isobutyrate	cyclohexanone	50%	81%	Wallach, Ann. 360, 26 (1908).
Ethyl butyrate	cyclohexanone	68%	76%	Wallach, ibid.
Ethyl butyrate	cyclopentanone	44%	75%	Macllard, et. al., Bull. Soc. Chem. Fr., 1958, 244.
Ethyl isobutyrate	propionaldehyde	24%	75%	Reformatsky, J. Prakt. Chem., 54, 469, 477 (1896).
Ethyl isobutyrate	benzaldehyde	78%	66%	Dain, J. Russ. Phys. Chem. Soc., 28, 283 (1896).

[a]From 2-bromoester, Zn + carbonyl

Yield

Carbony
Acetald
Isovale
Benzald
Acetone

TABLE IV

Yields of β-Hydroxyester Formed from Ethyl α-Bromoisovalerate, Zinc, and Carbonyl Compound

Carbonyl Compound	Yield of Hydroxyester	Reference
Acetaldehyde	None Reported	Maturewitsch, J. Russ. Phys. Chem. Soc., 41, 1319 (1909).
Isovaleraldehyde	None Reported	Reformatsky, ibid., 33, 242 (1901).
Benzaldehyde	60%	Reformatsky, J. Prakt. Chem., 54, 469, 477 (1896).
Acetone	50%	ibid.

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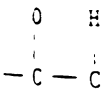

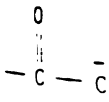

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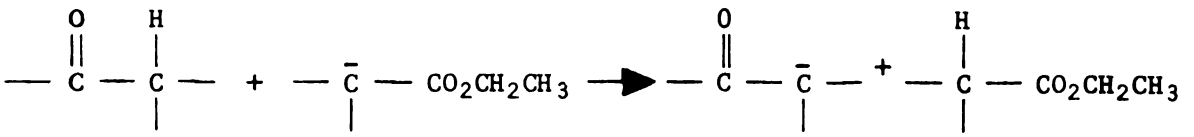
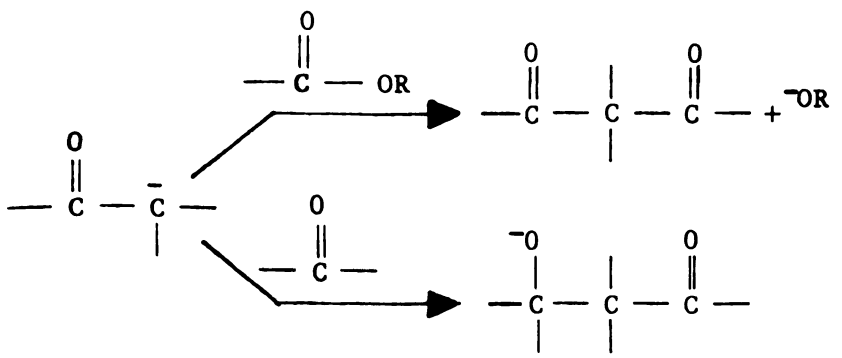




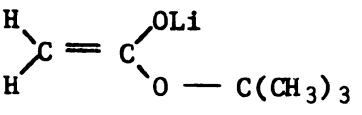
Since no difficulty was encountered with ethyl isobutyrate, these results are probably due to an increase in branching remote from the α carbon in the ester, rather than increased substitution on the α carbon itself. Such behavior has precedent in the literature.

The primary Grignard reagent, neopentyl magnesium bromide, added to diisopropyl ketone only to the extent of 4%. Ninety percent of the Grignard reagent was consumed enolizing the ketone. Under the same conditions, the secondary Grignard reagent, diisopropyl magnesium bromide enolized 29% of the diisopropyl ketone. (11).

When ethyl 2-bromopropionate was treated with zinc in the presence of 1-keto-2-phenyl-1,2,3,4-tetrahydronaphthalene, 27% of the ketone was enolized and recovered unchanged after hydrolysis, and thirty-eight percent of the corresponding β-hydroxy acid was obtained. If ethyl α-bromobutyrate was used in place of the ethyl β-bromopropionate, the amount of enolization was increased to 48% and only 28% of the β-hydroxyester was formed.

An examination of the probable transition state involved in the reaction of the lithium enolates with carbonyl compounds explains the effect of remote branching in the enolate on the course of the reaction.

The structure of lithio t-butyl acetate in THF and benzene has been determined to be I, rather than II. (13).



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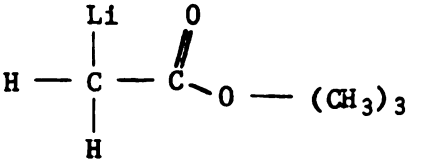


II

A complexation of reactants prior to reaction may favor a six-membered ring transition state leading to the β-oxido esters obtained. (Figure 1).

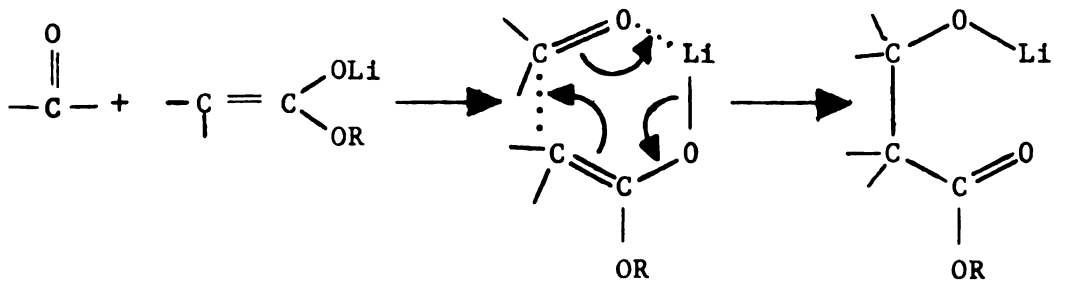


Figure 1. Reaction of Ester Enolate and Carbonyl Compound

The sterochemistry of this transition state suggests that there may be a substantial difference in the relative energies of the transition states of different enolates, as β-substitution in the enolate (Figure 2) is increased (i.e. as the size of R,R' increases).

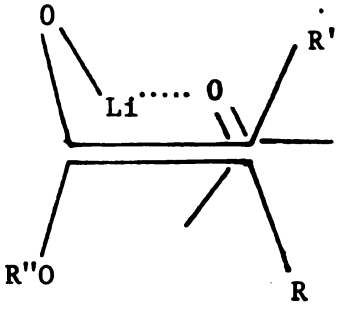
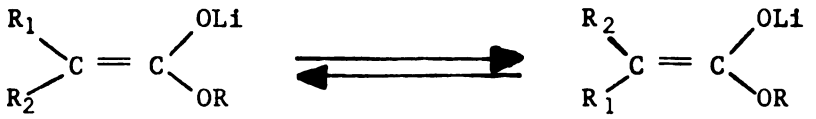


Figure 2. Stereochemistry of Transition State in Reaction of Ester Enolate and Carbonyl Compound

Before a more quantitative description can be obtained, the preferred configuration of the enolate must be established, and the rate at which the two possible configurations interconvert under the reaction conditions must be determined.



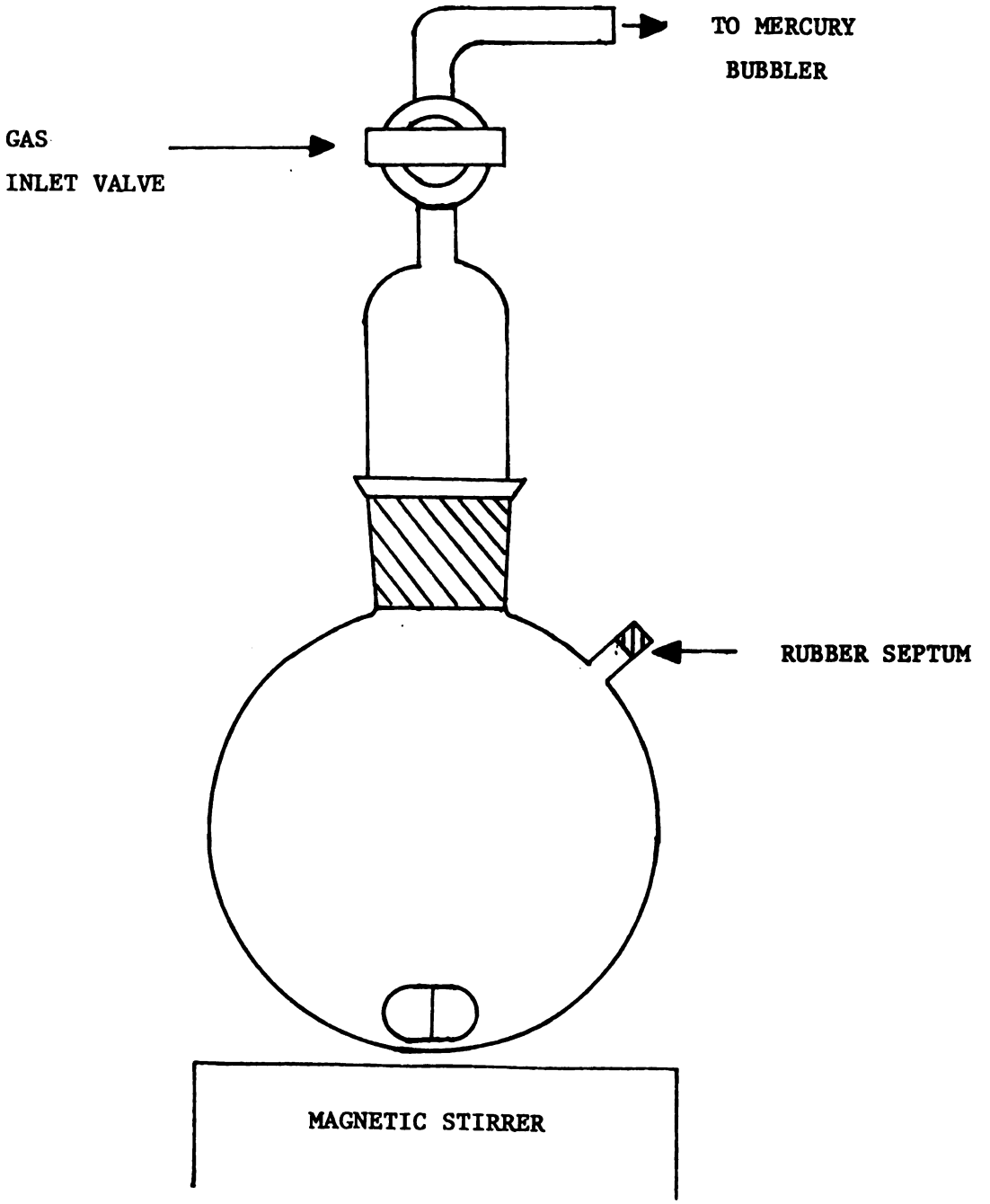


Figure 3. Reaction Apparatus

EXPERIMENTAL

I. Materials

Esters

All esters were commercially available and were used without further purification.

Carbonyls

All ketones and aldehydes were commercially available and used without further purification.

II. Preparation of Ester Enolates and their Reaction with Ketones and Aldehydes

The ester enolates were prepared and reacted in a manner similar to that described for ethyl acetate. All analyses were performed using a ¼ inch by 6 foot SE-30 column with appropriate internal standards.

A. Preparation of Lithio Ethyl Acetate

A 50 ml flask equipped as in Figure 3 was flame dried under nitrogen. To this flask was added 2.38 ml (5.25 mmoles) of a 2.2 M commercial solution of butyllithium in hexane. The flask was cooled in an ice bath and 0.89 ml (5.25 mmoles) of N-isopropylcyclohexylamine was added dropwise with stirring. When the evolution of butane was complete, a vacuum was applied until the hexane removal was complete. The flask was flushed with nitrogen and 5 ml of tetrahydrofuran was

added. After dissolution of the oily residue of lithium N-isopropylcyclohexylamide was complete, the flask was cooled in a dry ice-acetone bath. The ethyl acetate (0.495 ml; 5.0 mmoles) was added dropwise and after 15 minutes quenched with 5 ml of a 2 M solution of HCl. The mixture was warmed to room temperature and extracted with pentane. Recovery of the ethyl acetate was essentially quantitative.

B. Reaction of Ester Enolates with Carbonyl Compounds

The preparation of the enolate was as described above. After 15 minutes at -78°, the carbonyl compound was added dropwise. After an additional 15 minutes, the solution was quenched at -78°, as above, and extracted with pentane. The organic layers were collected, dried over K_2CO_3 and examined by glpc.

C. Modified Procedure with Lithio Ethyl Isovalerate

The procedure as described for diethyl ketone is representative. The enolate of ethyl isovalerate (5.0 mmoles) was prepared, as above. The ketone (0.52 ml; 5.0 mmoles) was added slowly and, after 15 minutes at -78°, the solution was placed in an ice bath. After 30 minutes, the solution was quenched with 2 M HCl and worked-up as described. The glpc yield of ethyl 2-isopropyl-3-ethyl-3-hydroxypenanoate was 41%.

Product Analysis

The hydroxyesters synthesized were examined by NMR and/or their

physical constants compared with published values.

Ethyl 2-(1-hydroxycyclopentyl)acetate

NMR(CCl_4): 4.1δ (q,2H), 3.1δ (5,1H), 2.2δ (s,2H), 1.5δ (broad s, 8H), 1.3δ (t,3H).

Ethyl 2-(1-hydroxycyclohexyl)-2-methylpropanoate

B.p. 126-128°/11 mm. Refractive index $n_D^{23°}$ 1.4637. NMR(CCl_4): 4.1δ (q,2H), 3.15δ (s,1H), 1.3δ (m,19H).

Ethyl 2,2-dimethyl-3-hydroxypentanoate

Refractive index $n_D^{22.5°}$ 1.4411. NMR(CCl_4): 4.1δ (q,2H), 3.5δ (m,1H), 3.4δ (s,1H), 1.1δ (m,14H).

Ethyl 2,2-dimethyl-3-phenyl-3-hydroxypropanoate

B.p. 115°/0.05 mm. Refractive index $n_D^{23°}$ 1.5075. NMR(CCl_4): 7.5δ (s,5H), 5.0δ (s,1H), 4.3δ (q,2H), 3.85δ (s,1H), 1.5δ (t,3H) 1.3δ (d,6H).

Ethyl 2-(1-hydroxycyclopentyl)-2-methylpropanoate

Refractive index $n_D^{22.5°}$ 1.4593. NMR(CCl_4): 4.1δ (q,2H), 3.0δ (s,1H), 1.6δ (broad s,8H), 1.1δ (m,9H)

Ethyl-2-(1-hydroxycyclohexyl)butanoate

Refractive index $n_D^{23.5°}$ 1.4616. NMR(CCl_4): 4.1δ (q,2H), 2.65δ (s,1H), 2.1δ (t,1H), 1.4δ (m, 18H).

Ethyl 2-(1-hydroxycyclopentyl)butanoate

B.p. 70°/0.02 mm. Refractive index $n_D^{23.5°}$ 1.4540. NMR(CCl_4): 4.1δ (q,2H), 2.65δ (s,1H), 1.50δ (m,11H), 1.1δ (t,3H), 0.98δ (t,3H).

Ethyl 3-ethyl-3-hydroxy-2-isopropylpentanoate

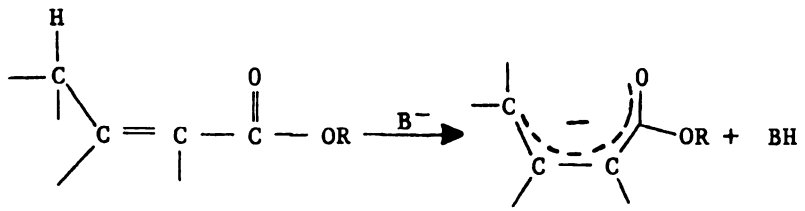
Refractive index $n_D^{23.5°}$ 1.4412. NMR(CCl_4): 4.15δ (q,2H), 3.15δ (s,1H), 2.3δ (m,1H), 1.1δ (m,20H).

CHAPTER II

THE PREPARATION AND REACTIONS OF α,β-UNSATURATED ESTER ENOLATES

INTRODUCTION

Since Bauer's initial observations (15, 16) it has been well established that enolate anions derived from α,β-unsaturated ketones react predominantly at the alpha carbon. In contrast, almost nothing is known about the chemistry of enolate anions derived from α,β-unsaturated ester derivatives of carboxylic acids.

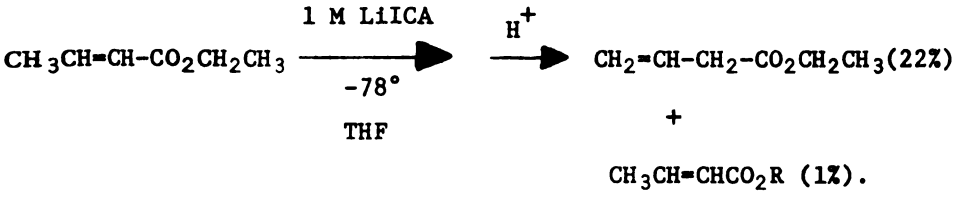


Early investigations into the chemistry of the α,β-unsaturated ester system involved attempts to isomerize the double bond to the β,γ-position. (17). Except in cases involving unusual steric or electronic requirements, poor yields of the β,γ-unsaturated material were obtained. As a result, more elaborate synthetic methods have been developed to prepare these compounds; (18, 19) however, none involve generation of enolate anions of the α,β-unsaturated esters.

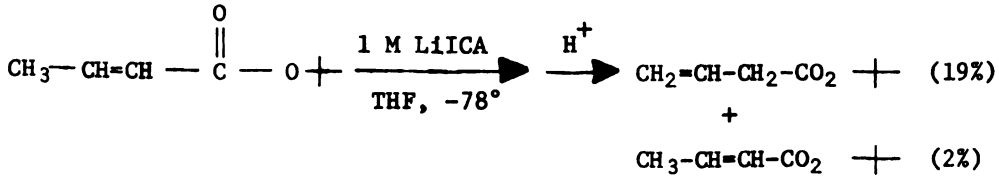
Although methods now exist for generating metal enolates of α,β-unsaturated esters, they are not as general or as convenient as the formation of simple lithium ester enolates from a lithium dialkyl amide and the corresponding ester. With this in mind, we attempted to develop a parallel procedure which would provide a convenient synthetic source of the lithium enolate anions of α,β-unsaturated esters.

RESULTS

Treatment of a 1 M solution of lithium isopropylcyclohexylamide (LiICA) in THF at -78° with ethyl crotonate, followed by quenching with dilute HCl, yielded two products, the starting ester and its β,γ-unsaturated isomer in yields of 1 and 22% respectively.



The total recovery of material and the relative product ratio was only slightly affected by replacing ethyl crotonate with its t-butyl analog or by prolonged reaction times with LiICA at -78°.



When hexamethylphosphoramide (HMPA), dimethylsulfoxide (DMSO) or bis(2-methoxy)diethyl ether (diglyme) were used as co-solvents, the total yield and product ratio changed. (Table V).

Replacing LiICA as the amide base with lithio-2,2,6,6-tetramethyl-

TABLE V

Results of Quenching the Enolate of Ethyl Crotonate

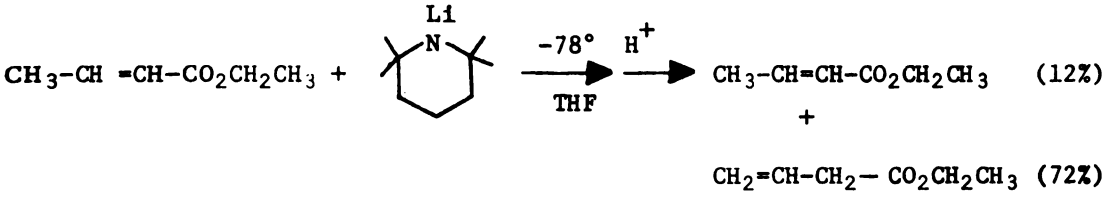
Solvent	Base	Ester[a] Concentration	%α,β	%β,γ
THF	LiICA[b]	1.0 M	1	22
THF	LiTMP[c]	1.0 M	12	72
THF-HMPA (20% by vol.)	LiICA	1.0 M	9	55
THF-HMPA (40% by vol.)	LiICA	1.0 M	14	39
THF-DMSO (20% by vol.)	LiICA	1.0 M	9	21
THF-Diglyme (20% by vol.)	LiICA	1.0 M	13	27
THF	LiICA	0.5 M	3	31
THF-HMPA (20% by vol.)	LiICA	0.5 M	13	87

[a]Ethyl crotonate was used throughout as the ester substrate

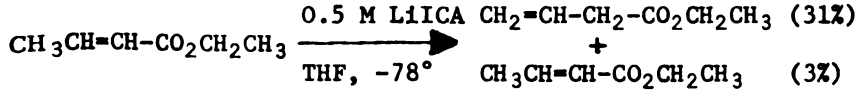
[b]Lithium N-isopropylcyclohexyl amide

[c]Lithium 2,2,66,-tetramethylpiperidine

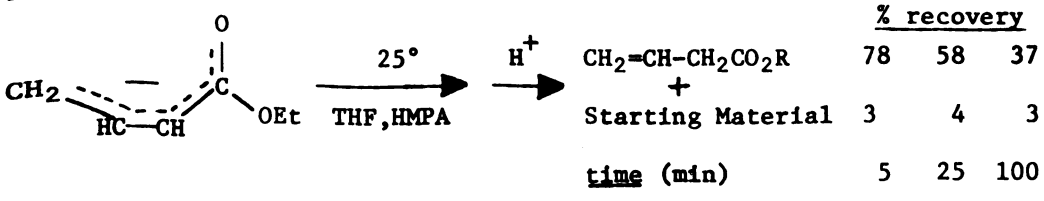
piperidine resulted in an 84% total product recovery (72% non-conjugated ester and 12% starting material):



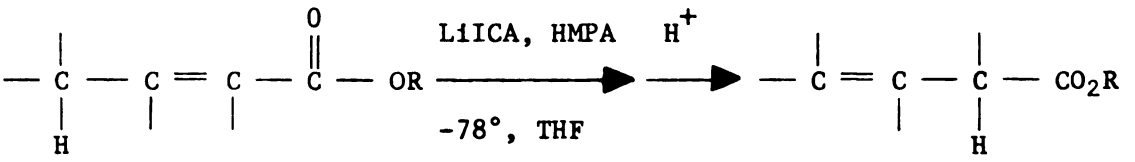
The yield of recovered material was also dependent on concentration. Treatment of a 0.5 M solution of LiICA in THF, with an equivalent amount of ethyl crotonate gave, after quenching, 31% of the non-conjugated material and 3% starting ester.



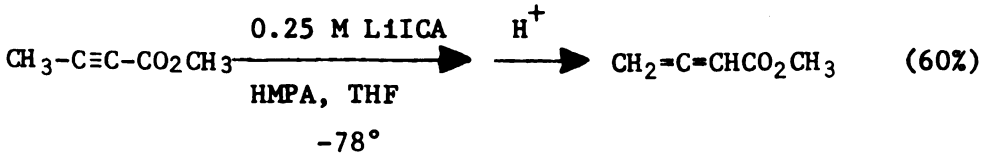
Finally, when a 0.5 M solution of LiICA was used with 20% (by volume) added HMPA, a quantitative yield of the non-conjugated and conjugated products was obtained in a ratio of 87:13. Under these conditions, the lithium enolate of ethyl crotonate was stable indefinitely at -78°, but decomposed slowly (½ life = 1 hour) at room temperature to undetermined products.



This procedure for isomerizing an α,β-unsaturated ester to its β,γ-unsaturated isomer was then applied to a variety of unsaturated esters with the results shown in Table VI.



The result obtained with methyl 2-butynoate was especially interesting. Quenching of the anion derived from this ester provided a simple synthesis of the allenic ester, methyl 2,3-butadienoate.



The enolate derived from ethyl crotonate was alkylated with methyl iodide by addition of the enolate solution at 0° to a 50:50 mixture of THF-HMPA containing excess alkyl halide. The non-conjugated, alkylated ester was obtained exclusively in an 87% yield.

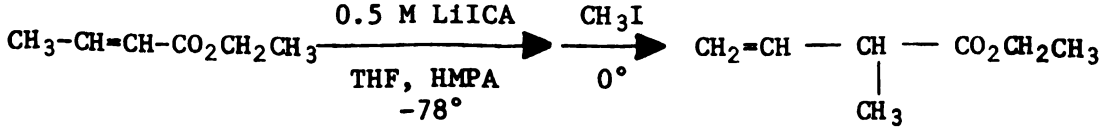


TABLE VI

Results of Quenching Various α,β-Unsaturated Ester Enolates

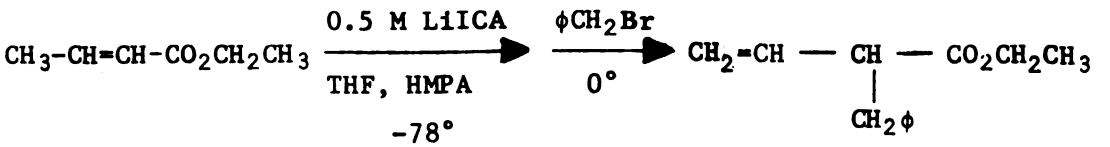
Ester	Conjugated Ester, %[a]	Non-Conjugated Ester, %[b]
Ethyl crotonate	13	87
Ethyl 3-methyl-2-butenoate	19	81
Ethyl 2-hexenoate	12	88
Methyl 2-butynoate	<0.5	60[c]

[a]Determined by glpc analysis using internal standards

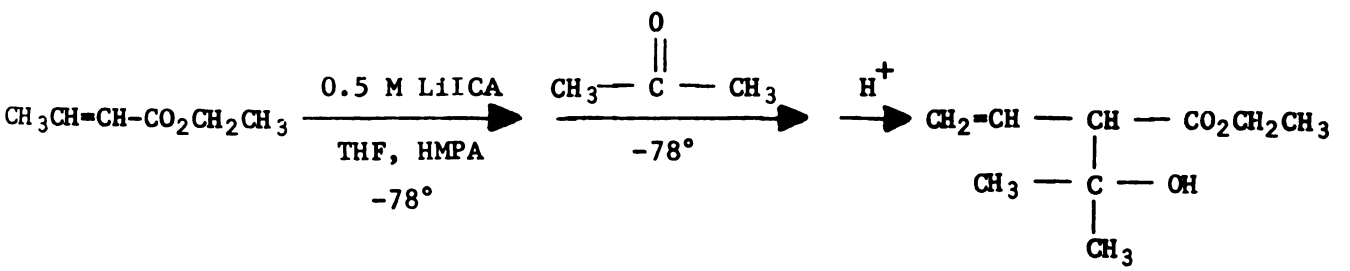
[b]Products were isolated by preparative glpc and exhibited satisfactory spectral properties.

[c]Reaction solution was 0.25M in starting ester. Reaction run at 0.5M concentration produced 40% of the non-conjugated ester.

In a similar fashion, alkylation with benzyl bromide afforded 62% of ethyl 2-benzyl-3-butenoate.

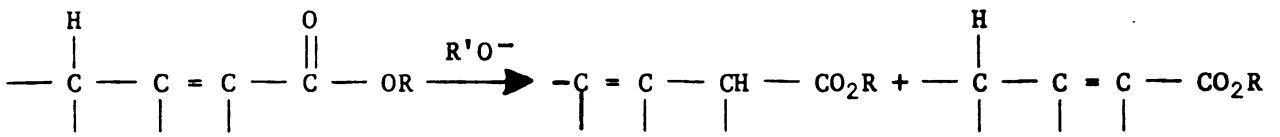


Finally, treatment of the enolate of ethyl crotonate with 1 equivalent of acetone at -78°, followed by the addition of dilute HCl, yielded ethyl 2-vinyl-3-hydroxy-3-methylbutenoate.



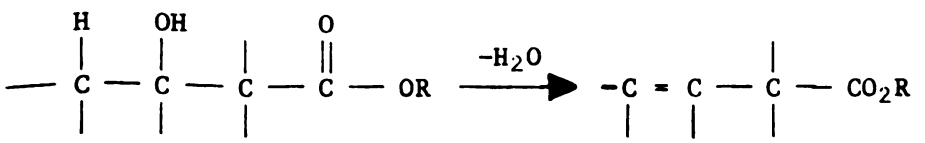
DISCUSSION

Treatment of α,β-unsaturated esters with alkoxide bases yields an equilibrium mixture of starting material and the isomeric β,γ-unsaturated ester. The conjugated ester predominates



over the non-conjugated material in almost all cases.

Dehydration of β-hydroxyesters, readily available via the Reformatsky reaction, yields more of the desired isomer but significant amounts of the conjugated isomer (Table VII) are also formed. (3).

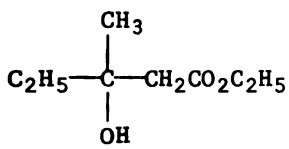
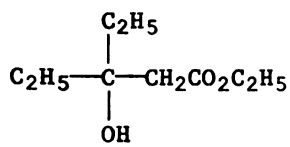
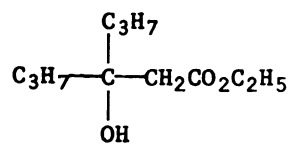
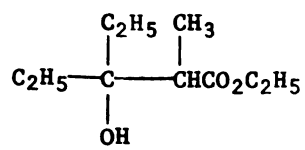
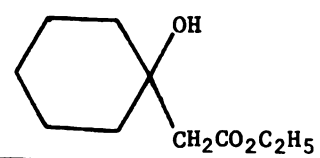
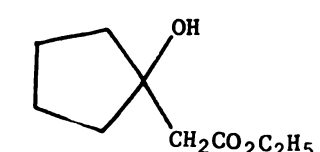


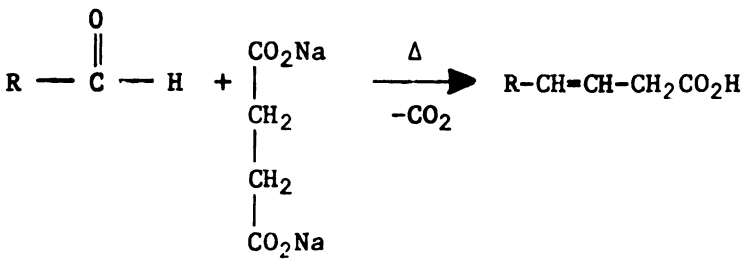
As a result of these limitations, more elaborate methods for the synthesis of β,γ-unsaturated esters have been devised.

Fittig's procedure for condensing sodium succinate with aliphatic aldehydes yielded β,γ-unsaturated acids. (20).

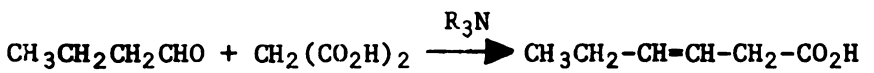
TABLE VII

Results of Dehydrating Hydroxyesters with Various Reagents

β-Hydroxyester	Percentage of α,β-Unsaturated Ester			
	P_2O_5	$POCl_3$	$SOCl_2$	(fused) $KHSO_4$
	39	62	53	57
	23	68	50	63
	24	51	31	51
	28	43	33	28
	19	43	32	45
	30	58	50	38



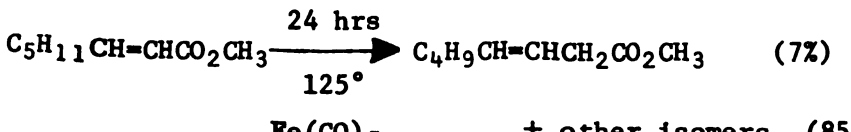
Malonic acid condensed with butyl aldehyde in the presence of a variety of amines to yield major amounts of 3-hexenoic acid. (21).



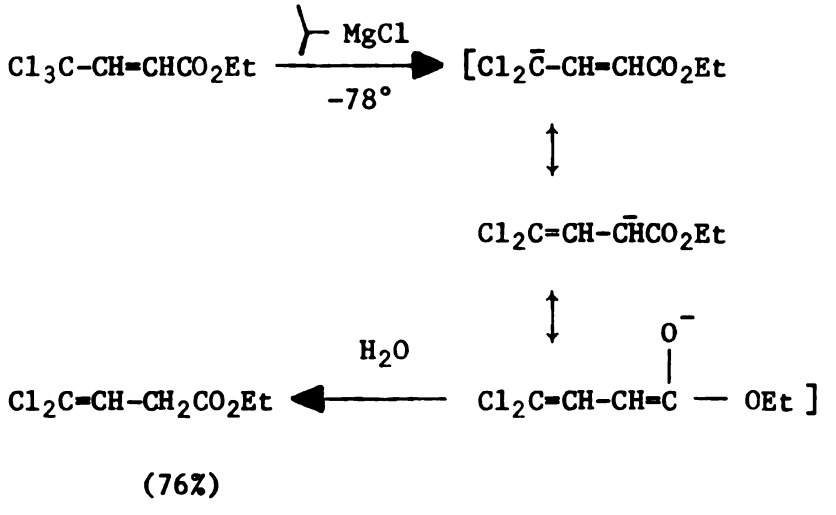
With triethanolamine a 37% yield of the β,γ-unsaturated acid alone was realized.

More recently, conjugated esters have been transformed into their non-conjugated isomers via irradiation (22, 23). The yields were high (85%) and the procedure has been applied in a number of syntheses.

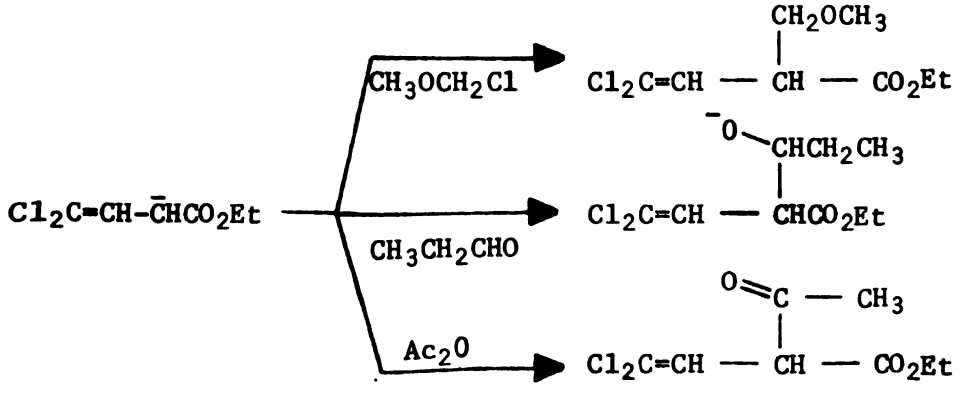
Iron pentacarbonyl has been used as an isomerization catalyst, but other isomers, in addition to the β,γ-unsaturated material, were formed.



Isomerization via the metal enolate of an α,β-unsaturated ester has been accomplished in the case of ethyl γ,γ,γ-trichlorocrotonate (25). Treatment of the ester with isopropyl magnesium chloride at -78° in THF, followed by addition of H_2O, gave ethyl 4,4-dichloro-3-butenoate in 76% yield.



The presence of the Mg enolate was confirmed by its ready reaction with a variety of electrophiles to yield the corresponding ethyl-3-butenoates, substituted exclusively in the α-position.



Similar behavior was observed in the reactions of the dianions of 2-hexenoic acid. (26). Treatment of 2-hexenoic acid with two equivalents of LiDIPA in THF followed by addition of H_2O, yielded the non-conjugated isomer exclusively. Alkylation of the

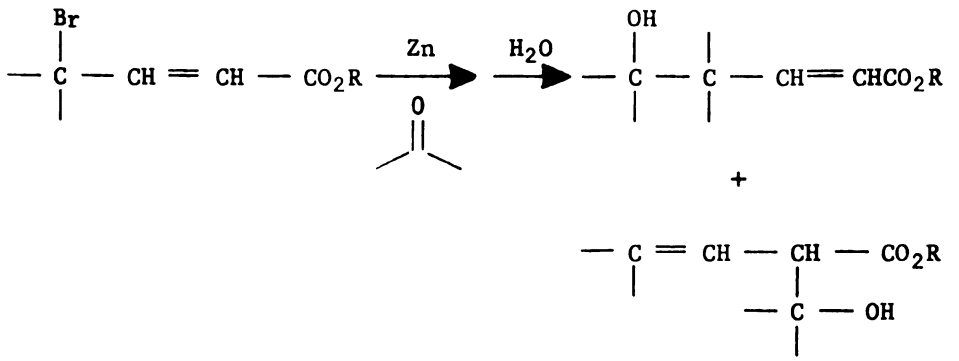
$$CH_3CH_2CH_2CH{=}CHCO_2H \xrightarrow{2\text{LiDIPA}} \xrightarrow[H^+]{H_2O} CH_3CH_2CH{=}CHCH_2CO_2H$$

dianion with CH_3I proceeded solely at the α carbon resulting in formation of 2-methyl-3-hexenoic acid.

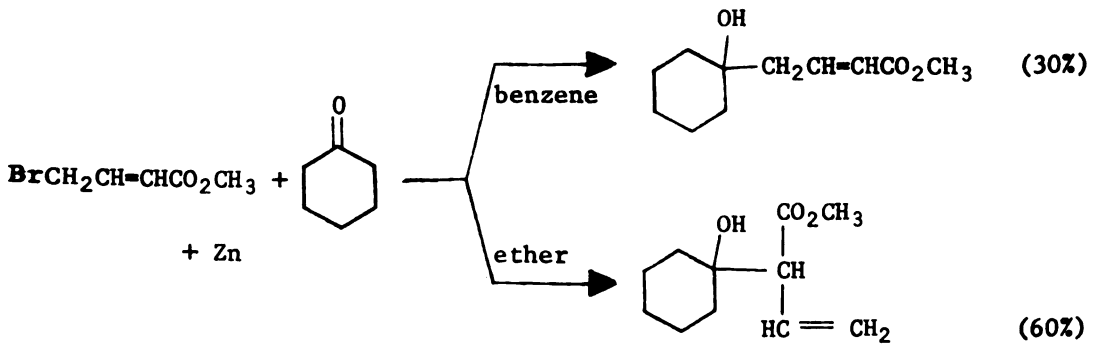
A more general procedure for generating α,β-unsaturated ester enolates used $NaNH_2$ as base. (27). No β,γ-unsaturated esters were reported synthesized in this fashion, but several different ester enolates were alkylated with butyl bromide to give β,γ-unsaturated esters substituted in the 2-position.

$$R_2CH{-}CH{=}CH{-}CO_2CH_3 \xrightarrow[NH_3(l)]{NaNH_2} \xrightarrow{n\text{-BuBr}} R_2C{=}CH{-}\underset{\displaystyle Bu}{\underset{|}{C}}HCO_2CH_3$$

4-Bromocrotonate esters, when added to zinc, reacted at the 2-position to give non-conjugated products. However attack also occurred

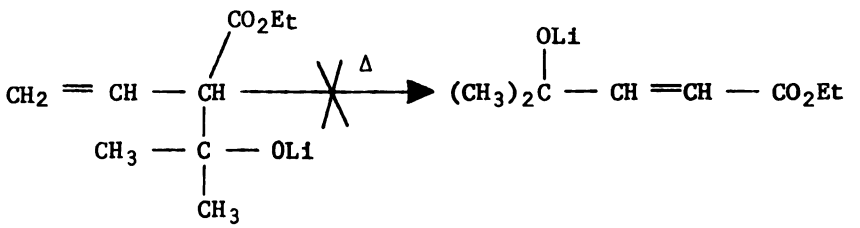


at the 4-position. This product ratio was affected by substitution in the ester and in the carbonyl substrate. Choice of reaction conditions was also important. Cyclohexanone reacted to give predominantly the 4-substituted product in refluxing benzene and the 2-substituted product in refluxing ether. (30).



Protonation of the lithium enolates of α,β-unsaturated ester enolates, generated from dialkyl amide bases, produced the β,γ-unsaturated isomer in high yield. The generality of the procedure has been demonstrated and it also provides a convenient method for the generation of stable, unsaturated ester enolates under these reactions conditions.

These enolates reacted with other electrophiles at the α position. Heating, as in the Reformatsky reaction, did not affect the course of addition to carbonyls. Attempts to isomerize the addition product formed with acetone to the 4-substituted isomer resulted only in loss of the α-substituted product.



EXPERIMENTAL

I. Materials

The ethyl crotonate, diethyl isopropylidenemalonate, and ethyl 2-hexenoate were obtained commercially and used without further purification. The methyl 2-butynoate was provided by Dr. E. LeGoff and used directly. The ethyl 3-methyl-2-butenoate was prepared from the commercially available acid in 88% yield by the procedure described in Org. Syn., 3, 714.

II. Isomerization of α,β-Unsaturated Esters

The procedure using ethyl crotonate is representative. A 50 ml flask as shown in Figure 3 was flame-dried. A hexane solution of 5.25 mmoles of lithium N-isopropylcyclohexyl amide was prepared as described in Chapter 1. After removal of the hexane, 10 ml of tetrahydrofuran were added and, after dissolution of the amide, the flask was cooled to -78°. Two ml of HMPA were added (f.p. 7.2). The ethyl crotonate (0.62 ml; 5.0 mmoles) was added slowly. After 15 minutes the solution was quenched with 5 ml of a 2 M solution of HCl. The solution was extracted with pentane; the organic layers were combined and dried over K_2CO_3. The product mixture was examined by glpc and shown to contain 87% ethyl 3-butenoate and 13% ethyl crotonate.

Product Analysis

All α,β-unsaturated esters produced in the above manner were

separated from isomeric starting ester by a ¼ inch by 6 foot column of SE - 30. The products were collected directly from the gas chromatograph and analyzed by NMR.

Ethyl 2-deuterio-3-butenoate

NMR(CCl_4): 5.8δ (m,1H), 5.25δ (d,1H), 5.0δ (m,1H), 4.1δ (q,2H), 3.0δ (m,1H), 1.2δ (t,3H).

Ethyl 4-deuteriocrotonate

NMR(CCl_4): 6.95δ (m,1H), 6.05δ (m,1H), 5.75δ (m,1H), 4.2δ (q,2H), 2.0δ (d,2H), 1.3δ (t,3H).

Methyl 2,3-butadienoate

NMR(CCl_4): 5.5δ (m,1H), 5.1δ (m,2H), 3.7δ (s,3H).

Ethyl 3-methyl-3-butenoate

NMR(CCl_4): 4.85δ (m,2H), 4.1δ (q,2H), 2.95δ (d,2H), 1.8δ (d,3H), 1.1δ (t,3H)

Diethyl (2-isopropenyl)malonate

NMR(CCl_4): 5.0δ (m,2H), 4.2δ (q,4H), 4.0δ (s,1H), 1.9δ (m,3H), 1.3δ (t,3H).

Ethyl 3-hexenoate

NMR(CCl_4): 5.5δ (m,2H), 4.15δ (q,2H), 3.0δ (m,2H), 2.0δ (m,2H), 1.3δ (m,6H).

III. Reactions of Lithio Ethyl Crotonate

A. Alkylation

The reaction of the enolate with CH_3I is representative. The 5.0 mmoles of enolate was prepared as described above. A 1 M solution of methyl iodide (1.25 ml; 10 mmoles) in THF (6 ml)-HMPA (4 ml) at 0° was prepared in a 50 ml round-bottom flask. The cold (-78°) enolate solution was added to the methyl iodide solution over the course of 3-5 minutes. After 60 minutes the solution was quenched with 2 M HCl and extracted. After the usual work-up, 87% of ethyl 2-methylbutenoate was obtained. NMR (CCl_4): 5.95δ (septet, 1H), 5.1δ (m, (m,2H), 4.1δ (q,4H), 3.1δ (m,2H), 1.3δ (t,3H), 1.28δ (d,3H).

B. With Carbonyls

The enolate (5.0 mmoles) was generated as described above. To the cold (-78°) enolate solution was added 0.37 ml (5.0 mmoles) of acetone, dropwise. After 15 minutes the solution was quenched with HCl and worked-up in the usual fashion with pentane. The yield of ethyl 3-hydroxy-3-methyl-2-vinylbutanoate was 78%. NMR (CCl_4): 6.0δ (m,1H), 5.3δ (s,1H), 5.05δ (doublet of doublets, 1H), 4.15δ (q,2H), 2.9δ (d+s,2H), 1.2δ (m,9H).

CHAPTER III

THE SILYLATION OF ESTER ENOLATES AND THE REACTIONS OF α-SILYLATED ESTERS AND TRIALKYL KETENE ACETALS

INTRODUCTION

Ester enolates are ambident anions capable of undergoing reaction with electrophiles at either carbon or oxygen. (Figure 4).

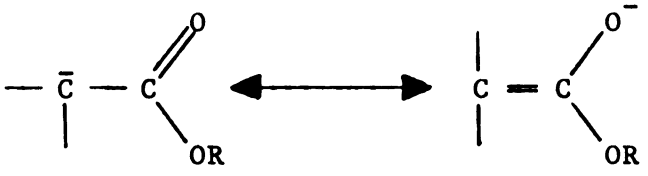
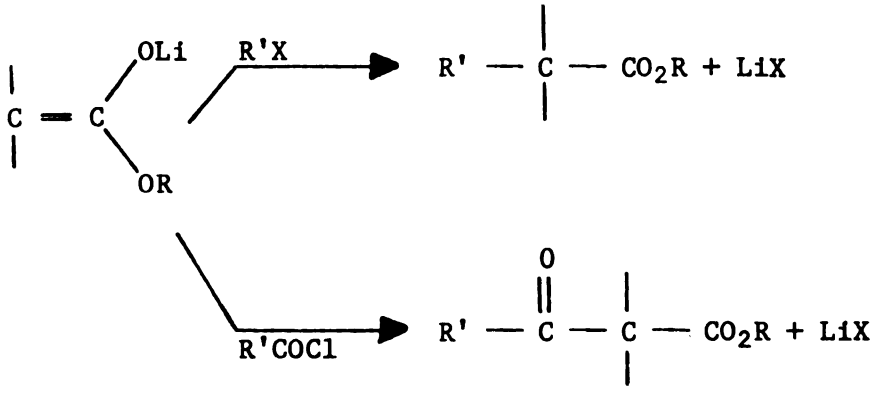
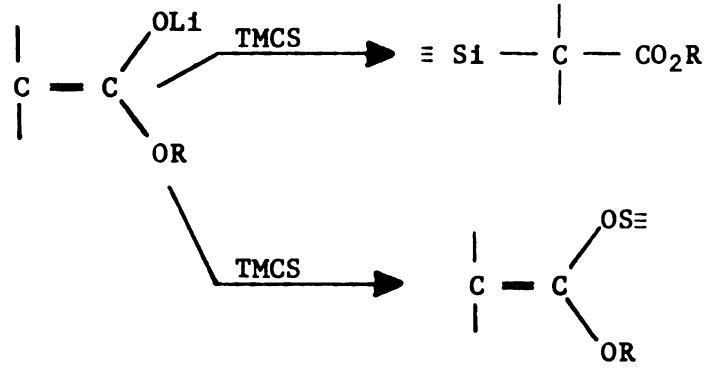


Figure 4. Ester Enolate Resonance Hybrid

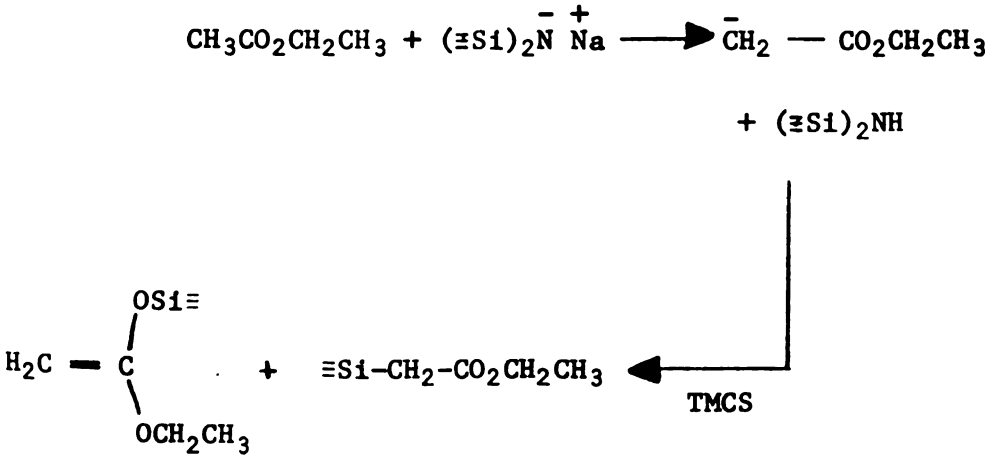
Alkyl halides (10) and acyl halides (31) react with lithium ester enolates at carbon, producing the corresponding chain-extended esters and β-keto esters.



Reaction of ester enolates with trimethylchlorosilane (TMCS) can generate α-silyl esters and/or O-trialkylsilyl-O'-alkyl ketene acetals.

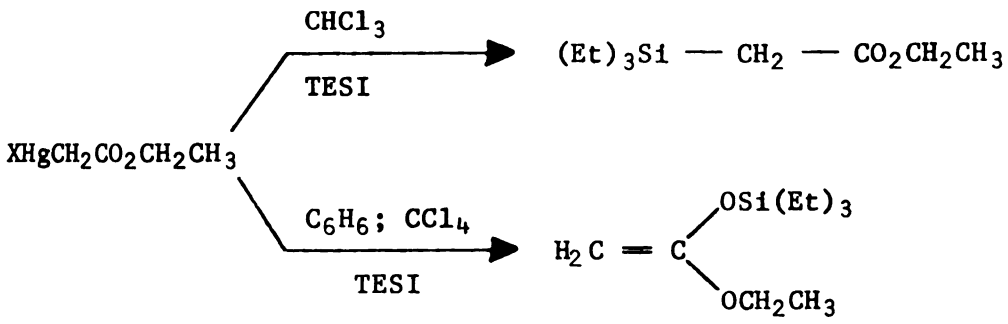


Hauser (32) first prepared C-silylated esters by reaction of the enolates of acetates with TMCS. Rochow (8) has synthesized a mixture of both C- and O-silylated ethyl acetate via the sodium enolate of ethyl acetate using NaHMDS.

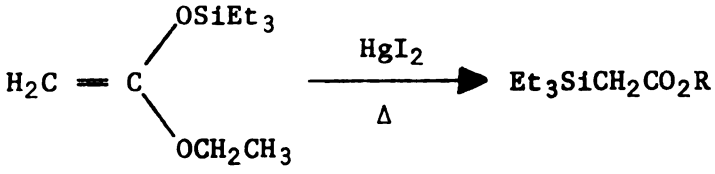


(13.7%) (22.3%)

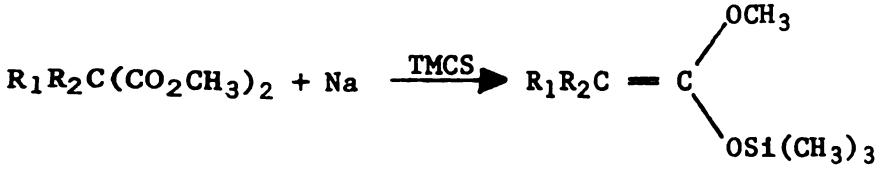
Choice of solvent has been shown to affect the course of silylation of mercuric salts of acetate anions with triethylsilyl iodide (TESI). (33).

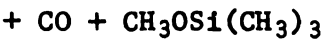


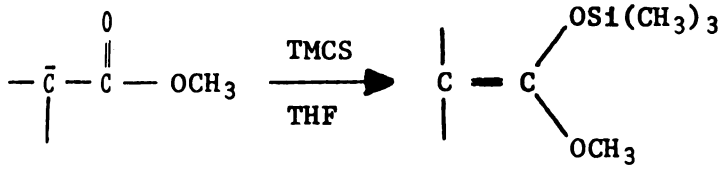
The O-silylated acetal obtained was rearranged to the C-silylated ester *by* mercuric iodide.



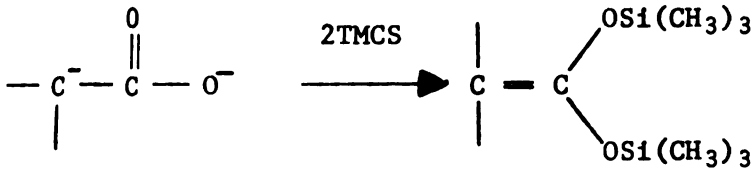
More recently, trialkylsilyl ketene acetals have been prepared via the reaction of disubstituted malonic esters with sodium in xylene (34) and by the direct silylation of lithium ester enolates with TMCS. (35).







In a similar manner, disilyl dialkyl ketene acetals have been prepared from metalated carboxylic acids using TMCS. (36).



Ketene acetals react with a variety of electrophilic reagents. (37). The simple resonance picture (Figure 5) of ketene acetals predicts the α carbon to be the preferred site of reaction with electrophiles, and this qualitative representation can be used to predict the structure of products in these reactions.

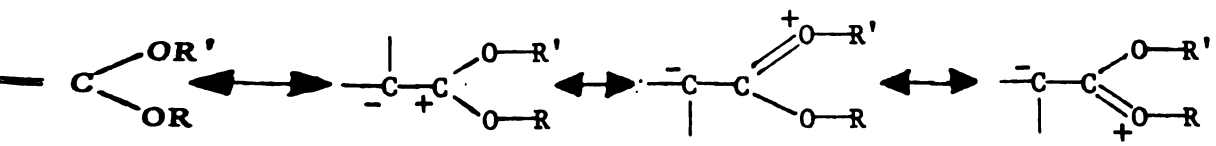
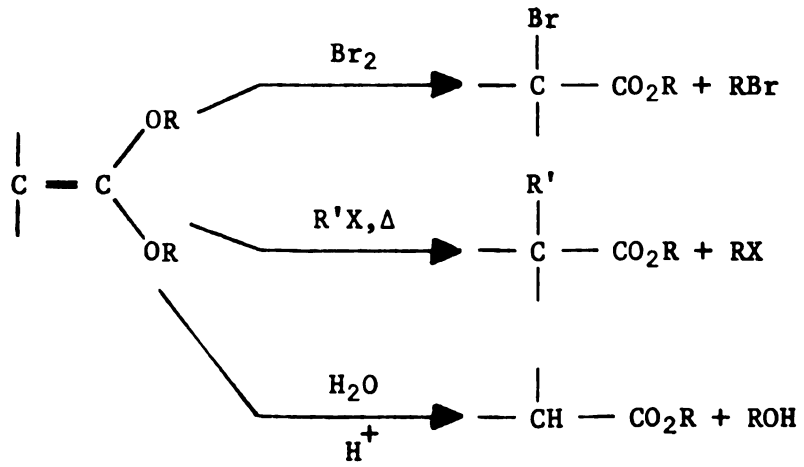


Figure 5. Resonance Contributors of a Ketene Acetal

In such a fashion, ketene acetals reacted with bromine to give the α-bromo esters, alkylhalides to give chain-extended esters, acid halides to give β-keto ester derivatives, and water to regenerate the ester.

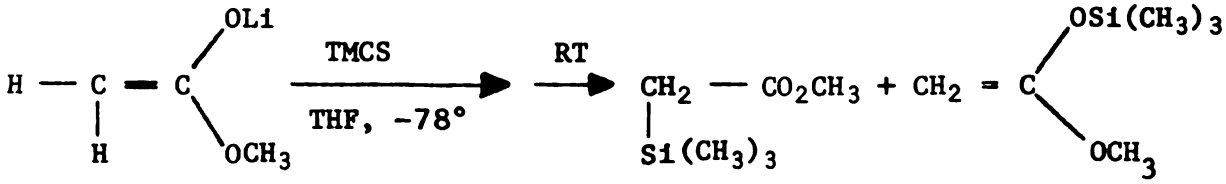


Our purpose in this study was to determine the products of reaction of lithium ester enolates with various electrophiles, including silyl halides, and to investigate the value of these products for more elaborate synthetic procedures.

RESULTS

I. Preparation of O- and C-Silylated Esters

Addition of TMCS to a THF solution of lithio methyl acetate at -78° produced a mixture of O-silylated (65%) and C-silylated (35%) products.



35% 65%

With lithio ethyl acetate, slightly more C-silylated material was obtained (40%), while lithio t-butyl acetate gave almost exclusively C-silylated product (98%). Addition of either hexamethylphosphoramide (HMPA) or tetramethylethylene diamine (TMEDA) to the lithio ethyl acetate solution prior to addition of the trimethylchlorosilane increased the amount of C-silylated ester formed. With HMPA (20% by vol.), 90% of the C-silylated product was obtained, while addition of one equivalent of TMEDA yielded 60% of this ester.

The ethyl esters of butyric, hexanoic, and cyclohexylacetic acids all gave, exclusively, the O-silylated products. t-Butyl butyrate yielded a mixture of 60% C-silylated and 40% O-silylated products. (Table VIII).

TABLE VIII

Results of Silylation of Ester Enolates

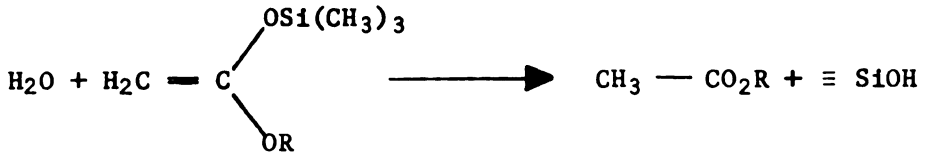
Ester	Solvent	Silane	% C-silylation	% O-silylation
Ethyl acetate	THF	TMCS	45	55
	THF-HMPA(20%)	TMCS	90	<10
Ethyl acetate	THF-HMPA (1 eq.)	BDCS	<1	<99
Methyl acetate	THF	TMCS	40	60
t-Butyl acetate	THF	TMCS	99	<1
	THF-HMPA(20%)	TMCS	99	<1
t-Butyl butanoate	THF	TMCS	60	40
Ethyl isobutyrate	THF	TMCS	<1	99
	THF-HMPA(20%)	TMCS	<1	99
	THF-HMPA (1 eq.)	BDCS[a]	<1	99
Ethyl hexanoate	THF	TMCS	<1	99
	THF-HMPA (1 eq.)	BDCS	<1	99
Ethyl 1-cyclohexylacetate	THF	TMCS	<1	99
Ethyl crotonate	THF-HMPA (1 eq.)	BDCS	<1	99

[a]BDCS ≡ t-Butyldimethylchlorosilane

When t-butyldimethylchlorosilane was used in place of TMCS, only O-silylated products were obtained, regardless of the ester enolate used. This was the case for ethyl acetate, t-butyl acetate, ethyl isobutyrate, ethyl hexanoate, and ethyl crotonate. It was necessary to add HMPA to these reactions in order to increase the rate of ester silylation to a practical level.

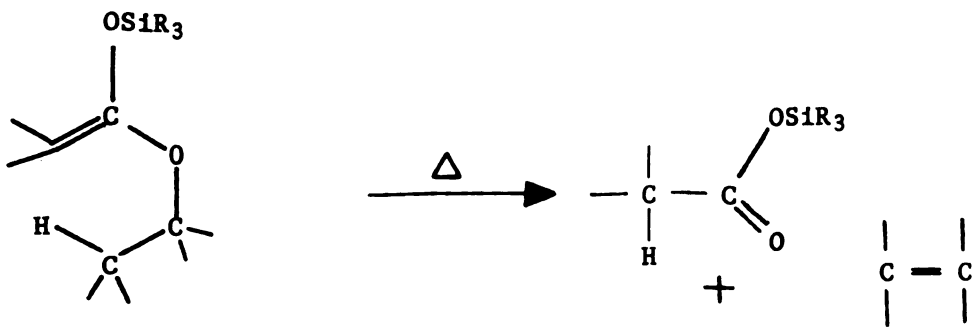
The C-silylated acetate esters were insensitive to acid. The amine used to generate the enolates was easily removed by treatment with dilute HCl. Evaporation of the THF yielded the C-silyl esters in 95% - 100% purity.

The O-silylated esters were more difficult to purify. Their sensitivity to acid was dependent on the degree of substitution on the double bond of the ketene acetal. O-silyl-O'-ethyl dimethyl ketene acetal and O-trimethylsilyl-O'-ethyl cyclohexylideneketene acetal were purified by acid treatment (HCl), removing the ICA present. However, the O-silyl ketene acetal obtained from ethyl hexanoate was much more sensitive to acid and even cold acetic acid treatment of the reaction mixture resulted in extensive decomposition of the ketene acetal. In the case of O-trimethylsilyl ketene acetals derived from the acetates, water was sufficiently acidic to convert them entirely into the corresponding esters.



The O-t-butyldimethylsilyl ketene acetals were more resistant to hydrolysis (38). The ICA could be removed from the reaction mixture by treatment with cold acetic acid without significant decomposition for most of the ketene acetals. Only O-t-butyldimethylsilyl ketene acetal derivatives of the acetates were converted back to their starting esters. O-t-butyldimethylsilyl-Ȯ-ethyl ketene acetal was prepared by using the more volatile diisopropyl amine to generate the ester enolate. The amine and solvent were then evaporated, without an acid wash, yielding product with greater than 95% purity (glpc).

The ketene acetals are also sensitive to thermal decomposition. O-Silyl-Ȯ-alkyl ketene acetals have been shown to decompose to give olefin and silyl ester when heated (39).

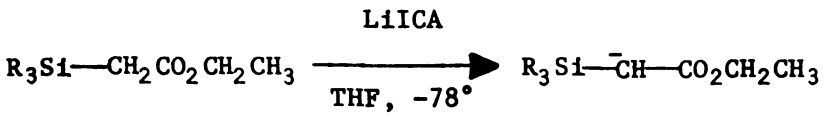


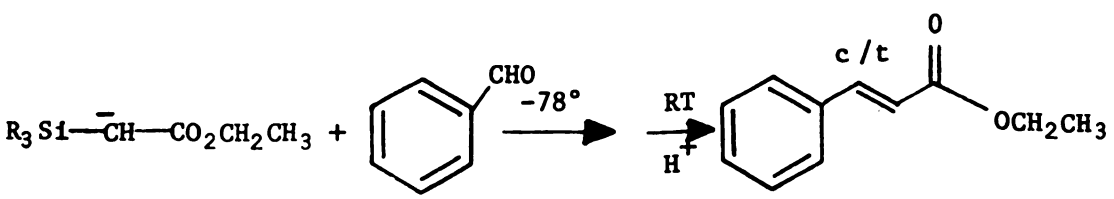
Fortunately, the crude ketene acetals were usually of sufficient

purity for further use after removal of amine and evaporation of solvent, making distillation unnecessary.

II. Reactions of C-silylated Esters

Trimethylsilyl ethyl acetate when treated with LiICA at -78° in THF formed a stable enolate. The ester was recovered quantitatively upon addition of acid. Addition of benzaldehyde to the enolate solution at -78°, followed by warming and quenching with HCl, yielded a mixture of cis/trans ethyl cinnamates.

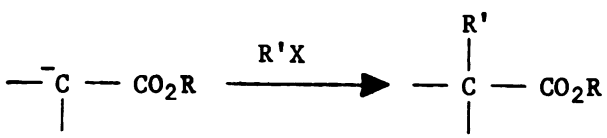




The scope of this reaction has subsequently been studied by another worker. (40).

II. Attempted O-Alkylation of Ester Enolates

Only TMCS gives ketene acetals when reacted with ester enolates. Methyl iodide, triethyloxonium fluoroborate, methyl sulfate, and methyl-fluorosulfonate all gave C-alkylated products when reacted with variety of lithium ester enolates.



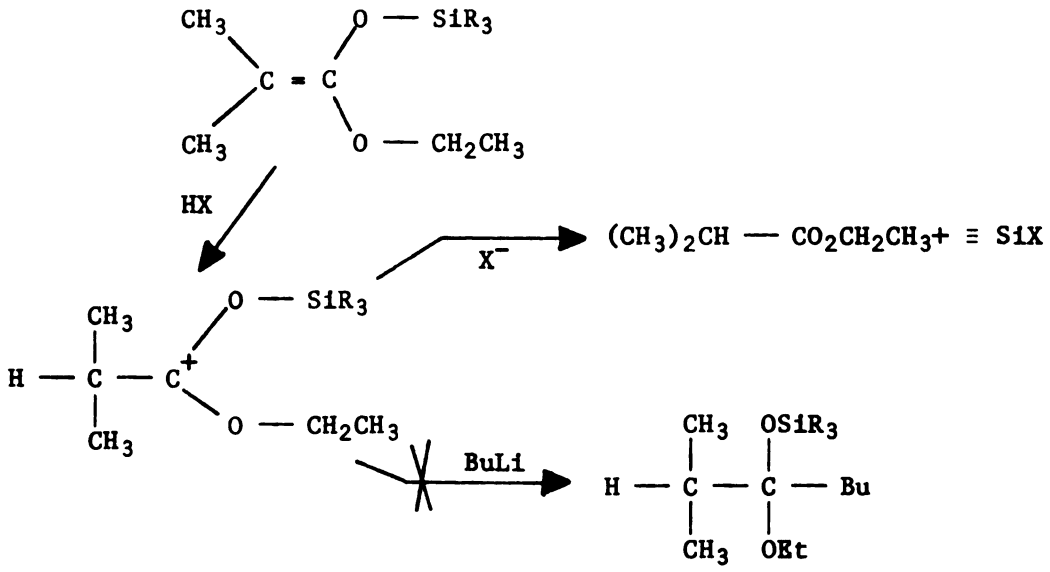
$R'X = Et_3OBF_4, \quad CH_3I, \quad (CH_3)_2SO_4, \quad FSO_3CH_3$

Addition of HMPA or TMEDA to the solvent increased the rate of reaction, but again only C-alkylated products were obtained.

III. Reactions of O-trialkylsilyl-O'-alkyl Ketene Acetals

A. With Acids

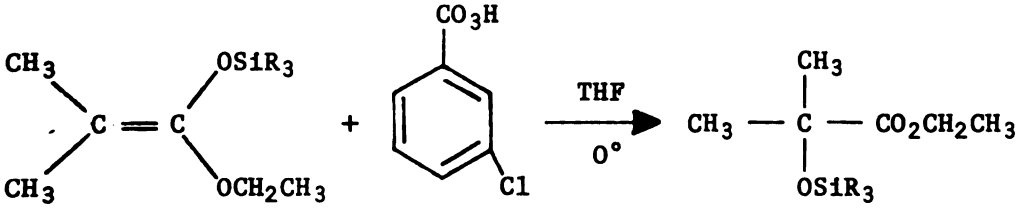
Addition of strong acids to O-trimethylsilyl-O'-ethyl dimethylketene acetal (DMA) resulted in formation of the starting ester. All attempts to trap the intermediate oxonium ion with butyllithium failed.



HX = HCl, HBF_3Cl, HSO_3F

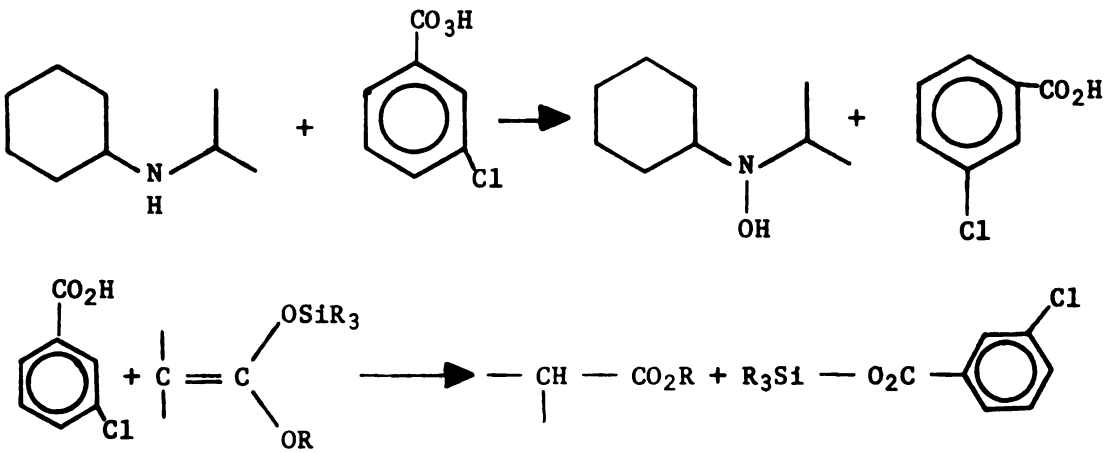
B. With Peracids

DMA reacted with m-chloroperbenzoic acid at 0° in THF to give ethyl 2-trimethylsiloxyisobutyrate in 64% yield.

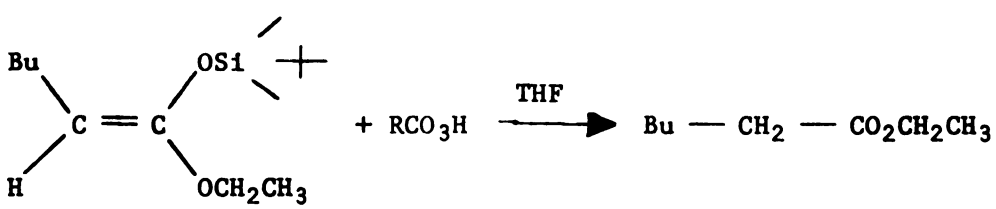


In the presence of ICA, the O-silyl ketene acetal derivatives of both ethyl isobutyrate and ethyl hexanoate were converted back to the starting esters upon peracid treatment followed by water work-up.

Reaction of the ICA with the perbenzoic acid to form hydroxylamine and m-chlorobenzoic acid could explain the formation of the esters (41).



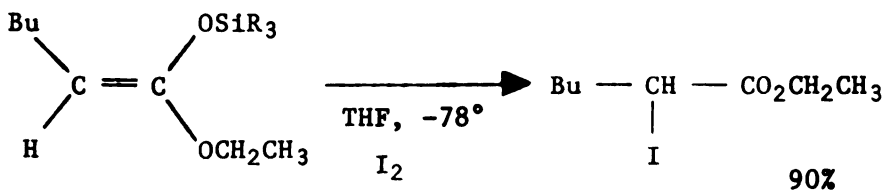
The more acid-resistant t-butyldimethylsilyl derivative of ethyl hexanoate was prepared and reacted with m-chloroperbenzoic acid under the same conditions that proved successful in the oxidation of the ketene acetal of ethyl isobutyrate. Only ethyl hexanoate was identified in the reaction mixture.



C. With Iodine

Due to the inability to separate acid sensitive ketene acetals from ICA, only electrophiles which can tolerate the presence of the

amine appear to have general synthetic value. Thus, addition of I_2 to a solution of O-trimethylsilyl-O'-ethyl butylketene acetal and ICA in THF at -78° yielded the α-iodo ester in 90% yield on work-up.



D. With Acid Chloride and Triethylamine

The trialkylsilyl ketene acetal, I, reacted with THF solutions of acid chlorides in the presence of triethylamine to yield silylated derivatives of β-keto esters. (Table IX).

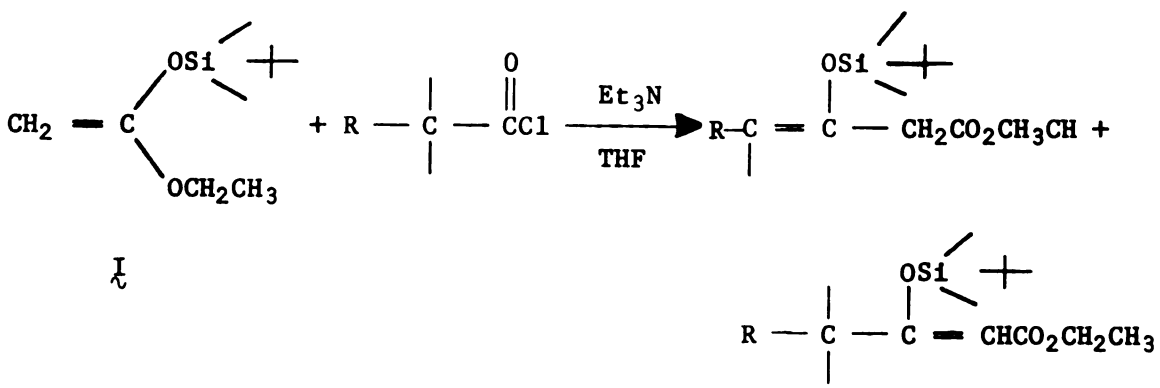
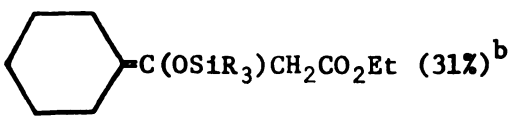
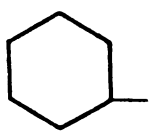


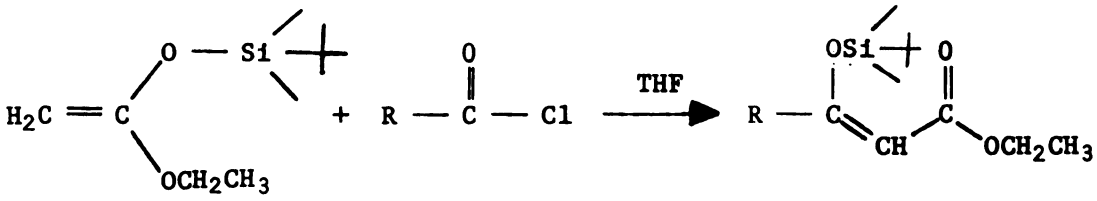
TABLE IX

Reaction of O-t-Butyldimethylsilyl-O'-ethyl Ketene Acetal with Acid Chlorides

Acid Chloride	Product (yield, glpc)[a]
Acetyl chloride	$CH_2=C(OSiR_3)CH_2CO_2Et$ (86%)
Butyryl chloride	$CH_3CH_2CH=C(OSiR_3)CH_2CO_2Et$ (85%)
Isobutyryl chloride	$(CH_3)_2C=C(OSiR_3)CH_2CO_2Et$ (35%) + $(CH_3)_2CHC(OSiR_3)=CHCO_2Et$ (35%)
Crotonoyl chloride	$CH_2=CHCH=C(OSiR_3)CH_2CO_2Et$ (35%)
Benzoyl chloride	$C_6H_5C(OSiR_3)=CHCO_2Et$ (62%)
Pivaloyl chloride	$(CH_3)_3CC(OSiR_3)=CHCO_2Et$ (40%)
Cyclohexanecarboxoyl chloride	 $=C(OSiR_3)CH_2CO_2Et$ (31%)[b] +  $C(OSiR_3)=CHCO_2Et$ (58%)

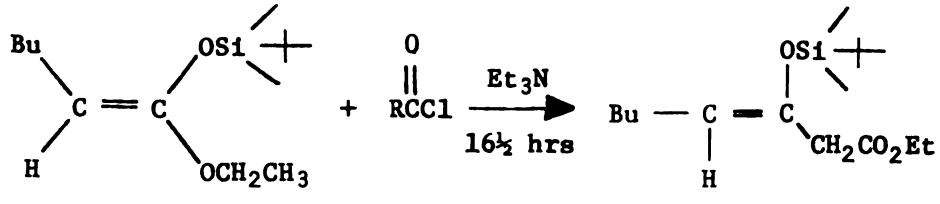
(a) All products were isolated by vacuum distillation. Structures were established by proton nmr and by hydrolysis to the corresponding β-keto esters.

Reaction of the ketene acetal with acetyl or butyryl chloride in the absence of triethylamine was slow and generated only small amounts (10-25%) of the siloxy-α,β-unsaturated esters.



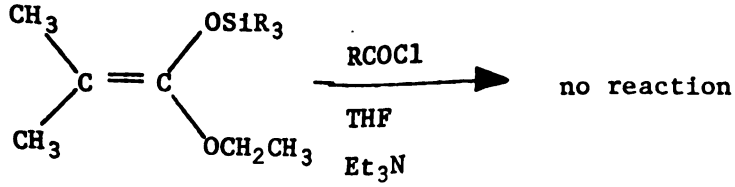
I

Ketene acetals substituted with one group on the alpha carbon underwent the reaction only after prolonged treatment with acid chloride and Et_3N.



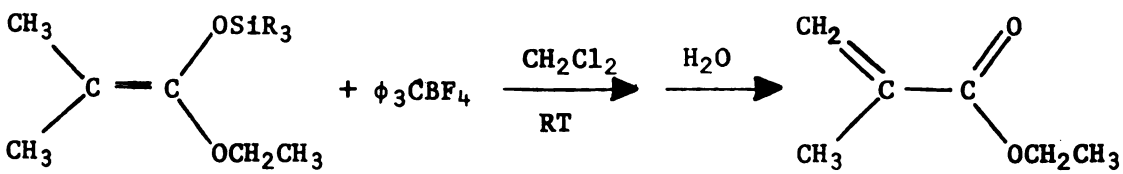
61%

α,α-Disubstituted ketene acetals, under the same conditions, were inert.



V. Reaction of Electron-rich Double Bonds with ϕ_3CBF_4

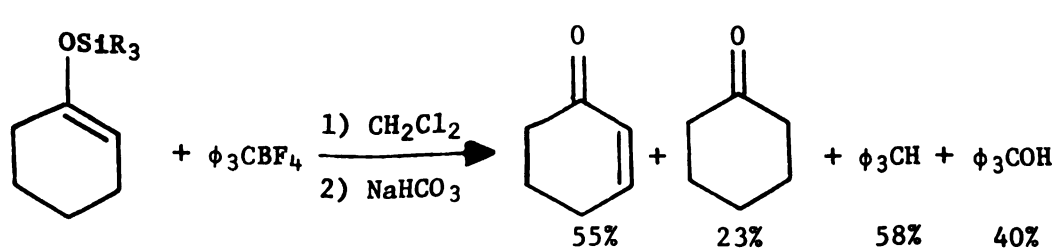
Addition of ϕ_3CBF_4 to a 1 M solution of O-trimethylsilyl-O'-ethyl dimethyl ketene acetal in CH_2Cl_2, followed by addition of H_2O after 5 minutes, resulted in a 1:1 mixture of ethyl isobutyrate and ethyl 2-methyl-2-propenoate.



+ $(CH_3)_2CHCO_2Et$

Since there were a limited number of substituted ketene acetals available free of contaminating amine, the synthetic utility of this reaction was investigated using a variety of siloxyolefins (42).

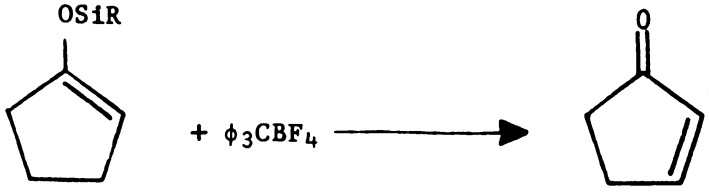
1-Siloxycyclohexene was prepared and reacted with ϕ_3CBF_4 in CH_2Cl_2 at room temperature. After addition of one equivalent of a Na_2CO_3 solution, a mixture of cyclohexenone (55%) and cyclohexane (23%) was obtained.



Triphenylmethane (58%) and triphenylmethanol (40%) were also present in the reaction mixture.

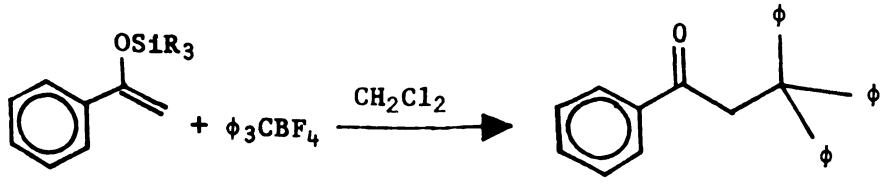
The yield of cyclohexenone could not be improved upon any manipulation of the reaction conditions. The use of acetonitrile, pentane, DMSO, or benzonitrile as solvent afforded no increase in the amount of cyclohexenone formed. Tropylium fluoroborate, trityl antimonyhexafluorate, DDQ, and trityl perchlorate all proved less effective than trityl fluoroborate in generating cyclohexenone from 1-silyoxycyclohexene.

Trityl fluoroborate was subsequently reacted with a number of siloxyalkenes. 1-Siloxycyclopentene afforded 33% of the corresponding α,β-unsaturated ketone.



33%

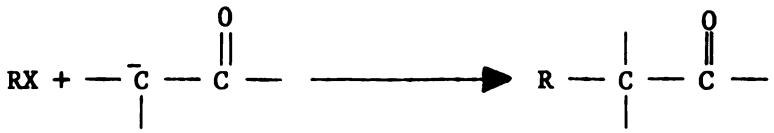
All other substrates used in the reaction failed to react as expected, returning only ester on work-up; α-siloxy styrene yielded an addition product, 3,3,3-triphenylpropiophenone.



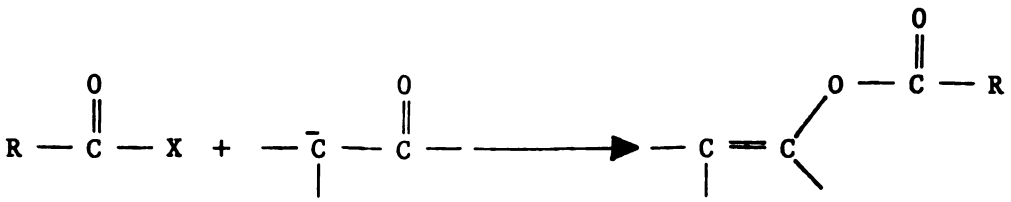
DISCUSSION

I. Preparation of O-, C-Silylated Esters

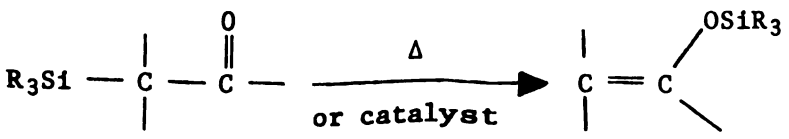
The alkali metal enolates of ketones react with alkyl halides to produce α-substituted ketones (1).



Only when more reactive electrophiles such as acid chlorides and acid anhydrides are employed does reaction at oxygen predominate.

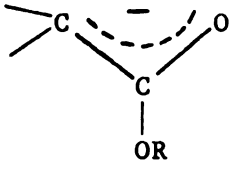


Trialkylhalosilanes react with ketones or their enolates to produce siloxyalkenes exclusively (42-46). Ketones substituted in the α position with trialkylsilyl groups are unstable relative to their O-silylated isomers (47), and readily rearrange under the influence of heat or a variety of catalysts (48).



Ester enolates did not invariably produce O-silylated products when reacted with trimethylchlorosilane. The products obtained depended heavily on the structure of the ester enolate used.

Although the results suggest that the reaction path was determined by steric considerations, an explanation of the results obtained is not easily provided. The reaction at oxygen of the more highly α-substituted esters was easily attributed to the steric inaccessability of the α carbon of the ester enolate. But increased substitution on the alcohol portion of the ester can not be used to explain the preference for C-silylation of t-butyl ester enolates. The availability of the carbon or the oxygen for reaction in an ester enolate appears to be equally affected by a change in substitution in the alcohol portion of an ester enolate.



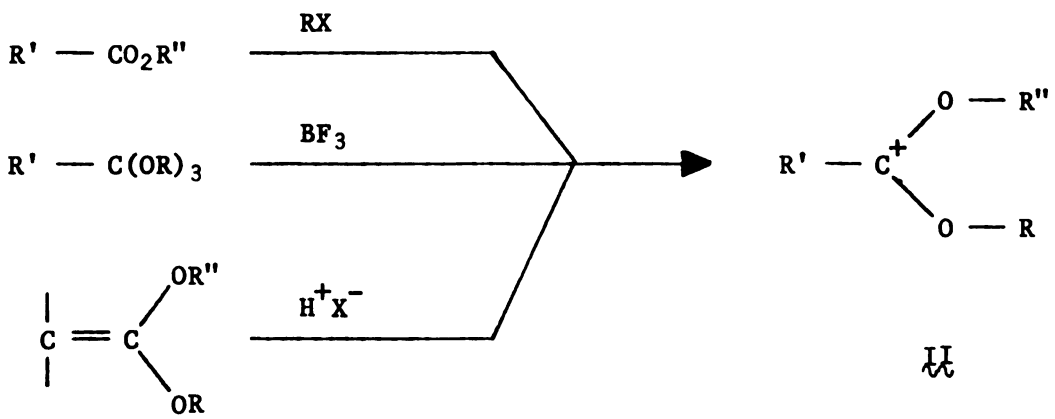
Based on these results, this simple description is not sufficient for predicting the course of reaction of ester enolates. A more elaborate description is required, possibly including the amine used to generate the enolate. Evidence for a strong association of amine with ester enolates and acid dianions has been presented (10, 49). Any attempt to predict the outcome of the reaction of such an associated

species without more information on its conformation is impossible.

II. Reaction of O-Trialkylsilyl-O'-alkyl Ketene Acetals

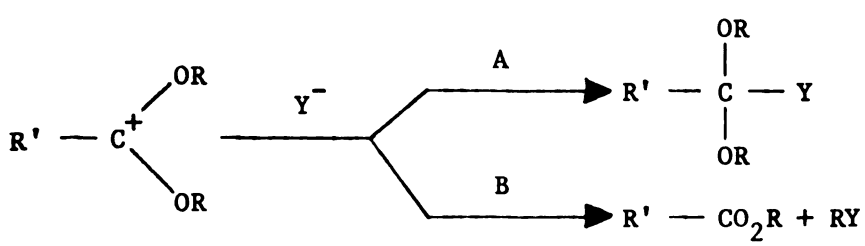
A. With Acids

Alkylation of an ester, treatment of an ortho-ester with a Lewis acid, and protonation of ketene acetals at low temperature produce 2-alkyl-1,3-dioxolenium ions, II. (50).



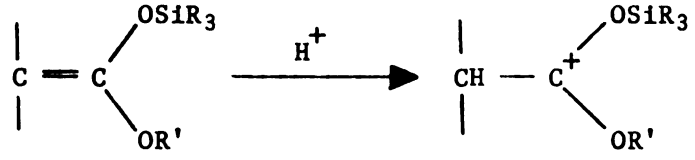
II

When treated with a nucleophile, the oxonium ions react by one of two pathways: addition to the central carbon bearing positive charge (route A) to form an ortho-ester derivative or displacement of one of the alkyl groups on oxygen to generate an ester (route B).



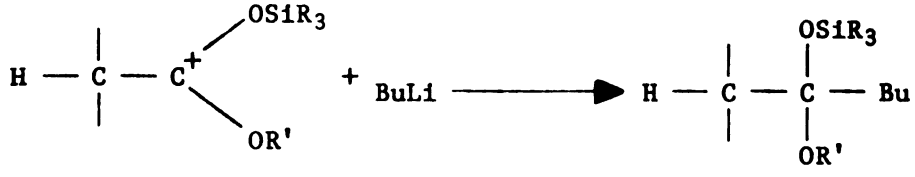
Dioxolenium ions usually react to give orthoester derivatives only with more nucleophilic anions such as alkoxide or cyanide.

O-trialkylsilyl-O'-alkyl ketene acetals when treated with acid were expected to initially produce the silyl analogs of 1,3-dioxolenium ions, III.



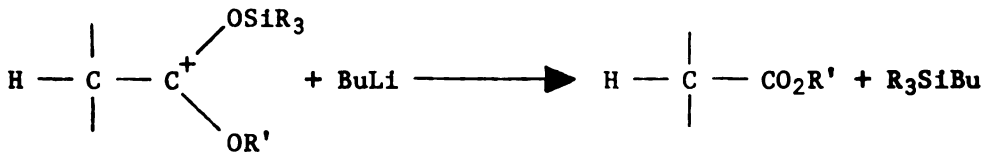
III

Reaction of these oxonium ions with the potent nucleophile butyllithium was expected to yield the O-trialkylsilyl-O'-alkyl ketal as product.

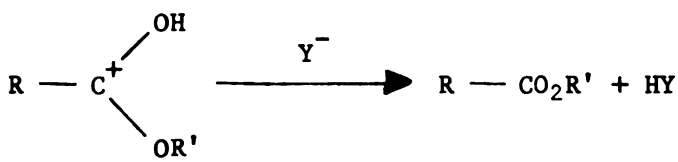


However, when O-trimethylsilyl-O'-ethyl dimethylketene acetal was subjected to these reaction conditions only ethyl isobutyrate was identified as a product. In the case of the 1-trialkylsilyl-1,3-dioxolenium ions, route B, displacement of the trialkylsilyl group, was

preferred.



The reactions of the trialkylsilyl dioxolenium ions parallel the reactions of protonated esters, IV. Treatment of these dioxolenium ions with a nucleophile also results in regeneration of ester.

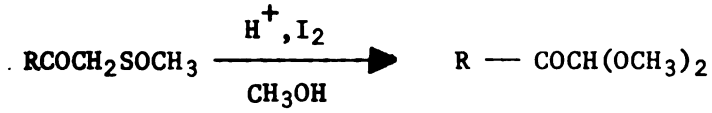


IV

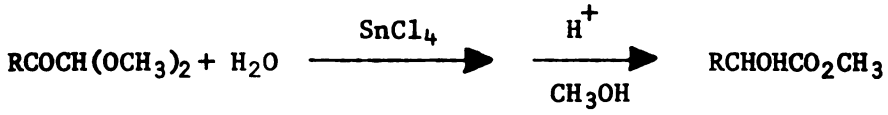
This parallel behavior may be due to the greater electropositive character of the silicon.

B. Reactions with Peracids and Iodine

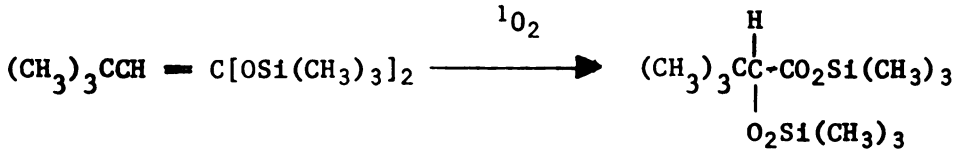
Only one useful preparation of α-hydroxyesters has been demonstrated in the past 10 years (51). The procedure required prior synthesis of α-keto ketals which were prepared from ester and methylsulfinyl carbanion (52).



Treatment of the α-keto ketal with stannic chloride resulted in good yields of the corresponding α-hydroxyester.



The oxidation of the reactive double bond in O-trialkylsilyl-O'-alkyl ketene acetals to form α-hydroxyesters would be a more convenient source of these compounds. However, the use of peracids to effect the oxidation must be ruled out except for the most acid-insensitive ketene acetals. A more acid-resistant silyl ketene acetal must be synthesized, or a non-acidic oxidizing reagent is needed. Partial success in preparing oxidized esters from silyl ketene acetals has been reported using non-acidic reagents. Treatment of O-trimethylsilyl-O'-trimethylsilyl t-butylketene acetal with singlet oxygen yielded the silylated peroxyester derivative (53).

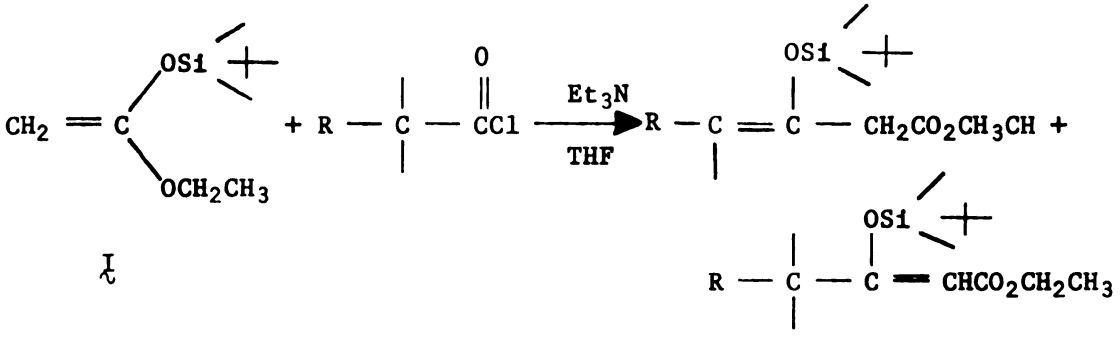


The value of this approach was verified by the reaction of ketene acetals with iodine. Although α-iodoesters can be prepared in high yield by direct iodination of ester enolates (54), the preparation of ethyl α-iodohexanoate from the corresponding ketene acetal demonstrated that synthetically valuable reactions using silyl ketene acetals required non-acidic electrophiles.

Ideally, these reagents should also be able to tolerate the presence of the amine used to generate the silyl ketene acetal. However, this difficulty may be circumvented by the use of more volatile secondary amines in the preparation of ester enolates. Evaporation of solvent and amine yielded silyl ketene acetals of sufficient purity for further reaction.

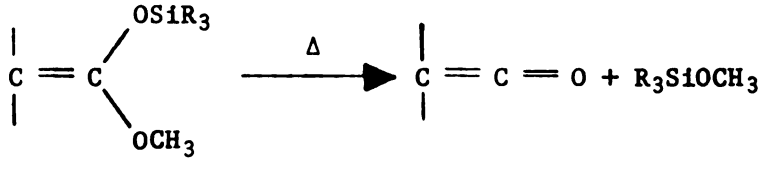
C. With Acid Halides and Triethylamine

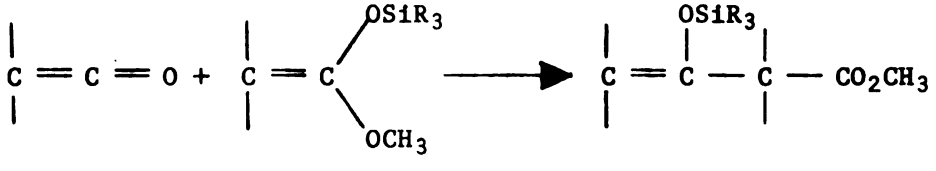
O-t-butyldimethylsilyl ketene acetal, I, is the first trialkylsilyl ketene acetal to be used as a reagent in the preparation of β-keto esters via their silyl enol ether derivatives.



I

Although the reaction of trialkylsilyl ketene acetals had been previously known (11, 39, 55), the ketenes used were generated from the trialkylsilyl ketene acetals themselves and the reaction was limited to the formation of "Claisen-type" β-keto ester derivatives.





The reaction has been proposed to proceed through a six-membered transition state (39). (Figure 6).

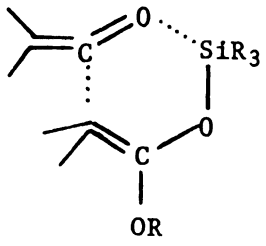
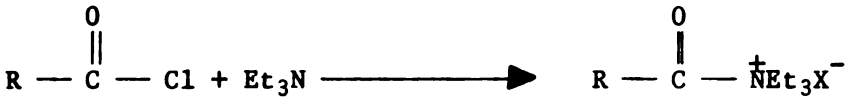
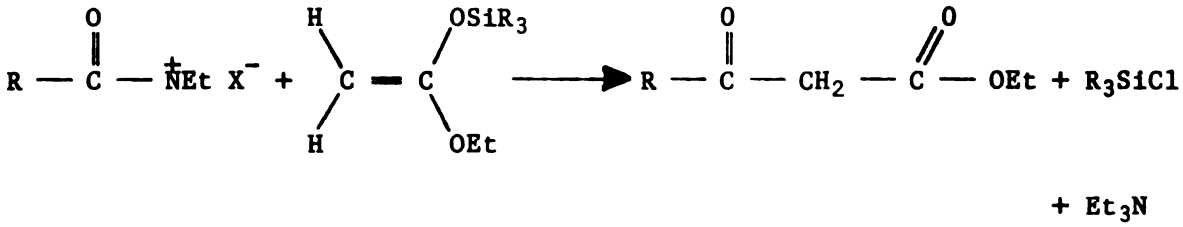
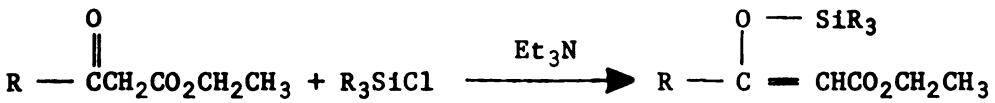


Figure 6. Transition State of Reaction Between Ketenes and Ketene Acetals

However, in view of the results obtained with pivaloyl and benzoyl chloride, the intermediate acyl ammonium salt formed must also be capable of reaction.

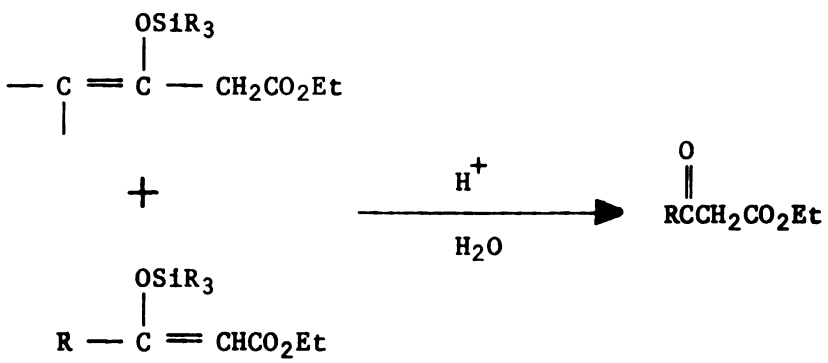






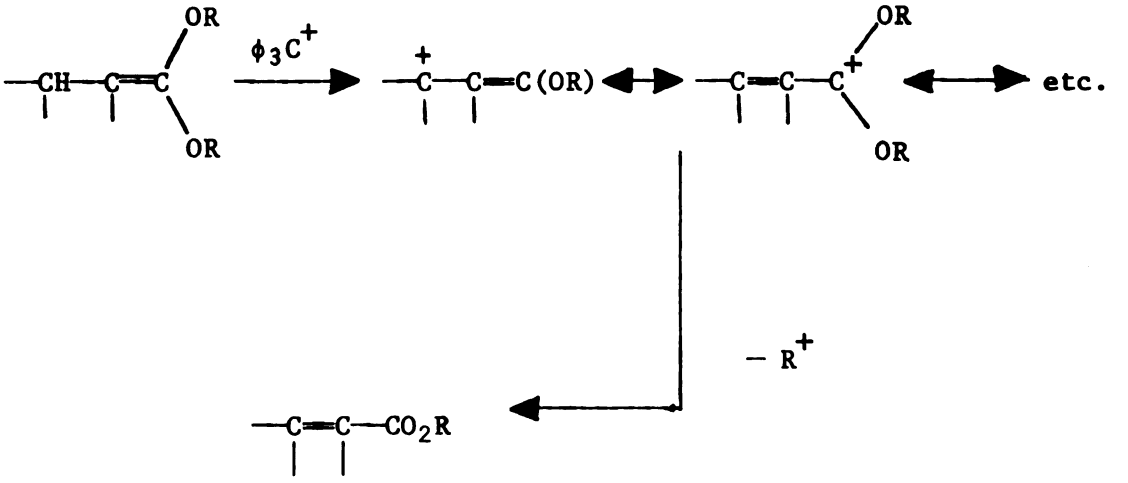
The last step, the silylation of a α-keto ester, is a rapid process catalyzed by the triethylamine (56).

Since free β-keto esters are sensitive to decarboxylation, this procedure provides a method of synthesizing these labile compounds in a derivatized form of long shelf life. The β-keto ester can be generated as needed by mild acid treatment of the siloxy derivative.



III. Reaction of Electron-rich Double Bonds with Trityl Fluoroborate

Ionic trityl compounds of the form ϕ_3CX have long been used as hydride abstractors in organic synthesis (57, 58). In view of the potential stabilization inherent in the two oxygens present, ketene acetals should behave as ready hydride donors when treated with trityl salts. β,γ-Unsaturated esters are the expected products of this reaction.



Indeed, when 0,0'-dimethyl dimethylketene acetal was treated with trityl bromide in the presence of mercuric bromide, an intermediate compound was formed which when heated further yielded methyl 2-methyl-2-propenoate and triphenylmethane (59).

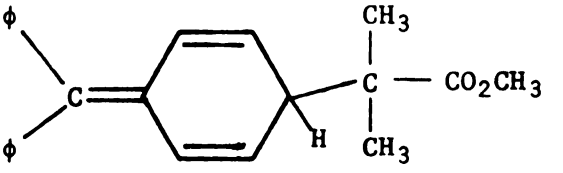
$$(CH_3)_2C{=}C(OCH_3)_2 \xrightarrow[HgBr_2]{\phi_3CBr} [\ X\ ] \xrightarrow{\Delta} \underset{CH_3}{\overset{|}{CH}}{=}\underset{H}{\overset{|}{C}}CO_2CH_3 + \phi_3CH$$

Although formally a hydride abstraction, the reaction has been proposed to be an addition-elimination reaction with the intermediate first formed having the structure of methyl 2-tritylisobutyrate, V.

$$X \equiv (CH_3)_2\underset{C\phi_3}{\overset{|}{C}}CO_2CH_3$$

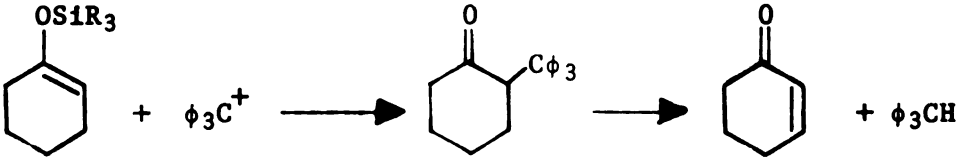
V

Subsequent work (60) has shown that the intermediate actually had the quinoid structure, VI, and the elimination step was an early example of a 1,5-sigmatropic rearrangement.



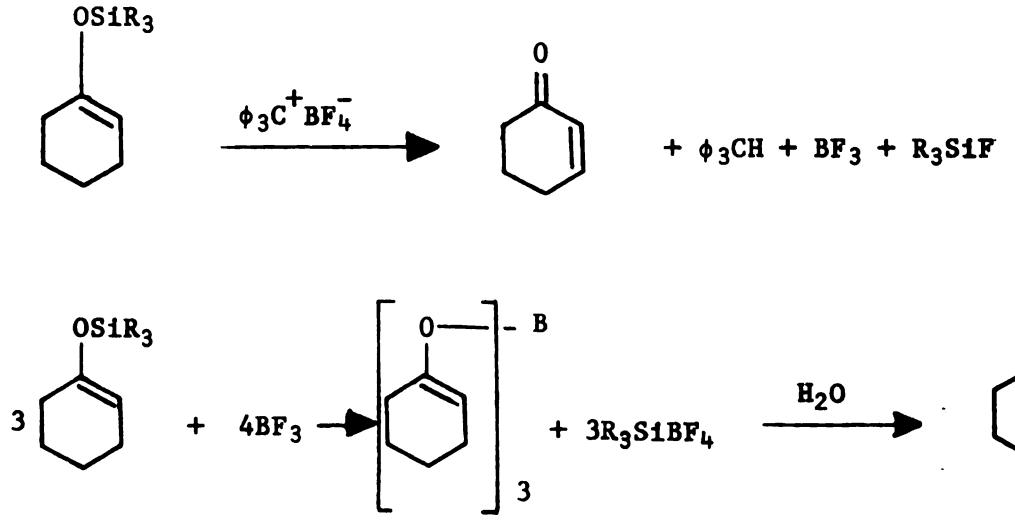
VI

The addition compound obtained when α-trimethylsiloxystyrene was added to trityl fluoroborate suggests that an addition-elimination reaction may be operating in our reaction.



However, attempts to isolate an intermediate addition compound for other silyl enol ethers failed.

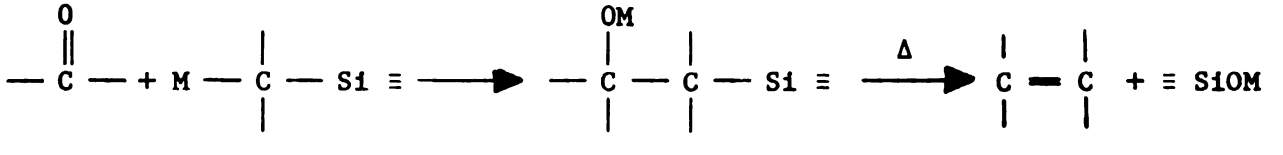
The difficulties encountered in attempting to improve this procedure may be due to a completing reaction at the oxygen of the enol ether.



The effect of boron trifluoride on the reaction of siloxyalkenes with water has been substantiated. The siloxyalkenes themselves were inert when treated with 2 M carbonate solutions. However, treatment of the enol ethers with $BF_3.OEt_2$, followed by addition of carbonate solution, did produce ketone.

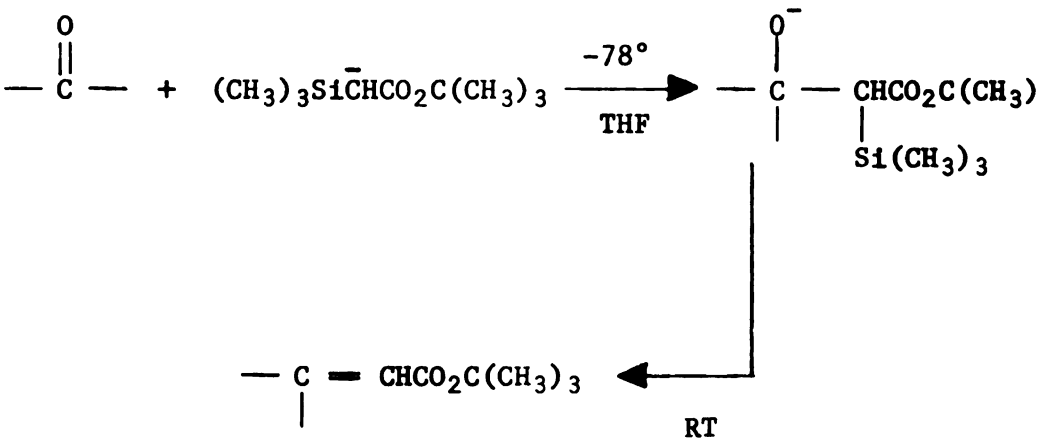
IV. Reactions of C-silylated Esters

β-Oxidosilanes undergo elimination reactions (61) when heated in an inert solvent. They have been used in a number of olefin-forming reactions starting from a silane and a carbonyl compound.

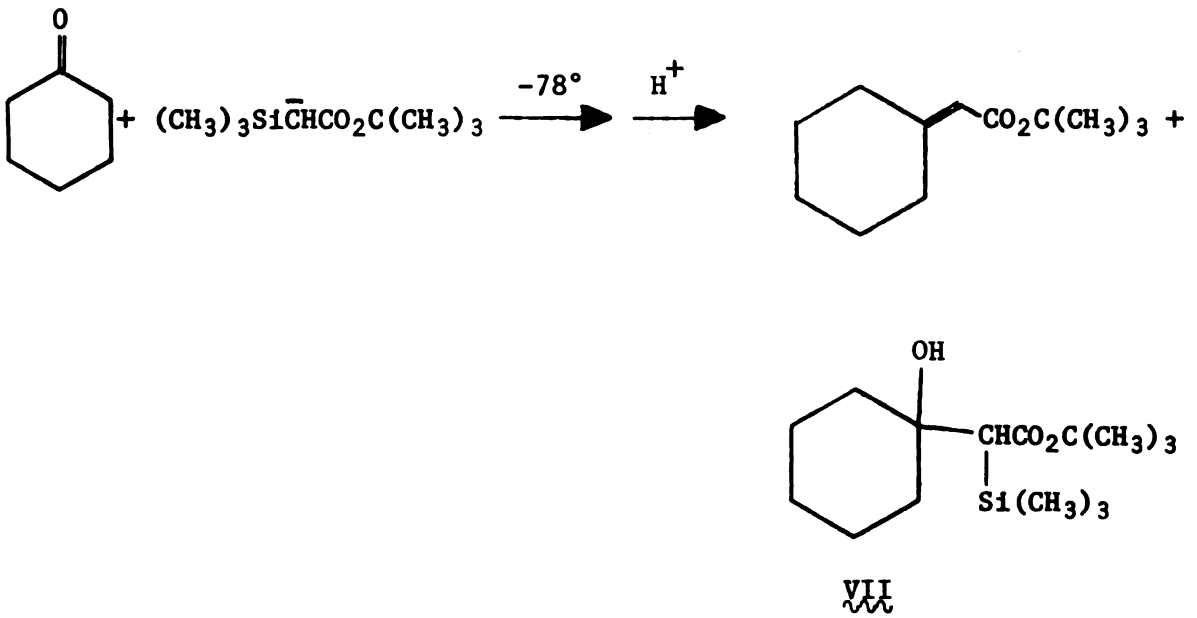


M = metal

Addition of carbonyl compounds to 1 M THF solutions of lithio t-butyl 2-trimethylsilylacetate at -78° produced β-oxido intermediates which when warmed eliminated the elements of lithio trimethylsiloxide to generate α,β-unsaturated esters.

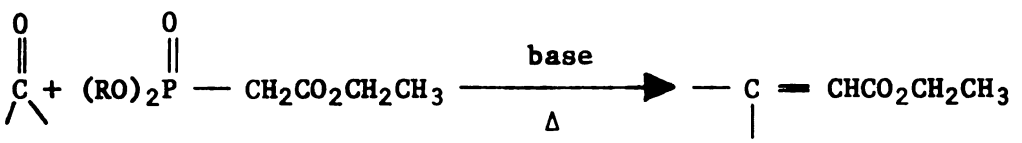


The unsaturated esters were free of any α,β-unsaturated isomers (< 1%). When cyclohexanone was added to a 1 M solution of lithio t-butyl 2-trimethylsilylacetate at -78° and then warmed to room temperature, t-butyl 2-cyclohexylideneacetate was the only product obtained. Rapid quenching of this solution at -78°, after mixing, yielded 90% of the same product and 5% of VII. This compound was readily isolable and supports the claim that elimination of lithium trimethylsiloxide occurred rapidly at -78° to form the α,β-unsaturated ester (40).



VII

The modification of the Wittig reaction (62) using phosphonate esters is the only comparable method capable of producing α,β-unsaturated esters, essentially free of contaminating β,γ-unsaturated isomers.



However, this procedure requires much more vigorous reaction conditions than the addition of carbonyl compounds to the enolates of α-silyl esters, and care must be taken to exclude any excess base used to generate the ylid to avoid isomerization of the products.

EXPERIMENTAL

I. Materials

All esters and ketones were used without further purification. The trimethylchlorosilane was obtained from Aldrich and distilled (b.p. 57°/atm. press.) prior to use. The N-isopropylcyclohexyl amine (b.p. 172°/atm. press.) and the diisopropyl amine (b.p. 83°/atm. press.) were also distilled.

All solvents employed were used directly except for the HMPA which was distilled from sodium.

The t-butyldimethylchlorosilane (BDCS) was prepared as described by Corey, et. al., JACS, 6190, 94 (1972). The silane was dissolved in pentane to form a 3.6 M solution that was used in all reactions requiring BDMS.

II. Preparation of C-silylated Acetates

This procedure applies equally well to the preparation of ethyl or t-butyl 2-trimethylsilylacetate. The use of HMPA was optional in the preparation of the C-silylated t-butyl acetate. The procedure described here used ethyl acetate as the ester substrate.

A 1 M THF solution of LiICA (5.25 mmoles) was prepared as described in Chapter I and cooled to -78°. One ml of HMPA was added and the ethyl acetate (0.495 ml; 5.0 mmoles) was added slowly. After 15 minutes,

0.70 ml (5.5 mmoles) of trimethylchlorosilane was added. After 15 additional minutes, the solution was allowed to warm to room temperature. The reaction mixture was extracted with 2 M HCl and pentane. The yield of ethyl 2-trimethylsilylacetate obtained was 90%.

Ethyl 2-Trimethylsilylacetate

B.p. 154°/atm. press. Refractive index $n_D^{23^\circ}$ 1.4150.

NMR(CCl_4): 4.05δ (q,2H), 1.8δ (s,2H), 1.2δ (t,3H), 0.1δ (s,9H).

t-Butyl 2-Trimethylsilylacetate

B.p. 169°/atm. press. Refractive index $n_D^{24.5^\circ}$ 1.4166.

NMR(CCl_4): 1.75δ (s,2H), 1.45δ (s,9H), 0.15δ (s,9H).

III. Preparation of O-Silylated Acetals

The use of trimethylchlorosilane is recommended only for the more acid-insensitive ketene acetals such as O-trimethylsilyl-O'-ethyl dimethylketene acetal. To obtain less substituted acetals free of amine, the t-butyldimethylsilyl derivative is the preferred one. Both procedures are given here.

A. O-Trimethylsilyl-O'-ethyl Dimethylketene Acetal

A 1 M solution of 5.25 mmoles of LiICA was prepared as described previously. The solution was cooled to -78° and 1.34 ml (5.0 mmoles) of ethyl isobutyrate was added slowly. After 15 minutes, a 10% excess (0.70 ml; 5.5 mmoles) of trimethylchlorosilane was added.

The reaction mixture was warmed to 0° after 5 minutes at -78°. Pentane was added. The amine may be extracted from the cold solution using dilute HCl, but the use of acetic acid (0.30 ml; 5.25 mmoles) in 5 ml of H_2O afforded much milder conditions while being just as effective. The O-trimethylsilyl-O'-ethyl dimethyl-ketene acetal was obtained in 90% yield.

O-Trimethylsilyl-O'-ethyl Butylketene Acetal

B.p. 96.5°/19 mm. Refractive index $n_D^{24.5^\circ}$ 1.4264.
NMR(CCl_4): 3.75δ (m,3H), 1.9δ (m,2H), 1.1δ (m,10H), 0.2δ (s,9H).

O-Trimethylsilyl-O'-ethyl Dimethyl Ketene Acetal

B.p. 75°/41 mm. NMR(CCl_4): 3.7δ (q,2H), 1.55δ (s,3H), 1.5δ (s,3H), 1.2δ (t,3H), 0.18δ (s,9H).

O-Trimethylsilyl-O'-ethyl Cyclohexylideneketene Acetal

NMR(CCl_4): 3.7δ (q,2H), 2.0δ (broad band, 4H), 1.45δ (broad band, 6H), 1.1δ (t,3H), 0.15δ (s,9H).

O-t-Butyl-O'-trimethylsilyl Ethylketene Acetal

NMR(CCl_4): 3.75δ (t,1H), 1.9δ (m,2H), 1.3δ (s,9H), 0.2δ (s,9H).

t-Butyl 2-Trimethylsilylbutanoate

NMR(CCl_4): 1.8δ (t,1H), 1.5δ (s,9H), 1.1δ (m,5H), 0.1δ (s,9H).

B. 0-t-Butyldimethylsilyl-0'-ethyl Butylketene Acetal

The ester enolate (5.0 mmoles) of ethyl hexanoate (0.825 ml) was prepared in the same manner as lithio ethyl isobutyrate. Prior to addition of 1.4 ml of the 3.6 M solution of BDCS in pentane, 0.4 ml of HMPA (2.5 mmoles) was injected in to the solution. The solution was warmed to room temperature. Pentane was added and the solution was extracted with H_2O to remove the HMPA. The reaction mixture was then cooled to 0° and 0.30 ml (5.25 mmole) of HOAC in 5 ml of H_2O was added slowly with stirring. Enough water was added to dissolve any precipitate. The organic layers were collected, dried and evaporated. The 0-t-butyldimethylsilyl-0'-ethyl butylketene was obtained quantitatively. This crude reaction product was sufficiently pure to be used further without distillation, thereby avoiding any thermal decomposition.

NMR(CCl_4): 3.95δ (t,1H), 3.75δ (q,2H), 2.0δ (m,2H), 1.35δ (m,10H), 1.05δ (s,9H), 1.05δ (s,9H), 0.25δ (s,6H).

0-t-Butyldimethylsilyl-0'-ethyl Ketene Acetal

B.p. 30°/0.2 mm. NMR(CCl_4): 3.73δ (q,2H), 3.1δ (d,1H), 2.9δ (d,1H), 1.3δ (t,3H), 0.95δ (s,9H), 0.15δ (s,6H).

0-t-Butyldimethylsilyl-0'-ethyl Vinylketene Acetal

B.p. 60°/0.4 mm. NMR(CCl_4): 6.4δ (doublet of triplets,1H), 4.55δ (m,3H), 3.85δ (q,2H), 1.3δ (t,3H), 1.0δ (s,9H), 0.15δ (s,6H).

IV. Reactions of O-Trialkylsilyl-O-alkyl Ketene Acetals

A. Oxidation of O-Trimethylsilyl Dimethylketene Acetal

A 2.5 ml, 2 M solution of 85% m-chloroperbenzoic acid (8.6 g) in THF was added to a 1 M THF-ketene acetal (5.0 mmoles) solution at 0°. After 5 minutes the solution was warmed to room temperature and the THF evaporated. The solid precipitate (m-chlorobenzoic acid) was filtered and washed with pentane. The lone product of ethyl 2-trimethylsiloxyisobutyrate was obtained in 64% yield. NMR(CCl_4): 4.2δ (q,2H), 1.3δ (t,3H), 0.15δ (s,9H).

B. Iodination of O-Trimethylsilyl-O'-ethyl Butylketene Acetal

The ketene acetal was generated at -78° as described above. (Section IIIA). To this solution, 1.4 g (5.5 mmoles) of iodine was added and after 15 minutes the solution was warmed to room temperature. Pentane was added and the solution was washed twice with a 2 M $NaHSO_3$ solution after removal of the amine with 2 M HCl (2.6 ml; 5.2 mmoles). The organic layer was dried and the solvent evaporated. Ethyl 2-iodohexanoate was obtained in a 90% yield. NMR(CCl_4): 4.15δ (t,1H), 4.1δ (q,2H), 1.9δ (q,2H), 1.0δ (m,10H).

C. Condensation with Acid Chlorides in the Presence of Triethyl Amine

The reaction using acetyl chloride is representative. The usual 50 ml round-bottom flask with septum inlet (Figure 3) was used.

The triethyl amine (0.695 ml; 5 mmoles) was added slowly to a 1 M solution of acetyl chloride (0.355 ml; 5 mmoles) and O-t-butyldimethyl-O'-ethyl ketene acetal (1.18 ml; 5.0 mmole) in THF at 0°. The reaction was monitored by glpc. After 6 hours the ketene acetal was completely reacted. Pentane was added with an equal volume of water. The organic layer was collected, dried and evaporated. The yield of ethyl 3-trimethylsiloxy-3-butenoate was 86%. The spectral and physical data of the silylated β-keto esters produced in this fashion are listed here:

Ethyl 3-t-Butyldimethylsiloxy-3-butenoate:

B.p. 69°/1.25 mm. Refractive index $n_D^{25°}$ 1.4374.
NMR(CCl_4): 4.15δ (s,2H), 4.1δ (q,2H), 3.0δ (s,2H), 1.3δ (t,3H), 0.95δ (s,9H), 0.2δ (s,6H).

Ethyl 3-t-Butyldimethylsiloxy-3-hexenoate:

B.p. 80°/0.2 mm. Refractive index $n_D^{24.5°}$ 1.4449.
NMR(CCl_4): 4.6δ (t,1H), 4.15δ (q,2H), 2.95δ (s,2H), 2.1δ (t,2H), 1.3δ (t,3H), 1.0δ (t+s, 12H), 0.2δ (s,6H).

Ethyl 3-t-Butyldimethylsiloxy-3-phenyl-2-propenoate:

B.p. 135°/0.3 mm. Refractive index $n_D^{25°}$ 1.5145
NMR(CCl_4): 7.5δ (m,5H), 5.65δ (s,1H), 4.2δ (q,2H), 1.35δ (t,3H), 1.0δ (s,9H), 0.2δ (s,6H).

Ethyl 3-t-Butyldimethylsiloxy-3-isohexenoate and Ethyl 3-t-Butyldimethylsilyl-siloxy-2-isohexenoate (50:50 mixture)

B.p. 78°/0.1 mm. NMR(CCl_4): 5.0δ (s,1H), 4.15δ (q,4H), 3.1δ (s,2H), 2.25δ (m,1H), 1.65δ (s,6H), 1.25δ (sextet,6H), 1.0δ (s,18H), 0.2δ (s,6H), 0.1δ (s,6H).

Ethyl 3-t-Butyldimethylsiloxy-4,4-dimethyl-2-penenoate

NMR(CCl_4): 5.0δ (s,1H), 4.1δ (q,2H), 1.3δ (t,3H), 1.15δ (s,9H), 1.0δ (s,1H), 2.5δ (s,6H).

Ethyl 3-t-Butyldimethysiloxy-3-cyclohexylidenepropionate and ethyl 3-t-Butyldimethylsiloxy-3-cyclohexyl-2-propenoate (38:51 mixture)

B.p. 120°/0.7 mm. NMR(CCl_4): 5.0δ (s), 4.1δ (m), 3.07δ (s), 1.75δ (broad signal), 1.3δ (sextet), 1.0δ (s), 0.3δ (s), 0.15δ (s).

Ethyl 3-t-Butyldimethylsiloxy-3,5-hexadienoate

B.p. 85°/0.2 mm. Refractive index $n_D^{24.5°}$ 1.4677.
NMR(CCl_4): 6.6δ (doublet of triplets,1H), 5.1δ (m,3H), 4.15δ (q,2H), 3.0δ (s,2H), 1.3δ (t,3H), 1.0δ (s,9H), 0.2δ (s,6H).

V. Alkylation of Ester Enolates

A. With Triethyloxonium Fluoroborate

Triethyloxonium fluoroborate (10.0 mmoles) was prepared in a 50 ml round bottom flask with septum inlet as described in Org. Syn. 52, 1080. The separated crystals were washed with ether (by

syringe) and cooled under N_2 to -78°. The flask was then charged with a cold solution (-78°) of lithio ethyl isobutyrate (10 mmoles). After 3.5 hours the solution was quenched with H_2O. Pentane was added. The organic layer was collected, dried and evaporated. The only high boiling material present was collected and identified as ethyl 2,2-dimethylbutanoate. NMR(CCl_4): 4.1δ (q,2H), 1.40δ (q,2H), 1.25δ (t,3H), 1.14δ (s,6H), 0.85δ (t,3H). Addition of 2 ml of HMPA still yielded no O-alkylated products but the reaction was complete in a shorter time.

B. With Magic Methyl

The enolate of lithio ethyl isobutyrate (10 mmoles) (see Chapter I - Experimental) was generated at -78°. Two ml of HMPA was added. The methylfluorosulfonate (0.76 ml; 10 mmoles) was then added. After 10 ml pentane were added, the solution was examined by glpc. Only ethyl pivaloate was present as determined by NMR of a collected sample. NMR(CCl_4): 4.1δ (q,2H), 1.3δ (q,2H), 1.3δ (t,3H), 1.17δ (s,9H).

C. With Methylsulfate and TMEDA

The lithio ethyl isobutyrate (10.0 mmoles) was generated as above. The tetramethylethylenediamine (1.51 ml) was then added. After 5 minutes, 0.95 ml (10.0 mmoles) of dimethylsulfate was added. Pentane was added and the solution was examined by glpc. Only

ethyl pivaloate was present (compared with authentic material).

VI. Addition of Acids to O-Trimethylsilyl-O'-ethyl Dimethylketene Acetal

To a 1 M solution of 5.0 mmoles of the ketene acetal in THF (2.09 ml), 0.74 ml of a 6.77 M solution of HCl in THF was added at -78°. Butyllithium (10.0 mmoles) was then added to the solution. After addition of H_2O only ethyl isobutyrate was found on glpc examination. Other acids used include HBF_4, generated from the HCl/THF solution and $NaBF_4$, $HCl-BF_3.OEt_2$, and FSO_3H. Only starting ester was formed.

Using hexane as solvent and a reaction temperature of 0° or -78° still resulted in formation of ethyl isobutyrate when fluorosulfonic acid was added to the ketene acetal.

VII. Oxidation of O-Substituted Double Bonds by Trityl Carbonium Ions

A. Reaction of O-Trimethylsilyl-O'-Ethyl Dimethylketene Acetal with Trityl Fluoroborate

A 50 ml round-bottom flask equipped as in Figure 3 was charged with 2.5 ml of CH_2Cl_2. To this was added 0.83g of triphenylcarbenium fluoroborate (2.5 mmoles) and the solution was cooled at -78°. The ketene acetal was dropped into this solution slowly. After 15 minutes the solution was "quenched" with one equivalent of a 2 M K_2CO_3 solution. Only starting ester and ethyl 2-butenoate in the ratio of 13:19, were identified by glpc and NMR. NMR(CCl_4) of

ethyl 2-methyl 2-butenoate: 6.2δ (d,1H), 5.6δ (d,1H), 4.1δ (q,4H), 1.95δ (s,3H), 1.3δ (t, 3H).

B. Reaction of 1-Siloxyalkenes with Trityl Fluoroborate

All the starting 1-siloxyalkenes were prepared by the method of House, et. al., J.O.C., 34, 2324 (1969). The physical and spectra data of these compounds are given below.

1-Trimethylsiloxycyclohexene

NMR(CCl_4): 4.75δ (m,1H), 1.8δ (m,8H), 0.15δ (s,9H).

1-Trimethylsiloxy Cyclopentene

NMR(CCl_4): 4.55δ (t,1H), 2.15δ (m,6H), 0.2δ (s,9H).

3-Trimethylsiloxy-2-pentene

NMR(CCl_4): 4.5δ (m,1H), 2.02δ (m,2H), 1.5δ (m,3H), 1.0δ (t,3H), 0.2δ (s,9H).

1-Trimethylsiloxy-1-phenylpropene

NMR(CCl_4): 7.25δ (m,5H), 5.3δ (q,1H), 1.7δ (d,3H), 0.1δ (s,9H).

α-Trimethylsiloxystyrene

B.p. 45°/0.5 mm. NMR(CCl_4): 7.1δ (m,5H), 4.1δ (d,1H), 4.25δ (d,1H), 0.25δ (s,9H).

To a 1 M solution of trityl fluoroborate (1.65 g; 5.0 mmoles) in CH_2Cl_2, 0.97 ml (5.0 mmoles) of 1-trimethylsiloxycyclohexene was

added. After 15 minutes at room temperature, the solution was analyzed by glpc after quenching with 1 equivalent of 2 M K_2CO_3 solution. Only cyclohexenone (55%) and cyclohexanone (23%) were identified by comparison with authentic material. When 1-trimethylsiloxycyclopentene was used 33% cyclopentenone and 16% cyclopentanone were recovered. All other siloxyalkenes examined returned only varying amounts of starting ketone under these conditions except for α-trimethylsiloxystyrene which, under the above conditions, yielded 3,3,3-triphenylpropiophenone. NMR(CCl_4): 7.2δ (s,20H), 4.25δ (s,2H), M. S. parent peak 362. [See Can. J. Chem., 42, 298 (1964).]

VIII. Preparation of (cis/trans) Ethyl Cinnamate from Ethyl 2-Trimethylsilylacetate

A 50 ml round-bottom flask as shown in Figure 3 was used to prepare 5.25 mmoles of LiICA in THF as described in Chapter I. The solution was cooled to -78° and 5.0 mmoles of the silylated ester (0.90 ml) were added dropwise. After 5 minutes, 0.51 ml of benzaldehyde (5.0 mmoles) was also added dropwise. In 15 minutes the solution was warmed to room temperature for 15 minutes. The solution was quenched with two equivalents of dilute HCl after an equal volume of pentane had been added. The organic layers were collected, dried and the solvent evaporated. The yield of cis(1)/trans(5) ethyl cinnamate was 67%. NMR (CCl_4): (Trans isomer) 7.42δ (m,5H), 7.7δ (d,1H), 6.38δ (d,1H), 4.25δ (q,2H), 1.35δ (t,3H). (Cis isomer) 7.5δ (m,5H), 6.92δ (d,1H), 5.9δ (d,1H), 4.18δ (q,2H), 1.25δ (t,3H).

CHAPTER IV

THE STRUCTURE AND DECOMPOSITION OF ESTER ENOLATES IN SOLUTION

INTRODUCTION

Although the chemistry of ester enolates has been studied extensively for the last few years, nothing is known of enolate structure in solution or the mode of decomposition of ester enolates when warmed above -78°.

There are two possible structures for an ester enolate in solution, the carbon-metalated ester, I, or the oxygen-metalated enolate, II.

M = metal

I II

The NMR spectra of these two species are expected to be appreciably different and examination of a solution of ester enolate at -78° should disclose which of the two structures is preferred.

The isolation of an ester enolate, besides providing a useful synthetic intermediate, would allow spectral examination of enolate structure in a variety of solvents, in the absence of amines. It would also be of interest to determine whether the enolate structure, I or II, is dependent on solvent.

The products of ester enolate decompositions have been tentatively identified as β-keto esters. (10). With this in mind, three possible decomposition routes present themselves for further consideration. These are: first, formation of a ketene which then reacts with more enolate; second, direct coupling of two moles of ester enolate; and third, proton abstraction by the enolate from solvent or amine to form free ester which then reacts with ester enolate to form a β-keto ester. (Figure 7). Application of the kinetic method to solutions of decomposing ester enolates should differentiate between these possible reaction paths.

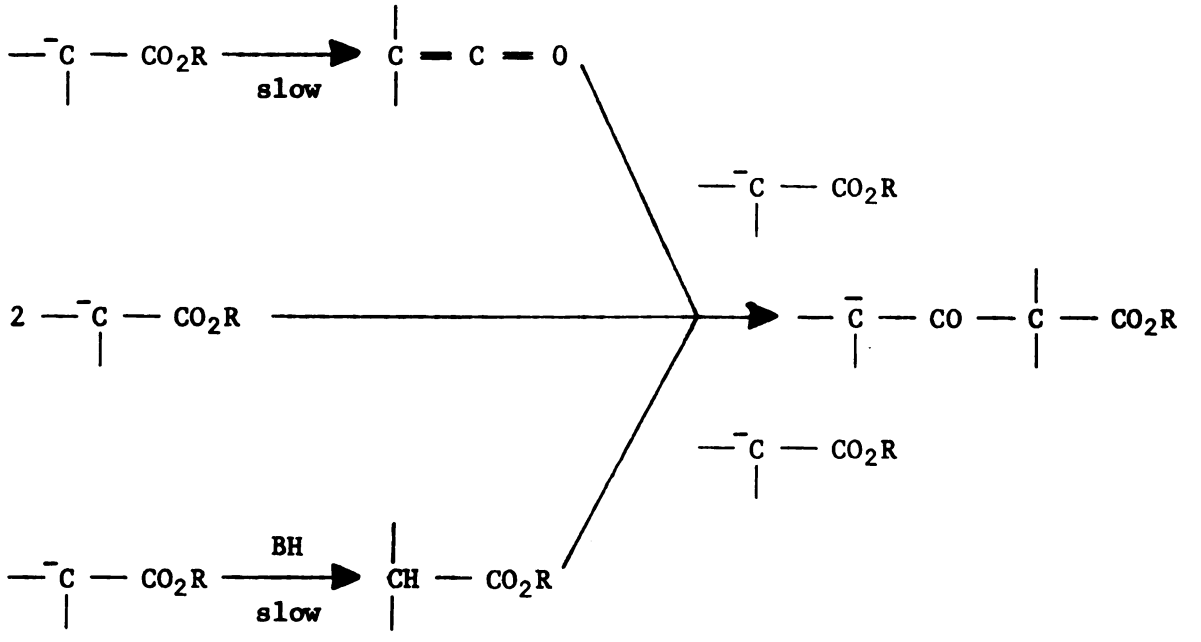


Figure 7. Possible Decomposition Routes of Ester Enolates

RESULTS

An NMR spectrum of lithio t-butyl acetate generated from lithium hexamethyldisilazane in THF at -60°, revealed two broad signals at δ2.72 and δ2.55 (relative to the HMDS) and two singlets, the larger at δ1.3 and the smaller at δ1.35. As the solution was warmed to 35°, the smaller singlet increased in intensity at the expense of the singlet at δ1.3. New singlets appeared at δ1.05, δ1.68, and δ4.5. The broad signals at δ2.72 and δ2.55 also disappeared. The new singlets were in the approximate ratio of 1:3:9:9 (low field to high field). The decomposition product has been assigned the structure of the enolate of t-butyl acetoacetate.

$$2H_2\bar{C} - CO_2C(CH_3)_3 \longrightarrow CH_3CO - \bar{C}H - CO_2C(CH_3)_3$$

Lithio t-butyl acetate has also been isolated free from contaminating amine, taking advantage of the fact that this low molecular weight enolate is relatively insoluble in non-polar solvents. A solution of lithio t-butyl acetate in hexane was prepared in the usual fashion, using lithium isopropylcyclohexyl amide as base. The enolate solution was clear at -78°; however, a precipitate formed on warming the solution to room temperature. Removal of the supernatant liquid resulted in a 40-42% yield of solid lithio t-butyl acetate. Quenching of the supernatant liquid with dilute acid produced an additional 50% recovery of t-butyl acetate. The solubility of lithio t-butyl acetate

in hexane was attributed to the presence of amine. Indeed, isolated lithio t-butyl acetate had no solubility in hexane at room temperature, as shown by glpc examination of a hexane-lithio t-butyl acetate mixture. Addition of an amine to this mixture, either HMDS or ICA, resulted in greatly enhanced enolate solubility. It has been found that two moles of amine are required to dissolve one mole of lithio t-butyl acetate in hexane at room temperature.

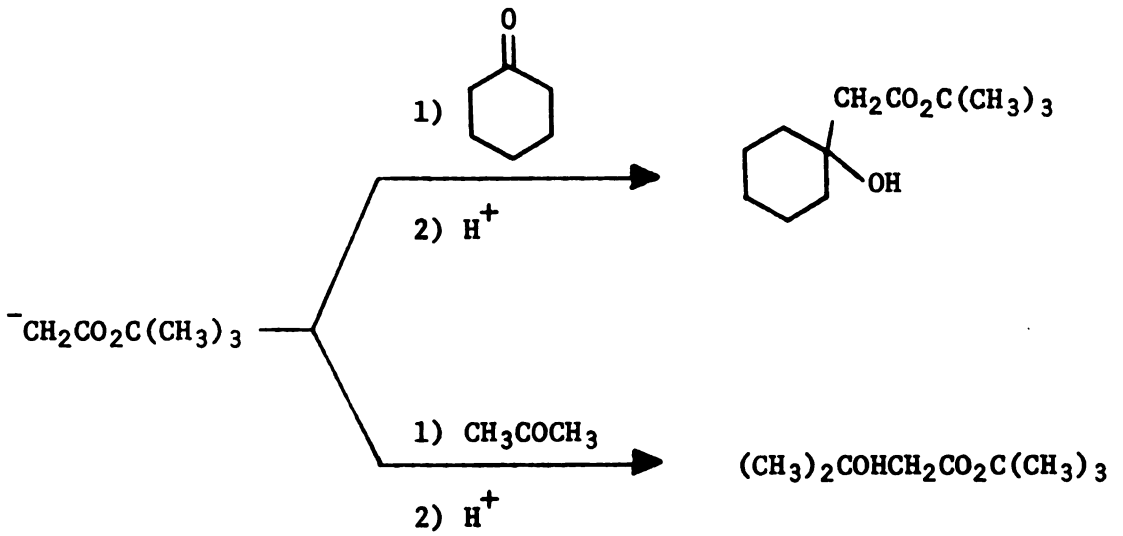
$$\underset{\text{[insoluble in hexane]}}{{}^{-}CH_2CO_2C(CH_3)_3} \xrightarrow{2 \text{ amines}} \underset{\text{[soluble in hexane]}}{({}^{-}CH_2CO_2R)\cdot(2 \text{ amines})}$$

When lithium diisopropyl amide was used to generate the lithio t-butyl acetate in hexane, a precipitate again formed upon warming of the enolate solution. However, the use of this more volatile amine permitted evaporation of amine with solvent, producing a 90% yield of solid lithio t-butyl acetate.

The NMR spectrum of lithio t-butyl acetate in benzene showed two broad singlets at 2.45 and δ2.2 (relative to benzene at δ7.25). In addition there was a sharp singlet at δ1.6. Integration of these peaks showed their ratio to be 1:1:9 (low field to high field).

Solutions of lithio t-butyl acetate reacted exothermically with one equivalent of cyclohexanone in toluene to produce the corresponding

β-hydroxyester. Acetone reacted in a similar fashion. Both β-hydroxyesters were produced quantitatively.



Solutions of lithio t-butyl acetate, generated using LiICA in THF, decomposed at 23 ± 1° following a first order rate law (63). A graph of the log of the change in recovered t-butyl acetate concentration vs time yielded a straight line (Figure 8).

Solutions of lithio ethyl isobutyrate and lithio ethyl hexanoate showed approximately the same first order decomposition kinetics (Figures 9, 10).

This kinetic data discounted a direct dimerization route in the decomposition of the enolates.

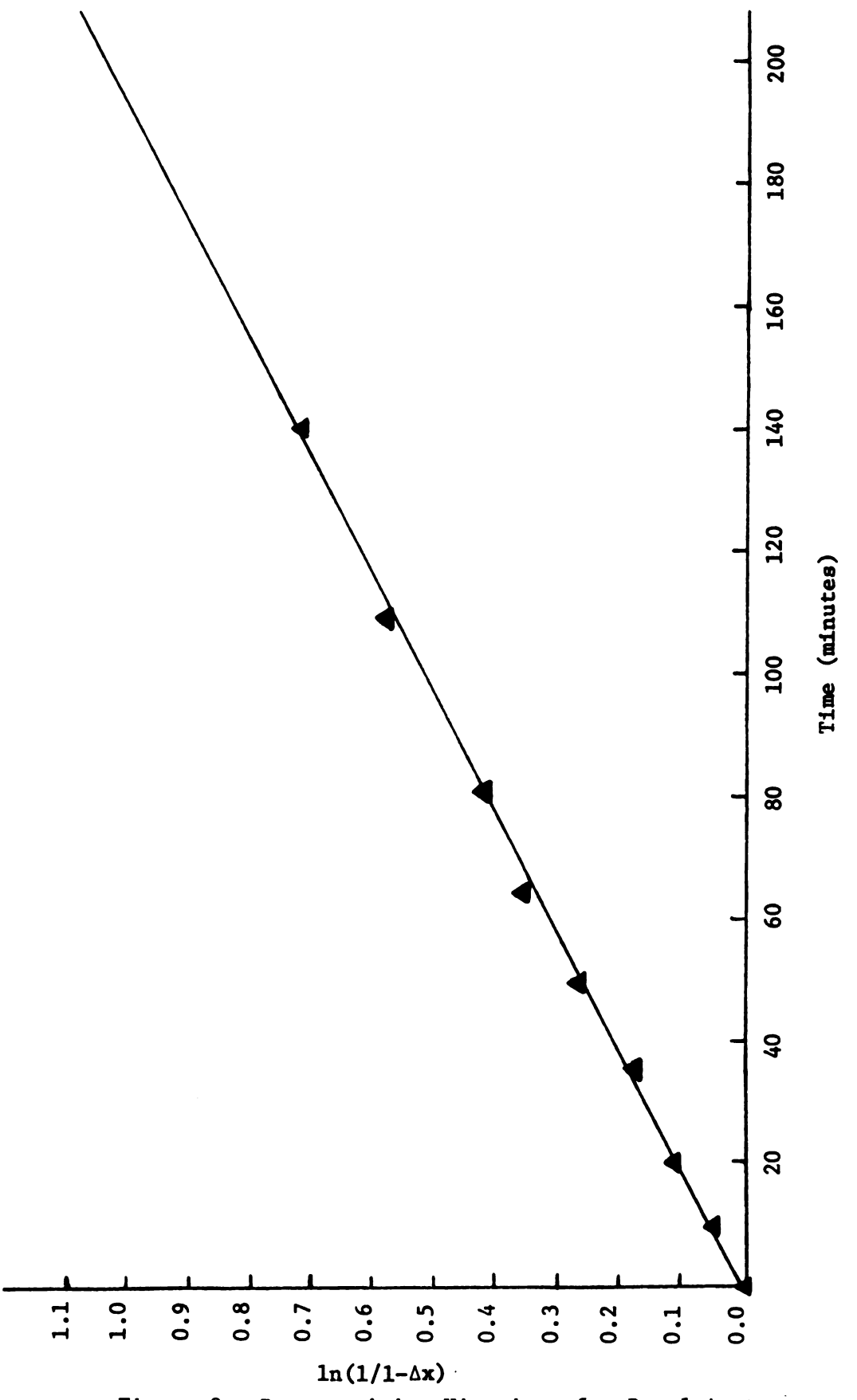


Figure 8. Decomposition Kinetics of t-Butyl Acetate

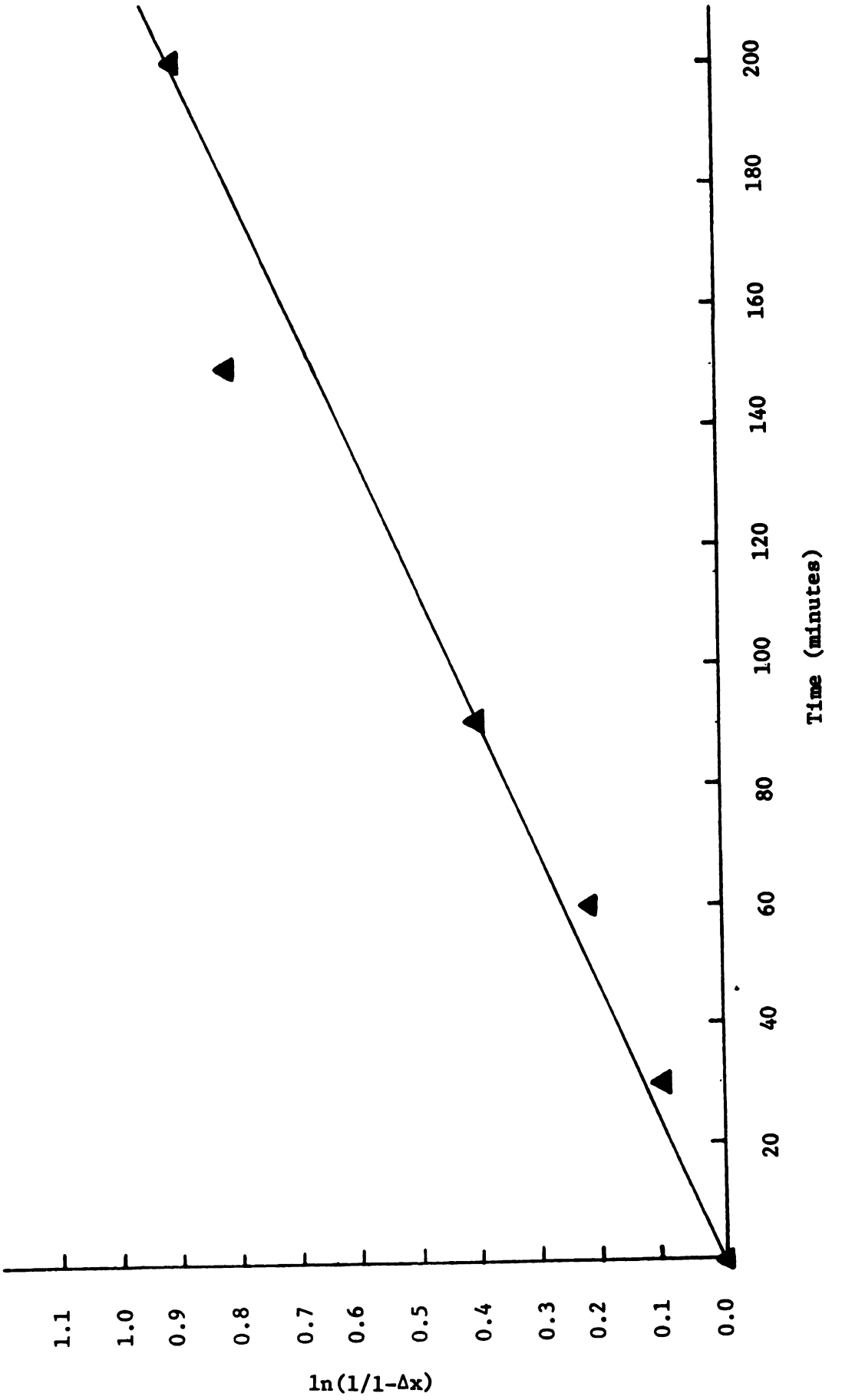


Figure 9. Decomposition Kinetics of Ethyl Hexanoate

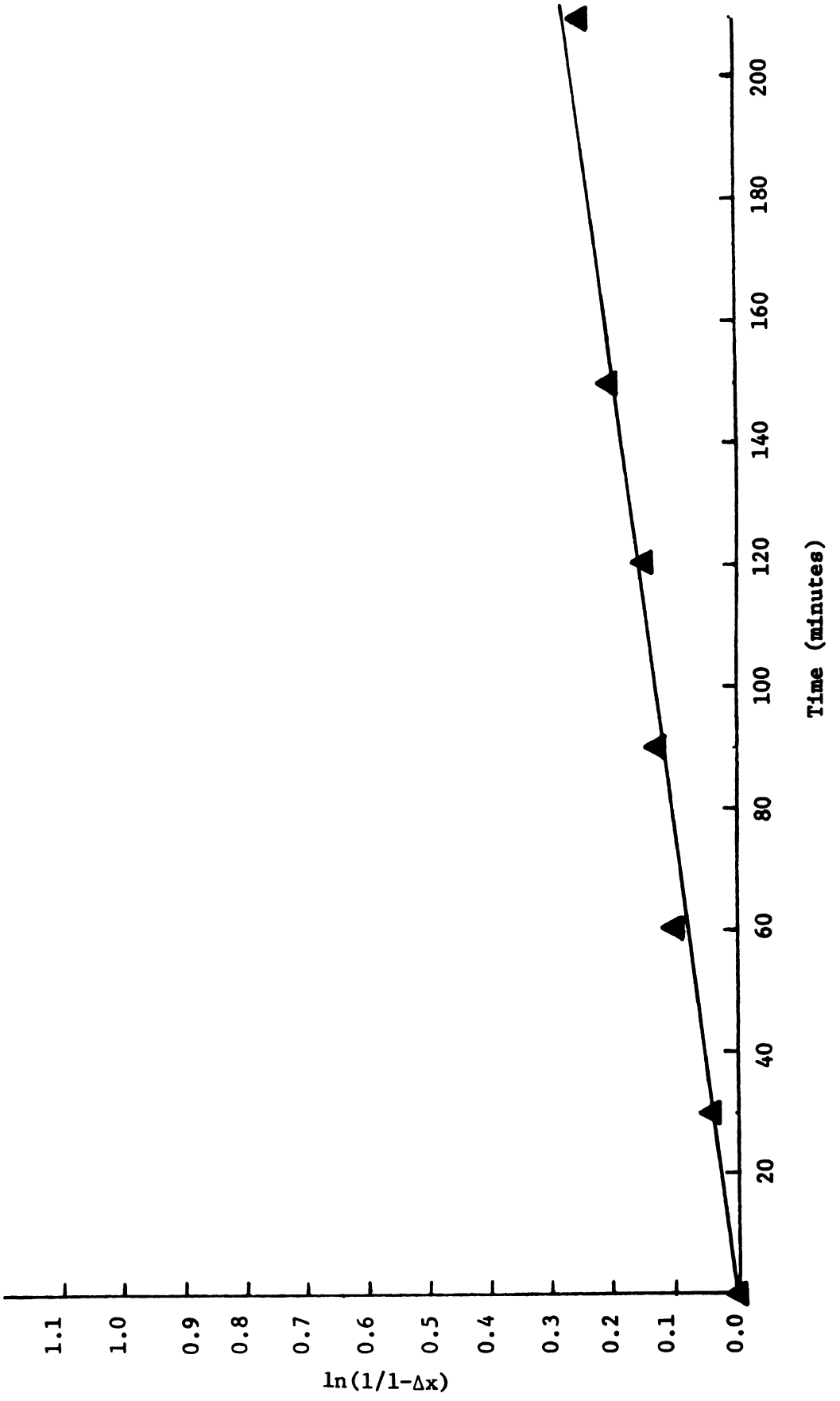


Figure 10. Decomposition Kinetics of Ethyl Isobutyrate

$$2\ LiCH_2CO_2C(CH_3)_3 \longrightarrow LiCH_2COCH_2CO_2C(CH_3)_3$$

Two other possible routes remained under consideration (see Figure 7): proton abstraction by the enolate from solvent or amine to form ester or formation of ketene. Of these, the formation of ketene was the most appealing, and steps to trap or isolate such an intermediate were undertaken.

Addition of two equivalents of phenyl magnesium bromide to a solution of lithio t-butyl acetate at -78° produced, on warming, a 13% yield of acetophenone. Acetophenone was the expected product of reaction of the Grignard reagent with ketene.

$$LiCH_2CO_2C(CH_3)_3 \longrightarrow CH_2 = C = O + LiCO(CH_3)_3$$

$$CH_2 = C = O + C_6H_5MgBr \longrightarrow {}^{-}CH_2COC_6H_5 \xrightarrow{H^+} CH_3COC_6H_5$$

However, acetophenone may also be formed by reaction of the Grignard with free ester.

$$LiCH_2CO_2C(CH_3)_3 \xrightarrow{SH} CH_3CO_2C(CH_3)_3$$

$$CH_3CO_2C(CH_3)_3 + C_6H_5MgBr \longrightarrow CH_3COC_6H_5$$

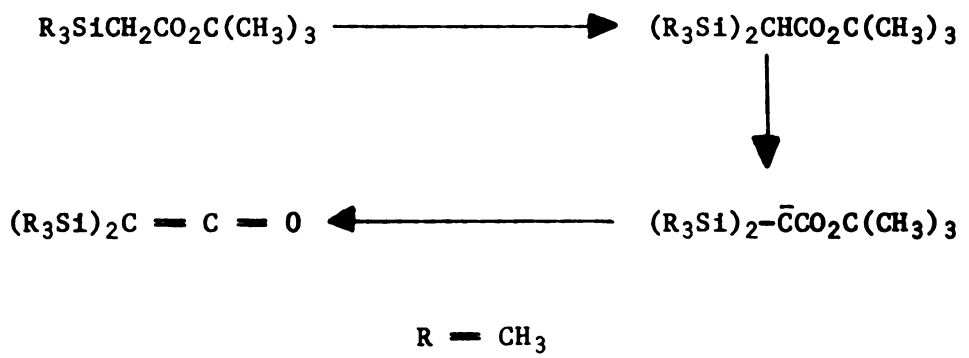
$$CH_3COC_6H_5 + B^- \longrightarrow {}^-CH_2COC_6H_5 + BH$$

$$B^- = C_6H_5^- \quad \text{or} \quad R_2N^-$$

The excess Grignard reagent, or amide formed by reaction with the excess Grignard reagent, may enolize any acetophenone formed, preventing any further reaction. No diphenylmethylcarbinol was found in the reaction mixture. The replacement of the Grignard reagent with other nucleophiles yielded no identifiable additional products.

Due to the ambiguous results obtained in the trapping experiments, our attention was turned toward the possible isolation of a ketene intermediate. The reactivity of ketenes is largely dependent on the degree of substitution at the methylene carbon of the ketene. Substitution of the methylene carbon with groups having large steric requirements produces a less reactive ketene (64). Since t-butyl 2-trimethylsilylacetate had previously been prepared, the introduction of a second trimethylsilyl group α to the carbonyl would produce an

ester whose enolate could generate an extremely hindered ketene, bis (trimethylsilyl)ketene.



The enolate of t-butyl 2-trimethylsilylacetate was generated at -78° using lithium diisopropyl amide as base. The enolate was recovered quantitatively on quenching with HCl. Addition of one equivalent of trimethylchlorosilane to this enolate solution at -78°, followed by warming to room temperature, yielded two products. Treatment of the solution with water removed the lower boiling material and distillation of the water-washed reaction mixture yielded 60% of t-butyl 2,2-bis(trimethylsilyl)acetate and 31% recovered starting material.

The enolate of t-butyl 2,2-bis(trimethylsilyl)acetate was generated at -78°, again using lithium diisopropyl amide. Upon warming, the enolate solution produced only one product, which was isolated by preparative glpc. The NMR showed one peak at δ0.28 and the infrared spectrum revealed intense signals at 2965, 2075 and

1260 cm^{-1} (65). Addition of two drops of concentrated H_2SO_4 to an ethanol solution of this material yielded ethyl 2,2-bis(trimethylsilyl)-acetate as the only product.

$$[(CH_3)_3Si]_2CHCO_2C(CH_3)_3 \xrightarrow[EtOH]{H^+} [(CH_3)_3Si]_2\overset{H}{\overset{|}{C}}CO_2C(CH_3)_3$$

On the basis of this information, the structure of the product isolated in the decomposition of t-butyl 2,2-bis(trimethylsilyl)acetate has been assigned that of bis(trimethylsilyl)ketene.

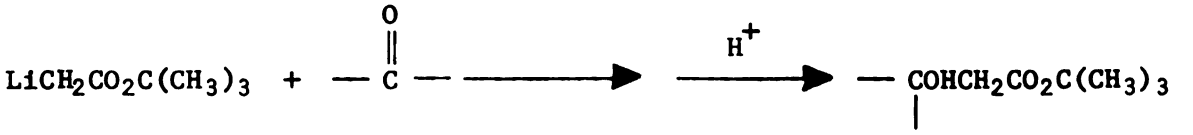
DISCUSSION

The oxygen-metalated enolate, II, rather than the carbon-metalated ester, I, is thought to be the preferred structure of the enolates of Reformatsky reagents and halomagnesium enolates (67, 68, 69, 14).

M = -ZnX, -MgX, -Li

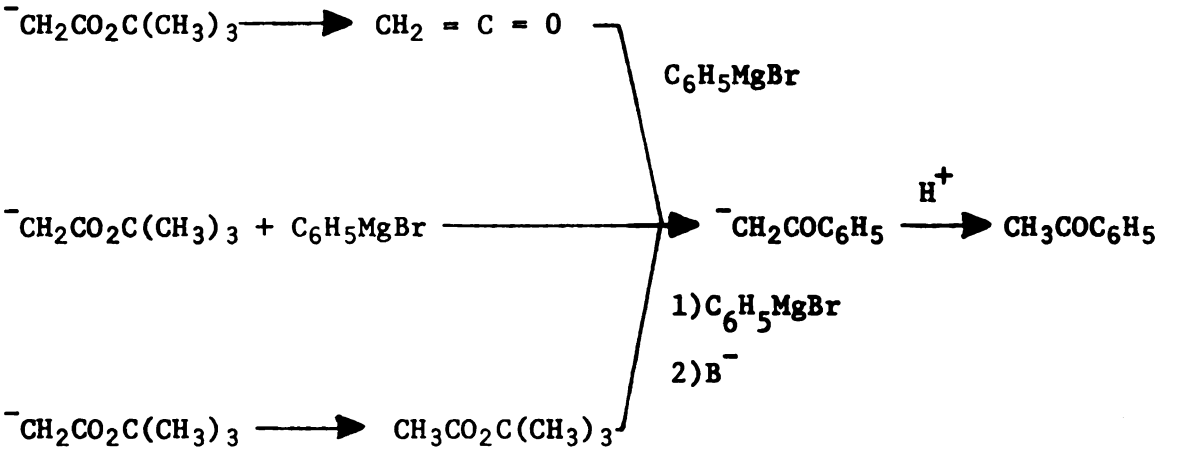
The NMR of lithio t-butyl acetate in benzene and THF also suggests that II (M=Li) is the preferred structure of a lithium ester enolate. The protons of a carbon-metalated structure would be expected to be equivalent. The non-equivalence of the α protons in the NMR of lithio t-butyl acetate indicates a large degree of double bond character in the anion.

The reactions of t-butyl acetate are those of a typical lithium ester enolate, and the isolation of lithio t-butyl acetate provides a convenient reagent for the facile introduction of a t-butyl acetate moiety into a compound via a Reformatsky-type reaction.

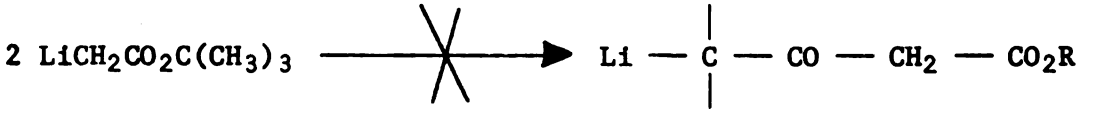


Although the structure of ester enolates in solution appears well established, the decomposition path of ester enolates is less certain.

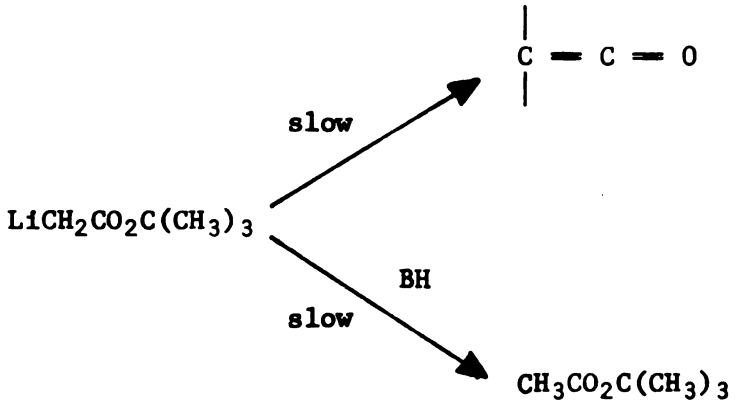
The fact that acetophenone was obtained when phenylmagnesium bromide was added to an enolate solution supports all three suggested mechanisms.



However, the kinetics of decomposition displayed by the enolates eliminates the direct enolate coupling. This path requires that the decomposition be second order in enolate concentration.

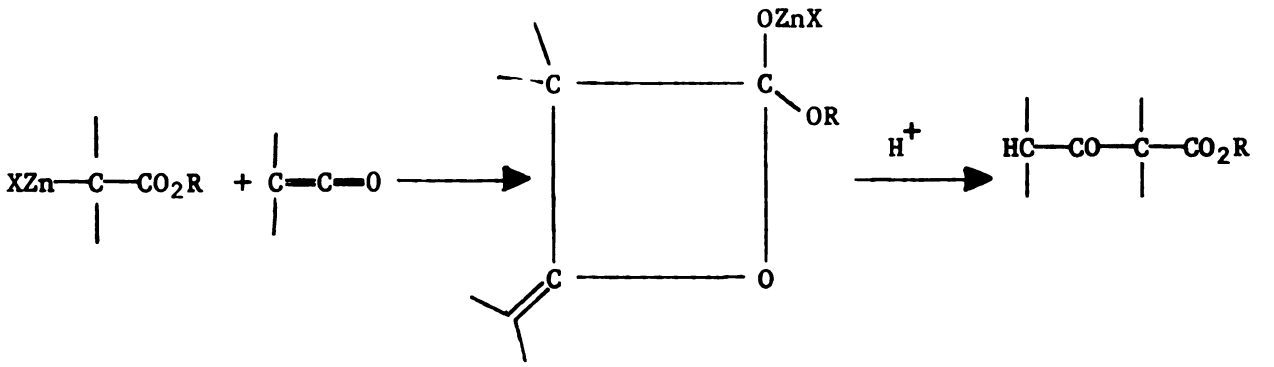


Either of the two remaining schemes under consideration was expected to display first order kinetics if the rate determining step was the formation of either a ketene intermediate or ester.

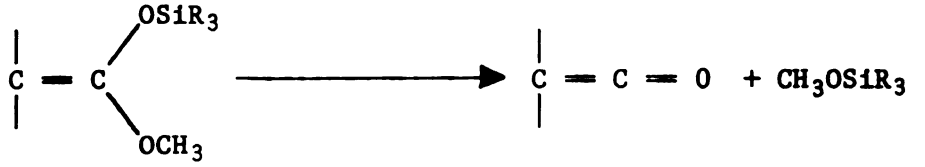


The assumption that the first step in each suggested mechanism (see Figure 7) is the rate-determining step is a reasonable one. Since, ketenes react with organometallic reagents readily, even at low temperatures (65), the reaction of a ketene with ester enolate was expected to be rapid. The reaction of an ester with an enolate was also expected to be a rapid reaction at room temperature (63).

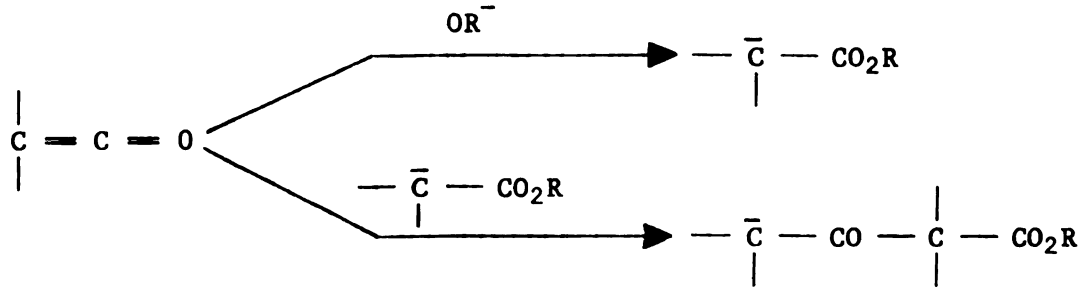
A ketene intermediate has been proposed in the decomposition of zinc ester enolates. The resultant ketene reacted with the ester enolate to produce a dimer, which gave β-keto esters on hydrolysis (14).



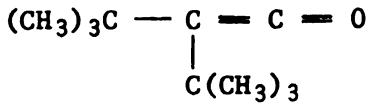
Ketenes are also produced in the thermal decomposition of silicon ester enolates (39).



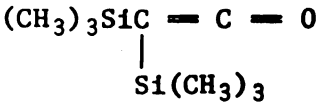
A ketene intermediate in the decomposition of lithium ester enolates could be isolated provided the reaction with alkoxide or with ester enolate can be prevented.



Increased substitution at the methylene carbon of a ketene has been shown to produce unreactive ketenes. Di-t-butyl ketene, III, has been prepared and proved to be remarkably unreactive (70).



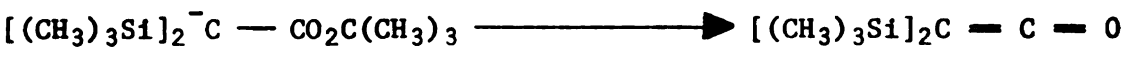
III



IV

The silyl analogue of di-t-butyl ketene, bis(trimethylsilylketene), IV, is expected to have similar properties. In fact, the larger steric requirements of the silicons may increase the silyl ketene's unreactivity. With this in mind, the t-butyl ester of 2,2-bis(trimethylsilyl)acetic acid was prepared and the enolate of this ester allowed to decompose. While other esters invariably produce higher boiling decomposition products, the only product obtained from the enolate of t-butyl 2,2-bis(trimethylsilyl)acetate was bis(trimethylsilyl)ketene

in quantitative yield.



The isolation of this ketene provides firm support for the suggestion that ester enolates decompose via ketene intermediates.

EXPERIMENTAL

I. Decomposition of Ester Enolates

The enolate of t-butyl acetate (13.4 ml) was prepared on a 50.0 mmole scale using LiICA (50.0 mmoles) as described in Chapter I. An internal standard was added, toluene, and the flask removed from the dry-ice bath and placed in an oil bath at 23° ± 1°C after a sample had been removed and examined by glpc. All samples removed were quenched with a 2 M solution of NH_4Cl. The organic layers were collected and dried. The samples were removed according to the schedule below and the recovery of t-butyl acetate noted.

t (min.)	Δx, Change in Enolate Conc. $(1M - \frac{\%\ \text{Recovery TBA}}{100})$	$\ln(1/1-\Delta X)$
0	0.00	0.000
10	0.01	0.004
20	0.11	0.050
30	0.23	0.113
45	0.33	0.172
60	0.46	0.264
75	0.56	0.358
90	0.62	0.418
120	0.74	0.592
150	0.80	0.700

The enolates of ethyl hexanoate and ethyl isobutyrate decomposed much more slowly. The recovery of starting esters at 50° ± 1° are given below:

Ethyl Hexanoate			Ethyl Isobutyrate		
t(min.)	Δx	ln(1/1-Δx)	t(min.)	Δx	ln(1/1-Δx)
0	.00	0.000	0	.000	0.000
30	.20	0.097	30	.090	0.042
60	.39	0.232	60	.210	0.102
90	.58	0.394	90	.255	0.128
150	.84	0.813	120	.300	0.154
300	.87	0.996	150	.383	0.210
			210	.418	0.236

II. NMR of Lithio t-Butyl Acetate in THF with HMDS as Base

The enolate was prepared on a 5.0 mmole scale in the usual fashion using hexamethyldisilazane (1.05 ml) as the amide base. THF-(D_8) was used as solvent. The solution was added by syringe to an NMR tube maintained at -78°. An NMR obtained at -60° on a Varian A 56/60 revealed two singlets at δ1.3 and δ1.35 (relative to the methyls of the silyl amine), a broad band at δ2.72 and a broad band at δ2.55. As the solution

was warmed to 35°, the band at δ1.3 diminished while the signal at δ1.35 increased. A singlet at δ1.05 appeared as did a singlet at δ4.5. A sharp signal also appeared at δ1.68. When the sample reached 35°, the signals at 2.55, 2.72, and δ1.3 were gone, and the peaks at 4.5, 1.68, 1.35 and δ1.05 integrated as 1H: 3H: 9H: 9H.

III. Preparation of Solid Lithio t-Butyl Acetate

A 50.0 ml flask equipped as in Figure 1 was charged with 26.25 mmoles (11.2 ml of 2.34 M in hexane) of butyllithium. Fourteen ml of hexane were added to the solution and the flask was cooled to 0°. Diisopropyl amine (26.25 mmoles; 3.5 ml) was added dropwise. The LiDIPA - hexane in solution was cooled to -78° and the t-butyl acetate (25.0 mmoles; 3.35 ml) was added slowly. After 15 minutes, the solution was warmed to room temperature and the solvent evaporated. Any yellow discoloration was removed by trituration with hexane at 0°. The yield of the vacuum - dried, white powder was 90%.

IV. Spectrum and Reactions of Lithio t-Butyl Acetate

To a 50 ml flask equipped as in Figure 1 was charged 5.0 mmoles (0.61 g) of lithio t-butyl acetate. Benzene (5 ml) was added. When toluene was used as internal standard, glpc examination of a quenched aliquot of this clear solution afforded a quantitative recovery of t-butyl acetate. The NMR of this solution revealed two broad singlets at δ3.45 and δ3.2 (relative to benzene at δ7.25) and a singlet at δ1.6. The relative peak intensities were 1:1:9.

When toluene (5 ml) was used in place of the benzene, and the solution cooled to 0°, addition of one equivalent of cyclohexanone (0.49 ml), followed by acid addition in 5 minutes, produced t-butyl (1-hydroxycyclohexyl)acetate in quantitative yield. Addition of acetone (0.37 ml; 5.0 mmoles), rather than cyclohexanone, yielded t-butyl-3-methyl-3-hydroxybutyrate quantitatively.

V. Reaction of Lithio t-Butyl Acetate with Phenyl Magnesium Bromide

The enolate (5.0 mmoles) was prepared at -78° as described above. To this solution was added two equivalents of phenyl magnesium bromide in 10 ml of THF. The solution was warmed to room temperature for 3 hours. After quenching with dilute HCl, the mixture was examined by glpc and found to contain 13% acetophenone, as identified by comparison of glpc retention times with authentic material.

VI. Preparation of Bis(trimethylsilyl)ketene

t-Butyl 2-(trimethylsilyl)acetate (2.50 mmoles; 55 ml) was added to a 1 M solution of LiDIPA (262.5 mmoles) in THF at -78°. The amide was prepared as described previously (Chapter I and above). After 15 minutes, trimethylchlorosilane (262.5 mmoles; 33.6 ml) was added, and the solution was warmed to room temperature for 30 minutes. Two product peaks were observed by glpc. Treatment of the reaction mixture with 25 ml of H_2O for one hour replaced the lower boiling peak with starting ester. The organic layers were then separated and dried,

evaporated and the residue distilled under vacuum. Starting material (31%) and 60% of t-butyl 2,2-bis(trimethylsilyl)acetate were obtained. B.p. 60°/1 mm. NMR(CCl_4): 1.41δ (s,10H), 0.1δ (s,18H). An NMR of neat material revealed a third signal at δ1.33.

A 50 ml flask with 5.0 mmoles of LiDIPA at -78° was again prepared. To the flask was added 5.0 mmoles of t-butyl 2,2-bis(trimethylsilyl)-acetate (1.50 ml). The solution was maintained at -78° for 45 minutes. The flask was removed from the dry-ice bath for ½ hour. Only one product, in quantitative amounts, was present as revealed by glpc. The bis(trimethylsilyl)ketene had the expected NMR, in CCl_4: a singlet at δ0.2 (relative to benzene at δ7.25). The mass spectrum showed a parent peak at 186 (calc. 186.40). Ketene was inert to short treatment with weak acid or weak base. The ketene reacted with a trace of sulfuric acid in ethanol (anhydrous) to yield ethyl 2,2-bis(trimethylsilyl)-acetate quantitatively, which was identified by NMR.

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