PREPARATION AND REACTIONS OF ALPHA TRIMETHYLSILYL ESTER ENOLATES

Dissertation for the Degree of Ph. D.

MICHIGAN STATE UNIVERSITY
STEPHEN LEE HARTZELL

1975

This is to certify that the

thesis entitled

PREPARATION AND REACTIONS OF

ALPHA TRIMETHYLSILYL ESTER ENOLATES

presented by

Stephen Lee Hartzell

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in **Chemistry**

Michael Rathke

Major professor

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ABSTRACT

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Lithium diisopropylamide reacts with t-butyl acetate at low temperatures to give stable tetrahydrofuran solutions of lithio t-butyl acetate. Tert-butyl α-trimethylsilylacetate is obtained in good yields from the reaction of lithio t-butyl acetate with trimethylchlorosilane. Tert-butyl α-trimethylsilylacetate is metalated with lithium diisopropylamide in tetrahydrofuran to give indefinitely stable suspensions of the carbon silylated ester enolate at dry ice temperatures. Tetrahydrofuran solutions of lithio t-butyl α-trimethylsilylacetate condense with aldehydes and ketones to give the corresponding α,β-unsaturated esters in excellent yields.

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The carbon silylated ester enolate reacts with trimethylchlorosilane at low temperatures to give t-butyl bis(trimethylsilyl)acetate in moderate yields. Lithium diisopropylamide generates lithio t-butyl bis(trimethylsilyl)acetate at low temperatures in tetrahydrofuran. Aliphatic and aromatic aldehydes condense with the bis carbon silylated ester enolate to produce α-trimethylsilyl α,β-unsaturated esters in good yields. However, ketones fail to react with the ester enolate.

N-Acylimidazoles condense with lithio t-butyl α-trimethylsilylacetate in tetrahydrofuran at low temperatures to produce, after hydrolysis, β-keto esters in excellent yields. Lithio t-butyl acetoacetate is obtained directly from the reaction of N-acetylimidazole with the carbon silylated ester enolate after removal of the solvent.

PREPARATION AND REACTIONS OF
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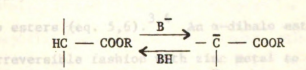
CHAPTER I

THE GENERATION OF α-HALO ESTER ENOLATES

INTRODUCTION

The α-protons in α-halo esters are acidic, and the corresponding ester enolates can be obtained through acid-base reactions (eq. 1). In the past, these enolates were normally generated only in equilibrium concentrations, using metal alkoxide bases.



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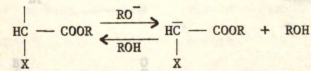
The Darzens condensation employs this approach to prepare glycidic esters (eq. 2,3).[1,2] An α-halo ester reacts with a ketone or aromatic aldehyde in the presence of a metal alkoxide or amide base. The



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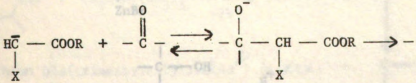

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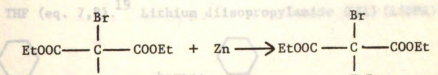
reaction is usually most successful with α-chloro esters. Alpha-iodo esters, and α-bromo esters to a lesser extent, often alkylate enolizable ketones to give γ-keto esters (eq. 4).[1] In addition, formaldehyde and

$$C_6H_5COCH(CH_3)_2 + ICH_2COOEt \xrightarrow{NaNH_2} C_6H_5COC(CH_3)_2CH_2COOEt \qquad (4)$$

monosubstituted acetaldehydes usually give poor yields of the desired products.[1] The scope of the reaction is further limited by the availability of the appropriate α-halo ester.

The Reformatsky reaction is a second method used to obtain metalated α-halo esters (eq. 5,6).[3,4] An α-dihalo ester[5,6,7,8,9] is reduced in an irreversible fashion with zinc metal to produce a halo-zinc ester enolate (I).[5] Because of the instability of the zinc enolate, I is usually trapped as it is formed by reaction with a carbonyl compound.



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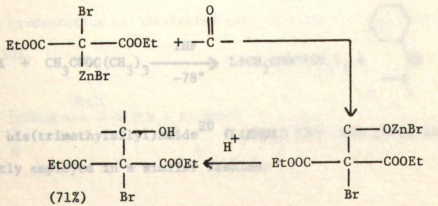
I



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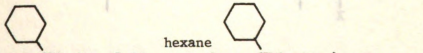
The two most common side reactions of the halozinc reagent are condensation with the starting α-halo ester[10] or enolization of the carbonyl component. This latter reaction is especially prevalent with aliphatic aldehydes.[11,12]

Recently, a two-step Reformatsky sequence was developed involving initial generation of halozinc ester enolates.[13,14,15] However, this method apparently has not been extended to the dihalo esters.

Direct proton removal from an ester ($pk_a \simeq 24$)[16] with lithium dialkylamide bases provides a convenient method to generate ester enolates from simple aliphatic esters. These strong bases (pk_a of $NH_3 > 34$)[17] are weakly nucleophilic,[18] soluble in many organic solvents, and capable of quantitatively generating ester enolates at low temperatures.

Lithium isopropylcyclohexylamide (II) (LiICA), formed in hexane by reaction of the amine with a commercial n-butyllithium solution, quantitatively generated the ester enolate of tert-butyl acetate at -78° in THF (eq. 7,8).[19] Lithium diisopropylamide (III) (LiDPA)[19] and



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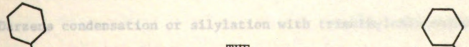

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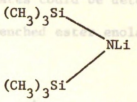
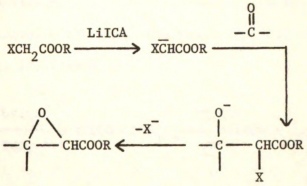
lithium bis(trimethylsilyl)amide[20] (LiHMDA) (IV) are prepared and frequently employed in a similar fashion.

III



IV

An investigation was undertaken to extend this two-step reaction sequence to the formation of α-halo ester enolates (eq. 9), which could then be used as discrete synthetic intermediates without the complications caused by the presence of the generating base.



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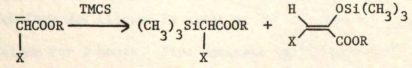
The actual anion formation might be demonstrated by successful Darzens condensation or silylation with trimethylchlorosilane (TMCS)[21] (eq. 9,10).



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The stability of α-halo ester enolates could be determined by glpc analysis for recoverable ester from quenched ester enolate solutions (eq. 11).

$$XCH_2COOR \xrightarrow{LiICA} \underset{\displaystyle X}{LiCHCOOR} \xrightarrow{H^+} XCH_2COOR \qquad (11)$$

RESULTS

Quenching and Decomposition of α-Halo Ester Enolates

Several α-halo esters were reacted with LiICA in THF at -78°. After 10 to 120 minutes, these solutions were quenched with dilute hydrochloric acid followed by glpc analysis for recovered ester. The chloro esters were returned in higher yields than the bromo esters. Ethyl bromoacetate and t-butyl bromoacetate were recovered in 11% and 63% yields respectively. Ethyl chloroacetate, t-butyl chloroacetate, and t-butyl dichloroacetate were returned in 80, 83, and 96% yields respectively (eq. 12) (Table 1).

$$XCH_2COOC(CH_3)_3 \xrightarrow[THF,-78°]{LiICA} \bar{X}CHCOOC(CH_3)_3 \xrightarrow[-78°]{3N\ HCl} XCH_2COOC(CH_3)_3 \qquad (12)$$

When warmed to 25° for 100 minutes, the lithio t-butyl chloroacetate solution gave, on quenching, only a five per cent return of the chloro ester. After stirring overnight in THF at 25°, lithio t-butyl chloroacetate gave t-butyl 2,4-dichloro-3-oxobutanoate (V) and 1,3-dichloroacetone (VI) as the major isolable products (eq. 13). This ester enolate was allowed to react at 25° in presence of cyclohexene or 1-octene for 3 hours. Glpc analysis indicated a 100% recovery of unchanged olefin.

TABLE 1

Quenching Results of α-Halo Ester Enolates

Ester	Solvent	Temp. °C	Time (min.)	% Return[a]
Ethyl bromoacetate	THF	-78	15	11
Ethyl chloroacetate	THF	-78	110	80
t-Butyl bromoacetate	THF	-78	10	63
t-Butyl chloroacetate	THF	-78	30	83
	THF	-78	120	75
	THF	25	100	5
	Pentane	-78	30	27
t-Butyl dichloracetate	THF	-78	120	96

[a] Determined by glpc analysis of aliquots quenched with 3N hydrochloric acid.

$$\underset{\text{Cl}}{\overset{|}{\overline{\text{C}}}}\text{HCOOC(CH}_3\text{)}_3 \xrightarrow[\text{THF}\\ \text{overnight}]{\text{RT}} \xrightarrow{\text{H}^+} \underset{\text{Cl}}{\overset{|}{\text{CH}_2}}\text{COCH}\underset{\text{Cl}}{\overset{|}{\text{C}}}\text{OOC(CH}_3\text{)}_3 \text{ (V)} + \underset{\text{Cl}}{\overset{|}{\text{CH}_2}}\text{COCH}_2\underset{\text{Cl}}{\overset{|}{\text{C}}}\text{l} \text{ (VI)} \qquad (13)$$

Darzens Condensation of α-Halo Ester Enolates

Darzens condensation of the α-halo esters provided additional evidence for enolate formation. The lithium enolates of ethyl chloroacetate and t-butyl chloroacetate reacted with aldehydes or ketones at -78° in THF to give the corresponding glycidic esters in 40 to 64% yields (eq. 14) (Table 2). These condensations gave predominately the trans glycidic esters in the case of ethyl β-phenylglycidate and t-butyl β-ethylglycidate.

$$\text{Cl}\overline{\text{C}}\text{HCOOC(CH}_3\text{)}_3 + \text{RCOR}' \xrightarrow[\text{then to RT}]{\text{THF, -78°}} \underset{\text{R}'}{\overset{\text{R}}{\text{C}}}\!\!\overset{\text{O}}{\diagup\diagdown}\!\!\underset{\text{COOC(CH}_3\text{)}_3}{\overset{\text{H}}{\text{C}}} \qquad (14)$$

The stereoisomers of ethyl β-phenylglycidate were separated on an SE-30 column. The first eluted glycidic ester exhibited a coupling constant of 2Hz for the oxirane protons, consistent for the trans isomer.[22] It was assumed that the stereoisomers of t-butyl β-ethylglycidate were eluted in the same order on an SE-30 column.

The corresponding chlorohydroxy esters were isolated from the condensation of lithio t-butyl chloroacetate with propionaldehyde and butyraldehyde (eq. 15).

TABLE 2

Yields of Glycidic Esters Using Lithium Halo Ester Enolates

Ester	Substrate	% Yield[c]	Cis/Trans Ratio	Lit. Yield[e]
Ethyl chloroacetate	Benzaldehyde	64[a]	16/84	50
t-Butyl chloroacetate	Acetone	40 (77.5)[b]		60
t-Butyl chloroacetate	Butyraldehyde	50[d]		
t-Butyl chloroacetate	Propionaldehyde	(56.5)	7.5/92.5	20-30

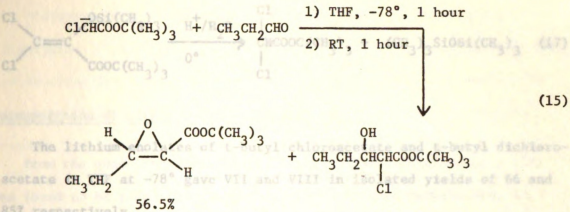
[a] Isolated yields.

[b] Glpc yields are parenthesized.

[c] All compounds exhibited spectral properties consistent with assigned structures.

[d] Tentatively identified as t-butyl 2-chloro-3-hydroxyhexanoate.

[e] Literature yield comparison to the ethyl glycidic esters (reference 1).



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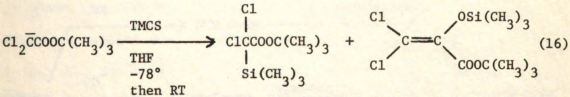
Reaction of α-Halo Ester Enolates with Trimethylchlorosilane

The lithium t-butyl ester enolates reacted with TMCS to give the C-silylated ester together with a minor product observed by glpc analysis (eq. 16). The minor product was sensitive to acid and presumed to be the O-silylated ketene acetal, since such compounds are usually readily hydrolized by such treatment (eq. 17).[21] Lithio t-butyl chloroacetate silylated exclusively at carbon. The reaction of lithio t-butyl dichloroacetate with TMCS gave 97% C- and 3% O-silylation.



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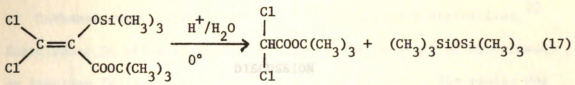
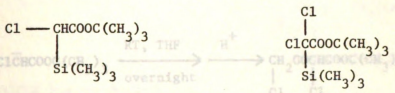


The lithium enolates of t-butyl chloroacetate and t-butyl dichloroacetate in THF at -78° gave VII and VIII in isolated yields of 66 and 85% respectively.



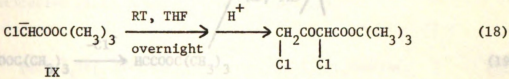
VII VIII

Lithio ethyl bromoacetate, generated with either LiHMDS or LiDPA in THF at -78°, gave several unidentified products from reaction with TMCS. Attempted condensation of ethyl bromoacetate with benzaldehyde or acetone employing LiICA or LIHMDS again resulted in several unidentified products. The aldehyde was returned unchanged.

DISCUSSION

Decomposition of Lithio t-Butyl Chloroacetate

From the quenching experiments, lithio t-butyl chloroacetate (IX) was found to be reasonably stable at -78°. At room temperature, IX decomposed to t-butyl 2,4-dichloro-3-oxobutanoate (eq. 18).



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The α-halo ester enolate IX could conceivably decompose by three pathways. The ester anion might react by proton abstraction from the solvent or amine to give the starting halo ester which then condenses with another molecule of IX. Alternatively, the halo ester enolate could collapse to a ketene or a carbene (Figure 1).

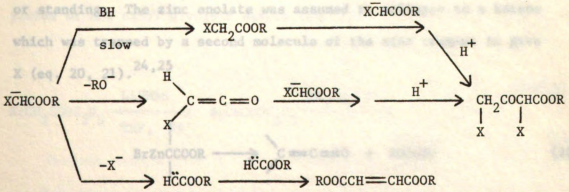
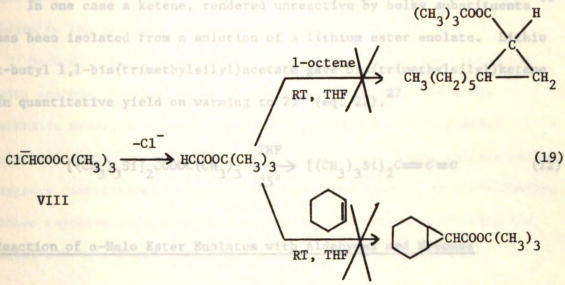


Figure 1. Possible α-Halo Ester Enolate Decomposition Routes

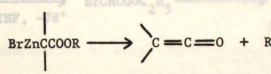
Carbenes react with olefins to give cyclopropane derivatives.[23] Experiments in which IX was decomposed in the presence of cyclohexane or 1-octene failed to give any cyclopropane product. The olefin was recovered unchanged even after total decomposition of the starting enolate had occurred, arguing against a carbene intermediate (eq. 19).



(19)

VIII

Of the two remaining decomposition routes, a ketene intermediate appears most attractive. Thus, a ketene intermediate was proposed to account for the slow dimerization of Reformatsky reagents upon heating or standing. The zinc enolate was assumed to collapse to a ketene which was trapped by a second molecule of the zinc reagent to give X (eq. 20, 21).[24,25]



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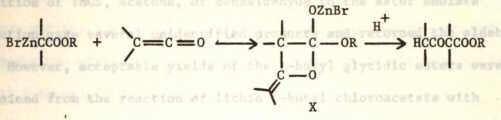

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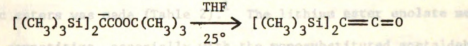
In one case a ketene, rendered unreactive by bulky substituents,[26] has been isolated from a solution of a lithium ester enolate. Lithio t-butyl 1,1-bis(trimethylsilyl)acetate gave bis(trimethylsilyl)ketene in quantitative yield on warming to 25° (eq. 22).[27]



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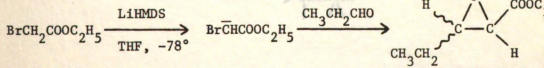
Reaction of α-Halo Ester Enolates with Aldehydes and Ketones

After our research was initiated, the Darzens condensation of ethyl bromoacetate was reported, using LiHMDS as base.[28] Borch reported THF solutions of the ester enolate were stable at -78° for one hour. The addition of aldehydes or ketones to the ester enolate gave excellent yields of the ethyl glycidic esters (eq. 23).



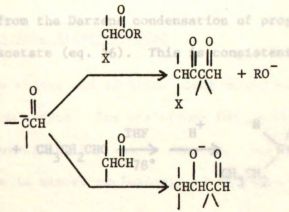
(23)

Our attempts to duplicate this procedure with ethyl bromoacetate, using LiHMDS, LiICA, or LiDPA as the base, were unsuccessful.

Addition of TMCS, acetone, or benzaldehyde to the ester enolate solution gave several unidentified products and returned the aldehyde.

However, acceptable yields of the t-butyl glycidic esters were obtained from the reaction of lithio t-butyl chloroacetate with aldehydes and ketones (Table 2). The reaction was complete within two hours under mild reaction conditions. No attempts were made to maximize the glycidic ester yields.

Because t-butyl chloroacetate apparently has not been condensed with acetone, butyraldehyde or propionaldehyde using the metal alkoxide bases, a comparison with the literature yield of ethyl glycidic esters was made (Table 2).[1] The lithium ester enolate method appears competitive, especially with the monosubstituted acetaldehydes. These reactive aldehydes probably suffer self-condensation with the metal alkoxide bases (eq. 24).

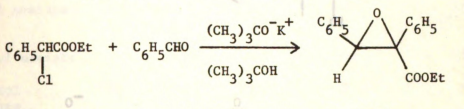


(24)

Darzens condensation of ethyl chloroacetate with benzaldehyde gave predominately the trans isomer as did condensation of t-butyl chloroacetate with propionaldehyde. Because the configuration of t-butyl

β-ethylglycidate could not be determined from the coupling constants of the oxirane protons, the cis/trans isomer ratio was determined by assuming the elution order on an SE-30 column to be the same as for ethyl β-phenylglycidate isomers.

The trans glycidic ester is often favored in the Darzens condensation. Thus, condensation of benzaldehyde with ethyl α-chlorophenylacetate gave exclusively the isomer trans to the carboalkoxy function (eq. 25).[29]



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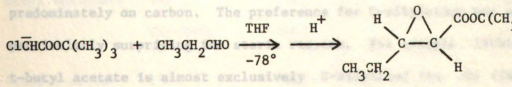
The hydroxychloro ester, glycidic ester, and starting materials were isolated from the Darzens condensation of propionaldehyde and t-butyl chloroacetate (eq. 26). This is consistent for a rate-limiting



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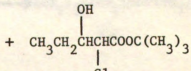


ring-closure step permitting an equilibration of the aldol intermediates (eq. 28). Such an equilibrium might explain the cis/trans isomer ratio of 7.5/92.5 for the propionaldehyde adduct.

$$ClCH_2COOR + LiICA \longrightarrow Cl\bar{C}HCOOR + ICA \qquad (27)$$

$$Cl\bar{C}HCOOR + \underset{\displaystyle O}{\overset{\displaystyle \|}{-C-}} \rightleftharpoons \underset{\displaystyle Cl}{\overset{\displaystyle O^-}{\overset{|}{-C-}}}\overset{|}{CHCOOR} \qquad (28)$$

$$\underset{\displaystyle Cl}{\overset{\displaystyle O^-}{\overset{|}{-C-}}}\overset{|}{CHCOOR} \longrightarrow \underset{}{\overset{\displaystyle O}{\overset{/\!\backslash}{-C-}}}\overset{|}{CHCOOR} + Cl^- \qquad (29)$$

Silylation of α-Halo Ester Enolates

The lithium chloro and dichloro ester enolates silylated with TMCS predominately on carbon. The preference for C-silylation was not particularly surprising for steric reasons. For example, lithio t-butyl acetate is almost exclusively C-silylated (eq. 30) (Table 3)[21]

$$\bar{C}H_2COOC(CH_3)_3 \xrightarrow[THF,\ -78°]{TMCS} \begin{cases} (CH_3)_3SiCH_2COOC(CH_3)_3 \\ \quad 98\% \\ \\ \begin{matrix} H \\ H \end{matrix}\!\!>\!C=C\!<\!\begin{matrix} OSi(CH_3)_3 \\ OC(CH_3)_3 \end{matrix} \\ \quad 2\% \end{cases} \qquad (30)$$

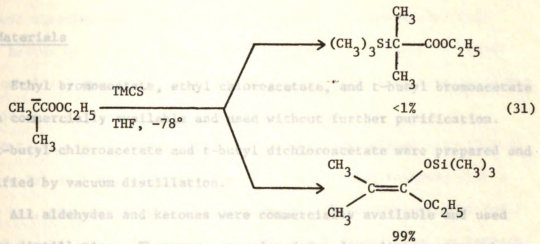
TABLE 3

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-cyclo-hexylacetate	THF	TMCS	<1	99
Ethyl crotonate	THF-HMPA (1 eq.)	BDCS	<1	99

[a] BDCS ≡ t-Butyldimethylchlorosilane

However, lithio ethyl isobutyrate is silylated predominately on oxygen (eq. 31) (Table 3).[21]



(31)

Thus it appears that substitution on the alcohol portion of the ester favors C-silylation while substitution on the alpha carbon favors O-silylation.

EXPERIMENTAL

I. Materials

Ethyl bromoacetate, ethyl chloroacetate, and t-butyl bromoacetate were commercially available and used without further purification. Tert-butyl chloroacetate and t-butyl dichloroacetate were prepared and purified by vacuum distillation.

All aldehydes and ketones were commercially available and used after distillation. They were stored under a dry nitrogen atmosphere.

Trimethylchlorosilane was obtained from Aldrich and distilled (bp 57°/atm. pressure) prior to use. Diisopropylamine (bp 83°/atm. pressure) was distilled and stored over molecular sieves. Isopropylcyclohexylamine and hexamethyldisilazane were commercially available and used without further purification. THF was commercially available and stored over molecular sieves.

II. Preparation, Decomposition, and Quenching Analysis of Ester Enolates

Tert-butyl chloroacetate is representative of all esters used for conversion into the enolate and ester recovery. Glpc analysis utilized a 1/4 inch by 6 foot SE-30 column. Each reaction run had an appropriate internal standard.

A. Preparation of tert-Butyl Chloroacetate

Into a 200 ml flask fitted with a stir bar, Vigreux condenser with an attached bent adapter and receiver, one mole (116 ml) of benzoyl chloride and one-half mole (47.25 g) of chloroacetic acid were heated to reflux. After ninety minutes, chloroacetyl chloride had completed distillation at 83° yielding 45.4 g (80%) of a colorless liquid.

Chloroacetyl chloride (45.4 g, 0.4 mole) was placed with 50.5 ml (0.4 mole) of N,N-dimethylaniline in a 500 ml flask equipped with a stir bar, dropping funnel, and thermometer. Tert-butyl alcohol (37.5 ml, 0.4 mole) was added dropwise to the flask maintaining the temperature under 30° with the aid of an ice bath. The mixture was stirred for an additional 45 minutes at room temperature after the addition was completed. After pouring the reaction mixture into 75 ml of water, the layers were separated, the aqueous phase washed with ether and combined with the crude ester. The organic phase was washed thrice with 10% sulfuric acid, then with 10% sodium hydroxide solution, and dried over anhydrous sodium sulfate. The product distilled at 56-9°/13 mm (lit.[30] 48-9/11 mm) giving 37.8g (63%) of a colorless oil.

B. Preparation of tert-Butyl Dichloroacetate

The acid chloride was prepared as described for chloroacetyl chloride. A one-half mole reaction gave 53.6 g (72.7%) of a colorless oil distilling at 106° (lit.[31] 106°).

Dichloroacetyl chloride (0.36 mole) and DMF (.364 mole, 28.4 ml) were placed together in a 500 ml flask immersed in an ice bath. The

procedure is carried out in the manner described for the monochloroester. The dichloroester distilled at 48-9°/3 mm yielding 42 g (61%) of a colorless oil.

C. Preparation of Lithio tert-Butyl Chloroacetate

A 50 ml flask equipped with a stir bar, septum, gas inlet valve, and mercury bubbler was flame dried while a stream of dry nitrogen was flowing through the system. A 2.4 M (2.1 ml, 5 mmoles) aliquot of commercial n-butyllithium in hexane was added to the flask. The flask was immersed in an ice bath and 0.85 ml (5 moles) of N-isopropylcyclohexylamine was added dropwise with stirring. After the evolution of butane had ceased, the hexane was removed by vacuum which was broken with nitrogen. The white solid was dissolved in 5 ml of THF and cooled in an acetone-dry ice bath. Tert-butyl chloroacetate (0.5 ml, 4 mmoles) was added dropwise, and after 15 minutes, a yellow color had developed. After 30 minutes, the reaction was quenched with 5 ml (3N, 15 moles) of HCl. Upon warming to room temperature, 0.62 ml (4 moles) of n-butyl benzene (internal standard) was added, and the resulting solution extracted with pentane. The organic layer was dried over anhydrous sodium sulfate before glpc analysis. Recovery of tert-butyl chloroacetate was 83%.

D. Decomposition of Lithio tert-Butyl Chloroacetate

The lithio ester enolate (40 mmoles) was generated as previously described. The enolate was stirred at room temperature overnight and quenched with 100 mmoles (33 ml) of 3N HCl at 0°. The aqueous solution was extracted with ether, and the organic phase dried with

sodium sulfate. An initial glpc trace showed one major product. However, a white solid and high boiling liquid were collected. The solid was a decomposition product from the initial oil since attempted vacuum distillation transformed the liquid into a white solid. This same decomposition resulted on an SE-30 column when 50 ml injections were made. The solid gave a positive Beilstein test and melted at 42-3° (lit.[32] 42.5°) consistent with 1,3-dichloroacetone. The oil was identified by spectral properties which were consistent with t-butyl 2,4-dichloroacetoacetate.

III. Darzens Condensation of Lithio Halo Ester Enolates

The procedure for tert-butyl β,β-dimethylglycidate is representative. Twenty millimoles of LiICA in 20 ml of THF was prepared in the usual manner. The basic solution was cooled with a dry ice-acetone bath, and the ester (2.0 ml, 20 mmoles) was added dropwise with stirring. After five minutes, acetone (1.84 ml, 20 mmoles) was added slowly to the yellow solution. The mixture was stirred for one hour at -78° and an additional hour at 25°, quenched with 13 ml of 3N acetic acid and extracted with ether. The organic extracts were washed with water, saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The product was vacuum distilled yielding 1.32 g (40%) of a colorless liquid.

The chlorohydroxyester was isolated by glpc from the tert-butyl β-ethylglycidate preparation. The chlorohydroxy ester was the only product isolated from the t-butyl β-propylglycidate preparation. This latter reaction mixture was stirred for 2.5 hours at -78° followed by quenching.

IV. Reaction of Lithio Ester Enolates with Trimethylchlorosilane

This procedure is representative for all ester enolate silylations. One-half mole of lithio N,N-diisopropylamide is prepared in a similar manner to LiICA. After the lithium amide was dissolved in 300 ml of dry THF and cooled in a dry ice-acetone bath, 500 millimoles of t-butyl acetate was added over a 20 minute period and stirred for an additional 5 minutes. The TMCS was rapidly added, the bath removed, and the mixture warmed to room temperature. The mixture was cooled to 0°, an equal volume of pentane added, the organic phased washed with 3N sodium hydroxide and finally dried over sodium sulfate. The solvent was removed on the roto-evaporator and the product vacuum distilled giving 130 g (69%) of a colorless liquid.

Tert-butyl chlorotrimethylsilylacetate and tert-butyl dichlorotrimethylsilylacetate gave 66% and 85% yields respectively.

V. Product Analysis

The products synthesized were examined by NMR and/or IR. TMS was the internal standard for NMR spectra.

Chloroacetyl chloride

Bp 83°. NMR (CCl_4): δ 4.5 (s, 2H).

tert-Butyl chloroacetate

Bp 56-9°/13 mm. NMR(CCl_4): δ 3.88 (s, 2H), δ 1.48 (s, 9H).

1,3-Dichloroacetone

Mp 42-3°. NMR(CCl_4): δ 4.3 (s).

tert-Butyl 2,4-dichloroacetoacetate

NMR(CCl_4): δ 4.9 (s, 1H), δ 4.4 (s, 2H), δ 1.6 (s, 9H). IR(neat): 1750 cm^{-1} (broad, C=O).

tert-Butyl 2-chloro-3-hydroxyhexanoate

Bp 74-8°/0.3 mm. NMR(CCl_4): δ 0.8-1.1 (m, 7H), δ 1.5 (s, 9H), δ 3.8-4.2 (m, 2H), δ 4.66 (broad, 1H).

Ethyl β-phenylglycidate

Bp 110°/0.8 mm. NMR(CCl_4): δ 3.25, δ 3.95 (d, J=2Hz, trans, 2H), δ 7.3 (s, 5H), δ 4.2 (q, 2H), δ 1.25 (t, 3H).

tert-Butyl β,β-dimethylglycidate

Bp 40-41°/0.5 mm. NMR(CCl_4): δ 2.98 (m, 2H), δ 1.6 (m) and δ 1.52 (s), total 11H, δ 1.0 (t, 3H). IR(neat): 1740 cm^{-1} (C=O), 1725 cm^{-1} (shoulder, C=O).

tert-Butyl 3-hydroxy-2-chloropentanoate

Refractive index $n_D^{25°}$ 1.4444. NMR(CCl_4): δ 3.6-4.2 (m, 2H), δ 2.9 (s, 1H, disappeared with D_2O), δ 1.5 (s, 9H), δ 1.0 (t, 3H). IR(neat): 3200-3600 cm^{-1} (OH), 1725 cm^{-1} (broad, C=O).

tert-Butyl α-trimethylsilylacetate

Bp 67°/13 mm. Density 0.84. NMR(CCl_4): δ 1.7 (s, 2H), δ 1.4 (s, 9H), δ 0.1 (s, 9H). IR(neat):1725 cm^{-1} (broad, C=O).

tert-Butyl α-chloro-α-trimethylsilylacetate

Bp 50-4°/1.0 mm. NMR(CCl_4): δ 3.64 (s, 1H), δ 1.48 (s, 9H), δ 0.18 (s, 9H). IR(neat): 1740 cm^{-1} and 1700 cm^{-1} (shoulder, C=O).

tert-Butyl α,α-dichloro-α-trimethylsilylacetate

Bp 65-7°/2 mm. NMR(CCl_4): δ 1.56 (s, 9H), δ 0.30 (s, 9H). IR(neat): 1750 and 1725 cm^{-1} (C=O).

CHAPTER II

THE PREPARATION OF α,β-UNSATURATED ESTERS WITH C-SILYLATED ESTER ENOLATES

INTRODUCTION

Lithium ester enolates are ambident anions capable of combining with an electrophile at either carbon or oxygen (Figure 2).

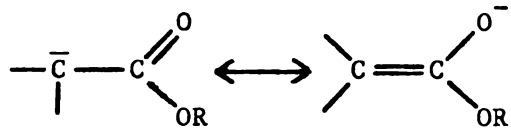
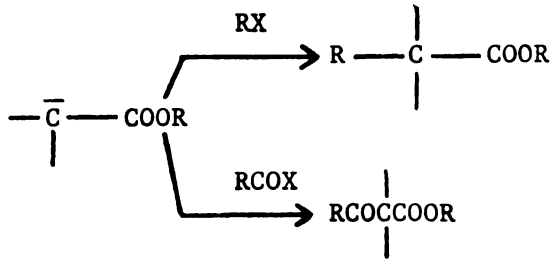


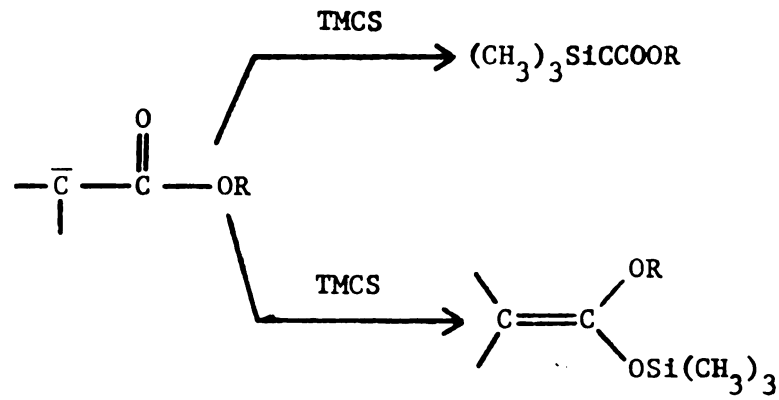
Figure 2. Ester Enolate Resonance Hybrid

These metalated esters preferentially react at carbon with alkyl halides[19] or acyl halides[33] giving chain-extended esters and β-keto esters respectively (eq. 1).



(1)

Silyl halides give both C- and O-silyl products in relative amounts depending on the structure of the ester, the silylating agent, and the reaction conditions (eq. 2) Lithio tert-butyl acetate is almost



(2)

exclusively silylated at carbon to provide a convenient synthesis of t-butyl trimethylsilylacetate (eq. 3).[21]

$$LiCH_2COOC(CH_3)_3 \xrightarrow[THF,\ -78°]{TMCS} (CH_3)_3SiCH_2COOC(CH_3)_3 \qquad (3)$$

The trimethylsilylmethyl lithium and magnesium compounds, I and II, are synthetically useful intermediates for preparing olefins. Tetramethylsilane is metalated[34] with the reactive n-butyllithium-N,N,N,N-tetramethylethylenediamine (TMEDA) complex[35] (eq. 4). Tri-

$$(CH_3)_3SiCH_3 + \text{n-BuLi}\cdot\text{TMEDA} \xrightarrow[3\ \text{days}]{\text{hexane}} (CH_3)_3SiCH_2Li \qquad (4)$$

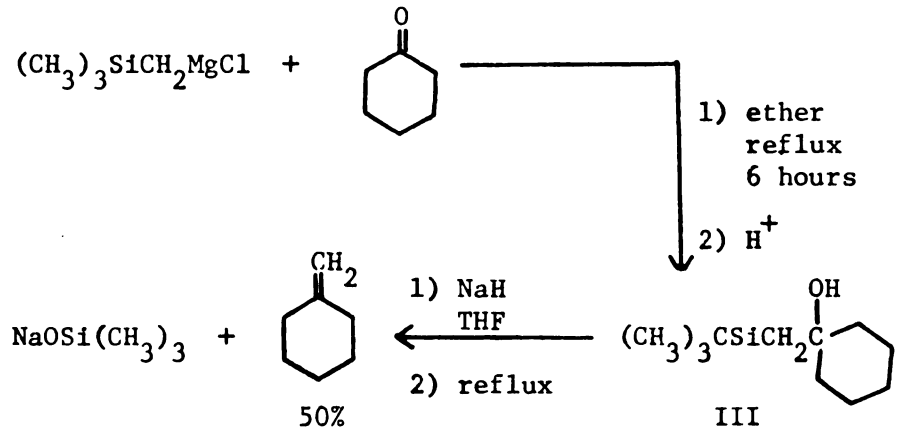
I 36%

methylsilylmethyl magnesium chloride is prepared in a Grignard fashion[36] (eq. 5).

$$(CH_3)_3SiCH_2Cl + Mg \xrightarrow[\text{reflux}]{\text{ether}} (CH_3)_3SiCH_2MgCl \qquad (5)$$

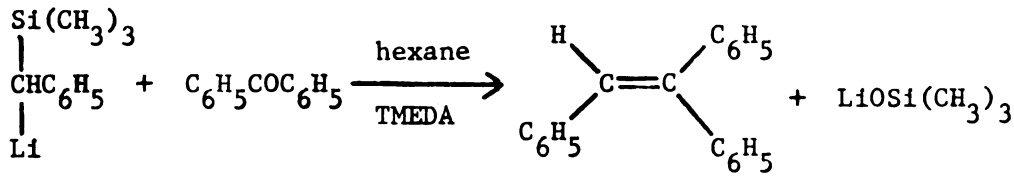
II

The silylated Grignard reagent II reacts with aldehydes and ketones to give the β-silylcarbinol III after hydrolysis. The sodium salt of III eliminates in refluxing THF providing the corresponding olefin (eq. 6).[37]



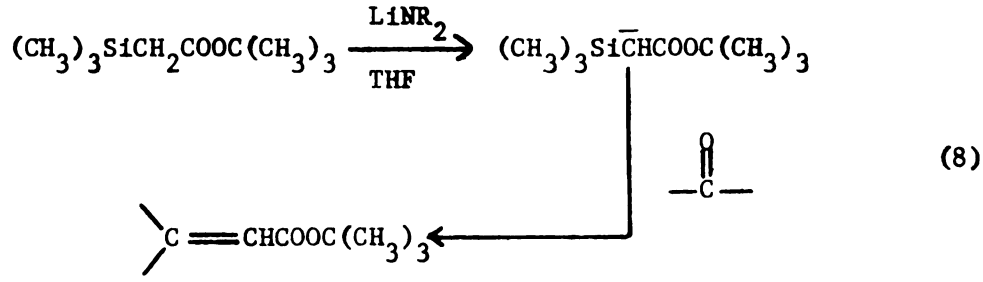
(6)

Reaction of lithium benzyltrimethylsilane with the carbonyl component is reported to yield the olefin directly (eq. 7).[38]



(7)

This facile trimethylsiloxy elimination suggested that t-butyl trimethylsilylacetate may be a synthetically useful precursor to unsaturated esters. It was hoped stable THF solutions of lithio t-butyl trimethylsilylacetate could be prepared using a lithium dialkylamide base. The silylated ester enolate might then react with aldehydes or ketones to provide the unsaturated ester directly (eq. 8).



(8)

RESULTS

Preparation of Lithio tert-Butyl Trimethylsilylacetate

Treatment of lithio t-butyl acetate with TMCS in THF at -78° gave t-butyl trimethylsilylacetate IV in 69% isolated yield (eq. 9).

$$LiCH_2COOC(CH_3)_3 \xrightarrow[THF,\ -78°]{TMCS} (CH_3)_3SiCH_2COOC(CH_3)_3 \qquad (9)$$

IV

Addition of IV to THF solutions of LiDPA at -78° quantitatively generated lithio t-butyl trimethylsilylacetate within five minutes to give a white precipitate of V (eq. 10) which was indefinitely stable at dry ice temperatures, as determined by quenching aliquots with dilute acid and analyzing for recovered ester.

$$(CH_3)_3SiCH_2COOC(CH_3)_3 \xrightarrow[THF,\ -78°]{LiDPA} (CH_3)_3SiCHCOOC(CH_3)_3 \qquad (10)$$

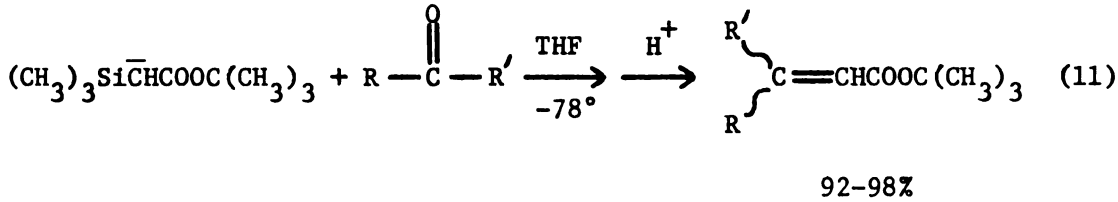
Li

V

Attempts to isolate V were undertaken. A white solid material was isolable at ice bath temperatures under vacuum. This material turned yellow if the ice bath was removed and rapidly charred upon exposure to the atmosphere.

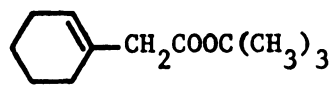
Reaction of Lithio tert-Butyl Trimethylsilylacetate with Aldehydes and Ketones

A one molar solution of lithio t-butyl trimethylacetate readily condensed with benzaldehyde at -78° in THF. On slowly warming the mixture to room temperature complete elimination to t-butyl cinnamate was complete in 30 minutes. This procedure was extended to a variety of aldehydes and ketones to produce the corresponding α,β-unsaturated esters in 92 to 98% yields (eq. 11) (Table 4). All α,β-unsaturated esters prepared in this manner gave satisfactory elemental analyses (Table 6) and their structures were confirmed by pmr.



92-98%

Reaction of cyclohexanone with lithio t-butyl trimethylsilyl-acetate gave only 0.6% of the corresponding nonconjugated ester (VI).



VI

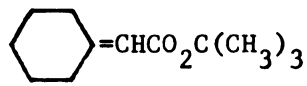
Quenching THF reaction mixtures of V and acetone, benzaldehyde, or cyclohexanone at -78° with dilute HCl gave small amounts of the corresponding β-hydroxy esters. Repeating the quenching procedure in

TABLE 4

Reaction of Carbonyl Compounds with Lithio tert-Butyl Trimethylsilylacetate

Carbonyl Compound	Product[a]	Yield, %[b]		Bp/mmHg	N^{22}_D
Acetaldehyde	$CH_3CH=CHCO_2C(CH_3)_3$	98	(93)	150/760	1.4249
Isobutyraldehyde	$(CH_3)_2CHCH=CHCO_2C(CH_3)_3$	94	(66)	98/41	1.4327
Benzaldehyde	$C_6H_5CH=CHCO_2C(CH_3)_3$	97	(75)	103-105/0.5	1.5300
Crotonaldehyde	$CH_3CH=CH-CH=CHCO_2C(CH_3)_3$	92	(78)	85-90/8	1.4784
Cinnamaldehyde	$C_6H_5CH=CH-CH=CHCO_2C(CH_3)_3$	95	(58)	171-178/7	1.5858
Acetone	$(CH_3)_2C=CHCO_2C(CH_3)_3$	96	(53)	164/760	1.4391

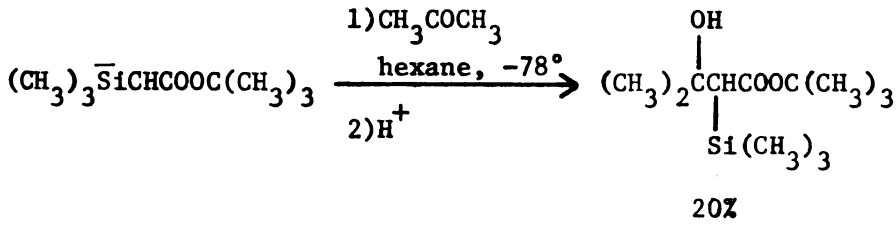
TABLE 4 (cont.)

Carbonyl Compound	Product[a]	Yield, %[b]	Bp/mmHg	N^{22}_D
Cyclohexanone		95 (90)	121-123/16	1.4738

[a] All products exhibited spectral properties in accordance with assigned structures.

[b] Glpc yields, isolated yields in parentheses.

hexane solution gave larger amounts of the β-hydroxy esters, which were isolated by preparative glpc (eq. 12).



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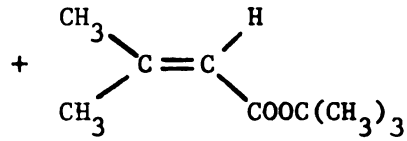
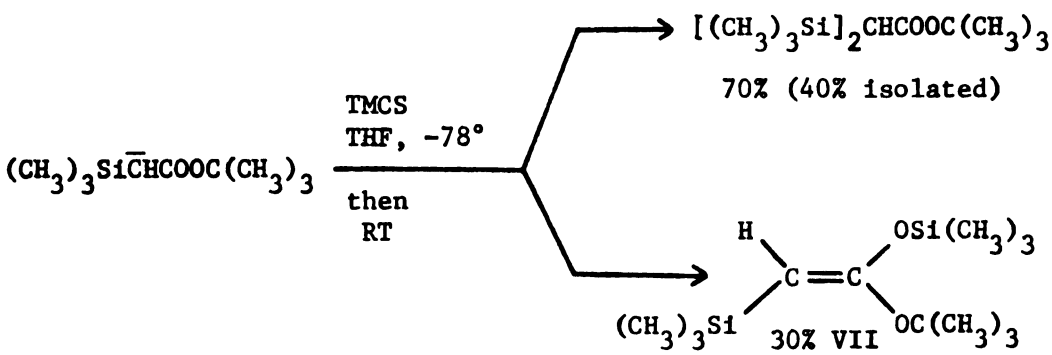


Preparation of Lithio tert-Butyl bis(trimethylsilyl)acetate

Reaction of TMCS with a 1.67 molar solution of V, followed by warming to room temperature, gave (glpc analysis) a mixture of 70% C- and 30% O-silylated products (eq. 13). The C-silylated product, tert-butyl bis(trimethylsilyl)acetate, was isolated in 40% yield after the acid catalyzed hydrolysis of the O-silyl ketene acetal (VII) to t-butyl trimethylsilylacetate.

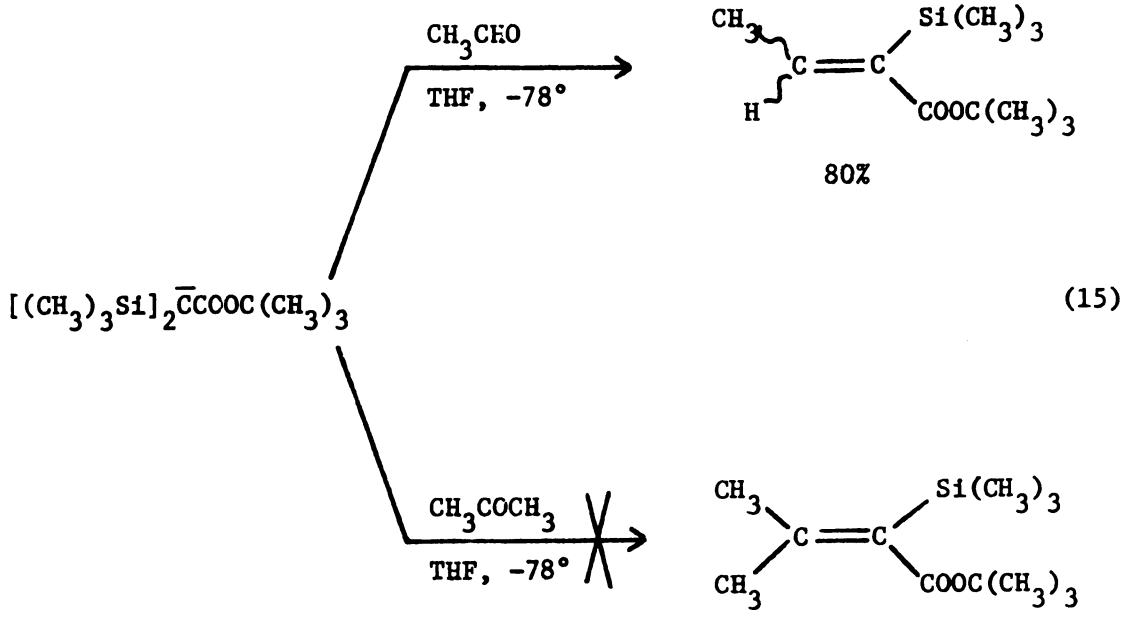


(13)

Reaction of Lithio tert-Butyl bis(trimethylsilyl)acetate with Aldehydes and Ketones

The bis silylated ester was converted into the ester enolate VIII with LiDPA in THF at -78° (eq. 14). The bis silyl ester enolate was then condensed with aliphatic or aromatic aldehydes in THF at -78° to give 70 to 85% glpc yields of the corresponding α,β-unsaturated trimethylsilyl esters. However, the reaction failed to give any condensation products with cyclohexanone or acetone, returning the bis silylated ester unchanged (eq. 14) (Table 5).

$$[(CH_3)_3Si]_2CHCOOC(CH_3)_3 \xrightarrow[THF,\ -78°]{LiDPA} [(CH_3)_3Si]_2\bar{C}COOC(CH_3)_3 \qquad (14)$$



(15)

TABLE 5

Reaction of Aldehydes with Lithio tert-Butyl bis(trimethylsilyl)acetate

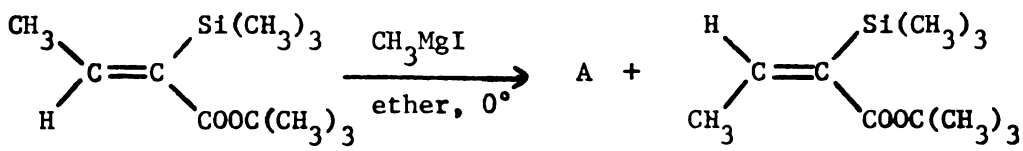
Aldehyde	Product[a]	Yield, %[b]		Bp/mmHg	N^{20}_D
Benzaldehyde	$C_6H_5CH=C[Si(CH_3)_3]CO_2C(CH_3)_3$	79	(65)	109/0.1	1.5095
Acetaldehyde	$CH_3CH=C[Si(CH_3)_3]CO_2C(CH_3)_3$	80	(58)	59/0.3	1.4430
Isobutyraldehyde	$(CH_3)_2CH-CH=C[Si(CH_3)_3]CO_2C(CH_3)_3$		(74)	63/0.4	1.4385
Crotonaldehyde	$CH_3CH=CH-CH=C[Si(CH_3)_3]CO_2C(CH_3)_3$	85			
Formaldehyde	$CH_2=C[Si(CH_3)_3]CO_2C(CH_3)_3$	70	(35)	34/0.2	

[a] All products exhibited spectral properties in accordance with assigned structures.

[b] Glpc yields, isolated yields in parentheses.

Reactions of tert-Butyl α-Trimethylsilyl α,β-Unsaturated Esters

Treatment of cis/trans t-butyl α-trimethylsilylcrotonate with methyl Grignard in ether at 0° gave, after hydrolysis with aqueous NH_4Cl, an unidentified material and the ketone (IX). The cis isomer, identified by pmr, was recovered unchanged, apparently being more resistant toward Grignard addition (eq. 16).



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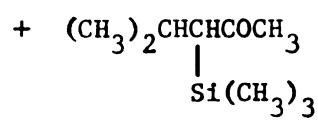
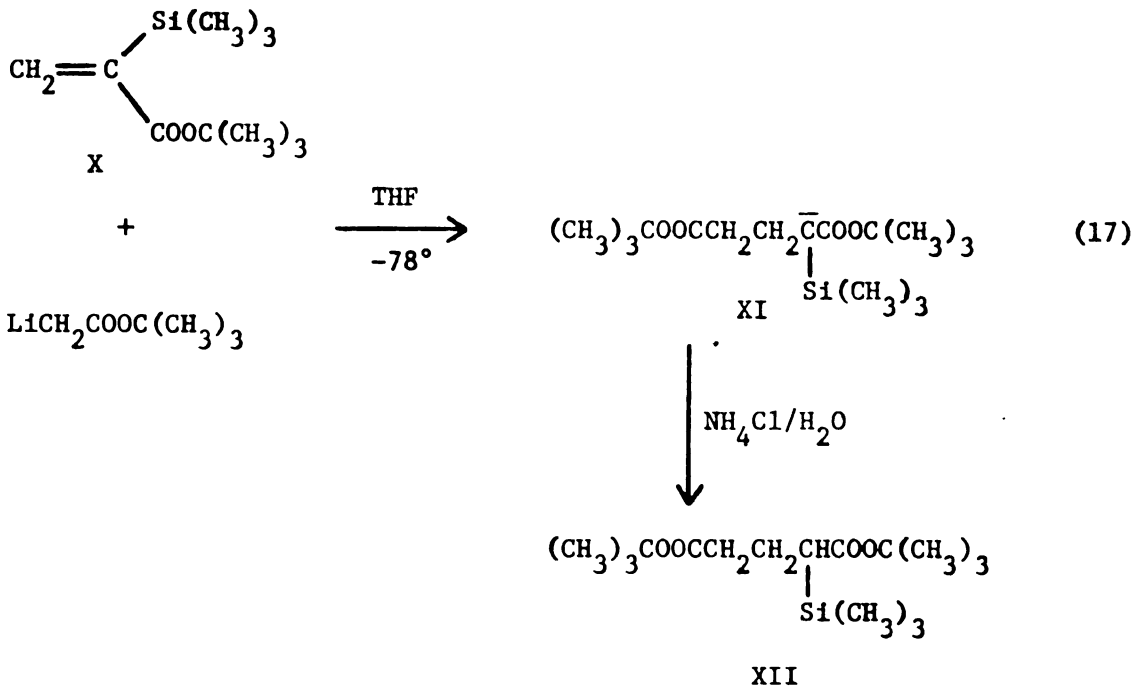


IX

Freshly prepared lithio t-butyl acetate added in a 1,4-fashion to the silylated acrylate (X) to give, after hydrolysis, the t-butyl glutarate (XII) (eq. 17). A sample of previously prepared solid ester[39] enolate gave no reaction under similar conditions.



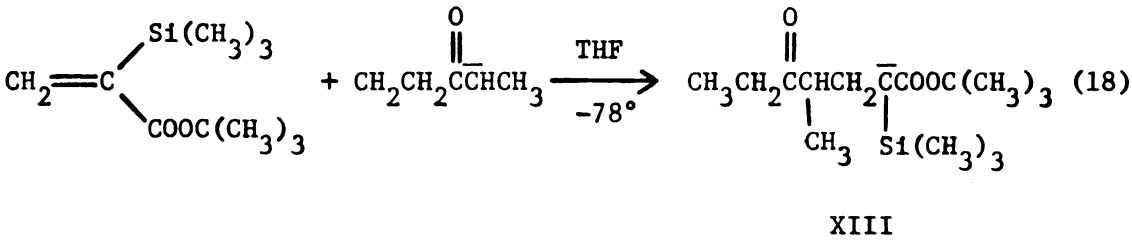
X

XI

XII

(17)

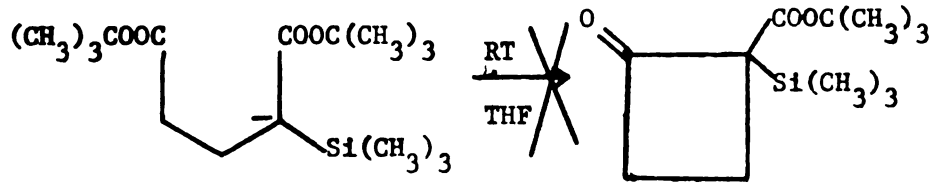
The lithium enolate of diethyl ketone combined in a Michael reaction with t-butyl α-trimethylsilylacrylate (eq. 18).



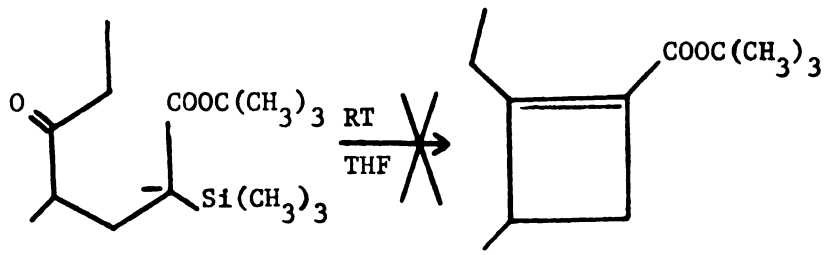
XIII

(18)

Both silylated ester enolates XI and XIII failed to cyclize in THF solution at room temperature (eq. 19, 20).


(CH3)3COOC
COOC(CH3)3
Si(CH3)3
RT
THF
O
COOC(CH3)3
Si(CH3)3

(19)


O
COOC(CH3)3
Si(CH3)3
RT
THF
COOC(CH3)3

(20)

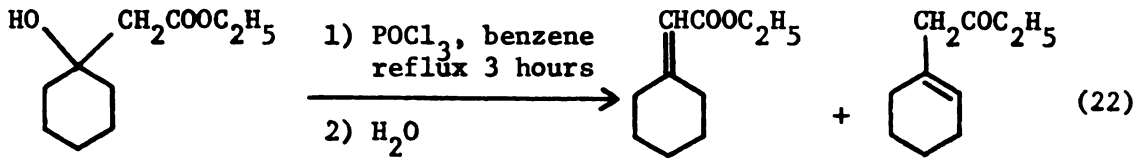
DISCUSSION

Reaction of Lithio t-Butyl Trimethylsilylacetate with Aldehydes and Ketones

Proton removal from t-butyl trimethylsilylacetate with LiDPA is facile to produce lithio t-butyl trimethylsilylacetate. This ester enolate rapidly condensed with aldehydes and ketones to give excellent yields of α,β-unsaturated esters free from the non-conjugated isomer. The reaction is particularly advantageous since the position of the new double bond is certain. In addition, loss of the trimethylsiloxide group irreversibly rendered the product (eq. 21).

$$(CH_3)_3Si\bar{C}HCOOC(CH_3)_3 \xrightarrow[THF,\ -78°]{C_6H_5CHO} C_6H_5CH(O^-)-CH(Si(CH_3)_3)COOC(CH_3)_3 \longrightarrow (CH_3)_3SiOLi + C_6H_5CH{=}CHCOOC(CH_3)_3 \qquad (21)$$

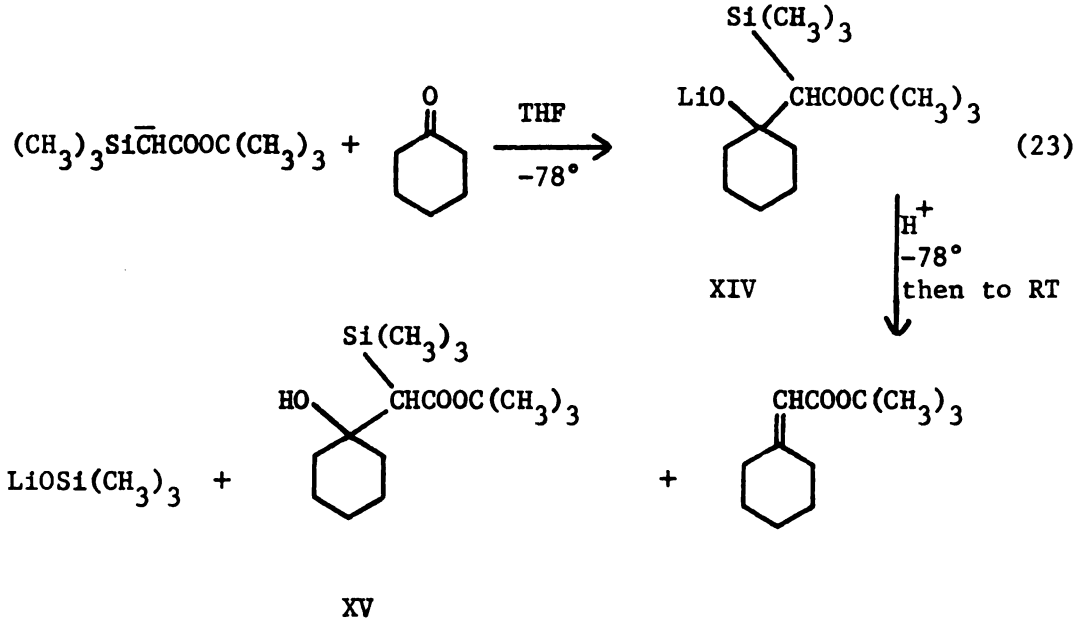
Established preparations of α,β-unsaturated esters have usually relied upon acid-catalyzed dehydration of β-hydroxy esters, which usually gives a mixture of the conjugated and unconjugated esters (eq. 22).[40]



(22)

43% 57%
(64% combined yield)

In the silylated ester enolate sequence, the α,β-unsaturated t-butyl esters are formed prior to quenching since the hydroxy ester (XV) is stable to acid at room temperature (eq. 23). Replacing THF with the nonpolar solvent hexane and quenching the reaction mixture within five minutes at -78° afforded increased amounts of the hydroxy ester derived from benzaldehyde, acetone, or cyclohexanone. The olefin function is most likely formed by loss of lithium trimethylsiloxide from the intermediate XIV. The lithium trimethylsiloxide grouping has been reported to be a good leaving group.[38]



(23)

The conjugated aldehydes, cinnamaldehyde and crotonaldehyde, gave excellent yields of the conjugated esters. Exclusive 1,2-addition occurred providing a convenient synthesis for extended conjugated esters (eq. 24).

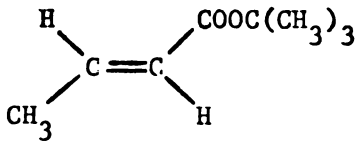
$$(CH_3)_3Si\bar{C}HCOOC(CH_3)_3 + CH_3CH{=}CHCHO \xrightarrow[-78°]{THF} CH_3CH{=}CHCH{=}CHCOOC(CH_3)_3 \quad (24)$$

Acetaldehyde and isobutyraldehyde, possessing highly enolizable hydrogens, were nevertheless smoothly converted into the corresponding α,β-unsaturated esters (eq. 25).

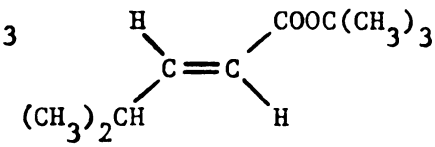
$$(CH_3)_3Si\bar{C}HCOOC(CH_3)_3 + CH_3CHO \xrightarrow[-78°]{THF} \underset{98\%}{CH_3CH{=}CHCOOC(CH_3)_3} \quad (25)$$

Determination of Stereoisomers

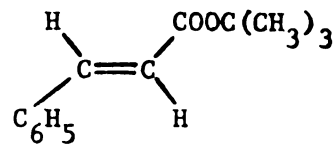
Acetaldehyde, isobutyraldehyde, and benzaldehyde condensed with lithio t-butyl trimethylsilyl acetate to give a mixture of the corresponding cis/trans conjugated ester (XVI-XVIII). The trans α,β-unsaturated ester was favored in each of these cases.



XVI



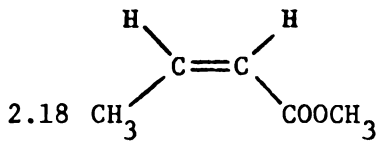
XVII



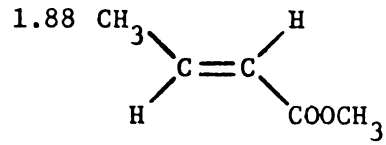
XVIII

	XVI	XVII	XVIII
trans	70	78	78
cis	30	22	22

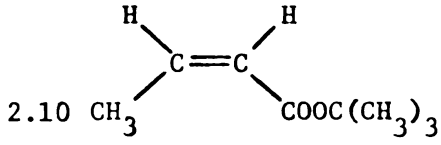
The cis/trans ratio for t-butyl cinnamate (XVIII) and t-butyl 4-methyl-2-pentenoate (XVII) were determined by glpc analysis. Pmr spectra of XVII and XVIII revealed the major isolable products had coupling constants of 16 Hz for the vinyl protons confirming the trans assignment (J≈16 Hz, trans; J≈11 Hz, cis).[41] The cis/trans ratio for t-butyl crotonate (XVI) was determined by pmr analysis of the mixture since the isomers were not readily separated on an SE-30 column. The major vinyl protons also had a coupling constant of 16 Hz. The cis/trans ratio was conveniently determined from the integration ratio of the allylic methyl groups. This was possible since the cis methyl group β to a carbonyl function is generally found further downfield than the corresponding trans β-methyl.[41,42,43] For example, cis/trans methyl crotonate (XIX, XX) have chemical shifts of δ2.14 and δ 1.88 respectively.[41] Cis/trans t-butyl crotonate (XXI, XXII) had nearly identical chemical shifts of δ 2.10 and δ 1.86.



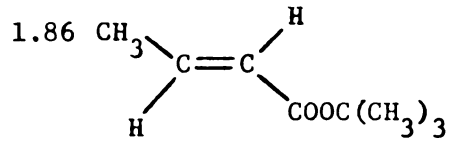
XIX



XX



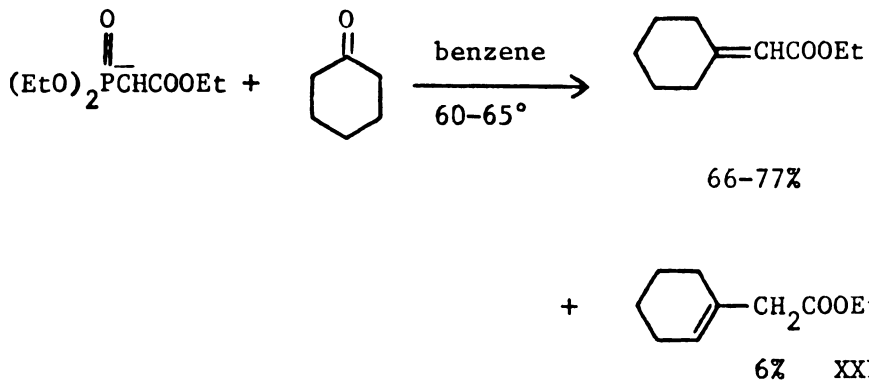
XXI



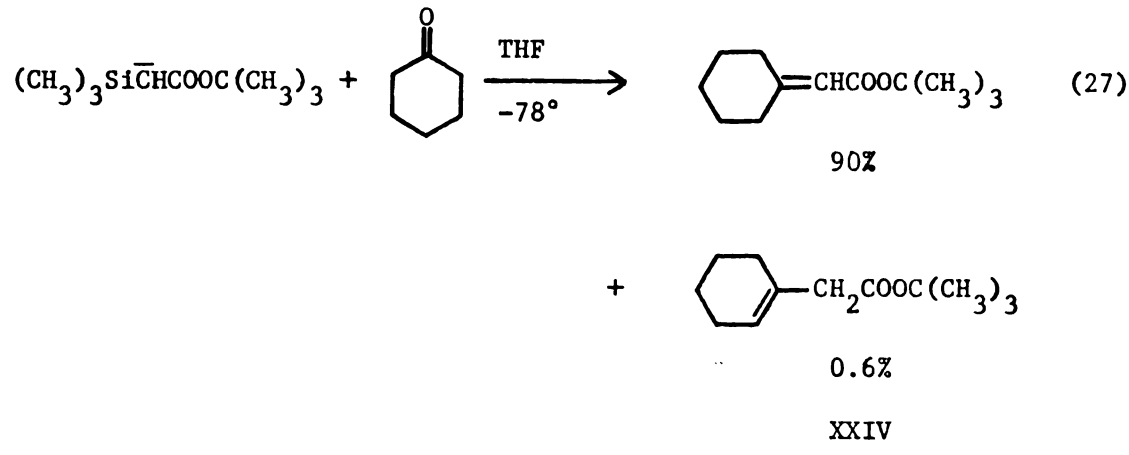
XXII

Comparison to Wittig Reaction

The Wittig reaction,[44] including the phosphonate modification,[45] is presently the most useful method for converting aldehydes and ketones into α,β-unsaturated esters. However, the silylated ester enolate method offers an attractive alternative, being complete within a short time at -78° in THF. Phosphorus ylides react with similar carbonyls either at room temperature or in refluxing solvents such as benzene or ethanol.[44] Equations 26[46] and 27 compare yields of similar products using the different methods.



(26)



(27)

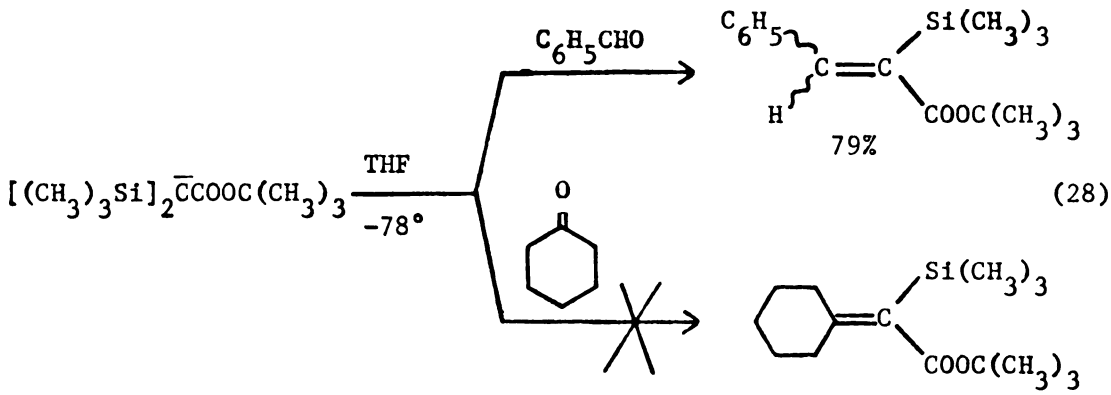
The Wittig method reportedly gave six per cent of the unconjugated isomer (XXIII) (eq. 26).[47] From the present procedure, only 0.6 per cent of the unconjugated isomer (XXIV) was detected by glpc analysis.

tert-Butyl bis(trimethylsilyl)acetate

Tert-butyl bis(trimethylsilyl)acetate and O-trimethylsilyl-O-t-butyl trimethylsilylketene acetal (VII) (eq. 13) were obtained unexpectedly in a 70/30 ratio from the silylation reaction. As Table 3 illustrates, increased substitution at carbon promoted O-silylation. For example, t-butyl acetate gave 99% C-silylation but decreased to 60% with t-butyl butanoate. Thus, the 70% C-silylation observed with t-butyl trimethylsilylacetate seems difficult to explain solely on steric arguments.

Reaction of Lithio t-Butyl Trimethylsilylacetate with Aldehydes and Ketones

Proton removal from t-butyl bis(trimethylsilyl)acetate with LiDPA, requiring about one hour, encountered some difficulty. The bis silylated ester enolate condensed with aldehydes affording conjugated vinyl silylated esters in excellent yields (eq. 28). Like the mono silylated ester enolate condensation, the position of the new double bond is certain and loss of the trimethylsiloxy group irreversibly gives the α,β-unsaturated α-silylated ester.



(28)

Presumably for steric reasons, the bis silyl ester enolate failed to condense with acetone or cyclohexanone (eq. 28). Glpc analysis only detected the bis silylated ester and cyclohexanone in the quenched reaction mixture. The bulky ester enolate might serve as a base to generate the ketone enolate.

The reaction with crotonaldehyde gave exclusive 1,2-addition providing an extended conjugated ester in excellent yield (eq. 29).

$$[(CH_3)_3Si]_2\overline{C}COOC(CH_3)_3$$

$$+ \qquad \xrightarrow[\text{then RT}]{\text{THF, } -78^\circ} CH_3CH{=}CHCH{=}C\begin{matrix}\diagup Si(CH_3)_3 \\ \diagdown COOC(CH_3)_3\end{matrix} \qquad (29)$$

$$CH_3CH{=}CHCHO$$

Reactions of t-Butyl α-Trimethylsilyl α,β-Unsaturated Esters

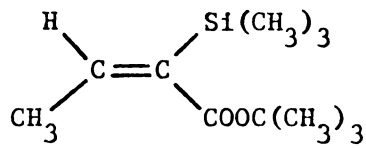
With the vinyl silylated esters easily accessible in good yields, it was of interest to further investigate their synthetic utility. Three major products were obtained from reaction of methyl magnesium iodide with t-butyl 2-trimethylsilyl-2-butenoate. These products consisted of a low boiling component A, a tentatively identified ketone (IX), and the cis isomer of the starting ester (eq. 16).

An ir spectrum revealed a carbonyl band at 1680 cm^{-1} consistent with a saturated ketone. The pmr spectrum showed the trimethylsilyl moiety at δ 0.06, most likely bonded to carbon.[21] The pmr also revealed a methyl group attached to the carbonyl moiety (singlet, δ 1.93). Both the pmr and ir spectra confirmed the absence of the olefinic function.

$$(CH_3)_2CHCHCOCH_3$$
$$\qquad\quad |$$
$$\qquad Si(CH_3)_3$$

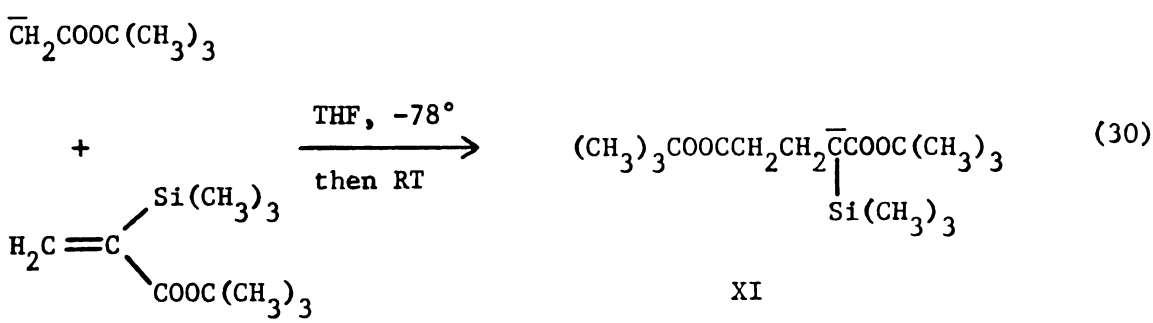
IX

The pmr spectrum of the isolated ester was identical to a previously obtained spectrum for cis t-butyl 2-trimethylsilyl-2-butenoate. It was assumed the cis β-methyl group, in respect to the carboalkoxy function, was shifted further downfield than the tran β-methyl. The unexpected stability of the cis isomer was not further investigated.



Pure compound A eluded isolation. A pmr spectrum was obtained of the crude material only showing with certainty the trimethylsilyl group at δ 0.27.

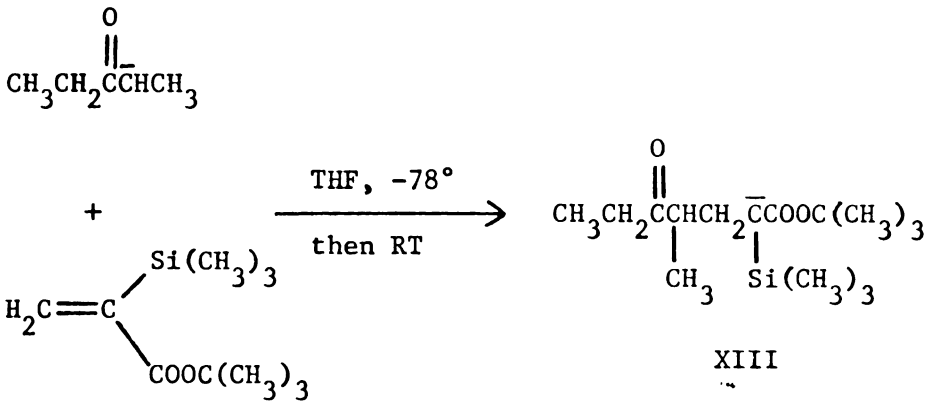
Solid lithio t-butyl acetate failed to undergo a Michael reaction with t-butyl α-trimethylsilylacrylate. However, freshly prepared solutions of lithio t-butyl acetate added to the vinyl silyl ester at -78° in THF followed by warming to room temperature (eq. 30).



(30)

XI

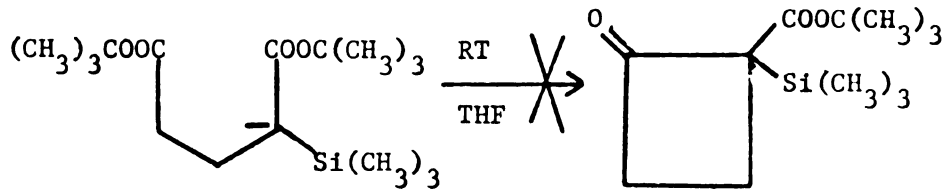
The enolate of diethyl ketone similarly gave the Michael addition product (eq. 31).



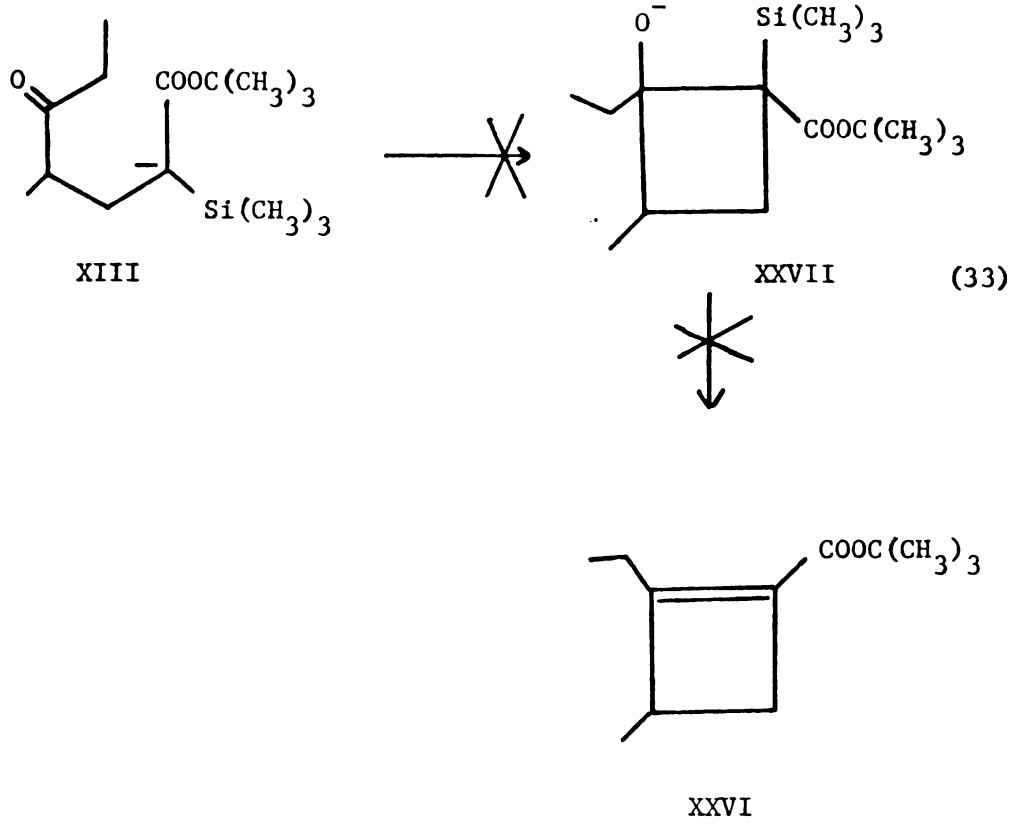
(31)

XIII

The silylated ester enolates XI and XIII are conceivably precursors to the cyclobutanone (XXV) and the cyclobutene (XXVI) (eq. 32, 33). Elimination of the trimethylsiloxy group from intermediate XXVII would irreversibly render the cyclobutene (XXVI). Unfortunately, XI and XIII apparently did not undergo cyclization after 18 hours in THF at room temperature. The failure of XI to undergo a Dieckmann condensation is not surprising since the Dieckmann cyclization is normally only successful for five- and six-membered rings.



(32)



XIII XXVII (33)

XXVI

EXPERIMENTAL

I. Materials

Esters

The preparation of t-butyl trimethylsilylacetate is described in Chapter I. Tert-butyl bis(trimethylsilyl)acetate (bp 61°/0.4 mm) is prepared in a similar fashion.

Carbonyls

All aldehydes and ketones were commercially available. All carbonyls, except acetone, were distilled and stored under a nitrogen atmosphere. Acetone was stored over molecular sieves.

Amine and Solvent

N,N-Diisopropylamine (bp 83°/atm. pressure) was distilled and stored over molecular sieves under a nitrogen atmosphere. Tetrahydrofuran was used without further purification.

II. Preparation of t-Butyl α,β-Unsaturated Esters

Tert-butyl cyclohexylideneacetate is representative for the preparation of α,β-unsaturated esters. Glpc analysis utilized a 1/4 inch by 6 foot SE-30 column. Each reaction run on a 5 mmole scale had an appropriate internal standard.

A. General Procedure

A 100 ml round-bottomed flask equipped with magnetic stirring, septum inlet, and mercury bubbler is flushed with nitrogen and immersed in an ice-water bath. The flask is charged with a hexane solution of n-butyllithium (12.5 ml, 25 mmole) and 3.6 ml (25 mmole) of diisopropylamine is injected over a 2 minute period. Following complete addition, the hexane is removed under reduced pressure and the flask is immersed in a dry ice-acetone bath and tert-butyl trimethylsilylacetate (5.5 ml, 25 mmoles) is added dropwise over a 2 minute period. After an additional 10 minutes of stirring, 2.6 ml of cyclohexanone (25 mmoles) is injected. The solution is then allowed to reach room temperature and quenched by the addition of 25 ml of 3N hydrochloric acid. Extraction with pentane and vacuum distillation of the organic phase gives 4.5 g (90% yield) of tert-butyl cyclohexylideneacetate, bp 121-3°/16 mm.

B. Product Analysis

tert-Butyl cyclohexylideneacetate

NMR(CCl_4): δ 5.43 (s, 1H), δ 2.97 (m, 2H), δ 2.13 (m, 2H), δ 1.60 (m, 6H), δ 1.43 (s, 9H). IR(neat): 1715 cm^{-1} (C=O), 1655 cm^{-1} (C=C).

tert-Butyl cinnamate

NMR($CDCl_3$): δ 7.5 (m, 6H), δ 7.83, δ 6.56, δ 6.30 (2 doublets, 1 H, J=16Hz), δ 1.56 (s, 9H).

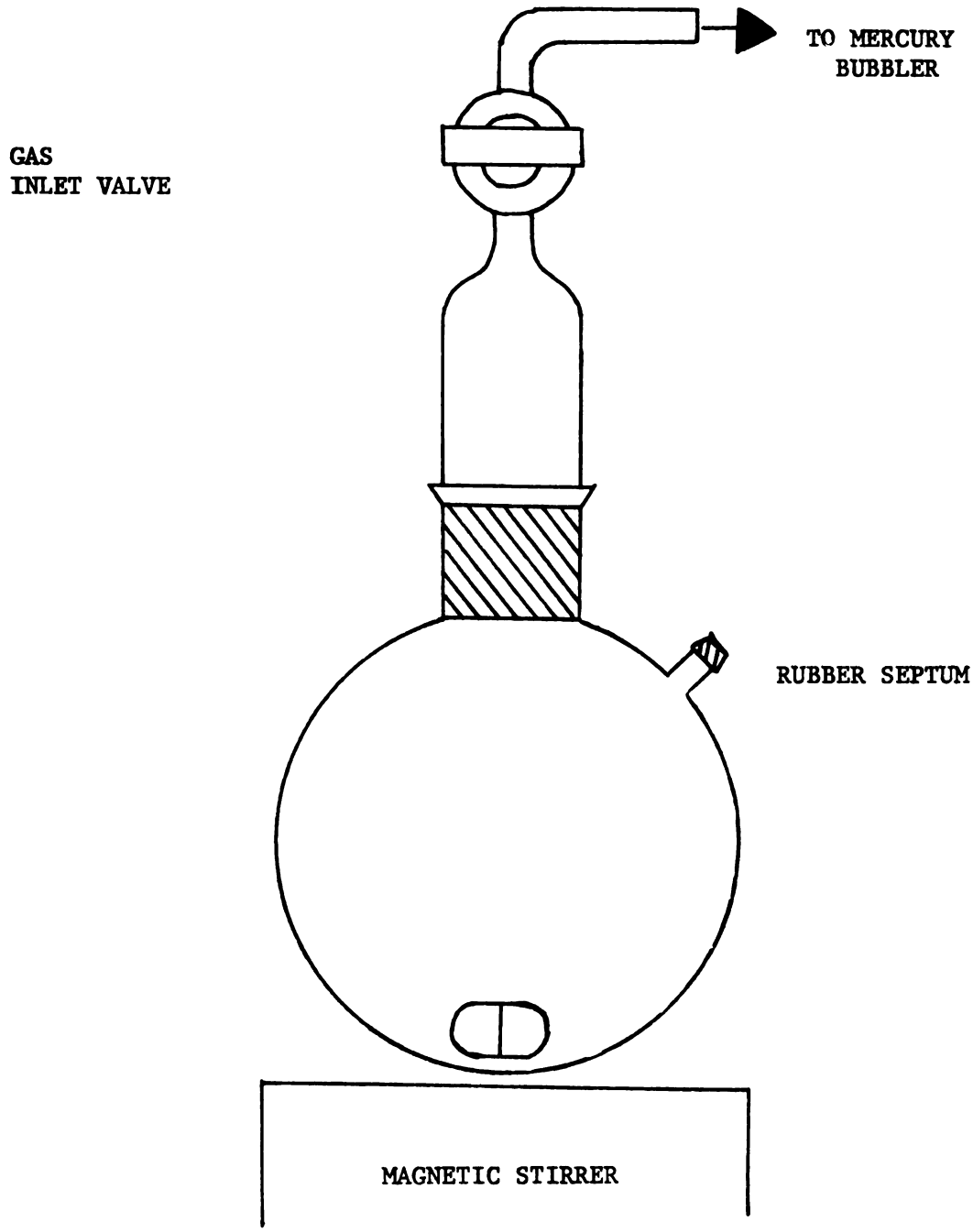


Figure 3. Reaction Apparatus

tert-Butyl 3-methyl-2-butenoate

NMR(CCl_4): δ 5.53 (broad, 1H), δ 2.13 (d, 3H, cis methyl), δ 1.87 (d, 3H, trans methyl),δ 1.43 (s, 9H). IR(neat): 1715 cm^{-1} (C=O), 1600 cm^{-1} (C=C).

tert-Butyl 2-butenoate

NMR(CCl_4): δ 5.57-7.13 (multiplets, 2H), δ 1.80, δ 1.90, δ 2.03, δ 2.17 (4 doublets, 3H), δ 1.47 (s, 9H). IR(neat): 1720 cm^{-1} (C=O), 1660 cm^{-1} (C=C).

tert-Butyl 4-methyl-2-pentenoate

NMR(CCl_4): δ 6.90, δ 6.60, δ 5.57 (3 doublets, 2H), δ 2.33 (m, 1H), δ 0.97,δ 1.10 (d, 6H), δ 1.43 (s, 9H). IR(neat): 1725 cm^{-1} (C=O), 1655 cm^{-1} (C=C).

tert-Butyl 2,4-hexadienoate

NMR(CCl_4): δ 5.2-7.7 (multiplets, 4H), δ 1.87 (m, 3H), δ 1.50 (s, 9H).

tert-Butyl 5-phenyl-2,4-pentadienoate

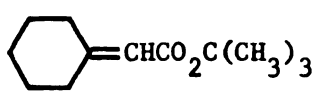
NMR(CCl_4): δ 5.4-8.2 (multiplets, 9H), δ 1.50 (s, 9H).

tert-Butyl 3-phenyl-3-hydroxy-2-trimethylsilylpropanoate

NMR(CCl_4): δ 7.4 (s, 5H), δ 4.90 (d, 1H), δ 4.30 (broad, 1H), δ 2.57 (d, 1H), δ 1.40 (s, 9H), δ 0.20 (s, 9H).

TABLE 6

Elemental Analysis[a] of the α,β-Unsaturated Esters

Ester	Calculated		Found	
	C %	H %	C %	H %
$CH_3CH{=}CHCO_2C(CH_3)_3$	67.51	9.93	67.37	9.86
$(CH_3)_2CHCH{=}CHCO_2C(CH_3)_3$	70.56	10.62	70.56	10.67
$C_6H_5CH{=}CHCO_2C(CH_3)_3$	76.30	7.78	76.18	7.72
$CH_3CH{=}CH{-}CH{=}CHCO_2C(CH_3)_3$	71.45	9.58	71.18	9.43
$C_6H_5CH{=}CH{-}CH{=}CHCO_2C(CH_3)_3$	78.10	7.86	78.21	7.94
$(CH_3)_2C{=}CO_2C(CH_3)_3$	69.20	10.32	69.33	10.37
	73.40	10.24	73.39	10.16

[a] Performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

tert-Butyl 3-hydroxy-3-methyl-2-trimethylsilylacetate

NMR(CCl_4): δ 3.40 (broad, 1H, disappears with D_2O), δ 2.07 (s, 1H), δ 1.50 (s, 9H), δ 1.23 (s, 6H), δ 0.20 (s, 9H).

tert-Butyl 3-cyclohexyl-3- hydroxy-2-trimethylsilylacetate

Elemental Analysis: Calc.: 62.85% C, 9.79% Si, 10.55%H;
Found: 62.12% C, 10.44% Si, 9.22% H.

tert-Butyl 1-cyclohexenylacetate

NMR(CCl_4): δ 5.37 (broad, 1H), δ 2.67 (s, 2H), δ 1.93 (m, 4H), δ 1.53 (m, 4H), δ 1.40 (s, 9H).

III. Preparation of tert-Butyl α-Trimethylsilyl α,β-Unsaturated Esters

A. General Procedure

The following procedure for the conversion of acetaldehyde into tert-butyl 2-trimethylsilyl-2-butenoate is representative for most aldehydes. A 100 ml round-bottomed flask equipped with magnetic stirring, septum inlet, and mercury bubbler is flushed with nitrogen and immersed in an ice-water bath. The lithium diisopropylamide is generated in a similar manner as described previously. The THF solution of the lithium amide is cooled in a dry ice-acetone bath and tert-butyl bis(trimethylsilyl)acetate (13.3 ml, 50 mmoles) is added dropwise over a 5 minute period. After an additional one hour of stirring, 2.8 ml of acetaldehyde (50 mmoles) is injected. The solution is then allowed to reach room temperature and quenched by the

addition of 35 ml of 3N hydrochloric acid. After pentane extraction, the organic phase is washed with saturated sodium bicarbonate. Vacuum distillation of the organic layer gives 6.2 g (58% yield) of tert-butyl 2-trimethylsilyl-2-butenoate, bp 59°/0.3 mm.

B. tert-Butyl α-Trimethylsilylacrylate

A 250 ml round-bottomed 3-necked flask, equipped with a mechanical stirrer, gas inlet valve, mercury bubbler, and rubber septum, is flushed with nitrogen. After preparation of 100 mmoles of the lithium amide, the bis silyl ester (26.6 ml, 100 mmoles) is added dropwise to the -78° solution and stirred for one hour. Meanwhile, a 50 ml flask containing 5 g of paraformaldehyde (170 mm formaldehyde), is fitted with a T-tube through a rubber septum. A mercury bubbler, containing excess mercury (pressure valve), and a 10 mm diameter glass tube are attached to the T-tube (Figure 4). After the ester enolate is generated, the glass tube is placed 2 cm above the surface of the reaction mixture. With rapid stirring, the formaldehyde, produced by flame heating paraformaldehyde, is entrained in a slow stream of nitrogen flowing into the reaction flask. After 20 minutes, the addition is complete, and the reaction mixture warmed to room temperature. A mixture of 60 ml water and 150 ml pentane is added and the layers separated. Vacuum distillation of the organic phase gives 6.7 g (35% yield) of product, bp 34°/0.2 mm.

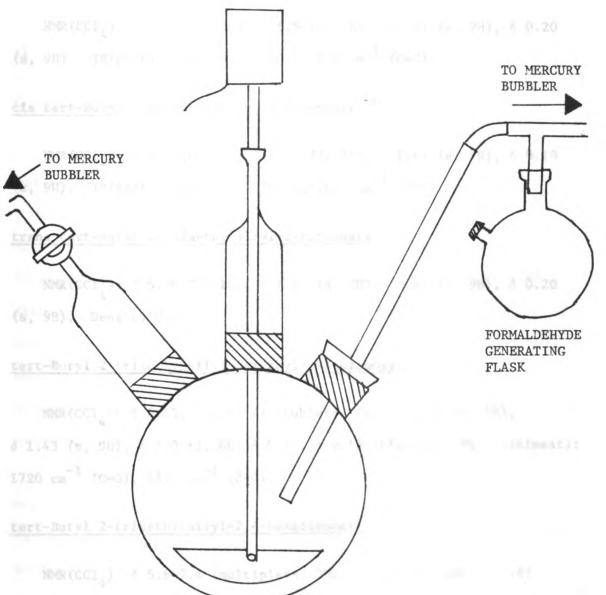


Figure 4. Reaction Apparatus

C. Product Analysis

tert-Butyl 2-trimethylsilyl-3-phenyl-2-propenoate

NMR(CCl_4): δ 7.13 (s, 5H), δ 6.5 (s, 1H), δ 1.37 (s, 9H), δ 0.20 (s, 9H). IR(neat): 1710 cm^{-1} (C=O), 1600 cm^{-1} (C=C).

cis tert-Butyl 2-trimethylsilyl-2-butenoate

NMR(CCl_4): δ 6.0 (q, 1H), δ 1.90 (d, 3H), δ 1.47 (s, 9H), δ 0.10 (s, 9H). IR(neat): 1715 cm^{-1} (C=O), 1610 cm^{-1} (C=C).

trans tert-Butyl 2-trimethylsilyl-2-butenoate

NMR(CCl_4): δ 6.90 (q, 1H), δ 1.87 (d, 3H),δ 1.47 (s, 9H), δ 0.20 (s, 9H). Density 0.90.

tert-Butyl 2-trimethylsilyl-4-methyl-2-pentanoate

NMR(CCl_4): δ 6.53, δ 5.60 (2 doublets, 1H), δ 2.87 (m, 1H), δ 1.43 (s, 9H), δ 1.0 (d, 6H),δ 0.17, δ 0.10 (singlets, 9H). IR(neat): 1720 cm^{-1} (C=O), 1610 cm^{-1} (C=C).

tert-Butyl 2-trimethylsilyl-2,4-hexadienoate

NMR(CCl_4): δ 5.6-7.4 (multiplets, 3H), δ 1.80 (d, 3H), δ 1.47 (s, 9H), δ 0.13, δ 0.23 (singlets, 9H). IR(neat): 1705 cm^{-1} (C=O), 1640 cm^{-1} (C=C).

tert-Butyl 2-trimethylsilyl-2-propenoate

NMR(CCl_4): δ 5.77, δ 6.50 (d, 2H), δ 1.47 (s, 9H), δ 0.17 (s, 9H). IR(neat): 1700, 1720 cm^{-1} (C=O), 1590 cm^{-1} (C=C). Density 0.88.

IV. Reaction of t-Butyl 2-Silylated Unsaturated Esters

A. tert-Butyl 2-Trimethylsilyl-2-butenoate with Methyl Grignard

A 50 ml round-bottomed flask, equipped with magnetic stirring, septum inlet, and mercury bubbler, is flushed with nitrogen and immersed in an ice-water bath. The flask is charged with 1.9 ml of methyl magnesium iodide in ether (2.1 mmoles) and 0.50 ml of ester (2.1 mmoles) is injected dropwise. After 15 minutes, the reaction mixture is warmed to room temperature for one hour giving a white precipitate. Ether is added and the reaction quenched with aqueous ammonium chloride. Glpc isolated an impure low-boiling fraction, 3-trimethylsilyl-4-methyl-2-pentanone, and cis t-butyl 2-trimethylsilyl-2-butenoate as the only products from the reaction mixture.

An NMR spectrum of 3-trimethyl-4-methyl-2-pentanone revealed signals at δ 2.2 (m, 1H), δ 2.03 (d, 1H), δ 1.94 (s, 3H), δ 0.90 (m, 6H), and δ 0.06 (s, 9H). The IR spectrum showed a carbonyl band at 1680 cm^{-1} (ketone).

B. tert-Butyl 2-Trimethylsilylacrylate with Methyl Grignard

The reaction flask, as described above, is charged with 3.6 ml of methyl magnesium iodide (4 mmoles) and cooled in an ice-water bath. The ester (0.90 ml, 4 mmoles) is injected into the reaction vessel

giving a white precipitate within a few minutes. The reaction is quenched after 30 minutes with aqueous ammonium chloride. Glpc of the organic phase showed an almost complete conversion of the acrylate into t-butyl 2-trimethylsilylbutanoate. NMR(CCl_4): δ 2.0 (m, 1H), δ 1.83 (m, 2H), δ 1.40 (s, 9H), δ 1.0 (m, 3H), δ 0.06 (s, 9H). IR(neat): 1710 cm^{-1} (C=O).

C. tert-Butyl 2-Trimethylsilylacrylate with Lithio t-Butylacetate

Lithio t-butyl acetate (0.25 g, 2 mmoles) is placed into a 50 ml round-bottomed flask and dissolved in 4 ml of THF. The flask is immersed in a dry ice-acetone bath and 2 mmoles of ester (0.45 ml) is injected. After 15 minutes, the reaction mixture is warmed to room temperature and stirred for an additional 2 hours. After dilution with pentane, the reaction is quenched with water. Glpc showed much starting material and an abundant number of products. No t-butyl acetate was detected.

The reaction was repeated with freshly prepared lithio t-butyl acetate. Lithium diisopropylamide is generated in the usual manner. To the 1M solution of base at -78°, t-butyl acetate (0.53 ml, 4 mmoles) is injected dropwise and stirred for 10 minutes. The acrylate (0.90 ml, 4 mmoles) is added, diluted with pentane after 5 minutes, and quenched with water. Tert-butyl 2-trimethylsilylglutarate was isolated by preparative glpc. NMR(CCl_4): δ 1.40 (s, 18H), δ 0.10(s, 9H).δ 1.87 (m, 3H). IR(neat): 1715, 1730 cm^{-1} (C=O).

D. tert-Butyl 2-Trimethylsilylacrylate with 3-Pentanone Enolate

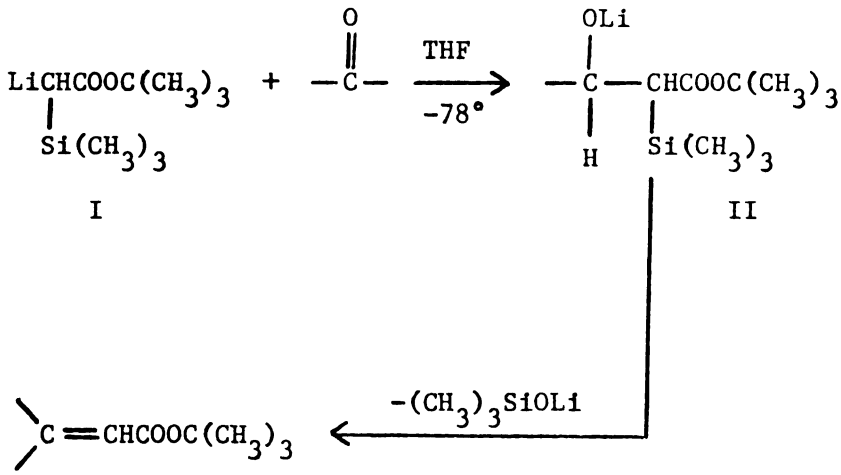
Lithium diisopropylamide (20 mmoles) is prepared in the usual manner and dissolved in 20 ml of THF. The flask is immersed in a dry ice-acetone bath and 2.1 ml of 3-pentanone (20 mmoles) is injected. After 10 minutes, the reaction is stirred for an additional 2 hours at room temperature. After dilution with ether, the reaction is quenched with water. Vacuum distillation of the organic phase gave 2.1 g (37% yield) of t-butyl 2-trimethylsilyl-5-oxo-4-methylheptanoate. NMR(CCl_4): δ 2.40 (m, 3H), δ 1.70 (m, 1H), δ 1.47 (s) and δ 1.07 (m) total 17H, and δ 0.17 (s, 9H). IR(neat): 1710 cm^{-1} (C=O)

CHAPTER III

THE REACTION OF ACYL COMPOUNDS WITH α-TRIMETHYLSILYL ESTER ENOLATES

INTRODUCTION

Lithio tert-butyl trimethylsilylacetate (I) reacts with aldehydes or ketones to give α,β-unsaturated esters (eq. 1).[48] The products are assumed to form by elimination of lithium trimethylsiloxide from the intermediate II. This elimination occurs rapidly at dry ice temperatures.



(1)

It was of interest to further investigate the reactions of I. In particular, reaction of I with acylating reagents could conceivably take three paths, two of which involve elimination of the trimethylsilyl group (IV, V).

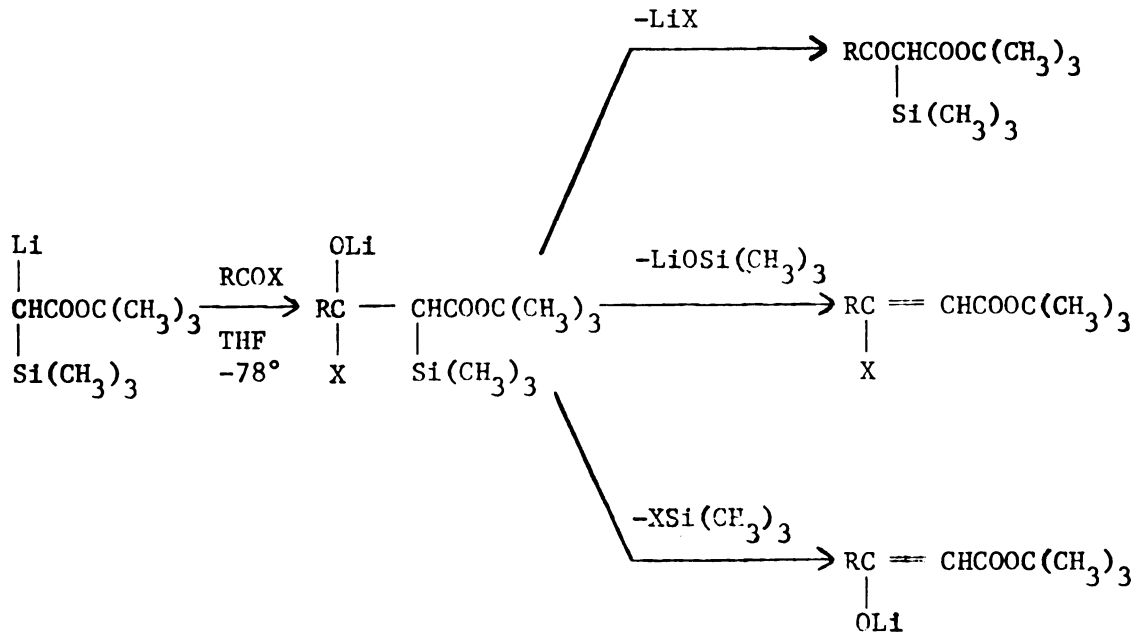
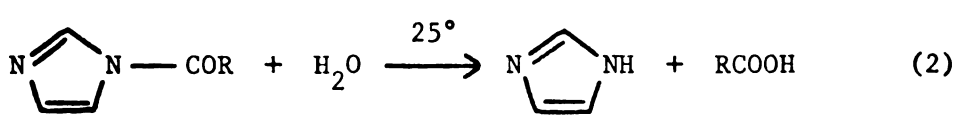


Figure 5. Possible Reaction Paths for Lithio t-Butyl Trimethylsilyl-acetate with Acylating Reagents

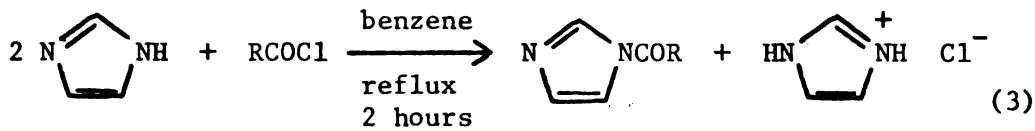
Acyl halides, esters, and amides all might be used as successful acylating reagents for silyl ester enolates. Although amides are normally not very reactive toward nucleophilic attack, the N-acyl-imidazoles (VI) are about as reactive as acyl halides or anhydrides. For example, they react with water at room temperature (eq. 2).[49]



(2)

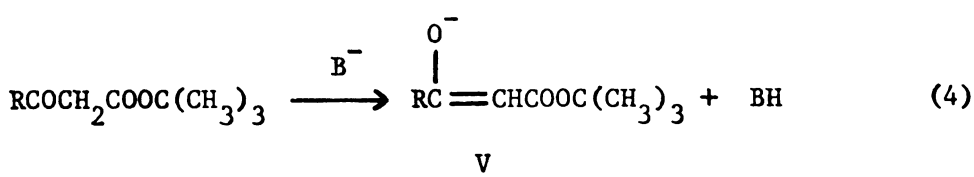
VI

The N-acylimidazoles are conveniently prepared by reaction of an acid halide with two equivalents of imidazole (eq. 3), or by reaction of carboxylic acids with carbonyl diimidazole.[49]



(3)

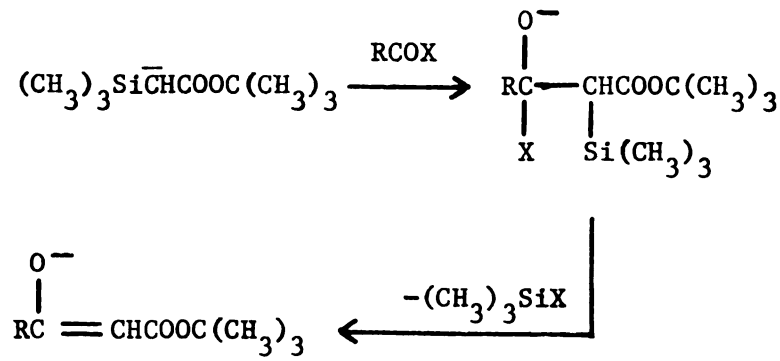
The reaction path in Figure 4 which leads to the condensation product IV would constitute a unique synthesis of an enamine[50] if an acylimidazole is employed. Regardless of the acylating reagent or possible reaction path, the products (Figure 4) would all be converted to a β-keto ester upon acid-catalyzed hydrolysis. β-Keto esters are relatively acidic compounds, and the alpha proton flanked by two carbonyl groupings is easily removed to give a β-keto ester enolate (V) (eq. 4).



V

(4)

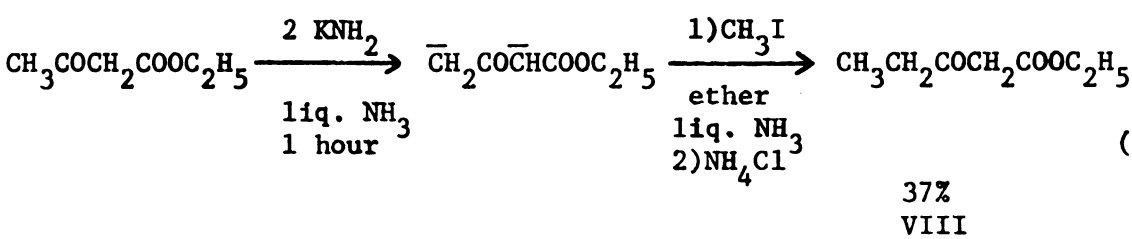
The condensation of I with an acylating reagent may give the β-keto ester enolate (V) directly (eq. 5). Such enolates are known to be stable[51] and may be isolated in a similar fashion to lithio t-butyl acetate.[39]



(5)

More Complex Enolate Sytems

The β-keto ester enolates are susceptible to additional proton removal with a strong base to give a dianion.[52,53] Thus, ethyl acetoacetate reacts with two equivalents of potassium amide to give the corresponding dianion (VI) (eq. 6). The low yield of the γ-alkylated product (VII) is probably due to incomplete dianion formation or slow alkylation at liquid ammonia temperatures.[52,53]



(6)

The use of n-butyllithium or LiDPA[54] as bases to generate the dianion gave more satisfactory results upon alkylation (eq. 7).[53]

$$CH_3COCH_2COOCH_3 \xrightarrow[0°]{NaH,\ THF} CH_3C\bar{O}CHCOOCH_3 \xrightarrow[0°]{n\text{-}BuLi} \qquad (7)$$

$$\bar{C}H_2C\bar{O}CHCOOCH_3 \xrightarrow[2)H^+]{1)CH_3I,\ 25°,\ 15\ min.} CH_3CH_2COCH_2COOCH_3$$

99%

The γ-position, the most basic site in the dicarbanionic β-keto ester, apparently undergoes reaction exclusively with one equivalent of an electrophilic reagent (eq. 7).[53] Consequently, reaction of TMCS with a β-keto ester dianion should give the γ-silylated enolate (VIII) (eq. 8). The dianion of VIII could conceivably undergo a subsequent elimination reaction analogous to equation 1 (eq. 9).

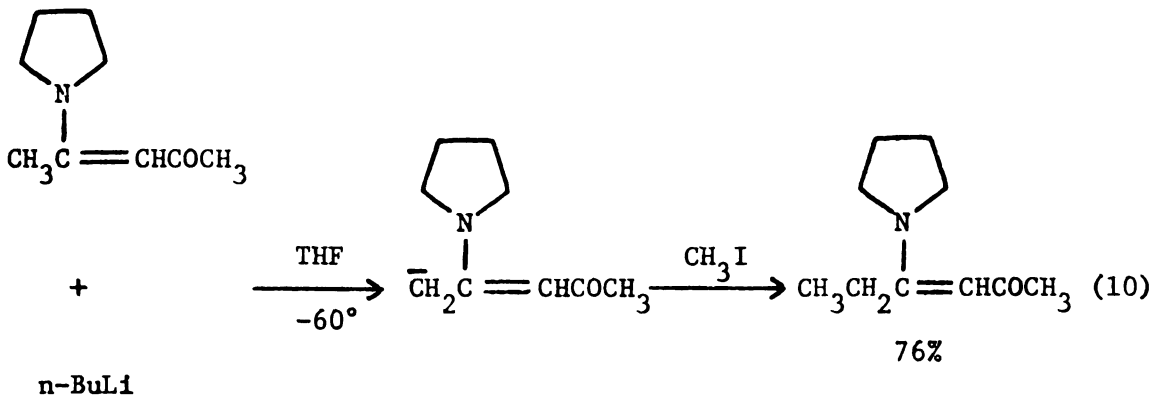
$$LiCH_2C(OLi)=CHCOOC(CH_3)_3 \xrightarrow[THF]{TMCS} (CH_3)_3SiCH_2C(OLi)=CHCOOC(CH_3)_3 \qquad (8)$$

VIII

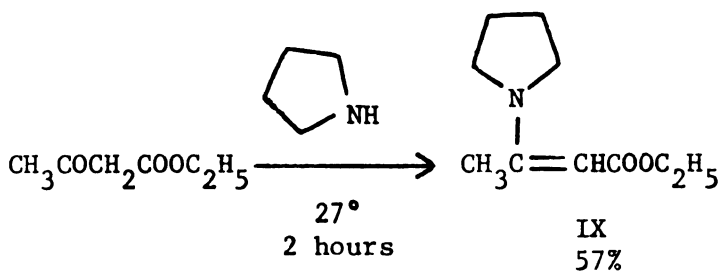
$$(CH_3)_3SiCH_2C(OLi)=CHCOOC(CH_3)_3 \xrightarrow[2)\ O=C]{1)BuLi,\ THF} -C(O^-)-CH(Si(CH_3)_3)-C(OLi)=CHCOOC(CH_3)_3$$

$$-C(O^-)-CH(Si(CH_3)_3)-C(OLi)=CHCOOC(CH_3)_3 \xrightarrow{-(CH_3)_3SiO^-} >C=CHC(OLi)=CHCOOC(CH_3)_3 \qquad (9)$$

Anions of β-enamino ketones also undergo alkylation exclusively at the γ-carbon affording chain extended β-keto esters (eq. 10).[55] The β-enamino esters are conveniently prepared from a β-keto ester and a secondary amine (eq. 11)[56] and might be expected to react in a similar fashion.

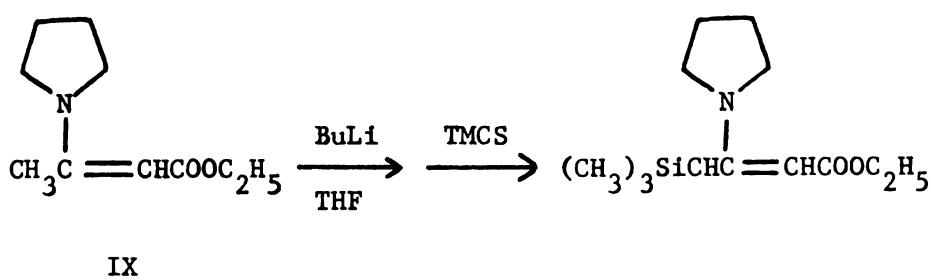


(10)

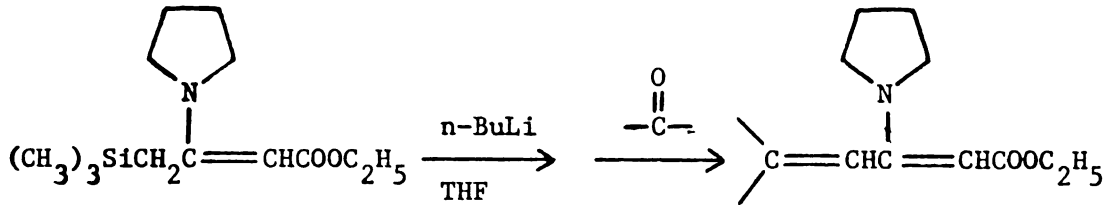


(11)

Silylation of IX rather than alkylation should lead to a precursor for further condensation, analogous to equation 1 (eq. 12, 13).



(12)



(13)

It was the intention of this investigation to explore the synthetic utility of I. The possible products from different acylating reagents, Figure 5, appeared a promising way to extend the silylated anion method to more complex systems.

RESULTS

Preparation of β-Keto Esters

Lithio tert-butyl trimethylsilylacetate in THF at -78° was reacted with a variety of acylating reagents. With acetyl chloride, only a complicated mixture of products was obtained. With ethyl acetate or N,N-dimethylacetamide, I was recovered unchanged. However, reaction of I with N-acetylimidazole in THF at -78° gave, following removal of the solvent, the lithiated β-keto ester V in 85% yield (eq. 14). Reaction of I with a variety of N-acylimidazoles in THF at dry ice temperatures, followed by quenching with dilute hydrochloric acid, gave the corresponding β-keto esters (X) in 70 to 94% yields (eq. 15) (Table 8).

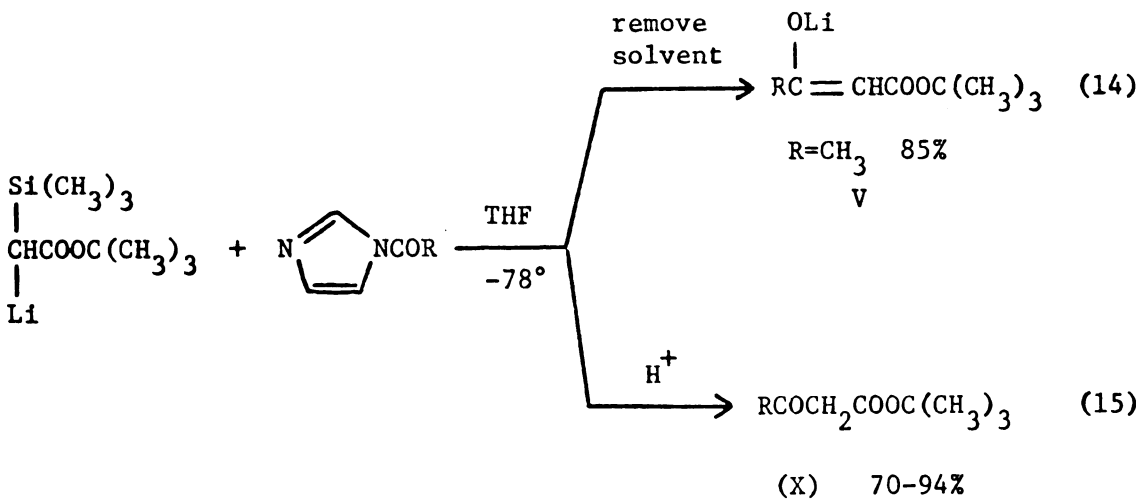


TABLE 7

Reaction of Acid Chlorides with Imidazole

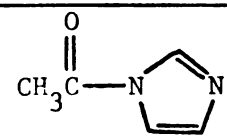
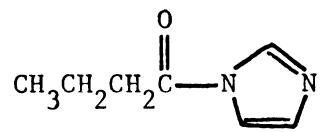
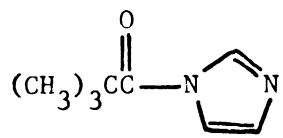
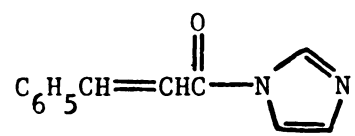
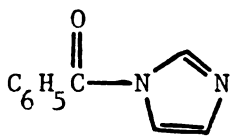
Acid Chloride	Product	Yield, %[a]	Mp (Bp/mmHg)	Lit. Mp
CH_3COCl		68	103-4°	104° [57]
$CH_3CH_2CH_2COCl$		86	(110-12°/6)	19° [58]
$(CH_3)_3CCOCl$		47	53-4°	56° [59]
$C_6H_5CH{=}CHCOCl$		68	133-4°	134° [60]

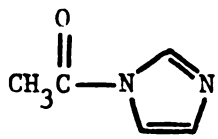
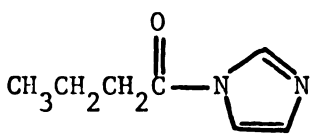
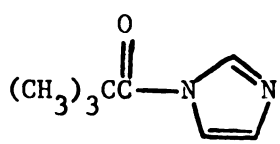
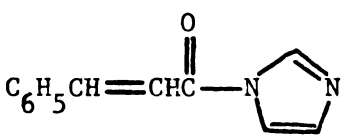
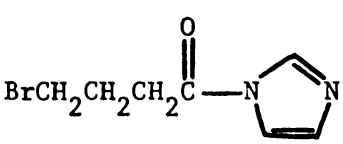
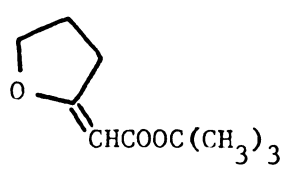
TABLE 7 (cont.)

Acid Chloride	Product	Yield, %[a]	Mp (Bp/mmHg)	Lit. Mp
C_6H_5COCl		87		19-20° 60

[a] Isolated yields.

TABLE 8

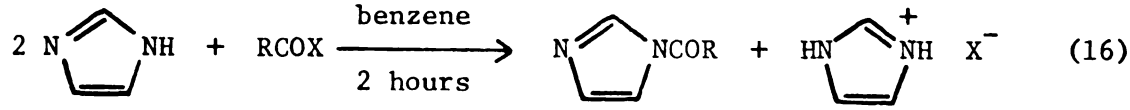
Reaction of N-Acylimidazoles with
Lithio tert-Butyl Trimethylsilylacetate

N-Acylimidazole	Product	Yield, %[a]
	$CH_3COCH_2COOC(CH_3)_3$	94
	$CH_3CH_2CH_2COCH_2COOC(CH_3)_3$	81
	$(CH_3)_3CCOCH_2COOC(CH_3)_3$	70
	$C_6H_5CH{=}CHCOCH_2COOC(CH_3)_3$	(50)
		75

[a] Glpc yields, isolated yields in parentheses.

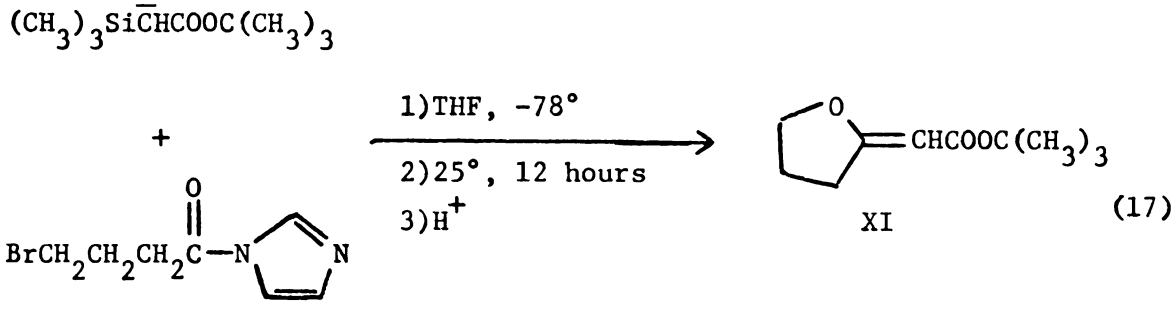
Preparation of N-Acylimidazoles

The N-acylimidazoles were prepared by the method developed by Staab.[49] Reaction of two equivalents of imidazole with an acyl halide in benzene gave the corresponding N-acylimidazoles in 47-87% isolated yields (eq. 16) (Table 7).



47-87% (16)

Condensation of I with 4-bromobutanoylimidazole gave the heterocyclic ester XI in 75% yield (eq. 17).

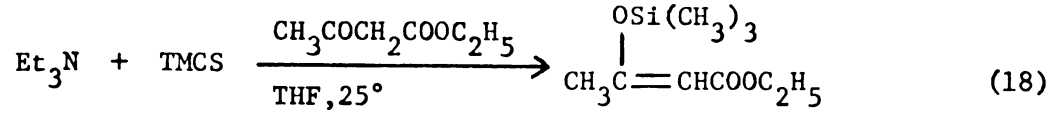


XI (17)

Preparation of β-Keto Ester Derivatives

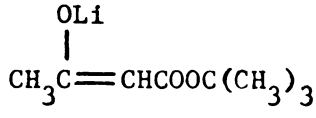
The lithiated β-keto ester XII could be isolated directly from the reaction of I with N-acetylimidazole (eq. 14). The O-silylated derivative XIII was obtained in 76% yield from the reaction of triethylamine, TMCS, and ethyl acetoacetate in THF at 25° (eq. 18). Reaction of pyrrolidine with ethyl acetoacetate at room temperature

gave the β-enamino ester IX.

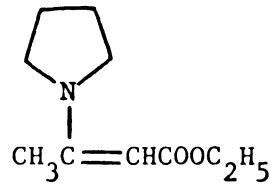


(18)

XIII 76%



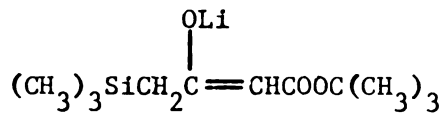
XII



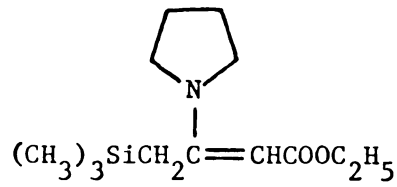
IX

Silylation or Alkylation of β-Keto Ester Derivatives

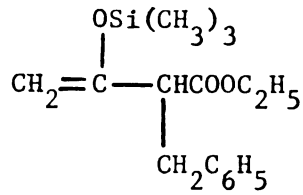
The metalated β-keto ester XII tolerated exposure to the atmosphere for days without decomposition. Conversion of XII to a dianion was accomplished by treatment with n-butyllithium in THF at 25°. Alternatively, this dianion was prepared by reaction of t-butyl acetoacetate with two equivalents of LiDPA. Reaction of the dianion with TMCS at -78° gave a 70% yield of the γ-silylated material VIII. The mono anion of the β-enamino ester IX, generated with n-butyllithium in THF at -78°, was likewise silylated at the γ-position to give XIV. However, generation of the mono anion of XIII with LiDPA in THF at -78° gave the α-alkylated product XV on reaction with benzyl bromide.



VIII



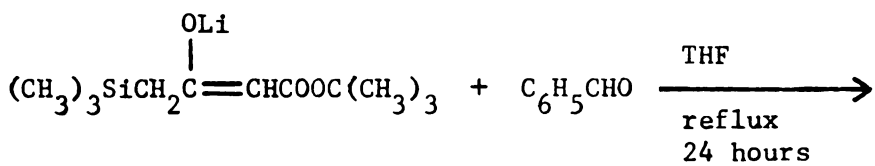
XIV



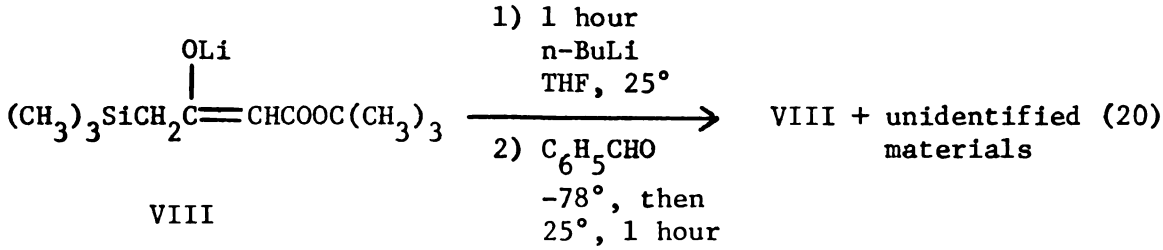
XV

Attempted Reaction of VIII and XIV with Benzaldehyde

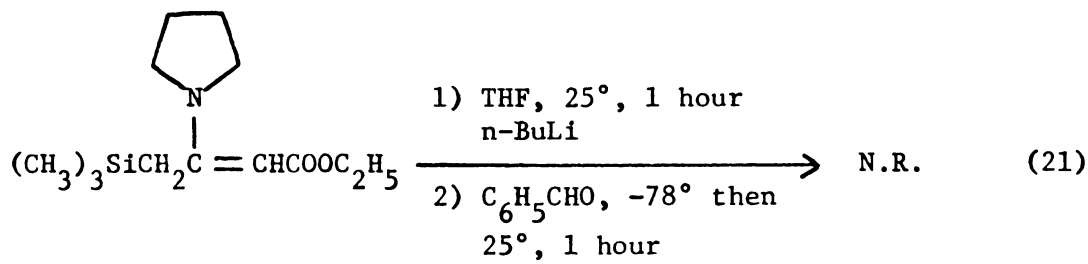
Efforts to induce reaction of VIII with benzaldehyde in refluxing THF resulted in the recovery of VIII (eq. 19). Reaction of the dianion of VIII with benzaldehyde in THF, with or without HMPA or TMEDA added, only resulted in the recovery of the γ-silylated mono anion (eq. 20). Interestingly, a camphor-like odor was detected from the latter reaction when acetone was substituted for benzaldehyde.



(19)



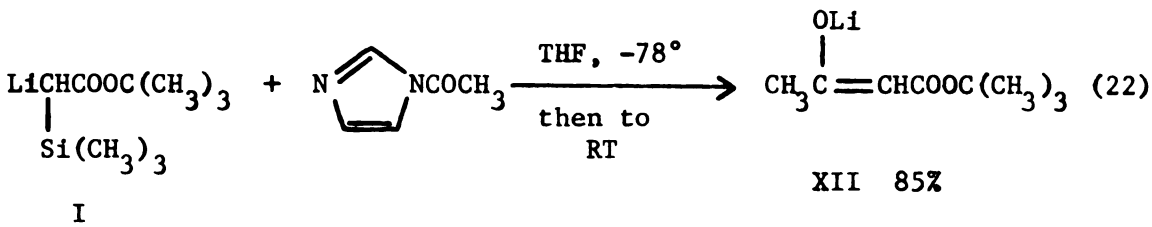
Attempted generation of the β-enamino ester anion in THF at room temperature, followed by the addition of benzaldehyde, returned XIV unchanged (eq. 21).



DISCUSSION

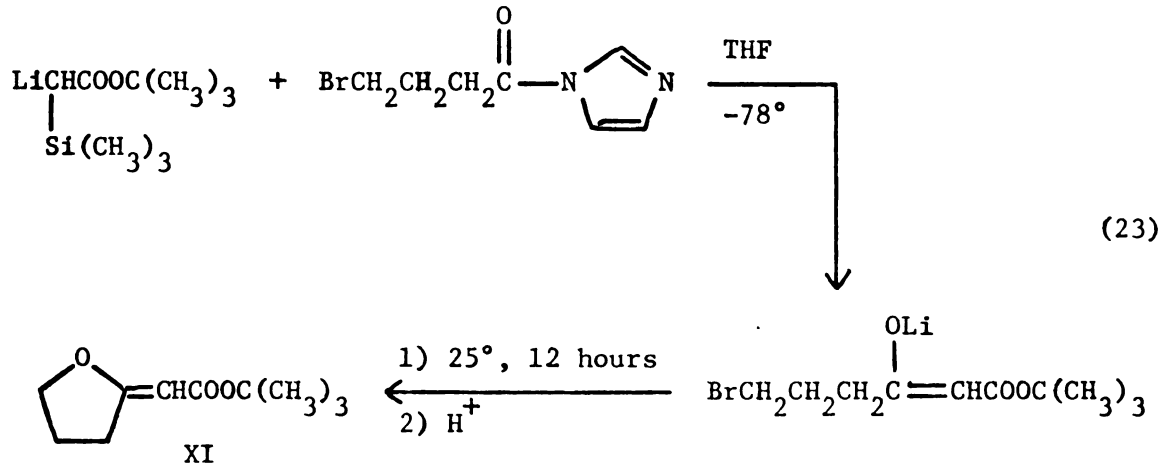
Preparation of β-Keto Esters

Treatment of lithio t-butyl trimethylsilylacetate with N-acetylimidazole gave the lithium salt XII by selective elimination of the imidazole and trimethylsiloxy moieties (eq. 22). The mechanism for loss of these groups was not established.



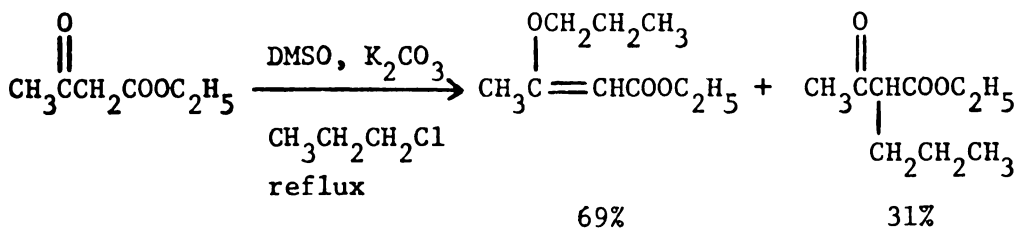
(22)

The preparation of β-keto esters by acylation of ester enolates is normally complicated by the acidic nature of the product.[33] This usually results in the neutralization of 50% of the starting enolate. The present procedure avoids this difficulty by directly generating the anion of the β-keto ester, and also offers obvious advantages when further synthetic sequences with the anion are desired. For example, reaction of I with 4-bromobutanoylimidazole, prepared in THF and used immediately, gave in one step a 75% yield of tert-butyl 2-tetrahydrofurylideneacetate (eq. 23).



(23)

Cyclization of the lithiated intermediate through oxygen was surprising. Although O-alkylation is frequently observed with relatively acidic methylene compounds,[61] the site of alkylation is dependent upon solvent, temperature, the counterion, and alkylating reagent. For example, lithium enolates are normally alkylated at carbon while the larger counterions, such as potassium, favor O-alkylation (eq. 24).[62]



(24)

γ-Silylation of tert-Butyl Acetoacetate

With the lithium salt XII on hand, the dianion could be generated with an appropriate strong base. However, it was more convenient to generate the dianion directly from t-butyl acetoacetate with two

equivalents of LiDPA [54] (eq. 25).

$$CH_3COCH_2COOC(CH_3)_3 \xrightarrow[THF,\ 0°]{2\ LiDPA} \bar{C}H_2CO\bar{C}HCOOC(CH_3)_3 \qquad (25)$$

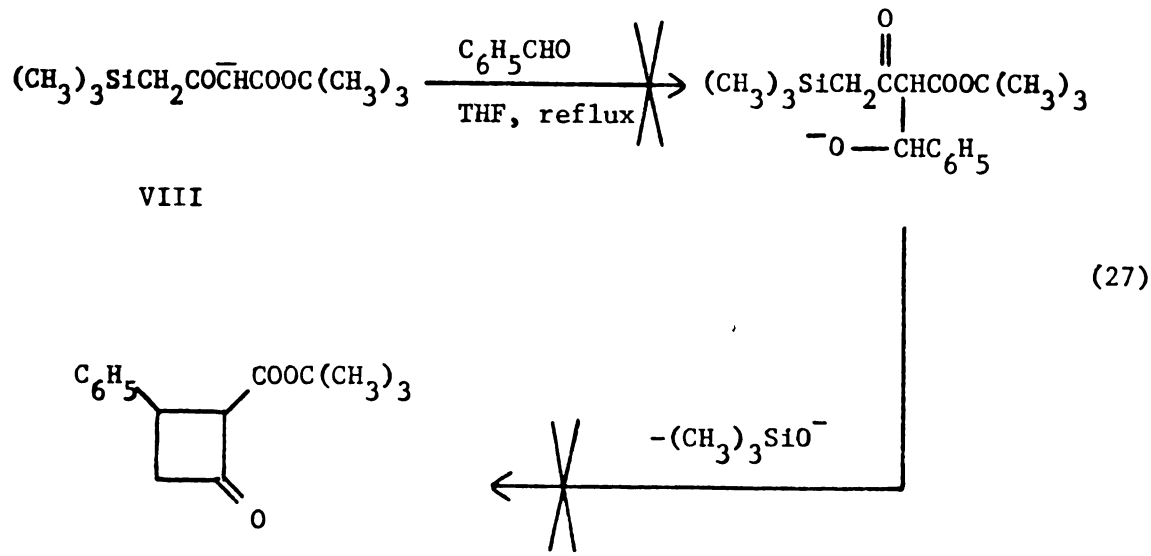
Silylation of the dianion with one equivalent of TMCS gave VIII (eq. 26), as expected from previous studies of alkylations in dianion systems.[53, 54, 63]

$$\bar{C}H_2CO\bar{C}HCOOC(CH_3)_3 \xrightarrow[-78°,\ then\ to\ 25°]{TMCS,\ THF,} (CH_3)_3SiCH_2CO\bar{C}HCOOC(CH_3)_3 \qquad (26)$$

VIII 70%

Attempted Reaction of Lithio t-Butyl γ-Trimethylsilylacetoacetate with Benzaldehyde

Our attempts to condense VIII with benzaldehyde to give a substituted cyclobutane were unsuccessful (eq. 27). Acidification of the reaction mixture, after 24 hours at reflux in THF, returned t-butyl acetoacetate.

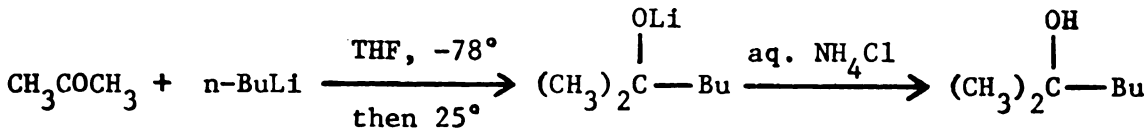


VIII

(27)

Attempted Reaction of the Dianion of VIII with Benzaldehyde

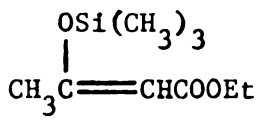
Apparently, attempts to generate the dianion of VIII with n-butyllithium failed. Addition of HMPA or TMEDA did not appreciably facilitate dianion formation. Addition of acetone to these reaction mixtures resulted in camphoric odors after quenching, indicative of tertiary alcohol formation. A 1,2-addition of base to the carbonyl component would explain the presence of a tertiary alcohol reflecting incomplete dianion formation (eq. 28). Failure to generate the dianion system is not unusual since such reactions have been shown sensitive to the base used, solvent, temperature and reaction time.[53,64]



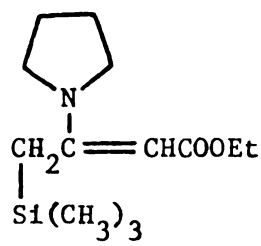
(28)

Attempted Reaction at the γ-Position of XIII and XIV

Compounds XIII and XIV were prepared in hopes their monoanions would undergo alkylation or aldol condensation at the γ-carbon. For

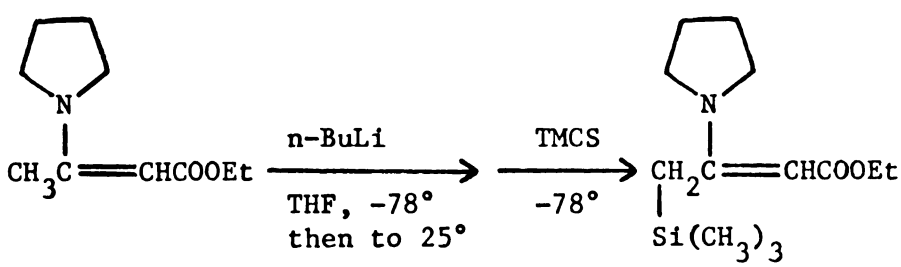


XIII



XIV

example, the anion of 4-pyrrolidino-3-penten-2-one readily undergoes reaction exclusively at the γ-position (eq. 10).[55] The silylated enamino ester XIV was obtained in a similar fashion (eq. 29).

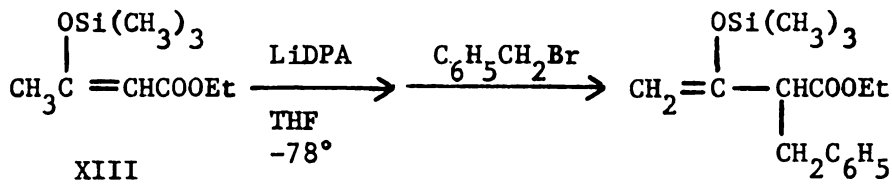


(29)

Treatment of XIV with n-butyllithium in THF at -78° followed by benzaldehyde addition returned starting material. Apparently the

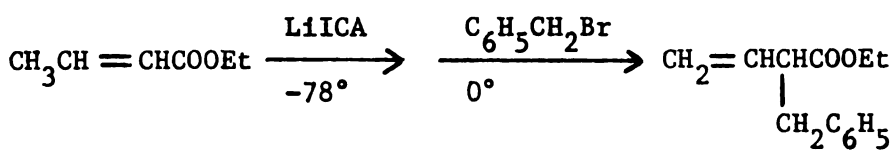
C-trimethylsilyl group seriously interferes with proton removal from the γ-position in XIV.

Proton removal from the crotonate XIII with LiDPA and quenching the anion with benzyl bromide gave the alkylated unconjugated ester XV (eq. 30) and not the γ-substituted product. This result was not



(30)

particularly surprising since such ester enolate systems are known to react predominately at the alpha carbon[65,66] (eq. 31).



(31)

62%

EXPERIMENTAL

I. Materials

Tert-butyl trimethylsilylacetate was prepared and purified as described in Chapter 1. Tert-butyl and ethyl acetoacetate were commercially available and used without further purification. Trimethylchlorosilane was obtained from Aldrich and distilled (bp 57°/atm. pressure) prior to use. Diisopropylamine (bp 83°/atm. pressure) was distilled and stored over molecular sieves. All acid chlorides and imidazole were commercially available and used without further purification. Tetrahydrofuran was stored over molecular sieves, and the HMPA was distilled from sodium before use.

II. Preparation of N-Acylimidazoles

The preparation of N-acetylimidazole is representative. A 250 ml round-bottomed flask, equipped with magnetic stirring, septum inlet, and mercury bubbler, is flushed with nitrogen. The flask is charged with 6.8 g (100 mmoles) of imidazole and 125 ml of dry benzene. After the imidazole has dissolved, 3.5 ml (50 mmoles) of acetyl chloride is injected, and the mixture stirred for 3 hours. The hydrochloride salt is removed by vacuum filtration followed by evaporation of the filtrate. The crude imidazole is recrystallized from benzene, washed with cold hexane, and dried in vacuum giving 3.75 g (68%) of product (mp 103-4°).

III. Preparation of β-Keto Esters

A. tert-Butyl Cinnamoylacetate

The following procedure for the conversion of cinnamoyl imidazole into tert-butyl cinnamoylacetate is representative. A 100 ml round-bottomed flask equipped with magnetic stirring, septum inlet, and mercury bubbler is flushed with nitrogen and immersed in an ice-water bath. The flask is charged with a hexane solution of n-butyllithium (12.5 ml, 25 mmoles), and 3.6 ml (25 mmoles) of diisopropylamine is injected over a 2 minute period. Following complete addition, the hexane is removed under vacuum, and the residue of lithium diisopropylamide is dissolved in 25 ml of THF. The flask is immersed in a dry ice-acetone bath, and t-butyl trimethylsilylacetate (5.5 ml, 25 mmoles) is added dropwise over a 2 minute period. After an additional 10 minutes of stirring, a warm solution of cinnamoyl imidazole (4.95 g, 25 mmoles) in 25 ml of THF is added dropwise. The red reaction mixture is stirred for an hour and then allowed to reach room temperature followed by quenching with 25 ml of 3N hydrochloric acid. Addition of 100 ml of pentane followed by separation and evaporation of the organic phase gave 5.85 g (95%) of a yellow solid. Recrystallization from methanol gave pure tert-butyl cinnamoylacetate; 3.1 g (50%), mp 87-87.5°.

B. Product Analysis

tert-Butyl cinnamoylacetate

NMR($CDCl_3$): δ 7.52 (m, 5H), δ 7.80, δ 7.00, δ 6.62 (all singlets, 2H), δ 5.17, δ 3.66 (2 singlets, 2H), δ 1.50 (overlapping singlets, 9H).

tert-Butyl acetoacetate

NMR(CCl_4): δ 4.67, δ 3.13 (2 singlets, 2H), δ 2.13, δ 1.83 (2 singlets, 3H),δ 1.43 (s, 9H).

tert-Butyl 3-oxohexanoate

NMR(CCl_4): δ 3,16 (s, 2H), δ 2.30-2.60 (m, 2H), δ 1.46 (s, 9H), δ 1.16 (m, 2H), δ 0.90 (t, 3H).

tert-Butyl 3-oxo-4,4-dimethylpentanoate

NMR(CCl_4): δ 4.83, δ 3.30 (2 singlets, 2H), δ 1.46 (overlapping singlets, 9H), δ 1.12 (s, 9H).

tert-Butyl 2-furylideneacetate

NMR($CDCl_3$): δ 5.17 (broad, 1H), δ 4.12 (t, 2H), δ 3.03 (t, 2H), δ 2.03 (m, 2H), δ 2.46 (s, 9H).

C. Isolation of Lithio tert-Butyl Acetoacetate

The reaction flask and lithium amide are prepared as previously described. To the THF solution of base at -78°, 1.1 ml (5 mmoles) of t-butyl trimethylsilylacetate is added dropwise and stirred for 5 minutes. N-Acetylimidazole (0.55 g, 5 mmoles) is added, and the reaction mixture allowed to warm to room temperature. After two hours, pentane and water are added, the organic layer separated, dried, and removed by vacuum leaving 0.7 g (85%) of product. The solid decomposes upon burning imparting a pink color to the flame and leaving a charred residue. The lithium salt is soluble in pyridine or DMF.

NMR(pyridine): δ 5.12 (s, 1H), δ 2.08 (s, 3H), δ 1.57 (s, 9H).

IV. Reactions Involving Dianion Systems

A. Lithio tert-Butyl Acetoacetate with Trimethylchlorosilane

Lithium diisopropylamide (10 mmoles) is prepared and dissolved in 25 ml of THF. The 100 ml round-bottomed flask is immersed in an ice-water bath, and 0.85 ml (5 mmoles) of t-butyl acetoacetate is injected. After 20 minutes, 5 mmoles (0.63 ml) of TMCS is added, and the mixture stirred for another 15 minutes. The THF is removed on the roto-evaporator, and the residue dissolved in ether. After a few minutes the lithium chloride separates. With a good vacuum, the ether and amine are removed leaving a white solid. Lithio t-butyl 4-trimethylsilylacetoacetate is soluble in pyridine and imparts a pink color to a flame upon burning.

NMR(pyridine): δ 4.93 (s, 1H), δ 1.97 (s, 2H), δ 1.50 (s, 9H), δ 0.12 (s, 9H).

B. Lithio tert-Butyl Trimethylsilylacetoacetate with Benzaldehyde

The procedure is general. The silylated monoanion (1.18 g, 5 mmoles) is dissolved in 15 ml of THF and 5 mmoles of LiDPA in THF or n-butyllithium in hexane is added at -78°. Alternatively, the monoanion my be added to the base. In some trials, 1 mmole of TMEDA or HMPA was added at this point. In some trials, the monoanion and base were mixed at 0°. In any case, the mixture is stirred for one hour at room temperature, cooled in a dry ice-acetone bath, 5 mmoles of benzaldehyde added (or acetone), and the reaction mixture warmed to 25°. After one hour, the THF is removed in vacuum leaving a gel. Washing the gel with ether gave a white solid. Treatment of this material with aqueous ammonium chloride resulted in a camphoric odor (when acetone is used) but glpc detected an array of products. Removal of ether from the gel extract often resulted in as much as a 70% return of starting material.

V. Reactions Involving Monoanion Systems

A. Ethyl 3-Pyrrolidinocrotonate with Trimethylchlorosilane

A 500 ml round-bottomed flask equipped with magnetic stirring, septum inlet, and mercury bubbler is charged with 9.16 g (50 mmoles) of the enamine and 200 ml of THF. The contents, under nitrogen, are cooled in a dry ice-acetone bath, and 23 ml (50 mmoles) of n-butyllithium is injected. The mixture is allowed to reach room

temperature and after 90 minutes is cooled again to -78°. TMCS is added dropwise, and the mixture is stirred overnight at 25°. The THF is removed by vacuum, the red oil dissolved in pentane separating the lithium chloride. Vacuum distillation of the organic phase gave ethyl 4-trimethylsilyl-3-pyrrolidinocrotonate (bp 118-120°/0.5 mm) which seriously decomposed under these conditions.

NMR(CCl_4): δ 4.13 (s, 1H), δ 3.80 (q, 2H), δ 3.17 (m, 4H), δ 2.53 (s, 2H), δ 1.83 (m, 4H), δ 1.13 (t, 3H), δ 0.06 (s, 9H).

B. Ethyl 4-Trimethylsilyl-3-pyrrolidinocrotonate with Benzaldehyde

A 100 ml round-bottomed flask, equipped as usual, is flushed with nitrogen and charged with 1.13 g of the silylated enamine (5 mmoles) and 20 ml of THF. The flask is immersed in a dry ice-acetone bath and 2.45 ml of n-butyllithium in hexane is injected. The mixture is stirred for 1 hour and allowed to reach 25°. After cooling to -78°, 0.51 ml (5 mmoles) of benzaldehyde is added dropwise and stirred for an additional hour coming to room temperature. The reaction contents are mixed with pentane and water, the organic phase dried, and subjected to glpc revealing no reaction had occurred.

C. Preparation of Ethyl 3-Trimethylsiloxycrotonate

A 2-liter round-bottomed flask, equipped with a dropping funnel, condenser, and thermometer, is charged with 137 ml (1 mole) of triethylamine and 145 ml (1.1 moles) of TMCS. The system is kept under nitrogen and ethylacetoacetate added dropwise. The temperature is maintained at 25° frequently requiring an ice-water bath. The

addition required 1 hour, and after 2 more hours, the amine hydrochloride is removed by filtration. The salt is washed with hexane, the solvents combined, and removed by vacuum. The product distilled at 75°/7mm giving 153 g (76%) of a colorless oil (density 1.06).

NMR(CCl_4): δ 4.87 (s, 1H), δ 3.97 (q, 2H), δ 2.13 (s, 3H), δ 1.10 (t, 3H),δ 0.26 (s, 9H).

D. Ethyl 3-Trimethylsiloxycrotonate with Benzyl bromide

A 50 ml round-bottomed flask, equipped with magnetic stirring, septum inlet, and mercury bubbler, is flushed with nitrogen and flame dried. LiDPA (5 mmoles) is prepared in the usual fashion, dissolved in 10 ml of THF and immersed in a dry ice-acetone bath. The silyl enol crotonate (0.95 ml, 5 mmoles) is injected and stirred for 15 minutes. The benzyl bromide (0.60 ml, 5 mmoles) is added, and the flask is warmed to 25°. The solvent is removed on the roto-evaporator, pentane added to the residue, and lithium bromide separated. The pentane is removed by vacuum leaving an oil. The product is purified by glpc.

NMR(CCl_4): δ 6.97 (m), δ 5.03, δ 4.83 (2 doublets), δ 3.90 (m), δ 2.92 (m), δ 1.18 (t), δ 0.20 (s). IR(neat): 1735 cm^{-1} (C=O), 1625 cm^{-1} (C=C).

E. tert-Butyl 4-Trimethylsilylacetoacetate with Benzaldehyde

A 50 ml round-bottomed flask, equipped with magnetic stirring, septum inlet, and mercury bubbler, is flushed with nitrogen and charged with 1.18 g (5 mmoles) of the lithium salt and 10 ml of THF.

The flask is immersed in an ice-water bath, and 0.51 ml (5 mmoles) of benzaldehyde is injected. After 1 hour, glpc detected no reaction had occurred. The mixture was refluxed for 24 hours, the solvent removed, and an orange oil remained with an odor of benzaldehyde. Washing the oil with pentane separated the unreacted lithium salt.

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