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THE CHEMISTRY OF DICARBOXYLIC
ESTER ENOLATES

By

Nathan Roy Long

A DISSERTATION

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ABSTRACT

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By

Nathan Roy Long

Di-enolates of diethyl succinate, glutarate, and suberate were generated by addition of the dicarboxylic ester to two equivalents of lithium diisopropylamide in dilute THF at -78° . Attempts to prepare di-enolates of diethyl adipate and pimelate resulted in the formation of β -keto esters. Attempts to prepare stable solutions of mono-enolates by direct proton removal failed for all dicarboxylic esters studied.

The dicarboxylic ester di-enolates were found to be stable indefinitely at -78° . Warming the di-enolate solutions resulted in decomposition at rates faster than those for simple ester enolates.

Diethyl dilithiosuccinate was isolated quantitatively as a pale yellow solid. Exposure to air causes rapid decomposition. A PMR spectrum was obtained in dilute THF d_8 : $\delta 1.16(t, 6H)$, $\delta 3.34(q, 4H)$, $\delta 3.54(s, 2H)$. An oxygen metalated structure was proposed for the structure of diethyl dilithiosuccinate.

Reaction of diethyl dilithiosuccinate with chlorotrimethylsilane produced 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene in 88% yield. Hydrolysis of 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene with 3N hydrochloric acid returned 92% diethyl succinate.

Reaction of diethyl succinate with one equivalent of lithium diisopropylamide, followed by quenching with chlorotrimethylsilane yielded 45%, 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene and 30% diethyl succinate. Apparently formation of di-enolate is favored over formation of mono-enolate. Coordination of lithium diisopropylamide with the first lithium atom to speed up proton removal may favor di-enolate formation.

Reaction of diethyl dilithiosuccinate with two equivalents of organic halide in THF-HMPA gave high yields of α,α' -di-alkylated derivatives of diethyl succinate. Reaction of diethyl dilithiosuccinate with one equivalent of organic halide in the absence of HMPA gave high yields of α -alkylated derivatives of diethyl succinate.

Reaction of diethyl dilithiosuccinate with aldehydes or ketones formed γ -butyrolactones in high yields. The α -metalated- γ -butyrolactone intermediate can be α -alkylated in moderate yield.

Dicarboxylic ester di-enolates react with copper(II) salts or iodine to form double bonds or cyclic products depending on the structure of the starting dicarboxylic

ester. Yields for the formation of double bonds or three-membered rings were excellent.

A series of anhydrous metal salts were reacted with diethyl dithiosuccinate at -78° . Cobalt bromide formed a solution which was stable at room temperature.

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To my late father, I hope that someday I might fulfill your hopes and expectations.

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CHAPTER 1

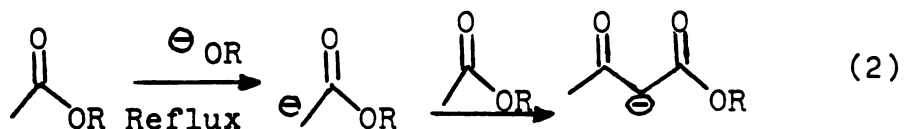
PREPARATION OF MONO- AND DI-ENOLATES OF DICARBOXYLIC ESTERS

INTRODUCTION

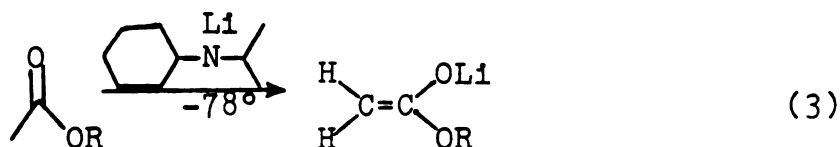
Protons on a carbon alpha to a carbonyl are acidic and can be removed by base to form a resonance stabilized anion (Eq. 1). Reactions of such enolate anions obtained from aldehydes and ketones with electrophiles have long provided some of the most useful and versatile methods for the synthesis of organic compounds.¹



For many years the use of esters for organic synthesis was limited to simple condensation reactions because the bases employed, commonly alkoxides, were not potent enough to completely convert the ester function to enolate (Eq. 2).² In 1971 a general procedure was reported for preparing stable solutions of simple ester



enolates by using lithium N-isopropylcyclohexylamide as the base (Eq. 3).³ Since 1971 lithium ester enolates



have been studied extensively to determine their reactivity, structure, and stability.

Ester enolates react with a variety of reagents such as trialkylhalosilanes,⁴ alkyl halides,³ aldehydes and ketones,⁵ halogens,⁶ copper(II) salts,⁷ and acid chlorides⁸ to form respectively, silylated esters, chain-extended esters, β -hydroxy esters, α -halogenated ester, substituted succinate esters and β -keto esters (Figure 1).

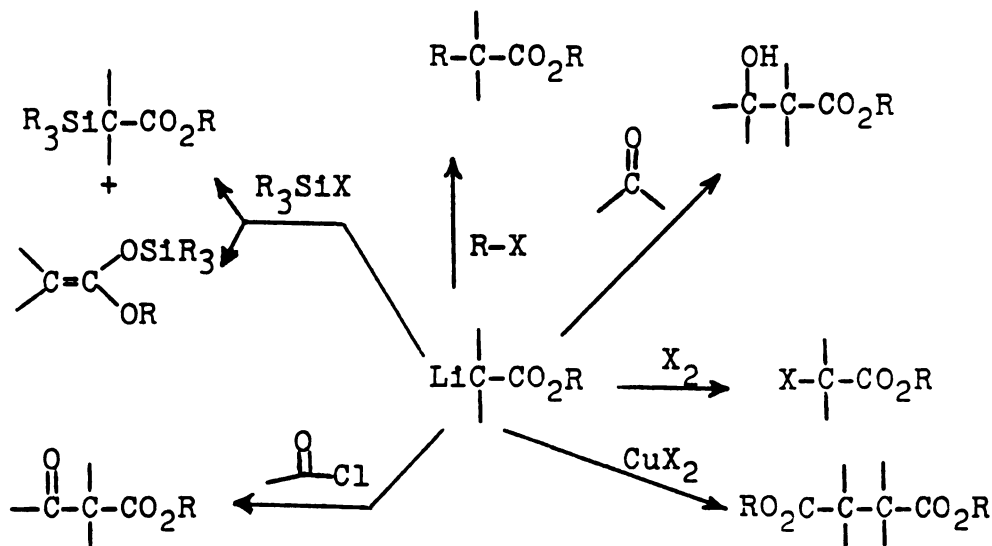
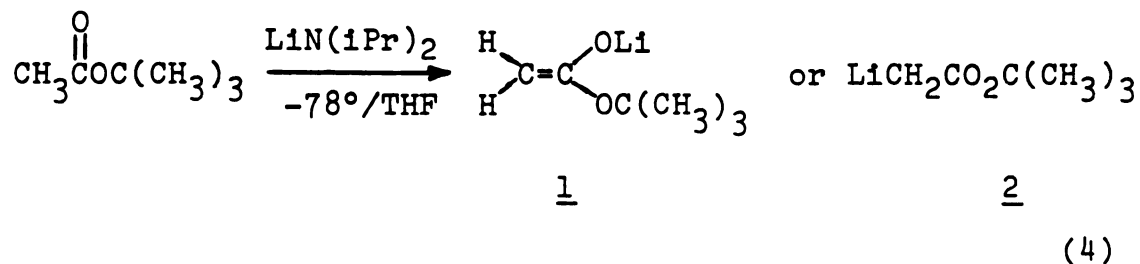
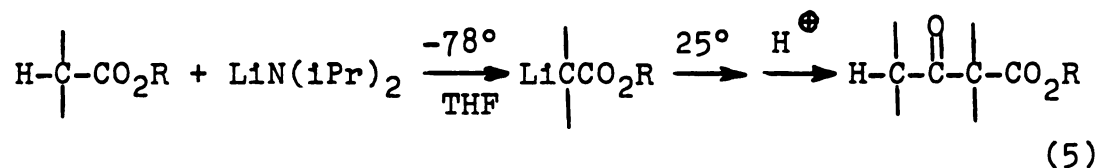


Figure 1. Reactions of Ester Enolates.

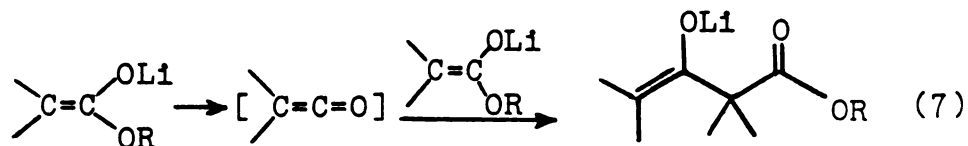
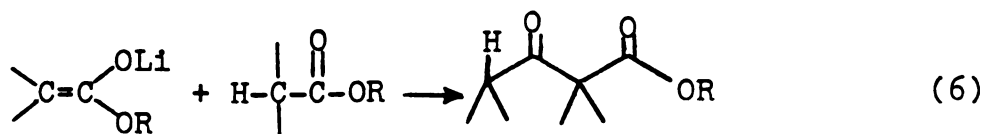
In 1973 *t*-butyl lithioacetate was isolated as a stable white solid.⁹ Its structure was characterized by proton NMR (PMR) as the oxygen metalated enolate 1, rather than the carbon metalated enolate 2 (Eq. 4).



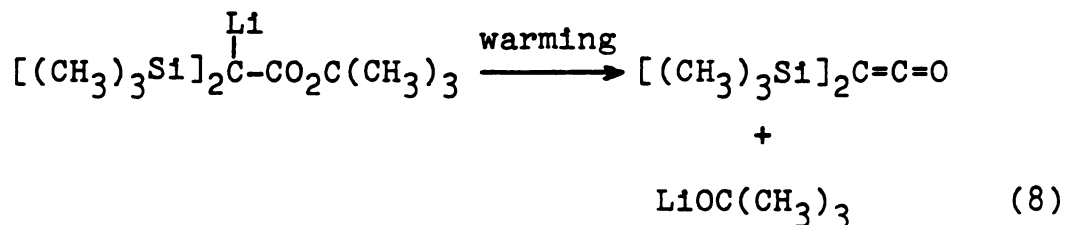
It was also found that lithio ester enolates which are generated at -78° in THF are stable indefinitely at that temperature.³ However warming the THF solution above -78° leads to decomposition and the formation of β -keto esters (Eq. 5).



Two possible pathways for the decomposition of ester enolates have been proposed.¹⁰ Condensation of enolate with unreacted starting ester or regenerated ester in an "Inverse Claisen" mechanism (Eq. 6) or formation of ketene followed by enolate attack can also lead to β -keto ester (Eq. 7).



Quantitative isolation of bis(trimethylsilyl)ketene from the decomposition of t-butyl lithio-1,1-bis(trimethylsilyl)acetate was reported in 1971 (Eq. 8).¹¹



The preceding survey briefly describes recent advances in simple ester enolate chemistry, while the following will survey reactions involving enolates of dicarboxylic esters.

The Stobbe condensation, the reaction of a ketone with an enolate of diethyl succinate, has long been used to prepare alkylidene derivatives 3 of diethyl succinate (Figure 2).²

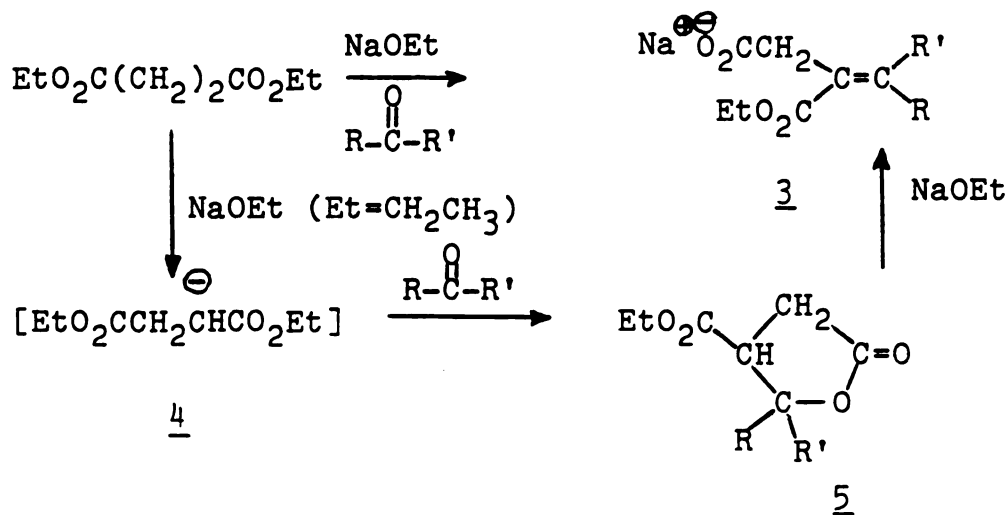
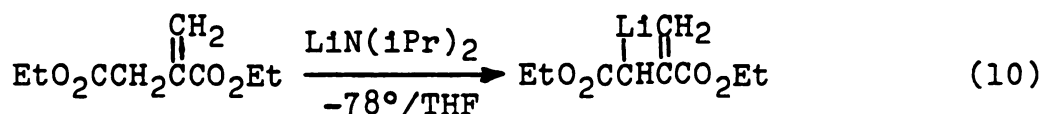
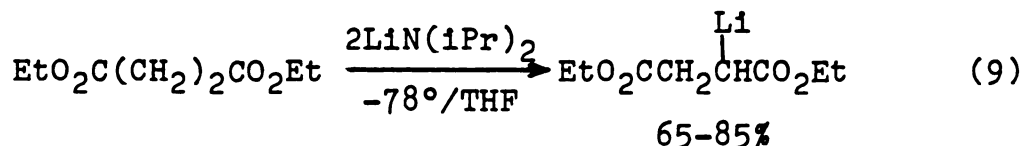


Figure 2. The Stobbe Condensation.

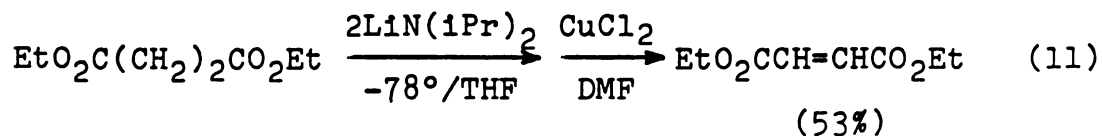
The mono-enolate 4 is not prepared as a discrete reagent but 4 is trapped as it is formed, by ketone, $R-\overset{\overset{O}{\parallel}}{C}-R'$, present in the reaction mixture. This usually requires that the ketone have no enolizable protons.

Recent studies,^{12,13} using lithium amide bases to generate the enolate, have enabled workers to isolate the γ -butyrolactone intermediate 5 (Figure 2) which had long been postulated for the Stobbe condensation.

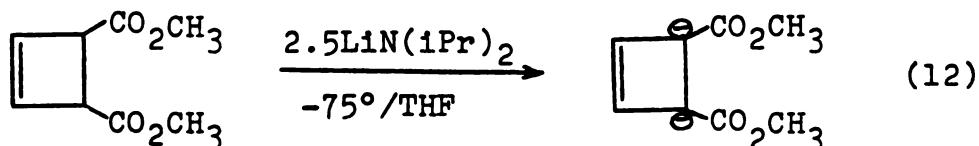
Reutrakul¹⁴ claimed preparation of the mono-enolate of diethyl succinate (Eq. 9) in high yield reactions; yet Carlson¹⁵ was unable to generate a stable mono-enolate of dimethyl itaconate (Eq. 10).



While studying the oxidative coupling of ketone enolates with cupric chloride, Saegusa briefly reported that diethyl fumarate could be formed in moderate yield from diethyl succinate (Eq. 11).¹⁶ The di-enolate of diethyl succinate may be an intermediate in this reaction.

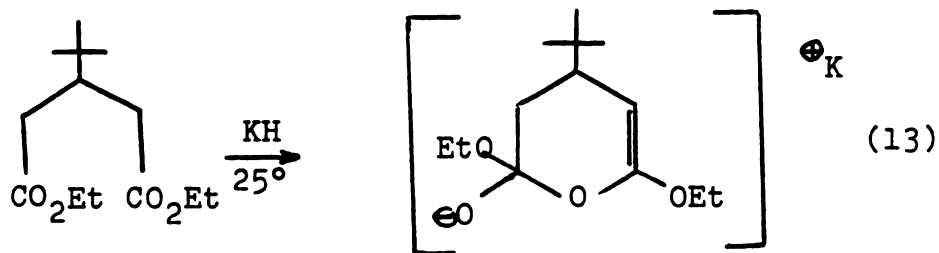


Garrett¹⁷ reported that stable solutions of dimethyl dilithiocyclobut-3-ene-1,2-dicarboxylate could be prepared by reaction of dimethyl cyclobut-3-ene-1,2-dicarboxylate with 2.5 equivalents of lithium diisopropylamide (Eq. 12).



Although the dianion was not isolated, the PMR spectrum in deuterated tetrahydrofuran was taken. It showed two signals as broad singlets at $\delta 5.94(2H)$ and $\delta 3.73(6H)$. Quenching the dianion with acid returned dimethyl cyclobut-3-ene-1,2-dicarboxylate in 50% yield. The dianion exhibited additional spectroscopic and chemical data which indicated that it does not benefit from aromatic delocalization, despite the fact that monocyclic anions and dianions containing $[4n+2]$ π electrons are unusually stable.

Willer recently found evidence for a cyclic intermediate in the reaction of substituted glutarate esters with potassium hydride (Eq. 13).¹⁸



The primary objective of this investigation was to find a general procedure for the preparation of mono- and di-enolates for a series of dicarboxylic esters. Several solvents, concentrations, and bases were tested in order to find a satisfactory procedure. After a general procedure was found, the stabilities of the enolates were studied with hopes that their decomposition would give some insight into the mechanism of simple ester enolate decomposition.

A second objective of this investigation was to isolate a di-enolate of a diester as a crystalline solid. The structure of the di-enolate could then be characterized by proton NMR.

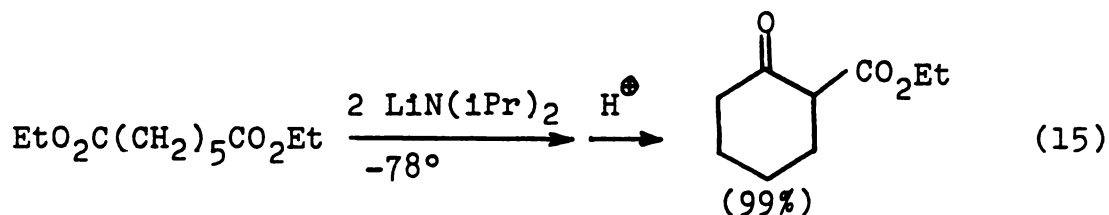
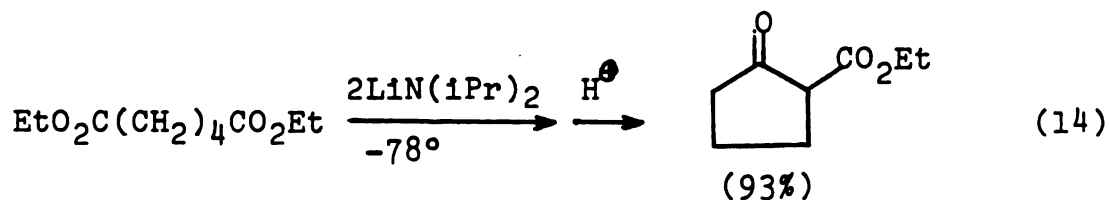
RESULTS

Quenching Enolates of Dicarboxylic Esters

A series of dicarboxylic esters were reacted with one or two equivalents of lithium diisopropylamide (LDA) in dilute THF at -78° . After 60 minutes, these solutions were quenched with 3N hydrochloric acid, and followed by glpc analysis for recovered diester. With the exception of the adipate and pimelate esters, reactions of the diester with two equivalents of base invariably returned a higher percentage of starting diester, after quenching, than reactions of the diester with one equivalent of

base (Table 1).

Cyclization products were isolated in high yields from the reactions of adipate and pimelate esters with two equivalents of lithium diisopropylamide, thus explaining the low recovery of starting diester (Eqs. 14 and 15).



Attempts were made to slow the cyclization process to allow complete formation of the dienolate. However, use of the more sterically hindered di-*t*-butyl esters, and running the reactions at -100° did not increase the amount of di-enolate formed.

Concentration Dependence Studies

Concentration of the dicarboxylic ester was very important in forming stable enolate solutions. At concentrations normally used (1M) for preparing simple ester enolates, gel formation occurred. This slowed complete formation of enolate and competing side reactions could

Table 1. Quenching Results of Dicarboxylic Ester Enolates.

Diester	Percent Recovered Diester ^a		
	1 eq / $\frac{-78^{\circ}}{1h}$ LDA	2 eq / $\frac{-78^{\circ}}{1h}$ LDA	2 eq / $\frac{25^{\circ}}{1h}$ LDA
diethyl succinate	74	100	74
di-t-butyl succinate	67	98	51
diethyl glutarate	58	98	60
diethyl adipate	42	0	--
di-t-butyl adipate	41	0	--
diethyl pimelate	25	1	--
diethyl suberate	47	92	56
diethyl apellate	60	61	8

^aDetermined by glpc analysis of aliquots quenched with 3N hydrochloric acid. Reactions were done in dilute THF.

occur. Attempts to make enolates in 1M THF resulted in very poor recovery of diester after quenching (30-60%); while almost quantitative recovery was possible when dilute solutions were used.

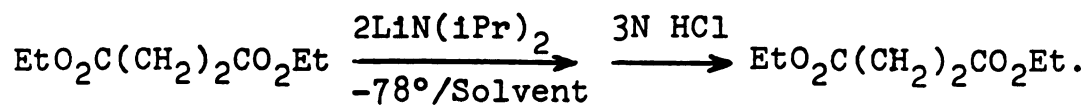
For the reactions of diesters with two equivalents of lithium diisopropylamide, quantitative recovery was possible for succinate, glutarate, and suberate esters if the final concentration of enolate in THF was approximately .125M, .1M, and .085M, respectively. At these concentrations the enolates stirred freely.

Because of the low solubility of the enolates in THF, attempts were made to find a suitable solvent or co-solvent which would allow enolate formation in more concentrated solution.

The results listed (Table 2) indicate that none was successful in forming a more concentrated solution of enolate.

Another attempt to circumvent low solubility of diester enolates was to change the alcohol portion of the ester to something which could internally chelate with lithium to prevent the supposed polymeric gel from forming. Ethylene glycol monomethyl ether when reacted with succinic acid formed bis(ethyleneglycol monomethyl ether) succinate 6 (Eq. 16).¹⁹ This reacted with lithium diisopropylamide to give an orange gel which returned little of the diester upon quenching (Eq. 17).

Table 2. Effect of Solvent on Enolate Formation

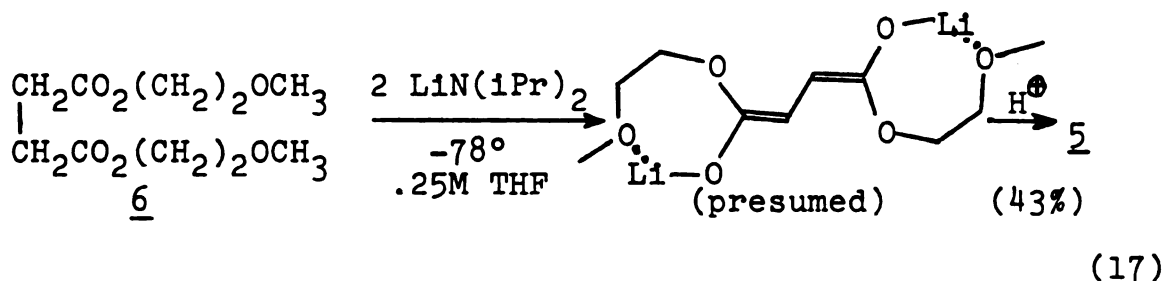
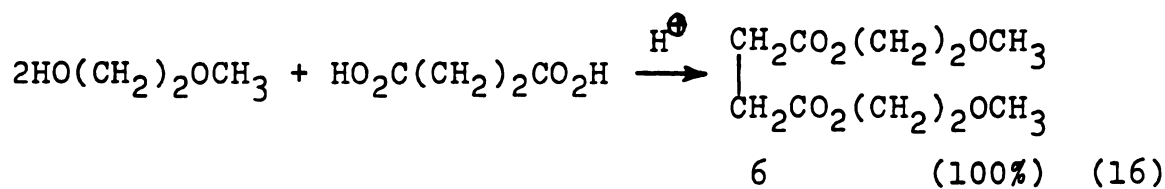


Solvent (or Co-solvent)	Conc. (M) of Di-enolate	% Recovered Diethyl succinate ^a
THF ^b	0.125	100
THF	0.25	76
Glyme	0.25	54
Diglyme	0.25	59
HMPA ^{bc}	0.50	0
2 eq. HMPA:THF ^{bc}	0.5	23
2 eq. TMEDA:THF	0.25	72
Pentane ^{bc}	0.25	19

^aAll yields were determined by glpc analysis.

^bSolution stirred freely.

^cOrange color.



Reaction of diethyl succinate with potassium hydride resulted in a rapid quantitative evolution of hydrogen as monitored by a gas burette. The solution turned yellow and quenching with methyl iodide failed to give detectable new products by glpc analysis. Only (19%) starting material and intractable tar were observed.

Decomposition Studies of Diester Di-enolates

The di-enolates of the diesters, which gave a quantitative recovery in the quenching study listed in Table 1 (Page 10), were warmed to 25° so that their stability might be studied and their method of decomposition determined. The results of this study are listed in Table 3.

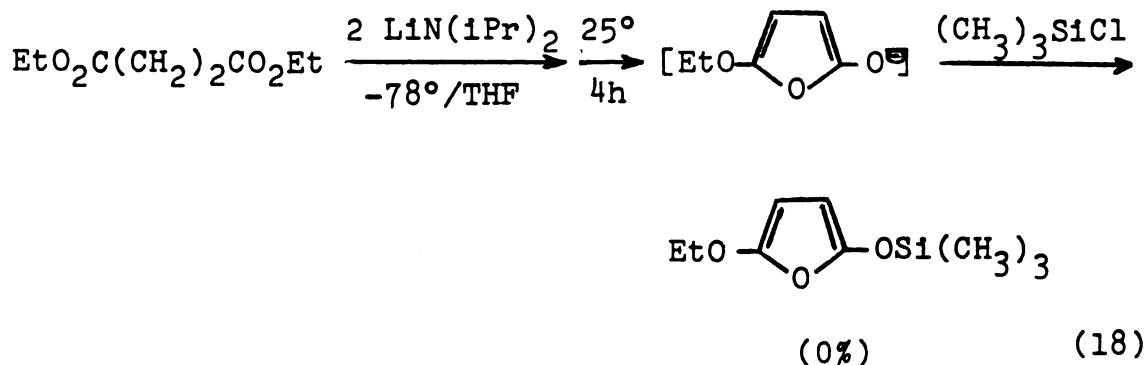
Also the decomposition of diethyl dilithiosuccinate was carefully examined to see if cyclic intermediates, similar to those postulated by Willer,¹⁸ might be found

Table 3. Decomposition Study of Dicarboxylic Ester Di-enolates.

Diester	Time (hours)	% Recovered Diester ^a
Diethyl succinate	0	100
	1	74
	2	46
	3	19
	4	5
	5	0
Di-t-butyl succinate	0	98
	1	51
	2	7
	3	0
Diethyl glutarate	0	98
	1	60
	2	11
	3	0
Diethyl suberate	0	92
	1	56
	2	6
	3	0

^aYields were determined by glpc analysis.

perhaps by a ketene decomposition route (Eq. 18).



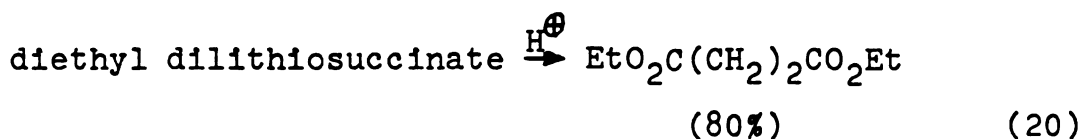
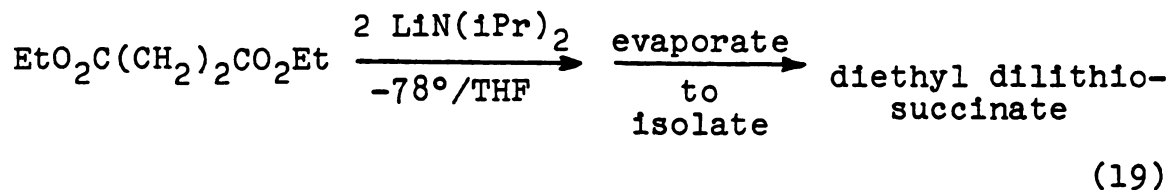
An orange solution resulted from warming to 25° but quenching with acid, chlorotrimethylsilane or methyl iodide did not give the expected cyclic product.

Isolation of Diethyl Dilithiosuccinate

Addition of diethyl succinate to a dilute THF solution containing 2 equivalents of lithium diisopropylamide, at -78°, produced diethyl dilithiosuccinate quantitatively (Eq. 19).

Removal of the solvent and volatile diisopropylamine under reduced pressure and cold temperatures (-78°→) gave diethyl dilithiosuccinate as a pale yellow solid. The diester di-enolate was stable only under a moisture-free inert atmosphere. Exposure to the air caused the pale yellow solid to turn rust-brown almost instantly. The di-enolate could be dissolved in excess THF and quenching

with acid resulted in 80% recovered starting diethyl succinate (Eq. 20).



Proton NMR Spectrum of Diethyl Dilithiosuccinate

Solid diethyl dilithiosuccinate is insoluble in DMSO and benzene, decomposes rapidly in pyridine, and can be dissolved only in a large excess of THF (.01M). Its high reactivity and these solubility restrictions precluded obtaining a conclusive PMR spectrum of diethyl dilithiosuccinate.

It was possible to generate diethyl dilithiosuccinate in .125M deuterated tetrahydrofuran (d_8 THF) and obtain a spectrum of the di-enolate contaminated by the diisopropylamine which was used to generate the di-enolate. The chemical shift of diisopropylamine's protons were in regions which did not interfere with the interpretation of the PMR spectrum of diethyl dilithiosuccinate.

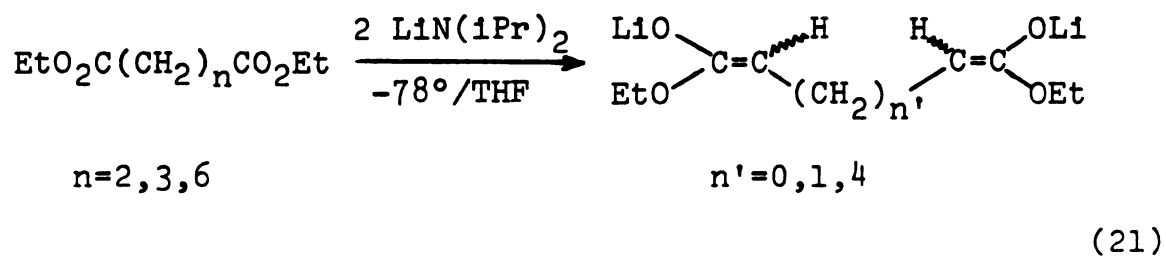
The PMR spectrum of diethyl dilithiosuccinate exhibits a sharp 2⁴ proton doublet at 1.08 ppm (relative to TMS), a 6 proton triplet at 1.16 ppm, a broad 3 proton singlet at 1.76 ppm, a 2 proton multiplet at 2.86 ppm, a 4 proton quartet at 3.3⁴ ppm, and a 2 proton singlet at 3.5⁴ (Figure 3).

The PMR spectrum of the starting material, diethyl succinate, was taken for comparison. The spectrum consisted of a 3 carbon triplet at 1.1 ppm, a 2 carbon singlet at 2.45 ppm, and a 2 carbon quartet at 4.1 ppm (Figure 4).

DISCUSSION

Quenching Enolates of Dicarboxylic Esters

The di-enolates of succinic, glutaric, and suberic esters have been generated in a simple procedure and were found to be stable. The method of choice was to add the dicarboxylic ester to a solution of two equivalents of diisopropylamide in dilute THF (0.125M, .1M, .085M, respectively) at -78° for 15 minutes (Eq. 21).



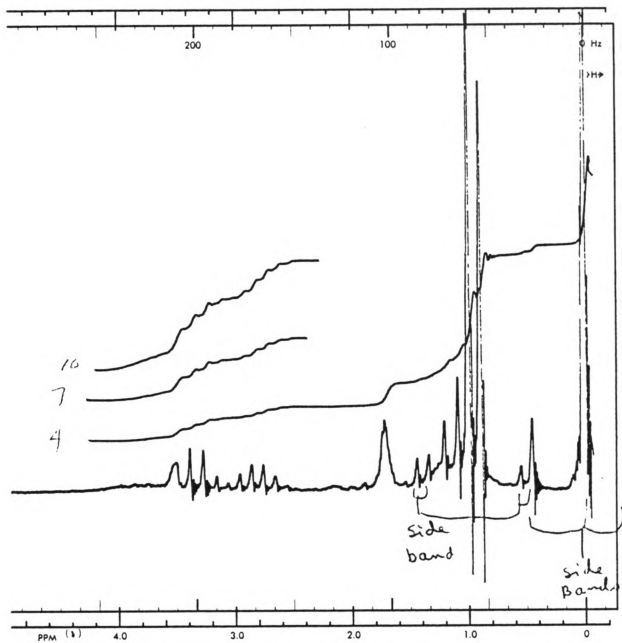


Figure 3. Proton NMR Spectrum of Diethyl Dilithiosuccinate in d_8 THF.

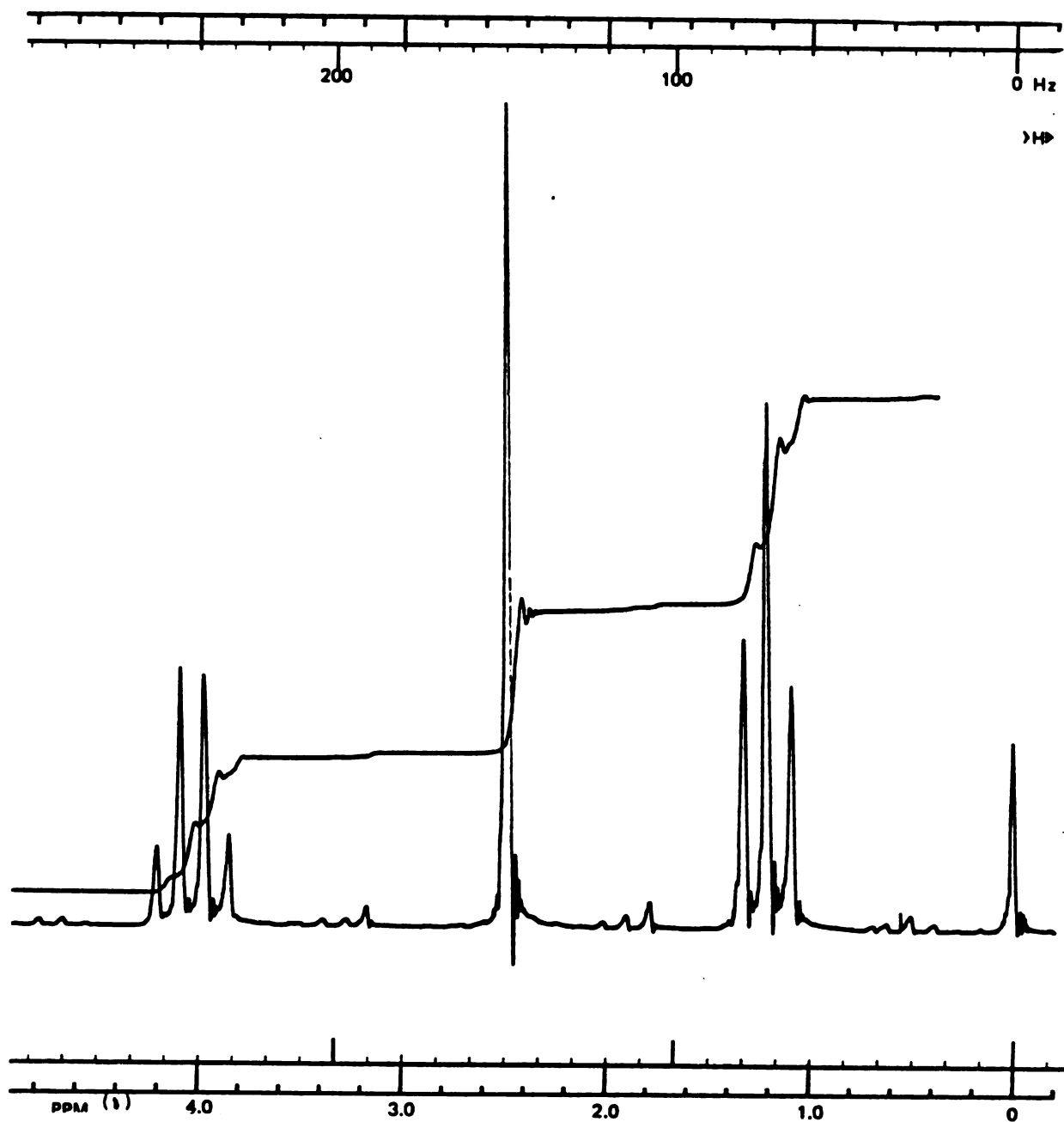


Figure 4. Proton NMR Spectrum of Diethyl Succinate in Carbon Tetrachloride.

Attempts to prepare di-enolates of adipic and pimelic ester resulted in the formation of five- and six-membered rings, respectively. The reaction of a diester with sodium ethoxide to form a cyclic β -keto ester is a name reaction, called the Dieckmann condensation. The mechanism of the Dieckmann condensation is listed below (Figure 5).

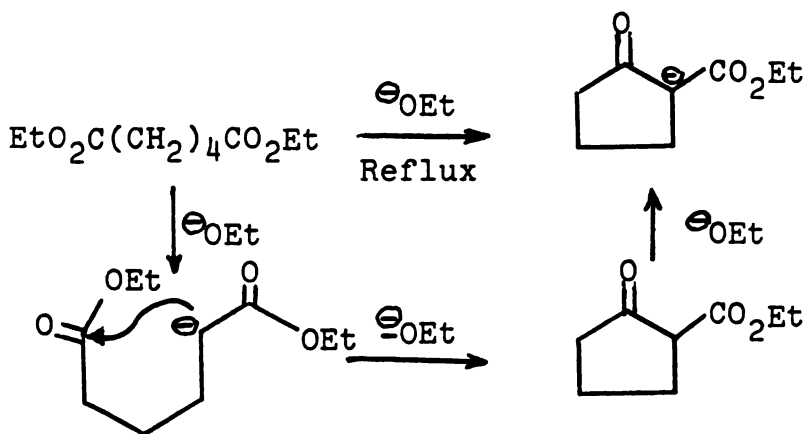
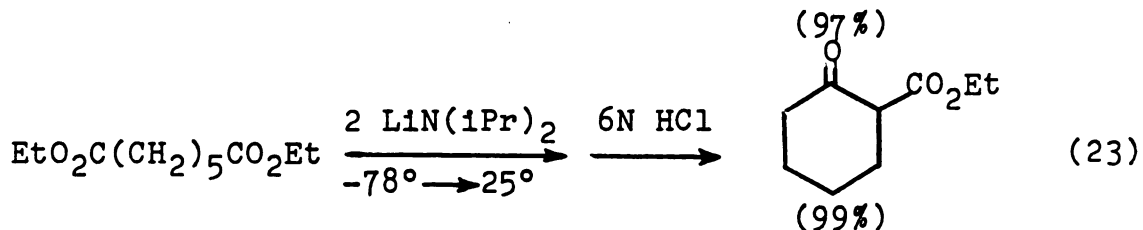
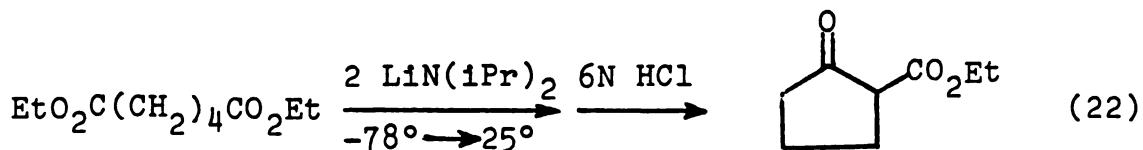


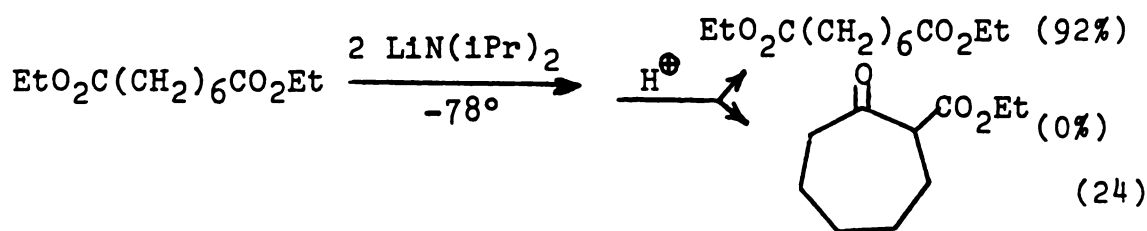
Figure 5. The Dieckmann Condensation.



Listed above (Eqs. 22 and 23) are results obtained by using lithium diisopropylamide as the base to bring about cyclization. It should be noted that the Dieckmann

condensation is most successful for the formation of five-, six-, and seven-membered rings. Attempts to prevent five- and six-membered ring formation by use of lithium diisopropylamide failed; probably because ring closure was more rapid than proton removal to form the di-enolate. Once formed, the di-enolate should be stable at -78° .

However, for diethyl suberate, formation of the seven-membered ring apparently is not as rapid as di-enolate formation, since it formed stable solutions when it was reacted with two equivalents of diisopropylamide at -78° . Since the Dieckmann condensation under these conditions should be irreversible, quantitative recovery of diethyl suberate indicates that cyclization did not occur (Eq. 24).



Attempts to prepare stable solutions of mono-enolate by direct proton removal failed for all dicarboxylic esters studied. Possibly a Claisen mechanism is acting to condense the dicarboxylic ester.

Concentration Dependence Studies

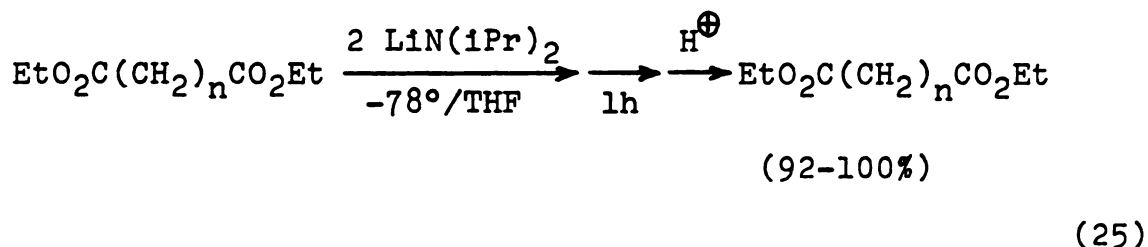
The major limitation to forming diester di-enolates by direct proton removal from the diester was the need to use dilute tetrahydrofuran ($\sim 0.1M$). Dilution may be necessary either to slow intermolecular Claisen condensation or to allow complete reaction by preventing gel formation. The gel appears to be polymeric in nature, possibly the lithium atoms are intermolecularly bonded to several oxygen atoms. Once the gel forms, addition of enough THF, which would ordinarily prevent gel formation, will not dissolve the gel. Only when a ten-fold excess of THF was added did the gel slowly dissolve.

Attempts to find a better solvent than THF failed. Glyme, diglyme, and TMEDA:THF did not prevent the gel from forming, and also did not return a higher percentage of diester upon quenching. When pentane, HMPA, and HMPA:THF were studied, a decomposition reaction seemed to take place even at -78° ; quenching returned little of the starting diester. No products were isolated.

The orange gel, which formed when bis(ethylene glycol monomethyl ether) succinate was reacted with two equivalents of lithium diisopropylamide, returned little of the starting diester upon quenching. The hoped for chelation did not help prevent gel formation. Also the quenching results indicated that either decomposition or side reactions were occurring. Product determination was not attempted.

Decomposition Studies of Diester Di-enolates

Di-enolates of dicarboxylic esters can be generated quantitatively in dilute THF at -78° (Eq. 25), and are stable indefinitely at -78° .



Solutions of diester di-enolate rapidly condense when warmed to 25° ; however the initial decomposition products which result cannot be isolated, as only intractable tars are formed.

The rate of decomposition for diester di-enolates is appreciably faster than for simple ester enolates. Woodbury²⁰ found that various ethyl lithio esters decomposed completely between 8-80 hours; the diester di-enolates studied were completely decomposed within 5 hours. The increased rate of decomposition may be due to intramolecular factors similar to the cyclic structure postulated by Willer¹⁸ (page 7). The cyclic intermediate which he proposed was sufficiently stable to be trapped by methyl iodide. Perhaps for the dilithio di-enolates decomposition may be facilitated by intramolecular factors, perhaps even proceeding through a cyclic intermediate, but further

condensation occurred so that the intermediate could not be trapped.

Several attempts were made to trap the expected furan 7 intermediate but none was successful (Figure 6).

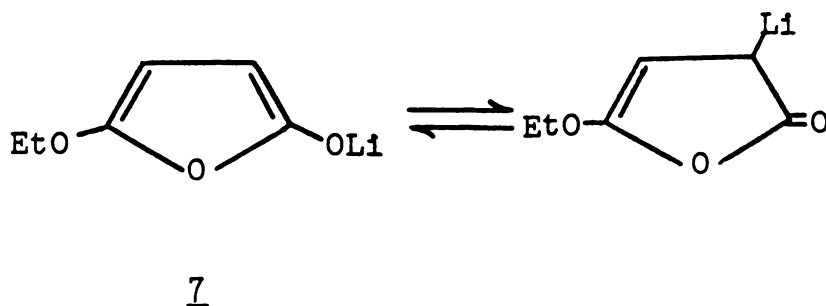


Figure 6. Proposed Decomposition Intermediate.

Isolation of Diethyl Dilithiosuccinate

Diethyl dilithiosuccinate was more difficult to isolate than simple ester enolates, because it was more reactive. Isolation of simple ester enolates can most easily be done by generating the enolate in pentane and then evaporating the solvent by use of a rotary evaporator at room temperature to isolate the white solid. Simple ester enolates in the solid form can be weighed in air with only a very slow decrease in weight as hydrolysis and evaporation occur. Even in solution they can be rapidly transferred without excessive hydrolysis and decomposition.

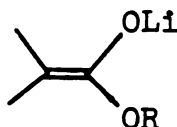
However diethyl dilithiosuccinate was much more reactive and could not be generated in pentane (Table 3).

Exposure to air caused the solution to turn brown immediately; quenching indicated an appreciable loss in diester. Decomposition was rapid enough that rapid removal of the solvent in vacuum and heat resulted in a lower yield of diester after quenching. Only when care was taken to avoid the introduction of air, and solvent was removed by high vacuum with only slight warming, could a reasonable yield of diethyl dilithiosuccinate be isolated.

The high reactivity of solid diethyl dilithiosuccinate limits its use as a discrete reagent. Unlike simple ester enolates, which can be weighed in air and stored on the shelf, isolating diethyl dilithiosuccinate as a solid has no synthetic advantage over generating the di-enolate and using it in situ.

Proton NMR of Diethyl Dilithiosuccinate

The structure of a lithium ester enolate has been characterized as the oxygen-metalated species 8.⁹ Since the actual structure of a particular enolate probably



8

depends on the metal cation and its association with the enolate, it was predicted that diethyl dilithiosuccinate

would exist as an oxygen-metalated species 9, 10, or 11 (Figure 7).

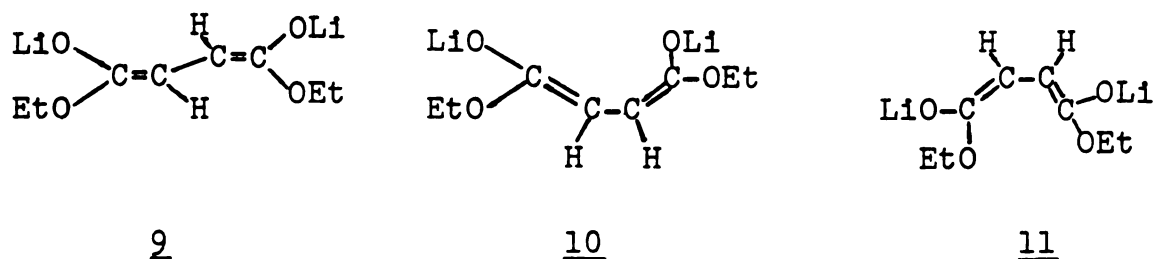


Figure 7. Proposed Structures for Diethyl Dilithiosuccinate.

A PMR spectrum could not be obtained for pure diethyl dilithiosuccinate; the PMR spectrum obtained (Figure 3) was inherently contaminated with diisopropylamine. Analysis showed the doublet at 1.08 ppm, the singlet at 1.76 ppm, and the multiplet at 2.86 ppm could be assigned to diisopropylamine. Only the triplet at 1.16 ppm, the quartet at 3.34 ppm, and the singlet at 3.54 ppm remained to be assigned. From examination of the possible structures 9, 10, and 11, it was obvious from chemical shifts and splitting patterns that the peaks at 1.16 and 3.34 ppm correspond to the ethyl groups of the di-enolate. Therefore, the peak at 3.54 ppm must correspond to the vinyl protons of the di-enolate. Based on this PMR data the structure of diethyl dilithiosuccinate could not definitely be assigned to any of the three possible structures 9, 10, or 11; it may be a mixture of all three.

The chemical shifts of the vinyl protons (3.54 ppm) were compared with related structures (Table 4).

Table 4. Comparison of Proton NMR.

Structure	Chemical Shift of Vinyl Protons
$\begin{array}{c} \text{H} \\ \diagdown \\ \text{C}=\text{C} \diagup \text{OLi} \\ \diagup \text{H} \quad \diagdown \text{O}^+ \end{array}$	3.14 and 3.44 ppm
<u>9</u> , <u>10</u> , or <u>11</u>	3.54 ppm
$\begin{array}{c} \text{H} \quad \text{OSi(CH}_3)_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{EtO} \quad \text{H} \end{array}$	4.1 and 4.29 ppm
$\begin{array}{c} \text{H} \quad \text{OEt} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{EtO} \quad \text{OEt} \end{array}$	4.45 ppm ²¹

This comparison shows that the vinyl protons of ester enolates and diester di-enolates are shifted upfield from ordinary vinyl protons, indicating that there is less electron density at the alpha carbon.

EXPERIMENTAL

1. MaterialsDicarboxylic Esters

Diethyl succinate, glutarate, adipate, pimelate, suberate, and azelate were obtained from Aldrich Chemical Company and distilled prior to use. Di-t-butyl succinate and di-t-butyl adipate were prepared from the commercially available acid chlorides as described in Organic Synthesis, Vol. 4.²² Bis(ethyleneglycol monomethylether)succinate was prepared as adapted from the procedure for preparing diethyl adipate in Organic Synthesis Vol. 2.¹⁹

Bases

Diisopropylamine and tetramethylenediamine were obtained from Aldrich and distilled from CaH_2 prior to use. n-BuLi was obtained from Aldrich as 1.6M solutions in hexane and used without further purification. Potassium hydride was obtained from Alfa Products as a 5M solution and used without further purification.

Solvents

Tetrahydrofuran was commercially available and distilled from the sodium ketyl of benzophenone. THF d_8

was obtained from Aldrich and used without further purification. Glyme and diglyme were commercially available and distilled from lithium aluminum hydride prior to use. Commercially available hexamethylphosphoramide (HMPA) was distilled prior to use.

2. Preparation of Lithium Diisopropylamide

A dry 100-ml flask is equipped with magnetic stirrer, septum inlet, and mercury bubbler. The flask is flushed with argon, charged with 5 ml of dry pentane, and then cooled to 0°. Then 6.6 ml (10.8 mmoles) of 1.6M n-BuLi was added, followed by dropwise addition of 1.40 ml (11 mmoles) of diisopropylamine. The reaction mixture was warmed to room temperature and stirred for 10 minutes. The solvent was then removed under reduced pressure, leaving a white solid.

3. Preparation of Dicarboxylic Ester Di-enolates

Diethyl Dilithiosuccinate

Lithium diisopropylamide (10.8 mmoles) was prepared as described above, dissolved in 20 ml of THF, and was cooled to -78°. In a separate flask under argon, 20 ml of THF and 0.83 ml (5 mmoles) of diethyl succinate were combined and added to the lithium diisopropylamide solution in a rapid dropwise fashion. The solution was stirred

for 15 minutes at -78° and slowly turned a very pale yellow-green.

Diethyl Dilithioglutarate

The identical procedure used for diethyl dilithio-succinate preparation was followed, except 25 ml of THF was added at each step (total 50 ml) and .92 ml of diethyl glutarate was needed.

Diethyl Dilithiosuberate

The identical procedure used for diethyl dilithio-succinate preparation was followed, except 30 ml of THF was added at each step (total 60 ml) and 1.17 ml of diethyl suberate was needed.

4. Quenching, Concentration Dependence, and Decomposition Studies

Dicarboxylic ester enolates were prepared by procedures listed above. Quenching studies with 3N hydrochloric acid were done at -78° after the appropriate time and reaction conditions. After quenching, the reaction mixture was allowed to warm to 25° and 5 ml of pentane was added before separation of layers. The organic layer was dried over anhydrous potassium carbonate and then analyzed using glpc with a six foot by 1/4 inch column. The most efficient

packing used was 2-1/2% SE-30 on neutral Chromosorb G. Some tailing of the diester peaks occurred, but no better packing material could be found.

For concentration dependence studies the co-solvent HMPA or TMEDA was introduced to the reaction before the dicarboxylic ester was added. For decomposition studies the enolate solution was allowed to stir at -78° for 15 minutes to allow complete formation of the enolate. Solutions were then warmed to 25° by immersion in a warm water bath and allowed to stir for the appropriate time. A colored solution normally resulted. Prior to quenching, solutions were cooled to -78° .

5. Isolation of Cyclization Products

The procedure for the reaction of diethyl adipate and pimelate with two equivalents of lithium diisopropylamide was the same as listed above for preparing diethyl dilithiosuccinate. The solution was maintained at -78° for 15 minutes and then warmed to 25° for 60 minutes. The colored solution was then cooled to -78° and quenched with 6N hydrochloric acid. The nearly colorless solution was then warmed to 25° and a little diethyl ether was added to help separate the layers. The organic layer was dried over K_2CO_3 . Glpc analysis was done on 2-1/2% SE-30.

6. Isolation of Diethyl Dilithiosuccinate

Diethyl dilithiosuccinate was prepared as described above. After stirring for 15 minutes at -78° , solvent and amine were removed by high-vacuum, without any exposure to air. Titration with cold pentane removed very little of the resulting yellow color. Removal of excess pentane by vacuum yielded a pale yellow powder.

When the yellow solid, diethyl dilithiosuccinate, is dissolved in THF (.01M) and then quenched with 3N HCl or chlorotrimethylsilane at -78° , diethyl succinate and disilylated diester were formed, respectively, in 78% and 80% yields. Yields did not vary much with time but any exposure to air immediately caused the pale yellow solid, diethyl dilithiosuccinate, to brown and quenching yields were then much lower.

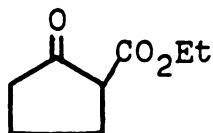
7. Preparation of Diethyl Dilithiosuccinate for PMR

Analysis

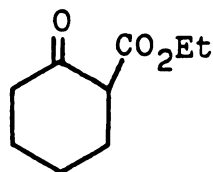
Lithium diisopropylamide (.025 mmoles) was prepared as described above by the reaction of 82.5 μl of 1.6M n-BuLi with 9.6 μl of diisopropylamine at 0° . The solvent was then removed under reduced pressure, leaving a white solid. Deuterated tetrahydrofuran (25 μl THF d_8) was added and the resultant solution was cooled to -78° . Diethyl succinate (10.4 μl) was mixed with 25 μl of THF d_8

and then added dropwise to the lithium diisopropylamide solution. After 15 minutes of stirring, the solution was transferred via a cold syringe to a cold (-78°) argon flushed NMR tube. The NMR tube was immediately sealed. All NMR studies were run immediately on a Varian T-60 NMR spectrometer.

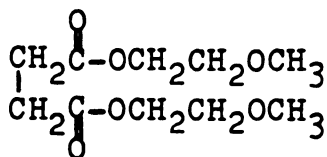
8. Product Analyses:



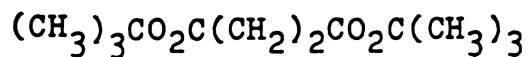
NMR(DCCl₃): $\delta 4.1$ (q, 2H), $\delta 3.3$ (m, 1H), $\delta 2.3$ (m, 4H),
 $\delta 1.8$ (m, 2H), $\delta 1.3$ (t, 3H).



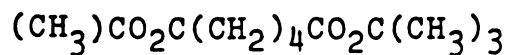
NMR(DCCl₃): $\delta 4.1$ (q, 2H), $\delta 3.3$ (t, 1H), $\delta 2.2$ (m, 8H),
 $\delta 1.7$ (m, 8H), $\delta 1.3$ (t, 3H).



NMR(CCl₄): B.P. $145^{\circ}/3\text{mm}$ $\delta 4.0$ (t, 4H), $\delta 3.4$ (t, 4H),
 $\delta 3.1$ (s, 6H), $\delta 2.4$ (s, 4H).



NMR(CCl₄): $\delta 2.3$ (s, 4H), $\delta 1.4$ (s, 18H).



NMR(CCl₄): $\delta 2.1$ (m, 4H), $\delta 1.5$ (m, 4H) $\delta 1.4$ (s, 18H).

CHAPTER 2

SILYLATION OF MONO- AND DI-ENOLATES OF DIETHYL SUCCINATE

INTRODUCTION

Ester enolates are ambident anions capable of reacting with electrophiles at either carbon or oxygen (Figure 8).

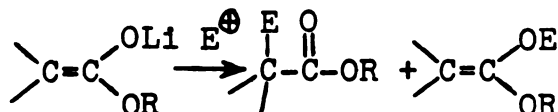
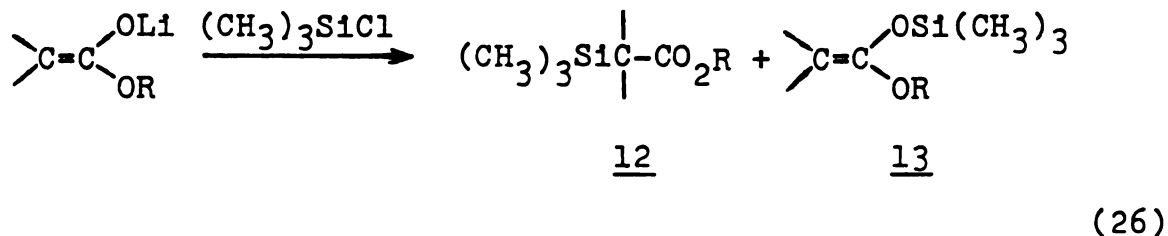


Figure 8. Reaction of Ester Enolates with Electrophiles.

Reaction of ester enolates with chlorotrimethylsilane can form α -silyl esters 12 and/or O-trimethylsilyl-O'-alkyl ketene acetals 13 (Eq. 26). Substitution on the



alcohol portion of the ester favors C-silylation, while substitution on the alpha carbon favors O-silylation.⁴ Ethyl esters excluding acetates give predominately O-silylation products, 13.

Ketene silyl acetals react with a variety of electrophilic reagents. Acid chlorides,²³ ketenes,^{24,25} and aldehydes²⁶ react to form β -keto esters and β -hydroxy

esters (Figure 9).

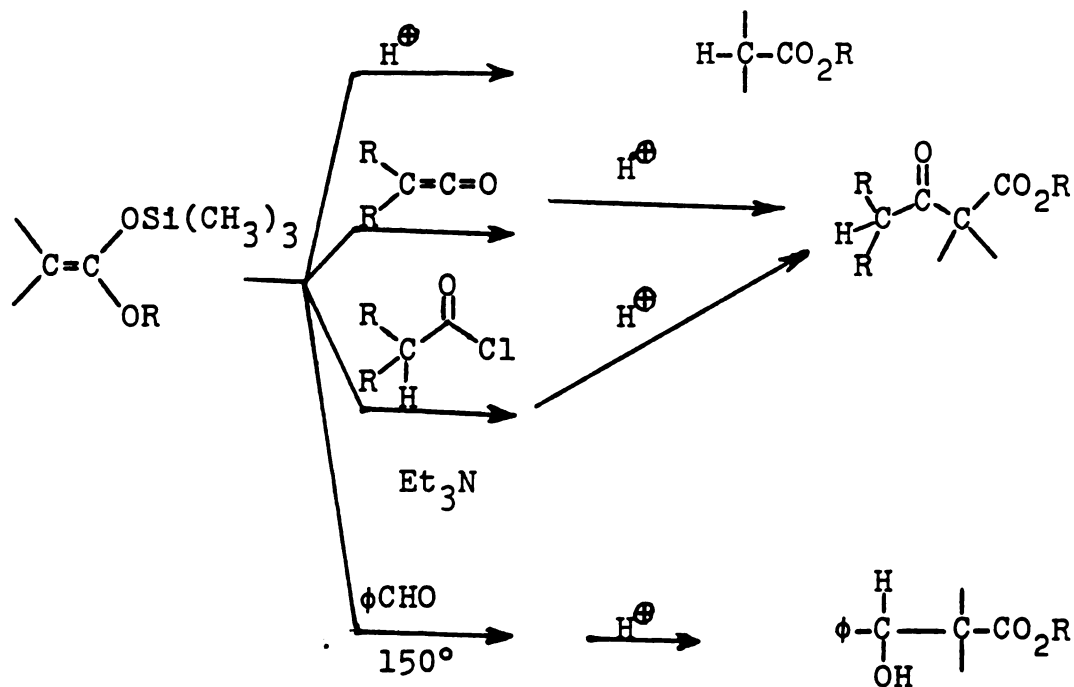
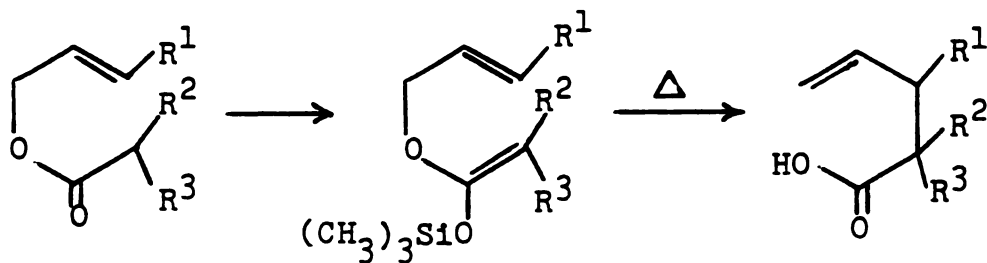


Figure 9. Reactions of Ketene Silyl Acetals with Electrophiles.

Ireland²⁷ has found that allyl esters via the intermediacy of ketene silyl acetals can undergo a Claisen rearrangement under mild conditions (Eq. 27).



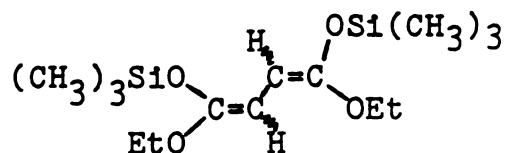
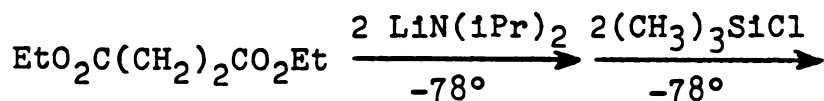
(27)

The objective of this investigation was to explore the reaction of silyl halides with the mono- and di-enolates of diethyl succinate. It was hoped that this study might lead to a better understanding of the enolate forming reaction in Chapter 1 as well as providing a synthetic route to new compounds.

RESULTS

Silylation of Diethyl Dilithiosuccinate

Addition of diethyl succinate to two equivalents of lithium diisopropylamide at -78° formed a stable solution. Addition of chlorotrimethylsilane produced a single product 14 (88%) as determined by glpc analysis (Eq. 28). There was no evidence of C-silylated product by glpc. The

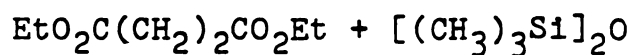
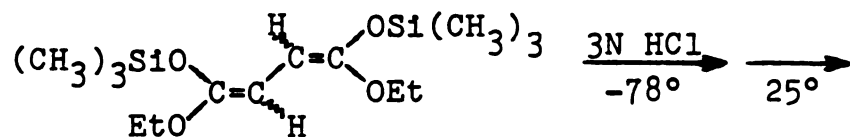


14 (88%)

(28)

stability of 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene 14 was studied. Hydrolysis of 14 with 3N

hydrochloric acid readily formed diethyl succinate and bis(trimethylsilyl) ether (Eq. 29).



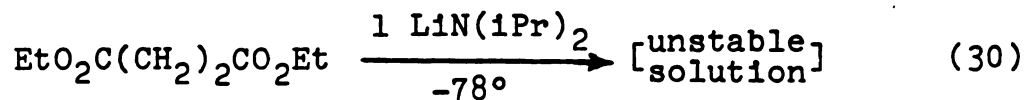
92%

(29)

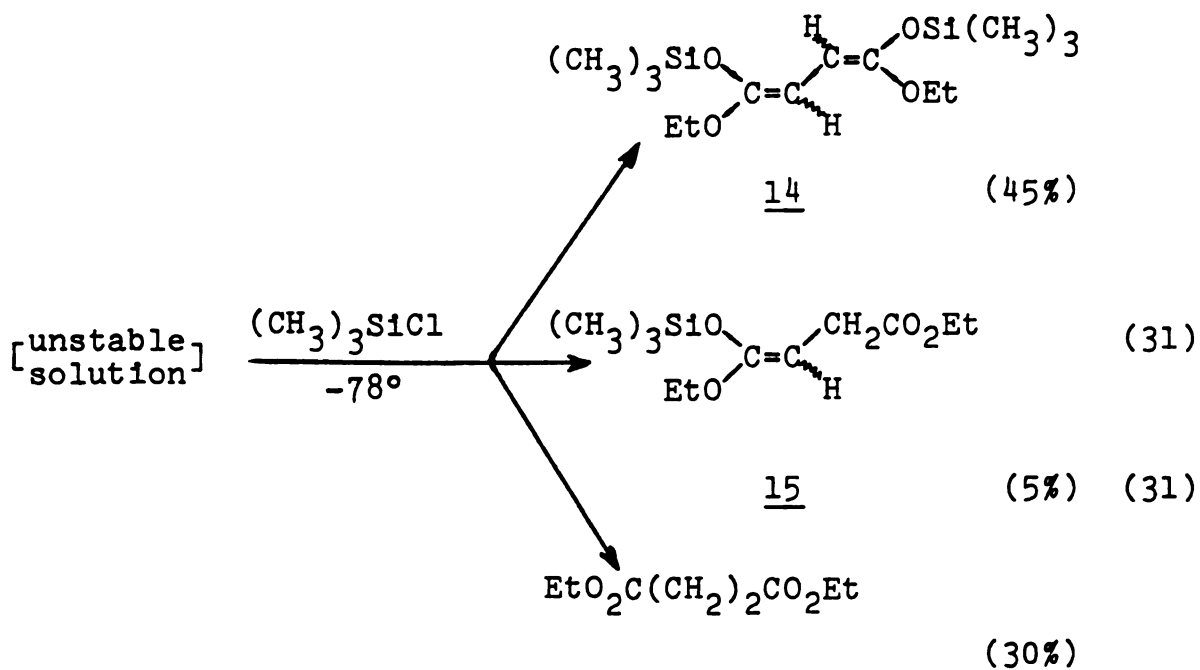
Exposure to air also caused 14 to slowly form diethyl succinate, so pure samples of 14 must be stored under argon in tightly sealed vessels to prevent hydrolysis.

Attempted Silylation of the Mono-enolate of Diethyl Succinate

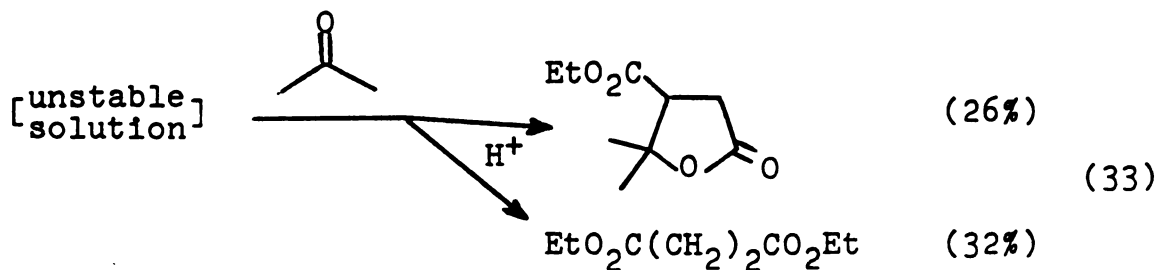
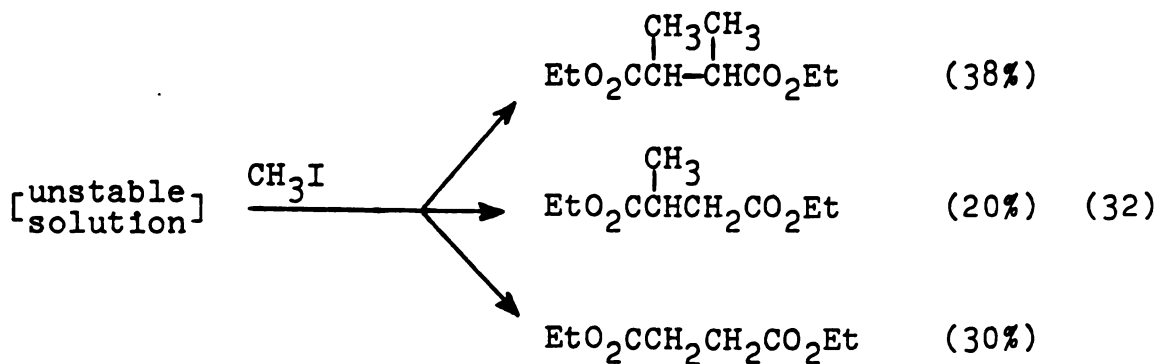
Addition of diethyl succinate to one equivalent of lithium diisopropylamide at -78° did not form a stable solution (Eq. 30). Addition of chlorotrimethylsilane



produced three products 14, 15, and starting diethyl succinate as determined by glpc analysis (Eq. 31).



Similar quenching studies using methyl iodide or acetone gave similar product ratios (Eqs. 32 and 33).



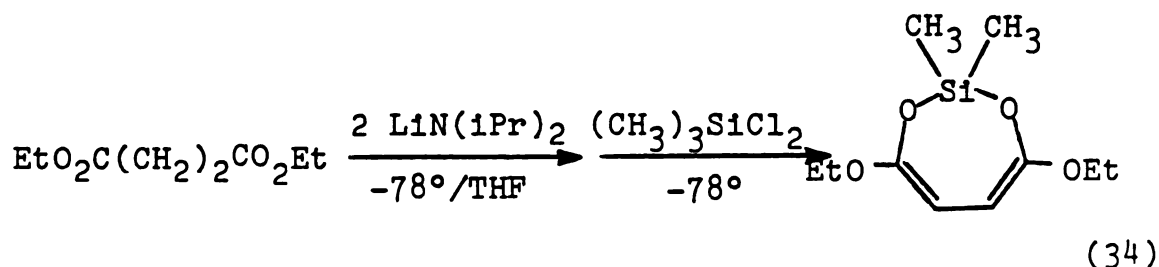
Proton NMR Spectrum of 1,4-Bis(trimethylsiloxy)-1,4-dieethoxy-1,3-butadiene

Proton NMR spectral analysis of the product 14 (Eq. 28) showed it to be a mixture of geometrical isomers. The PMR spectrum (Figure 10A) showed an eighteen proton singlet at 0.05 ppm, a pair of 3 proton triplets at 0.95 and 1.05 ppm, a pair of 2 proton quartets at 3.35 and 3.45 ppm, and a pair of singlets at 4.1 and 4.29 ppm.

The geometrical isomers could be separated by repeated crystallization in pentane at -78° . The crystals which formed at -78° were collected by filtration through a cold (-78°) frit. The PMR spectrum (Figure 10B) of the isolated sample showed a nine proton singlet at 0.05 ppm, a 3 proton triplet at 1.05 ppm, a 2 proton quartet at 3.45 ppm, and a singlet at 4.30 ppm. This proton NMR spectrum corresponds to the major (80%) isomer of the mixture studied above.

Related Reactions

Reaction of diethyl dilithiosuccinate with dichlorodimethylsilane failed to form a stable product (Eq. 34).



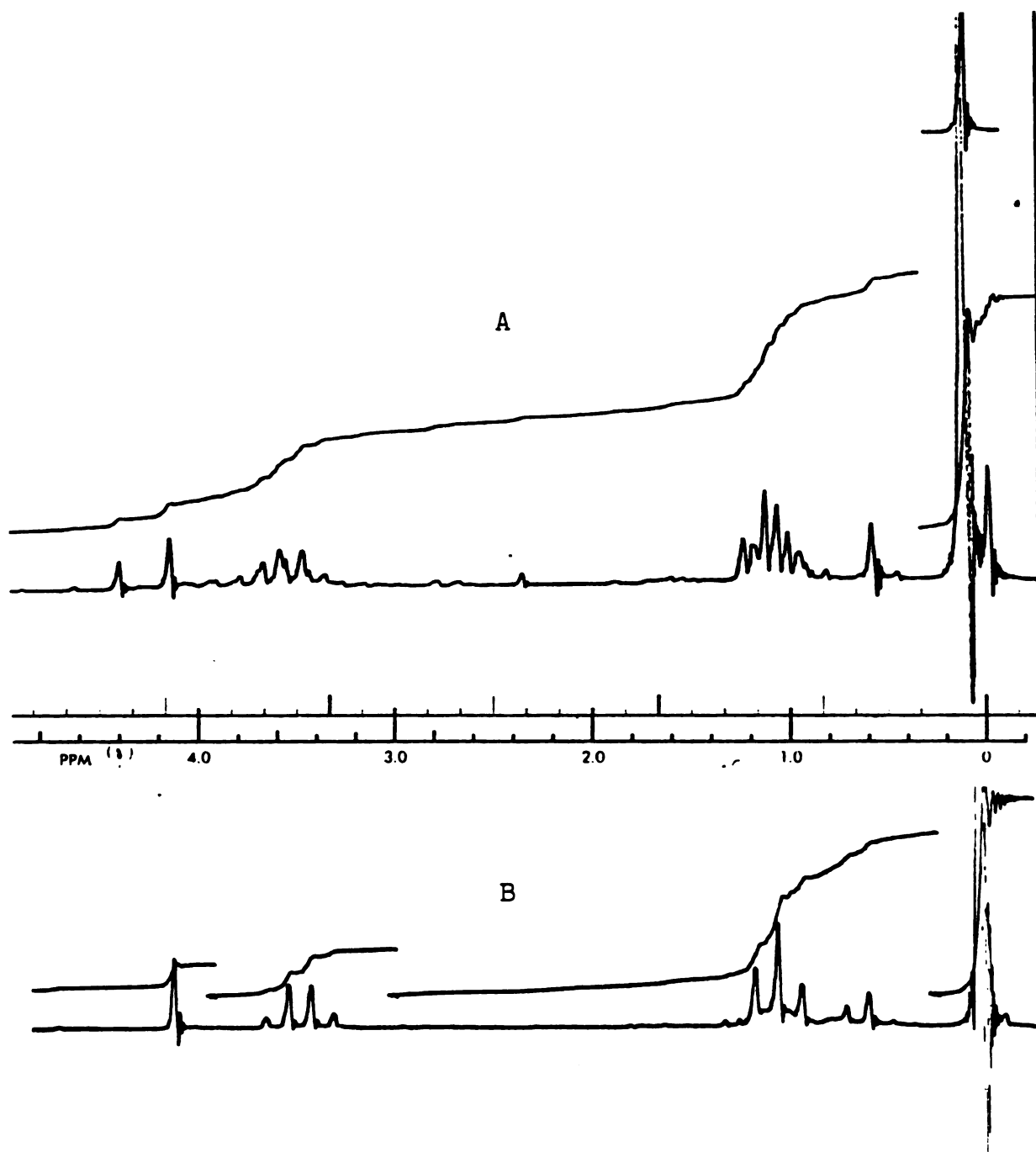
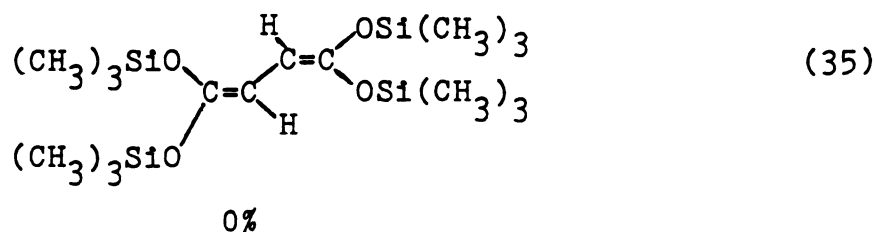
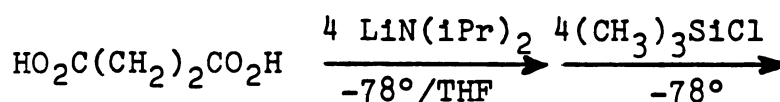


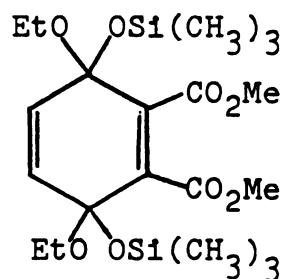
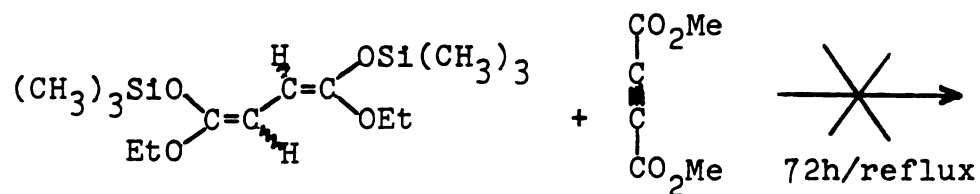
Figure 10. Proton NMR Spectrum of 1,4-Bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene in Carbon Tetrachloride.

Glpc analysis showed starting diethyl succinate was present after quenching with dichlorodimethylsilane.

Reaction of succinic acid with four equivalents of lithium diisopropylamide formed a yellow gel. Quenching with four equivalents of chlorotrimethylsilane did not form the desired product (Eq. 35).

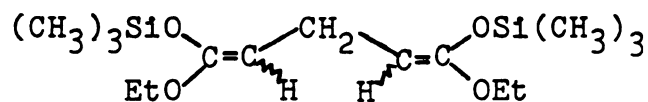
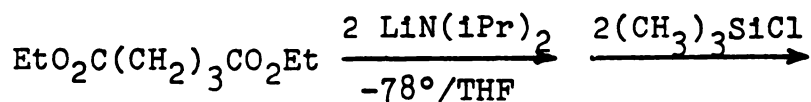


A Diels-Alder reaction between 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene and acetylene-1,2-dimethyl-dicarboxylate was unsuccessfully attempted (Eq. 36). Starting material (99%) remained after 72 hours at reflux.



(36)

Addition of diethyl glutarate to two equivalents of lithium diisopropylamide, followed by quenching with chlorotrimethylsilane yielded a single product 16 (Eq. 37).



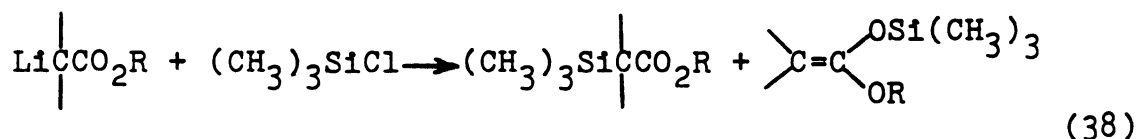
(37)

85%

DISCUSSION

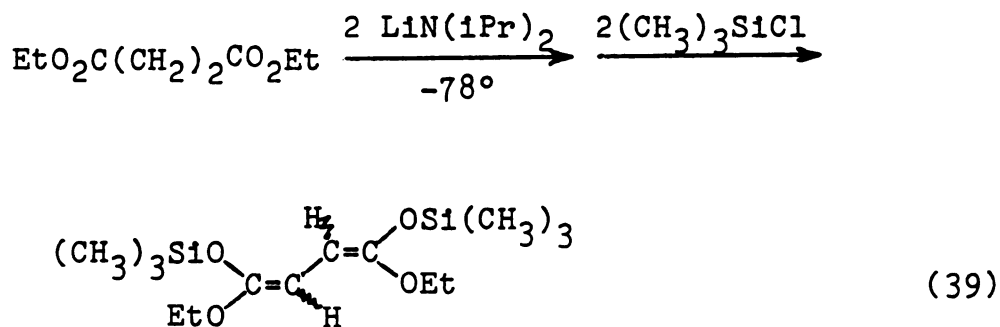
Silylation of Diethyl Dilithiosuccinate

The reaction of ester enolates with trialkylhalo-silanes has been studied extensively, and has been found to silylate on either carbon or oxygen depending on the structure of the ester (Eq. 38).⁴ The ratio of O to C



silylation depends on the substitution at the alpha carbon and on the substitution in the alcohol portion of the ester.

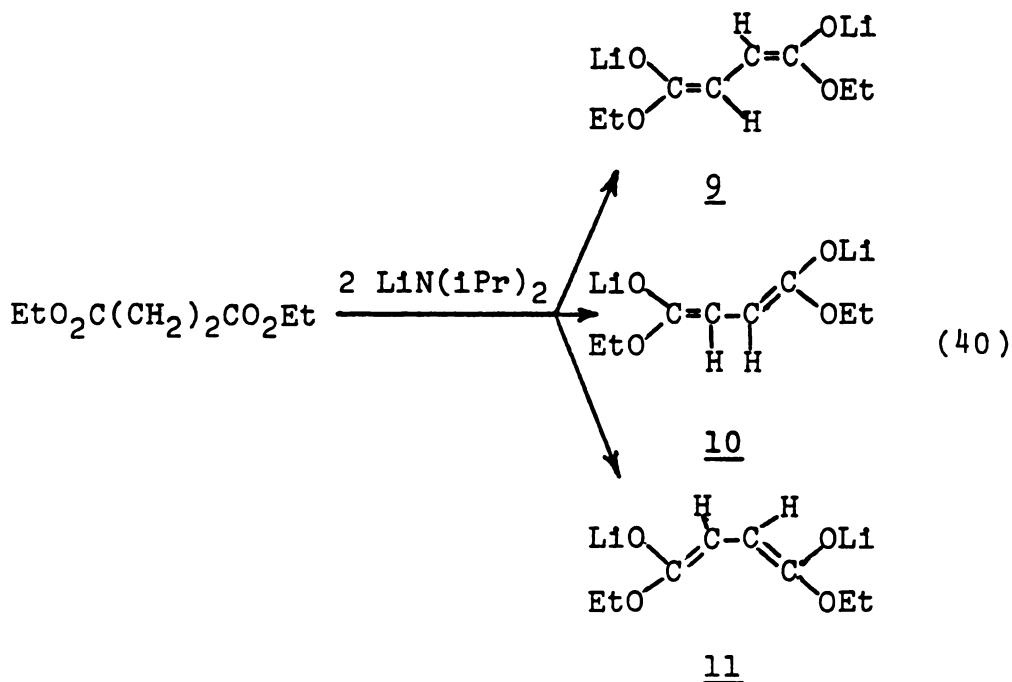
With diethyl dilithiosuccinate, silylation occurred exclusively to form O-silylated product (Eq. 39). No C-silylated product or starting diethyl succinate was found.



Hydrolysis of the O-silylated product to diethyl succinate

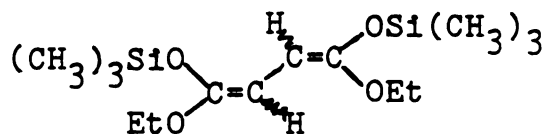
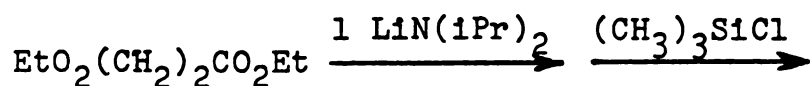
under mild conditions confirms the structure as 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene 14. C-silylated esters are more stable than O-silylated esters toward hydrolysis.⁴

A mixture of geometrical isomers of 14 was formed which could be separated by crystallization from pentane at -78° . The existence of geometrical isomers for 14 makes it probable that the solution of diethyl dilithiosuccinate existed as a mixture of geometrical isomers before quenching. These geometrical isomers (structures 9, 10, 11 in Chapter 1) are formed by non-stereospecific proton abstraction by lithium diisopropylamide (Eq. 40).

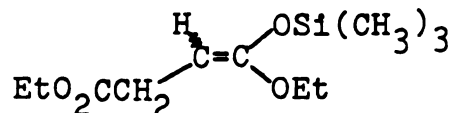


Attempted Silylation of the Mono-enolate of Diethyl Succinate

Reaction of diethyl succinate with one equivalent of lithium diisopropylamide, followed by quenching with chlorotrimethylsilane yielded three products 14, 15, and diethyl succinate (Eq. 41).

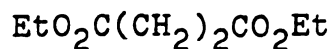


(45%) 14



(41)

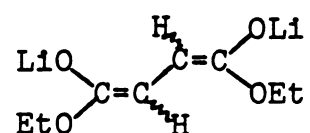
(5%) 15



(30%)

These results were not expected. Formation of 14 in high yield and return of starting diethyl succinate indicates that the di-enolate was formed more efficiently than the mono-enolate.

Two explanations are possible. The di-enolate may be more stable than the mono-enolate, and the observed product distribution may represent an equilibrium mixture of enolate anions. The structure of diethyl dilithio-succinate, 9, 10, 11, contains a conjugated diene structure. These thermodynamic considerations do not seem

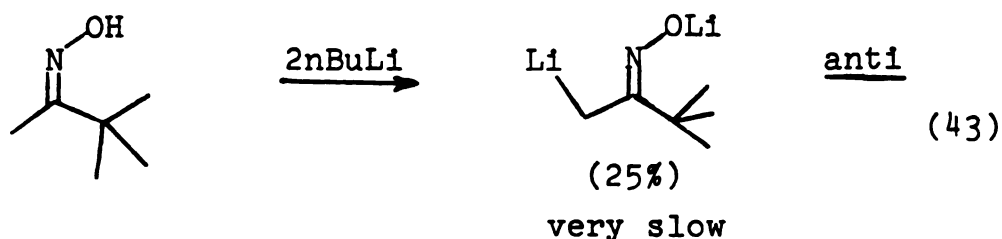
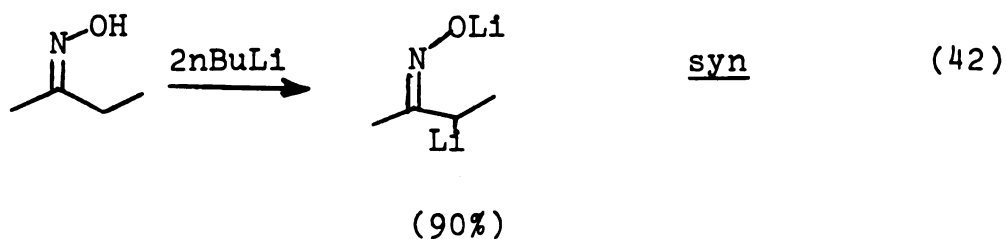


9, 10, 11

reasonable since they require that the dianion be more stable than the monoanion and the second proton must be appreciably more acidic to account for the formation of 14 in high yield.

Another explanation is that the observed product distribution may represent kinetically controlled enolate formation. The mono-enolate may assist the formation of the di-enolate.

Jung²⁸ has found for oxime dianions that the hydrogen which is syn to the oxygen is removed by base (Eq. 42). Oximes which have no protons syn to the oxygen and are forced to react anti, do so sluggishly and in low yields (Eq. 43). His explanation is that the second equivalent of base coordinates with the first lithium atom to

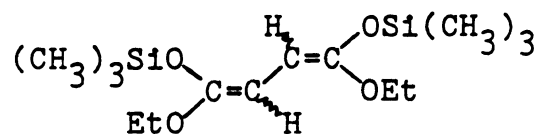


kinetically facilitate removal of the second proton.

A similar coordination of the second equivalent of lithium diisopropylamide with the diester mono-enolate may account for the di-enolate being formed preferentially. This could then explain the observed product distribution (Eq. 39).

Proton NMR Spectrum of 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene

The proton NMR spectrum (Figure 10) shows that a mixture of geometrical isomers is formed when diethyl dilithiosuccinate is quenched with chlorotrimethylsilane. Assignment of the structure as the O-silylated molecule 14 was based on hydrolysis reactions and the proton NMR spectrum.

14

An 18 proton singlet at 0.05 ppm was assigned to the methyl groups on the silicons; 3 proton triplets at 0.95 and 1.05 ppm and 2 proton quartets at 3.35 and 3.45 ppm were assigned to the ethyl groups; and singlets at 4.1 and 4.29 ppm were assigned to the vinyl protons.

Related Reactions

Reaction of diethyl dilithiosuccinate with dichlorodimethylsilane failed to give the postulated cyclic product. Also reaction of succinic acid with lithium diisopropylamide failed to form the tetra anion. Possibly low solubility was the problem.

Trapping the di-enolate of diethyl glutarate with chlorotrimethylsilane was successful.

EXPERIMENTAL

1. Materials

Diethyl succinate and glutarate were distilled prior to use. Chlorotrimethylsilane and dichlorodimethylsilane were commercially available and were distilled and stored

under argon. $n\text{-BuLi}$ was obtained from Aldrich as 1.6M solutions and used without further purification. Diisopropylamine was obtained from Aldrich and distilled from CaH_2 prior to use. Tetrahydrofuran was commercially available and distilled from the sodium ketyl of benzophenone. Succinic acid and maleic anhydride were commercially available and used without further purification.

2. Preparation of 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene

Diethyl dilithiosuccinate (50 mmoles) was prepared as described in Chapter 1. After stirring at -78° for 15 minutes, 7.0 ml chlorotrimethylsilane (55 mmoles) was added dropwise. The solution was stirred 15 minutes at -78° before warming to room temperature for 30 minutes. Solvent and amine were evaporated by use of a rotary evaporator. Pentane was added to the resulting oil and the solution was filtered to remove lithium chloride. Vacuum distillation at $92^\circ/.65$ mm yielded 11.6 g (73%) of 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene.

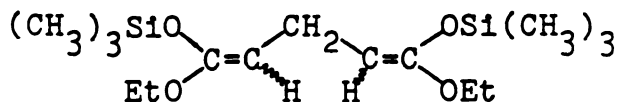
3. Attempted Silylation of the Mono-enolate of Diethyl Succinate

Lithium diisopropylamide (5 mmoles) was prepared and isolated as described in Chapter 1. 10 ml of tetrahydrofuran

was added and the solution was cooled to -78° . Diethyl succinate (5 mmoles) was mixed with 10 ml of tetrahydrofuran and then added slowly dropwise. A yellow solution resulted. After stirring 15 minutes at -78° , chlorotrimethylsilane (5.5 mmoles) was added dropwise. The solution was stirred 15 minutes at -78° , and then 30 minutes at room temperature. Glpc analysis indicated three products.

4. Preparation of 1,5-bis(trimethylsiloxy)-1,5-diethoxy-1,4-pentadiene

The identical procedure used for 1,4-bis(trimethylsiloxy)-1,4-diethoxy-1,3-butadiene preparation was followed except dilithioglutamate was prepared by the procedure in Chapter 1. Vacuum distillation at $108^{\circ}/.65$ mm yielded 10.8 g (65%) of 1,5-bis(trimethylsiloxy)-1,5-diethoxy-1,4-pentadiene.



NMR(CCl_4): $\delta 3.6(\text{q}, 4\text{H})$, $\delta 3.45(\text{t}, 2\text{H})$, $\delta 2.4(\text{t}, 2\text{H})$,
 $\delta 1.05(5, 6\text{H})$, $\delta 0.05(\text{s}, 18\text{H})$.

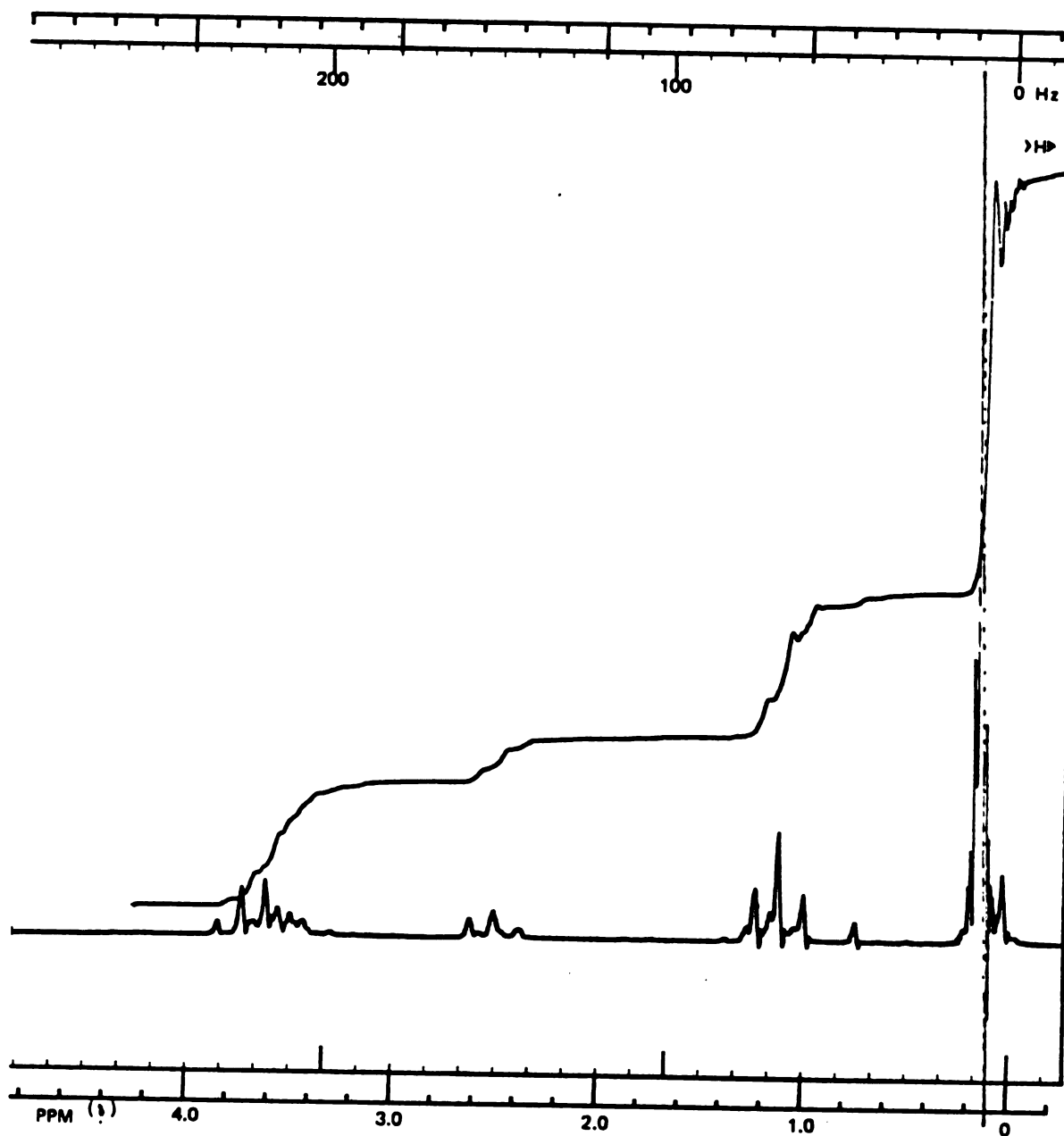


Figure 11. Proton NMR Spectrum of 1,5-Bis(trimethylsiloxy)-1,5-diethoxy-1,4-pentadiene in Carbon Tetrachloride.

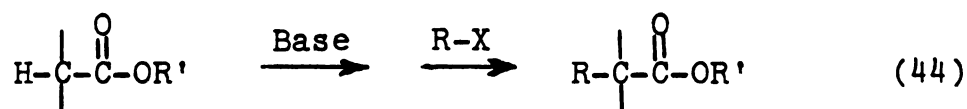
CHAPTER 3

ALKYLATION OF MONO- AND DI-ENOLATES OF DIETHYL SUCCINATE

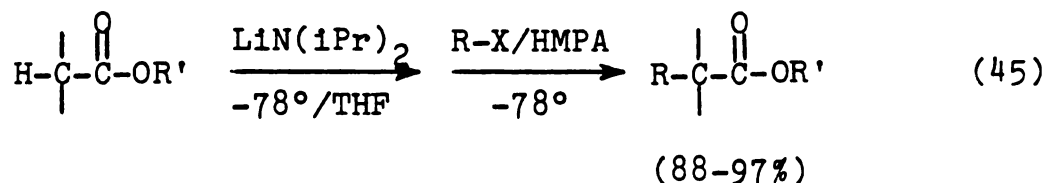
INTRODUCTION

In Chapters 1 and 2 it was established that stable solutions of diethyl dilithiosuccinate could be generated by reaction of diethyl succinate with two equivalents of lithium diisopropylamide in tetrahydrofuran at -78° . This ability to generate diethyl dilithiosuccinate as a discrete reagent should be synthetically useful.

Several authors²⁹⁻³¹ have reported alkylation of simple ester enolates (Eq. 44). Reaction conditions vary,



but most use strong bases, reactive alkylating agents, and cold temperatures. Schlessinger³⁰ reported a general method for the alkylation of esters in high yield (Eq. 45).



Hexamethylphosphoramide (HMPA) is used as co-solvent.

In 1972 it was reported¹² that dicarboxylic esters could be alkylated in very low yields (1-29%) by using lithium amide as the base. Previous attempts to alkylate

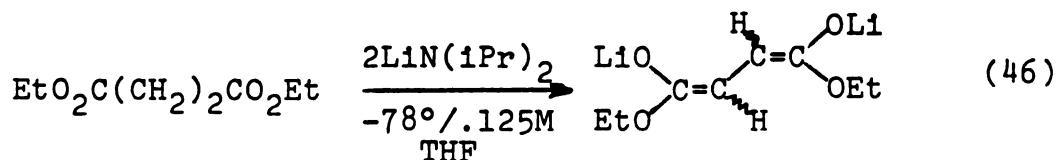
dicarboxylic esters using alkoxide bases invariably failed to give desired products. The main problem is that the enolate generated by alkoxide is not a discrete reagent so it must be trapped as it forms or competing condensation reactions will occur. It is not possible to alkylate in high yield in refluxing alkoxide.

The objective of this investigation was to explore the reaction of diethyl dilithiosuccinate with alkylating agents. New products were characterized and known products were compared with previous investigations. The use of the mono-enolate of diethyl succinate for alkylation reactions was also studied.

RESULTS

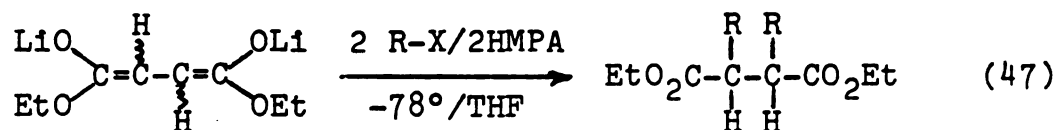
Di-alkylation of Diethyl Dilithiosuccinate

Diethyl dilithiosuccinate was prepared by addition of diethyl succinate to a tetrahydrofuran solution containing two equivalents of lithium diisopropylamide at -78° (Eq. 46).



9, 10, 11

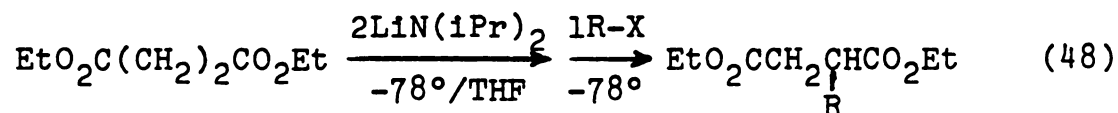
This stable solution was then di-alkylated by adding two equivalents of an organic halide in hexamethylphosphoramide (HMPA) to the THF solution of diethyl dilithiosuccinate at -78° (Eq. 47) (Table 5). Yields of these



reactions varied depending on the structure of the alkylating agent. Product analysis by proton NMR and glpc indicated that diastereomers were formed. No O-alkylation or di-alkylation at the same carbon was observed.

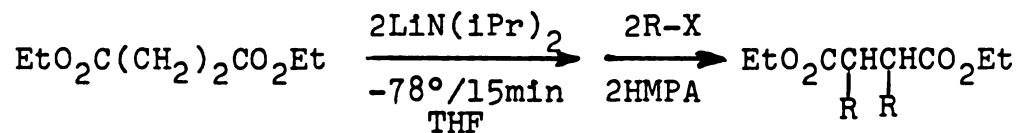
Mono-alkylation of Diethyl Dilithiosuccinate

Addition of only one equivalent of an organic halide to a solution containing diethyl dilithiosuccinate produced mono-alkylated derivatives of diethyl succinate, after quenching with acid (Eq. 48) (Table 6).



Higher yields were obtained when HMPA was not added as co-solvent.

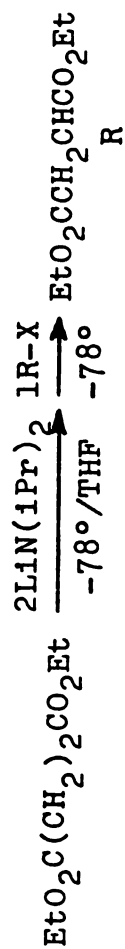
Table 5. Di-alkylation of Diethyl Dilithiosuccinate.



R-X	EtO ₂ C(CH ₂) ₂ CO ₂ Et	EtO ₂ CCH ₂ $\underset{\text{R}}{\text{C}}$ CHCO ₂ Et	EtO ₂ C $\underset{\text{R}}{\text{C}}$ CH $\underset{\text{R}}{\text{C}}$ CHCO ₂ Et
2CH ₃ I	----	----	82% ^a
2CH ₃ CH ₂ I	----	----	84%
2φCH ₂ Br	----	12%	68%

^aYields were determined by glpc analysis.

Table 6. Mono-alkylation of Diethyl Dilitiosuccinate.



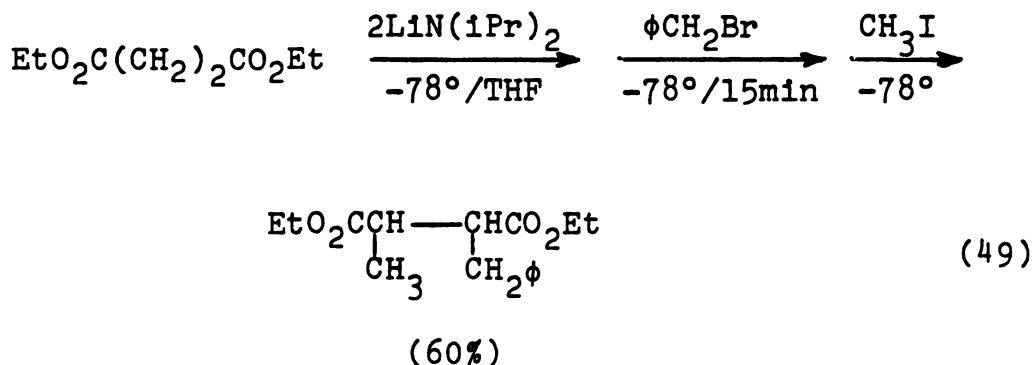
R-X	Time/Temp.	$\text{EtO}_2\text{C}(\text{CH}_2)_2\text{CO}_2\text{Et}$	$\text{EtO}_2\text{C}(\text{CH}_2)_2\text{CH}(\text{R})\text{CO}_2\text{Et}$	$\text{EtO}_2\text{C}(\text{CH}_2)_2\text{CH}(\text{R})\text{CH}(\text{R})\text{CO}_2\text{Et}$	% Yield ^a
$\text{1CH}_3\text{I}$	30 min/-78°	9	66	10	
	1h/-100°	20	40	1	
$\text{1CH}_3\text{CH}_2\text{I}$	15min/-78°+25°	20	46	17	
	1h/-78°	39	53	1	
	4h/-78°	20	68	2	
	18h/-70°	4	58	--	
$\text{1.5CH}_3\text{CH}_2\text{I}$	2h/-78°	18	68	--	
	4h/-78°	8	69	4	
$\text{1}\phi\text{CH}_2\text{Br}$	15min/-78°	--	83	6	

^aYields were determined by glpc analysis.

The time necessary for mono-alkylation varied, depending on the nature of the alkylating agent. Less reactive alkylating reagents ($\text{CH}_3\text{CH}_2\text{I}$) required more time for complete reaction. Competing side reactions also were a problem for the longer reaction times.

Mixed Alkylations

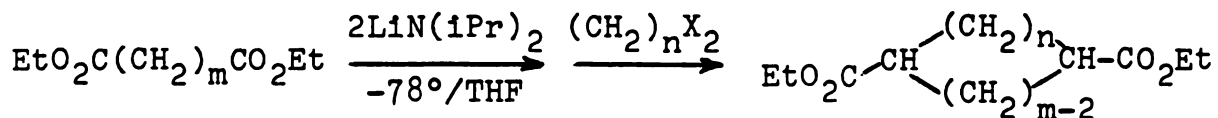
Addition of one equivalent of an organic halide to a solution containing diethyl dilithiosuccinate, followed by addition of a different organic halide, produced mixed alkylated derivatives of diethyl succinate (Eq. 49).

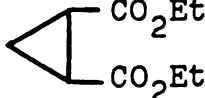
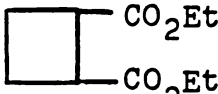
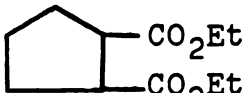
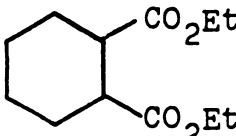
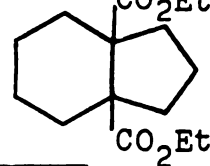
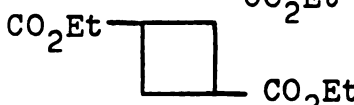
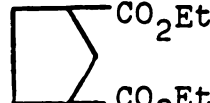
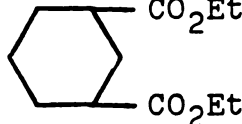


Cyclic Alkylations

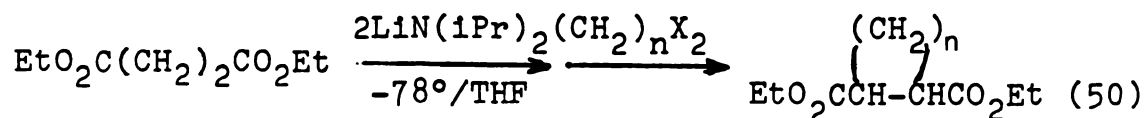
Addition of one equivalent of an organic dihalide to a solution containing diethyl dilithiosuccinate produced cyclic products (Eq. 50) (Table 7). Since organic dihalides are ordinarily less reactive toward alkylation processes,

Table 7. Cyclic Alkylation Reactions.



Diester	RX ₂	Product	% Yield ^a
diethyl succinate	CH ₂ I ₂		23
diethyl succinate	(CH ₂) ₂ I ₂		0
diethyl succinate	(CH ₂) ₃ Br ₂		44
	(CH ₂) ₃ Br ₂		55
diethyl glutarate	CH ₂ I ₂		0
diethyl glutarate	(CH ₂) ₂ I ₂		17
diethyl glutarate	(CH ₂) ₃ Br ₂		22

^aYields were determined by glpc analysis.



$$n = 1, 2, 3$$

$$x = \text{I or Br}$$

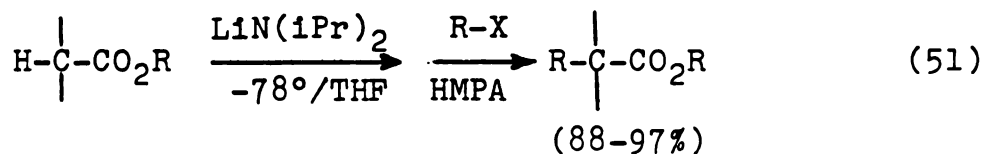
the yields of cyclic products by this reaction were low, as expected.

DISCUSSION

Di-alkylation of Diethyl Dilithiosuccinate

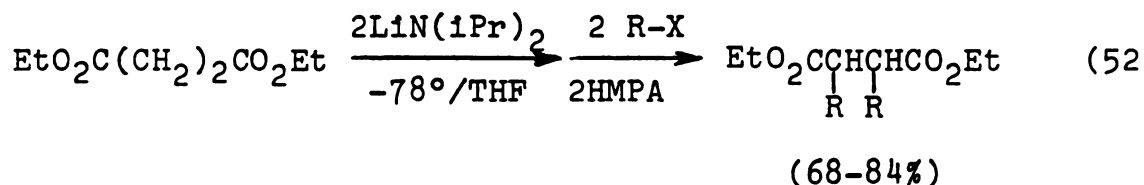
Diethyl dilithiosuccinate can be generated as a discrete reagent. This makes alkylation reactions possible since competing condensation reactions are minimized at the cold temperatures employed. Also the generating base is not present for competitive reaction with the alkyl halide as it would be under Stobbe reaction conditions.

Simple ester enolate can be alkylated easily at -78° by use of hexamethylphosphoramide as co-solvent (Eq. 51).³⁰



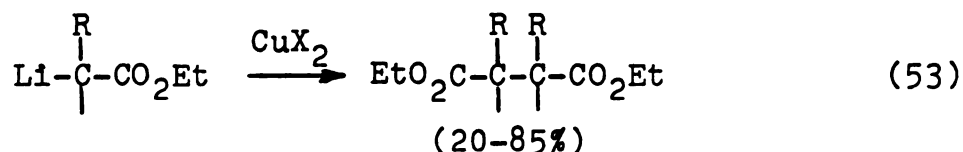
Reaction of diethyl dilithiosuccinate with two

equivalents of organic halide proceeded smoothly to yield di-alkylated derivatives of diethyl succinate (Eq. 52).



Yields of di-alkylated product reported in this work were far superior and cleaner than those reported in earlier studies by Kofron.¹²

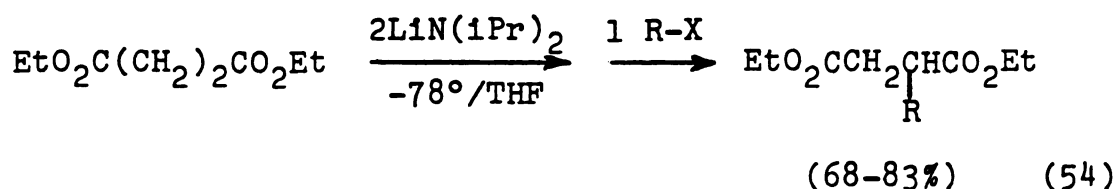
Simple ester enolates can be coupled with copper(II) salts to form di-substituted succinate esters (Eq. 52).⁷ Yields of di-alkylated succinates reported in this work



were found to be greater than or equal to those reported for the copper coupling reaction of simple ester enolates (Eq. 53). The two methods compliment each other. In many cases the availability of starting materials might determine which method should be used for preparing di-substituted succinates.

Mono-alkylation of Diethyl Dilithiosuccinate

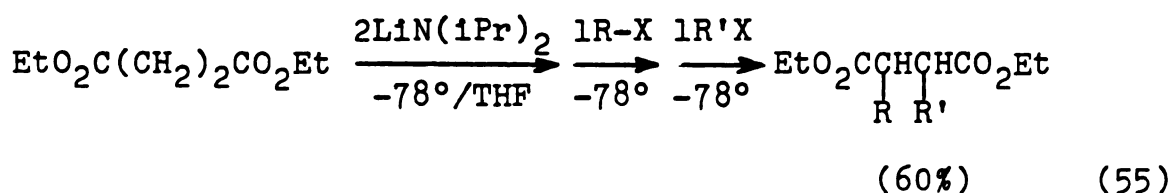
Reaction of diethyl dilithiosuccinate with one equivalent of organic halide in the absence of hexamethylphosphoramide gave high yields of mono-alkylated succinates (Eq. 54).



These mono-alkylated succinates cannot be made efficiently by copper coupling reactions of simple ester enolates. A several-step method³² involving the addition of sodium cyanide to an α - β unsaturated ester as the key step has been used to prepare mono-substituted diethyl succinate derivatives in yields slightly less than those obtained in this study. The major limitation to preparing mono-alkylated succinates via direct alkylation of diethyl dilithiosuccinate is difficulty in separating the desired product from the side products. In many cases the non-alkylated succinates and di-alkylated succinates have similar physical properties.

Mixed Alkylation

Reaction of diethyl dilithiosuccinate with one equivalent of organic halide, followed by addition of a different organic halide gave high yields of the mixed alkylated product (Eq. 55). No products were found in which alkylation



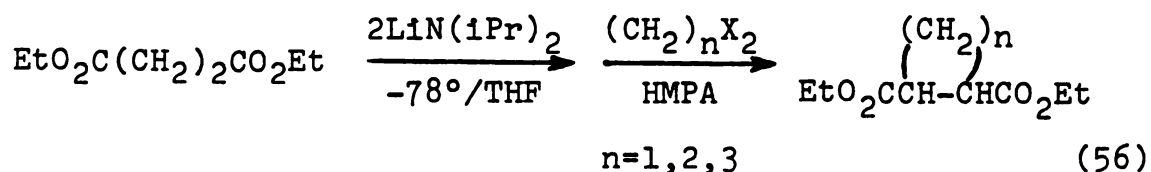
occurred twice at the same carbon. This indicates that diester di-enolates are similar to simple ester enolates in that they do not undergo enolate exchange at cold temperatures unless the stability of the enolates is markedly different.

This suggests that the di-enolate of diethyl succinate is not thermodynamically more stable than the mono-enolate. Also the ability to mono-alkylate the di-enolate suggests that the di-enolate may in fact be thermodynamically less stable than the mono-enolate. Or alternatively the di-enolate may kinetically be more reactive. In either case the ability to mono-alkylate the di-enolate provided a method for preparing the mono-enolate of a diethyl succinate derivative. An examination of the yields for the mono-alkylation and mixed alkylation reactions (Table 6)

and (Eq. 48) showed that material recovery was quite low. Apparently the mono-enolate is slightly more prone to condensation reactions than is the di-enolate.

Cyclic Alkylations

Reaction of diethyl dilithiosuccinate with an organic dihalide gave low yields of cyclic product (Eq. 56). The formation of a five-membered ring was the only



synthetically useful reaction.

EXPERIMENTAL

1. Materials

Alkyl halides and organic dihalides were obtained commercially and distilled prior to use. Alkyl iodides were stored over copper turnings. Diethyl succinate and glutarate were distilled prior to use. Diethyl cyclohexane dicarboxylate was prepared from the commercially available cis-1,2-cyclohexane dicarboxylic anhydride by reaction with ethanol. nBuLi was obtained from Aldrich

as 1.6M solutions and used without further purification. Diisopropylamine was obtained from Aldrich and distilled from CaH_2 prior to use. Tetrahydrofuran was commercially available and distilled from the sodium ketyl of benzophenone. Hexamethylphosphoramide was obtained from Aldrich and distilled prior to use.

2. Di-alkylation of Diethyl Dilithiosuccinate

The preparation of diethyl α,α' -dimethylsuccinate will be representative. Diethyl dilithiosuccinate (50 mmoles) was prepared by procedures described in Chapter 1. After stirring at -78° for 15 minutes, 18 ml hexamethylphosphoramide (100 mmoles) in 18 ml tetrahydrofuran was added. 6.8 ml (110 mmoles) Methyl iodide was added dropwise, stirred at -78° for 15 minutes, and then allowed to warm to room temperature for 45 minutes. The solution was cooled to -78° and quenched with 50 ml of 3N hydrochloric acid. After warming to room temperature, 50 ml of pentane was added, and the layers were separated. The organic layer was washed twice with 50 ml 3N hydrochloric acid to remove hexamethylphosphoramide. The solution was dried with anhydrous potassium carbonate and distilled at 71° (3mm) to yield 6.9 g (68%) of diethyl α,α' -dimethylsuccinate.

3. Mono-Alkylation of Diethyl Dilithiosuccinate

The preparation of diethyl α -methylsuccinate will be representative. Diethyl dilithiosuccinate (5 mmoles) was prepared by the procedure described in Chapter 1. After stirring at -78° for 15 minutes, 0.34 ml (5 mmoles) methyl iodide was added dropwise. No hexamethylphosphoramide was added. The solution was stirred at -78° for 30 minutes and then quenched with 5 ml 3N hydrochloric acid. Pentane was added and the layers were separated. After drying with anhydrous potassium carbonate, the organic layer was analyzed by glpc.

4. Mixed Alkylation of Diethyl Dilithiosuccinate

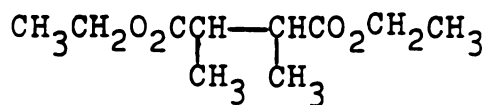
Diethyl dilithiosuccinate (5 mmoles) was prepared by the procedure described in Chapter 1. After stirring at -78° for 15 minutes, 0.60 ml (5 mmoles) benzyl bromide was added dropwise. The solution was stirred at -78° for 50 minutes, and then 0.90 ml (5 mmoles) hexamethylphosphoramide in 1 ml THF was added and stirred 10 minutes. 0.44 ml (6 mmoles) Methyl iodide was added dropwise and stirred 15 minutes at -78° before warming to room temperature. After 30 minutes the solution was cooled to -78° and quenched with 5 ml 3N hydrochloric acid. After warming to room temperature 5 ml of pentane was added, and the layers were separated. After drying with anhydrous potassium carbonate, the organic layer was analyzed by glpc.

5. Cyclic Alkylation of Dicarboxylic Ester Di-enolates

The preparation of diethyl cyclopentane dicarboxylate will be representative. Diethyl dilithiosuccinate (50 mmoles) was prepared by the procedure described in Chapter 1. After stirring at -78° for 15 minutes, 18 ml (100 mmoles) hexamethylphosphoramide in 18 ml tetrahydrofuran was added. 5.2 ml (52 mmoles) 1,3-Dibromopropane was added dropwise, stirred at -78° for 15 minutes, and allowed to warm to room temperature for 45 minutes. The solution was cooled to -78° and quenched with 50 ml of 3N hydrochloric acid. After warming to room temperature, 50 ml of pentane was added, and the layers were separated. The organic layer was washed twice with 50 ml 3N hydrochloric acid and then dried with anhydrous potassium carbonate. Distillation at $95^{\circ}/3\text{mm}$ yielded 3.6 g (33%) of diethyl cyclopentane dicarboxylate.

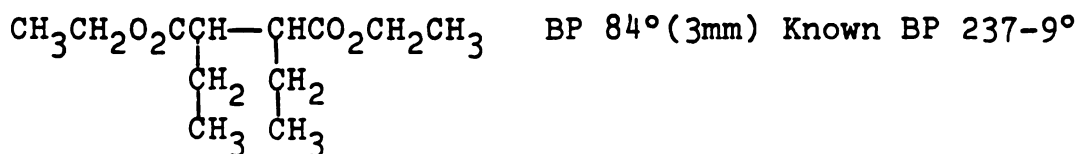
6. Product Analyses

All proton NMR spectra were recorded on a Varian T-60 Spectrometer. The IR spectra were recorded on a Perkin-Elmer 237B Grating Infrared Spectrophotometer.

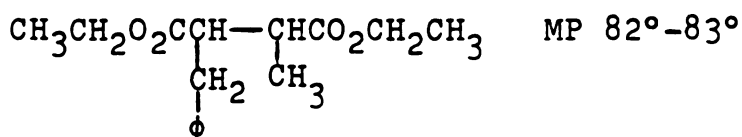


NMR(CCl₄): δ 4.0(q, 4H), δ 2.65(m-2q, 2H), δ 1.15(d, 6H)
 δ 1.20(t, 6H).

IR (CCl₄): 1740 cm⁻¹ (-CO₂R).

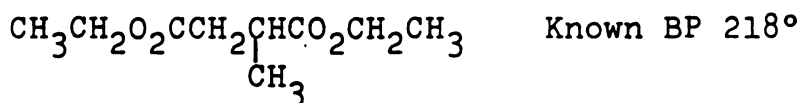


NMR(CCl₄): δ 4.05(q, 4H), δ 2.55(m, 2H), δ 1.5(m, 4H)
 δ 1.25(t, 6H), δ .95(t, 6H).

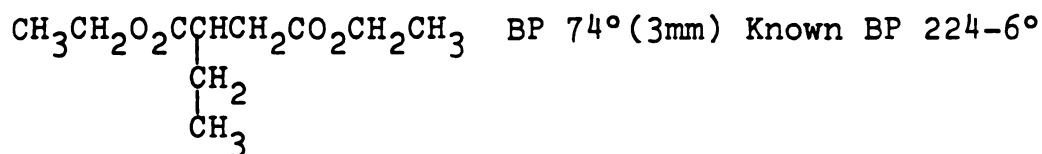


NMR(CCl₄): δ 7.05(s, 5H), δ 3.95(m-2q, 4H), δ 2.85(m-2d, 4H)
 δ 2.35(m, 2H), δ 1.10(t, 3H), δ 1.05(t, 3H).

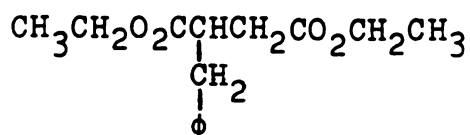
IR(CCl₄): 1740 cm⁻¹ (-CO₂R)



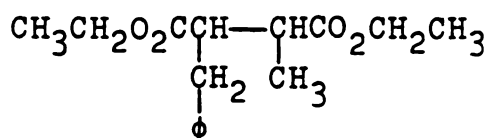
NMR(CCl₄): δ 4.05(q, 4H), δ 2.5(m, 3H) δ 1.1(t, 6H),
 δ 1.05(d, 3H).



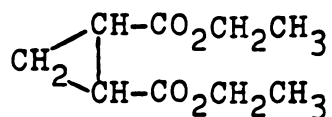
NMR(CCl₄): $\delta 4.05(\text{q}, 4\text{H}), \delta 2.50(\text{m}, 3\text{H}), \delta 1.5(\text{m}, 2\text{H}),$
 $\delta 1.20(\text{t}, 6\text{H}), \delta 1.00(\text{t}, 3\text{H}).$



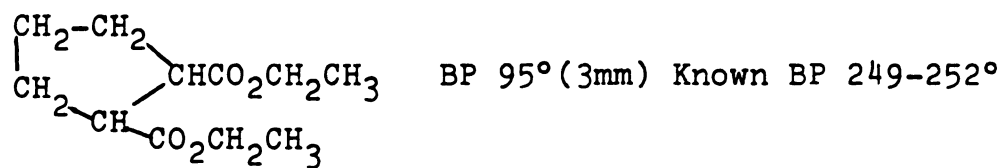
NMR(CCl₄): $\delta 7.05(\text{s}, 5\text{H}), \delta 4.0(\text{q}, 4\text{H}), \delta 2.8(\text{m}, 3\text{H}),$
 $\delta 2.4(\text{m}, 2\text{H}), \delta 1.1(\text{t}, 3\text{H}), \delta 1.05(\text{t}, 3\text{H}).$



NMR(CCl₄): $\delta 7.0(\text{s}, 5\text{H}), \delta 4.0(\text{m}-2\text{q}, 4\text{H}), \delta 2.75(\text{m}, 4\text{H}),$
 $\delta 1.15(\text{d}, 3\text{H}), \delta 1.1(\text{t}, 3\text{H}), \delta 1.05(\text{t}, 3\text{H}).$

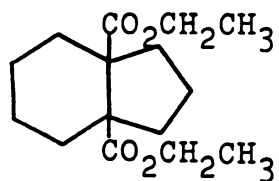


NMR(CCl₄): $\delta 4.05(\text{q}, 4\text{H}), \delta 2.1(\text{m}, 2\text{H}), \delta 1.5(\text{t}, 2\text{H}),$
 $\delta 1.3(\text{t}, 6\text{H}).$



NMR(CCl₄): δ 4.0(q, 4H), δ 2.95(m, 2H), δ 1.95(m, 6H),
 δ 1.25(t, 6H).

IR(CCl₄): 1740 cm⁻¹ (-CO₂R), 1200 cm⁻¹ (C-O).



NMR(CCl₄): δ 4.0(q, 4H), δ 2.4-1.6(m, 14H), δ 1.2(t, 6H).

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CHAPTER 4

REACTIONS OF DIETHYL DILITHIOSUCCINATE WITH CARBONYL COMPOUNDS

INTRODUCTION

The Stobbe condensation is a well-known reaction which has found numerous applications in organic synthesis. The reaction involves treatment of diethyl succinate with a ketone in refluxing alkoxide to yield a more functionalized half acid-half ester.² Ring opening occurs (Figure 12).

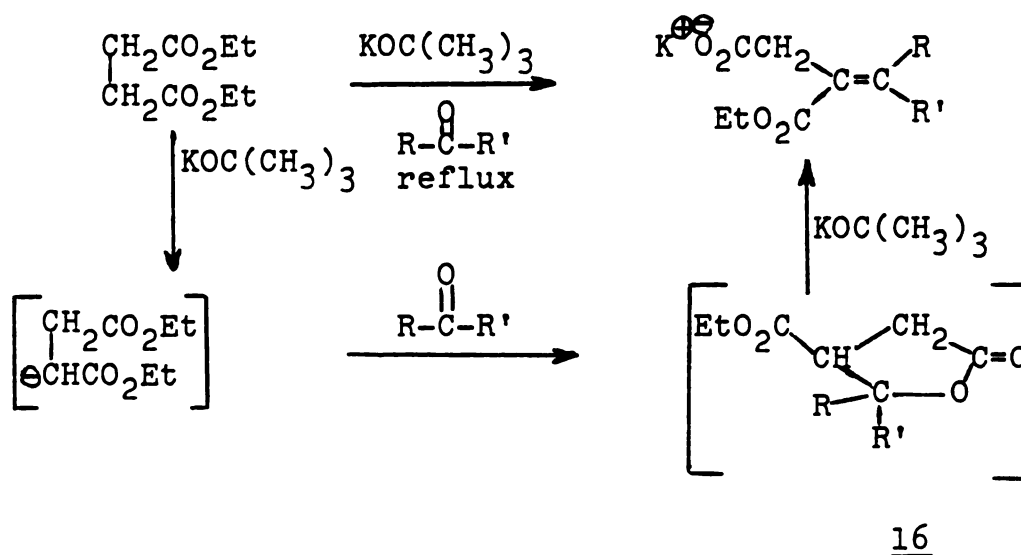
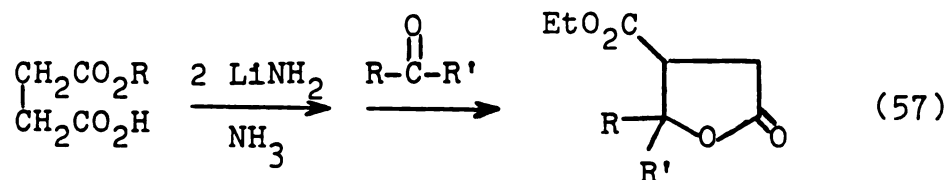


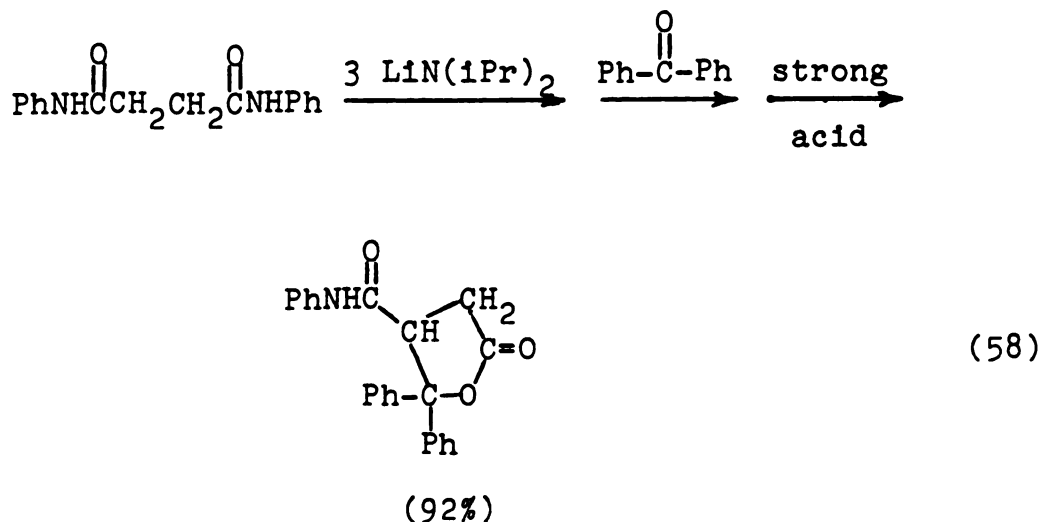
Figure 12. The Stobbe Condensation.

Recently a few methods have been developed to trap the useful γ -butyrolactone intermediate 16. Kofron and Wideman were the first to successfully trap the γ -butyrolactone intermediate.¹² Their method involves treating mono-ethyl succinate with lithium amide in dilute liquid

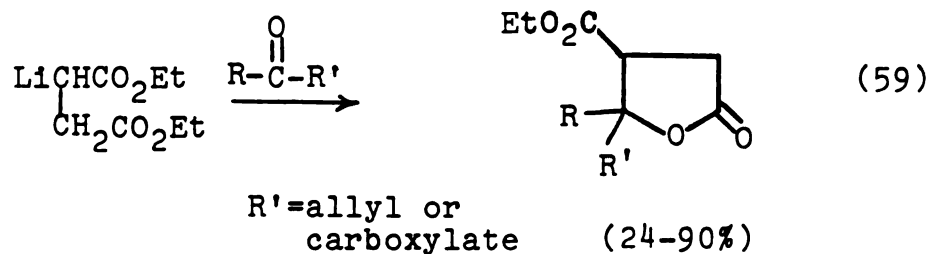
ammonia, followed by addition of ketone (Eq. 57). Yields were low (21-49%).



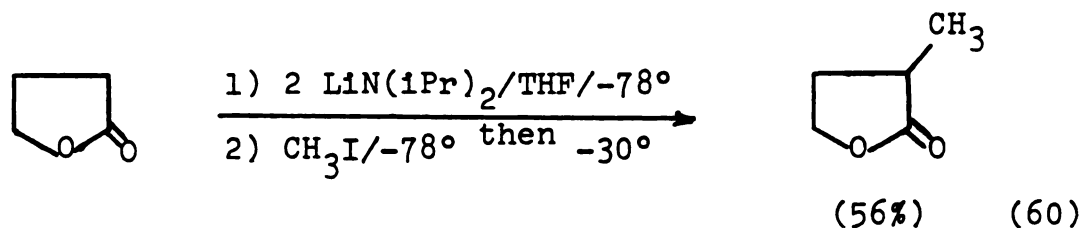
In 1977 Adams³³ reported formation of the α -butyrolactone by reaction of a trilithiosuccinamide with benzophenone (Eq. 58). One disadvantage of this method is that strong acid is required to form the lactone.



In 1977 Reutrakul reported a convenient procedure for preparing α -butyrolactones by reaction of the monoanion of diethyl succinate with ketones¹³, and α -keto esters¹⁴ (Eq. 59).

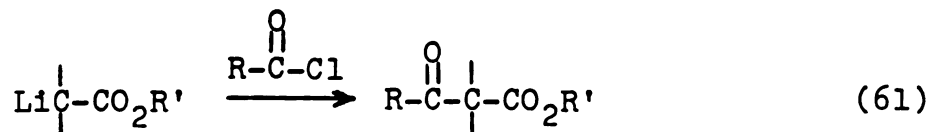


In 1972 Posner³⁴ reported a direct procedure for α -methylating γ -butyrolactones (Eq. 60). Yields for this



reaction varied with the amount of lithium diisopropylamide used. Higher yields of methylated product could be obtained by increasing the amount of amide base used; however, by-products also increased.

Simple ester enolates react with acid chlorides to form β -keto esters in moderate yields (37-81%) (Eq. 61).⁸



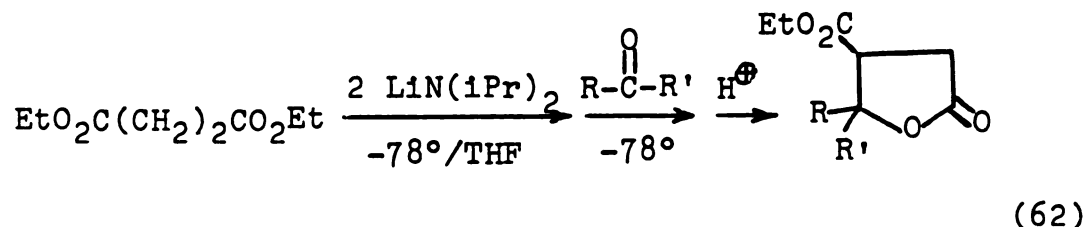
Use of different acetylating reagents can improve the yield some,³⁵ but even better results are obtained when O-silyl ketene acetals are reacted with ketenes.²³⁻²⁵

The objective of this investigation was to explore the reactions of diethyl dilithiosuccinate with various carbonyl compounds.

RESULTS

Reactions of Diethyl Dilithiosuccinate with Ketones and Aldehydes

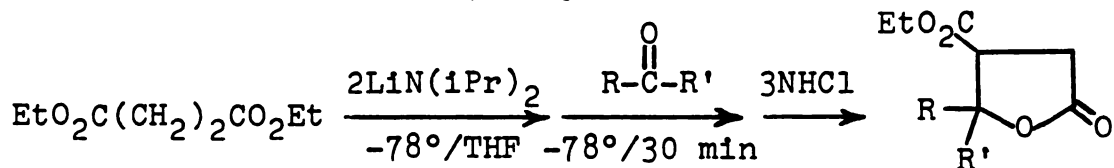
Diethyl dilithiosuccinate was prepared as described in Chapter 1. Dropwise addition of ketones or aldehydes to the THF solution at -78° produced high yields of the corresponding γ -butyrolactones (Eq. 62) (Table 8).

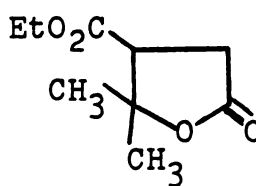
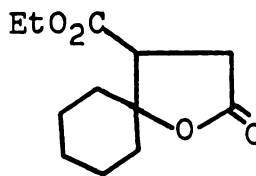
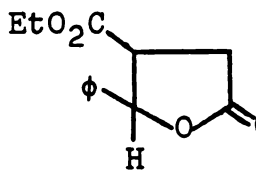
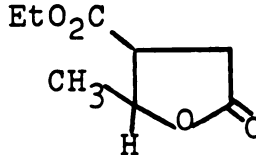


These reactions were complete within 30 minutes and were quenched with 3N hydrochloric acid. All products were identified using proton NMR and mass spectrometry.

Alkylation of α -Metalated- γ -butyrolactones

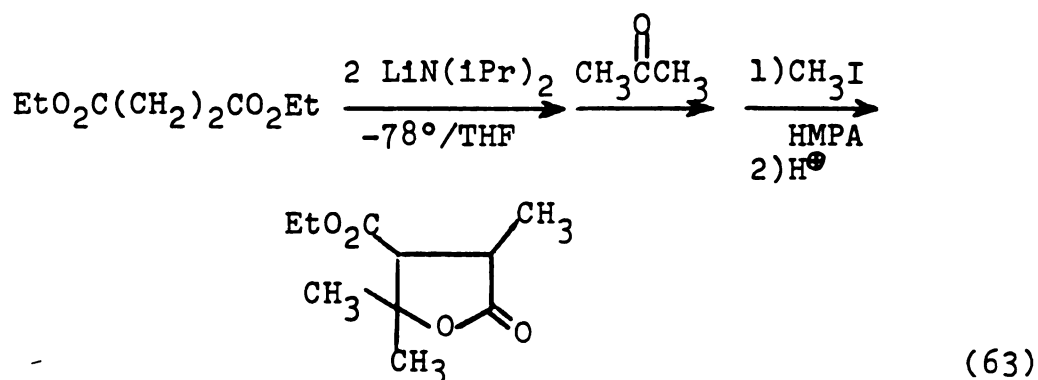
Reaction of diethyl dilithiosuccinate with one equivalent of ketone at -78° rapidly formed γ -butyrolactone in high yield. Addition of one equivalent of methyl iodide

Table 8. Formation of γ -Butyrolactones.

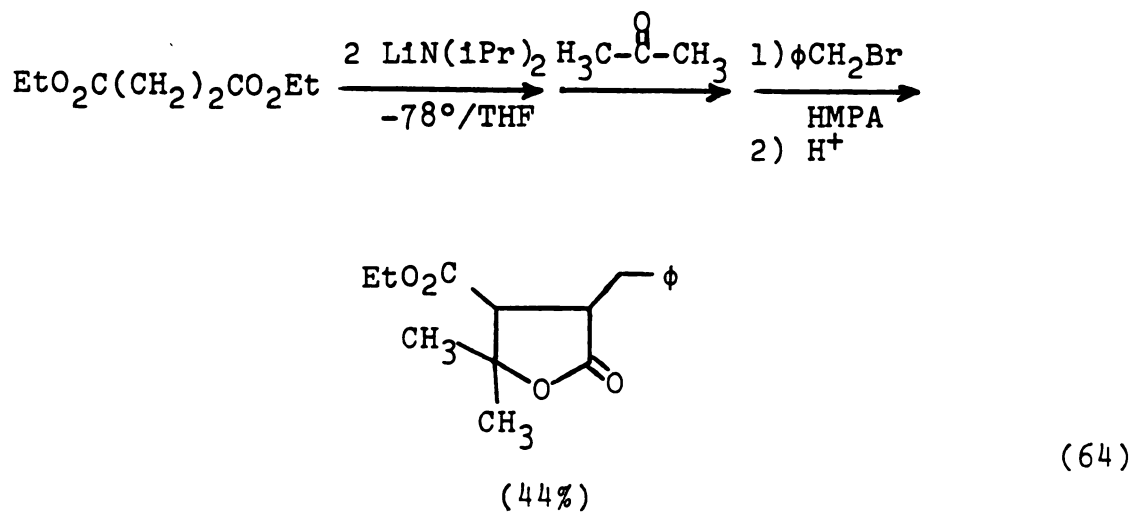
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$	Product	% Yield ^a
acetone		90
cyclohexanone		78
benzaldehyde		55
acetaldehyde		48

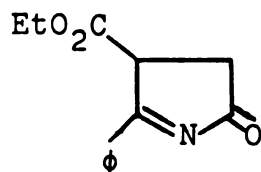
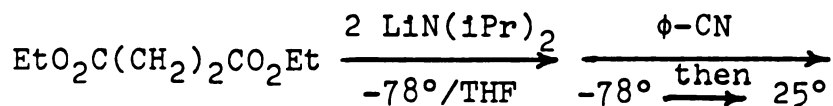
^aYields were determined by glpc analysis.

formed the α -methylated- γ -butyrolactone (Eq. 63). Due to similar physical properties, separation of pure α -methylated- γ -butyrolactone from non-methylated- γ -butyrolactone was not possible. Glpc analysis showed two partially resolved peaks. The larger peak was assumed to be α -methylated- γ -butyrolactone ($\sim 45\%$ yield) and the smaller peak, slightly higher retention time, had the same retention time as the non-methylated- γ -butyrolactone ($\sim 25\%$ yield).



Addition of one equivalent of benzyl bromide formed the α -benzylated- γ -butyrolactone in moderate yield (Eq. 64).



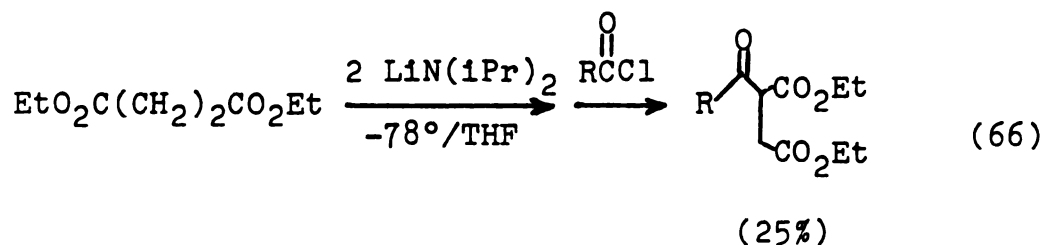


(0%)

(65)

Reaction of Diethyl Dilithiosuccinate with Acid Chlorides

Reaction of diethyl dilithiosuccinate with one equivalent of acid chloride formed a small amount (25%) of the β -keto ester (Eq. 66). Both benzoyl and acetyl chlorides

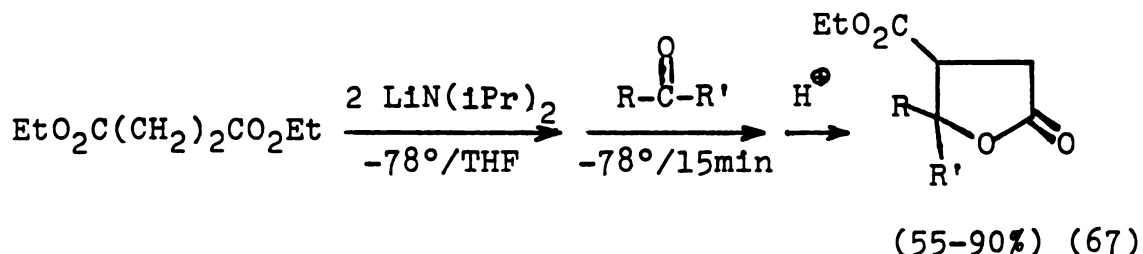


failed to give good yields of desired products despite several attempts at various reaction conditions. Perhaps O-acetylation and/or condensation are competing processes. Reaction of diethyl lithiosuccinate with nitriles or acid chlorides would not be synthetically useful.

DISCUSSION

Reactions of Diethyl Dilithiosuccinate with Ketones and Aldehydes

The addition of diethyl succinate to a solution of tetrahydrofuran containing two equivalents of lithium diisopropylamide at -78° forms diethyl dilithiosuccinate quantitatively. Reaction of diethyl dilithiosuccinate with aldehydes or ketones forms γ -butyrolactones in high yields (67).

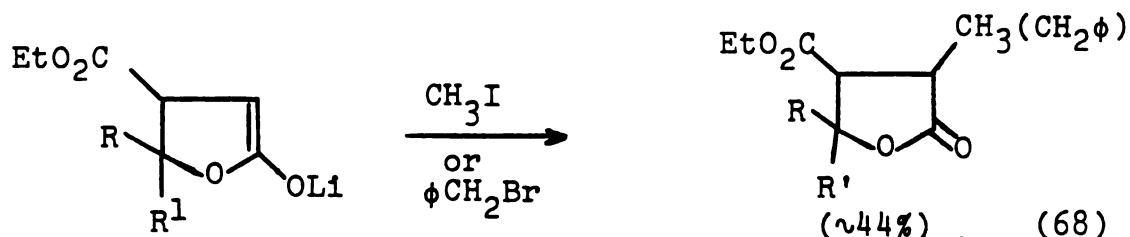


The reaction (Eq. 61) is essentially the same as Reutra-kul reported in 1977.¹³ One major difference is that he claimed preparation of the mono-enolate of diethyl succinate by reaction of diethyl succinate with two equivalents of lithium diisopropylamide. This study in Chapter 1 and 2 established that the mono-enolate of diethyl succinate does not form by direct proton abstraction as efficiently as does the di-enolate. Actually the di-enolate of diethyl succinate must be reacting with ketones to form the γ -butyrolactone.

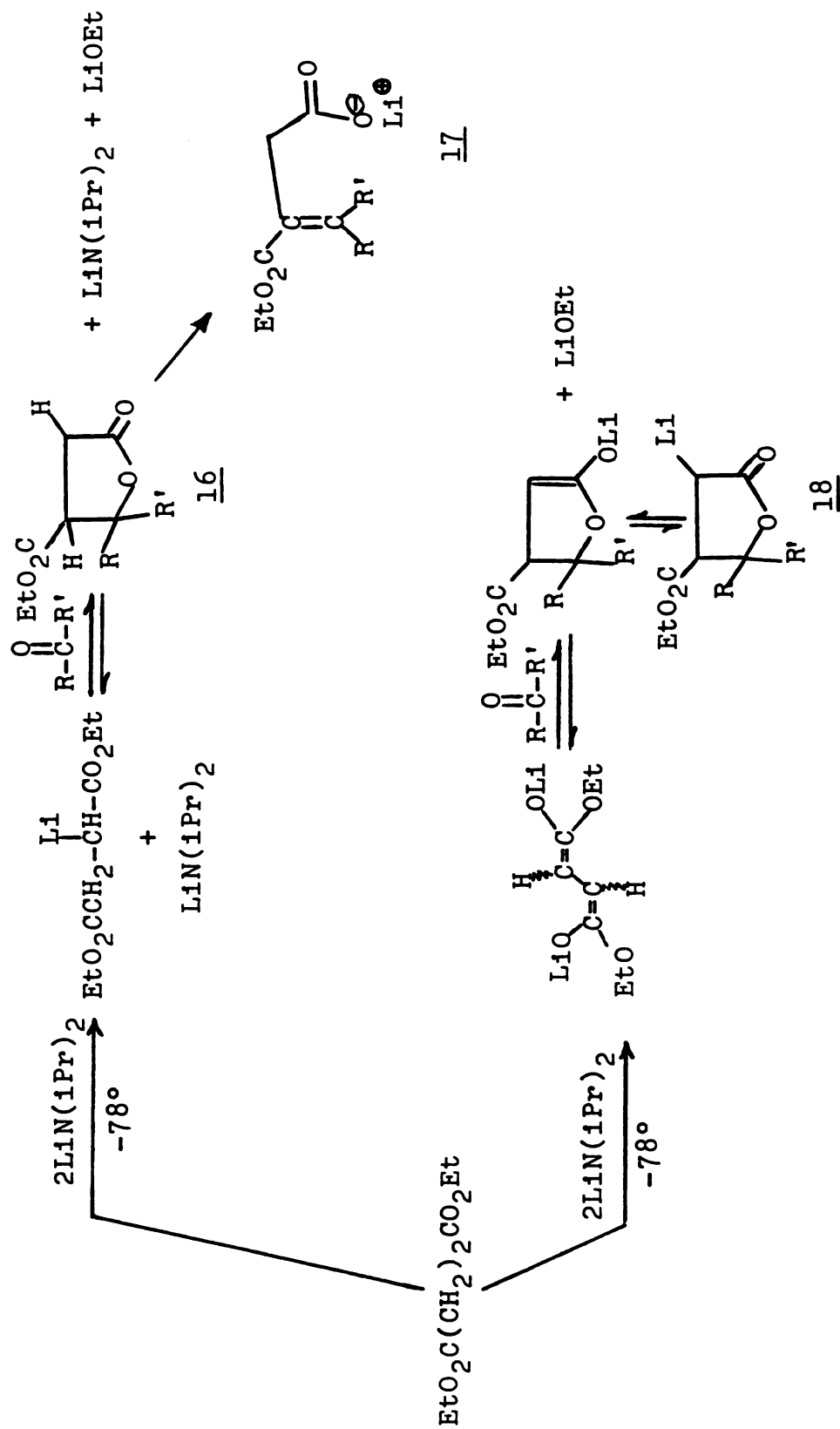
A comparison of the two different reaction schemes to form γ -butyrolactone is listed (Figure 13). If the non-melated γ -butyrolactone 16 were formed in the reaction, one equivalent of lithium diisopropylamide would still be present in solution. It is highly probable that proton abstraction by the lithium diisopropylamide would occur to form the ring opened product 17. This provides additional evidence that the intermediate for this reaction must be the α -metalated- γ -butyrolactone 18 which could be formed directly by reaction of diethyl dilithiosuccinate with a ketone (Figure 13).

Alkylation of α -Metalated- γ -Butyrolactones

Since the α -metalated- γ -butyrolactone intermediate was postulated for this reaction mechanism, attempts were made to trap the enolate by alkylation reactions (Eq. 68). Yields were unexpectedly low.

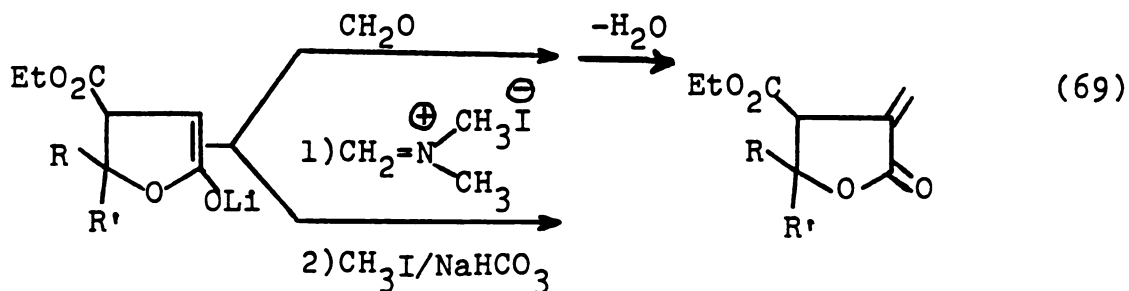


The ability to form α -methylated- γ -butyrolactones directly from diethyl succinate would be of great synthetic utility. The α -methylated- γ -butyrolactone unit is found in

Figure 13. Comparison of Reaction Schemes to form γ -Butyrolactones.

many naturally occurring eudesmanolides, guaiamanolides, germacranolides, and pseudoguaianolides.³⁴

In addition to being useful in forming α -methylated- γ -butyrolactones, this reaction scheme could be used to form α -methylene- γ -butyrolactones. Products obtained from the reaction of the α -metalated- γ -butyrolactone with formaldehyde or Eschenmoser's salt³⁶ could readily be transformed into the α -methylene- γ -butyrolactone functional unit (Eq. 69). Compounds possessing this functional unit have been found to be potent antitumor agents.³⁷



This reaction sequence was not attempted.

EXPERIMENTAL

1. Materials

Aldehydes, ketones, and nitriles were obtained commercially and distilled prior to use. Commercially available alkyl halides, chlorotrimethylsilane, and acid

chlorides were distilled and stored under argon prior to use. Diethyl succinate was distilled prior to use. nBuLi was obtained from Aldrich as 1.6M solutions and used without further purification. Diisopropylamine was obtained from Aldrich and distilled from CaH_2 prior to use. Tetrahydrofuran was commercially available and distilled from the sodium ketyl of benzophenone.

2. Formation of γ -Butyrolactones

Preparation of ethyl γ,γ -dimethyl- γ -butyrolactone- β -carboxylate will be representative. Diethyl dilithiosuccinate (50 mmoles) was prepared by procedures described in Chapter 1. After stirring at -78° for 15 minutes, 3.8 ml (50 mmoles) acetone was added dropwise. After stirring at -78° for 30 minutes, the solution was quenched with 50 ml of cold 3N hydrochloric acid. After warming to room temperature, 50 ml of pentane was added, and the layers were separated. The organic layer was washed twice with 50 ml water and dried with anhydrous potassium carbonate. Distillation at 107° (3mm) yielded 7.6 g (82%) of ethyl β -carboxylate- γ,γ -dimethyl- γ -butyrolactone.

3. Alkylation of γ -Butyrolactones

Diethyl dilithiosuccinate (50 mmoles) was prepared by procedures described in Chapter 1. After stirring at -78° for 15 minutes, 3.8 ml (50 mmoles) acetone was added

dropwise. After stirring at -78° for 30 minutes 9 ml (50 mmoles) hexamethylphosphoramide in 10 ml tetrahydrofuran was added. 6.0 ml benzyl bromide was added dropwise and the solution was allowed to warm to room temperature for 30 minutes. 50 ml Diethyl ether was added and the organic layer was washed three times with cold 3N hydrochloric acid. After drying with anhydrous potassium carbonate, distillation at $152^{\circ}/3$ mm yielded α -benzylated γ -butyrolactone. The γ -butyrolactone was then dissolved in hot pentane and then cooled to 0° to allow crystals to form 4.64 g (32%) pure α -benzyl- γ,γ -dimethyl- β -ethyl carboxylate- γ -butyrolactone was isolated, MP $69-70^{\circ}$. Glpc yield was 44%.

4. Reaction of Benzyl Nitrile with Diethyl Dilithiosuccinate

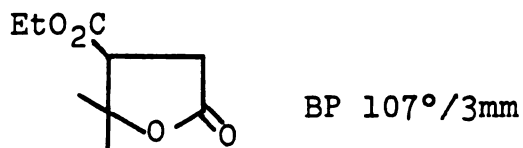
Diethyl dilithiosuccinate (5 mmoles) was prepared by procedures described in Chapter 1. After stirring at -78° for 15 minutes, 0.56 ml of benzyl nitrile (5.5 mmoles) was added dropwise. After stirring at -78° for 30 minutes, the solution was warmed to room temperature and stirred three hours. The caramel-colored solution was then cooled to -78° and quenched with 5 ml cold 3N hydrochloric acid. 5 ml Pentane was added and the layers were separated. After drying with anhydrous potassium carbonate, glpc analysis showed 99% recovered benzyl nitrile and 12%

diethyl succinate.

5. Reaction of Diethyl Dilithiosuccinate with Acid Chlorides

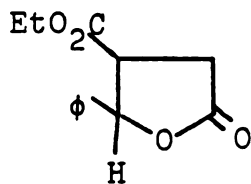
The reaction of diethyl dilithiosuccinate with acetyl chloride will be representative. Diethyl dilithiosuccinate (50 mmoles) was prepared by procedures described in Chapter 1. After stirring at -78° for 15 minutes, 3.6 ml acetyl chloride (50 mmoles) was added dropwise. After stirring at -78° for 15 minutes the solution was warmed to room temperature for 15 minutes. The yellow solution was cooled to -78° , quenched with 50 ml 3N hydrochloric acid, and warmed to room temperature. 50 ml Diethyl ether was added and the layers were separated. The water layer was washed twice with 50 ml of diethyl ether. The combined ether washes were dried over anhydrous potassium carbonate. Distillation at $118-122^{\circ}/3\text{mm}$ yielded 2.45 g (25%) of diethyl α -acetylsuccinate.

6. Product Analyses



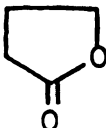
NMR(CCl₄): $\delta 4.1(\text{q}, 2\text{H})$, $\delta 3.3-2.7(\text{m}, 3\text{H})$, $\delta 2.55(\text{s}, 6\text{H})$,
 $\delta 1.15(\text{t}, 3\text{H})$.

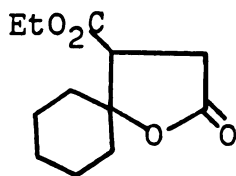
IR(CCl₄): 1785 cm^{-1} (), 1740 cm^{-1} ($-\text{CO}_2\text{R}$).



NMR(CCl₄): δ 7.05(s, 5H), δ 5.8(t, 1H), δ 4.05(q, 2H)

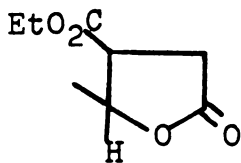
δ 3.5-3.0(m, 3H), δ 1.15(t, 3H).

IR(CCl₄): 1795 cm⁻¹ (, 1740 cm⁻¹ (-CO₂R).



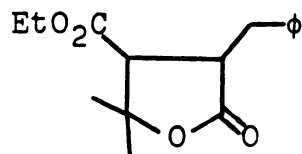
NMR(CCl₄): δ 4.00(q, 2H), δ 2.8(m, 3H), δ 1.6(m, 10H),

δ 1.2(t, 3H).



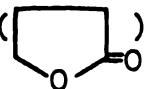
NMR(CCl₄): δ 4.05(q, 2H), δ 3.4-2.8(m, 4H), δ 1.50(d, 3H),

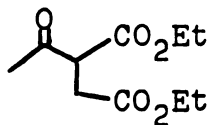
δ 1.15(t, 3H).



 MP 69-70°, BP 152°/3mm

NMR(CCl₄): δ7.1(s,5H), δ4.0(q,2H), δ3.0(m,4H), δ2.4
(s,3H), δ1.4(s,3H), δ1.2(t,3H).

IR(CCl₄): 1785 (), 1735 (CO₂R), 1200-1250(C-O).



BP 118°-122°/3mm

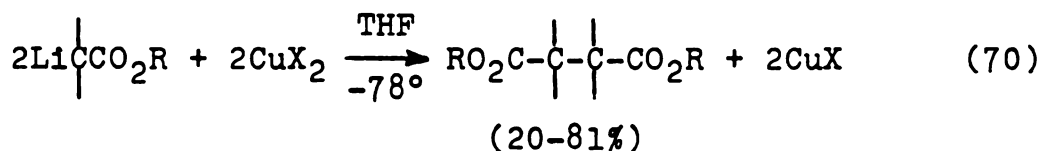
NMR(CCl₄): δ4.15(m-q,4H), δ4.0(m,1H), δ2.9(d,2H),
δ2.35(s,3H), δ1.25(m-2t,6H).

CHAPTER 5

COUPLING AND COMPLEXATION REACTIONS OF DICARBOXYLIC ESTER DI-ENOLATES

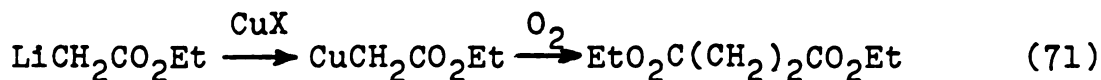
INTRODUCTION

Lithium ester enolates react with copper(II) salts to give the corresponding dimerized esters (Eq. 70).

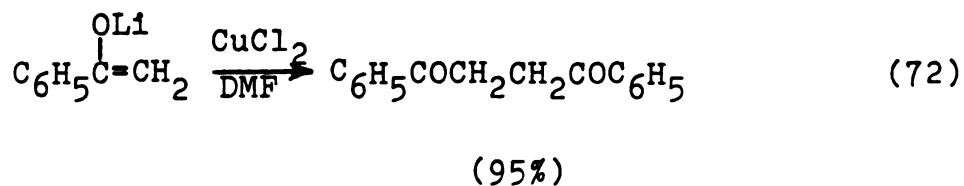


The yield of dimer decreases with increasing substitution at the alpha carbon of the ester.

Kuwajima and Doi³⁸ have reported that lithio ethyl acetate forms a stable copper(I) derivative when added to an equivalent amount of copper(I) halide. Air oxidation of this enolate gave diethyl succinate (Eq. 71).



Saegusa recently reported a dimerization of ketone enolates using copper(II) chloride in dimethylformamide (Eq. 72) and also an oxidative dehydrogenation procedure for diketones and diesters (Eq. 73).¹⁶





R=alkyl or OR'

The objective of this investigation was to study the reaction of dicarboxylic ester di-enolates with various coupling reagents. It was hoped that cyclic compounds and double bonds might be formed by coupling reactions.

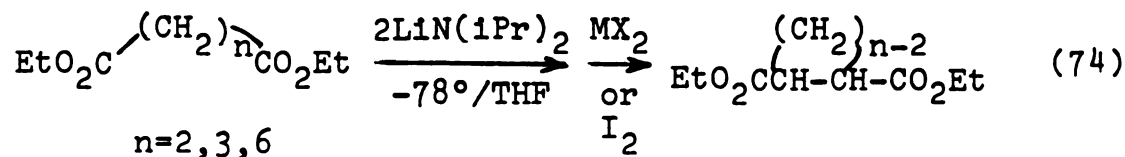
House³⁹ has shown that the chemistry of aldol condensations can be changed markedly by the choice of the metal ion. Lithium often serves as an effective chelating metal cation in non-polar solvents at low temperatures. However, addition of a divalent metal salt, such as anhydrous MgBr_2 or ZnCl_2 , can form a complex which has the ability to chelate better. This can change product distribution markedly.

The objective of this investigation was to survey a series of anhydrous metal salts to see if any might form stable solutions with diethyl dilithiosuccinate. Those metal salts which gave promising results were then studied to see if the metalated di-enolate of diethyl succinate might be formed directly from diethyl succinate. It was hoped that this might alleviate the problem of low solubility of diethyl dilithiosuccinate in tetrahydrofuran.

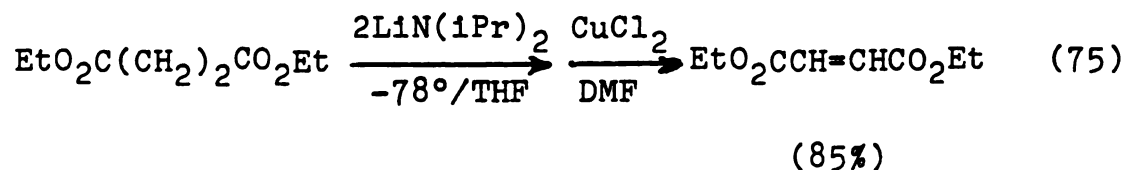
RESULTS

Coupling of Dicarboxylic Ester Di-enolates

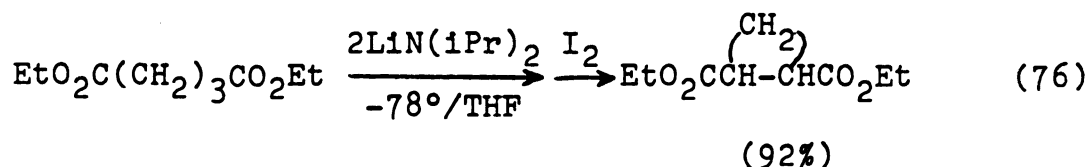
In Chapter 1 it was established that a stable solution of dicarboxylic ester di-enolate could be generated by reaction of a dicarboxylic ester with two equivalents of lithium diisopropylamide in tetrahydrofuran at -78° . Addition of metal salts or iodine to the di-enolate formed double bonds or cyclic products (Eq. 74).



Diethyl fumarate was formed in high yield by using cupric chloride in DMF to couple the di-enolate of diethyl succinate (Eq. 75).



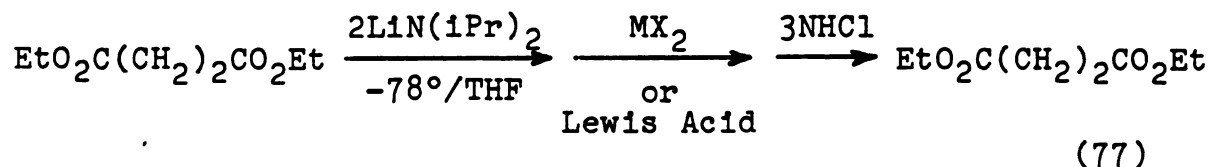
Also reaction of diethyl dilithioglutamate with iodine formed the cyclopropane ring in high yield (Eq. 76).



Other results are listed in Table 9.

Complexation Reactions

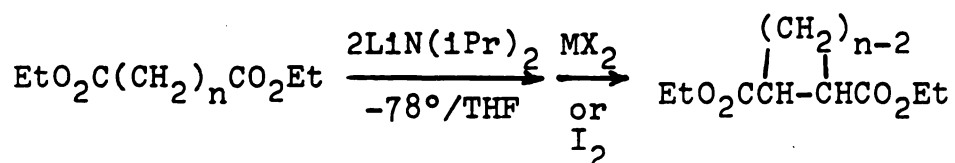
A series of anhydrous metal salts or Lewis acids were reacted with diethyl dilithiosuccinate at -78° . After 60 minutes at -78° the solutions were quenched with 3N hydrochloric acid, and followed by glpc analysis for recovered diethyl succinate (Eq. 77).

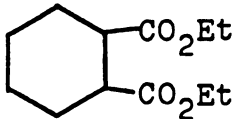
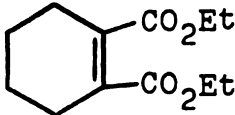
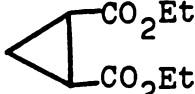
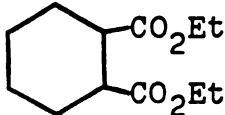


The effect of time and temperature on the recovery of diethyl succinate was also studied (Table 10).

The addition of cobalt bromide or $\text{BF}_3 \cdot \text{OEt}_2$ to diethyl dilithiosuccinate formed a stable solution. It was of interest to see if the stable solution obtained for the cobalt bromide reaction could be generated directly from the reaction of cobalt amide and diethyl succinate. Cobalt bis(diisopropylamide) was prepared by adding anhydrous

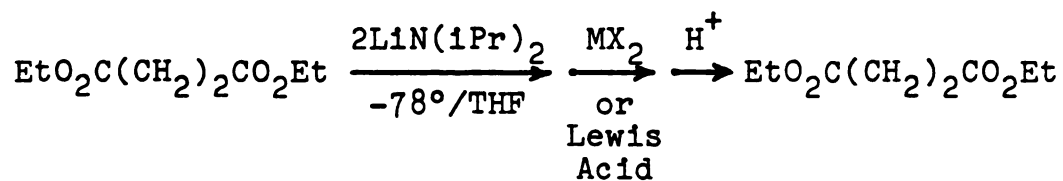
Table 9. Coupling Reactions.



Diester	MX ₂ or I ₂	Product	% Yield ^a
diethyl succinate	CuCl ₂ /DMF	EtO ₂ CCH=CHCO ₂ Et	85
	I ₂	"	12
	CuCl ₂ /DMF		89
	I ₂		46
diethyl glutarate	I ₂	 cis/trans	92
diethyl suberate	CuBr ₂		34
	TiCl ₄		33
	FeCl ₃		18
	I ₂	cis/trans	25

^aYields were determined by glpc analysis.

Table 10. Complexation Reactions.



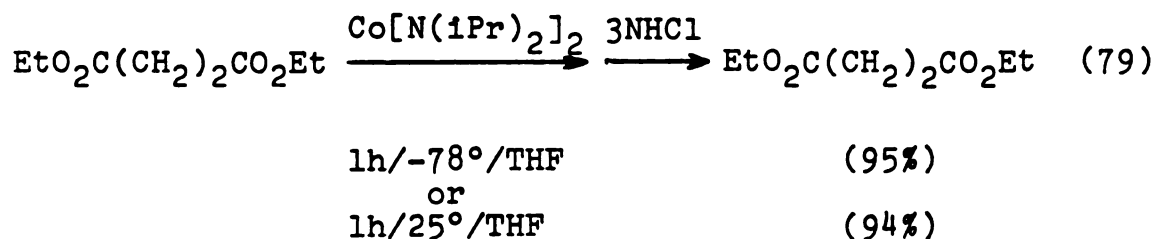
Anhydrous Metal Salt or Lewis Acid	Percent Recovered Diethyl Succinate ^a			
	1h/-78°	1h/25°	5h/25°	24h/25°
Li	100	58	5	0
MgCl ₂	85	20	0	--
CaCl ₂	did not dissolve	9	0	--
CoBr ₂	95	80	79	77
ZnI ₂	91	24	0	--
Al (O-) ₃	93	13	0	--
B(OMe) ₃	65	0	--	--
BF ₃ ·OEt ₂	86	81	80	80

^aYields were determined by glpc analysis.

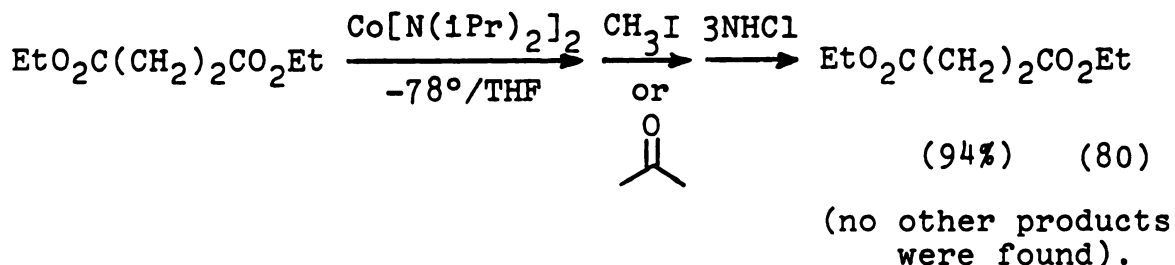
cobalt bromide to lithium diisopropylamide (Eq. 78). A black solution formed upon mixing. The cobalt diisopropylamide was not isolated or characterized.



Addition of diethyl succinate to the cobalt amide, followed by quenching with 3N hydrochloric acid, returned essentially quantitative amounts of diester (Eq. 79).



When the reaction of diethyl succinate and cobalt bromide was reacted further with methyl iodide or acetone, only diethyl succinate was formed after quenching (Eq. 80).



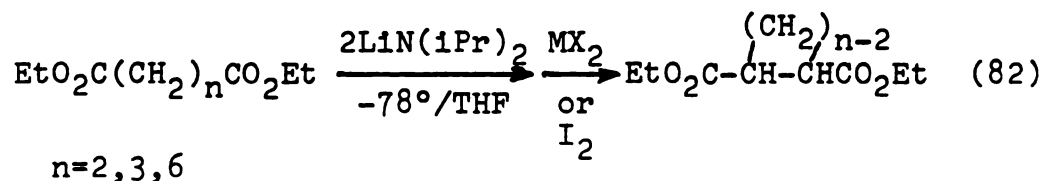
Cobalt diisopropylamide bromide was prepared by reaction of cobalt bromide with only one equivalent of diisopropylamide (Eq. 81).



DISCUSSION

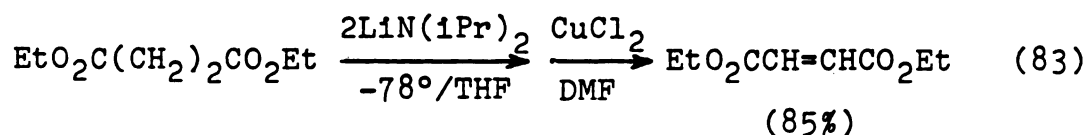
Coupling of Dicarboxylic Ester Di-enolates

Dicarboxylic ester di-enolates react with copper(II) salts or iodine to form double bonds or cyclic products, depending on the structure of the starting dicarboxylic ester (Eq. 82). Yields for this reaction were excellent,



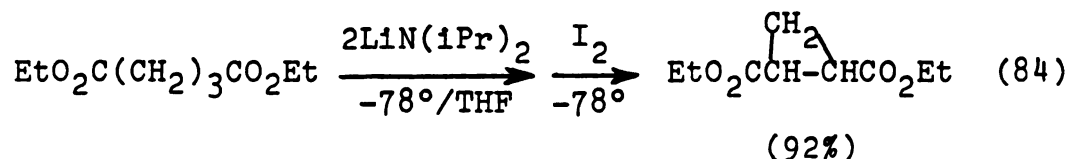
especially to form double bonds and three-membered rings.

The yield of diethyl fumarate obtained by this process (85%) (Eq. 83) exceeds that obtained by Saegusa for his oxidative dehydrogenation reaction (53%).¹⁶



The two reactions were essentially the same, except Saegusa was not forming the di-enolate completely in the more concentrated solutions with which he was working. Complete formation of diethyl dilithiosuccinate in .125M tetrahydrofuran permitted formation of the coupled product in much higher yields.

Diethyl cyclopropane dicarboxylate was prepared by a simple procedure in high yields (Eq. 84).

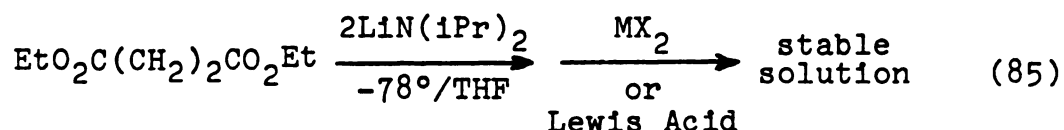


Diethyl cyclohexane dicarboxylate could not be prepared efficiently by coupling the di-enolate of diethyl suberate. Ring closure for the six-membered ring must not be as efficient, and competing condensation reactions can occur. This may account for the low yields.

Complexation Reactions

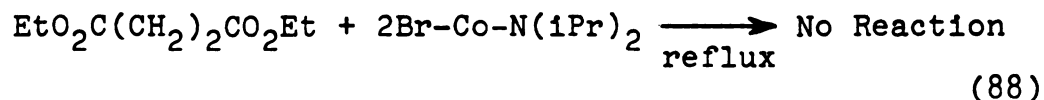
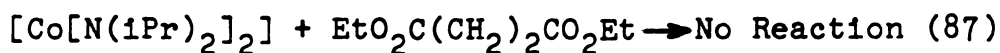
A series of anhydrous metal salts or Lewis acids were reacted with diethyl dilithiosuccinate at -78° (Eq. 85). The results (Table 10) showed that only cobalt bromide and

$\text{BF}_3 \cdot \text{OEt}_2$ formed solutions which were indefinitely stable.



It was of interest to see if the stable solution obtained for the cobalt bromide reaction could be generated directly from the reaction of cobalt amide with diethyl succinate.

Cobalt bis(diisopropylamide) was prepared by adding anhydrous cobalt bromide to two equivalents of lithium diisopropylamide at -78° (Eq. 86). Cobalt bis(diisopropylamide) was found to be unreactive toward diethyl succinate. Stable solutions were formed, but reactions with alkyl halides or ketones failed, even at reflux (Eq. 87).



It was hoped that cobalt diisopropylamide bromide might be more reactive. However, it also was too stable to enolize diethyl succinate (Eq. 88).

EXPERIMENTAL

1. Materials

Anhydrous cupric chloride, cupric bromide, ferric chloride, calcium chloride, cobalt(II) bromide, and zinc(II) iodide were obtained commercially and stored under argon. Anhydrous magnesium chloride was prepared by reaction of excess thionyl chloride with magnesium chloride·hexahydrate.⁴⁰ Titanium tetrachloride, aluminum isopropoxide, trimethyl borate, and boron trifluoride etherate were obtained commercially, distilled, and stored under argon. Diethyl succinate, glutarate, and suberate were obtained commercially and distilled. *n*-BuLi was obtained from Aldrich as 1.6M solutions and used without further purification. Diisopropylamine was obtained from Aldrich and distilled from CaH_2 prior to use. Tetrahydrofuran was commercially available and distilled from the sodium ketyl of benzophenone. Dimethylformamide was distilled.

2. Coupling of Dicarboxylic Ester Di-enolates with Iodine

The preparation of diethyl cyclopropane-1,2-dicarboxylate from diethyl glutarate will be representative. Diethyl

dilithioglutarate (50 mmoles) was prepared by procedures described in Chapter 1. Iodine 12.7 g (50 mmoles) was dissolved in tetrahydrofuran and added dropwise to the diethyl dilithioglutarate at -78° . The rust-brown iodine color disappeared instantly. Iodine was added until the rust-brown color persisted. The solution was stirred at -78° for 15 minutes and then quenched with 25 ml of 3N hydrochloric acid. Pentane was added and the layers were separated. The organic layer was washed with a saturated sodium thiosulfate solution to remove excess iodine. The colorless organic layer was dried with anhydrous potassium carbonate. Distillation at 64° (3mm) yielded 7.1 g (76%) diethyl cyclopropane-1,2-dicarboxylate.

3. Coupling of Dicarboxylic Ester Di-enolates with Cupric Chloride

The preparation of diethyl fumarate will be representative. Diethyl dilithiosuccinate (5 mmoles) was prepared in dilute tetrahydrofuran as described in Chapter 1. After stirring at -78° for 15 minutes, 10 ml dimethylformamide was added, followed by addition of 1.4 g cupric chloride. The solution was stirred at -78° for 30 minutes and then warmed to room temperature. Glpc analysis showed 85% diethyl fumarate.

4. Complexation Reactions of Diethyl Dilithiosuccinate with Metal Halides

Diethyl dilithiosuccinate (5 mmoles) was prepared by procedures described in Chapter 1. After stirring at -78° for 15 minutes, an anhydrous metal halide (5.5 mmoles) was added through a powder funnel. After stirring at varied reaction conditions, the solution was quenched with 5 ml 3N hydrochloric acid at -78° . Pentane was added. After separation the organic layer was dried with anhydrous potassium carbonate and analyzed by glpc.

5. Complexation Reactions of Diethyl Dilithiosuccinate with Lewis Acids

Diethyl dilithiosuccinate (5 mmoles) was prepared by procedures described in Chapter 1. After stirring at -78° for 15 minutes, a Lewis acid (5.5 mmoles) was added dropwise. After stirring at various reaction conditions, the solution was quenched with 5 ml 3N hydrochloric acid at -78° . Pentane was added and the solution was neutralized with saturated sodium bicarbonate. After separation the organic layer was dried with anhydrous potassium carbonate and analyzed by glpc.

6. Preparation of Cobalt(II) Bis(diisopropylamide)

Lithium diisopropylamide (10 mmoles) was prepared as described in Chapter 1. Cobalt(II) bromide was added to the dilute tetrahydrofuran solution at -78° and stirred at -78° for 15 minutes.

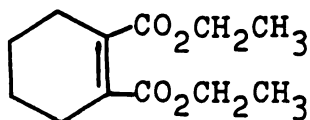
7. Reaction of Diethyl Succinate with Cobalt(II) Bis(diisopropylamide)

Cobalt(II) bis(diisopropylamide) (5 mmoles) was prepared as described above. Diethyl succinate (5 mmoles) in 5 ml tetrahydrofuran was added dropwise. Stirring at various reaction conditions, followed by quenching with acetone, methyl iodide, or acid at -78° returned by glpc analysis (94%) diethyl succinate.

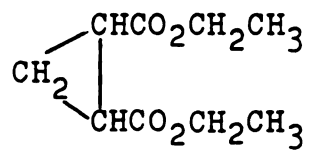
8. Product Analyses

$\text{CH}_3\text{CH}_2\text{O}_2\text{CCH}=\text{CHCO}_2\text{CH}_2\text{CH}_3$ BP $66-67^{\circ}$ (3mm) Known BP $213-15^{\circ}$

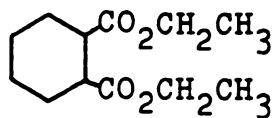
NMR(CCl_4): $\delta 6.7(\text{s}, 1.5\text{H})$, $\delta 6.0(\text{s}, 0.5\text{H})$, $\delta 4.05(\text{q}, 4\text{H})$,
 $\delta 1.15(\text{t}, 6\text{H})$.



NMR(CCl_4): $\delta 4.0(\text{q}, 4\text{H})$, $\delta 2.3(\text{m}, 4\text{H})$, $\delta 1.75(\text{m}, 4\text{H})$,
 $\delta 1.2(\text{t}, 6\text{H})$.



NMR(CCl₄): $\delta 4.05(\text{q}, 4\text{H}), \delta 2.1(\text{t}, 2\text{H}), \delta 1.3(\text{t}, 2\text{H}),$
 $\delta 1.1(\text{t}, 6\text{H}).$



BP 120° (3mm)

NMR(CCl₄): $\delta 4.0(\text{q}, 4\text{H}), \delta 2.9(\text{m}, 2\text{H}), \delta 1.9(\text{m}, 4\text{H}),$
 $\delta 1.5(\text{m}, 4\text{H}), \delta 1.1(\text{t}, 6\text{H}).$

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