THE SYNTHESIS OF ESTERS OF DI TERT BUTYLACETIC ACID AND THEIR ATTEMPTED REACTION WITH STRONG BASES

By

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ABSTRACT

THE SYNTHESIS OF ESTERS OF DI-TERT-BUTYLACETIC ACID AND THEIR ATTEMPTED REACTION WITH STRONG BASES

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Di-t-butylketene prepared by a modified version of a method developed by Newman, was converted into the esters of di-t-butylacetic acid, by reaction with various alcohols in the presence of Lewis acids.

An attempt was made to prepare the enolate conjugate base of these esters to determine if decomposition to di-t-butylketene occurs. Though ester enolates are stable indefinitely at -78°, upon warming they decompose to β-keto esters, there is evidence that this decomposition occurs through a ketene intermediate. Surprisingly, di-t-butylacetic acid esters were found to be inert to LDA.

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TABLE OF CONTENTS

Chapter		Page
LIST OF TABLES		v
INTRODUCTION		1
RESULTS		8
I.	Synthesis of Di-t-butylketene	8
II.	Preparation of the Ester Series	10
III.	Reactions of Esters with Bases	11
DISCUSSION		14
EXPERIMENTAL		16
I.	Materials	16
II.	Preparation of 2,2,4,4-Tetramethyl-3-pentanone (II)	16
III.	Preparation of 1,1-Di-t-butylethanol (III)	17
IV.	Preparation of 1,1-Di-t-butylethylene (IV)	18
V.	Preparation of 2,2-Di-t-butylethanol (V)	18
VI.	Preparation of Di-t-butylacetic acid (VI)	19
VII.	Preparation of Di-t-butylacetyl chloride (VII)	20
VIII.	Preparation of Di-t-butylketene (VIII)	20
IX.	Preparation of Ethyl Di-t-butylacetate (IX)	20

Chapter Page

X. Preparation of t-Butyl Di-t-butylacetate (X). 21

XI. Reactions of Esters with Strong Bases 21

A. Materials. 21

B. Apparatus and General Procedure. 21

C. Mixture of IX and LDA. 22

D. Mixture of X and LDA 23

E. ^{1}H NMR of 1:1 Mixture of X and LDA. 24

F. Mixture of X and n-Butyllithium 24

G. Mixture of X and Methyllithium. 24

H. Mixture of X and Sodium Amide. 25

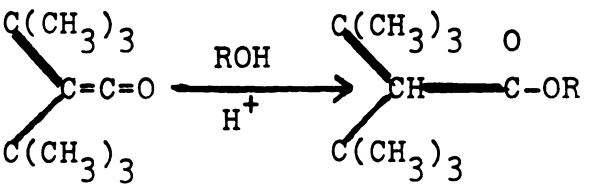
BIBLIOGRAPHY. 26

LIST OF TABLES

Table		Page
I	Results of Quenching 1:1 Mixtures of X and Base.	13
II	Results of Quenching 1:1 Mixtures of IX and Base	23

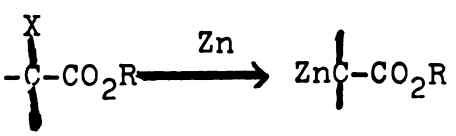
INTRODUCTION

In this thesis we will present a method for the synthesis of di-t-butylketene by a modified version of the procedure developed by Newman (13). We will also describe reactions of this ketene with various alcohols in the presence of Lewis acids, which lead to esters of di-t-butylacetic acid.



Our purpose in making these esters is to prepare and study their enolate conjugate bases under various conditions to determine whether decomposition to di-t-butylketene occurs.

There are two methods by which ester enolates may be prepared, one method utilizes the action of zinc metal on α-haloesters (Reformatsky reaction) (1)



However, the zinc enolates are unstable at the temperatures required for their formation and their usefulness depends on the availability of the corresponding α-haloesters. The second method consists of treating the ester with a relatively strong (pka of an ester ≅ 25) (2) organic base.

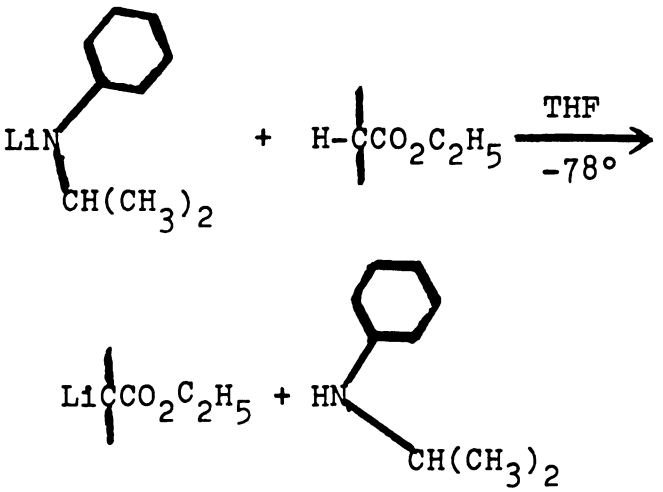
In an early study of ester enolates Hauser (3) used sodium triphenylmethane as a base, and observed reaction of the enolates with acid chlorides. He later developed (4) an alternative procedure in which enolates of t-butylesters were generated in liquid ammonia using lithium amide as a base; such enolates proved to be stable at -37°.

Dialkylamide salts are strong (pka of amine >34) (2) soluble, nonnucleophilic bases capable of generating ester enolates quantitatively at -78°. At this temperature the resulting enolates are indefinitely stable.

Disilyl analogues of dialkylamide bases can also be used to prepare enolates of esters. Sodium bis(trimethylsilyl)amide generated the enolate of ethyl acetate (5), which upon reaction with trimethylchlorosilane, produced a mixture of ethyl trimethylsilylacetate (22.3%) and O-trimethylsilyl-O-ethyl ketene acetal (13.7%). Lithium bis(trimethylsilyl)amide, formed in hexane by the reaction of the amine with a commercial butyllithium solution, generated the enolate quantitatively at -78° in

tetrahydrofuran (6). However attempts to use this procedure to prepare other ester enolates were unsuccessful.

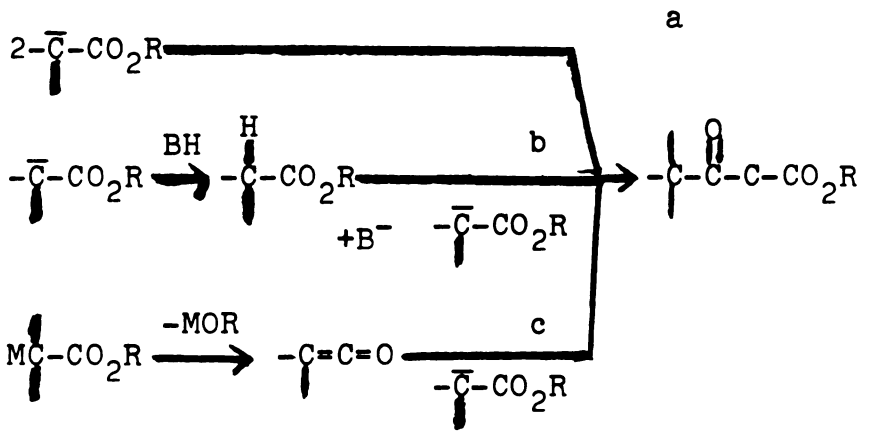
Lithium isopropylcyclohexylamide or lithium diisopropylamide, react with a wide variety of esters at low temperatures in tetrahydrofuran to produce quantitatively solutions of the corresponding lithium ester enolates (7)



This represented the first general method for the preparation of stable solutions of ester enolates. In a later study lithio t-butyl acetate was obtained in quantitative yield as a stable white solid free of amine (7) using lithium diisopropylamide in hexane and evaporating off the solvent and amine.

Ester enolates, unlike ketone enolates, are unstable upon warming to room temperature. The resulting decomposition to β-keto esters may occur by three pathways: (a) direct coupling of the ester enolate with a second mole of enolate; (b) removal of a proton from the solvent or

amine and condensation of the ester thus formed with another mole of enolate, a rapid process (8); (c) elimination of metal alkoxide and reaction of the resulting ketene with a second mole of enolate.



A study of the kinetic behavior of the decomposition of ester enolates (9) provided evidence against direct enolate coupling. Thus solutions of lithio t-butyl acetate, lithio ethyl isobutyrate, and lithio ethyl hexanoate showed first order decomposition kinetics. In the case of mechanism (b) it was discovered (10) that solutions of lithio t-butyl acetate, which are prepared free of amine, also formed condensation products at room temperature

$$2LiCH_2CO_2C(CH_3)_3 \xrightarrow[THF,\ 1h]{25^\circ C} \xrightarrow{H_3O^+} CH_3COCH_2CO_2C(CH_3)_3$$

(90% GLC)

$$+ (CH_3)_3COH$$

The ketene pathway to β-keto ester formation was suggested by Vaughan (11) for the self-condensation of the reagent prepared from ethyl α-bromoisobutyrate and zinc metal

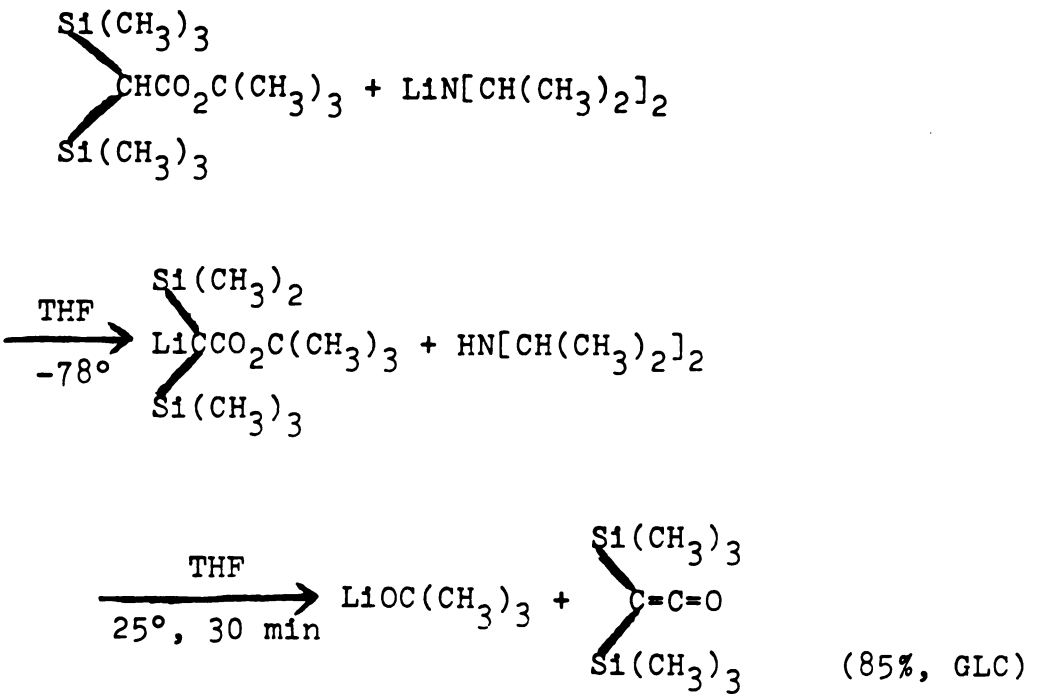
$$BrZnC(CH_3)_2CO_2C_2H_5 \rightarrow (CH_3)_2C{=}C{=}O + BrZnOC_2H_5$$

$$(CH_3)_2C{=}C{=}O + BrZnC(CH_3)_2CO_2C_2H_5 \rightarrow$$

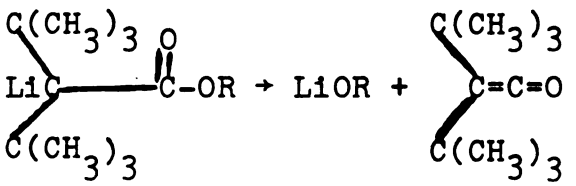
$$\xrightarrow{H_3O^+} (CH_3)_2CHCOC(CH_3)_2CO_2C_2H_5$$

Ketene intermediates have also been proposed for the E_1CB mechanism of hydrolysis of malonic and β-keto esters (12).

The first decomposition of an ester enolate leading to the isolation of a ketene (10) involved the enolate of t-butyl 2,2-bis(trimethylsilyl)acetate, prepared by the addition of the ester to an equivalent amount of lithium diisopropylamide at -78°. Warming solutions of the enolate to room temperatures gave the relatively stable bis(trimethylsilyl)ketene. Steric hindrance by the bulky trimethylsilyl groupings favored isolation of ketene rather than condensation products.



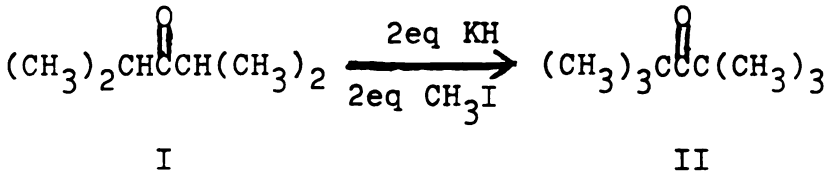
Ketene intermediates in the decomposition of lithium ester enolates can be isolated (as by the example of bis(trimethylsilyl)ketene) provided the reaction with alkoxide or with ester enolate can be prevented. Increased substitution at the methylene carbon of a ketene has been shown to result in unreactive ketenes. Di-t-butylketene is known to be remarkably unreactive (13), hence the esters of di-t-butylacetic acid were chosen for this study. It was desired to know if ketene is formed by loss of lithium alkoxide from such ester enolates and if so, how the rate of decomposition is affected by the structure of the alkoxide leaving group.


C(CH3)3
O
LiC
C-OR
LiOR +
C(CH3)3
C=C=O
C(CH3)3
C(CH3)3

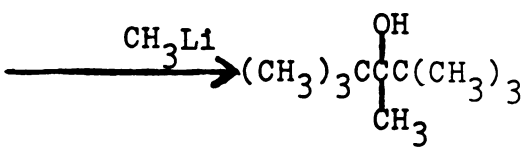
RESULTS

I. Synthesis of Di-t-butylketene

Di-t-butylketene was prepared by a modified version of the procedure developed by Newman (13) for synthesizing highly branched aliphatic compounds. The steps in the synthesis are outlined as follows:



I II



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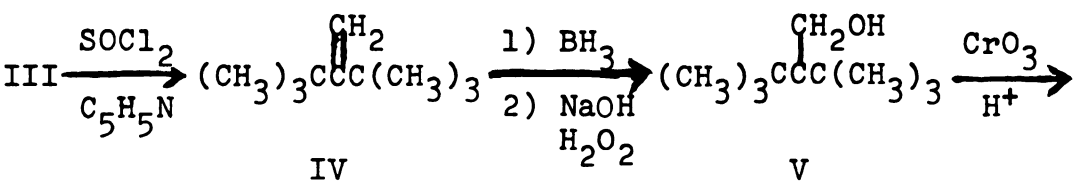
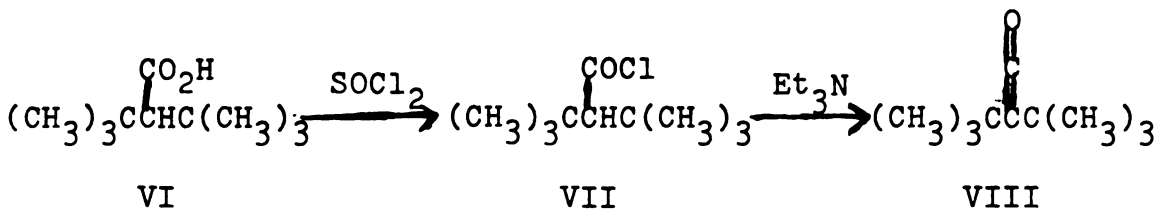


IV V

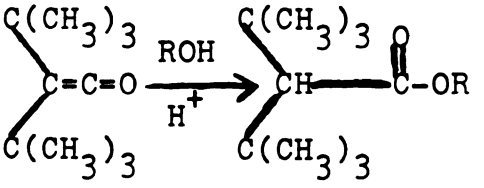


VI VII VIII

Permethylation of diisopropyl ketone I was achieved by treatment of I with a twofold excess of potassium hydride and methyl iodide. This procedure (14) gave a greater yield (60-70%) and provides a simpler route to hexamethylacetone II than the classical method used by Newman. Treatment of II with excess methyl lithium gave 2,2,3,4,4-pentamethyl-3-pentanol III in 71% yield. This was dehydrated with thionyl chloride and pyridine to the olefin 1,1-di-t-butylethylene IV in 86% yield. The olefin was then converted into 2,2-di-t-butylethanol V in 60-70% yield by treatment with diborane (prepared by treating sodium borohydride with borontrifluoride etherate instead of aluminum chloride as done by Newman), followed by oxidation with alkaline hydrogen peroxide and hydrolysis. Oxidation of V with chromium trioxide in aqueous acetic acid containing sulfuric acid gave di-t-butylacetic acid VI in 76% yield. This acid was converted to the acid chloride VII in 70-90% yield by the action of excess thionyl chloride. A better procedure for elimination of the acid chloride VII to ketene VIII than that described by Newman involved the use of triethylamine in place of sodium amide. This gave a greater yield of di-t-butylketene than that obtained by Newman, as well as providing a much simpler procedure.

II. Preparation of the Ester Series

The esters of di-t-butylacetic acid were prepared by addition of the appropriate alcohols to VIII in the presence of a Lewis acid catalyst.



This provides a simpler method of preparation of the esters than the more conventional methods such as esterification of the acid VI with the alcohols in the presence of acid catalyst, or acylation of the alcohols by the acid chloride. Such reactions were expected to be more difficult to effect, since in each case a tetrahedral intermediate would be generated. Such intermediates would be disfavored by branching at the α and β carbon atoms (15). Also, when R is tertiary, carbonium ion formation and elimination predominate under these conditions.

Ethyl Di-t-butylacetate IX, was prepared by adding VIII to a stirred solution of ethanol and a drop of sulfuric acid. Distillation (22 mm, 90°) gave IX in greater than 90% yield.

t-Butyl-Di-t-butylacetate X, could not be prepared in the same way as IX. Instead borontrifluoride etherate was added to a solution of VIII and tertiary butyl alcohol

in methylene chloride, and after a vigorous reaction occurred, GLC analysis showed the ketene peak had disappeared and a new peak had appeared. This reaction required only 3-5 minutes, and distillation (0.3 mm, 61°) gave X in quantitative yield.

III. Reactions of Esters with Bases

In a typical experiment one equivalent of ethyl ester IX was added to a stirred solution of lithium diisopropylamide LDA in tetrahydrofuran at -78°. This solution was stirred for 15 minutes, then warmed to room temperature and stirred an additional 5 minutes. After quenching with water, pentane and an internal standard (tridecane) were added and the mixture was dried over anhydrous potassium carbonate. Analysis of the supernatant liquid showed a 93-95% recovery of IX. When the 1:1 mixtures of IX and LDA was stirred for longer periods (1 to 8 hours) quenching resulted in a 85-95% recovery of IX. If the mixture was refluxed for an hour, 80% recovery of IX was observed. When the same experiments were tried with the t-butyl ester X similar results were obtained.

These results presented two possibilities: One, the enolates of both esters are formed and are stable with respect to decomposition to ketene. Two, the enolates of the esters are not formed in the presence of LDA.

To determine whether the enolate anion was formed, the ^{1}H NMR of a 1:1 mixture of LDA and X in benzene was taken and found to be identical to the ^{1}H NMR of the reactants.

Further experiments involving 1:1 mixtures of X and other bases were conducted, the results are given in Table I.

Table I. Results of Quenching 1:1 Mixtures of X and Base.

Base (Solvent)	Reaction Period (Temperature)	Recovered Ester, %[a]
LDA (THF)	1 h (reflux)	90-96
LDA/TMEDA[b] (THF)[c]	2 d (reflux)	80
n-butyllithium (THF)	5 min (40°)	100
n-butyllithium/TMEDA (THF)	5 min (40°)	100
methyllium/TMEDA (THF)	30 min (40-50°)	94
methyllium/TMEDA (pentane)	10 h (25°)	87
sodium amide (Et_2O)[d]	9 h (25°)	91

[a]Determined by GLC analysis.

[b]N,N,N',N'-tetramethylethylenediamine.

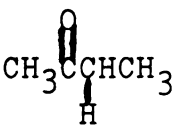
[c]The ratio of base to X was 5:1.

[d]The ratio of base to X was approximately 100:1.

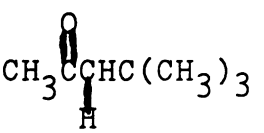
DISCUSSION

The exter X proved to be inert to LDA as opposed to its silyl analogue, t-butyl 2,2-bis(trimethylsilyl)acetate. This is a surprising result and X represents the only known ester to be inert to LDA.

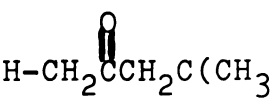
Steric hindrance to the approach of base is probably the major cause of the inactivity of X. The importance of such steric effects can be noted by comparing the relative rates of base catalyzed deuteration (16) of the CH_2 group in 2-butanone with the more hindered CH_2 group in 4,4-dimethyl-2-pentanone.



krel = 41.5



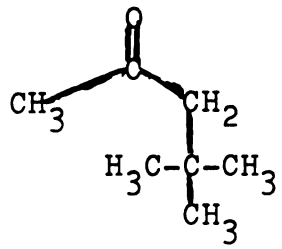
krel = 0.45



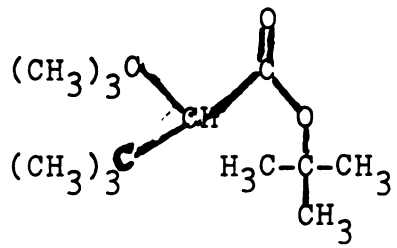
krel = 5.1

This steric hindrance effect should be less in the silyl analogue due to the longer bond length of the Si-C bond (1.87 Å) as opposed to the C-C bond (1.54 Å) (17).

The rather slow rate of exchange at the CH_3 group of 4,4-dimethyl-2-pentanone may also reflect a steric factor arising from the bulky nature of the neopentyl group (16).



The t-butoxy group in ester X may play a similar role.



The enhanced acidity of a Si-C-H grouping compared with C-C-H may also be an important factor in the different reactivity of t-butyl 2,2-bis(trimethylsilyl)acetate and t-butyl di-t-butylacetate with strong bases. Such acidity is due to the vacant d-orbitals of silicon which are of suitable energy for back bonding with a filled 2p orbital on the adjacent carbon atom, thus stabilizing an adjacent carbanion (18).

EXPERIMENTAL

I. Materials

All reagents were obtained commercially from Aldrich Chemical Company, Inc. unless otherwise stated.

Diisopropyl ketone was purified by simple distillation and stored under argon over molecular sieves. Methyl iodide was distilled and stored in a dark bottle over copper wire. Potassium hydride was obtained commercially from Ventron Corp. as a 23.6% in mineral oil dispersion. The dispersion was standardized by measuring the gas given off when a sample of known volume was treated with water. Methyllithium was obtained as a 1.6M solution in ether and used as received. Tetrahydrofuran was dried over sodium benzophenone ketyl, distilled and stored under argon over molecular sieves. Diglyme was purified by distillation from lithium aluminum hydride under reduced pressure and stored under argon over molecular sieves.

II. Preparation of 2,2,4,4-Tetramethyl-3-pentanone (II)

A 5000 mL three neck round bottom flask was equipped with a mechanical stirrer, dry ice condenser, and mercury bubbler. The system was heated in an oven and flushed

with argon. The flask was charged with 732 ml (4048 mmol) of potassium hydride in mineral oil, and immersed in an ice water bath. THF (1000 ml) was added followed by dropwise addition of 285-mL (2024-mmol) of diisopropyl ketone over a 4 h period. Methyl iodide 126 ml (4048 mmol) was added dropwise over a 3 h period. The reaction mixture was refluxed for 1 h, then immersed in an ice water bath. A second addition of methyl iodide 126 ml (4048 mmol) was added dropwise over a 3 h period. The mixture was allowed to stir for 1 h and the unreacted potassium hydride quenched cautiously with water. The aqueous layer was extracted with ether and the combined organic layers distilled to give 173 g, 60% yield, of 2,2,4,4-tetramethyl-3-pentanone; bp 154° (760 mm); ^{1}H NMR (CCl_4, internal Me_4Si) δ1.2 (s); IR (neat) 1670 cm^{-1}.

III. Preparation of 1,1-Di-t-butylethanol (III)

A 3000 ml three neck round bottom flask was equipped with a mechanical stirrer, condenser, and mercury bubbler. The system was heated in an oven and flushed with argon. The flask was charged with 678 ml of 1.6M methyllithium in ether, to this was added 140 ml (810 mmol) of II. After refluxing for 1 h excess methyllithium was destroyed carefully with water. The aqueous layer was extracted with ether and the ether removed from the combined organic layers under reduced pressure leaving behind an oil.

Crystallization at -78° from pentane gave 181.5 g, 76% yield, of 1,1-di-t-butylethanol: mp 42-44°; ^{1}H NMR (CCl_4, internal Me_4Si) δ1.05 (s, 18H), δ1.13 (s, 3H).

IV. Preparation of 1,1-Di-t-butylethylene (IV) (13)

A 1000 ml three neck round bottom flask was equipped with a mechanical stirrer. To this flask was added a solution of 131 g of III in 500 ml of pure dry pyridine. Thionyl chloride (90 ml) purified by distillation from raw linseed oil, was added dropwise so that the temperature never exceeded 20° during the addition. The liquid phase was passed through a filter to remove pyridine hydrochloride. Distillation from potassium hydroxide pellets produced a cloudy liquid which was dried over calcium hydride to yield 88 g, 86% of 1,1-di-t-butylethylene: bp 150° (760mm); ^{1}H NMR (CCl_4, internal Me_4Si) δ1.28 (s, 18H), δ4.95 (s, 2H).

V. Preparation of 2,2-Di-t-butylethanol (V)

The apparatus for this preparation consisted of a 2000 ml three neck round bottom flask, which was equipped with a condenser and mechanical stirrer. Boron trifluoride etherate (80 ml) was added dropwise to a slurry composed of 19.1 g of sodium borohydride, 106.3 g of IV and 135 ml of diglyme maintained at 20° by a water bath. After

stirring for 1 h at room temperature and then overnight on a steam bath, most of the diglyme was removed under reduced pressure. Ethanol (100 ml) was added followed by dropwise addition of 220 ml of 6N sodium hydroxide. 215 ml of 30% hydrogen peroxide was added at a rate to maintain gentle reflux. Excess peroxide was destroyed by careful addition of a sodium bisulfite solution. Extraction with pentane and removal of solvent under reduced pressure, followed by crystallization from pentane at -78° gave 96 g, 70% yield, of 2,2-di-t-butylethanol: mp 54-55°; ^{1}H NMR (CCl_4, external Me_4Si) δ1.05 (s, 18H), δ1.32 (broad s, 1H), δ3.61 (d,2H).

VI. Preparation of Di-t-butylacetic acid (VI)

To a stirred solution of 63.3 g of V in 450 ml of sulfuric-acetic acid solution (made by adding 50 ml of concentrated sulfuric acid to 50 ml of water and diluting to 450 ml with acetic acid) was added 250 ml of chromic acid solution (made by dissolving 106.6 g of chromic oxide in 105 ml of water and diluting to 240 ml with acetic acid, during 1.5 h. After standing overnight and heating on a steam bath for 1 h, 200 ml of water was added and the organic product taken up in methylene chloride. Addition of sodium hydroxide solution precipitated out the sodium salt of the acid, which was then filtered off. Acidification

gave 52.4 g, 76% yield, of di-t-butylacetic acid: ^{1}H NMR (CCl_4, internal Me_4Si) δ1.13 (s, 18H), δ2.1 (s, 1H), δ10.2 (s, 1HO.

VII. Preparation of Di-t-butylacetyl Chloride (VII)

A mixture of 52.4 g of VI and excess thionyl chloride was refluxed for 1 h. Distillation at 105-110° (50mm) gave 32 g, 55% of di-t-butylacetyl chloride: IR (neat) 1780 cm^{-1} 2075 cm^{-1}.

VIII. Preparation of Di-t-butylketene (VIII)

50 ml of triethylamine was added to a stirred solution of 32 g of acid chloride and 100 ml of methylene chloride. The solution was allowed to stir overnight and triethylammonium chloride was removed by filtration. Distillation 50-53° (26mm) gave 18 g, 68% of di-t-butyl-ketene: ^{1}H NMR (CCl_4, internal Me_4Si) δ1.18 (s); IR (neat) 2075 cm^{-1}.

IX. Preparation of Ethyl Di-t-butylacetate (IX)

3.3 ml of VIII was added to a large excess of ethanol and a drop of concentrated sulfuric acid. The mixture was stirred overnight, distillation 90° (22mm) gave 3.2 g, 90% yield, of ethyl di-t-butylacetate: ^{1}H NMR (CCl_4, external Me_4Si) δ4.0 (q, 2H), δ2.15 (s, 1H), δ1.33 (m, 3H), δ1.12 (s, 18H); IR (neat) 1740 cm^{-1}; m/e 201, base peak 57.

X. Preparation of t-Butyl Di-t-butylacetate (X)

To a mixture composed of 9.3 ml of VIII, 20 ml of methylene chloride and 10 ml of t-butyl alcohol, was added 1.23 ml of boron trifluoride etherate. The reaction was vigorous and rapid, requiring approximately 5 min, distillation 61° (0.3 mm) gave 11.4 g, 90% yield, of di-t-butylacetate: ^{1}H NMR (CCl_4, internal Me_4Si) δ1.9 (s, 1H), δ1.4 (s, 9H), δ1.1 (s, 18H); IR (neat) 1740 cm^{-1}; base peak 57.

XI. Reaction of Esters with Strong Bases

A. Materials

All reagents were obtained commercially from Aldrich Chemical Company, Inc.

Pentane was stored over molecular sieves and used without further purification. N,N,N',N'-Tetramethylethylenediamine was used as received. Diisopropylamine was distilled from calcium hydride and stored under argon. n-Butyllithium was obtained as a 1.6M solution in hexane and used as received.

B. Apparatus and General Procedure

All reactions unless indicated otherwise were conducted in a 5 to 10 ml round bottom flask with septum

inlet and containing a magnetic stir bar, the flask was also equipped with a mercury bubbler. This system in all cases was flame dried and flushed with argon.

All GLC analyses were performed on a Varian 920 Chromatograph using 1/4 inch by 6 foot stainless steel column packed with 2.5% SE-30 on Chromosorb G NAW.

Lithium diisopropylamide LDA was prepared by injecting n-butyllithium into the apparatus (described above) cooling to 0° by an ice bath and injecting pentane (1 to 5 ml as required). One equivalent of diisopropylamine was added dropwise while stirring vigorously, and stirring was continued for 15 min. Solvent was evaporated under reduced pressure leaving behind a white solid.

C. Mixture of IX and LDA

A typical experiment was as follows, 0.11 ml (0.5 mmol) of ethyl ester was added to a stirred solution of 0.55 mmol of LDA in 1 ml of THF at -78°. The solution was stirred for 15 min, then warmed to room temperature and stirred an additional 5 min. After quenching with 0.5 ml of water, 1 ml of pentane and 0.12 ml (0.5 mmol) of standard (tridecane) were added, the mixture was then dried over anhydrous potassium carbonate. GLC analysis of the supernatant liquid gave a 93-95% recovery of IX. Table

II contains further experiments involving 1:1 mixtures of IX and LDA, in each case 0.5 mmol of IX and 0.5 mmol of LDA were mixed, and worked up as done above.

Table II. Results of Quenching 1:1 Mixtures of IX and Bases.

Reaction Period (Temperature)	Recovered Ester %
1 h (25°)	94
8 h (25°)	85
1 h (reflux)	80

D. Mixture of X and LDA

0.13 ml (0.5 mmol) of X was added to a stirred solution of 0.5 mmol of LDA in 1 ml of THF at -78°. The mixture was refluxed for 1 h, quenched with 0.5 ml of water and worked up as in part A. GLC analysis (pentadecane as standard) showed a 96% recovery of X. A similar experiment was tried in which 0.26 ml (1 mmol) of X was added dropwise to a solution of 5 mmol of LDA in 6 ml of THF and 0.75 ml (5mmol) of TMEDA at -78°. This mixture was warmed to room temperature and stirred for two days. The usual workup (see part A) and GLC analysis showed 80% recovery of X.

E. ^{1}H NMR of 1:1 Mixture of X and LDA

0.26 ml (1mmol) of X in 1 ml of benzene was added to a solution of LDA in 3 ml of benzene at -78°. The mixture was stirred for 5 min, then warmed to room temperature and stirred an additional 15 min. 0.6 ml of this mixture was injected into a NMR tube that was evacuated with argon. The resulting ^{1}H NMR of the mixture showed the ester to be unaffected by LDA, since the α-proton of the ester remained in the NMR.

F. Mixture of X and n-butyllithium

0.26 ml (1mmol) of X was added to solution of 0.63 ml of 1.6M n-butyllithium in 1 ml of THF at -78°. The mixture was stirred for 5 min, warmed to 40° and stirred an additional 5 min. Work up of the mixture followed by GLC showed 100% recovery of X. The same experiment was tried again with the exception that 0.15 ml (1mmol) of TMEDA was added, GLC again showed 100% recovery of X.

G. Mixture of X and Methyllithium

0.26 ml (1mmol) of X was added to a solution of 0.63 ml of 1.6M methyllithium in 0.5 ml of THF and 0.15 ml (1mmol) of TMEDA at -78°. The mixture was stirred for 15 min at -78°, then warmed to 40-50° and stirred an additional 30 min. Work up followed by GLC showed 94%

recovery of X. When the same procedure was tried with a 1:5:5 mixture of X to methyllithium to TMEDA in 3 ml of pentane and the solution stirred at 25° for 10 h, upon GLC analysis showed 87% recovery of X.

H. Mixture of X and Sodium Amide

A 100 ml three neck round bottom flask was equipped with a dry ice condenser, mechanical stirrer with Hersberg stirrer, mercury bubbler, and rubber septum. This system was flame dried and flushed with argon. Sodium amide was prepared (19) by first adding 0.1854 g of anhydrous ferric chloride (oven dried) to flask, followed by condensation of approximately 50 ml of ammonia (Matheson Gas Co.). A few pieces of sodium were then added with vigorous stirring, to convert the iron salt into the catalytic form. The rest of the sodium was then added 2.90 g (total) and after 1.5 h of stirring a gray precipitate of sodium amide formed. X was then added in one portion at -78° and the solution allowed to stir for 1 h at -78°. Then 60 ml of ether was added and the ammonia evaporated off in a stream of argon. The solution was stirred for 9 h at room temperature, work up followed by GLC analysis showed 91% recovery of X.

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