THE SYNTHESIS AND REACTIONS OF A HINDERED SECONDARY AMINE

By

Zakaria A. Fataftah

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ABSTRACT

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HINDERED SECONDARY AMINE

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The unsaturated secondary amine, bis-(1-ethynylcyclohexyl) amine, 16, was successfully synthesized by coupling 1-chloro-1-ethynylcyclohexane with 1-ethynylcyclohexylamine in 65% yield. Raney nickel hydrogenation of 16 gave the corresponding saturated amine, bis-(1-ethylcyclohexyl) amine, 17, in 80% yield. Several reactions of 17 with typical electrophiles, including methyl iodide, boron trifluoride etherate, N-chlorosuccinimide, bromine and trimethylchlorosilane were investigated.

The lithio-bis-(1-ethylcyclohexyl) amide, 27, was prepared by reaction of 17 with n-butyllithium or sec-butyllithium in hexane at room temperature for several days. Amide 27 was formed at a much faster rate (less than 5 minutes), in the presence of an equivalent amount of N,N,N,N-tetramethylethylenediamine.

Several reactions of 27 with very weak acids including methyl iodide, toluene, α-methylstyrene and organoboranes were investigated.

Amide 27 reacted with 2-methyl-3-pentanone and 3-methylcyclohexanone to give almost exclusively the less substituted lithium enolate.

The stereochemistry of the enolates formed by deprotonation of a series of ketones with a variety of lithium dialkylamide bases was

investigated. Under kinetically controlled conditions, deprotonation of 3-pentanone and 2-methyl-3-pentanone gave mainly the E-enolate. The Z-enolate was the major product under equilibration conditions. Conditions required to obtain either thermodynamic or kinetic control of ketone deprotonation reactions were investigated. A mechanism was proposed for enolates equilibration.

To my wife, Nahla,
and my daughter, Joanne.

ACKNOWLEDGMENTS

I wish to extend my appreciation to a fine chemist and a fine friend, Dr. Michael W. Rathke, for his guidance, assistance and inspiration through this investigation. Thanks are also given to Dr. William H. Reusch for serving as Second Reader. Special thanks are extended to my loving parents for all their encouragement, and I hope that their expectations for me have been adequately fulfilled.

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Finally, I would like to express my gratitude to Yarmouk University for providing me with the full scholarship which made it possible for me to continue my graduate studies and complete this work.

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DMF	N,N-Dimethylformamide
HMPA	Hexamethylphosphoramide
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine
NCS	N-chlorosuccinimide
NHS	N-hydrosuccinimide
9BBN	9-borabicyclo[3.3.1]nonane
TMEDA	N,N,N,N-Tetramethylethylenediamine

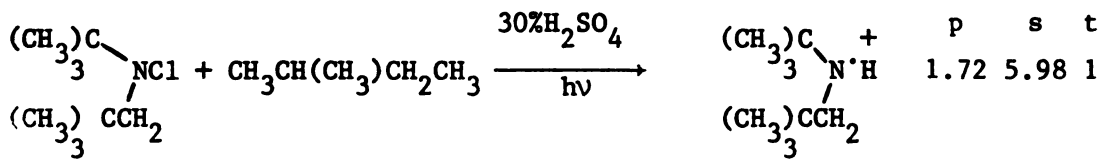
CHAPTER I

THE SYNTHESIS AND REACTIONS OF STERICALLY HINDERED SECONDARY AMINES

INTRODUCTION

Secondary amines with highly branched alkyl groupings are of general importance in synthetic organic chemistry. Major applications of such amines depend on their increased substrate selectivity, resulting from steric factors.

For example[1] the N-chloro-derivative 1 of t-butylneopentylamine in sulfuric acid solution generates radical cation 2 which exhibits an increased selectivity for primary hydrogen over tertiary hydrogen



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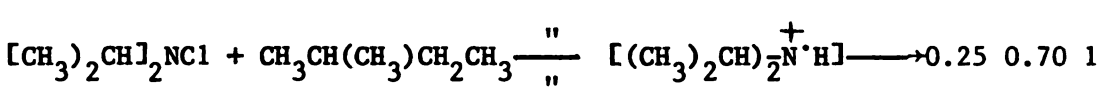


1' 2'

abstraction (eq. 1). This is presumably due to the greater steric hindrance of radical 2 compared to less hindered radicals such as 2'.

The alkali metal amides derived from hindered secondary amines are efficient proton abstractors but poor nucleophiles, and this characteristic is often of great synthetic value. For example, 2,2,6,6,-tetramethylpiperidine is probably the most hindered commercially available secondary amine, and its lithium salt (LiTMP) is a very poor nucleophile. Although bases of moderate steric requirements such as lithium

diethyl- or diisopropylamide do not give a metallated derivative with alkylboranes 3, or vinylboranes 4,[2] LiTMP produces boron-stabilized carbanions in both cases (eqs. 2 and 3). The failure of the smaller

$$R_2BCH_3 + LiTMP \xrightarrow[25^oC]{\text{benzene}} R_2BCH_2Li + TMP \qquad (2)$$

3 10-60%

$$RCH_2CH{=}CHBR'_2 + LiTMP \xrightarrow[25^oC]{THF} RCHLiCH{=}CHBR'_2 + TMP \qquad (3)$$

4 50-70%

bases to give proton abstraction is probably due to their coordination to boron (eq. 4). The bulky LiTMP is too hindered to bond to boron and

$$R_2BCH_3 + \bar{B}ase \longrightarrow R_2\bar{B}(CH_3)(Base) \qquad (4)$$

therefore reacts to form the carbanion.

A variety of related applications of LiTMP has been reported. Olofson[3] described the use of LiTMP for a practical synthesis of arylcyclopropanes 5 from benzylhalides (eq. 5). LDA was less effective

$$ArCH_2Cl + LiTMP \longrightarrow [Ar\ddot{C}H] \longrightarrow Ar \qquad (5)$$

5 (54%)

(39% yield), presumably because substitution reactions of the starting benzylhalide become more likely with this less hindered amide.

In all of these examples, it would be useful to know if secondary amines with more hindered alkyl groups would show even greater substrate selectivity.

An α,α'-enolisable non-symmetrical ketone may be deprotonated to two regioisomeric enolates 6 and 7 (eq. 6). The lack of regiocontrol in

$$RCH_2\overset{O}{\overset{\|}{C}}-CHR^1R^2 \xrightarrow{\text{base}} RCH=\overset{O^-}{\overset{|}{C}}-CHR^1R^2 + RCH_2\overset{O^-}{\overset{|}{C}}=CR^1R^2 \qquad (6)$$

$$\underline{6} \qquad\qquad \underline{7}$$

the formation of 6 and 7 is a significant problem which limits the use of such enolates in organic synthesis. It is possible that hindered amide bases might favor proton abstraction from the less hindered side of the carbonyl function.

A second reason for preparing highly hindered 2^o- amines is the possibility that their metal amide derivatives may be significantly stronger bases. C. A. Brown[4] investigated the effect of increased alkyl group size upon alkoxide basicity. He found that the base strength of alkoxides increases with alkyl group size. Potassium tricyclohexylmethoxide, for example is a stronger base, by about 1.2 pKa units, than potassium t-butoxide. Brown attributed this to a decrease in solvation or ion-pair formation in the more hindered base. It seems likely that such an effect would also occur with metal amide bases.

A major goal of this study was the development of a simple, inexpensive route to a secondary amine which is more hindered than secondary amines which are presently available. We then planned to investigate synthetic applications of such an amine in reactions where steric factors might lead to greater selectivity. In addition, we hoped to obtain information about the base strength of the lithium amide derived from such an amine.

The best procedure for the preparation of hindered secondary amines is probably that reported by Hennion[5]. This is illustrated by

the reaction of hindered primary amine 9 with tert-propargylic chloride 8 to give hindered N-tert-propargylic secondary amine 10 (eq. 7).

$$HC{\equiv}C\text{-}C(CH_3)_2Cl + HC{\equiv}CC(CH_3)_2NH_2 \xrightarrow[\text{Copper bronze, } Cu_2Cl_2]{40\%KOH,\ H_2O} [HC{\equiv}CC(CH_3)_2]_2NH \quad (7)$$

8 9 10 (47%)

Compound 10 was semihydrogenated to 11, using 10% palladium on charcoal as a catalyst, and then hydrogenated to the saturated amine 12, using Raney nickel in ethanol (eq. 8).

$$10 \xrightarrow[\text{Pet. ether}]{Pd/C} [CH_2{=}CH\ C(CH_3)_2]_2NH \xrightarrow[EtOH]{Raney\text{-}Ni} [CH_3CH_2C(CH_3)_2]_2NH \quad (8)$$

11 12 (41%)

Recently, Kopka[6] modified Hennion's procedure and prepared a series of highly hindered secondary amines. The sequence used to prepare this series of secondary amines is summarized in eqs. 9-13. Kopka found that the coupling procedure exemplified by equation 7 does not give significant yields when applied to more hindered

$$R_2CO + NaC{\equiv}CH \longrightarrow HC{\equiv}CR_2COH \quad (9)$$

$$HC{\equiv}CR_2COH + HCl \longrightarrow HC{\equiv}CR_2CCl \quad (10)$$

$$HC{\equiv}CR_2CCl + NH_2 \longrightarrow HC{\equiv}CR_2CNH_2 \quad (11)$$

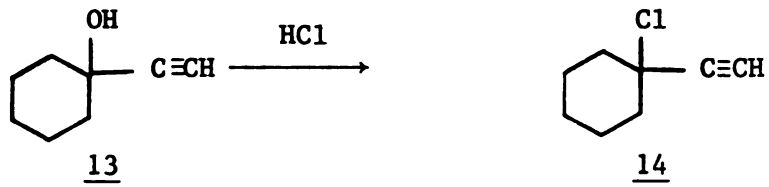
$$HC{\equiv}CR_2CCl + HC{\equiv}CR_2CNH_2 \longrightarrow (HC{\equiv}CR_2C)_2NH \quad (12)$$

$$(HC{\equiv}CR_2C)_2NH \xrightarrow{Ni/H_2} (CH_3CH_2R_2C)_2NH \quad (13)$$

reactants. The best yield (50-70%) of coupled product was obtained with an extra equivalent of the propargylamine serving as the base in place of

KOH (eq. 7 and 12). Kopka found also that Raney nickel W-2 was the most effective reducing catalyst (eq. 13).

One disadvantage of this scheme is the large number of steps. We chose bis-(1-ethylcyclohexyl) amine (17) as a target amine because the requisite alcohol (13) and 1^{o}-amine (15) are commercially available and inexpensive. This reduces the number of steps and seemed likely to make the projected synthesis of 17 both simple and inexpensive.



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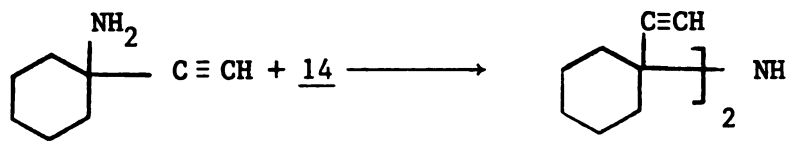


15 16 (15)

17 (16)

RESULTS

Synthesis of bis(1-ethylcyclohexyl) amine, 17.

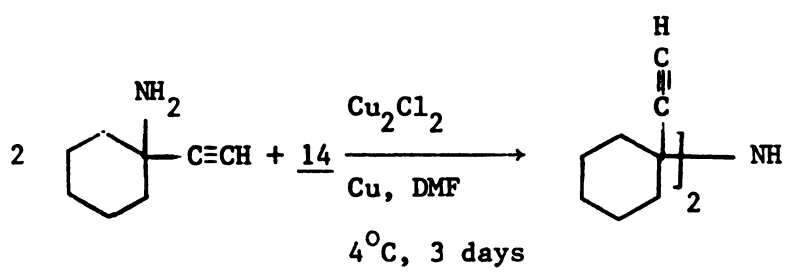
1-Chloro-1-ethynylcyclohexane, 14, was prepared[7] in 80% yield from the alcohol 13 by reaction of 13 with excess cold hydrochloric acid in the presence of copper bronze powder, calcium chloride and cuprous chloride (eq. 17). The chloride was sensitive to heat and was used

(17)

13 14

without further purification.

1-Ethynylcyclohexylamine 15, was coupled[8,6] in dimethylformamide (DMF) solution with the chloride 14 in the presence of cuprous chloride and copper bronze (eq. 18). The product 16 was purified by distillation



(18)

15 16

(65%). This unsaturated amine was hydrogenated in ethanol solution with Raney nickel, W_2, catalyst, activated as reported by Vexlearsche[9]. The hydrogenation was completed in 20 hr and GLC analysis of the crude

product showed a second, minor, component (9%) in addition to the saturated amine. The hydrogenation was conducted under basic (KOH) as well as acidic (CH_3COOH) conditions in efforts to obtain product of higher purity, but the results were inferior to those obtained under neutral conditions (basic media 80% purity, acidic media 87% purity). The saturated amine 17 was purified by distillation with a spinning band column. The isolated yield was 80%.

Reactions of bis(1-Ethylcyclohexyl) amine 17.

A number of experiments were done with amine 17 to compare its behavior with that of other, less hindered amines.

Reactions of secondary amines with methyl iodide.

The rate of reaction of diisopropylamine, 2,2,6,6,-tetramethylpiperidine and amine 17 with methyl iodide was briefly examined. The three amines were mixed with one equivalent of methyl iodide in deuterated chloroform solution at room temperature and allowed to react overnight. Analysis by H^1 NMR spectroscopy indicated that the first two amines reacted with methyl iodide to give the N-methylammonium iodide while 17 did not react. The methyl iodide NMR peak disappeared in the first two reactions, and white crystals were formed in the NMR-tube containing the 2,2,6,6,-tetramethylpiperidine reaction. These crystals were identified as the N-methylammonium iodide derivative[10]. There was no change in the NMR spectrum of a mixture of 17 and methyl iodide, even after one week. Refluxing a deuterated ethanol solution of 17 containing excess methyl iodide for 6 hr also did not lead to reaction (NMR analysis).

Reaction of Secondary Amines With $BF_3 \cdot OEt_2$.

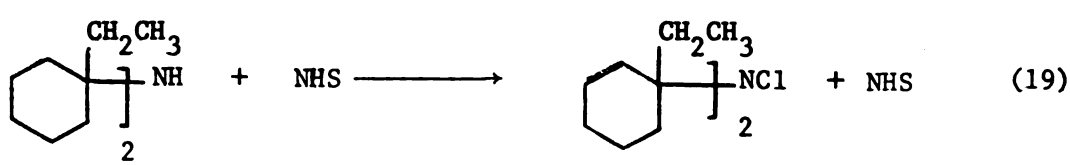
Addition of equimolar amounts of boron trifluoride etherate to a hexane solution of diisopropylamine, 2,2,6,6,-tetramethylpiperidine and 17, at room temperature gave, within a few minutes, a white precipitate. These reactions were repeated in $CDCl_3$. The NMR spectra showed an up-field shift of ~0.7 ppm, for the methylene hydrogens of the diethyl ether. This shift towards the free ether signal is an indication that BF_3 is no longer coordinated to the ether. The product from the reaction of 17 with $BF_3 \cdot OEt_2$ was found to be a stable white solid with a sharp melting point, 154.5-155°C. A sample of this solid was maintained under high vacuum overnight with no change either in weight or NMR spectrum.

Reaction of 17 with Trimethylchlorosilane.

Amine 17 was added to excess trimethylchlorosilane in $CDCl_3$ solution at room temperature and the mixture was stirred for four days. There was no evidence of reaction by NMR analysis.

Reaction of 17 with N-Chlorosuccinimide (NCS).

Amine 17 and N-chlorosuccinimide were stirred in methylene chloride[11] solution and the reaction was followed by NMR. The signal for NCS vanished and signal for NHS appeared after one week (eq. 19).



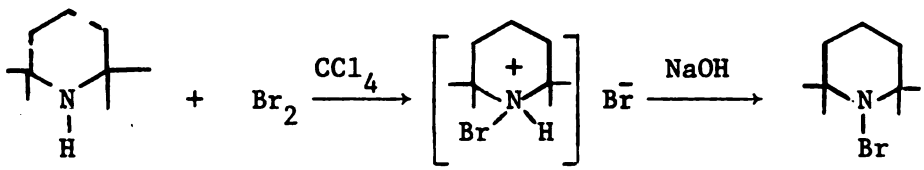
(19)

17 18

The reaction was repeated under more vigorous conditions, using a 1:1 mixture of CCl_4 and CH_2Cl_2 at reflux for 20 hrs. The signal for NCS also disappeared, as in the earlier experiment. The methylene hydrogen multiplet observed in the NMR spectrum of the residue in both reactions showed a down field shift of 0.2 ppm from the starting amine.

Reaction of Secondary Amines With Bromine.

A solution of bromine in CCl_4 was added to a solution of 2,2,6,6,-tetramethylpiperidine in CCl_4. A yellow solid 19 was formed which gave the N-bromo-derivative 20 on treatment with sodium hydroxide solution (eq. 20). The yield of 20 was 66% but a quantitative yield was

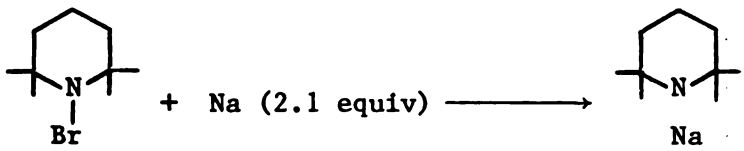


19 20 (20)

obtained by dropwise addition of bromine to a mixture of aqueous sodium hydroxide (1.18M) and a chloroform solution of the amine. A 95% yield was obtained (by NMR) with hexane as the solvent in place of chloroform. The NMR spectrum of a pure sample of 20 (obtained by distillation, 65°C/0.7 mm) fortunately could be distinguished from starting amine. Benzene was used as internal standard to determine the yield by integrating product signals relative to the benzene signal. In a parallel experiment, 17 formed a precipitate shortly after mixing with bromine, but the yield of the N-bromo-derivative of 17 was not determined because the NMR of the product is very similar to that of the starting amine.

Reaction of N-Bromoamines with Sodium.

The reaction of 20 with sodium dispersion was investigated in some detail in an attempt to form the sodium derivative 21 (eq. 21).



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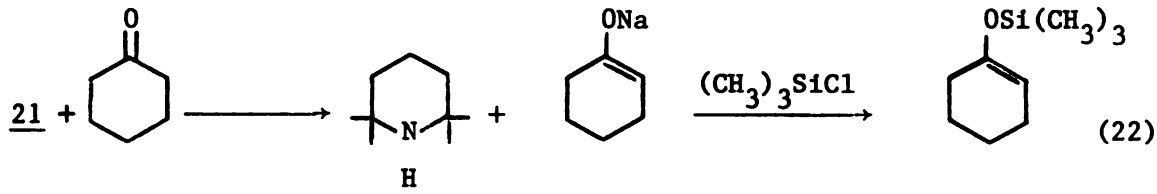
20 21

Dropwise addition of 20 to 2.1 equivalent of dispersed sodium in hexane was analyzed for formation of the sodium amide 21 by means of the sequence shown in equation 22. The yield of trimethylsilyl enol ether

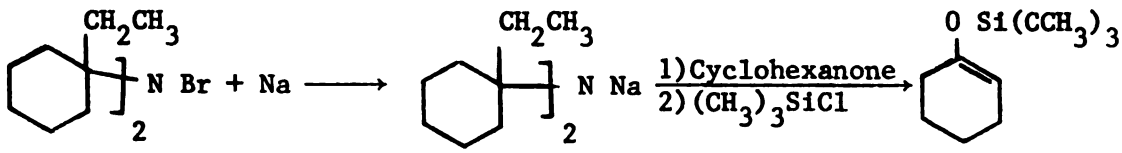


(22)

22 23

23, as determined by GLC, ranged from 15-77 percent. Table 1 summarizes the results of a few of the reactions studied.

The N-bromo-derivative of amine 17 was also reacted with sodium. The yield of trimethylsilyl enol ether 23, as determined by GLC, was 50% (eq. 23). When 20 was treated with n-butyllithium or lithium instead of



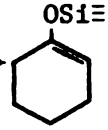
(23)

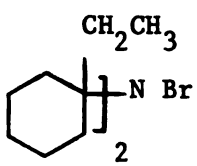
24 25 23

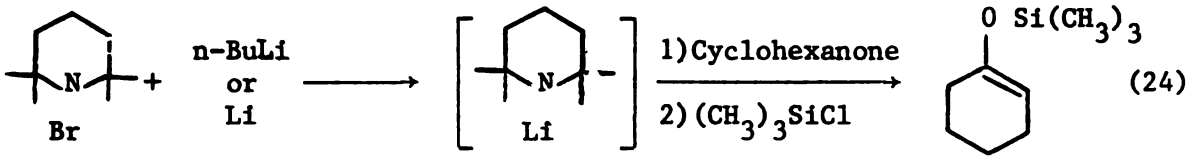
sodium, measurable amounts of 23 (eq. 24) were not obtained.

TABLE I.

Reaction of N-bromoamines with sodium dispersion.

Na(2.1 equiv) + N-bromoamine (1 equiv) $\xrightarrow[\text{R. T.}]{t_1}$ Na-amide $\xrightarrow[2)\equiv SiCl]{1)\text{Cyclo-hexanone}}$  (total yield)

	condition	t_1	(yield)
1.	hexane	50 min	77%
2.	"	16 hr	60%
3.	THF	30 min	43%
4.	EtOEt	1 min	55%
5.	"	1 hr	42%
6.	hexane and n-BuLi instead Na	1 hr	3%
7.	hexane and Li instead Na	1 hr	0%
8.	hexane, Amine instead of N-bromoamine	1 hr	15%
9.	hexane, 	3 hr	48%
10.	hexane, "	overnight	52%

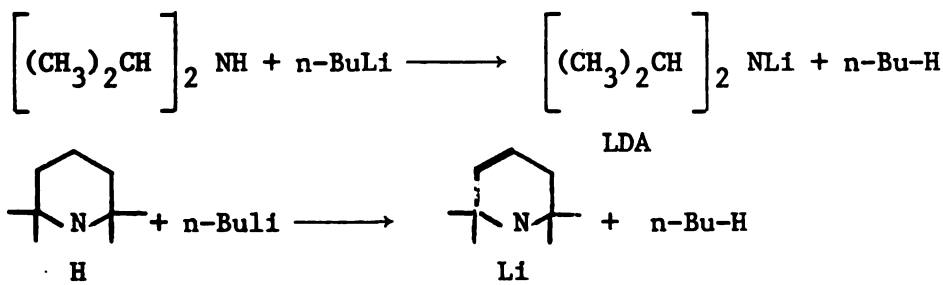


(24)

20 26 23

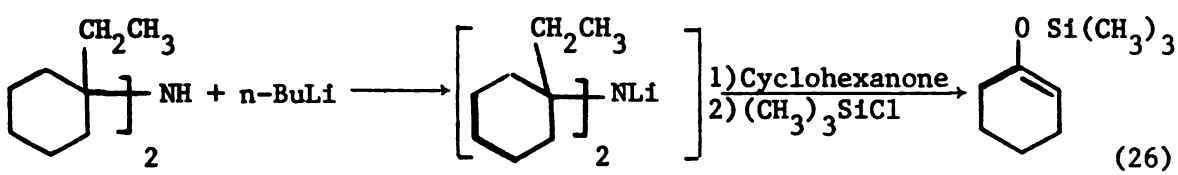
Reaction of 17 with n-Butyllithium.

n-Butyllithium reacts rapidly with diisopropylamine and 2,2,6,6,-tetramethylpiperidine at 0°C. These amines were added dropwise to an equivalent amount of n-butyllithium in hexane in a flask connected to a mercury bubbler, and the evolution of butane was readily observed (eq. 25).



(25)

When 17 was added to n-butyllithium, no butane evolution was observed, even after removal of the ice bath. The reaction mixture was allowed to stir overnight and then analyzed for the formation of amide 27 by the sequence shown in equation 26. The yield of the trimethylsilyl enol



(26)

17 27 23

ether, 23 obtained in this case, as determined by GLC, was 21%. The reaction of 17 with n-butyllithium was repeated at reflux (60-70°C) for 5 hrs. The yield of 23, as determined by GLC, was 60%.

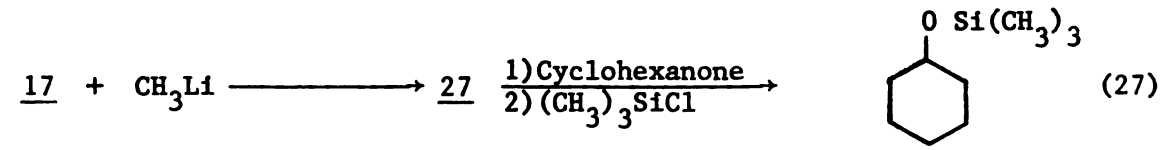
Since these experiments indicate that the rate of reaction of 17 with n-butyllithium is extremely slow, a kinetic study was carried out by gas analysis. A mercury burette was connected to the reaction flask containing two mmoles each of 17 and n-butyllithium in hexane. After 4 days, 30 ml (1.2 mmoles) of gas was evolved. The experiment was repeated with excess (3 mmoles) n-butyllithium. After 5 days, 32 ml (1.3 mmoles) of butane was obtained and this volume remained constant for two more days.

The reaction of 17 with n-butyllithium (2 mmoles) was repeated at reflux (72°C) and 29 ml (1.2 mmoles) of butane was obtained after 12 hrs. This increased to 39.5 ml (1.6 mmoles) of butane after the addition of 0.5 ml of water to the reaction mixture. The theoretical volume of butane gas from a 2 mmole scale reaction (eq. 25) was ~50.0 ml. We considered that the reason for the less than stoichiometric volume of butane is due to solubility of butane in the reaction mixture. Accordingly, the hexane solution of n-butyllithium (2 mmoles) was saturated with butane gas before the addition of the amine 17. Glass connections were used instead of rubber connections. In this case an evolution of 47 ml (1.9 mmoles) of butane after 5 days at room temperature was observed.

Reaction of 17 With Other Organolithium Reagents.

a. Methyllithium Amine 17 (2 mmoles) was added to an equivalent amount of methyllithium in ether at room temperature. The methane gas evolved was measured by a mercury burette and 94 ml (3.75 mmoles) of gas was accumulated over a 10 hr period. In a control experiment the reaction was repeated with diisopropylamine in place of 17 and over

100 ml (>4 mmoles) gas was obtained. The high vapour pressure of ether is possibly the reason for the excess volume observed. The reaction mixture of 17 and methyllithium was analyzed for the formation of the lithium amide 27. The sequence shown in equation 27 was used for the



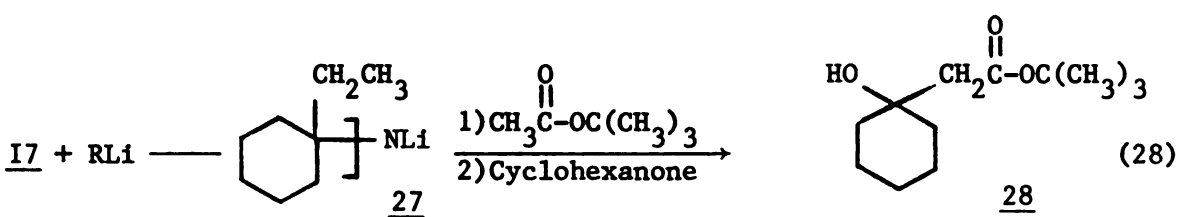
(27)

analysis. The yield of 23, as determined by GLC, was only 10%.

b. sec-Butyllithium. sec-Butyllithium (2 mmoles) was reacted with 17 in hexane at room temperature .45 ml (1.8 mmole) of butane was evolved after 44 hrs.

Analysis for the Formation of the Lithium Amide 27.

Since the yields in the analysis for the formation of the Li-amide 27, through the sequence shown in equation 27, were not large, the possibility existed that it was not accurate. The sequence was tried with LiTMP, an amide known to be formed quantitatively and a 71% yield of 23 was obtained. Consequently, we decided to analyze for amide by reaction with tert-butyl acetate in THF at -78°C, followed by addition of cyclohexanone (eq. 28). The reaction mixture was then analyzed for the

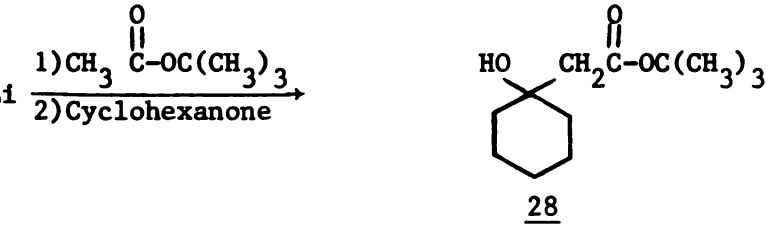


(28)

β-hydroxy ester 28. This method of analysis was tested first with LiTMP. LiTMP was prepared and dissolved in THF at -78°C. An equivalent amount of t-butyl acetate was added to this solution followed by cyclohexanone. The yield of the β-hydroxy ester 28 obtained in this case as determined by

GLC, was 95%.

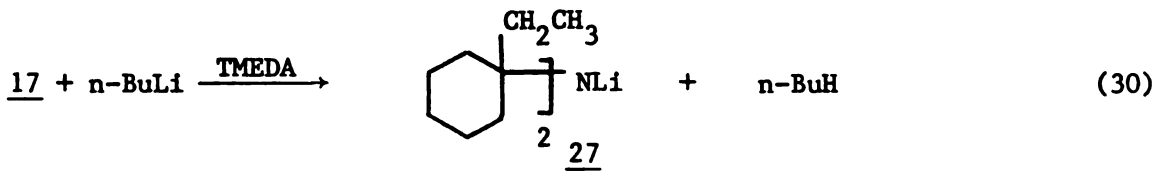
Amine 17 was mixed with equivalent amount of methyllithium in ether overnight at room temperature and the reaction mixture was worked up (eq. 28). The yield of the β-hydroxy ester 28, as determined by GLC was 36%. To check that all 28 was formed by the reaction of 27 and not by any other base, the reaction was repeated but without amine (eq. 29). No detectable amount of 28 was formed.



28 (29)

Reaction of 17 with n-BuLi in the Presence of N,N,N,N-tetramethylethylenediamine (TMEDA).

Equivalent amounts (2 mmoles) of 17 and n-butyllithium in hexane were mixed in a flask connected to a gas burette at room temperature. The reaction mixture was saturated with butane. An equivalent amount of TMEDA was added dropwise to this mixture. After the addition of TMEDA was completed (~1 min) 51 ml of gas were evolved (eq. 30). The reaction



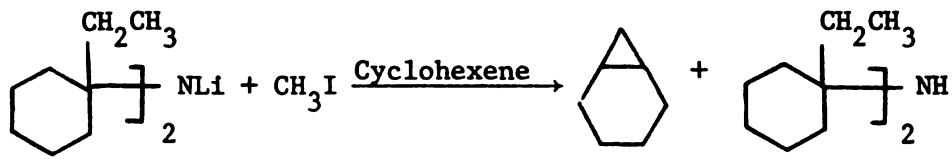
27 (30)

mixture was analyzed for the amide 27 by the sequence of equation 28. The yield of the β-hydroxy ester 28, as determined by GLC, was 100%.

TMEDA (0.1 equivalent) was added to equimolar amounts of 17 and n-butyllithium at room temperature. 49 ml of butane was obtained after 5 hrs. This reaction was worked up and analyzed by GLC. The yield of 28 was 92%.

Reaction of 27 With Methyl Iodide.

The amide 27 was prepared by the reaction of 17 with n-butyllithium and 10% TMEDA in hexane. Cyclohexene (1 ml) was added to the reaction mixture followed by two equivalents of methyl iodide at room temperature. The reaction mixture was stirred for two days and then was diluted with pentane (2 ml) to precipitate any LiI to facilitate GLC-analysis. GLC analysis indicated the presence of 17 (eq. 31). There was no peak on

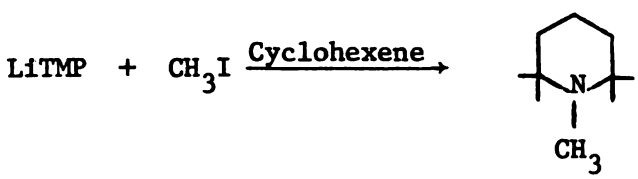


(31)

27 29 17

the GLC trace for 29. This conclusion was reached by co-injection of a sample of 29 prepared by another method,[12] with the reaction mixture. The reaction of 27 with methyl iodide was repeated. The reaction mixture was analyzed for unreacted 27 by the standard sequence of equation 28. The GLC yield of 28 was less than 5%.

For comparison, the reaction of LiTMP and methyl iodide was also investigated (eq. 32). GLC analysis showed 57% of the amide was



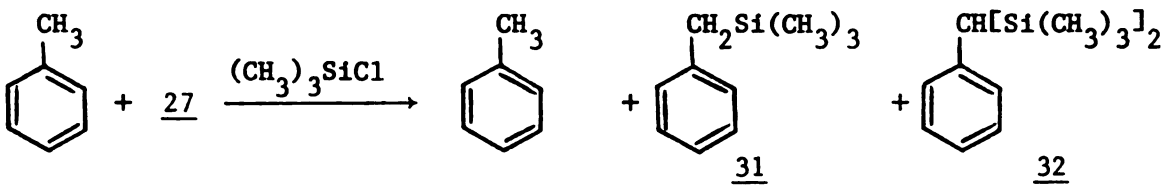
(32)

30 (57%)

methylated (1,2,2,6,6,-pentamethylpiperidine, 30). No norcarane 29 was formed.

Reaction of 27 With Toluene.

The reaction of 27 with toluene was investigated to determine if 27 is a sufficiently strong base to metallate toluene. Equivalent amounts of 27 and toluene were mixed in hexane at room temperature. The reaction mixture was stirred for 16 hrs then quenched with trimethylchlorosilane. GLC-mass spectral analysis indicated unreacted toluene (80%), mono-silylated toluene 31 (9%) and disilylated toluene 32 (5%) (eq. 33). We thought at first that metallation may be caused by unreacted



(33)

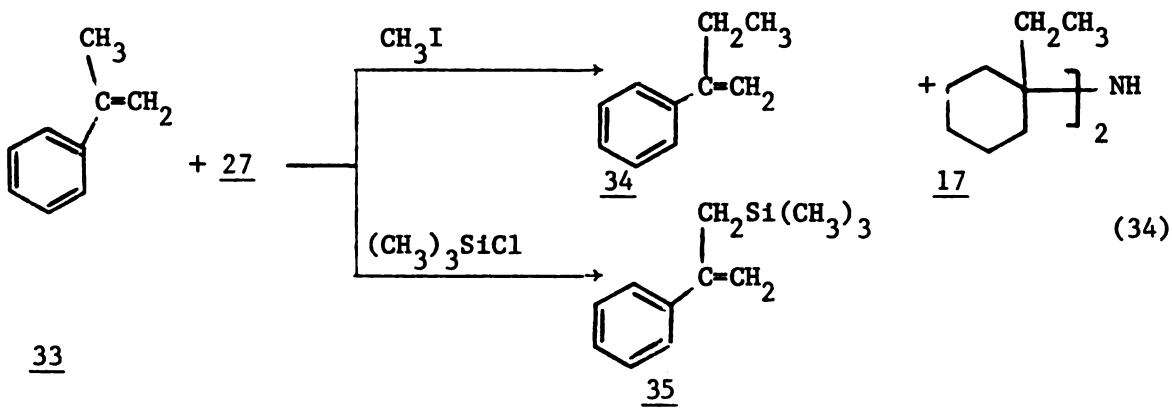
	↓	↓	↓
16 hrs	80%	9%	5%
46 hrs	56%	14%	7%
6 days	45%	18%	5%
2 weeks	<5%	<5%	<5%

n-butyllithium. Diisopropylamine (10%) was therefore added to consume any unreacted n-butyllithium before the addition of toluene. When the reaction mixtures was then quenched after 46 hrs and analyzed, the yield of unreacted toluene was 7%. However, the amount of unreacted toluene decreased when the reaction of 27 with toluene was repeated and quenched after 6-days. The starting toluene almost disappeared after two weeks.

Toluene was recovered quantitatively, without any of 31 or 32 formed, when it was stirred with LiTMP for 20 hrs at room temperature.

Reaction of 27 With α-Methylstyrene.

The reaction of 27 with α-methylstyrene was investigated. Equivalent amounts of 27 and α-methylstyrene were mixed in hexane at room temperature. The reaction mixture was quenched after 20 hrs, once with methyl iodide and another with trimethylchlorosilane (eq. 34). In the



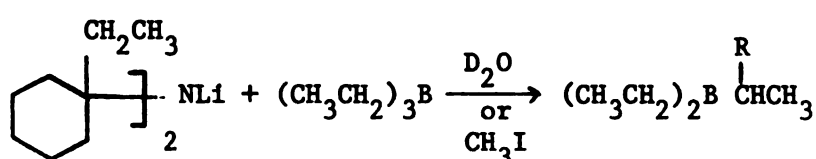
(34)

33 34 35 17

methyl iodide quenching, GLC analysis showed α-methylstyrene and amine 17. In the trimethylchlorosilane quenching, only α-methylstyrene was observed.

Reaction of 27 With Triethylboron.

The reactions of 27 with organoboranes were investigated to see if higher yield of metallated organoboranes could be achieved compared to the reaction with LiTMP. 27 was reacted with an equivalent amount of triethylboron in benzene for 42 hrs at room temperature. The reaction was then quenched with D_2O (eq. 35). The organic layer was analyzed by



(35)

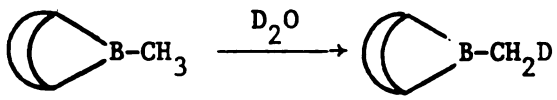
36 R=D

37 R=CH_3

GLC-mass spectrum for the deuterated product 36. The mass spectra showed only starting triethylboron and none of the deuterated product 36. The reaction sequence was repeated then quenched with methyliodide instead of D_2O. GLC-mass spectral analysis showed no methylated product 37 (eq. 35).

Reaction of 27 With 9-Methyl BBN.

The reaction of 27 with 9-methyl BBN,[13] 38 was carried out in the same fashion as with triethylboron (eq. 36). The deuterium incorboration

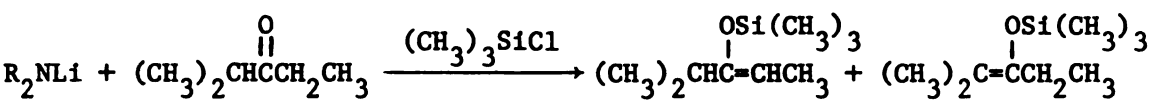


27 38 39 (36)

product 39 was found to be 40%.

Reaction of 27 and Other Li-Amides With 2-Methyl-3-pentanone.

The reactions of a series of lithium amides with 2-methyl-3-pentanone was investigated to determine how regiospecificity of enolate formation is related to size of R_2NLi (eq. 37). The lithium-amides shown

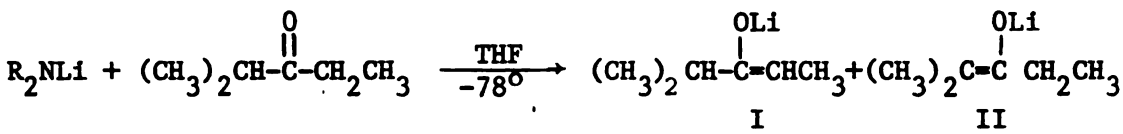


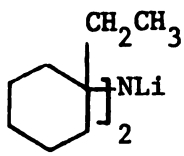
40 (E and Z) 41 (37)

in Table II were prepared by the reaction of the corresponding amine with n-butyllithium in the presence of an equivalent amount of TMEDA. After the formation of the amide in hexane was completed, the solvent hexane was replaced with THF. The reaction mixture was then cooled to -78°C. 2-Methyl-3-pentanone was added dropwise, followed by trimethylchlorosilane. After work up, the organic layer was analyzed by GLC for 40 and 41. The results are shown in Table II.

TABLE II

Reaction of R_2NLi with 2-methyl-3-pentanone.

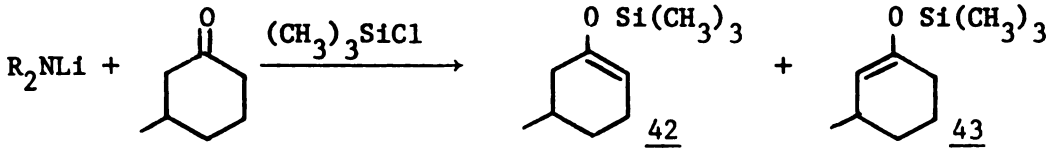


	R_2NLi[a]	I:II[b]	total yield
1	LDA	89:11	96%
2	LiTMP	92:8	98%
3		99:1	85%
4	$[CH_3CH_2(CH_3)_2C]NLi$	99:<1	98%
5	$CH_3CH_2(CH_3)_2C\ NLiC(CH_3)(CH_2CH_3)_2$	99.7:~0.3	94%
6	$[(CH_3CH_2)_2(CH_3)C]_2NLi$	99.1:<1	96%
7	$(CH_3CH_2)_2CH_3C\text{-}NLi\ C(CH_2CH_3)_3$	99:<1	93%
8	$[(CH_3CH_2)_3C]_2NLi$	99:1	91%

[a]The amides were prepared with equivalent amounts of TMEDA at room temperature. Entries 4 and 5 the amides were formed immediately. Entry 6, the amide was formed within 10 minutes. Entry 7, the amide was formed within 30 minutes. Entry 8, the amide was formed after 20 hrs.
[b]The ratio of I:II was determined by analysis for the corresponding silyl ethers (40 and 41). Pure samples of 40 and 41 were isolated by preparative glc and exhibited spectral properties in agreement with published values.[35]

Reaction of 27 and Other Li-Amides with 3-Methylcyclohexanone.

The reactions of the amides shown in Table III, with 3-methylcyclohexanone, were investigated. The reaction sequence was identical with that for 2-methyl-3-pentanone described above. The organic layer was analyzed by GLC for 42 and 43 (eq. 38). The results are shown in

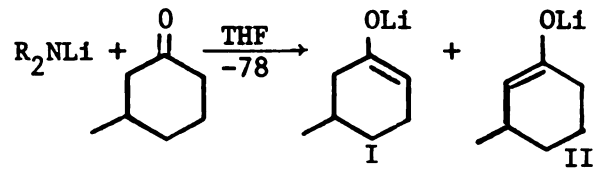


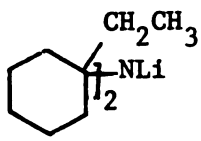
(38)

Table III. The position of thermodynamic equilibrium of 42 and 43 was determined by reaction of LDA with excess 3-methylcyclohexanone in the presence of equivalent amount of TMEDA in THF at room temperature. The equilibrium ratio of 42:43 was determined to be 59:41 (by both GLC and NMR), after 24 hrs of reaction and 57:43 after 48 hrs.

TABLE III

Reaction of R_2NLi with 3-methylcyclohexanone.

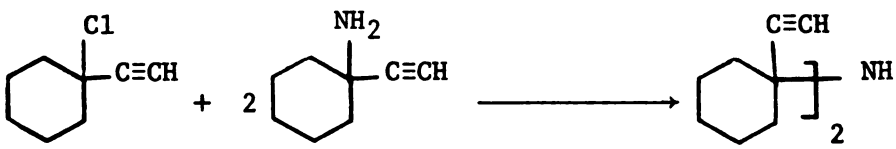


	R_2NLi[a]	I:II[b]	total yield
1	LDA	75:25[c]	97%
2	LiTMP	77:23	96%
3		90:10[c]	91%
4	$[CH_3CH_2(CH_3)_2C]_2NLi$	87:13	98%
5	$CH_3CH_2(CH_3)_2C\ NLiC(CH_3)(CH_2CH_3)_2$	91:9	81%
6	$[(CH_3CH_2)_2(CH_3)C]_2$-NLi	91:9	93%
7	$(CH_3CH_2)_2(CH_3)C\ NLiC(CH_2CH_3)_3$	96:4[c]	94%
8	$[(CH_3CH_2)_3]_2NLi$	95:5	87%

[a]The amides were formed with equivalent amount of TMEDA at room temperature. [b]The ratio of I:II and the total yield was obtained by glc and/or NMR. I was differentiated from II by NMR where the vinyl proton of I showed more splitting than the vinyl proton in II. [c]Entries 1, 3, and 7 were analyzed for the ratio by both NMR and GLC.

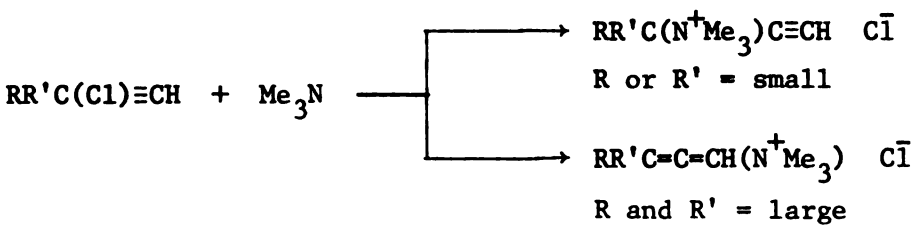
DISCUSSION

Hindered secondary amines are of great importance in organic synthesis, but their synthesis is usually difficult and requires a large number of steps. However the unsaturated secondary amine bis-(1-ethynylcyclohexyl) amine 16 was successfully synthesized by coupling 1-chloro-1-ethynylcyclohexane 14 with 1-ethynylcyclohexylamine 15 in good yield.



14 15 16 (65%)

The coupling occurred with 2:1 ratio of 15:14. The extra equivalent of 15 was used as a hydrochloric acid acceptor. The yield of the coupled amine was reduced greatly when other bases (KOH, KH, $KOC(CH_3)_3$ or Et_3N) were used as hydrochloric acid acceptors.[14,6] The reduction in the yield of 16 with these bases may be due to a competing substitution reaction of these base with chloride 14. Hennion studied the reaction of trimethylamine with tertiary propargylic chlorides in acetone[15] (eq. 39). He found that the reaction produces quaternary ammonium chlorides



(39)

with propargylic structure when R or R' is $-CH_3$. When R and R' are larger than methyl, the products are allenes.

The saturated secondary amine 17 was successfully obtained by hydrogenation of 16 with Raney nickel in ethanol. Unidentified side products (~10%) of the reduction could not be separated by simple distillation. However, distillation with a spinning band column gave 17 of greater than 99% purity (GLC). The simple and inexpensive synthesis of the very hindered amine 17, may be of great importance to organic synthesis.

Little is known about reactions of highly hindered secondary amines. However, work by Klages[16] in 1963 provides an example of how steric effect reduces the nucleophilicity of di-t-butylamine (44). Klages reacted 44 with methyl iodide for 5½ months and obtained 46 and 47 (eq. 40), possibly by initial formation of 45. 17 does not react with

$$\underset{\underline{44}}{[(CH_3)_3C]_2NH} \xrightarrow{CH_3I} \left[[(CH_3)_3C]_2\overset{+}{N}\begin{matrix}H\\CH_3\end{matrix}\right] I^- \longrightarrow \underset{\underline{46}}{\left[[(CH_3)_3C]_2N^+H_2\right] I^-} + \underset{\underline{47}}{[(CH_3)_3C\ N^+(CH_3)_3]\ I^-} \qquad (40)$$

methyl iodide or trimethylchlorosilane. This behavior was not unexpected because of steric hindrance in 17.

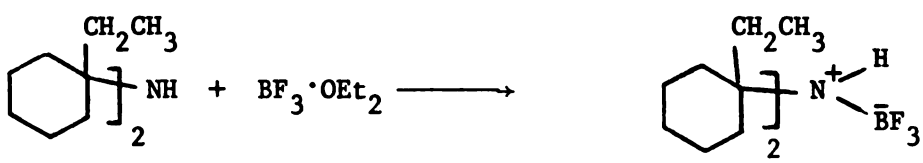
Boron trifluoride etherate, a powerful electrophile, reacts with diethylamine to give the addition product 48[17] (eq. 41). 48

$$(CH_3CH_2)_2NH \xrightarrow{BF_3\cdot OEt_2} \underset{\underline{48}}{(CH_3CH_2)_2\overset{+}{N}\overset{H}{\diagup}\underset{\diagdown}{\overset{-}{B}F_3}} \longrightarrow \underset{\underline{49}}{[(CH_3CH_2)_2\overset{+}{N}H_2]\overset{-}{B}F_4} + \underset{\underline{50}}{(CH_3CH_2)_2N\,BF_2} \tag{41}$$

disproportionate when heated above 250°C to give 49 and 50. Klages[16] found that di-t-butylamine reacts with boron trifluoride to give 52 and 53 possibly by initial formation of the simple adduct 51. Reaction of 17

$$\underset{\underline{44}\ R=t\text{-butyl}}{R_2NH} \xrightarrow{BF_3} \underset{\underline{51}}{R_2\overset{+}{N}\overset{H}{\diagup}\underset{\diagdown}{\overset{-}{B}F_3}} \longrightarrow \underset{\underline{52}}{[R_2\overset{+}{N}H_2]\,\overset{-}{B}F_4} + \underset{\underline{53}}{R_2NBF_2} \tag{42}$$

with boron trifluoride etherate gave a white precipitate, possessing a sharp melting point. Element analysis agreed with values calculated for structure 54. The formation of 54 and not disproportionation products

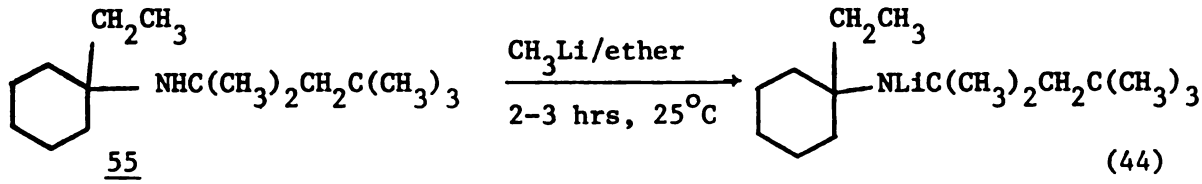


17 54 (43)

analogous to 52 and 53 may simply be due to a difference in reaction conditions.

Usually secondary amines such as diisopropylamine and 2,2,6,6,-tetramethylpiperidine react almost instantaneously with organolithium reagents. However, Olofson[3b] has reported that the sterically hindered amine, 55 requires 2-3 hr for complete reaction with methyllithium at

25°C. The exact time required for 17 to react with methyllithium could



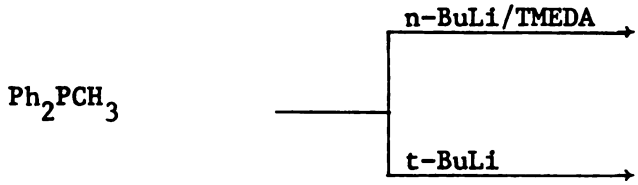
55 (44)

not be determined because the high vapor pressure of ether at 25°C interferes with an accurate measurement of the volume of methane produced. The time required for 17 to react completely with n-butyllithium in hexane is 4-5 days. If the time for metallation of an amine with an organolithium reagent can be taken as a measure of steric hindrance, then 17 is clearly exceptionally hindered.

In preliminary investigations of the rate of reaction of 17 with n-butyllithium, less than the expected volume of butane gas was observed. We considered that butane has an appreciable solubility in hexane, and may also penetrate or be adsorped by the rubber tubing used to connect the reaction flask with the measuring burrette. These effects probably become especially serious with long reaction times. The expected volume of butane was obtained when all rubber tubing was replaced with glass tubing and the n-butyllithium solution was saturated with n-butane gas prior to the addition of the amine.

The effect of the bidentate ligand TMEDA to enhance the rate of the reaction of n-butyllithium with 17 was not unexpected. This ligand is well known to increase rates of metallation because of its powerful ability to coordinate with lithium.[18] TMEDA coordination with lithium has the effect of diffusing the polarizing power of the metal atom and thus weakening the carbon lithium bond. In this manner, the carbanion becomes more independent of the lithium and consequently more reactive.

Also TMEDA converts the polymeric (tetrameric) organolithium structures to monomers and therefore increases the reactivity of these organolithium reagents. Peterson[18b] reported a similar effect of TMEDA for the metallation of diphenylmethylphosphine 56. With a stoichiometric amount of the n-butyllithium/TMEDA complex (eq. 45) complete metallation was achieved

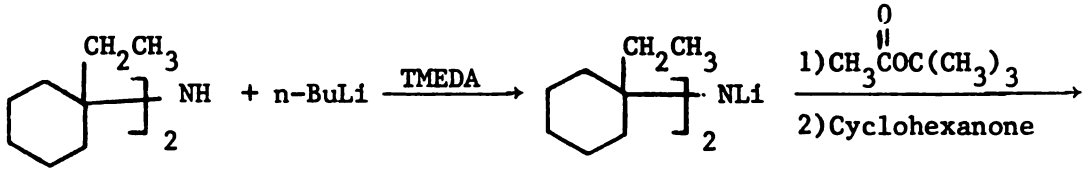


Ph_2PCH_3 → Ph_2PCH_2Li (45)

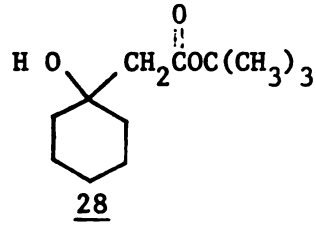
56 57

after only two hours reaction time. Metallation of the same methylphosphine with t-butyllithium alone required over 312 hrs.

The ultimate demonstration of the formation of amide 27 is the quantitative formation of 28 obtained when 27 was reacted with t-butyl acetate and cyclohexanone (eq. 28). This is because only lithium amide bases



27 (28)

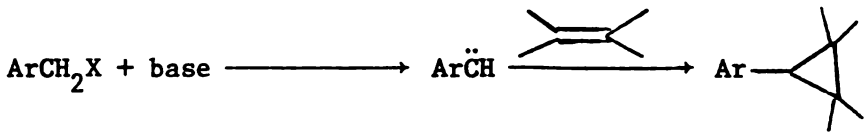


28

appear to generate enolates from esters. Both n-butyllithium and amine 17 failed to produce measurable amounts of 28 in control experiments.

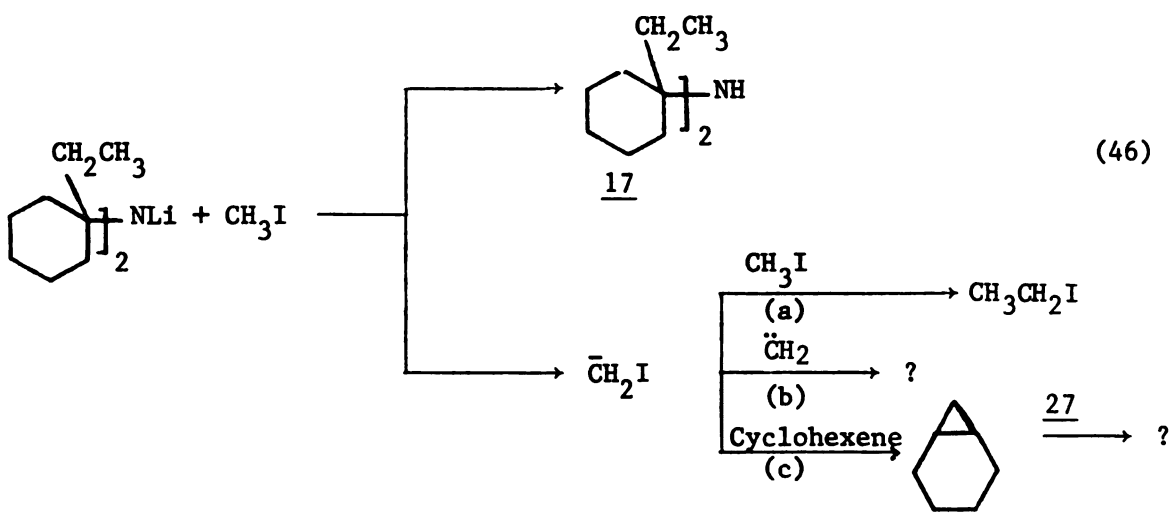
Carbenes are very important synthetic intermediates, especially for the formation of cyclopropane rings by addition to double bonds

(eq. 5). Olofson succeeded in generating benzyl carbenes from halides



(5)

by reaction with LiTMP. LiTMP does not form a carbene with methyl iodide. We considered that the generation of carbene from methyl iodide may require a stronger base or a poorer nucleophile than LiTMP. It seemed likely that 27 would meet these requirements. Therefore 27 was mixed with methyl iodide in the presence of cyclohexene and the reaction mixture was analyzed by GLC for norcarane. The amine 17 was observed but no norcarane was detected (eq. 31). A possible explanation for these results is that amide 27 removes a proton from methyl iodide to give 17 and methyl iodide anion. This anion may react with methyl iodide (path a, eq. 46) or may decompose to a carbene which for some reason fails to react with cyclohexene (path b, eq. 46). Another possibility is that

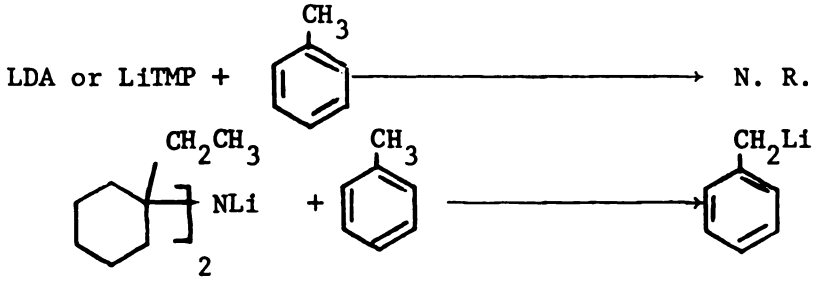


(46)

norcarane is formed but reacts with 27 (path c, eq. 46). Route (c) was ruled out because we observed in a separate experiment that 27 does not react with norcarane. Route (a) and (b) need more careful study before any final conclusion can be drawn because Olofson[2b] and others[19-21] have

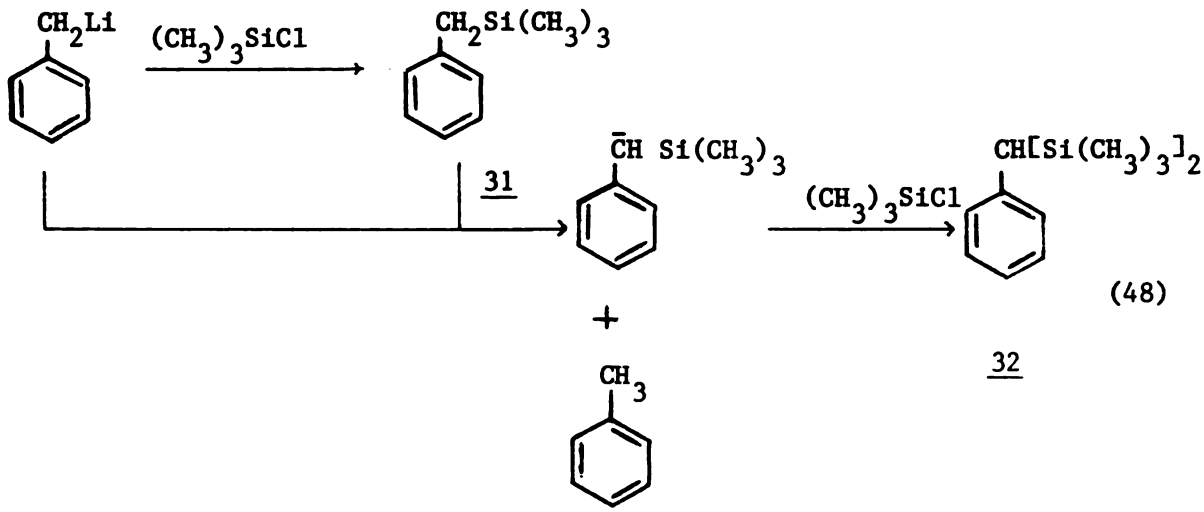
reported that the addition of carbenes or carbenoids to olefins often fails unless very specific reaction conditions are met.

Brown reported that alkoxide basicity is a function of the alkyl group size. If a similar effect applies with amide basicity, it seems likely that 27 is a stronger base than other less hindered amides such as LiTMP. One way of testing for this increase in basicity is to attempt metallation of toluene. The pKa of toluene is reported to be 40.9, while the pKa of diisopropylamine is reported to be ~38. As expected, we found no evidence for metallation of toluene by either LDA or LiTMP (eq. 47a). Amide 27



27

metallated toluene and we were able to obtain mono- as well as disilylated toluene when the reaction mixture of toluene and 27 was quenched with trimethylchlorosilane. At first, we considered that the observed metallation was due to the presence of unreacted n-butyllithium. This was excluded by the observation that the presence of diisopropylamine (which scavenges all n-butyllithium) has no effect on the amount of metallation observed. The disilylation product is not unexpected, because silicon is capable of stabilizing adjacent negative charge.[22] Therefore, it is possible that mono-silylated toluene reacts rapidly with benzyl anion to form toluene and disilylated toluene (eq. 48).



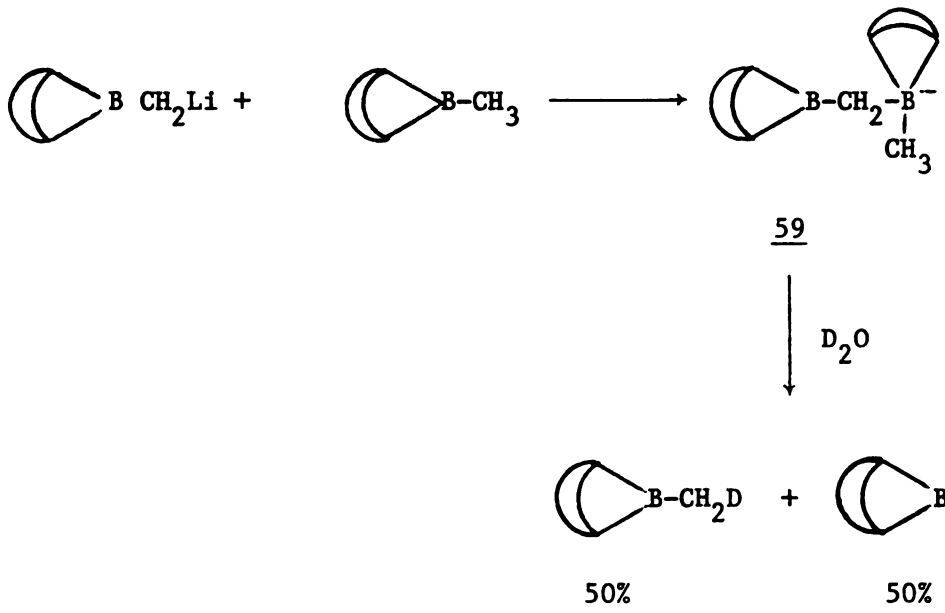
(48)

32

LiTMP reacts with 9-methyl BBN to form the boron stabilized anion in 50% yield. Excess base (LiTMP) gives a 60% yield of the

$$R_2B\ CH_3 + LiTMP \longrightarrow R_2B\ CH_2Li + TMP \qquad (2)$$

metallation product. LiTMP fails to react with triethylboron. We considered the degree of metallation would be increased if a base stronger than LiTMP were used. Unfortunately, the reaction of the amide 27 and 9-methyl BBN gave about the same results (40%) as LiTMP and no metallation was observed with triethylboron. These observations may be interpreted to mean the amide 27 is not a stronger base. But the metallation of toluene with 27 and not with LiTMP makes this interpretation unlikely. Another possibility is that the metallated organoborane 58 may coordinate to the boron atom of the starting organoborane to form complex 59. The formation of 59 will prevent at least half of the starting organoborane from participation in the reaction (eq. 49).



(49)

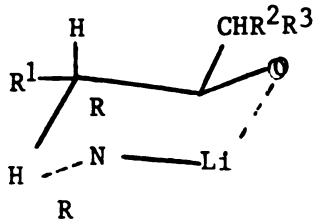
When the reaction mixture is quenched with D_2O, the complex 59 will dissociate to give 50% yield of the deuterated product. If this is the case, use of a stronger base would have no effect on the degree of metallation.

Lithium amide bases are known to deprotonate ketones to form lithium enolates. Non-symmetrical ketones may be deprotonated to two regioisomeric enolates. The lack of regiocontrol in the formation of

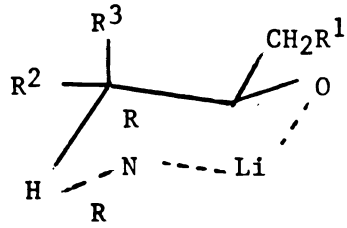
$$R^1CH_2\overset{O}{\overset{\|}{C}}CHR^2R^3 \xrightarrow{R_2NLi} R^1CH{=}\overset{OLi}{\overset{|}{C}}CHR^2R^3 + R^1CH_2\overset{OLi}{\overset{|}{C}}{=}CR^2R^3 \qquad (6)$$

these enolates is a significant problem which limits the use of enolates in organic synthesis. Amide 27 may provide an effective solution to this problem. Kinetically controlled deprotonation of 2-methyl-3-pentanone with 27 gave exclusively (99%) the less highly substituted enolate. Kinetically controlled deprotonation of 3-methylcyclohexanone with 27 gave a 90% selectivity favoring the less highly substituted enolate. The results shown in Table II and III also indicate the

preferential formation of the enolate on the less hindered side as the size of the alkyl groups of the amide increases. These results can be explained by considering the chair-like transition states 60 and 61.



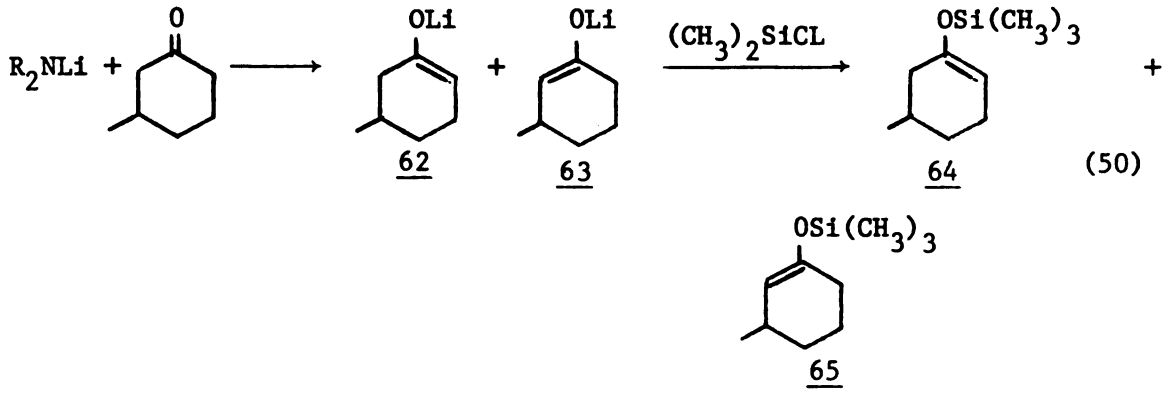
60 less substituted enolate



61 more substituted enolate

As the size of R increases the transition state 61 will be destabilized more than 60. Therefore, 60 will be preferred and the regioselectivity for the less substituted enolate will increase. Because the size of R of the amides, shown in Tables II and III (other than LDA and LiTMP) is very large, exclusive regioselectivity of enolate formation towards the less substituted side of the ketone was observed.

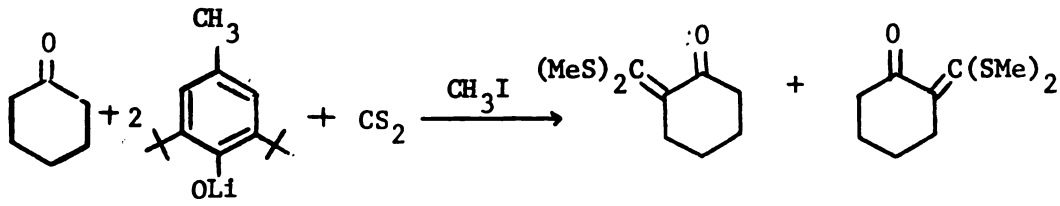
The assignment of structure to the two enolates (62 and 63) obtained by deprotonation of 3-methylcyclohexanone is not a simple task.



(50)

It seems reasonable to assign structure 62 to the major product of the reaction because hydrogens attached to C_6 (leading to enolate 62) appear to be more sterically accessible than the hydrogens attached to C_2 (leading to enolate 63). In line with this, Corey[23] has reported that

the major product formed by base-catalyzed reaction of 3-methylcyclohexanone with CS_2 is structure 67 and only minor amounts of the isomeric

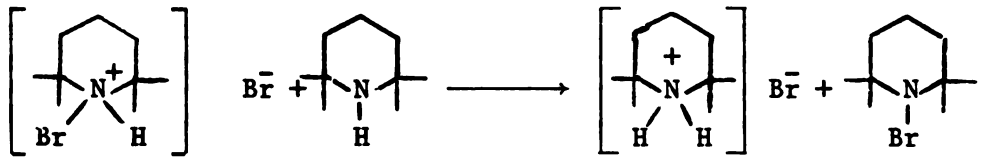


(51)

66 67 68

product 68 are formed. It is likely that Corey's results reflect a kinetically controlled enolate distibution because we observe almost equal amounts of 62 and 63 under equilibrating conditions (58% 62 and 42% 63). Additional evidence for the assignment of structures is based on the NMR spectra of the corresponding silyl enol ethers 64 and 65. The number of protons coupled to the vinyl hydrogen of 64 should be four while only three protons should couple to the vinyl hydrogen of 65. The signal for the vinyl hydrogen of the major isomer produced in the reaction does exhibit higher multiplicity.

The reactions of TMP with bromine is interesting. In our first experiments, a CCl_4 solution of bromine was added to TMP. An orange solid, presumed to have structure 19 was formed, but the yield was only 66%. Examination of the mother liquor by NMR showed the presence of 20 which may be formed by the reaction of TMP with 19 as shown in



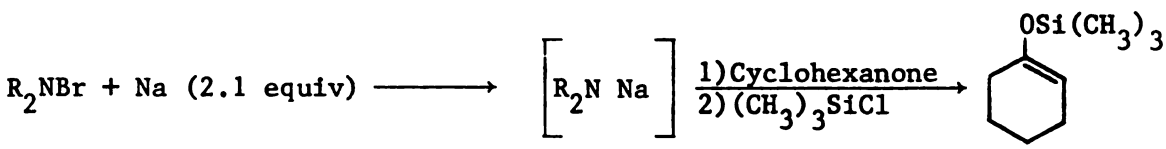
(52)

19 20

equation 52. Modification of the procedure by addition of bromine to a heterogenous mixture of sodium hydroxide and TMP gave a quantitative yield of 20.

Amine 17 likewise reacts with bromine to give the corresponding N-bromo-derivative.

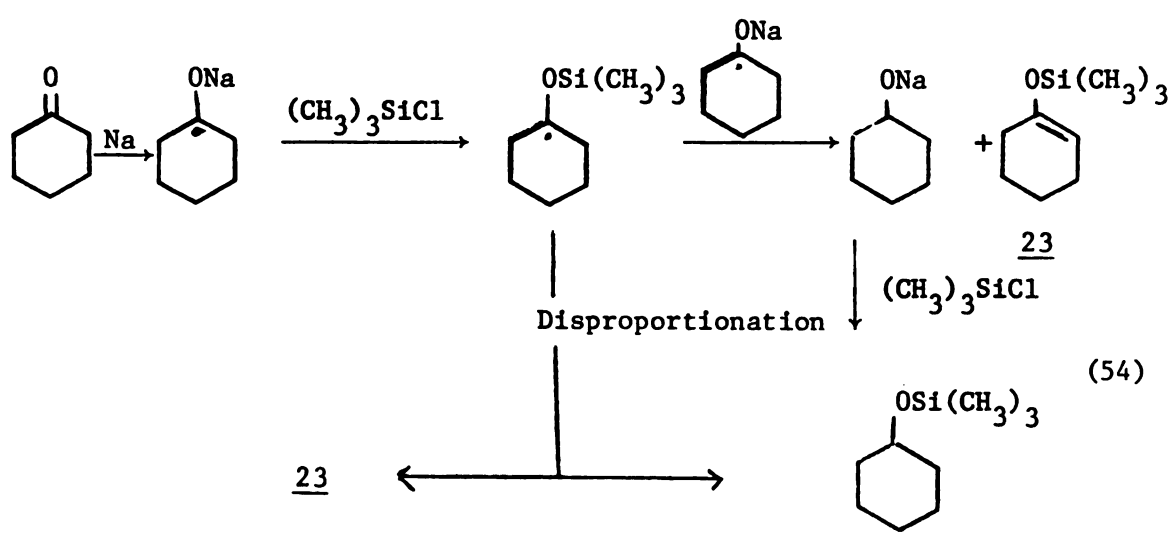
Reaction of the N-bromoamines with sodium to prepare the corresponding sodium amides was at least partially successful (Table I).



(53)

21 23

The yield of 23 as determined by GLC, was between 40-77%. However, 23 was obtained in ~ 15% yield, with R_2NH in place of R_2NBr.
A possible explanation for the formation of 23 is a radical mechanism (eq. 54).



(54)

EXPERIMENTAL

I. Materials

1-Ethynylcyclohexyl alcohol and 1-ethynylcyclohexylamine were commercially available and used without further purification.

Methyl iodide, N-chlorosuccinimide, cyclohexene, toluene, α-methylstyrene, and triethylboron were commercially available and used without further purification.

All organolithium reagents were commercially available and were used without further purification. Trimethylchlorosilane was commercially available and was distilled (bp 57%/atm. pressure) prior to use. Boron trifluoride etherate was distilled (126°C/atm. pressure) under argon atmosphere. Norcarane was prepared as described by LeGoff et al.[12]

Cyclohexanone, 3-methylcyclohexanone and tert-butyl acetate were commercially available and used without further purification. 2-methyl-3-pentanone was commercially available (95%) and was purified by distillation with a spinning band column (120°C/atm. pressure).

Diisopropylamine (bp 83°/atm. pressure) was distilled and stored over molecular sieves. 2,2,6,6,-tetramethylpiperidine was commercially available and used without further purification. The last five amines listed in Table II were obtained from I. Kopka and used directly.

Tetrahydrofuran was dried over sodium benzophenone ketyl,

distilled, and stored under argon over molecular sieves. Dimethylformamide was dried over calcium hydride, distilled under vacuum and stored over molecular sieves. U. S. P. grade absolute ethanol was used without further purification. N,N,N,N-Tetramethylethelenediamine was dried over calcium hydride and distilled before use. All other solvents were used without further purification.

All inorganic reagents were commercially available and used without further purification.

II. Preparation of bis(1-ethylcyclohexyl) amine (17)

a. Preparation of 1-chloro-ethynylcyclohexane (14).

A 1-L. 3-neck flask provided with a magnetic stir-bar, thermometer and dropping funnel was charged with 28 g (0.25 mole) of calcium chloride, 20 g (0.20 mole) of cuprous chloride, 0.2 g of copper bronze power and 220 ml of cold concentrated hydrochloric acid. The mixture was cooled in an ice bath. 62 g (0.5 mole) of 1-ethynylcyclohexanol was added and the mixture was stirred for 1.5 hr. The upper organic layer was separated and washed with two 50 ml portions of cold concentrated hydrochloric acid and then with three 50 ml portions of distilled water. The product was dried over anhydrous potassium carbonate. Analysis of the crude product by GLC (10% Carbowax 20-M on chromosorb-W column) showed the sample to be 95% pure. The chloride was used without further purification. Total isolated yield of pure chloride was 80%. The infrared spectrum showed the ethynyl band at 3050 cm^{-1}, and no band for the starting alcohol. NMR(CDl_3) (TMS internal standard): F 2.6 (S, 1H), δ 2.0 (bm 4H), δ 1.6 (bm, 6H).

b. Preparation of Bis(1-ethynylcyclohexyl) amine (16).

A 500 ml round bottom flask, equipped with a magnetic stir-bar, septum inlet and gas inlet value was flame dried under argon. The gas inlet value was removed. 0.22 g of copper bronze powder and 0.22 of cuprous chloride were added to the flask. Then 110 ml of DMF and 31.9 g (0.26 mole) of 1-ethynylcyclohexylamine were added to the flask. The gas inlet value was reattached and the flask was flushed with argon for a few minutes. The flask was then cooled to $4^{o}C$ in a cold room. 19.5 g (0.13 mole) of 95% 1-chloro-1-ethynylcyclohexane was added dropwise by syringe to the stirring solution. The solution was stirred at $4^{o}C$ for 72 hr. The solution was then diluted with 100 ml of water followed by 12 ml of 50% NaOH (0.15 mole) and stirred for 10 minutes. The solution was extracted with three 50 ml aliquots of ether. The ether extracts were combined and dried over magnesium sulfate. The ether and the unreacted primary amine were removed under reduced pressure. The coupled amine (16) was distilled under vacuum (bp $103-106^{o}/2$ mm Hg). There was obtained 16.4 g (65%) of (16). ν_{max} = 3290, 2300, 1070 cm^{-1}; mp. $71-72^{o}C$, NMR ($CDCl_3$) δ 1.55 (M,13H), δ 2.0 (M, 8H), δ 2.35 (S, 2H) mass spectrum m/e 230 ($M^+ + 1$), 229 (M^+), 228 (17). 200 (21), 186 (52), 172 (73), 118 (50), 80 (100), 67 (49), 41 (58).

c. Hydrogenation of bis(1-ethynylcyclohexylamine) with W_2 Raney Nickel Catalyst.

Raney nickel alloy was activated as reported previously.[9] Two and a half teaspoon (10 g) of W_2 Raney nickel was added to a solution of 250 ml absolute ethanol and 11.45 g (50 mmoles) of bis(1-ethynylcyclohexyl) amine in a 500 ml centrifuge bottle. The bottle was placed in a

Parr hydrogenation apparatus and purged with hydrogen 5 times. The bottle was pressurized to 60 psi and the shaker turned on. After 20 hr, the solution was filtered to remove the catalyst and the ethanol evaporated under reduced pressure. GLC analysis (5% OV 101 Chromosorb W, acid washed, DMSC treated) showed it to be 91% pure, the impurity was not identified. The saturated amine (17) was purified by distillation with a spinning band column (110-113°C/0.3 mmHg). The isolated yield of the saturated amine was 80% (9.5 g).

The hydrogenation was repeated under identical conditions except that 0.1 mole (5.6 g) of potassium hydroxide was added to the ethanolic solution of bis(1-ethynylcyclohexyl) amine before addition of the Raney nickel catalyst. After the hydrogentation was completed, the catalyst and ethanol were removed. The residue was dissolved in ether and extracted with water. GLC analysis of the organic layer as described above indicated an 80% purity of the saturated amine. The same experiment was performed under identical conditions except that acetic acid (0.1 mmole) was used in place of potassium hydroxide. GLC analysis of the product under these conditions showed 87% purity of the saturated amine.

NMR ($CDCl_3$) δ 0.8 (t, 7H), δ 1.40 (M, 24H); mass spectrum m/e 237 (M^+), 184 (4), 128 (5), 98 (11), 86 (100), 72 (15), 57 (20); elemental analysis calculated for $C_{16}H_{31}N$: C, 81.01; H, 13.08; N, 5.91. Found: C, 81.11; H, 12.94; N, 5.79.

III. Reactions of bis(1-ethylcyclohexyl) amine (17)

Reaction of 17 with Methyl Iodide.

Methyl iodide (2 mmoles, 0.14 ml) was added to a 10 ml round bottom flask containing a stir bar, side arm septum, gas inlet valve and 2 ml of $CDCl_3$ at room temperature. Then 2 mmoles (0.5 ml) of 17 was added by a syringe. The reaction mixture was stirred overnight. NMR showed only unreacted methyl iodide and 17. The same experiment was performed with diisopropylamine and 2,2,6,6,-tetramethylpiperidine. Both amines reacted and the N-methylammonium iodide derivatives were formed quantitatively by NMR. NMR ($CDCl_3$) of N-methyl, diisorpylammonium iodide δ 1.0 (S, 13H), δ 2.43 (5, 3H), δ 3.23 (M, 2H). NMR ($CDCl_3$) of N-methyl, 2,2,6,6,-tetramethylpiridium iodide, δ 1.03 (S, 6H), δ 1.23 (S, 6H), δ 1.46 (S, 6H), δ 2.20 (S, 3H). N-methyl-2,2,6,6,-tetramethylpiperidine iodide was also identified by a mixed melting point with an authentic[10] sample m. p. 280°C.

The reaction of 17 (2 mmoles) with excess methyl iodide (4 mmoles) was performed under identified conditions except the reaction mixture was stirred for one week. The NMR of the reaction mixture was identical to that of the starting amine and methyl iodide. The same experiment was performed in C_2H_5OD. The reaction mixture was refluxed (80°C) for 6 hrs. The NMR of the residue after the solvent was evaporated was identical to that of the starting amine.

Reaction of 17 with $BF_3 \cdot OEt_2$.

A 10 ml flask, equipped with a magnetic stir bar, septum inlet and gas inlet valve was flame dried under argon. One mmole of 17 and hexane (1 ml) were added to the flask followed by $BF_3 \cdot OEt_2$ (1 mmole, 0.12 ml) was added. A white solid was formed immediately. Evaporation of the solvent under vacuum gave a quantilative yield (0.3 g) of a white, air stable solid. Crystallization from benzene (m. p. 154.5-55). NMR ($CDCl_3$) δ 1.05 (t, 6H), δ 1.6 (bm, 20H), δ 1.95 (bq, 4H); mass spectrum m/e 237 (M^+)—identical to free amine. Elemental analysis calculated for $C_{16}H_{31}NBF_3$: C, 62.96; H, 10.23; N, 4.59, B, 3.54, F, 18.67. Found: C, 61.11; H, 10.43; N, 4.39; B, 4.83; F, 19.22. The same experiment was performed with diisopropylamine and with 2,2,6,6,-tetramethylpiperidine. A white solid was formed in both cases. The same experiment with the above three amines was performed in $CDCl_3$. The NMR spectrum of each reaction showed an upfield shift for the chemical shift of the methylene hydrogens in diethyl ether. δ 3.4 (free ether), δ 4.13 (BF_3OEt_2) and δ 3.42 (reaction mixture).

Reaction of 17 with trimethylchlorosilane.

Essentially the same procedure was followed for the reaction of 17 with trimethylchlorosilane as that described for the reaction of 17 with excess iodide. The reaction mixture was stirred for four days. The NMR showed unreacted 17 and trimethylchlorosilane.

Reaction of 17 with N-Chlorosuccinimide (NCS).

N-Chlorosuccinimide (0.14 g, 1 mmole) and 17 (o.25 ml, 1 mmole) were stirred in methylene chloride (2 ml) at room temperature. The reaction was followed by NMR. The NCS disappeared gradually and completely after a week. The NMR spectrum of the product showed a broadening with slight shift of the main resonance peak of the starting amine to lower field, NMR (CCl_4) δ 0.95 (t , 6H), δ 1.6 (bm, 24H). The same experiment was performed in CCl_4 and CH_2Cl_2 (1:1) mixture (10 ml). The reaction mixture was refluxed for 20 hrs. The solvent was removed under vacuum and the residue was dissolved in 5 ml CH_2Cl_2. The solution was extracted with three 10 ml portions of water. The organic layer was dried over Na_2SO_4. The NMR spectrum was identical with the one mentioned above. GLC analysis with OV 101 column showed only the solvent peak and no amine or N-chloroamine. Mass spectrum showed m/e 271 (M^+).

Reaction of 17 with Bromine.

A 0.5 M standard solution of bromine in CCl_4 was prepared by introducing 7.99 g (2.56 ml) bromine to a 100 ml volumetric flask then completed to 100 ml by CCl_4. In a 100 ml round bottom flask fitted with magnetic stir bar, side arm septum and gas inlet valve, 1.7 ml (10 mmoles) of 2,2,6,6,-tetramethylpiperidine and 20 ml CCl_4 were introduced. To this mixture, 20 ml of the standard solution of bromine in CCl_4 was added dropwise at 0^oC. The reaction mixture was stirred for 5 minutes, and an orange precipitate was formed. The solid was collected by filtration and washed three times with 5 ml portions of

hexane. The solid (2 g, 66%) was transferred to an erlenmeyer flask and 10 ml of 1.1825N NaOH solution was added. The solution was extracted with three 10 ml portions of ether and the organic layer was dried over magnesium sulfate. NMR (CCl_4) δ 1.2 (S, 12H), δ 1.56 (S, 6H). However, the NMR of the mother liquor showed similar resonance peaks. The same experiment was repeated but with a different sequence. 2,2,6,6,-tetramethylpiperidine (1 mmole) was added to a mixture of 1.18N NaOH (1 ml) and hexane (1 ml). To this mixture, bromine (1 mmole, 6.06 ml) was added dropwise by syringe with vigorous stirring. After 10 minutes, the organic layer was dried over $MgSO_4$ and hexane was removed under vacuum. To the residue 1 mmole of benzene was added (internal standard) and the NMR in $CDCl_3$ was taken. The yield of N-bromoamine was 95%. A large scale (100 mmole) experiment was performed exactly but the residue was distilled (65-70°C/0.7 mm). The isolated yield was 71% with identical spectral data as before. The last experiment was repeated with amine 17, but the N-bromo-derivative was not isolated but was reacted with sodium as described in the following section.

Reaction of N-Bromoamines with Sodium.

The procedure given below for the reaction of sodium with N-bromo-2,2,6,6,-tetramethylpiperidine is representative for the reactions shown in Table II.

A 10 ml round bottom flask equipped with a side arm septum, stir bar and gas inlet valve was flushed with argon and charged with sodium dispersion(40% in mineral oil) (0.15 ml, 2.2 mmoles) and hexane (1 ml). To this mixture, a 1 M solution of the N-bromoamine (1 ml) in hexane was added dropwise at room temperature. The mixture was stirred for 50

minutes and analyzed for the Na-amide as follows: Cyclohexanone (0.1 ml, 1 mmole) was added dropwise and stirred for 10 minutes. Then trimethylchlorosilane (0.13 ml, 1 mmole) was added all at once and $C_{11}H_{24}$ (0.21 ml, 1 mmole), internal standard, was also added. The reaction mixture was diluted with pentane (1 ml) and analyzed by GLC with an SE-30 column. A 74% yield of 1-trimethylsilyloxy-1-cyclohexene was established. A sample of this compound was isolated by preparative GLC; NMR ($CDCl_3$) δ 0.16 (S,9H), δ 1.5 (bm, 4H), δ 1.97 (bs, 4H), δ 4.8 (t of t, 1H).

Reaction of 17 with Organolithium Reagents.

The procedure given below for the reaction of n-butyllithium with 17 is representative.

A 10 ml round bottom flask equipped with side arm, magnetic bar, fitted with a gas measuring burrette was flame dried under argon and charged with 1.6M solution of n-butyllithium in hexane (2 mmoles, 1.25 ml). The reaction mixture was saturated with n-butane and amine 17 (2 mmole, 0.5 ml) was then added at room temperature. The reaction mixture was stirred for 4 days. 49 ml (2 mmoles) of butane gas was evolved.

Reaction of 17 with n-Butyllithium in the Presence of TMEDA.

The same experiment described above was repeated but after the addition of the amine 17, 2 mmole (0.3 ml) of TMEDA was added. 51 ml (2.01 mmoles) of butane gas was evolved immediately. The same experiment was repeated with 0.2 mmole (0.03 ml) TMEDA. A total of 2 mmoles of butane gas was evolved after 4 hrs of stirring at room temperature.

Analysis for Li-Amide Formation.

Hexane was removed from the amide solution formed above under vacuum. The residue was then dissolved in THF (2 ml) and cooled by dry ice acetone bath to -78°C. t-Butyl acetate (0.27 ml, 2 mmoles) was added dropwise and the reaction mixture was stirred for 15 minutes. Cyclohexanone (0.2 ml, 2 mmoles) was added dropwise and the reaction mixture was stirred for another 15 minutes. Then water (1 ml) was added. The dry ice acetone bath was removed and the reaction mixture was warmed to room temperature. n-$C_{15}H_{32}$ (0.55 ml, 2 mmoles) was added as internal standard for glc analysis. To this mixture ~0.2 g potassium carbonate was added followed by 2 ml pentane. The organic layer was dried over sodium sulfate and analyzed by GLC (SE-30 column) for the formation of the β-hydroxy ester. The yield was 99%.

IV. Reactions of the lithio-bis(1-ethylcyclohexyl) amide (27)

Reaction of the Amide 27 with Methyl Iodide.

A 1 mmole of 27 was prepared with 10% TMEDA as described above. 0.5 ml cyclohexene was added to the amide solution followed by 0.08 ml (1.3 mmole) of methyl iodide. The reaction mixture was stirred overnight and then analyzed for the formation of norcarane by GLC (OV 101 column). The GLC trace showed only a peak for the starting amine. The same experiment was performed and the reaction mixture was analyzed for unreacted amide, but the sequence described above for formation of the β-hydroxy ester. The amount of the amide found was less than 5%. The same experiment was performed with LiTMP instead of 27. GLC analysis

showed 57% of the amide was methylated but no norcarane was formed.

Reaction of 27 With Toluene.

One mmole of 27 was prepared with 10% TMEDA as described above. 0.11 ml (1 mmole) of toluene was added to the amide solution and the mixture was stirred for 16 h. Then 0.15 ml (1.1 mmole) of trimethylchlorosilane was added at 0°C. The reaction mixture was warmed to room temperature and quenched with 1 ml of water. The organic layer was dried over potassium carbonate and analyzed by GLC (SE-30 column). Relative to the amount of recovered amine the recovered unreacted toluene was 80%, mono-silylated tol ene was 9% and disilylated toluene was 5%. The silylation products were identified by GLC-mass spectrum analysis. Mono-silylated toluene mass spectrum m/e 164 (M^+), 149 (31), 121 (30), 91 (34), 73 (100), 65 (23), 43 (40). Disilylated toluene m/e 236 (M^+), 148 (88), 133 (17), 73 (100), 45 (58). The same experiment was performed for different periods of time prior to quenching with trimethylchlorosilane.

Reaction of 27 with α-Methylstyrene.

One mmole of 27 was prepared as described above and 0.13 ml (1 mmole) of α-methylstyrene was added to the amide solution. The mixture was stirred at room temperature for 20 h and quenched with trimethylchlorosilane (0.15 ml, 1.1 mmole). GLC analysis (SE-30 column) of the reaction mixture showed only unreacted α-methylstyrene. The experiment was performed again and quenched with methyl iodide after 20 h. Analysis of the reaction mixture by GLC showed unreacted α-methylstyrene and amine 17.

Reaction of 27 with triethylboron.

One mmole of 27 was prepared as described above. The solvent was evaporated under reduced pressure and 1 ml benzene was added. 0.14 ml of triethylboron (1 mmole) was then added to the reaction mixture and stirred for 42 hrs at room temperature. The mixture was quenched with 0.2 ml of deuterium oxide, followed by the addition of 0.2 ml 3N HCH a few minutes later. The water layer was removed with a syringe and the remaining organic layer was saturated with anhydrous potassium carbonate. The organic layer was then analyzed by GLC-mass spectra.

The same experiment was performed but quenched with methyl iodide instead of D_2O and was then analyzed for the methylation product by GLC-mass spectra.

Preparation of B-methyl-9-borabicyclo[3.3.1]nonane.

A 500 ml flask equipped with a reflux condenser, an addition funnel, a magnetic stirring bar, and a side-arm fitted with a rubber serum stopper was flushed with argon and maintained under a static argon atmosphere. 85 ml of a 1.18M solution of methyllithium (100 mmoles) in ether was placed in the cleaned dropping funnel and added dropwise to the solution of 9-borabicyclo[3.3.1]nonane at $0^{\circ}C$ over a period of one hour. This was immediately followed by dropwise addition of 6.5 ml of methanesulfonic acid (100 mmoles) and approximately 100 mmoles of hydrogen was rapidly evolved. The salt was allowed to settle, and the clear solution was transferred under argon to a distilling flask and the product distilled. A 74% yield of B-methyl-9-BBN b. p. $48-50^{\circ}C/6$ mm was obtained (12 ml).

Reaction of 27 with B-methyl-9BBN.

The same procedure described for the reaction of 27 with triethylboron was repeated exactly with B-methyl-9BBN. The reaction mixture was quenched with D_2O.

Reaction of 27 and other Li-amides with Unsymmetrical ketones.

The procedure given below for the reaction of 27 with 3-methylcyclohexanone is representative of the reactions shown in Tables II and III.

A 3.2 mmoles of 27 was prepared with equivalent amount of TMEDA (0.48 ml). The solvent was removed under vacuum which was broken with argon. The yellowish viscous residue was dissolved in 3 ml THF and cooled in a dry ice acetone bath. 3-Methylcyclohexanone (0.37 ml, 3 mmoles) was added dropwise and after 20 minutes, the reaction was quenched with 0.42 ml of trimethylchlorosilane (3.2 mmoles). The reaction mixture was stirred for 30 minutes and then the bath was removed. Upon warming to room temperature, 0.39 ml of decane (3 mmoles), internal standard, was added. The resulting solution was diluted with 3 ml pentane and then 6 ml saturated $NaltCO_3$ was added. The organic layer was dried over anhydrous sodium sulfate before glc analysis (1/8 in x 40 ft stainless steel column packed with 20% SE-30 on chromosorb W). The reaction mixture was analyzed by glc and/or NMR. NMR ($CDCl_2$) δ 4.82 (m, vinylic proton), δ 4.72 (m, vinylic proton), δ 1.95 (m, 6H), δ 1.02 (m, 4H), δ 0.28 (5, 9H).

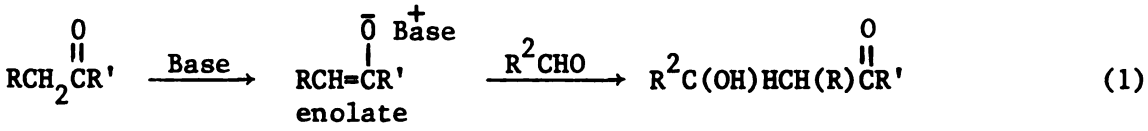
The NMR data for the products from the reaction of 2-methyl-3-pentanone were identical to the literature values.[35]

CHAPTER II

STEREOCHEMISTRY OF ENOLATE FORMATION

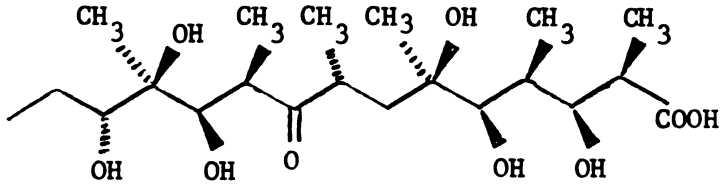
INTRODUCTION

The aldol condensation is a reaction of fundamental importance in biosynthesis (eq. 1). Compound 1, for example, which is the



(1)

open-chain form of the aglycone of the macrolide erythromycin A,[24] can be regarded as the result of a series of six aldol type condensations. The presence of ten chiral centers in this molecule requires that



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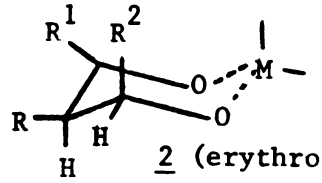
sufficient control be maintained over the stereochemical outcome of each condensation. This is typical of the biosynthesis of other macrolide aglycones in which the carbon skeleton originates from a series of condensations of acetyl- and propionyl-CoA units.[25]

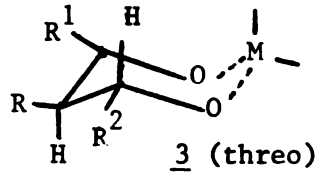
The formation of enolates from carbonyl compounds by the action of base is the first step in the aldol condensation (eq. 1). While the regiochemical aspects of this reaction have been studied extensively,[26] it is only recently that attention has been devoted to the stereochemistry of the reaction. The correlation of enolate geometry with the

stereochemical outcome of the aldol reaction has provided a strong incentive to such studies.

In 1973 House and coworkers[27] found that addition of chelating divalent cations such as Zn^{2+} or Mg^{2+} to preformed lithium enolates leads to aldol product mixtures rich in the threo product 3, regardless of enolate geometry. They attributed this preference to the greater stability of the threo chelate 3, in which the greater number of substituents on the cyclic intermediate occupy equatorial positions.

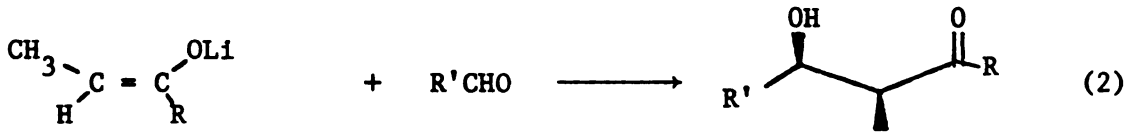


2 (erythro)



3 (threo)

Dubois[28] was apparently the first to relate the stereochemical outcome of the aldol to the geometry of the enolate. He showed that the condensation is subject to kinetic stereoselection with Z-enolates giving predominantly the erythro aldol 4 (eq. 2) and E-enolates leading predominantly to the threo isomer 5 (eq. 3).



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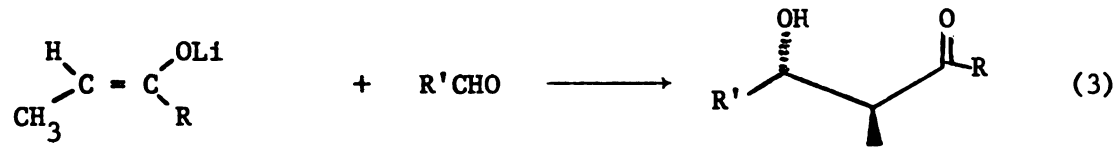
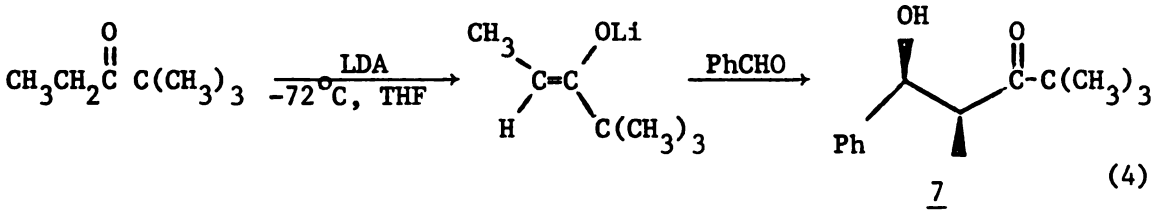


(3)

5

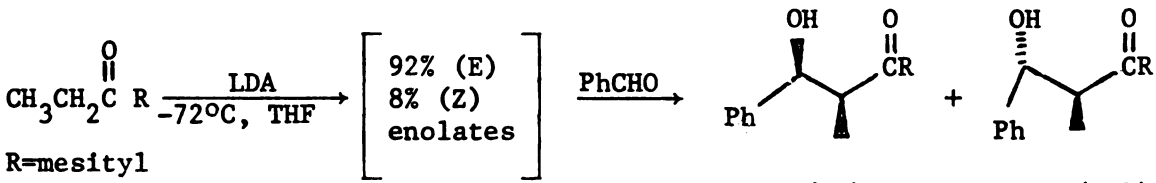
In 1977 Heathcock[29] examined the use of preformed lithium enolates and found that in some cases complete kinetic stereoselection may be achieved. For aldol condensations of the type typified by equations 2 and 3, complete kinetic stereoselection was observed when R

is bulky. The Z-enolate gave the erythro aldol and the E-enolate gave the threo aldol. For example, the condensation of 2,2,-dimethyl-3-pentanone (100% Z-enolate) with benzaldehyde gave erythro aldol 7 with no measurable amount of threo aldol. Ethyl mesityl ketone gave a



7 (4)

92% (E): 8% (Z) enolates mixture when reacted with LDA at -72°C. Reaction of this mixture with benzaldehyde generated a mixture of 92%

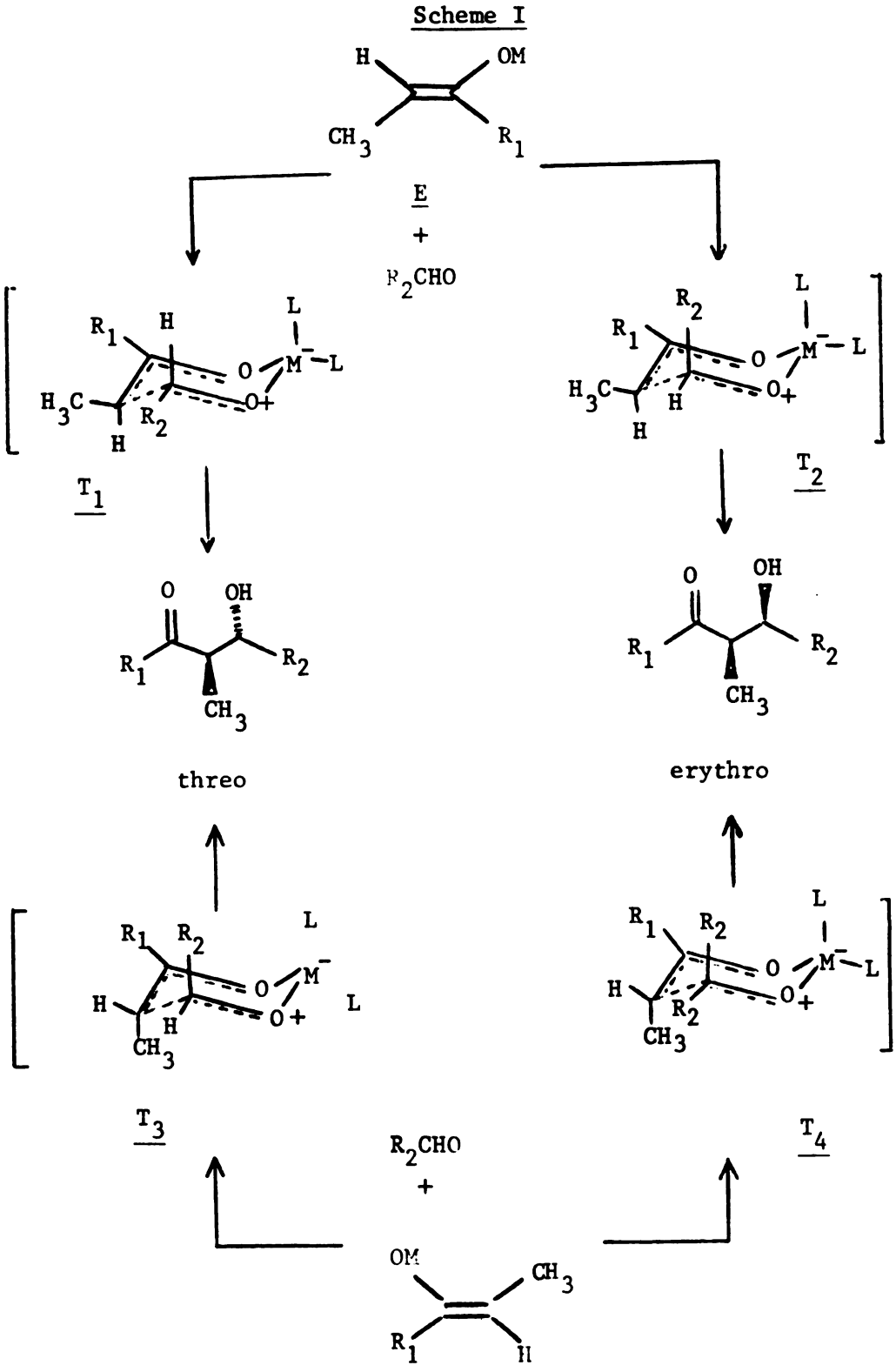


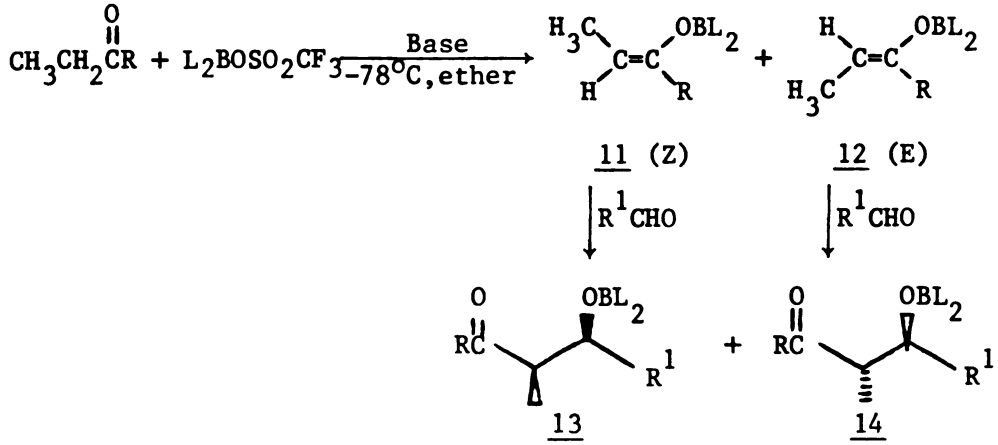
10, erythro (8%) 9, threo (92%) (5)

threo (9) and 8% erythro (10) condensation adducts. When R is smaller (ethyl, isopropyl,. . .) stereoselectivity diminished or disappeared.

In 1979 Evans and coworkers[30] investigated the stereochemistry of the aldol condensations of boron enolates. High kinetic stereoselection was observed, regardless of the size of R, the Z-enolate (11) giving the erythro adduct 13, and the E-enolate (12) giving the threo adduct 14 (eq. 6). Evans attributed the high steroselectivity to steric parameters involved in the pericyclic transition states leading to the diastereoisomeric adducts (Scheme I). In the case of an E-enolate, for example, transition state T_2 would be destabilized relative to T_1 by non-bonded interactions between R_2 and R_1 and between R_2 and L.

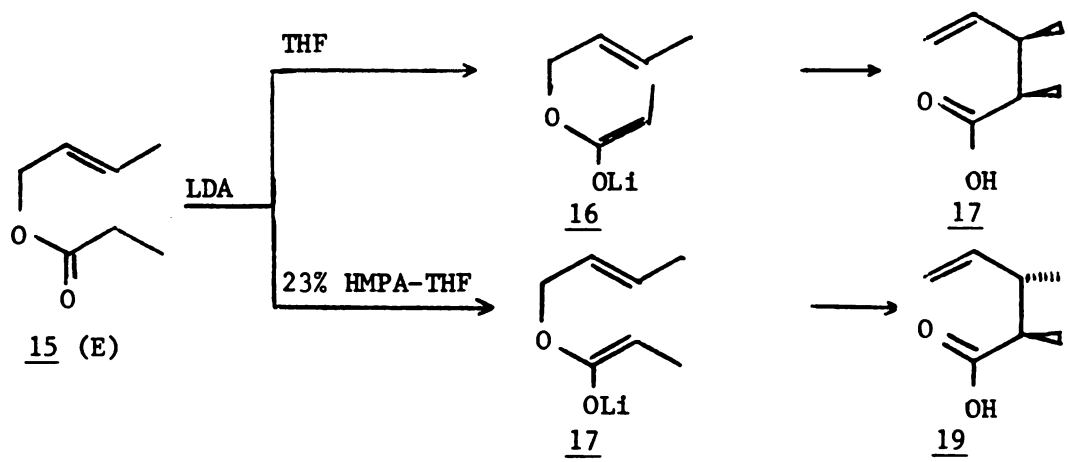
Scheme I





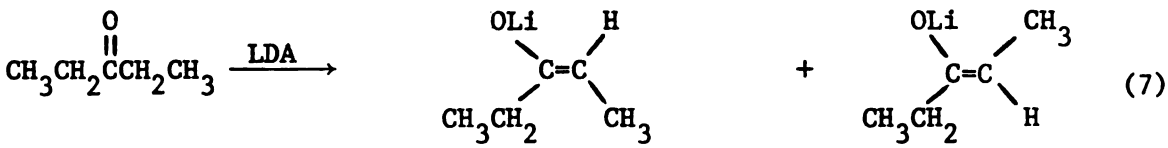
In 1976, Ireland and coworkers[31] investigated the ester enolate Claisen rearrangement with a variety of allylic esters. They found a stereochemical control operating through stereoselective enolate formation. Scheme II demonstrates the rearrangement of E-crotyl propanoate. In the THF solution, the enolate anion or the derived silyl

Scheme II



ketene acetal yielded the erythro rearrangement isomer 17. However, in the more coordinating solvent system 23% HMPA-THF, enolization took an alternative course and threo acid 19 was the major product. It was assumed that in THF the Z-type enolate 16 was preferentially formed and

trapped, but in 23% HMPA-THF the geometrically isomeric E-type enolate anion 18 was preferentially formed. Similar results were obtained with the symmetrical ketone 3-pentanone. A high degree of selectivity for the formation of one enolate in THF [77% (E): 23% (Z)] and the other

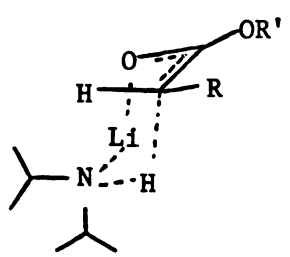


(7)

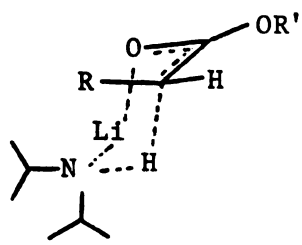
THF	77%	23%
23% HMPA-THF	5%	95%

enolate in HMPA-THF [5% (E): 95% (Z)] was observed.

Ireland rationalized this dramatic solvent effect by considering the steric requirements for enolization of the two transition states 20 and 21. In the less coordinating solvent, THF, the interaction of the carbonyl oxygen with the lithium cation is assumed to be quite important



20 (Z)

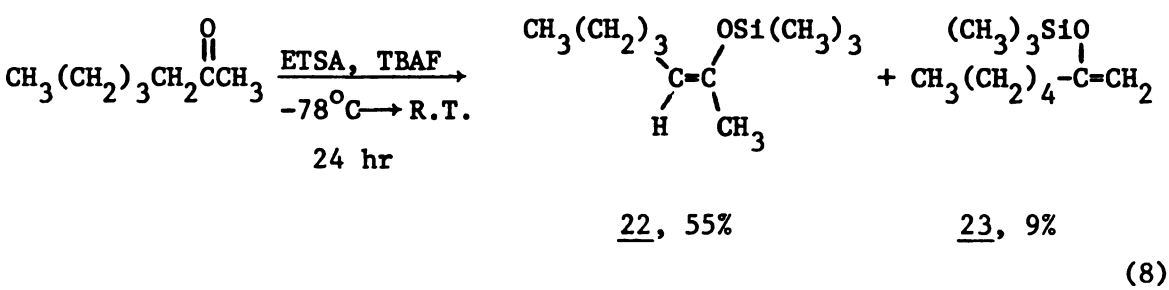


21 (E)

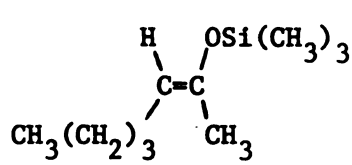
and the carbonyl oxygen became effectively bulkier than -OR'. The resulting non-bonded interactions raised the energy of transition state 21, and enolization proceeded through transition state 20. The presence of HMPA, on the other hand, resulted in greater solvation of the lithium cation and an enhanced reactivity of the amide base. The lithium-carbonyl oxygen interaction was assumed to be weaker and transition state 21, in which R becomes eclipsed with the now sterically smaller carbonyl

oxygen during enolization, was favored. Similar effects of HMPA on anion stereochemistry have been reported for deprotonation reactions of a variety of ketones,[29a] hydrazones,[32] and oxazolines.[33]

In 1978 Kuwajima and coworkers[34] investigated the formation of the silyl enol ethers of few acyclic ketones with ethyl trimethyl silyl acetate (ETSA) and catalytic amounts of tetrabutylammonium fluoride (TBAF) in THF. Silylation of 5-nonanone at 0°C gave exclusively the Z-silyl enol ether. Silylation of 2-heptanone gave the Z-silyl enol ether 22 in 55% yield together with the regio-isomer 23 in 9% yield (the E-isomer 24 was not detected).

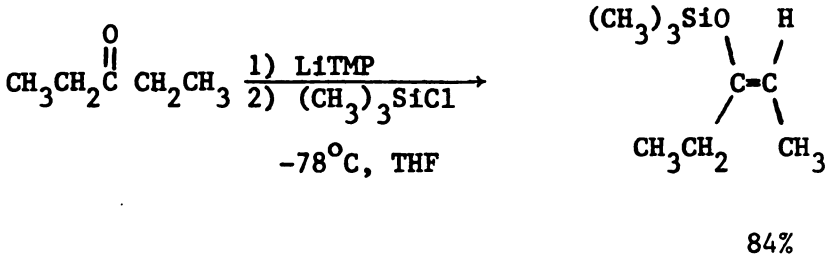


22, 55% 23, 9% (8)



24, 0%

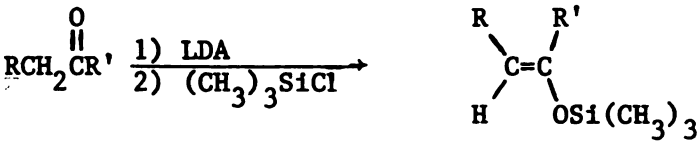
Kuwajima and coworkers also investigated the reaction of LiTMP with 3-pentanone and obtained 84% of the E-silyl enol ether. This E-selectivity is higher than that obtained by Ireland with LDA under similar conditions (77% E). This difference in selectivity was



84% (9)

attributed to the increased bulk of LiTMP over LDA (stabilizing 20 over 21).

In a study of the formation of silyl enol ethers from unsymmetrical ketones, House[35] found that deprotonation with LDA followed by enolate quenching with trimethylchlorosilane gave a mixture in which the less highly substituted silyl enol ether (except for case d eq. 10) is the principal product. When trimethylamine and trimethylchlorosilane were used, mixtures of both regio- and stereoisomers (except for case d eq. 10) were obtained, but it was not clear whether these results were



(10)

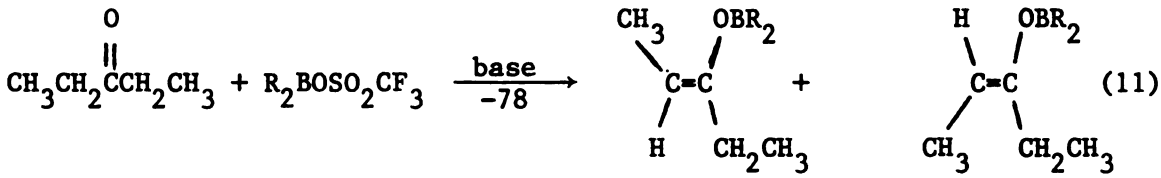
	25	26	27
a) R=Me, R'=isopropyl	53% (20%)	42% (62%)	5% (18%)
b) R=Me, R'=Me	16% (24%)	13% (64%)	71% (12%)
c) R=n-butyl, R'=Me	9% (29%)	7% (58%)	84% (13%)
d) R=Ph, R'=Me	86% (33%)	14% (67%)	0% (0%)

The results between ( ) are with triethylamine.

due to partial or complete equilibration of the enolates. House also observed that LDA slightly favors the formation of E-silyl enol ethers 25 rather than the Z-isomers 26.

In his study of the stereochemistry of aldol condensations of

boron enolates, Evans also investigated the stereochemistry of the enolates themselves. These were prepared by mixing dialkylboron triflates ($R_2BOSO_2CF_3$) and diisopropylethylamine with one equivalent of ketone. Evans obtained Z-enolates exclusively (>99%) in most cases; however, he found that the kinetically controlled enolate ratio (28:29) was a function of the base employed in the enolization process. Thus



(11)

	28 (Z)	29 (E)
Diisopropylethylamine	99%	1%
Lutidine	69%	31%

3-pentanone with diisopropylethylamine gave 99% (Z): 1% (E), whereas with lutidine it gave 69% (Z): 31% (E).

It is clear from the above review, that enolate geometry is a major factor in determining the stereochemical outcome of the aldol reaction. Consequently, we decided to study the factors which determine the stereoselectivity of the enolate formation reaction in greater detail.

RESULTS

The ratio of the two enolates (E and Z) obtained from the reaction of 3-pentanone with lithium dialkyl amides was studied. The lithium dialkyl amides were prepared by reaction of the corresponding secondary amine with n-butyllithium in hexane (eq. 12). 3-Pentanone was

$$R_2NH + \text{n-BuLi} \xrightarrow{\text{hexane}} R_2N\ Li + \text{n-BuH} \qquad (12)$$

added dropwise to a THF solution of the dialkyl amide. The resulting solution was analyzed for the two enolates 30 and 31 by quenching with trimethylchlorosilane and analyzing by GLC for the corresponding trimethylsilyl enol ethers 32 and 33 (eq. 13).

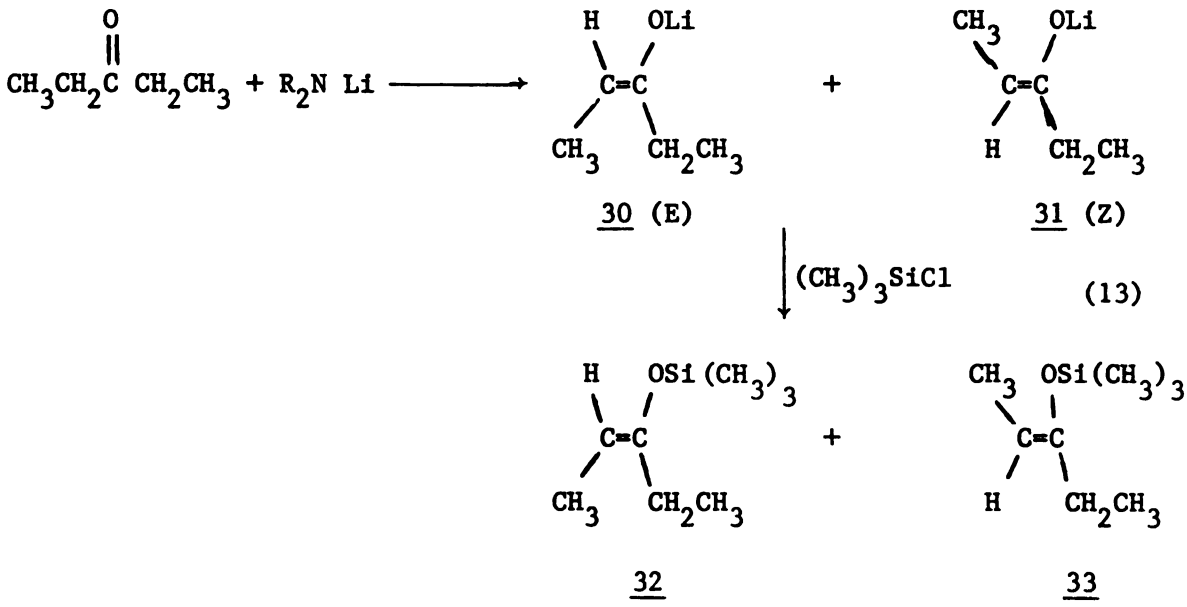


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TABLE IV

A Study of the Concentration Effect on the E and Z Enolate Ratio at 0°C with 10% Excess Amide.

3-Pentanone + LiTMP ⟶ E-(30) + Z-(31)

Entry	[Conc.]	E(30):Z(31)	Overall Yield
1	3.0M	38.5:61.5	94%
2	1.0M	86:14	100%
3	0.5M	89:11	83%
4	0.1M	90.6:9.4	100%
5	0.02M	92:8	90%

A Study of the Concentration Effects on the E and Z Enolate Ratio.

THF was chosen as the solvent for our initial study because it is the most commonly used solvent for enolate forming reactions. LiTMP was reacted with 3-pentanone at 0°C at various concentrations in THF. The results obtained are shown in Table IV.

A Study of the Stability of the Enolates, 30 and 31, and the Corresponding Silyl Ethers, 32 and 33.

The stability of the enolates, 30 and 31, and the trimethylsilyl enol ethers, 32 and 33, was investigated. Standard solutions of enolates 30 and 31 were prepared by addition of 3-pentanone to a slight excess (1.1 equiv.) of a 1.0 M solution of LiTMP in THF at 0°C. These solutions were quenched with trimethylchlorosilane after various periods of time at various temperatures and analyzed by GLC for the formation of 32 and 33. Both enolate total yield (92-100%) and 30 to 31 ratio (82-86):(18-14) did not change over a period of 24 h at 25°C in the absence of any solvent additive, or in the presence of 1-4 equivalent of HMPA or TMEDA.

A Study of the Temperature Effect on the E and Z Enolate Ratio.

The temperature effect was investigated by dissolving the amide (LiTMP) in THF (1 M). 3-Pentanone (0.9 equiv) was then added dropwise at the specified temperature to the amide solution, followed after 15 minutes by trimethylchlorosilane. The reaction mixture was then worked up and analyzed by GLC for 32 and 33. Reaction temperature was found to have only a slight effect on the ratio of E and Z enolates (30 and 31). The ratio of 30:31 was slightly lower at reflux temperature (70°C)

TABLE V

A Study of the Temperature Effect on the E and Z Enolate Ratio.

3-Pentanone + LiTMP ⟶ E-(30) + Z-(31)

Entry	Temperature	E:Z	Overall Yield
1	-78^{o}	84:16	100%
2	-23^{o}	87:13	92%
3	0^{o}	86:14	100%
4	70^{o}	73:27	97%
5	25^{o}	87:13	95%

but remained constant within experimental error, at the other temperatures studied. The results are presented in Table V.

A Study of the Solvent Effect on the E and Z Enolate Ratio.

Because only aprotic solvents can be used with lithium amides, a very limited number of solvents was tried. LiTMP was dissolved in the specified solvent (hexane, benzene, t-butylamine, diethyl ether or THF) at 0°C (25°C for benzene) and 3-pentanone (0.9 equiv) was added dropwise. Trimethylchlorosilane was then added and the reaction mixture was analyzed by GLC. The highest E:Z (32:33) ratio and highest enolate total yield was obtained with THF as solvent. The enolate total yields with the other solvents were low. However, a higher total yield was obtained with THF added during the silylation step. The results obtained are presented in Table VI.

A Study of the Effect of Excess Ketone on the E and Z Enolate Ratio.

A standard solution A of the enolates 30 and 31 was prepared by addition of 3-pentanone to a slight excess (1.1 equiv) of a 1.0 M solution of LiTMP in THF at 0°C. To this standard solution, 0.2 equivalent of 3-pentanone or 0.2 equivalent of benzophenone at 0°C was added and the solution was then quenched after various periods of time with trimethylchlorosilane. The results are presented in Figure I.

The results shown in Figure II were obtained by addition of equivalent amounts of TMEDA or HMPA (w. r. t. LiTMP) shortly after the addition of excess (0.2 equiv) 3-pentanone to solution A at 0°C.

The results shown in Figure III were obtained by addition of either 2 or 4 equivalents of TMEDA or HMPA shortly after the addition

TABLE VI

A Study of the Solvent Effect on the E and Z Enolate Ratio.

3-Pentanone + LiTMP ⟶ E-(30) + Z-(31)

Entry	Solvent	E:Z	Overall Yield
1	Hexane	12.5:87.5	<5%
2	Hexane (THF added to help silylation)	48:52	89%
3	$(CH_3)_3CNH_2$ (Silylation in THF)	10:90	35%
4	Benzene (THF added to help silylation)	56:44	76%
5	Diethyl ether	73:27	78%
6	THF	86:14	99%

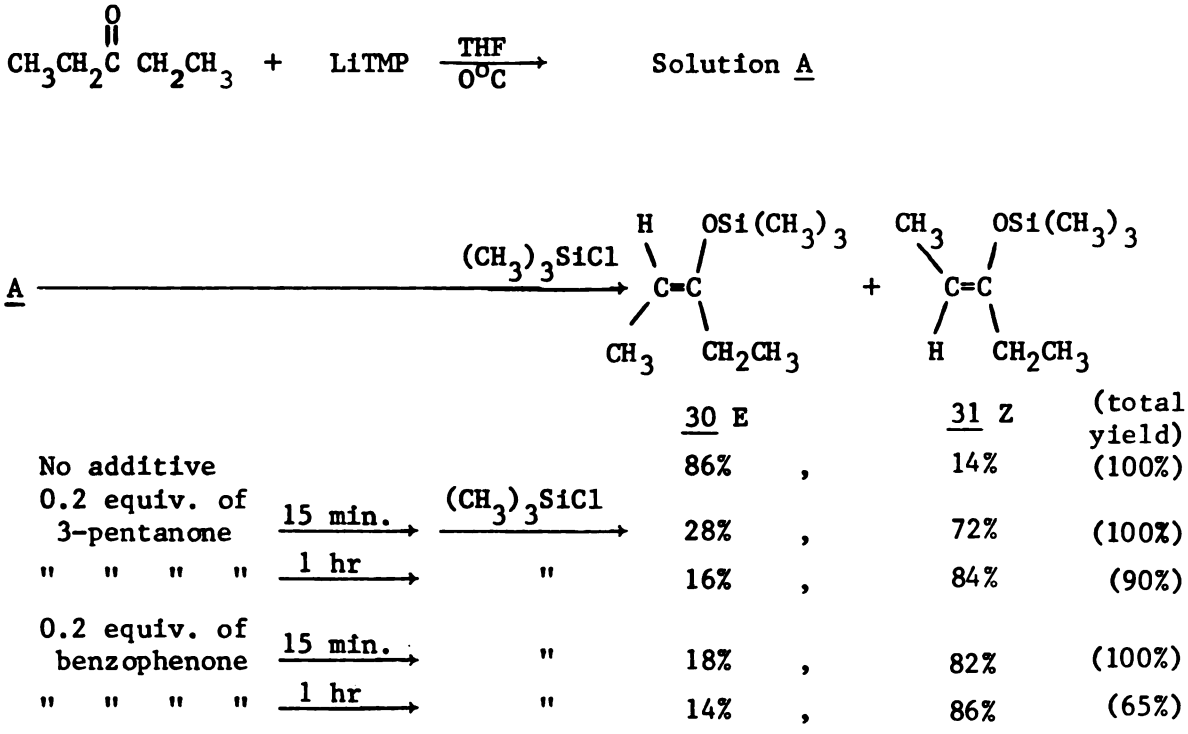


Figure I. The Effect of Excess Ketone on the E and Z Enolate Ratio.

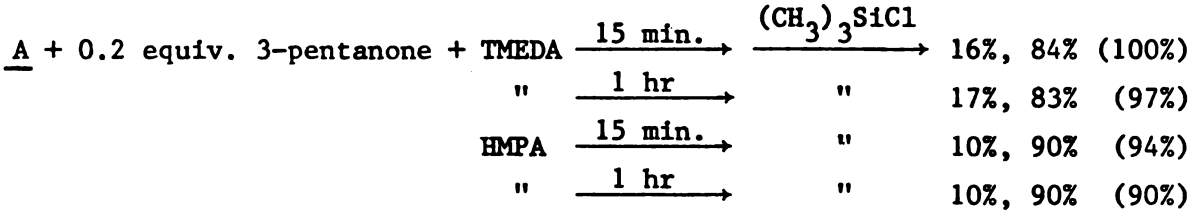


Figure II. The Effect of Excess Ketone in the Presence of TMEDA and HMPA on the E and Z Enolate Ratio.

of excess (0.2 equiv) 3-pentanone to solution A at 0°C.

The effect of excess ketone on the Z and E enolate ratio was also investigated in the presence and absence of TMEDA or HMPA at

A	15 min. $(CH_3)_3SiCl$	E , Z	(total yield)
A + 0.2 equiv 3-pentanone +	2.0 TMEDA, " "	15% , 85%	(83%)
	4.0 TMEDA, " "	11% , 89%	(65%)
	2.0 HMPA, " "	7% , 93%	(88%)
	4.0 HMPA, " "	6% , 94%	(68%)

Figure III. The Effect of Excess TMEDA or HMPA on the E and Z Enolate Ratio.

-78°C. In this study solution A was cooled to -78°C and then excess ketone (0.2 equiv) was added. The reaction mixture was quenched with trimethylchlorosilane at -78°C, and in the first reaction (Figure IV) TMEDA was added to activate the silylation at -78°C. The results obtained are presented in Figure IV .

A	$(CH_3)_3SiCl$		E , Z	(total yield)
A + 0.2 equiv 3-pentanone	$\xrightarrow[-78°C]{1\ hr}$	"	82% , 18%	(89%)
1.0 TMEDA	$\xrightarrow["]{"}$	"	88% , 12%	(99%)
1.0 HMPA	$\xrightarrow["]{"}$	"	67% , 33%	(49%)
1.0 HMPA	$\xrightarrow["]{"}$	$\xrightarrow[0°C]{1\ hr}$ "	7% , 93%	(83%)

Figure IV. The effect of Excess Ketone in the Presence or Absence of TMEDA or HMPA on the Z and E Enolate Ratio at -78°C.

The low enolate overall yield in the presence of HMPA at -78°C is possibly due to an irreversible aldol condensation (eq. 14).

$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 + LiTMP \xrightarrow[(CH_3)_3SiCl]{THF\text{-}HMPA} \underline{32} + \underline{33} + \underset{\underline{34}}{(CH_3CH_2)_2\overset{(CH_3)_3SiO}{\overset{|}{C}}CH(CH_3)\overset{O}{\overset{\|}{C}}CH_2CH_3} \qquad (14)$$

We examined for this possibility by reacting acetone with a slight excess (1.1 equiv) of LDA in THF at -78°C. An equivalent amount of both HMPA and 3- pentanone was then added to the reaction mixture. The solution was quenched with trimethylchlorosilane. GLC and NMR analysis indicated that the main product was the trimethylsilyl enol ether of 3-pentanone. The NMR spectrum of the reaction residue indicated that only a small amount, if any, of the aldol product 35 (eq. 15) was present. The same experiment was repeated with acetophenone in place of

$$CH_3\overset{O}{\overset{\|}{C}}-CH_3 + LDA \xrightarrow[3)\ (CH_3)_3SiCl]{1)HMPA\ 2)CH_3CH_2\overset{O}{\overset{\|}{C}}-CH_2CH_3} CH_3CH{=}\overset{OSi(CH_3)_3}{\overset{|}{C}}CH_2CH_3 + \underset{\underline{35}}{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{OSi(CH_3)_3}{\overset{|}{C}}(CH_2CH_3)_2} \qquad (15)$$

acetone. The NMR spectrum of the reaction residue indicated that the major component was the trimethylsilyl enol ether of acetophenone 36 (eq. 16).

$$PhCCH_3 + LDA \xrightarrow[3)\ (CH_3)_3SiCl]{1)HMPA\ 2)CH_3CH_2\overset{O}{\overset{\|}{C}}-CH_2CH_3} \underset{\underline{36}}{Ph\text{-}\overset{OSi(CH_3)_3}{\overset{|}{C}}{=}CH_2} \qquad (16)$$

A Study of the Effect of Excess Amide on the E and Z Enolate Ratio.

The relative amounts of 30 (E) and 31 (Z) enolates formed by reaction of various quantities of 3-pentanone with a fixed quantity of LiTMP or LDA at 0°C were determined. Addition of 0.9 equivalent of 3-pentanone to a THF solution of LiTMP produces mainly E-enolate (30). However, addition of 0.9 equivalent of 3-pentanone to THF solution containing LiTMP and either TMEDA or HMPA produces mainly Z-enolate (31). Addition of only 0.45 equivalent of 3-pentanone produces mainly E-enolate (30) in the presence or absence of TMEDA or HMPA. The maximum E-selectivity was obtained by addition of 0.25 equivalent of 3-pentanone to a solution of LiTMP and TMEDA. The results are shown in Table VII.

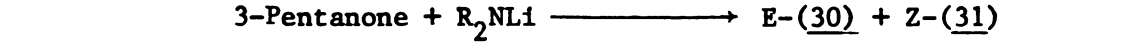
Similar trends were observed with LDA in place of LiTMP, but the ratio of 30:31 was slightly smaller with LDA (Table VII).

The ratio of enolates 30 (E) and 31 (Z) formed in the presence of excess amide (LiTMP) and excess HMPA and TMEDA was also investigated. A 2:1 or 4:1 ratio of LiTMP to 3-pentanone was used in this investigation to insure conditions of kinetic control. One equivalent of LiTMP was dissolved in THF at 0°C, then the specified amount of TMEDA or HMPA was added. 3-Pentanone was added dropwise to this mixture. The results are shown in Figure V.

The effect of excess amide on the Z and E enolate ratio was also investigated at -78°C. The THF solution of LiTMP was cooled to -78°C. One equivalent of TMEDA or HMPA was added to the reaction mixture followed by 0.9 equivalent of 3-pentanone. The reaction mixture was then quenched with trimethylchlorosilane and analyzed for 32

TABLE VII

Deprotonation of 3-Pentanone with LiTMP or LDA (1.0 mmole) in THF at 0°C.



Entry	3-Pentanone mmole	Additive, mmole	(E)-30:(Z)-31	(Overall Yield)
1	0.9	———	86:14	100%
2	0.45	———	88:12	90%
3	0.9	HMPA, 1.0	8:92	89%
4	0.45	HMPA, 1.0	65:35	75%
5	0.25	HMPA, 1.0	66:34	80%
6	0.9	TMEDA, 1.0	17:83	70%
7	0.45	TMEDA, 1.0	91:9	90%
8	0.25	TMEDA, 1.0	95:5	70%
9	0.9	HMPA[a], 1.0	53:47	91%
10	0.45	HMPA[a], 1.0	59:41	84%
11	0.9	TMEDA[a], 1.0	17:83	78%
12	0.45	TMEDA[a], 1.0	69:31	95%
13	0.9	TMEDA[b], 1.0	77:23	45%
14	0.9	LiCl[c], 5.0	40:60	96%
15	0.9[d]	———	90:10	100%

[a]Deprotonation of 3-pentanone by LDA. [b]Trimethylchlorosilane was in the reaction mixture during the deprotonation step. [c]LiCl was added prior to the deprotonation. [d]The ketone was added as 1M solution in THF.

LiTMP	+ TMEDA	3-Pentanone, 0°C, THF	$(CH_3)_3SiCl$	32 (E) , 33 (Z)	(total yield)
2.0	4.0	0.9	"	88% , 12%	(77%)
	9.0	0.9	"	85% , 15%	(90%)
	9.0	0.45	"	86% , 14%	(82%)
	4.0 (HMPA)	0.9	"	54% , 46%	(70%)
	9.0 (")	0.9	"	52% , 48%	(89%)
	9.0 (")	0.45	"	51% , 49%	(55%)

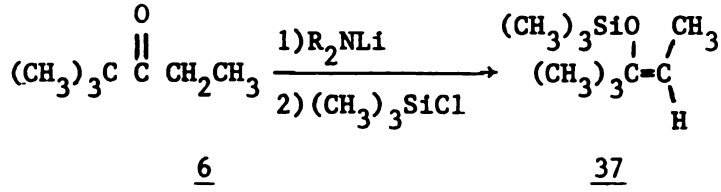
Figure V. The Effect of Both Excess Amide and TMEDA or HMPA on the Z and E Enolate Ratio.

and 33. The enolate (E and Z) ratios observed were 87:13 (81% total yield) with TMEDA and 40:60 (60% total yield) with HMPA. When 0.9 equivalent of 3-pentanone was dissolved in THF (1M) and then was added very slowly (25 min) to a mixture of TMEDA and LiTMP in THF at -78°C the ratio was 91:9 (97% total yield).

A Study of the Effect of Ketone Structure on the E and Z Enolate Ratio.

The reaction of 2,2-dimethyl-3-pentanone with LDA or LiTMP, gave only one product presumed to have the structure 37 (eq. 17), under all conditions studied (0°C or -78°C, excess ketone or excess amide, in the presence or absence of TMEDA).

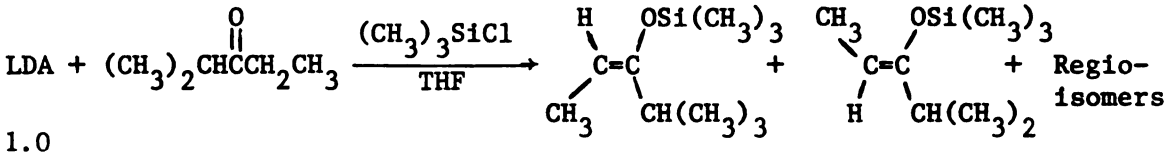
The reaction of 2-methyl-3-pentanone with excess LiTMP at -78°C gave mainly the E-enolate (38). However, reaction with excess LDA at



(17)

6 37

$-78^{\circ}C$ gave mainly the Z-enolate (39). The reaction of 2-methyl-3-pentanone with LDA in the presence of excess ketone at $0^{\circ}C$ or room temperature gave mainly the Z-enolate (39). The results obtained are shown in Figure VI (a study of the regio-isomers formed from deprotonation reactions of 2-methyl-3-pentanone was presented in Chapter I).

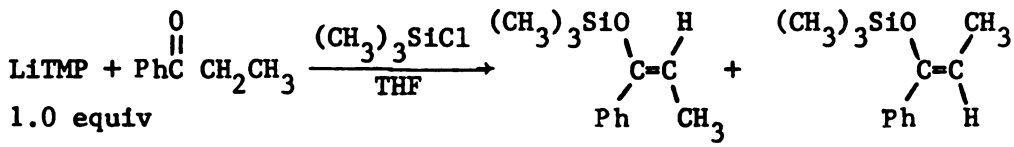


			38 (E)	39 (Z)
	0.9 equiv	$-78^{\circ}C$	36%	53%
LiTMP	0.9 equiv	$-78^{\circ}C$	64%	28%
LDA	1.1 equiv	$0^{\circ}C$	8%	82%
"	1.1 equiv	R. T.	8%	74%

Figure VI. The Ratio of Z and E Enolates Derived from 2-Methyl-3-pentanone.

The reaction of propiophenone with LDA or LiTMP gave mainly the Z-enolate (41) under all conditions studied (0° or $-78^{\circ}C$, excess

ketone or excess amide). The results are presented in Figure VII.



		40 (E)		41 (Z)	
	0.5 equiv , -78°C	8%	,	92%	(87%)
	0.25 equiv, -78°C	8%	,	92%	(81%)
	0.5 equiv , 0°C	17%	,	83%	(76%)
	1.1 equiv , 0°C	6%	,	94%	(80%)
LDA	0.5 equiv , -78°C	16%	,	84%	(90%)

Figure VII. The Ratio of Z and E Enolates Derived from Propiophenone.

A Study of the Effect of Amide Structure on the Z and E Enolate Ratio.

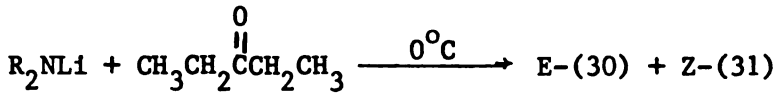
The ratio of 30 (E) and 31 (Z) formed by reaction of 3-pentanone with a wide variety of lithium-amides was investigated. In each case, the amide was prepared by reaction of the corresponding amine with n-butyllithium. 3-Pentanone was then added to a 1.0M solution of the amide in THF at 0°C. Trimethylchlorosilane was added and the reaction mixture was analyzed by GLC for 32 (E) and 33 (Z). The results obtained are presented in Table VIII.

The results presented in Table IX were obtained by reaction of the amide with 3-pentanone at -78°C. An equivalent amount of TMEDA was present in solution of these amides, for reasons described in Chapter I.

The effect of amide structure on the ratio of enolates derived

TABLE VIII

A Study of the Effect of the Amide Structure on the E and Z Enolate Ratio at 0°C.



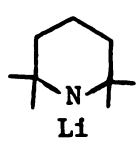
Amide:ketone	E:Z (total yield)		
Amide	1.1:1	2:1	5:1
$(CH_3)_3C\text{-}NHLi$	39:61 (28%)	———	———
$[(CH_3)_3Si]_2NLi$	40:60 (100%)	———	———
$(CH_3CH_2OCH_2CH_2)_2NLi$	50:50 (75%)	50:50 (78%)	49:51 (70%)
$(CH_3CH_2)_2NLi$	30:70 (73%)	35:65 (93%)	33:67 (89%)
$[(CH_3)_2CH]_2NLi$	69:31 (100%)	73:27 (100%)	72:28 (88%)
	86:14 (100%)	88:12 (91%)	86:14 (85%)

TABLE IX

The Effect of the Amide Structure on the Ratio of the Enolates Z and E Derived from 3-Pentanone at -78°C.

$$R_2NLi + \text{3-Pentanone} \xrightarrow{-78^{\circ}C} \text{E-(30)} + \text{Z-(31)}$$

Entry	Amide[a]	E:Z	(Total Yield)
1	LDA	71:29	(95%)
2	LiTMP	84:16	(76%)
3	$[CH_3CH_2(CH_3)_2C]_2NLi$	92:8	(72%)
4	$(CH_3CH_2)_2(CH_3)C\text{-}NLi\text{-}C(CH_3)_2CH_2CH_3$	93:7	(63%)
5	$[(CH_3CH_2)_2(CH_3)C]_2\text{-}NLi$	84:16	(80%)
6	$(CH_3CH_2)_3C\text{-}NLi\text{-}C(CH_3)(CH_2CH_3)_2$	81:19	(73%)
7	"	84:16	(69%)[b]
8	"	74:26	(57%)[c]
9	$[(CH_3CH_2)_3C]_2NLi$	60:40	(58%)
10	"	62:38	(69%)[d]
11	Amide 27	91:9	(81%)

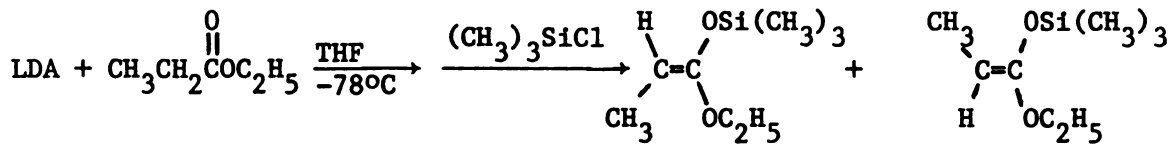
[a]All amides were formed with equivalent amount of TMEDA. [b]Equivalent amount of LiCl was added to the reaction mixture before the ketone addition. [c]The amide was formed with 10% TMEDA. [d]Amide:ketone ratio was 5:1.

from 2-methyl-3-pentanone at -78°C was also investigated. The results obtained are presented in Table X.

A Study of the Stereochemistry of Ester Enolates Formed by Deprotonation Reactions.

Deprotonation of esters with amide bases produces ester enolates. Because of their similarity to ketone enolates, we decided to investigate the stereochemistry of ester enolate formation.

Ethylpropanoate (0.9 equiv) was added dropwise to a 0.5M solution of LDA in THF at -78°C. Trimethylchlorosilane was added and the reaction mixture was analyzed by GLC for the formation of the two stereoisomers 43 and 44.



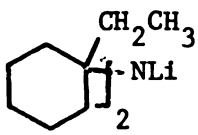
42	43	44
	80% , 20%	(77%)[a]
	70% , 30%	(57%)[b]
HMPA[c]	50% , 50%	(25%)
HMPA[c]	60% , 40%	(13%)
TMEDA[c]	75% , 25%	(68%)
Excess ester (10%)	No product	

Figure VIII. The Ratio of the Enolates Formed by Deprotonation of Ethyl Propanoate. a) The overall yield decreased with time, 43% after 24 h at R. T. and 15% after 3-days. b) The reaction mixture was warmed to 0°C for 15 min and then back to -78°C. c) HMPA or TMEDA was added to the reaction mixture before the ester additions.

TABLE X

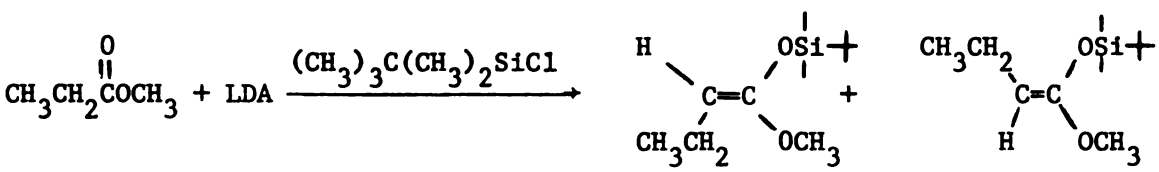
The Effect of the Amide Structure on the Ratio of the Enolates E and Z Derived from 2-Methyl-3-pentanone at -78°C.

$$R_2NLi + \text{2-Methyl-3-pentanone} \xrightarrow[-78^{\circ}C]{THF} \xrightarrow{(CH_3)_3SiCl} \text{E-(38)} + \text{Z-(39)}$$

Amide*	E:Z	(Total Yield)
LDA	42:58	(95%)
LiTMP	75:25	(95%)
	90:10	(85%)
$[CH_3CH_2(CH_3)_2C]_2NLi$	91:9	(98%)
$(CH_3CH_2)_2(CH_3)CNLiC(CH_3)_2CH_2CH_3$	90:10	(94%)
$[(CH_3CH_2)_2(CH_3)C]_2NLi$	92:8	(96%)
$(CH_3CH_2)_3CNLiC(CH_3)(CH_2CH_3)_2$	90:10	(93%)
$[(CH_3CH_2)_3C]_2NLi$	85:15	(91%)

*All amides (1.1 equiv) were formed in the presence of equivalent amount of TMEDA.

Because the low overall yield of the enolates in the reactions of ethyl propanoate may be due to susceptibility of this ester to condensation, we decided to study methyl butanoate. Ireland reported a quantitative overall yield of the enolates from the reaction of methyl butanoate with LDA, as determined by dimethyl-butylchlorosilane quenching (eq. 17). Ireland obtained mainly 46 (E) (91%) in THF solution and mainly 47 (Z) 84% in 23 vol % HMPA-THF.



45 46 (E) 47 (Z) (18)

For our study of this ester, three standard solutions (A, B, C) were prepared. Solution A was prepared by adding 5.0 mmoles of the ester 45 to 5.5 mmoles of LDA in THF (15 ml). Solution B was prepared by adding 5.0 mmoles of the ester 45 to a 5.5 mmoles of LDA in 23 vol % HMPA-THF (15 ml). Solution C was prepared by adding 2.5 mmoles of the ester 45 to 5.0 mmoles of LDA in THF (15 ml). These solutions were quenched with dimethyl-tert-butylchlorosilane. 2 ml HMPA was added to both A and C reaction mixture to facilitate the silylation reaction. The three reactions mixtures were then analyzed by H^1NMR for the silyl-derivatives 46 and 47. The spectra from solution A and C were identical, with 46 (E) as the major product. The NMR spectrum from reaction B showed 47 (Z) as the major product. A quantitative analysis for 46 and 47 was not possible because of incomplete resolution of NMR signals. We were unable to separate 46 and 47 by GLC even with 50'

column.

Addition of 1.5 mmoles of the ester 45 and 4.5 ml HMPA to solution A gave a mixture which could not be analyzed by NMR because the signals for $-OCH_3$ group of unreacted ester overlapped with product signals.

When 4.5 ml of HMPA was added to solution A and the mixture was stirred for 10 minutes before silylation, the NMR analysis of the residue indicated again that 46 (E) was the major product. The same result was obtained when 4.5 ml of HMPA was added to solution C and stirred for 10 minutes prior to silylation.

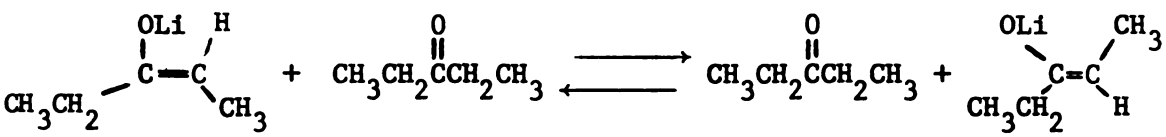
DISCUSSION

Ireland[31] reported that deprotonation of 3-pentanone with LDA in THF solution gave mainly the E-enolate [77% (E)-30, 23% (Z)-31]. The same sequence in a 23 vol % HMPA-THF solvent gave predominantly the Z-enolate [5% (E)-30, 95% (Z)-31]. Ireland suggested that the observed stereoselectivity arises in either case by a kinetically controlled process and that the increased Z-selectivity is a consequence of the lesser coordinating ability of lithium for carbonyl oxygen in a solvent mixture containing HMPA. Our results indicate that those deprotonation reactions of 3-pentanone with lithium amide bases which lead to predominant Z-stereoselectivity operate under conditions of thermodynamic control. Under conditions where kinetic control is ensured, predominant E-selectivity is observed in the presence or absence of HMPA or the related solvent additive, TMEDA.

Our initial investigation was carried out by preparing standard solutions which contained 86% (E)-30 and 14% (Z)-31. The stability of these standard solutions was studied under a variety of conditions. Both the (E)-30:(Z)-31 ratio and overall yield of the two enolates did not change over a period of 24 h at 25°C in the absence of any solvent additive, or in the presence of 1-4 equiv of HMPA or TMEDA. However, addition of 0.2 equivalent of 3-pentanone or 0.2 equivalent of benzophenon caused a rapid isomerization, complete in less than an hour at 0°C, to an equilibrium mixture of enolates with an (E)-30:(Z)-31 ratio

of 16:84, as shown in Figure I of the results section. The rate of this isomerization was appreciably faster in the presence of HMPA or TMEDA (complete in <10 min., Figure II of the results section). The rate of isomerization at -78°C with excess ketone was extremely slow in THF or TMEDA-THF mixtures. With HMPA-THF mixture at -78°C the overall yield of the enolates was low, <50%, and the rate of equilibration was also low. The effect of both HMPA and TMEDA on the position of enolate equilibrium at 0°C was to increase the amount of Z-enolate (84% (Z)-31 in THF alone, maximum of 94% (Z)-31 in HMPA-THF, and max 89% (Z)-31 in TMEDA-THF).

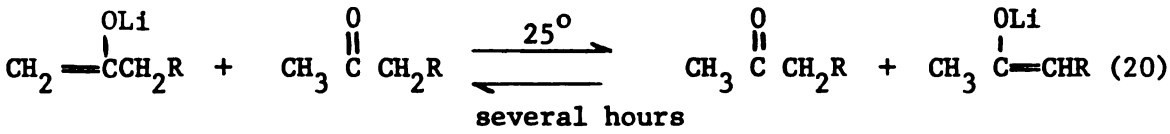
From these results we conclude that only unreacted ketone causes the equilibration of E ⇌ Z enolates. A possible mechanism for this equilibration is α-hydrogen exchange as shown in equation 19. However,



(19)

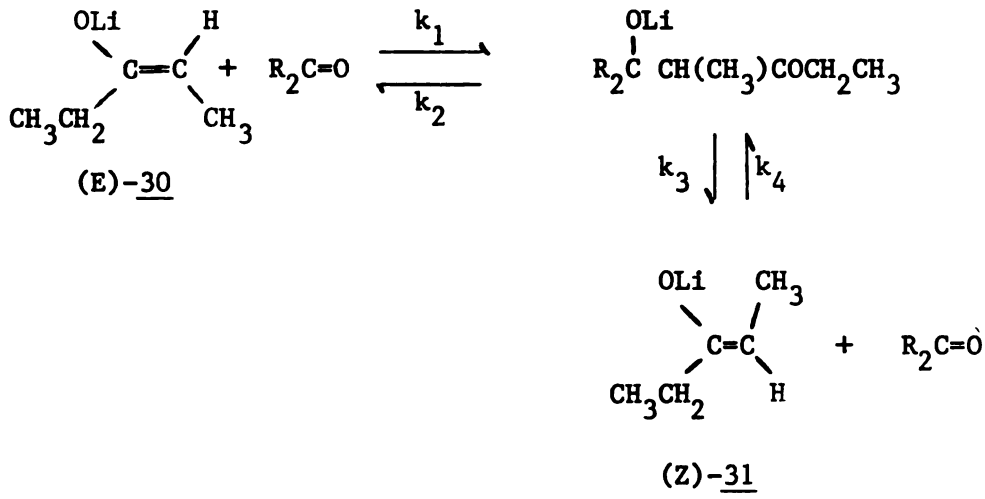
this mechanism is probably too slow to account for the rapid equilibration observed at 0°C (complete in less than 1 hr in THF alone). It is known[36] that the equilibration of regioisomers of ketone enolates, which is assumed to occur by the same α-hydrogen exchange mechanism, requires a period of several hours at 25°C even in the presence of a substantial excess (10-100%) of ketone (eq. 20).

Benzophenone is a ketone which has no α-hydrogens and therefore cannot possibly participate in an α-hydrogen exchange mechanism. Thus



our observation that benzophenone promotes enolate isomerization about as efficiently as 3-pentanone provides compelling evidence against the operation of the α-hydrogen exchange mechanism.

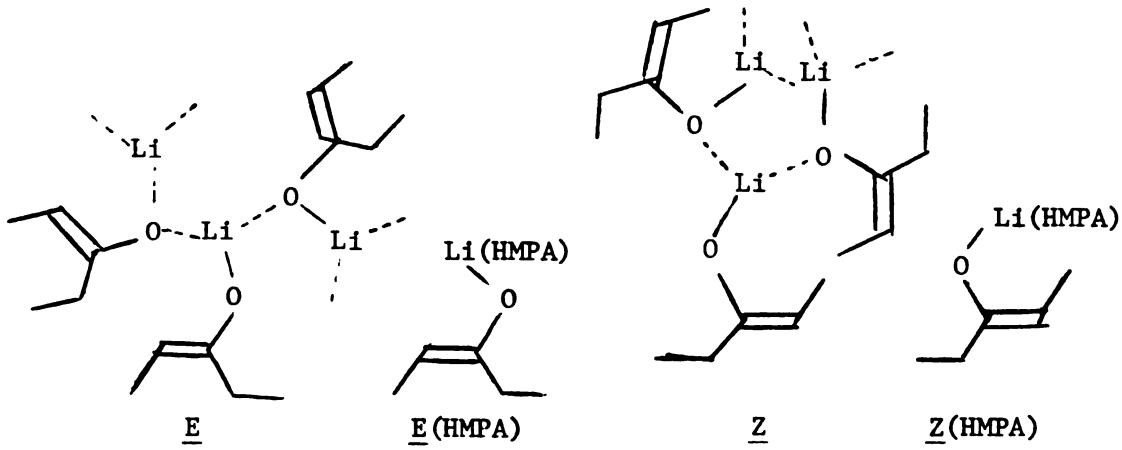
We consider that the most likely isomerization mechanism is a reversible aldol condensation as shown in equation 21. The aldol



(21)

condensation of ketones is known to be a reversible reaction with equilibrium favoring the starting ketone and enolate.[37-39]

The role of TMEDA and, more importantly, HMPA in increasing the equilibrium amount of Z-enolate may be interpreted in the following fashion. It is known[40] that lithium alkoxides are polymeric, with lithium bonded to four oxygen atoms in simple alkoxides ($LiOCH_3$), and to three oxygen atoms in more hindered ones ($LiOC(CH_3)_3$). If a similar polymeric structure is assumed for lithium enolates then the effect of HMPA may be to ligate with lithium and decrease the effective size of

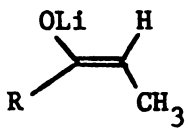


E E(HMPA) Z Z(HMPA)

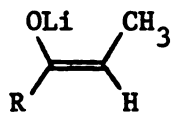
the lithium-oxygen grouping. This should result in an increased stability of the Z-enolate.

Both HMPA and TMEDA are known to strongly activate lithium enolates perhaps by coordination to lithium.[41] This ligation of lithium should increase the value of k_1 in equation 21, leading to a faster (compared to THF alone) rate of isomerization. We can explain the low yield of enolates obtained in the presence of HMPA at -78, by assuming the formation of a stable aldol at that temperature. We were able to get equilibration (7:93) and higher overall yield of enolates, (83%), when excess ketone was reacted with LiTMP in the presence of HMPA at -78°C for one hour and then warmed to 0°C for another hour before quenching with trimethylchlorosilane. But we were unable to trap the aldol product by silylation at -78°C.

The structure of the ketone has a marked effect on the composition of the enolate equilibrium mixture. For 2-methyl-3-pentanone, the enolate equilibrium composition in THF is 9:91 (E:Z, R=isopropyl).



E

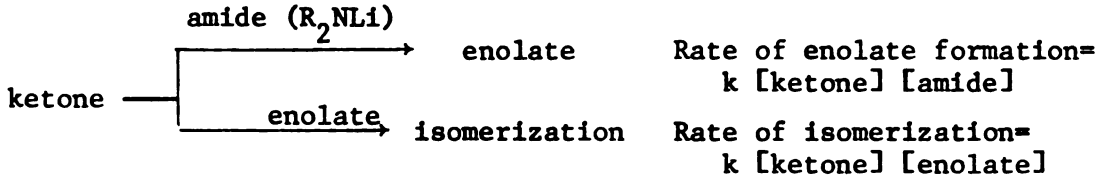


Z

2,2-dimethyl-3-pentanone gave only one enolate at equilibrium. Heathcock reported that this is the Z-enolate (100% Z R=C$(CH_3)_3$). For propiophenone, the equilibrium enolate composition in THF is 6:94 (E:Z, R=ph). In all cases, the most stable enolate is the Z- form, because the methyl group is trans to the bulkier group, R, and cis to the smaller -OLi. Also as the size of R increases the equilibrium composition of the Z- form increases.

The equilibrium mixtures of stereoisomeric enolates described above were prepared by reaction of 1·2 equivalent of the ketone with one equivalent of LDA or LiTMP in THF for 1 hr at 0°C. This is a new and very convenient method for the equilibration of enolate stereochemistry, and therefore it provides a simple method to study the position of enolate equilibrium.

Since enolate isomerization occurs only by reaction of enolate with starting ketone, (Scheme III), a true kinetically controlled deprotonation should be favored by: a) A high amide to ketone ratio



Scheme III

b) Low temperature deprotonation or c) Rapid trapping of the enolates. A high amide to ketone ratio should increase the rate of enolate formation and decrease the rate of isomerization. This is because the strating ketone will be rapidly consumed by deprotonation and will not be available for enolate isomerization. An amide to diethyl ketone ratio of 1.0:0.9 produces a kinetically controlled enolate distribution

in THF (86% (E)-30, 14% (Z)-31). Increasing the amide to ketone ratio to 2:1 does not greatly alter the ratio of the enolates [88% (E)-30, 12% (Z)-31]. However a kinetically controlled enolate distribution in the presence of TMEDA or HMPA was only obtained when a higher amide to ketone ratio (1.0:0.25) was used. This effect of both TMEDA and HMPA can be explained by the ability of these solvent additives to activate enolates, in this case to the aldol condensation, which leads to enolate isomerization. The enolate distribution [66% (E)-30, 34% (Z)-31] obtained in the presence of HMPA is puzzling. It is possible that the presence of HMPA does alter the kinetically controlled distribution of the two enolates. However, it is also possible that this ratio does not yet represent the results of the true kinetically controlled deprotonation. Unfortunately, we were unable to test this possibility by the use of even higher amide to ketone ratios because both enolate total yield and the reproducibility of the results decreased drastically in the presence of HMPA under these conditions.

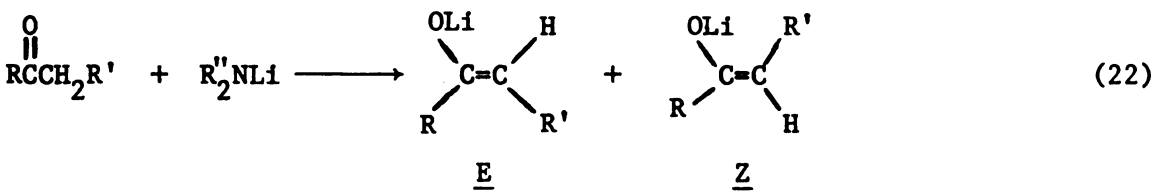
A low temperature deprotonation should favor kinetically controlled deprotonation because the rate of isomerization is very slow at -78°C, as shown by the results presented in Figure IV. It is important here to emphasize that either the trapping of the enolates must occur at -78°C or that no unreacted ketone is present prior to trapping. Otherwise, unreacted ketone will cause equilibration to occur once the enolate solution is warmed to higher temperatures. It seems likely that Ireland's[31] results [51% (E), 95% (Z)] obtained for the deprotonation of 3-pentanone with LDA in 23 vol % HMPA-THF at -78°C followed by trapping with dimethyl-tert-butylchlorosilane, are due to enolate equilibration. This is because of the slow reaction of the hindered dimethyl-tert-

butychlorosilane with enolates. Thus if unreacted ketone was present, equilibration would occur when the reaction mixture was warmed to room temperature.

Rapid trapping of the enolates by trimethylchlorosilane should favor kinetically controlled deprotonation. A rapid trapping of enolate will prevent further reaction of the enolate with unreacted ketone. The data presented in Table VII of the results section are in agreement with this point. The presence of trimethylchlorosilane in the reaction mixture, changed the ratio of enolates from 17%(E):83%(Z) to 77%(E): 23%(Z), during the deprotonation step rather than addition of trimethylchlorosilane after deprotonation in TMEDA-THF.

The kinetically controlled deprotonation of 3-pentanone at various temperature (-78°C-R. T.) in THF occurred with an almost constant ratio of E and Z enolates, as shown in Table V. A slight increase in the Z-selectivity was observed for the deprotonation at 70°C and this may simply be due to a slight isomerization during the deprotonation step at this high temperature.

The kinetically controlled enolate distribution obtained by reaction of a variety of ketones with lithium amide bases was determined. The Z-selectivity increases as the size of R (eq. 22) increases.



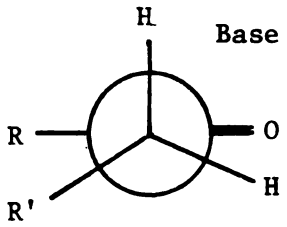
(22)

E Z

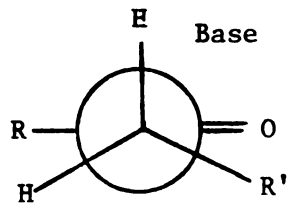
Deprotonation of 3-pentanone with LiTMP occurs with an E:Z ratio of 86:14. Deprotonation of 2-methyl-3-pentanone occurs with an E:Z ratio of 70:30. Deprotonation of propiophenone and 2,2-dimethyl-3-pentanone

produces mainly Z-enolate. Heathcock reported the formation of 100% Z-enolate with the last ketone.

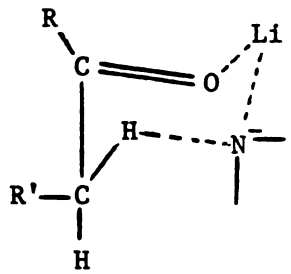
These results can be explained by considering the two chair transition states for the deprotonation step. When R is small (ethyl or

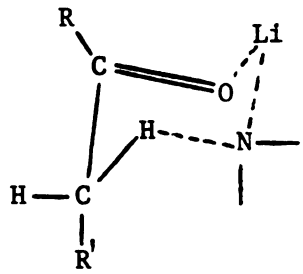


E-transition state

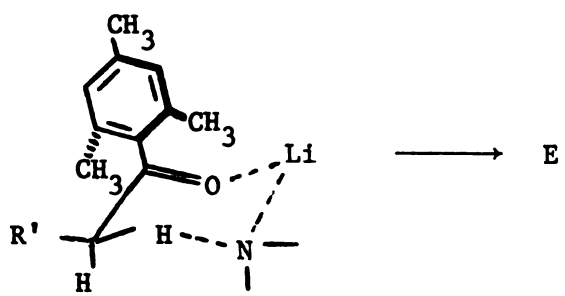


Z-transition state

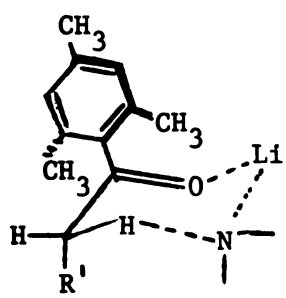




isopropyl), the E-transition state, with R' in the equatorial position, is more stable than the Z-transition state, which has R' in the axial position. However, as R becomes bulkier (t-butyl or phenyl) the interaction between R and R' becomes more severe and therefore the Z-transition state becomes more stable. The results reported by Heathcock[29a] for the deprotonation of ethyl mesityl ketone (92% (E), 8% Z) are suprising. It is possible that the benzene ring of the exceptionally bulky mesityl



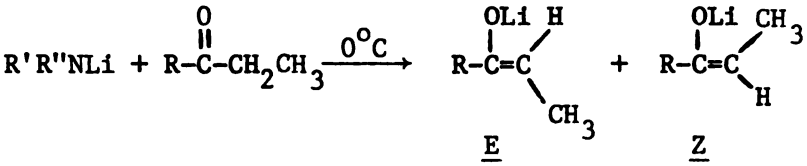
E



Z

group is forced to take a perpendicular conformation relative to the plane defined by the carbonyl grouping. Such an orientation will effectively lower any steric interaction with R' in the E transition state.

Kuwajima[34] reported a higher E-selectivity for deprotonation of 3-pentanone with LiTMP (84% E-enolate) compared to LDA (77% E-enolate). Our results, Table VIII also, indicate that under kinetically controlled reactions, an increase in the size of the alkyl groups of the amide (R', R") leads to a higher E-selectivity. These results can be explained



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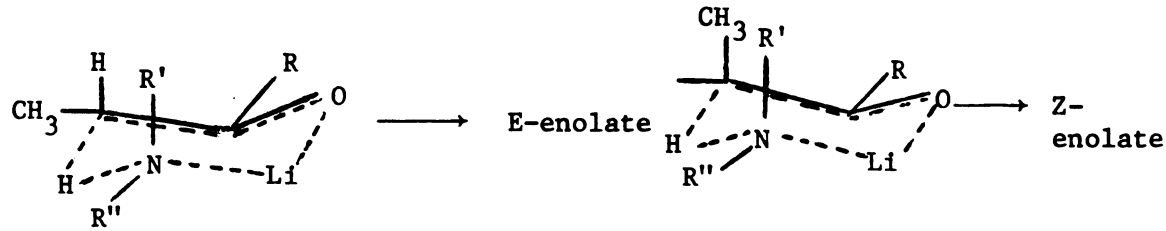
by considering the transition states A and B shown below. As the size



A B

of R' increases, transition state B will be destabilized by increasing axial-axial interaction of R' with CH_3. Therefore A becomes more stable and E-selectivity will increase. However, our results obtained with more hindered amides, shown in Tables IX and X indicate that there is a limit to this effect and after a certain point is reached, E-selectivity declines. As the size of R' becomes very bulky [$-C(CH_3)_2CH_2CH_3$ or $C(CH_2CH_3)_3$] it is possible that the transition state is no longer

chair-like and the decline in the E-selectivity results from a different transition state.

A very useful conclusion for the stereochemistry of enolate formation can be mentioned here. It is possible to control the deprotonation of 3-pentanone in THF solution alone. In order to produce predominantly E-enolate, 3-pentanone is added to 10% excess amide at $0^{o}C$ or to an equivalent amount of amide at $-78^{o}C$. To obtain predominantly Z-enolate 3-pentanone is added to a slight deficiency of the amide or a stoichiometric amount of amide is added dropwise to a solution of 3-pentanone at $0^{o}C$. The same procedure with 2-methyl-3-pentanone produces similar results.

Finally, the brief investigation of ester equilibration did not lead to any conclusive results. There were two main difficulties in the esters study: the instability of the silylketene acetal and the lack of a simple and easy way of analysis for the products. In fact, the first difficulty was solved by using dimethyl-tert-butylchlorosilane instead of trimethylchlorosilane. The second difficulty will probably be solved once the 250 MHz NMR will be more available for routine analysis. However, we still strongly believe that esters will behave as ketones regarding the enolate formation conditions.

EXPERIMENTAL

I. General

Spectra.

Proton magnetic resonance spectra were measured using a Varian T-60 spectometer.

Gas Chromatography.

Vapor phase chromatographic analysis and preparative work were carried out on a Varian Aerograph 920 thermal conductivity chromatograph. Relative peak areas were determined by a Varian disc chart integrator-model.

II. Materials

Handling of Materials.

All reactions were carried out under an argon atmosphere and all liquids were transferred with glass syringes. All solvents were carefully distilled[42] and stored uner an argon atmosphere over molecular sieves.

Amines, Amides and n-Butyllithium.

The following amines, diethylamine, diisopropylamine, tert-butylamine, 2,2,6,6,-tetramethylpiperidine, bis(trimethylsilyl) amine,

and bis(2-ethoxyethyl) amine were commercially available. All other amines were prepared as described in Chapter I. All Li-amides were prepared prior to use by reaction of n-butyllithium with the corresponding amine, as described in Chapter I. The n-BuLi was commercially available as a 1.6M solution in hexane and was used without further purification.

Silylating Reagents.

Trimethylchlorosilane, obtained commercially, was distilled and stored under argon. Dimethyl-tert-butylchlorosilane was prepared as described by Corey et al.[43] This silane was used as 3.6M solution in pentane.

Ketones and Esters.

3-Pentanone, propiophenone, 2,2-dimethyl-3-pentanone and ethyl propanoate were commercially available and were distilled before use. 2-Methyl-3-pentanone was 95% commercially available. This ketone was purified by distillation through a spinning band column. Methyl butanoate was prepared from the commercially available acid in 91% yield by the following procedure: One mole of butyric acid was refluxed with excess (1.2 equiv) thionyl chloride for two hours. The excess thionyl chloride was removed under reduced pressure. Methanol (1.5 equiv) was added dropwise at $0^{o}C$. The reaction mixture was stirred for 15 minutes at room temperature and then 200 ml of water was added. The aqueous layer was washed twice with ether (50 ml). The organic layers were combined and washed twice with saturated $NaHCO_3$ (30 ml). After drying the organic layer over anhydrous Na_2SO_4, the product was purified by a

spinning band distillation apparatus.

III. The Reactions of Ketones and Esters With Li-Amides

a. The Reaction of Excess Ketones With Li-Amides.

The following procedure for the reaction of 3-pentanone with LiTMP at $0^{o}C$ will be representative. A 10 ml flask equipped with a stir bar, septum, gas inlet valve, and mercury bubbler was flame dried while a stream of argon was flowing through the system. A 1.6M (1.25 ml, 2 mmoles) aliquot of n-butyllithium in hexane was added to the flask. The flask was immersed in an ice bath and 0.35 ml (2 mmoles) of 2,2,6,6,-tetramethylpiperidine was added dropwise with stirring. After the evolution of butane had ceased, the hexane was removed by vacuum which was broken with argon. The white solid was dissolved in 2 ml of THF and cooled in an ice bath. 3-Pentanone 0.19 ml, 1.8 mmoles) was added dropwise followed by (0.4 ml, 0.04 mmole) portion, and after 15 minutes, the reaction was quenched with 0.3 ml (2.3 mmoles) of trimethylchlorosilane. The reaction mixture was stirred for 30 minutes and then the ice bath was removed. Upon warming to room temperature, 0.34 ml (2 mmoles) of nonane (internal standard) was added. The resulting solution was diluted with 2 ml pentane and then 4 ml saturated $NaHCO_3$ was added. The organic layer was dried over anhydrous sodium sulfate before glc analysis.

b. The Reaction of Ketones With Excess Li-Amides.

The same procedures described above was used except the mmoles of 3-pentanone was less than the mmoles of LiTMP.

For reactions in the presence of solvent additives (TMEDA or HMPA), these solvents were added prior to the ketone addition.

c. The Reaction of Esters with Li-Amides.

The same procedure described above was used except the reaction mixture was not worked up with saturated $NaHCO_3$ in case of ethyl propanoate. The reaction mixture was diluted with pentane and then analyzed by glc.

IV. Product Analysis

The ratio of the enolates as well as the overall yield of the enolates was determined by glc (1/8 in x 40 ft stainless steel column packed with 20% SE-30 on Chromosorb W) analysis for the corresponding silyl enol ethers. Pure samples of each product were isolated by preparative glc and examined by NMR.

E-3-(Trimethylsilyloxy)-2-pentene (30).

NMR ($CDCl_3$): δ 0.18 (S, 9H), δ 1.01 (t, 3H), δ 1.54 (d, 3H), δ 2.08 (9, 2H), δ 4.6 (9, 1H) ($CHCl_3$ was the internal standard)

Z-3-(Trimethylsilyloxy)-2-pentene (31).

NMR ($CDCl_3$): δ 0.18 (S, 9H), δ 1.02 (t, 3H), δ 1.52 (d of t, 3H),

δ 2.03 (q, 2H), 4.53 (q, 1H) ($CHCl_3$ was the internal standard).

E-4-Methyl-3-(trimethylsilyloxy)-2-pentene (38).

NMR (CCl_4): δ 0.17 (S, 9H), δ 0.94 (d, 6H), δ 1.52 (d, 3H), δ 2.60 (m, 1H), δ 4.28 (q, 1H) (TMS was the internal standard).

Z-4-Methyl-3-(trimethylsilyloxy)-2-pentene (39).

NMR (CCl_4): δ 0.17 (S, 9H), δ 0.98 (d, 6H), δ 1.44 (d of d, 3H), δ 2.10 (m, 1H), δ 4.35 (q, 1H). (TMS was the internal standard).

2-Methyl-3-(trimethylsilyloxy)-2-pentene.

NMR ($CDCl_3$): δ 0.17 (S, 9H), δ 1.0 (t, 3H), δ 1.56 (bS, 6H), δ 2.07 (bq, 2H) (TMS was the internal standard).

Z-4,4-Dimethyl-3-(trimethylsilyloxy)-2-pentene (37).

NMR ($CDCl_3$): δ 0.17 (S, 9H), δ 0.97 (S, 9H), δ 1.24 (d, 3H), δ 4.50 (q, 1H).

E-3-Phenyl-3-(trimethylsilyloxy)-2-propene (40).

NMR ($CDCl_3$): δ 0.07 (S, 9H), δ 1.6 (d, 3H), δ 4.86 (q, 1H), δ 7.10 (S, 5H). UV (n-heptane) λ_{max} 235 nm.

Z-3-Phenyl-3-(trimethylsilyloxy)-2-propene (41).

NMR ($CDCl_3$): δ 0.1 (S, 9H), δ 1.65 (d, 3H), δ 5.10 (q, 1H), δ 7.07 (m, 5H). UV (n-heptane) λ_{max} 243 nm.

O-Trimethylsilyl-O'-ethyl Methyl Ketene Acetal.

NMR ($CDCl_3$): δ 0.18 (S, 9H), δ 1.19 (t, 3H), δ 1.5 (d, 3H), δ 3.73 (m, 3H).

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