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New Applications of the Mannich Reaction

Yu-Fang Wang
Western Kentucky University

Wang,

Yu-Fang

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NEW APPLICATIONS OF THE MANNICH REACTION

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Yu-Fang Wang

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NEW APPLICATIONS OF THE MANNICH REACTION

Recommended May 17, 1976
(Date)

Norman R. Holy
Director of Thesis

Earl F. Pearson

John W Reasoner

Approved 5-19-76
(Date)

Elmer Gray
Dean of the Graduate
College

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Yu-Fang Wang

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NEW APPLICATIONS OF THE MANNICH REACTION

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Director by: Norman L. Holy

Department of Chemistry Western Kentucky University

French chemists found that the reaction of trifluoroacetic anhydride with the N-oxide of trimethylamine leads to the methylenedimethylimmonium trifluoroacetate. This salt is considered to be the actual reagent in the Mannich reaction conducted with dimethylamine and formaldehyde. indeed use of this salt gives higher yields than those obtained via the classical Mannich procedure. This salt could be distilled under vacuum (5×10^{-2} mm) and reacted with phenylmagnesium bromide to give an 80% yield of benzyldimethylamine. The trimethylsilyl ethers of ketones were employed as intermediates and exhibited regioselectively. For unsymmetrical ketones, the more stable enol was formed thermodynamically and the less hindered enolate was produced kinetically. The silyl ether isomers were followed by quenching with immonium salt and resulted in the regiospecific products of Mannich base. For α,β-unsaturated ketones, the enolate was formed in high yield by 1,4-addition when lithium dimethylcuprate was employed. γ-Butyrolactone could be alkylated, providing an intermediate to the construction of an α-methylene lactone, a moiety present in several compound having appreciable anti-tumor activity.

INTRODUCTION

The earliest examples of the Mannich reaction were published in succession by Tollens and co-workers[1,2], Petrenko-Kritschenko and co-woekers[3-6], and by Mannich and Krosch[7]. Mannich was the first to recognize the reaction as a general one, and a detailed investigation was begun in 1917. The Mannich reaction was reviewed by Blicke[8], Karbe[9], Nobles[10,11], Reichert[12], and others [13,14]. Books by Reichert[15] and by Hellmann and Opitz[16], provide excellent coverage on practically the entire chemistry of Mannich bases up to 1960. In addition, in the last ten years many investigators have studied the numerous applications of the Mannich reaction[17], the problems of orientation and mechanism[18] and the reactivity of these bases in a reaction which allows the synthesis of numerous other products.

I. Synthesis of Mannich Bases

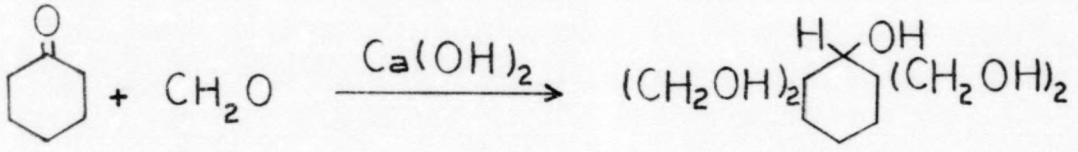
(A) The Classic Mannich Reaction

The aldol condensation of active hydrogen compounds with formaldehyde occurs readily[19]; this is called the Tollen's condensation when basic catalysis is used (eqn. 1). The reaction is often difficult to control in routine

$$CH_3NO_2 + CH_2O \xrightarrow[CH_3OH]{KOH} \xrightarrow{H_2SO_4} HO\text{-}CH_2\text{-}CH_2\text{-}NO_2 \quad (1)$$

laboratory preparations, and polycondensation often results. A further complication in base-catalyzed reaction arises from the fact that formaldehyde may reduce other carbonyl groups present (the Cannizzaro reaction). Examples of the reaction of carbonyl compounds with excess formaldehyde are provided (eqn. 2 & 3). A more satisfactory method for

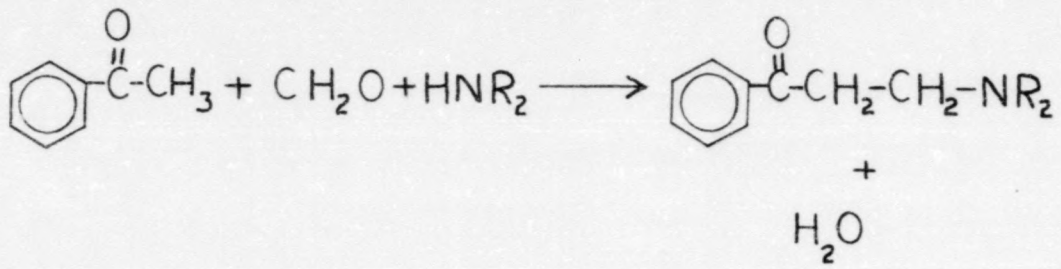
$$CH_3\text{-}CHO + CH_2O \xrightarrow[H_2O]{Ca(OH)_2} [(HOCH_2)_3C\text{-}CHO] \xrightarrow[OH^{\ominus}]{CH_2O} C(CH_2OH)_4 \quad (2)$$



(3)

the introduction of a single carbon atom is the reaction of ammonia or a primary or secondary amine (usually as the hydrochloride salt) with an aldehyde and a substrate (R–H) capable of supplying one or more active hydrogen. As a result of the reaction an aminomethyl group generally replaces the active hydrogen atom. This reaction, known as Mannich reaction, is usually run in protic solvents. Products of the condensation are known as "Mannich bases."

A typical condensation, with acetophenone as active hydrogen compound, is illustrated below (eqn. 4).



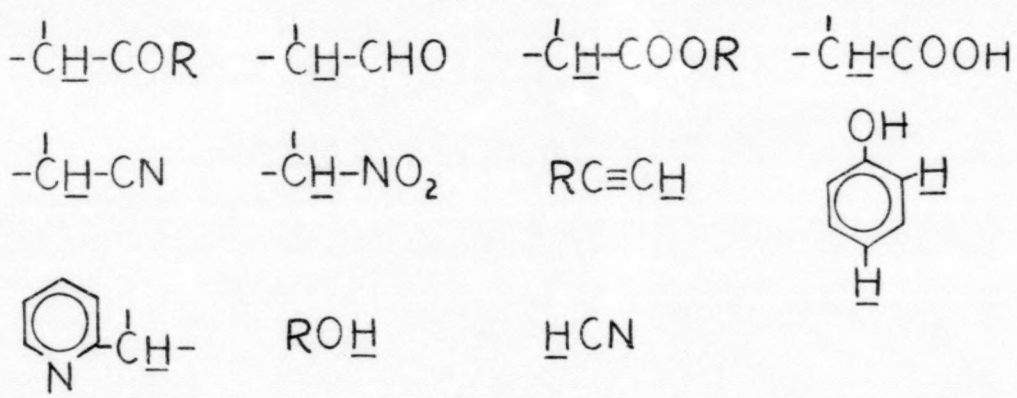
(4)

(B) Reactants and Reaction Conditions

Formaldehydes, either as aqueous solution, paraformaldehyde or 1,3,5-trioxan (trioxymethylene), is the aldehyde most frequently used. The amines are employed either as free bases or as hydrochlorides.

The most widely used solvents are ethanol or other alcohols such as methanol or isopropanol, water and acetic acid.

Many active hydrogen substrates undergo Mannich condensation. Among these are the types listed on the following with the active hydrogen underlined[20].



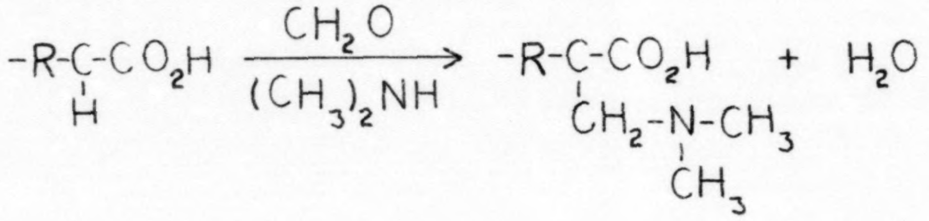
(5)

The most widely and successfully used reaction conditions for several groups of substrates are as follows[21].

ALKYL KETONES: Substrate, amine hydrochloride, and paraformaldehyde (sometimes 1,3,5-trioxan or aqueous formaldehyde) are refluxed in alcoholic solvents for several hours.

PHENOLS: Substrate, amine, and aqueous formaldehyde (sometimes paraformaldehyde) in alcoholic solvents are heated for a short time (up to several hours), or are allowed to stand at room temperature for a long time (up to a few days).

CARBOXYLIC ACID DERIVATIVES: Only "activated" carboxylic acid derivatives undergo substitution, where R in the following equation is $-CO_2H$, $-CN$, $R'SO_2-$, $-\underset{|}{C}=O$ (eqn. 6). Unactived



(6)

carboxylic acids, esters, and amides do not react. Substrate, amine, and aqueous formaldehyde are allowed to react in water (sometimes in alcoholic solvents) at room temperature.

HETEROCYCLIC COMPOUNDS: Substrate, amine, and aqueous formaldehyde are allowed to react in water or in alcoholic solvents at room temperature (sometimes with brief heating).

ALKYNES: Various reaction conditions as above are used;

the reaction is carried out in the presence of copper salts.

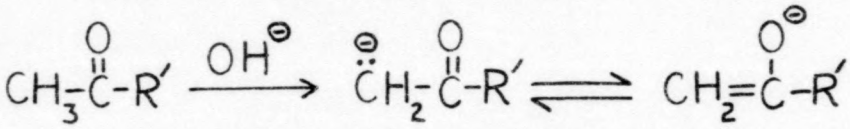
The reaction is generally carried out by mixing substrate, aldehyde, and amine in equimolar amounts.

Mannich bases often crystallize from the reaction mixture or the bases can be separated by extraction with aqueous hydrochloric acid.

(C) Mechanism

Over the years there has been much controversy about the mechanism of the Mannich reaction, especially as to whether the aldehyde is first attacked by the active hydrogen compound or by the ammonia or amine. The evidence seems to favor the latter course. Studies of the reaction kinetics have led to the following mechanistic proposals (eqn. 7-9).

The base-catalyzed reaction:



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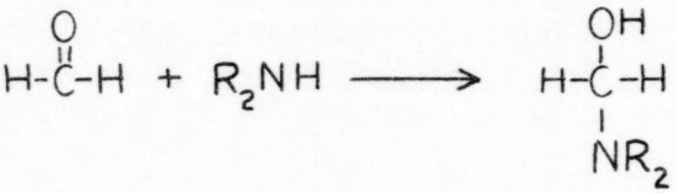

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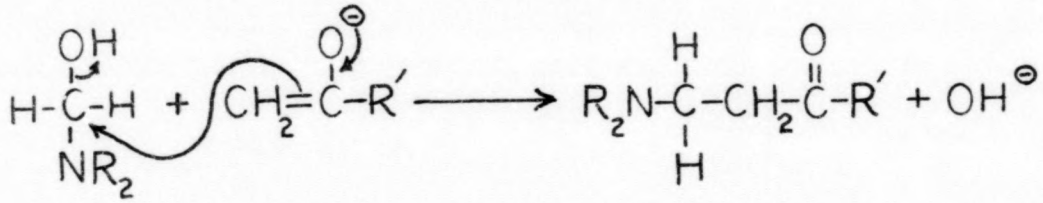


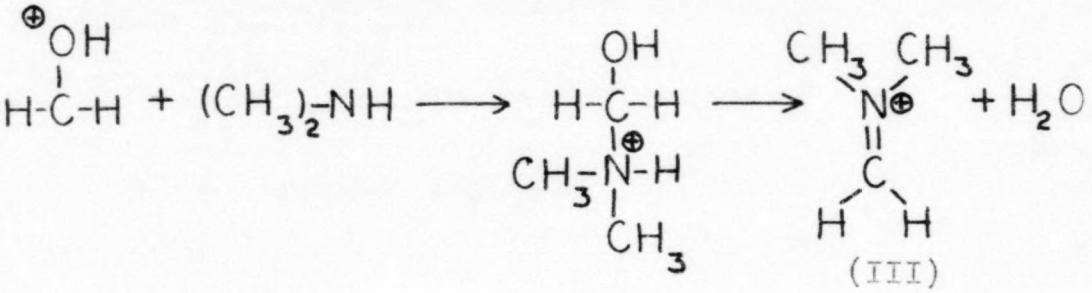
(9)

There is evidence that in basic media the intermediate which undergoes the nucleophilic substitution may be $H_2C(NR_2)_2$ (II) instead of (I)[23], but it has been shown that I is more reactive than II in this type of step[24].

Under the usual slightly acid reaction conditions, the mechanism of the Mannich reaction is believed to involve electrophilic attack by an iminium salt (III) on the enol (IV) of the active hydrogen compound (eqn. 10-13).

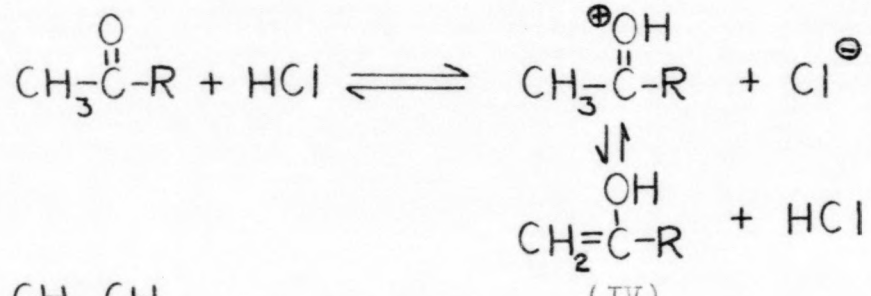
The acid-catalyzed reaction:

(10)



(11)

(III)



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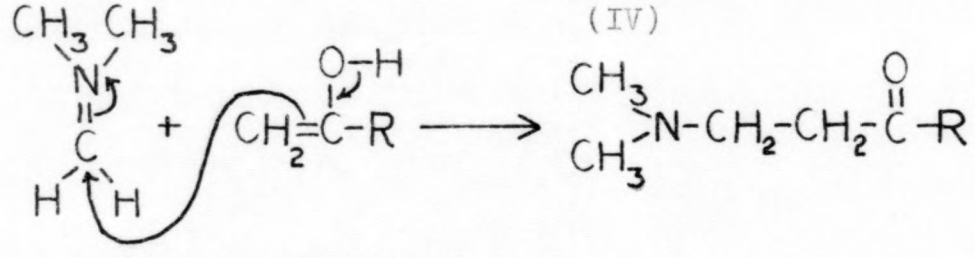
(IV)



(13)

(III) (IV)

(D) Side Reactions

In addition to ammonia, the reaction may be carried out with its salts of primary or secondary amine, or with an amide. Usually a secondary amine (e.g., dimethylamine, diethylamine, piperidine, morpholine, pyrrolidine) is employed to avoid side reactions such as might occur between the initially formed Mannich base and additional formaldehyde and active hydrogen compound, if a primary amine or ammonia were used (eqn. 14).

$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{CH_2O} HN(CH_2CH_2COR)_2$$

$$\xrightarrow[CH_3COR]{CH_2O} N(CH_2CH_2COR)_3 \qquad (14)$$

If the active hydrogen compound has two or three active hydrogens, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine (eqn. 15).

$$H_2NCH_2CH_2COR \xrightarrow[NH_3]{CH_2O} (H_2NCH_2)_2CHCOR$$

$$\xrightarrow[NH_3]{CH_2O} (H_2NCH_2)_3CCOR \qquad (15)$$

Another reaction consists of condensation of Mannich base with excess formaldehyde (eqn. 16).

$$H_2NCH_2CH_2COR + CH_2O \longrightarrow H_2C{=}NCH_2CH_2COR \qquad (16)$$

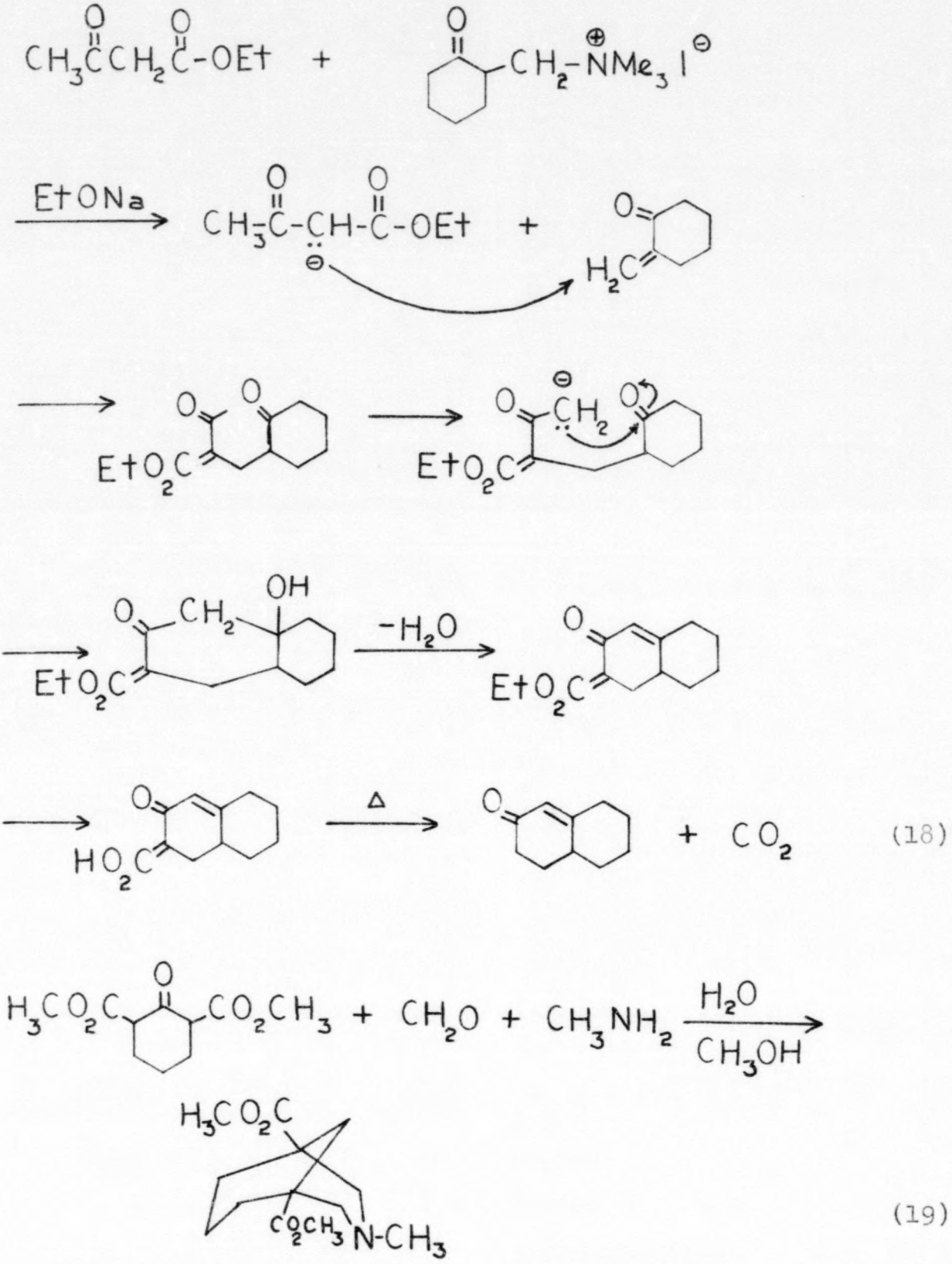
Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are only side products; when the Mannich base contains an amino group beta to a carbonyl, then ammonia is easily eliminated, and this is a route to α,β-unsaturated aldehydes, ketones, esters, etc. (eqn. 17).

$$H_2NCH_2CH_2COR \longrightarrow H_2C{=}CHCOR \qquad (17)$$

(E) The Characteristics of Mannich Bases

Studies on the chemistry of Mannich bases are of interest for several reasons:

1) The Mannich synthesis introduces a basic function which can render the molecule soluble in aqueous solvents when it is transformed into the ammonium salt.
2) Mannich bases are very reactive; in fact, they can easily be transformed into numerous other compounds (eqn. 18).
3) Mannich bases represent easily obtainable intermediate for the synthesis of other compounds, such as heterocycles, amino-alcohols etc. (eqn. 19).



(18)

(19)

4) Finally, Mannich bases have been investigated as potential biological agents, as dyes for synthetic fibers, as reactive dyes, and also as surface active compounds.

II. The New Mannich Reagent

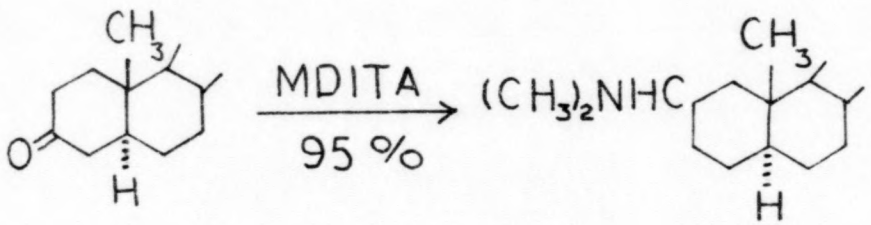
(A) Methylenedimethylimmonium Trifluoroacetate (MDITA); $(CH_3)_2\overset{\oplus}{N}=CH_2 \cdot CF_3CO_2^{\ominus}$; Mol. Wt. =171.12

French chemists reported that the reaction of trifluoroacetic anhydride with the N-oxide of trimethylamine lead to the trifluoroacetate of methylenedimethylimmonium (MDITA) (I; eqn. 20). This ion is considered to be the actural reagent in the Mannich reaction conducted with dimethylamine

$$(CH_3)_3N\text{-}O \xrightarrow{(CF_3CO)_2O} \left[(CH_3)_2\overset{\oplus}{N}=CH_2 \longleftrightarrow (CH_3)_2N\text{-}\overset{\oplus}{C}H\right] CF_3CO_2^{\ominus} \quad (20)$$

(I)

and formaldehyde, and indeed use of this salt gives higher yields (eqn. 21 & 22) than those obtained with the classical Mannich procedure[8].



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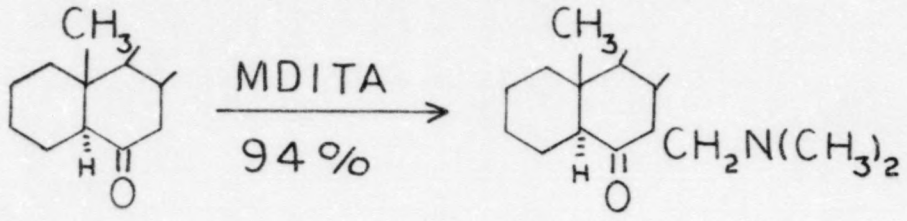


(22)

(B) Regioselective Characteristic of Mannich Bases

Isomeric Mannich bases derived from unsymmetrical ketones can be synthesised regioselectively simply by selecting the reaction conditions; reaction of methylenedimethylimmonium trifluoroacetate in trifluoroacetic acid yields the more substituted aminoketone while reaction of methylenediisopropylimmonium perchlorate (II) in an aprotic solvent such as acetonitrile leads to the less substituted aminoketone, as in the following table[26].

TABLE

Immonium salt	Solvent	Ketone RCOMe; R=	Total yield (%)	Ratio of III;IV
I	CF_3CO_2H	Cyclopentyl	90	95·5
		Isopropyl	90	85:15
		Cyclohexyl	70	69:31
II	MeCN	Cyclopentyl	80	0:100
		Isopropyl	95	0:100
		Cyclohexyl	90	0:100

II: $(CH_2\text{-}\underset{CH_2}{CH})_2N{=}CH_2 \cdot ClO_4$ III: $R_2NCH_2\text{-}C\text{-}COMe$

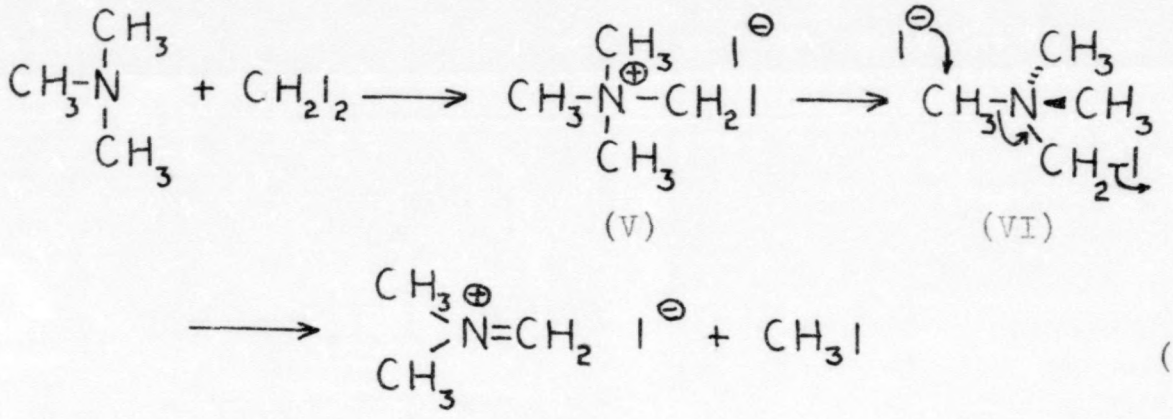
R=Me; R=i-Pr.

IV: $CHCOCH_2CH_2NR_2$

(C) Other Highly Reactive Mannich Reagents

Other reagents are methylenedimethylimmonium salts in which the counterion is iodide, bromide, or chloride.

If a solution of the immonium salt (V, readily obtained from trimethylamine and diiodomethane)[27] in tetrahydrothiophene dioxide is heated at ca. 150°C for 10-15 min methyl iodide distills off, and, on cooling, the methyleneimmonium salt (VI) crystallizes from the solution in greater than 80% yield (eqn. 23).



(23)

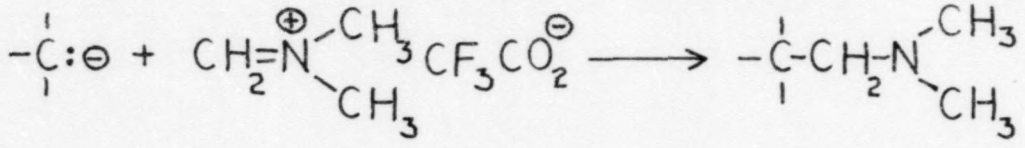
RESULTS & DISCUSSIONS

The Mannich reaction has been employed for years as an approach to the construction of molecules. The Mannich bases and their functional equivalents are useful intermediates for several important processes (e.g., Michael, Diels-Alder, Robinson annelation). Also, the present development illustrates that, by suitable choice of substrates, the simplicity and high yields of this method allow the unambiguous synthesis of certain Mannich bases which would not be readily available using conventional method.

The classic Mannich reaction involves the use of dimethylamine, formaldehyde and hydrochloric acid, all refluxed in the protic solvent (e.g., methanol) with activated hydrogen substrate. Some compounds of high pK values are not acidic enough to undergo this reaction (e.g., lactams, amides, carboxylic acids, alkanes and aromatics). Esters do not react unless an activating group (e.g., RSO_2-, NO_2-, $-\underset{|}{C}=O$) is present in the β-position.

In recent years new reagents have become available which are more reactive than the classic Mannich bases (see Introduction). The hypothesis under investigation here seeks to expand the known applications by recongnising the following consideration; these new reagents do not require protic conditions and therefore it should be possible to uncouple reac-

tivity from its present dependence on acidity of the substrate in protic media. Specifically, it should be possible to quench "carbanions" with these new reagents (eqn. 1).

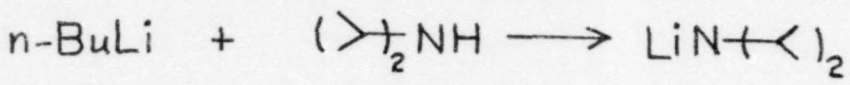


(1)

Methylenedimethylimmonium trifluoroacetate (MDITA) was prepared according to the procedure of A. Ahoud, A. Cave, C. Kan-fan, and P. Potier[28]. When it was treated with phenylmagnesium bromide (Grignard reagent), no trace of the expected benzyldimethylamine was found. Instead, benzene was generated. This phenomenon was ascribed to the presence of trifluoroactic acid in the reagent. In order to overcome this problem, the reagent was distilled on the vacuum line at 110-130°C (5×10^{-2} mm). Quenching this reagent with phenylmagnesium bromide resulted in benzyldimethylamine (80%).

After finding that carbanions could be alkylated successfully, attention was given to the question whether the ketones could be regiospecifically alkylated from both the kinetic and thermodynamic enolates. Lithium diisopropylamide (LDA) (eqn. 2) was employed as the base to generate the enolates. This was followed by quenching the solutions with immonium reagent (eqn. 3). No products of alkylation were produced. Instead, the starting ketones were regenerated (eqn. 4). It was concluded that the immonium salt reacted with the

diisopropylamine instead of the enolate through no direct proof of this was obtained.



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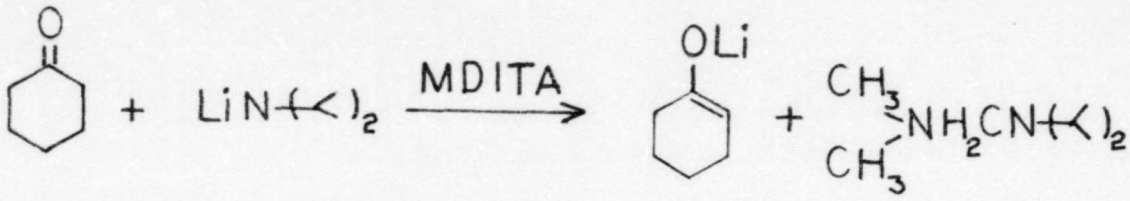

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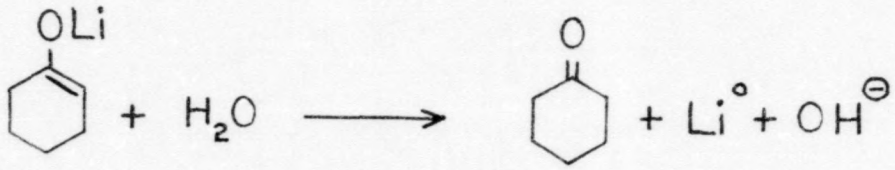
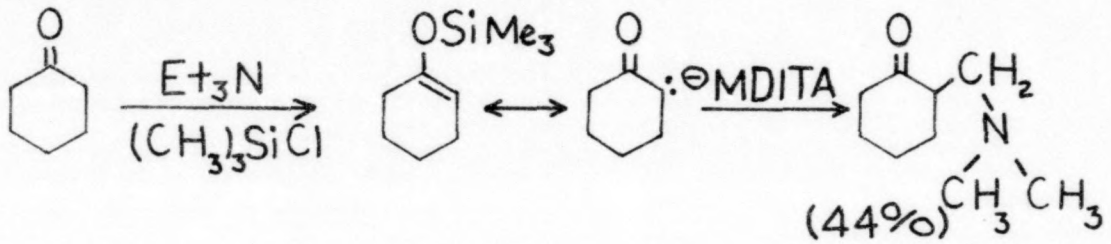


(4)

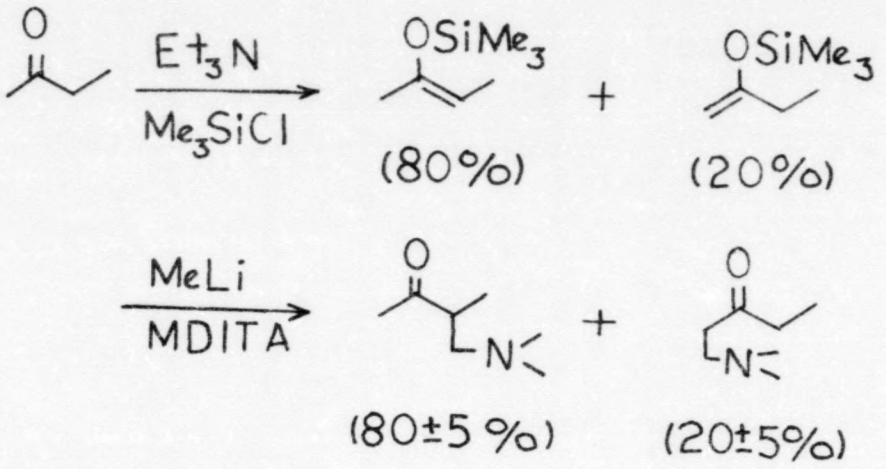
As a way of circumventing use of the amine base, the method of House[29] was evaluated. For symmetrical aldehydes or ketones, the silyl enol ethers were prepared by triethylamine and excess trimethylsilyl chloride in dimethylfromamide (DMF) solution (eqn. 5).



(5)

When the same preparative procedure was applied to unsymmetrical ketones, isomeric enol ethers were formed, with the proportions of each product determined by the relative

thermodynamic stabilities (eqn. 6 & 7).



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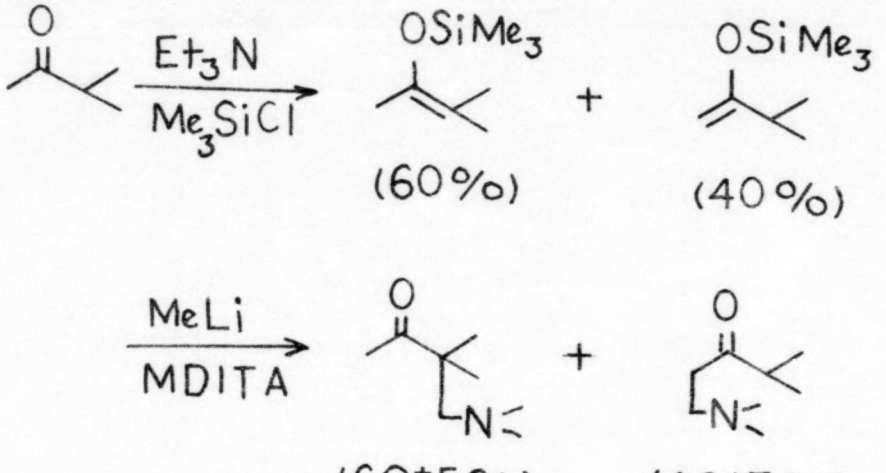
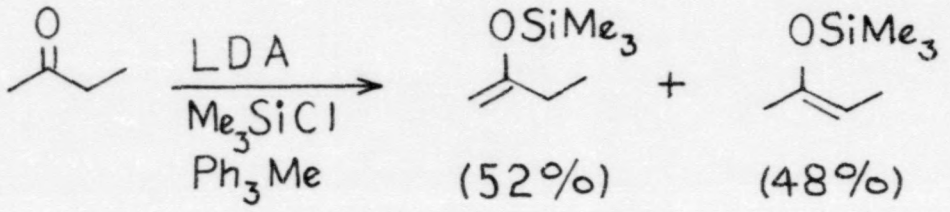
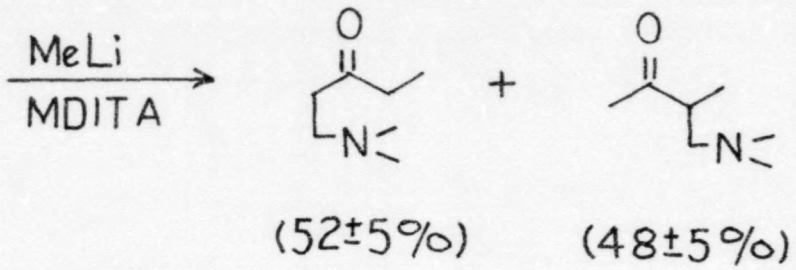


(7)

The less highly substituted silyl enol ethers were obtained by the initial reaction of the ketone with a strong base, lithium diisopropylamide (LDA), followed by addition of chlorotrimethyl silane; those conditions favor kinetically controlled deprotonation. Triphenylmethane was used as an indicator to prevent addition of excess ketone (eqn. 8 & 9).





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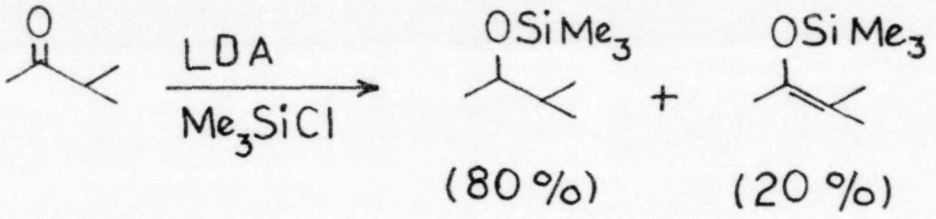
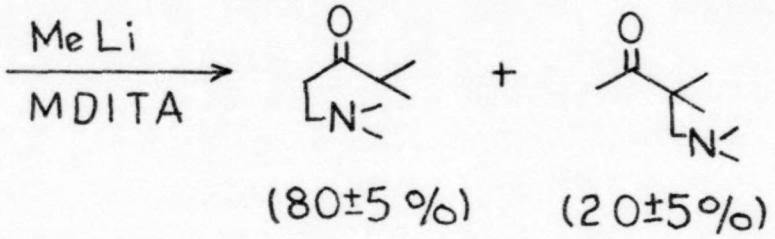
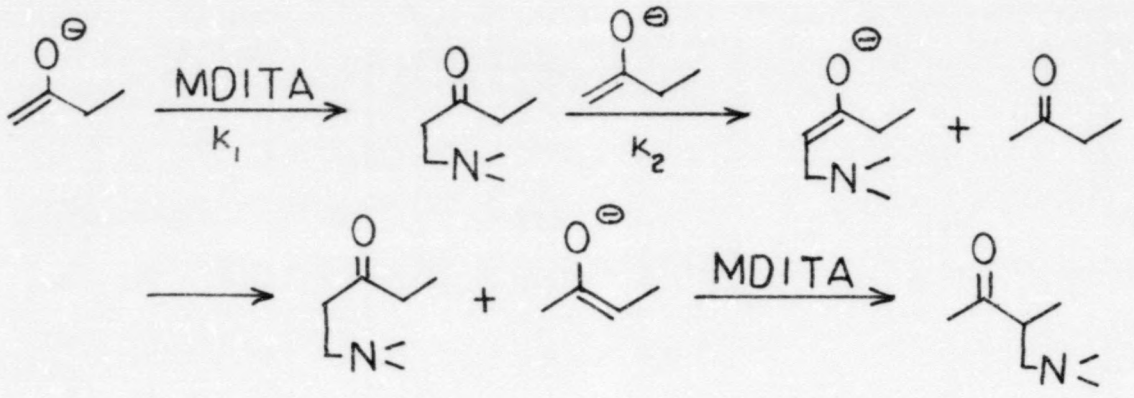




(9)

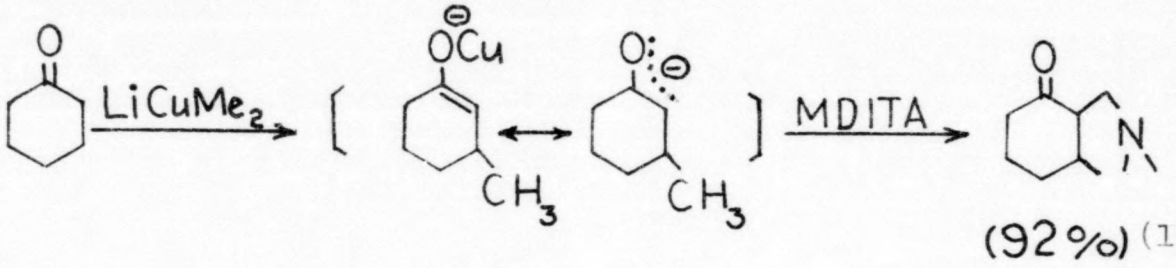
After treating the silyl ether with methyllithium, MDITA was added and the corresponding Mannich base was found regiospecifically. Observation of regiospecific behavior means that alkylation is faster than isomerization. This illustrated for 2-butanone (eqn. 10). Because of the overlap on the NMR spectra, the percentage of each isomer could not be



$k_1 >> k_2$ (10)

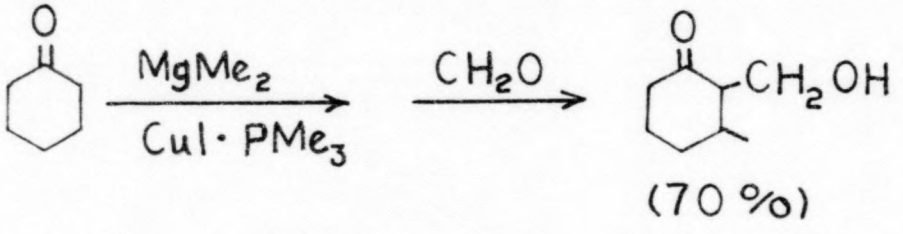
determined closer than ± 5%. Gas chromatography was unsatisfactory as an analytical tool since decomposition occurred on the 3% SE-30 column at 110°C. Decomposition was also observed upon thin-layer chromatography on silica gel.

Lithium dimethylcuprate was employed to produce the enolate by 1,4-addition to α,β-unsaturated ketones[34] (eqn. 11). The yield (92%) from this method was found to be higher



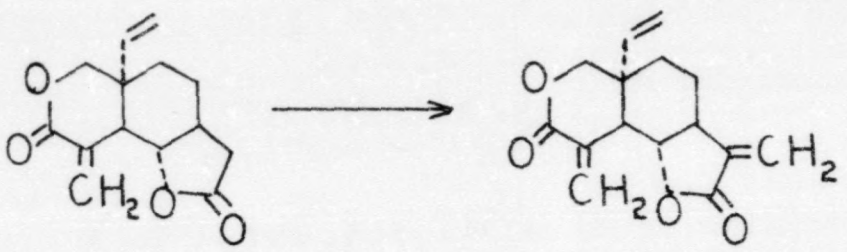
(11)

than that from Stork's method (70%)[30] (eqn. 12).



(12)

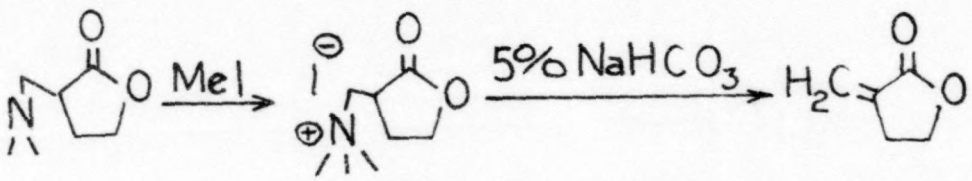
Several anti-tumor drugs have an α-methylene butyrolactone component (e.g., deoxyvernolepin[31], II; eqn. 13).



(13)

(II)

A principal goal of the research was to determine whether it was possible to synthesize the α-methylene-γ-butyrolactone moiety by taking advantage of the properties of the immonium salt. The silyl enol ether of γ-butyrolactone was generated and after quenching with MDITA the desired α-methylene-N,N-dimethylamine-γ-butyrolactone. The treatment of this with methyl iodide formed the trimethyl ammonium dervative. Conversion to the α-methylene product is known to occur upon addition of 5% sodium bicarbonate solution[32] (eqn. 14).



(14)

A variety of methods for generating the methylene lactones is available. But this approach gives the transformation to the unsaturated product at ambient temperatures

and may result in high yields. Unlike the formaldehyde condensation route, this approach dose not appear to suffer from multiple condensation.

EXPERIMENTAL

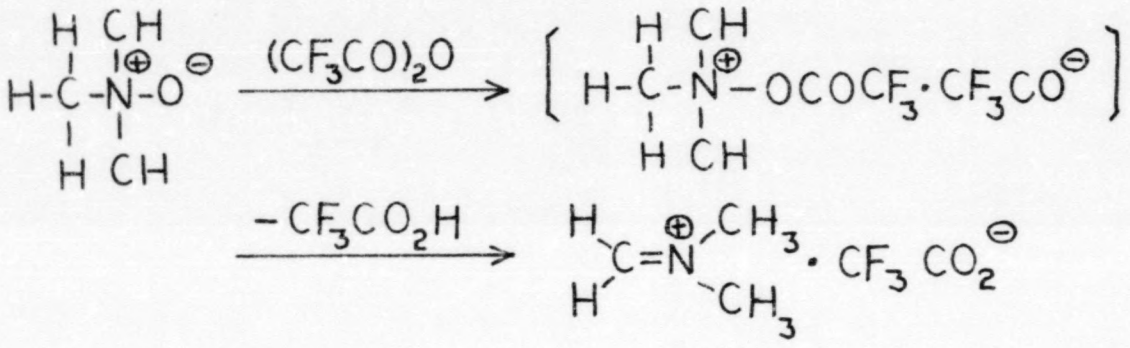
I. Preparation of Starting Materials

Commerical samples of the starting ketones were dried by magnesium sulfate followed by redistillation. 2-Cyclohexenone was used without further purification. Tetrahydrofuran was distilled from lithium aluminum hydride. Dimethylformamide was vacuum distilled from calcium hydride. Triethylamine and diisopropylamine were distilled from potassium hydroxide prior to use. Methyllithium (1.3 M in ethyl ether) was from Ventron Corp. and trimethylsilane chloride was from Matheson Coleman & Bell Corp. of America. Ventron Corp. 98% copper (I) iodide was used without further purification. In order to obtain a high yield of Mannich reagent, the water contained in the trimethylamine oxide was removed by either of the following two methods: (A) anhydrous trimethylamine oxide was propared by subliming the dihydrate at 120°C and 10 mm pressure[33]; (B) to a 500 ml round bottom flask, was added 300 ml of benzene and 20 g of trimethylamine oxide dihydrate. The solution was refluxed through a Dean-Stark trap for 48 hrs. Benzene was removed by rotary evaporation and anhydrous trimethylamine oxide (80%) was obtained : m.p. 92°C.

All reaction were conducted under a blanket of dry nitrogen in flame-dried reaction vessels.

NMR spectra were obtained on a Varian A-60A instrument and IR spectra were measured on Perkin Elemer 710; G.C. data were obtained on a Varian Aerograph 1700 instrument; mass spectra were taken on Perkin-Elmer RMU7 spectrometer.

II. Preparation of MDITA (Methylenedimethylimmonium Trifluoroacetate)



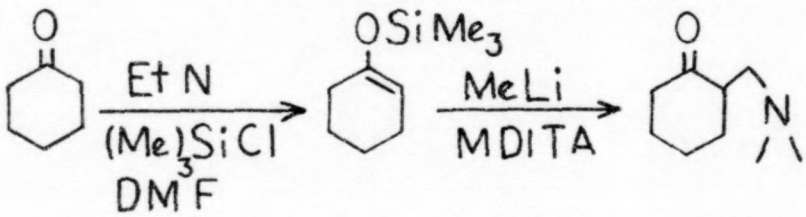
To a solution of 15.0 g (0.2 mole) of anhydrous trimethylamine oxide in 200 ml of dry methylene chloride cooled in an ice bath was added 81.6 g (0.4 mole) of trifluoroacetic anhydride. After stirring overnight, the methylene chloride was distilled at atmospheric pressure, and the residue was distilled at 110-130°C (5×10^{-2} mm). The product was MDITA 29.25 g (86%), which solidified upon storage in the freezer (-15°C). NMR (neat): 3.87 (6H, singlet, $-\underset{|}{N}-CH_3$), 7.95 (2H, singlet, $\diagdown N=CH_2$).

III. Reactions Developed with MDITA

(A) Reaction of MDITA with Phenylmagnesium Bromide

To a flask containing magnesium (1.0 g, 0.041 mole) and 5 ml of absolute ether was added dry bromobenzene (4.5 ml, 6.8 g, 0.043 mole). To the solution of phenylmagnesium bromide, cooled in an ice bath, was added dropwise 1.9 g (0.011 mole) of MDITA. After stirring for 5 min, 5 ml of ice water was added. The solution was extracted with 3 x 30 ml of ether. The combined organic extracts were washed with 2 x 20 ml of water, dried over anhydrous sodium sulfate and evaporated to yield 2.9 g (80%) of N,N-dimethylbenzylamine (b.p. 73-74°C/15 mm). NMR (CCl_4): 2.0-2.3 (6H, singlet, $-\underset{|}{N}-CH_3$), 3.35-3.5 (2H, singlet, $-CH_2-\underset{|}{N}-$), 7.2-7.4 (5H, broad singlet, phenyl).

(B) Reaction of MDITA with the Trimethylsilyl Ether of Cyclohexanone[29]

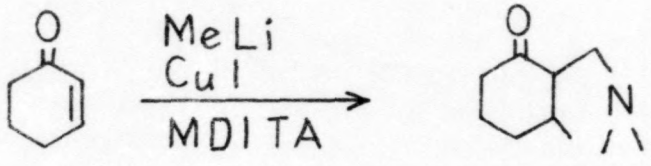


To a solution of 9.81 g (0.090 mole) of chlorotrimethylsilane and 18.18 g (0.18 mole) of distilled triethylamine in 30 ml of distilled dimethylformamide was added 7.36 g (0.075 mole) of cyclohexanone. The resulting mixture, from which some pale yellow solid (presumably triethylamine hydrochloride) separated immediately and more separated during the reaction, was refluxed with stirring for 4 hrs and then cooled, diluted with 60 ml of pentane, and washed with three 90 ml portions of cold aqueous $NaHCO_3$. The organic layer was combined with the pentane extract from the aqueous washes and washed rapidly in succession with portions of cold aqueous 1.5 M HCl and cold aqueous $NaHCO_3$. The resulting pentane solution was dried, concentrated and then distilled to yield the trimethylsilyl ether of cyclohexanone 7.17 g (56%): b.p. 74-75°C/20 mm. NMR (CCl_4): 0.0-0.1 (9H, singlet, $-C-CH_3$), 1.8-1.9 (4H, multiplet, methylene), 2.2-2.3 (4H, multiplet, methylene), 5.4-5.5 (1H, triplet, $-C=C-H$). IR: 1730 ($>C=C<$), 1260 ($Si-CH_3$), 1200 (C-O).

A flask containing 45 ml of dry tetrahydrofuran was cooled to -20°C and addition of 1.5 g (0.012 mole) of trimethylsilyl ether of cyclohexone was followed by the addition of 9.0 ml of methyllithium (0.015 mole, 1.7 M in ether). After stirring for 0.5 hr, 2.25 g (0.013 mole) of MDITA was added in one portion. The resulting mixture was stirred for 1 hr then allowed to warm to room temperature. Cold water

was added and the pH adjusted to 9. The aqueous layer was separated and washed with ether (3 x 20 ml). The organic portions were combined and washed with saturated aqueous NaCl (20 ml) and dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the residue was distilled under reduced pressure to obtain 0.82 g (44%) of 2-methylene-N,N-dimethylamine cyclohexanone (b.p. 105°C/1 mm). NMR (CCl_4): 3.6-3.7 (1H, quintet, α-H), 2.3 (2H, doublet, $-CH_2-N-$), 2.2 (1H, singlet, CH_3-N-), 1.4-1.7 (2H, quintet, β,γ,δ-methylene). IR: 1715 (C=O).

(C) Reaction of MDITA with the Trimethylsilyl Ether of 2-Cyclohexenone[34]

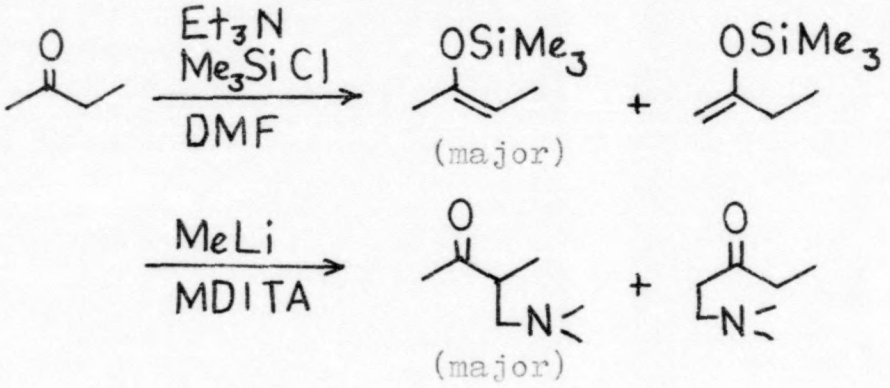


A solution of methyllithium in ether (4.4 mmol) was added to a stirred suspension of copper (I) iodide (2.1 g, 22 mmol) in 100 ml of ether and cooled to -75°C with a dry ice and acetone bath. After stirring for 0.5 hr, 2-cyclohexenone (10.0 mmol) was added over 3 min and followed by stirring an addition hour, MDITA (18.0 mmol) was added in one portion. The resulting mixture was stirred for 1 hr and then allowed to warm to room temperature and stand for 10 hrs. Cold water was added and the pH was adjusted to 9. The

aqueous layer was separated and washed with ether (3 x 20 ml). The combined ether extracts were washed with saturated aqueous sodium chloride solution (20 ml) and dried ($MgSO_4$). Removal of the solvent by rotary evaporation, followed by distillation, resulted in the isolation of 1.55 g (92%) of 2-(N,N-dimethylaminomethylene)-3-methyl cyclohexanone (75-80°C/0.8 mm). NMR ($CDCl_3$): 2.2-2.5 (2H, doublet, $-CH_2-N-$), 2.2-1.5 (3H, multiplet, CH_3-N-), 1.0-1.1 (3H, doublet, $-C-CH_3$). IR: 1710 (C=O). Mass spectrum: 169 (M), 155 ($M-CH_2$), 144 ($155-CH_2$), 124 ($M-NMe_3$), 45 (Me_2N^+).

(D) Reaction of MDITA with the Trimethylsilyl Ethers of 2-Butanone[29]

1) Procedure A for the Preparation of Trimethylsilyl Ether



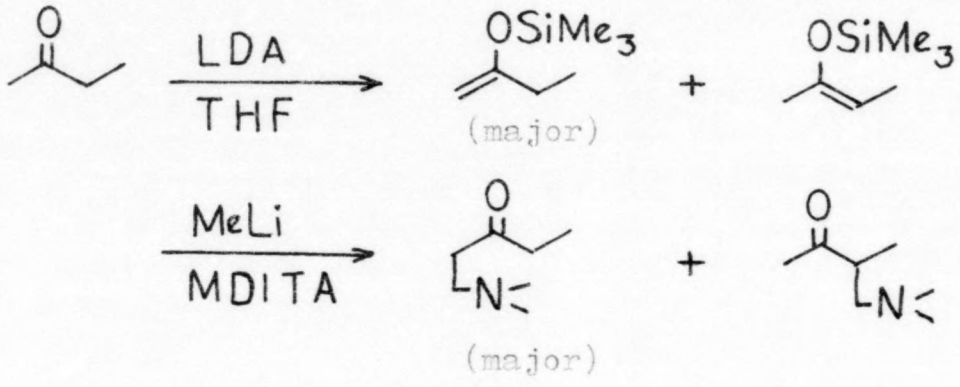
To a solution of 32.60 g (0.30 mole) of chlorotrimethylsilane and 60.60 g (0.60 mole) of triethylamine in 100 ml of dimethylformamide was added 18.00 g (0.25 mole) of 2-butanone. The resulting mixture, from which some pale yellow solid

(presumably triethylamine hydrochloride) separated immediately and more separated during the reaction, was refluxed with stirring for 16 hrs and then cooled, diluted with 200 ml of pentane, and washed with three 300 ml portions of cold saturated aqueous sodium bicarbonate. The organic layer was combined with the pentane extract from the aqueous washes and washed rapidly in succession with portions of cold aqueous 1.5 M HCl and cold aqueous $NaHCO_3$. The resulting pentane solution was dried and concentrated to leave 25.5 g of crude mixture of silyl ethers. Fractional distillation through a column separted 7.2 g of mixture (b.p. 100-115°C/760 mm), which contained about 80% of the major silyl ether and 20% of the minor silyl ether. NMR (CCl_4): 0.1-0.3 (9H, singlet, Si-CH_3), 1.4-1.6 (3H, doublet, C-CH_3), 1.7-1.8 (3H, singlet, CH_3-C-O-), 4.0-4.1 (2H, singlet, CH_2=C), 4.3-4.7 (1H, quetet, C=CH-). IR: 1680 (C=C), 1250 (Si-CH_3), 990 (Si-O).

To a flask containing 50 ml of dry tetrahydrofuran, cooled in a dry ice and isopropyl alcohol bath, was added 2.0 g (13.8 mmol) of the silyl ether mixture. Addition of methyllithium (15.2 mmol) and stirring for 0.5 hr, was followed by the addition of 2.83 g (16.6 mmol) of MDITA. The resulting mixture was stirring for 1 hr and allowed to warm to room temperature. Cold water was added and the pH was adjusted to 9. The aqueous layer was separated and washed with ether

(3 x 20 ml). The ether extracts were combined with the organic layer and washed with saturated aqueous sodium chloride (20 ml) and dried ($MgSO_4$). Solvent was removed by rotary evaporation; the residue, 0.22 g (14%), was 2-methyl-1-(N,N-dimethylamino)-3-butanone (80 ± 5 %) and 1-(N,N-dimethylamino)-3-pentanone (20 ± 5%) (b.p. 120°C/760 mm). NMR (CCl_4): 1.0-1.3 (3H, triplet, C-CH_3), 2.2 (3H, singlet, CH_3-CO-), 2.25-3.0 (6H, singlet, CH_3-N-), 2.65-2.8 (1H, multiplet, -CH-C-N-), 3.2 (2H, doublet, CH_2-N-). IR: 1710 (C=O).

2) Procedure B for the Preparation of Trimethylsilyl Ether



An etheral solution containing 200 mmol of methyllithium was concentrated under reduced pressure and the residual lithium reagent was dissolved in 200 ml of dry tetrahydrofuran containing several milligrams of triphenylmethane as an indicator. The resulting solution was cooled to 0°C and

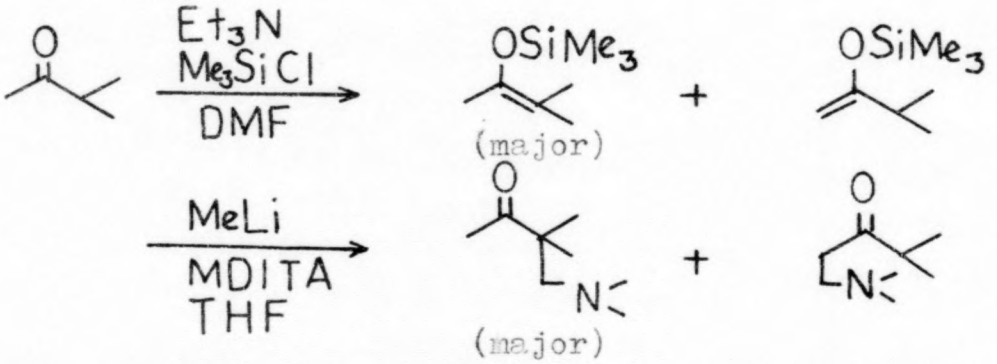
treated with 20.20 g (200 mmol) of diisopropylamine. To this solution of lithium diisopropylamide (LDA) was added dropwisely, 2-butanone (14.4 g, 200 mmol) until the red color of the triphenylmethide indicator was almost completely discharged. Meanwhile a quenching solution, prepared from 100 ml of tetrahydrofuran, 10.0 ml (88 mmol) of triethylamine, and 40 ml (338 mmol) of chlorotrimethylsilane solution was centrifuged to remove any of the insoluble triethylamine hydrochloride. By using of a syringe, this chlorotrimethylsilane solution was added, rapidly and with stirring, to a cold (0°C) solution of the lithium enolate. After the addition was complete, a white solid (LiCl) began to separate. The resulting mixture was stirred at room temperature for 1 hr and then partitioned between pentane and cold aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated to leave 16.46 g of residual liquid containing the crude silyl ether. Fractional distillation through a column separated a 8.23 g mixture of silyl ether (b.p. 85-120°C/760 mm), which contained 52% of the major silyl ether and 48% of the minor silyl ether. NMR (CCl_4): 0.1-0.2 (9H, singlet, $Si-CH_3$), 0.8-1.1 (3H, triplet, $C-CH_3$), 1.3-1.5 (3H, doublet, $C=C-CH_3$), 1.6-1.7 (3H, singlet, $CH_3-\overset{O-}{C}=C$), 1.7-2.1 (2H, quartet, $=\overset{O}{C}-CH_2-$), 4.0 (2H, singlet, $CH_2=C-O-$), 4.25-4.6 (2H, quartet, $-O-C=CH_2-$). IR: 1680 (C=C), 1250 ($Si-CH_3$).

A flask containing 50 ml of dry tetrahydrofuran was

cooled in a dry ice and isopropyl alcohol bath, 2.0 g (13.8 mmol) of silyl ether mixture and methyllithium (15.2 mmol, 1.3 M in ether) were added. After stirring for 0.5 hr, 2.83 g (16.6 mmol) of MDITA was added in one portion. The resulting mixture was stirred for 1 hr and then allowed to warm to room temperature. Cold water was added and the pH adjusted to 9. The aqueous layer was separated and washed with ether (3 x 20 ml). The organic portions were combined and washed with saturated aqueous sodium chloride (20 ml) and dried ($MgSO_4$). Solvent was removed by rotary evaporation, and the residue was distilled to obtain 0.41 g (26%) of mixture of 1-(N,N-dimethylamino)-3-pentanone (52 ± 5%) and 2-methyl-1-(N,N-dimethylamino)-3- butanone (48 ± 5%) (105-135°C/20 mm). NMR (CCl_4): 0.9-1.2 (3H, multiplet, C-CH_3), 2.16-2.17 (3H, singlet, CH_3-CO-), 2.2-2.3 (3H, singlet, N-CH_3), 2.4-2.6 (2H, multiplet, -CH-C-N-). IR: 1720 (C=O).

(E) Reaction of MDITA with the Trimethylsilyl Ethers of 3-Methyl-2-butanone[29]

1) Procedure A for the Preparation of Trimethylsilyl Ether

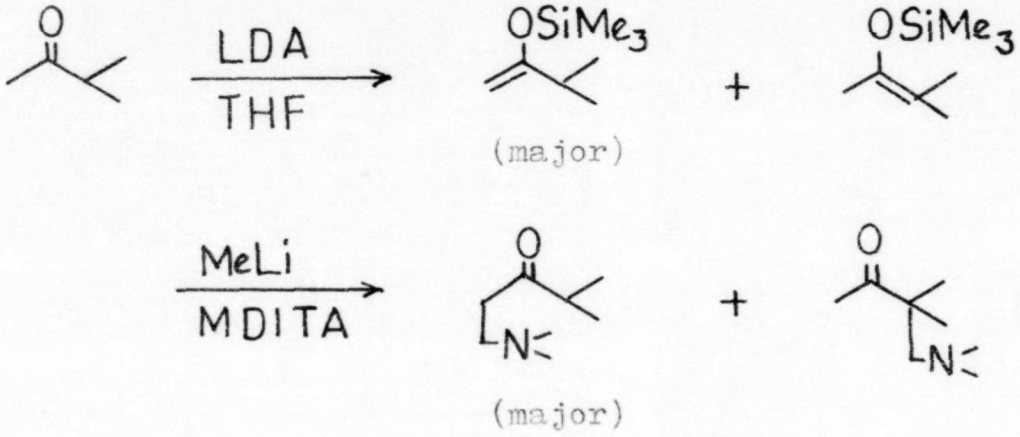


To a solution of 32.60 g (0.30 mol) of chlorotrimethylsilane and 60.60 g (0.60 mol) of triethylamine in 100 ml of dimethylformamide was added 21.50 g (0.25 mol) of 3-methyl-2-butanone. The resulting mixture, from which some pale yellow solid (presumably triethylamine hydrochloride) separated immediately and more sepatately during the reaction, was refluxed with stirring for 52 hrs and then cooled, diluted with 200 ml of pentane, and washed with three 300 ml portions of cold saturated aqueous sodium bicarbonate. The organic portions were combined and washed rapidly in succession with portions of cold aqueous 1.5 M HCl and cold aqueous $NaHCO_3$. The resulting pentane solution was dried and concentrated to leave 31.23 g of crude mixture of silyl ether. Distillation through a column separted 12.44 g of mixture (b.p. 110-140° C/760 mm), which contained about 60% of the major enol ether and 40% of the minor enol ether. NMR (CCl_4): 0.1-0.3 (9H, singlet, Si-CH_3), 0.9-1.1 (6H, doublet, C-CH_3), 1.5-1.6 (3H, singlet, C=C-CH_3), 1.7 (3H, singlet, CH_3-$\overset{O-}{C}$=C), 2.0-2.5 (2H, multiplet, -C-CH_2-), 3.9-4.1 (2H, doublet, CH_2=$\overset{O-}{C}$-C). IR: 1685 (C=C), 1250 (Si-CH_3).

To a flask containing 50 ml of dry tetrahydrofuran, cooled in a dry ice and isopropyl alcohol bath, were added 1.3 g (7.9 mmol) of enol ether mixture and methyllithium (8.8 mmol). After stirring for 0.5 hr, 1.5 g (8.8 mmol) of MDITA was added in one portion. The resulting mixture was stirred for 1 hr then allowed to warm to room temperature.

Cold water was added and the pH was adjusted to 9. The aqueous layer was separated and washed with either (3 x 20 ml). The extracts was combined with organic layer and were washed with saturated aqueous sodium chloride (20 ml) and dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the residue was obtained 0.41 g (40%) of 3-methyl-3-methylene-N,N-dimethylamine-2-butanone (60 ± 5%) and 1-methylene-N,N-dimethylamine-3-methyl-2-butanone (40 ± 5%) (b.p. 110°C/4 mm). NMR(CCl_4): 0.9-1.1 (6H, doublet, C-CH_3), 1.85-1.9 (6H, singlet, N-CH_3), 1.95 (3H, singlet, CH_3-CO-), 2.4-2.5 (2H, multiplet, CH-C-N-), 3.0-3.1 (2H, doublet, CH_2-N-). IR: 1710 (C=O).

2) Procedure B for the Preparation of Trimethylsilyl Ether



An etheral solution containing 100 mmol of methyllithium was concentrated under reduced pressure and the residual lithium reagent wa dissolved in 100 ml of dry

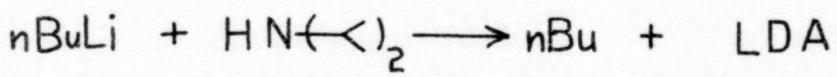
tetrahydrofuran containing 3 milligrams of triphenylmethane as an indicator. The resulting solution was cooled to 0°C and treated with 10.10 g (100 ml) of diisopropylamine. To this solution of lithium diisopropylamide was added, dropwise and with stirring over a 10 min period, 3-methyl-2-butanone (8.58 g, 99.8 mmol) until the red color of triphenylmethide indicator was almost completely discharged. Meanwhile a quenching solution, prepared from 50 ml of tetrahydrofuran, 5.0 ml (44 mmol) of triethylamine, and 20 ml (169 mmol) of chlorotrimethylsilane was centrifugated to remove any of the insoluble triethylamine hydrochloride. By using a syringe, this chlorotrimethylsilane solution was added, rapidly and with stirring, to a cold (0°C) solution of the lithium enolate. After the addition was complete, a white solid (LiCl) began to separate. The resulting mixture was stirred at room temperature for 1 hr and then partitioned between pentane and cold aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated to leave 12.24 g of residual liquid containing the crude silyl ether. Fractional distillation through a column separated a 3.8 g mixture of silyl enol ether (b.p. 120-140°C/760 mm), which contained about 80% of the major enol ether and 20% of the minor enol ether. NMR (CCl_4): 0.1-0.3 (9H, singlet, $Si-CH_3$), 0.9-1.1 (6H, doublet, $C-CH_3$), 1.5-1.6 (3H, singlet, $C=C-CH_3$), 1.65-1.75 (3H, singlet, $CH_3-\overset{O-}{C}=$), 1.9-2.4 (1H, multiplet, C-CH-), 3.9-4.1 (2H, doublet, $CH_2=\overset{O-}{C}-$). IR: 1680 (C=C), 1250

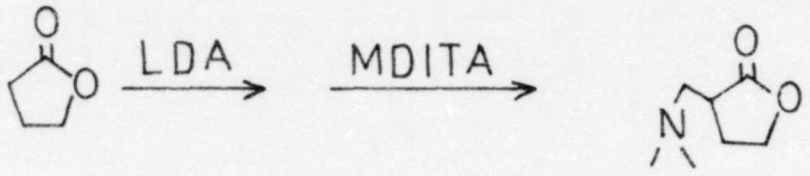
($Si-CH_3$), 1000 (Si-O).

To a flask containing 50 ml of dry tetrahydrofuran, cooled in dry ice and isopropyl alcohol bath, 1.16 g (7.35 mmol) of enol ethers and methyllithium (8.17 mmol) was added. After stirring for 0.5 hr, 1.4 g (8.2 mmol) of MDITA was added in one portion. The resulting mixture was stirred for 1 hr and then allowed to warm to room temperature. Cold water was added and the pH adjusted to 9. The aqueous layer was separated and washed with ether (3 x 20 ml) and followed by chloroform (3 x 20 ml). The extracts was combined with organic layer and were washed with saturated aqueous NaCl (20 ml) and dried ($MgSO_4$). Solvent was removed by rotary evaporation, and the residue was distilled to obtain 0.26 g (28%) of 1-methylene-N,N-dimethylamine-3-methyl-2-butanone (80 ± 5%) and 3-methyl-3-methylene-N,N-dimethylamine-2-butanone (20 ± 5%) (b.p. 110°C/4 mm). NMR (CCl_4): 1.0-1.2 (3H, doublet, $C-CH_3$), 1.9-2.0 (6H, singlet, $N-CH_3$), 2.2-2.25 (3H, singlet, CH_3-CO-), 2.4-2.6 (2H, multiplet, $-CH_2-C-N-$), 3.0-3.1 (2H, doublet, $-CH_2-N-$). IR: 1715 (C=O).

(F) Reaction of MDITA with -Butyrolactone

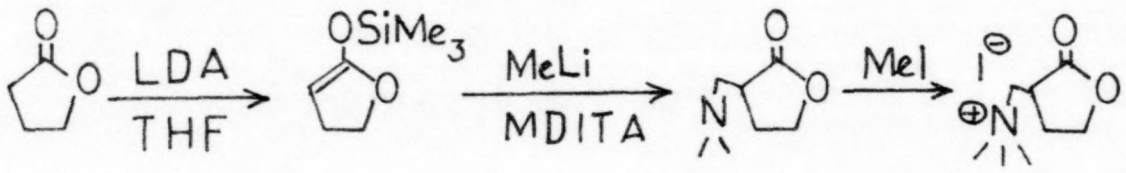
1) Use of LDA (Lithium Diisopropylamide) as Base





To a flask containing 15 ml of tetrahydrofuran, cooled in a dry ice and isopropyl alcohol bath, was added 1.01 g (10.0 mmol) of diisopropylamine. Addition of 4.3 ml (10.5 mmol) of n-butyllithium was followed by stirring for 5 min. γ-Butyrolactone 0.86 g (10 mmol) was added and stirred for an additional 5 min. The dry ice bath was removed and followed by the addition of MDITA (1.88 g, 11 mmol) and stirred for 15 min. 5 ml of saturated aqueous sodium chloride was added and stirred then removed water layer with medicine dropper. Dried the residue over sodium sulfate then evaporated without heating. The starting lactone was found.

2) Use of House's Procedure B to Generate the Trimethylsilyl Ether of γ-Butyrolactone[29]



An etheral solution containing 100 mmol of methyllithium was concentrated under reduced pressure and the residual lithium reagent was dissolved in 100 ml of dry THF containing 3 milligrams of triphenylmethane as an indicator. The resulting solution was cooled to 0°C and treated with 10.10

g (100 mmol) of diisopropylamine. To this solution of lithium diisopropylamide (LDA) was added, dropwise and with stirring over a 10 min period, γ-butyrolactone (8.58 g, 99.8 mmol) until the red color of the triphenylmethide indicator was almost completely discharged. Meanwhile a quenching so solution, prepared from 50 ml of tetrahydrofuran, 5.0 ml (44 mmol) of triethylamine, and 20 ml (169 mmol) of chlorotrimethylsilane was centrifugated to remove any of the insoluble triethylamine hydrochloride. By using of a syringe, this chlorotrimethylsilane solution was added, rapidly and with stirring, to a cold (0°C) solution of the lithium enolate. After the addition was complete, a white solid (LiCl) began to separate. The resulting mixture was stirred at room temperature for 10 hrs and then partitioned between pentane and cold aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and isolated to leave 14.42 g (91%) of trimethylsilyl enol ether of γ-butyrolactone (b.p. 120-150°C/5 mm). NMR(CCl_4): 0.1-0.3 (3H, singlet, $Si-CH_3$), 1.1-1.3 (2H, multiplet, CH_2-C), 3.4-3.7 (2H, triplet, $-CH_2-O-$), 4.15-4.4 (1H, triplet, HC=C). IR: 1680 (C=C), 1250 ($Si-CH_3$).

To a flask containing 30 ml of dry THF, cooled in dry ice and isopropyl alcohol bath, 0.83 g (5.85 mmol) of enol ether and methyllithium 4.5 ml (5.85 mmol) was added. After stirring for 0.5 hr, 1 g (5.85 mmol) of MDITA was added in one portion. The resulting mixture was stirring for 1 hr then allowed to warm to room temperature. Cold water was

added and the pH adjusted to 9. The aqueous layer was separated and washed with ether (3 x 20 ml) and followed by chloroform (3 x 20 ml). The extracts was combined with organic layer and were washed with saturated aqueous sodium chloride (20 ml) and dried ($MgSO_4$). Solvent was removed by rotary evaporation, and the residue was distilled to obtain 0.53 g (64%) of β-methyl-(N,N-dimethylamino)-γ-butyrolactone (b.p. 120-150°C/0.4 mm). NMR (CCl_4): 1.0-1.2 (2H, triplet, CH_2-C), 2.1-2.2 (3H, singlet, -N-CH_3), 2.5-2.7 (2H, doublet, CH_2-N-), 3.4-3.7 (2H, multiplet, -CH_2-O-), 4.1-4.4 (1H, multiplet, -CH-CO-). IR: 1720 (C=O).

To the β-methyl-(N,N-dimethylamino)-γ-butyrolactone, 5 drops of methyl iodide was added. The white quaternary iodide salt was precipited and the solvent was evaported of under room temperature (m.p. 170-176°C). NMR (DMSO-d_6): 1.0-1.2 (2H, multiplet, CH_2-C), 2.5-2.6 (1H, multiplet, CH-CO-O-), 3.0-3.4 (9H, singlet, N-CH_3), 3.7-3.9 (2H, multiplet, -CH_2-N-), 4.1-4.5 (2H, multiplet, -CH_2-O-).

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