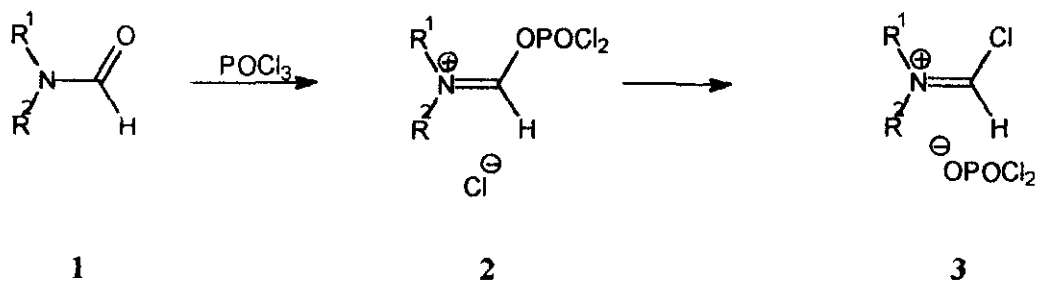


1

CHLOROMETHYLENEIMINIUM SALTS: METHODS OF GENERATION AND APPLICATIONS

1.1 Introduction

Reactions of electrophilic reagents with electron rich aromatic or aliphatic compounds or enolizable carbonyl compounds provide probably one of the most effective methods for the formation of new carbon-carbon bonds. In this class of reagents, chloromethyleneiminium salts, popularly known as Vilsmeier reagents, are highly versatile and possess excellent synthetic potential. Chloromethyleneiminium salts, usually generated *in situ* by the treatment of an acid chloride such as POCl_3 with an N,N-disubstituted formamide such as DMF¹⁻⁸, are the reactive intermediates in the Vilsmeier-Haack reaction which is very useful in the formylation of electron rich aromatic compounds or olefins.⁹⁻¹³ Today it is well established that the reaction proceeds via the attack of the carbonyl oxygen of the amide to POCl_3 to form the adduct **2** at first, which reacts further to give the chloromethyleneiminium salt **3** (Scheme 1).

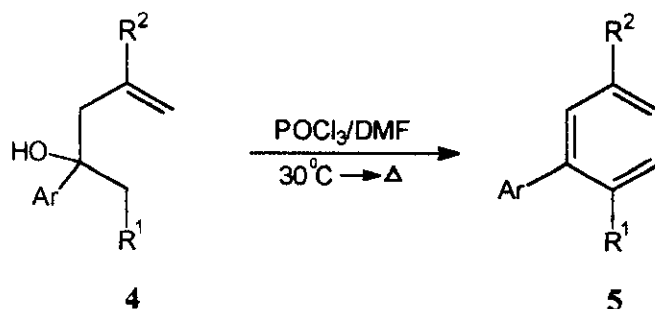


Scheme 1

Nevertheless, the chloromethyleneiminium salts are also useful in bringing about a variety of other synthetic transformations. Reactions involving olefins, carbonyl compounds and their derivatives are highly versatile. On treatment with chloromethyleneiminium salts, they provide multifunctional synthons having potential for further applications in organic synthesis. As part of an ongoing program to explore the synthetic applications of these intermediates, we have examined the reaction of the iminium salt intermediates generated from aliphatic tertiary alcohols. The studies have resulted in the development of valuable methods for the synthesis of a variety of functionalized pyridines and naphthyridines.¹⁹ These results are described in chapter two of this thesis. While exploring the reactions of iminium salt intermediates generated from α -hydroxyketenedithioacetals with chloromethyleneiminium salts, alkylthio substituted pyridines were obtained in good yields. Chapter three describes the results of our studies on the Vilsmeier-Haack reactions of these sulfur substituted allylic alcohols. Some earlier reports from our laboratory reveals that when a ketone flanked by two methylene groups is treated with Vilsmeier-Haack reagent, it undergoes multiple iminoalkylations followed by cyclization to afford substituted 4-pyrones.¹⁴ We envisaged that the above protocol could be developed further for the generation of functionalized pyridines. This approach for the synthesis of functionalized pyridines from ketones having two active methylene groups is described in chapter four of the thesis.

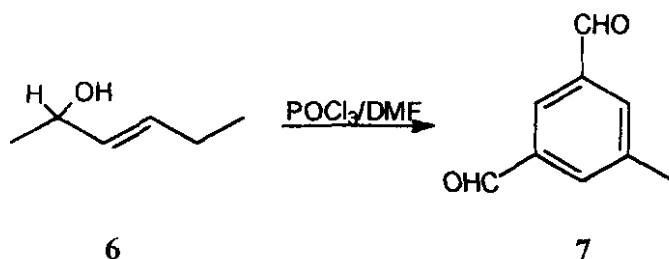
1.2 Reactions of Chloromethyleneiminium Salts with Tertiary Alcohols

The reactions of chloromethyleneiminium salts with aliphatic alcohols reported till date are very few. Biphenyl derivatives **5** have been synthesized by the Vilsmeier reaction of homoallyl alcohols **4**, obtained by the addition of allyl Grignard reagents to methyl ketones (Scheme 2).¹⁵



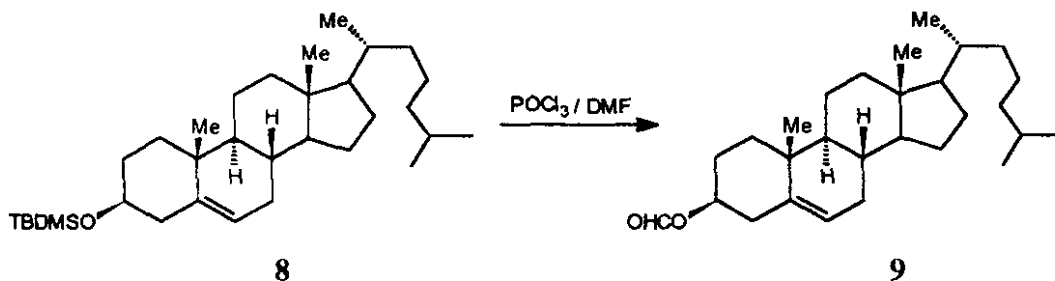
Scheme 2

The Vilsmeier reaction has been employed in the synthesis of aromatic aldehydes from acyclic compounds. For example, the acyclic unsaturated alcohol **6** on treatment with chloromethyleneiminium salts gave uvitaldehyde **7** (Scheme 3).¹⁶



Scheme 3

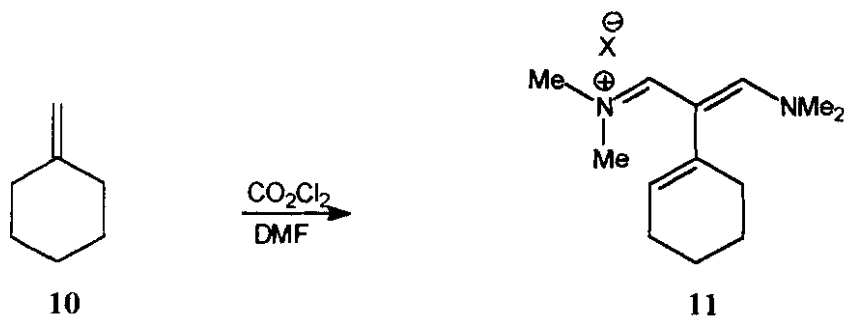
Lelouche and coworkers have converted *O*-*tert*-Butyldimethylsilylated or *O*-triethylsilylated alcohols **8** to their corresponding *O*-formyl derivatives **9** in a one step procedure using Vilsmeier reagents (Scheme 4).¹⁷



Scheme 4

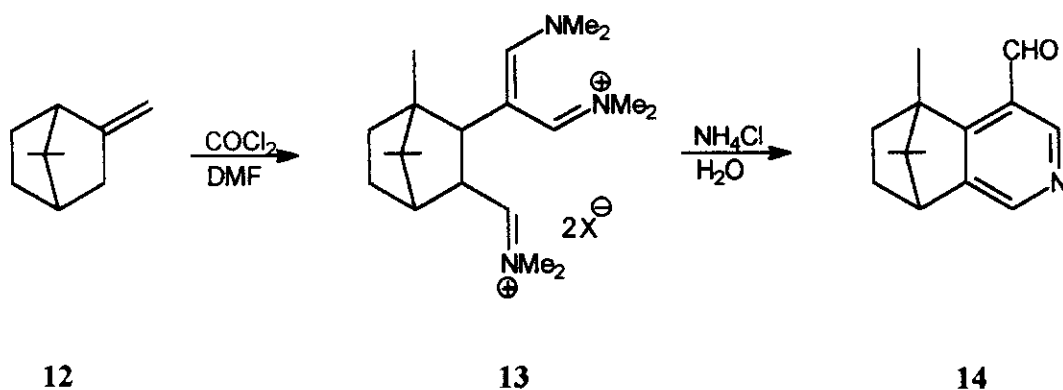
1.3 Chloromethyleneiminium Salts: Reactions with Alkenes

The reactions of simple alkenes possessing alkyl substituents are rather complex due to subsequent imino alkylations and migrations of carbon-carbon bonds. Methylene cyclohexene **10** underwent double iminoalkylation to produce **11** as its perchlorate salt (Scheme 5).¹⁸



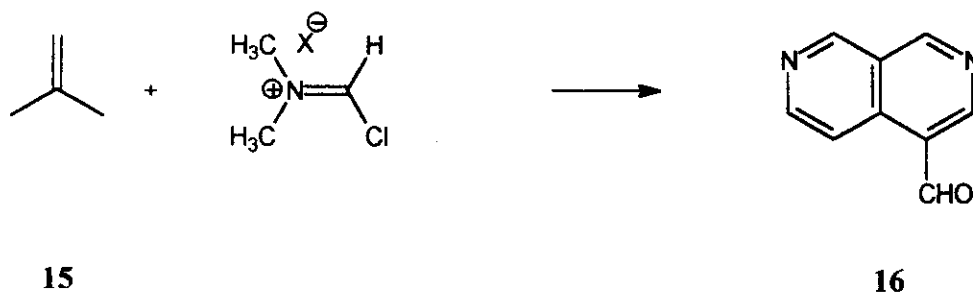
Scheme 5

The reaction of methylene bornane proceeded with multiple iminoalkylation to give the iminium salt **13** which could be converted to the pyridine **14** (Scheme 6).¹⁸

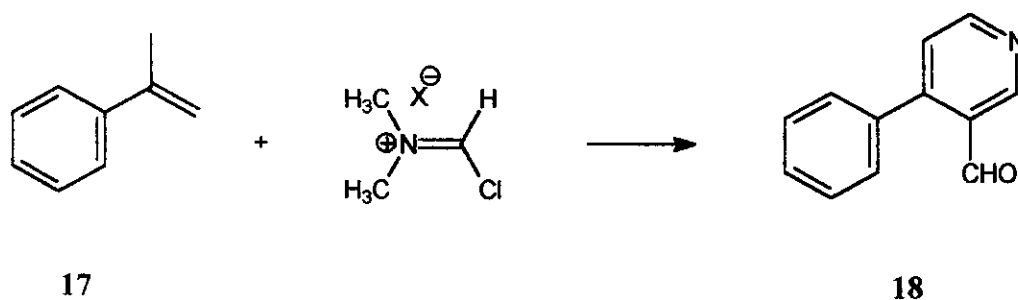


Scheme 6

Similar multiple formylations and subsequent conversions to 2,7-naphthyridine **16** or pyridine derivatives **18** have been described in the case of isobutene **15** and 2-phenyl propene **17** in Scheme 7 and Scheme 8 respectively.¹⁹



Scheme 7



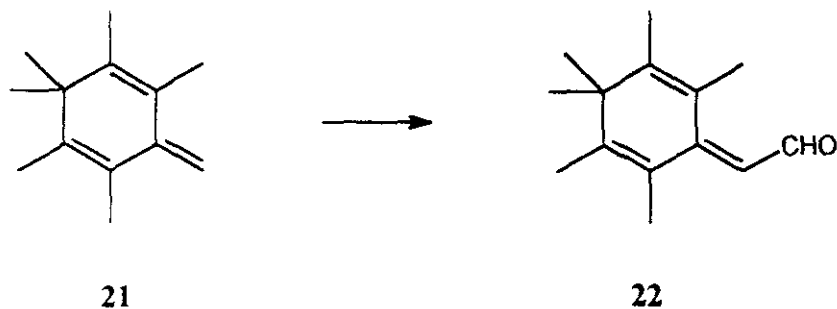
Scheme 8

However when the rearrangements are restricted by the substituents at the α -position monoformylated products are obtained. This is demonstrated by the reaction of *d,l*-camphene **19** which underwent reaction with the reagent prepared from POCl_3 and DMF to give the monoformylated product **20** (Scheme 9).



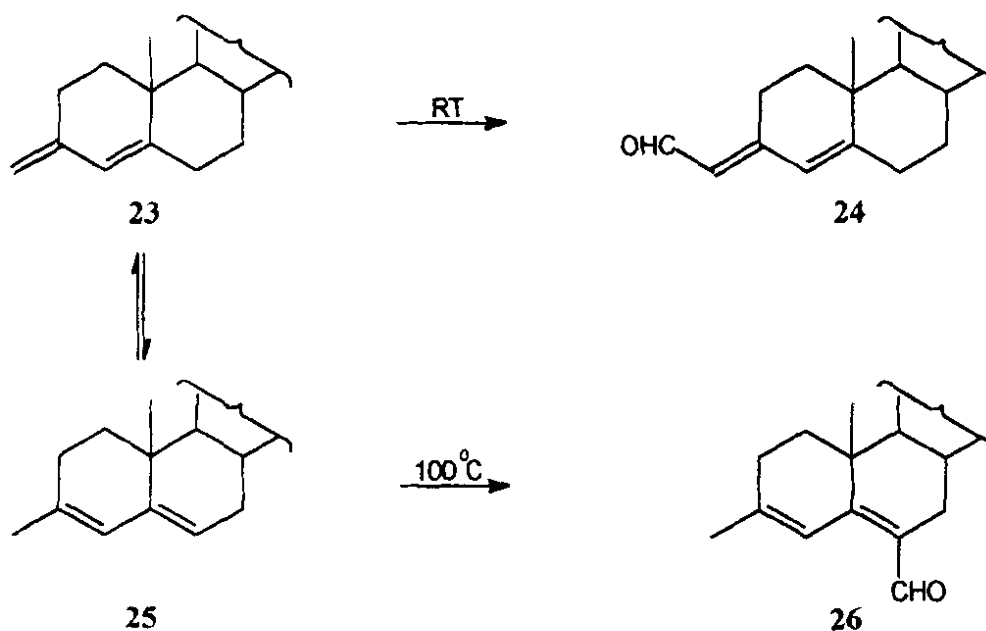
Scheme 9

Similarly the hexamethyl substituted 4-methylene cyclohexadiene **21** also underwent monoalkylation to give the corresponding α,β -unsaturated aldehyde **22** (Scheme 10).



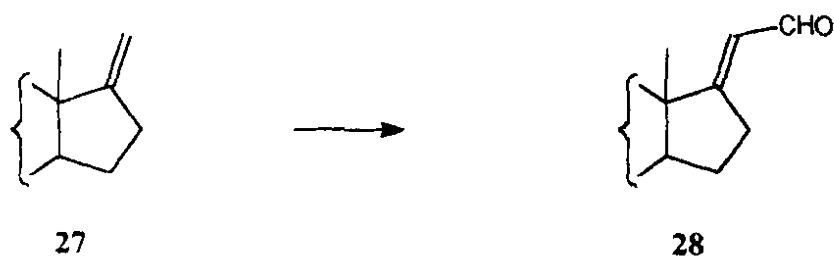
Scheme 10

The steroid diene **23** having exocyclic methylene group, gave the dienaldehyde **24** though the 3-methyl-3,5-diene is thermodynamically much more stable. However when the reaction was carried out at higher temperature the dienaldehyde **26** derived from the more stable diene **25** was obtained (Scheme 11).²⁰

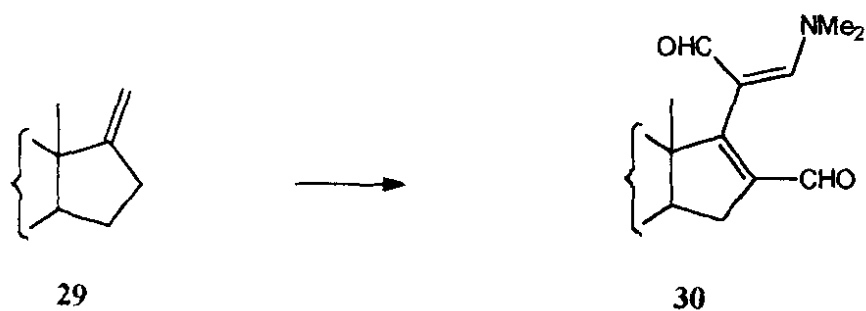


Scheme 11

Steroids 27 having exo methylene group at C-17 also underwent monoformylation leading to the formation of enaldehydes 28. However under more vigorous conditions multiple formylations did occur and the dialdehydes 30 have been isolated under such conditions (Scheme 12 and Scheme 13).²¹

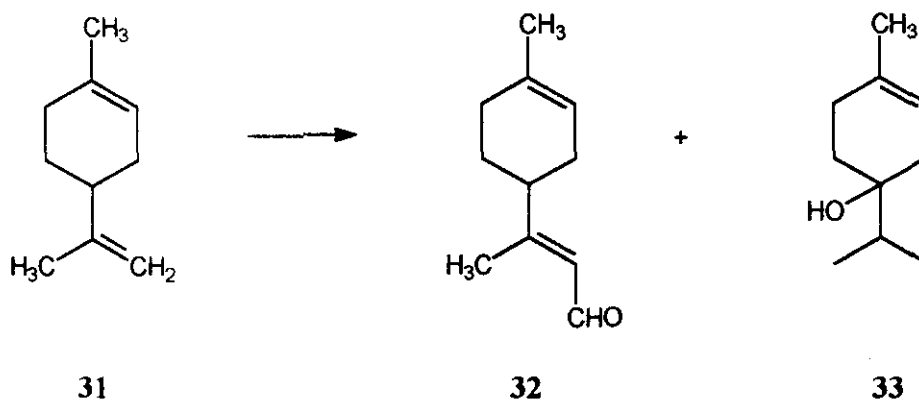


Scheme 12



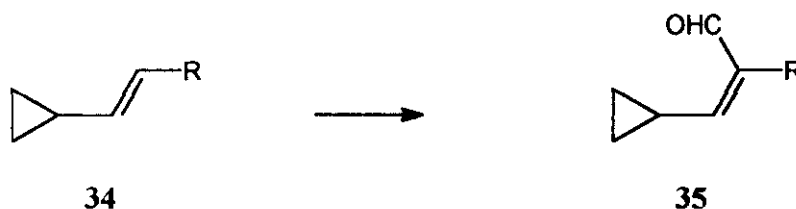
Scheme 13

Limonene **31** underwent monoformylation under Vilsmeier-Haack conditions to give the enaldehyde **32**, though the rearrangement product terpinolene **33** was also formed along with the aldehyde (Scheme 14).²²



Scheme 14

Vinyl cyclopropanes also react with the chloromethylene iminium salt leading to the formation of the mono formylated products **35** in good yields (Scheme 15).²³



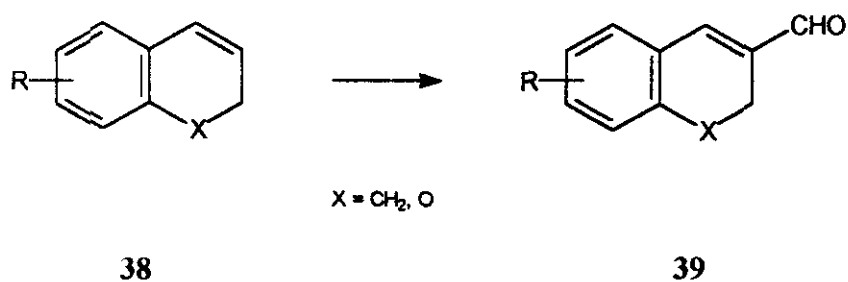
Scheme 15

Vilsmeier-Haack formylations of alkenes conjugated with aromatic systems are simple and straight forward. Thus the reaction of substituted styrenes with the Vilsmeier reagent leads to the formation of cinnamaldehyde derivatives on the hydrolysis of the intermediate iminium salts (Scheme 16).²⁴ Alternatively carbinols obtained by carbonyl group reduction of substituted acetophenones or addition of Grignard reagents to benzaldehydes may be directly used for the preparation of cinnamaldehydes by their treatment with Vilsmeier-Haack reagents.²⁵ Here the Vilsmeier reagent assisted elimination of hydroxy group and subsequent iminoalkylation leads to the formation of the (phenylvinyl)methyleneiminium salts.



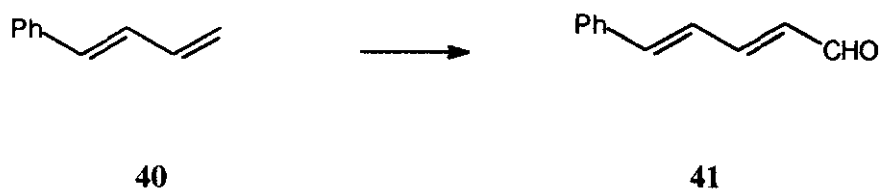
Scheme 16

1,2-Dihydronaphthalenes **38** ($\text{X} = \text{CH}_2$)²⁶ and chromene **38** ($\text{X} = \text{O}$) derivatives²⁷ also undergo similar formylation to afford the respective enaldehydes (Scheme 17).

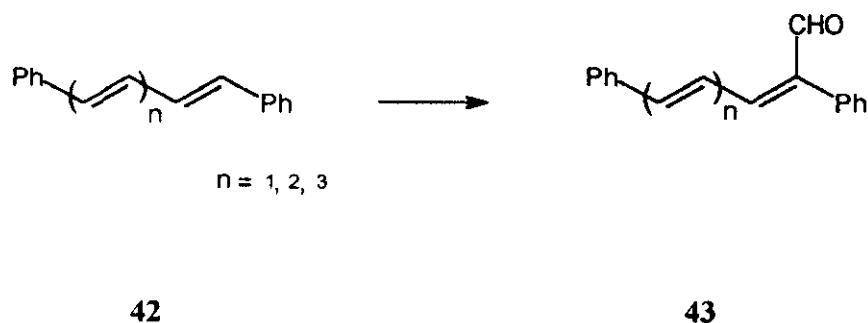


Scheme 17

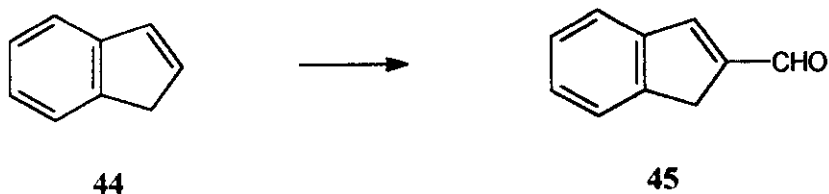
Other substrates that are reported to undergo similar formylations are phenyl substituted butadiene **40** (Scheme 18)²⁸ and hexatrienes **42** (Scheme 19)²⁹, indene **44** (Scheme 20)³⁰ and fulvene **46** (Scheme 21)³¹ derivatives.



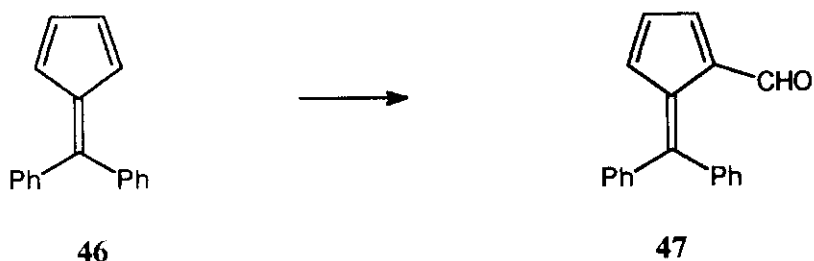
Scheme 18



Scheme 19



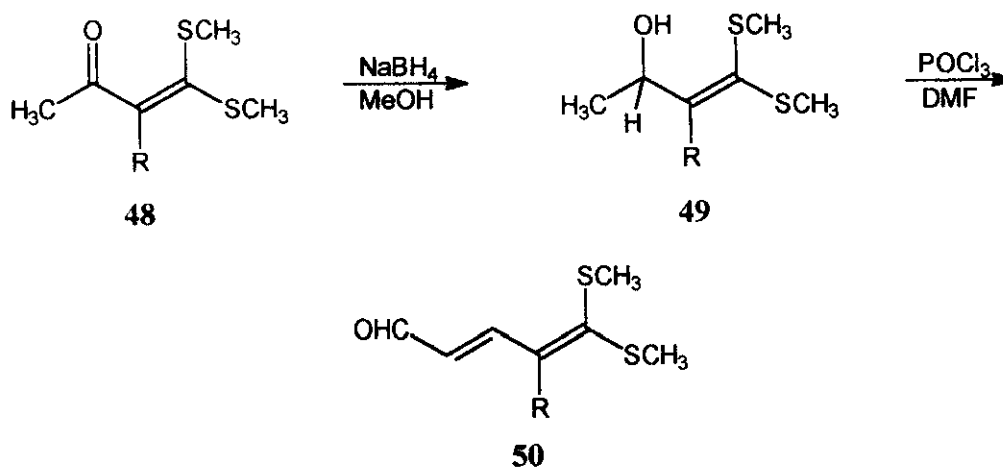
Scheme 20



Scheme 21

1.4 Reactions of Carbinols Derived from Acyl ketenedithioacetals

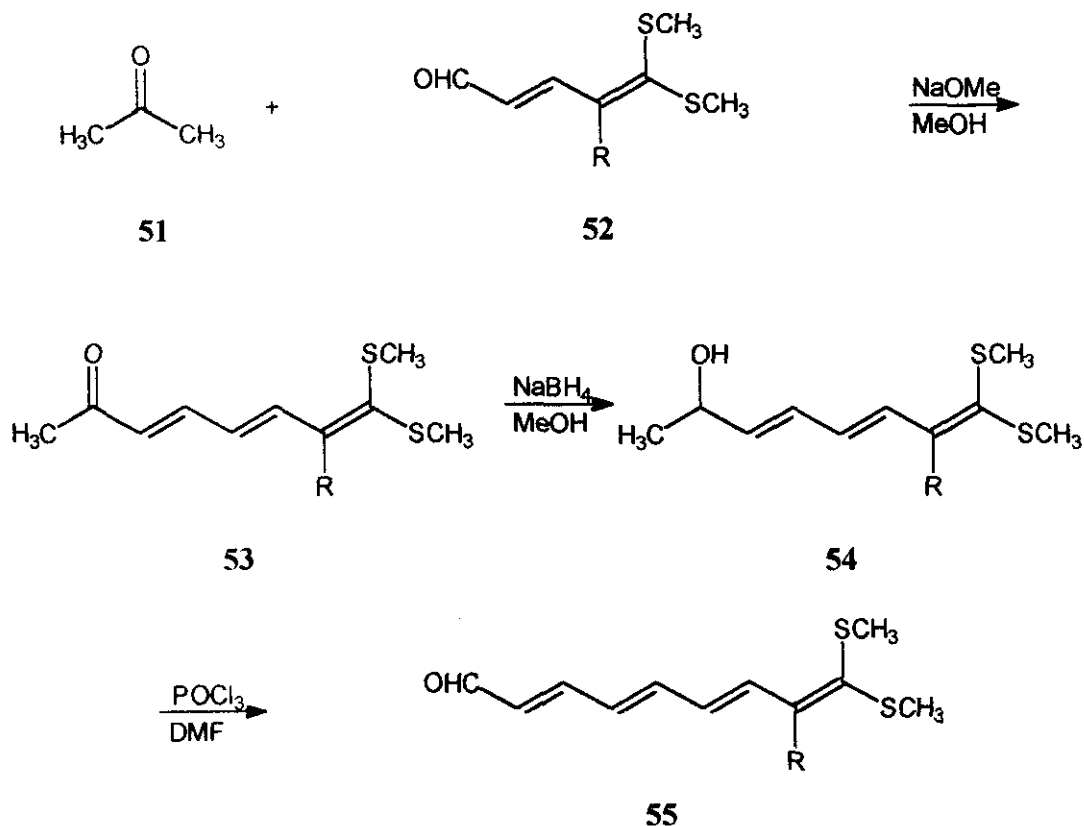
The carbinol derived from 1,2-reduction of acyl ketenedithioacetals **48** undergo facile Vilsmeier-Haack reaction to give 5,5-bis(methylthio)substituted pentadienaldehydes **50** (Scheme 22).³²



Scheme 22

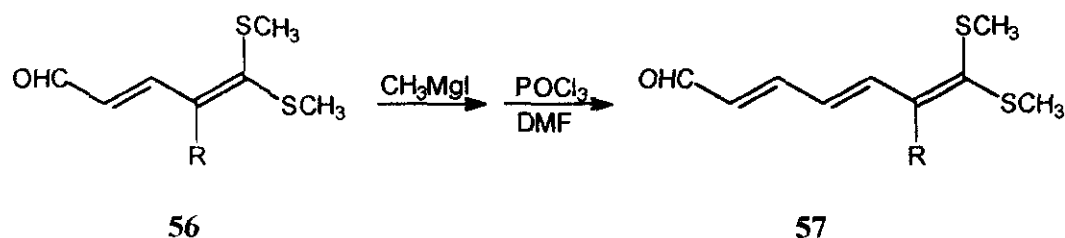
Ketene dithioacetals derived from cyclic ketones can also be similarly transformed to the respective pentadienaldehydes.

ω,ω -Bis(methylthio) substituted polyenaldehydes can be prepared by a combination of sequential aldol condensation, reduction and Vilsmeier-Haack reaction. This is exemplified by the synthesis of 9,9-bis(methylthio)nonapentaldehyde **55** (Scheme 23).



Scheme 23

Alternatively synthesis of similar polyenes can also be achieved by a combination of methyl Grignard addition and Vilsmeier-Haack formylation (Scheme 24).



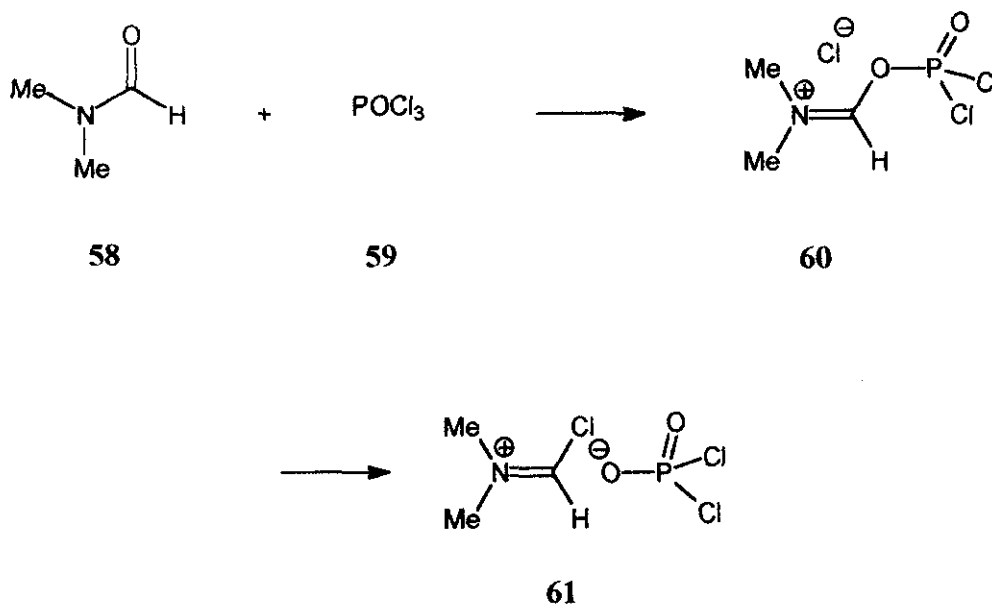
Scheme 24

The polyenaldehydes prepared by this method have been shown to be valuable intermediates in carbonyl group transposition reactions.

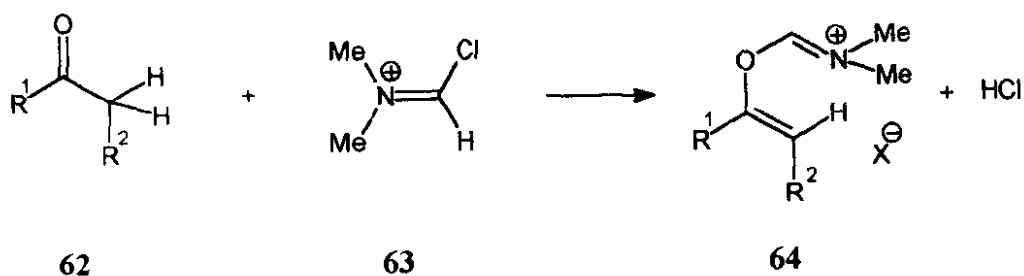
1.5 Chloromethyleneiminium Salts: Reactions with Carbonyl Compounds

The reactions of chloromethyleneiminium salts with carbonyl compounds and their derivatives are highly versatile. On treatment with chloromethyleneiminium salts they provide multifunctional synthons having potential for further application in synthesis as products.

Simple enolizable carbonyl compounds react with chloromethyleneiminium salts to afford the corresponding chloroethylenic aldehydes. Usually the reaction is carried out in a mixture of DMF and POCl_3 , where DMF will be in excess and often serve as the solvent as well. The treatment of POCl_3 with DMF leads to the formation of the chloromethyleneiminium salt **61** (Scheme 25) via the intermediate **60**. It has been suggested that the ketone enolizes prior to its reaction with Vilsmeier reagent.³³ The enolization enhanced due to the presence of HCl that would be formed as a result of the iminoalkylation at the oxygen of the carbonyl compound (Scheme 26).

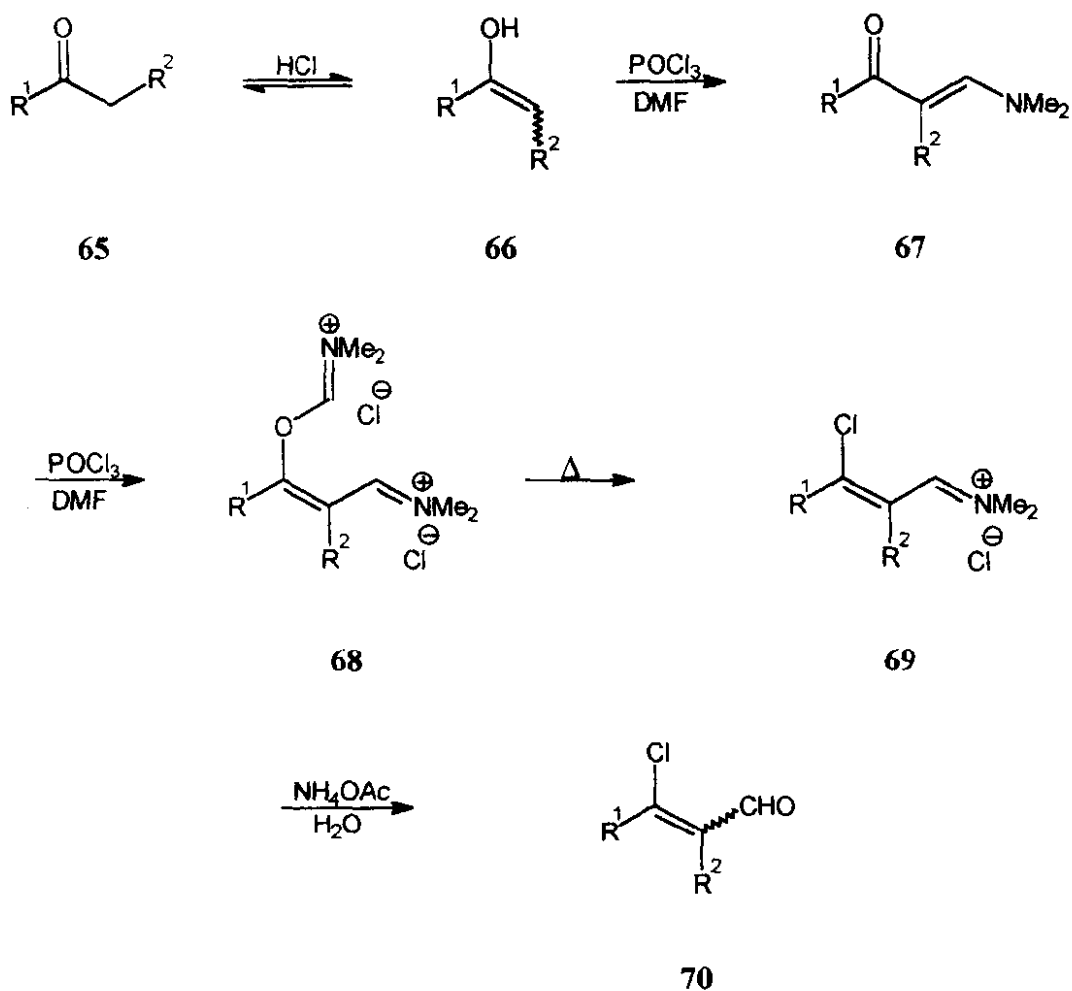


Scheme 25



Scheme 26

The enol form of the ketone reacts with the Vilsmeier reagent to afford the β -dimethylaminovinyl ketone 67 which undergo further reaction with the reagent to afford the iminium salt 69 which on alkaline hydrolysis lead to the formation of β -chloroethylenic aldehyde 70 (Scheme 27).



Scheme 27

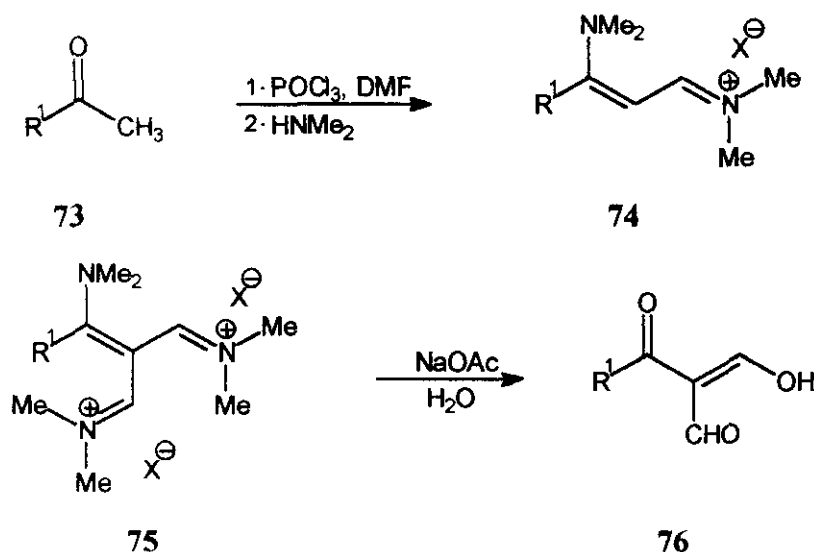
1.5.1 Reactions of Acyclic Ketones with Chloromethyleneiminium Salts

Simple aliphatic ketones can be conveniently transformed to the substituted β -chloroacrylaldehydes by the Vilsmeier-Haack reaction. The reaction is quite general and moderate to good yields of β -chloroacrylaldehydes^{2, 3, 6, 34} are obtained. The reactions are usually performed by the slow addition of ketones to a well cooled (0-5 °C) solution of Vilsmeier reagent in solvent such as DMF or chloroform. Excess Vilsmeier reagent (upto 5 equivalents) is often used. At higher temperatures multiple iminoalkylations are common and lead to complex reaction mixtures. When acetone was subjected to the reaction with Vilsmeier reagent, 3-chlorobut-2-enal **72** was obtained as a mixture of *E* and *Z* isomers in 39% yield (Scheme 28).³³



Scheme 28

There are several examples reported in the literature for the multiple iminoalkylations of acyclic ketones. When the chloro substituent of the intermediate iminium salt is replaced by N,N-dimethylamino group, subsequent iminoalkylation can be performed conveniently to afford malonaldehyde **76** as the final product after basic hydrolysis (Scheme 29).³⁵



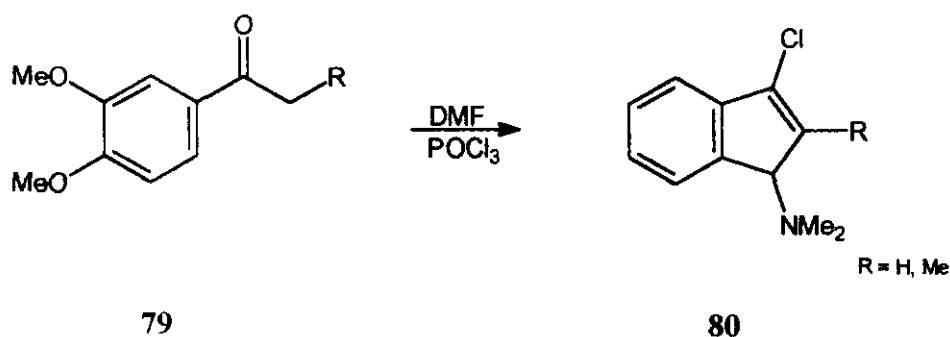
Scheme 29

The reaction of aryl alkyl ketone with Vilsmeier reagent is more selective. The respective chloraldehydes are formed in moderate to good yields. Substituted acetophenones give β -chlorocinnamaldehydes **78**^{33, 36, 37} (Scheme 30).



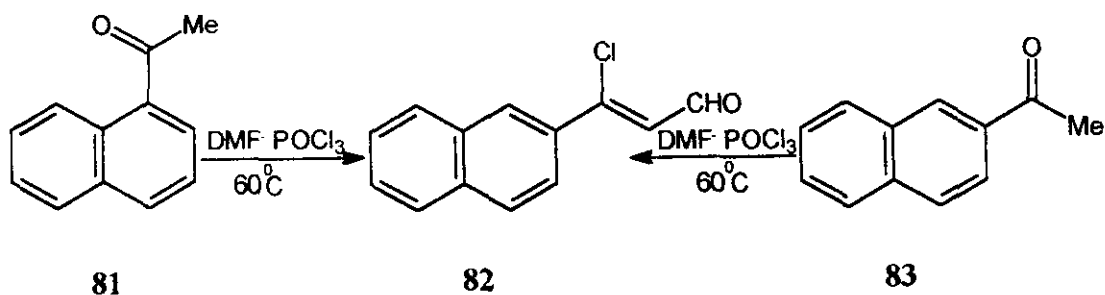
Scheme 30

In the case of diacetyl benzenes, all the acetyl group have been found to undergo chloroformylation with Vilsmeier-Haack reagent.^{38,39} Substituted propiophenones undergo cyclization to chloro substituted N,N-dimethylamino substituted indenes **80** (Scheme 31).⁴⁰ Aryl benzyl ketones on treatment with Vilsmeier reagent afforded the corresponding chloroindenes.⁴¹



Scheme 31

Bodendorf and Mayer have found that 1-acetyl naphthalene and 2-acetyl naphthalene undergo Vilsmeier reaction with the reagent prepared from DMF and POCl₃ to give the same chloroformylated product **82**. It has been proposed that the reaction of 1-acetyl naphthalene involve the migration of acetyl group (Scheme 32).⁴²

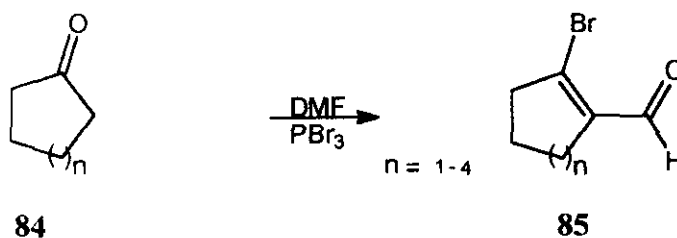


Scheme 32

Acetyl substituted pyrroles react with Vilsmeier reagent to afford the corresponding chlorovinyl pyrroles or acetylenic aldehydes.^{43,44}

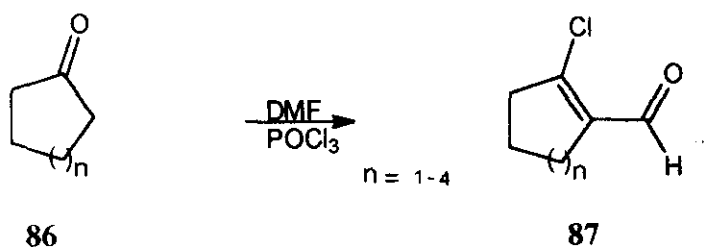
1.5.2 Reactions of Cyclic Ketones with Chloromethyleneiminium Salts

Like acyclic ketones cyclic ketones can also be transformed to the haloformylated products by the reaction with halomethyleneiminium salts. Arnold and Holy used a mixture of DMF and PBr_3 complex to synthesise bromo substituted cycloalkane carbaldehyde **85** (Scheme 33).⁴⁵



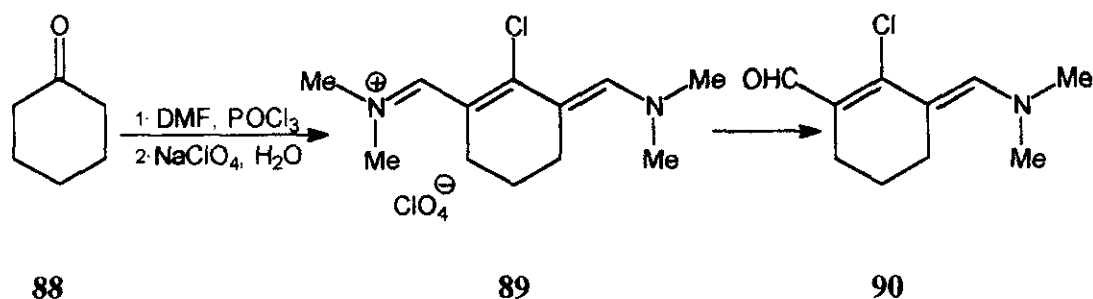
Scheme 33

Similarly corresponding β -chloroacrylaldehydes **87** can be obtained by the reaction of POCl_3 and DMF (Scheme 34).^{46,47,48}



Scheme 34

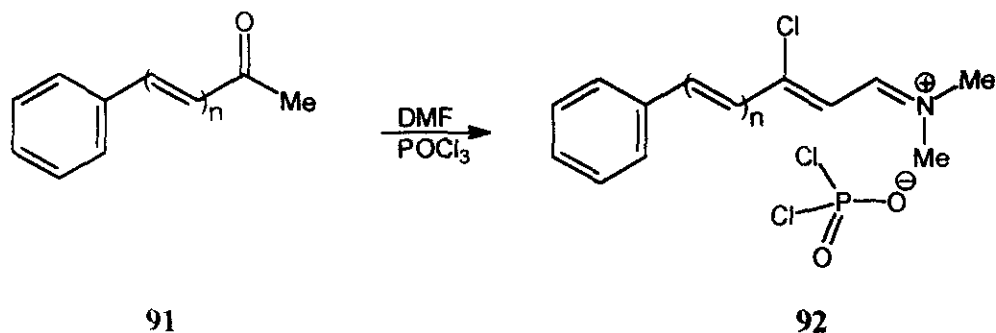
Cyclic ketones can undergo multiple iminoalkylations in the presence of large excess of Vilsmeier reagent. When cyclohexanone was allowed to react with excess Vilsmeier reagent prepared from POCl_3 and DMF the corresponding pentamethinium salt **89** was isolated as its perchlorate salt. This could be further hydrolysed to the N,N- dimethylamino substituted pentadienaldehyde **90** (Scheme 35).⁴⁹



Scheme 35

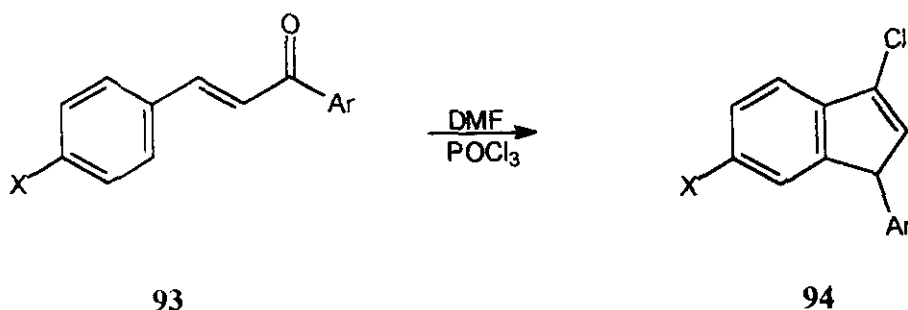
1.5.3 Reactions of α,β -Unsaturated Acyclic Ketones with Chloromethyleneiminium Salts

Benzilidene acetone **91** ($n=1$) and cinnamylidene acetone **91** ($n=2$) were smoothly converted into their iminium salts **92** (Scheme 36).⁵⁰



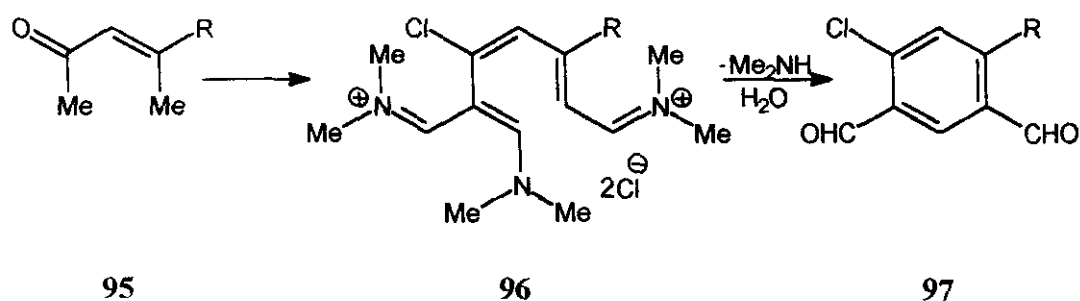
Scheme 36

Formation of similar iminium salts were reported by Arnold and Holy as well. Later Venugopal and Perumal have examined the reactions of benzal acetones and chalcones with Vilsmeier-Haack reagents.^{51,52} While benzal acetone gave chloroformylated products depending upon the substituents, chalcones cyclized to chlorosubstituted indene derivatives **94** in moderate yields in the presence of Vilsmeier-Haack reagent (Scheme 37).



Scheme 37

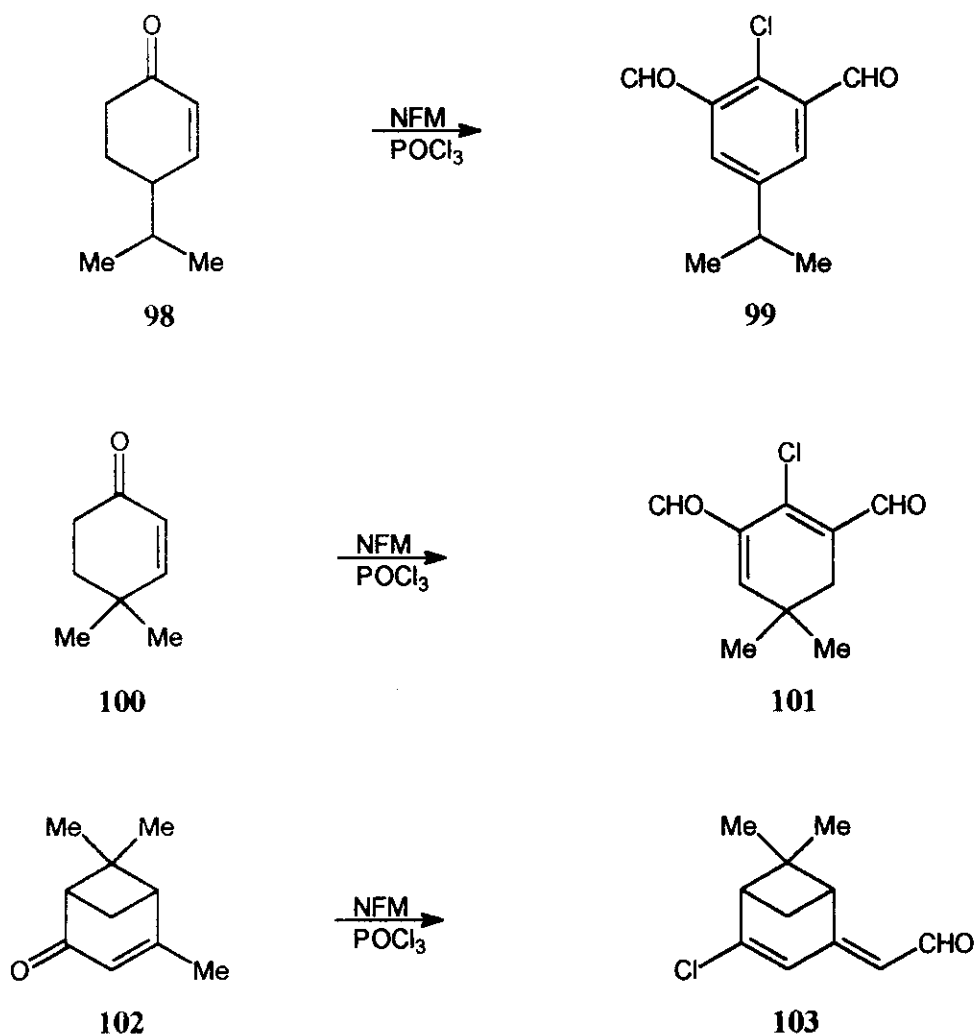
Aliphatic α, β -unsaturated ketones with appropriate substitutions can undergo cyclization to afford cycloaromatized products. Chlorosubstituted aromatic aldehydes are the major products in such reactions (Scheme 38).



Scheme 38

1.5.4 Reactions of α, β -Unsaturated Cyclic Ketones with Chloromethyleneiminium Salts

Katritzky and Marson have reported the reactions of α, β -unsaturated cyclic ketones under Vilsmeier-Haack conditions. Depending on the reaction conditions and the structure of the substrate, aromatized and formylated products or chlorosubstituted enaldehydes were formed. Selected examples showing the different reaction patterns of cyclohexanones are depicted in the following equations (Scheme 39).⁵³⁻⁵⁵



Scheme 39

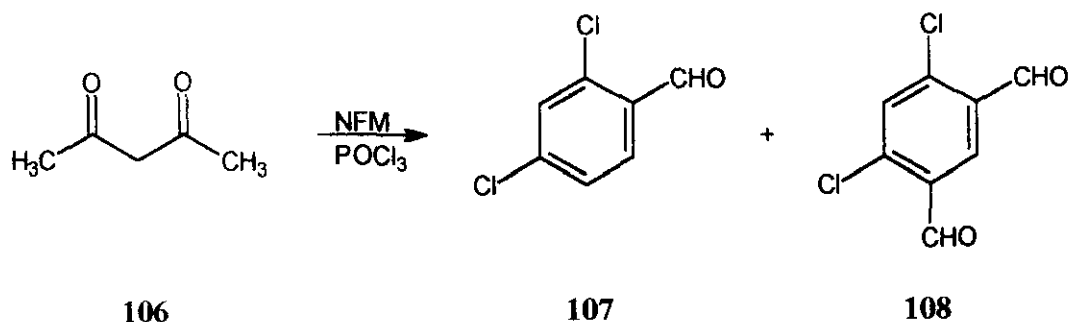
1.5.5 Reactions of Acyclic 1,3-Diketones with Chloromethyleneiminium Salts

When acetyl acetone was allowed to react with Vilsmeier reagent prepared from DMF and POCl₃, 2,4-dichlorobenzaldehyde 105 was obtained (Scheme 40).⁵⁰



Scheme 40

When the reaction was done using N-formyl morpholine instead of DMF 2,6-dichloroisophthalaldehyde **108** was also obtained along with 2,4-dichlorobenzaldehyde **107** (Scheme 41).⁵³



Scheme 41

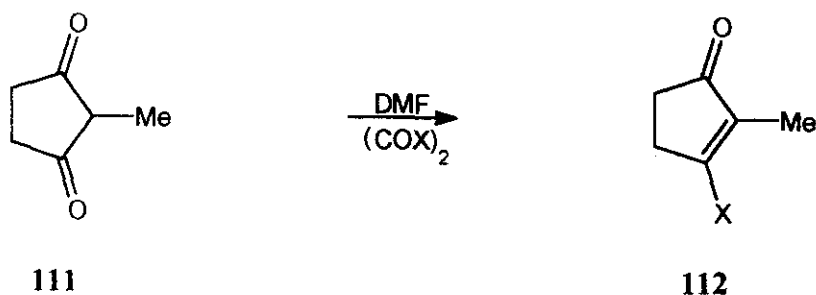
It has been proposed that when the Vilsmeier reagent prepared from formyl morpholine is used, cyclization of the intermediate iminium salt **109** becomes slow leading to further iminoalkylation to afford the bis iminium salt **110**, which leads to the formation of the isophthalaldehyde.



Scheme 42

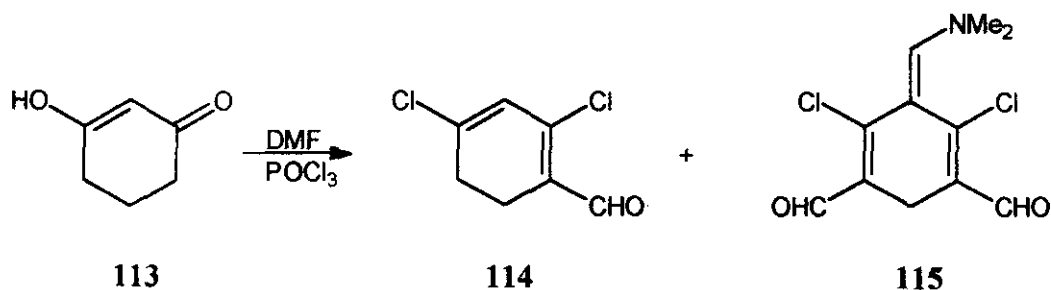
1.5.6 Reactions of Cyclic 1,3-Diketones with Chloromethyleneiminium Salts

1,3-Cyclopentadiones **111** undergo smooth conversion to β -halocyclopentanones **112** under Vilsmeier-Haack conditions.⁵⁶ The reagent is prepared from oxalyl chloride or bromide and DMF (Scheme 43).



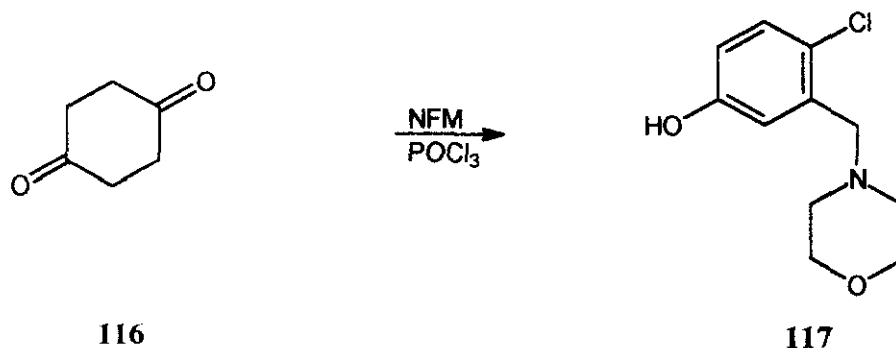
Scheme 43

1,3-Cyclohexanedione 113 affords a cross conjugated dialdehyde 115 along with dichlorosubstituted cyclohexadiene carbaldehyde 114 (Scheme 44).⁵⁷



Scheme 44

Cyclic 1,4-diketone 116 also has been shown to undergo aromatization in the presence of Vilsmeier-Haack reagent. Thus 1,4-cyclohexadione gave the substituted phenol 117 when it was allowed to react with the reagent prepared from N-formyl morpholine and POCl_3 (Scheme 45).⁵³

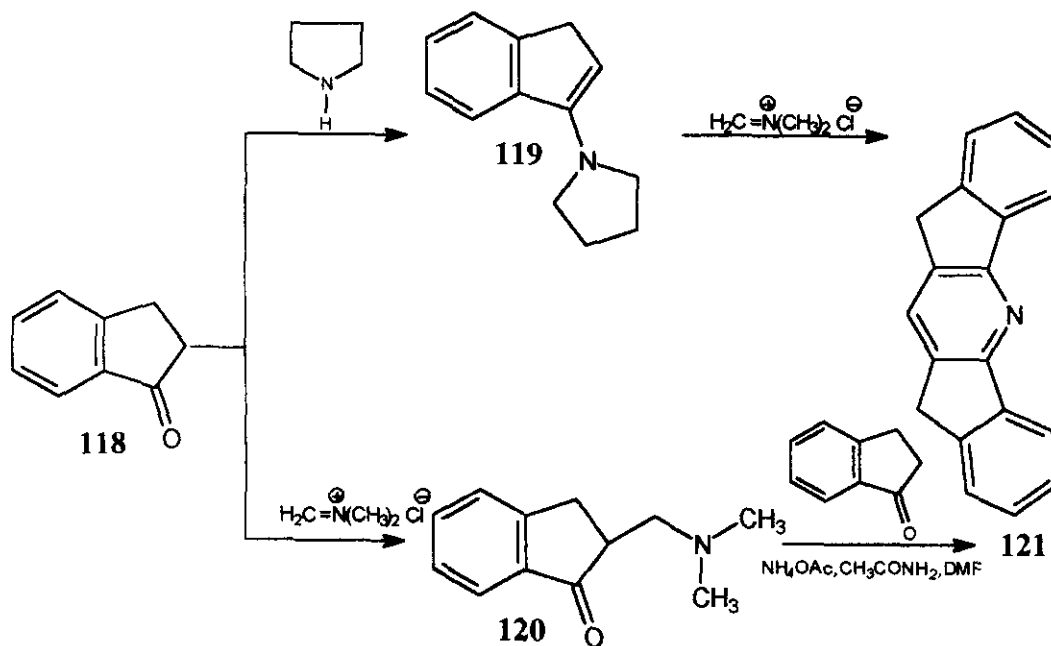


Scheme 45

In 1,5-cyclooctadione the carbonyl groups reacted independently to afford the corresponding chloroformylated product.⁵⁸

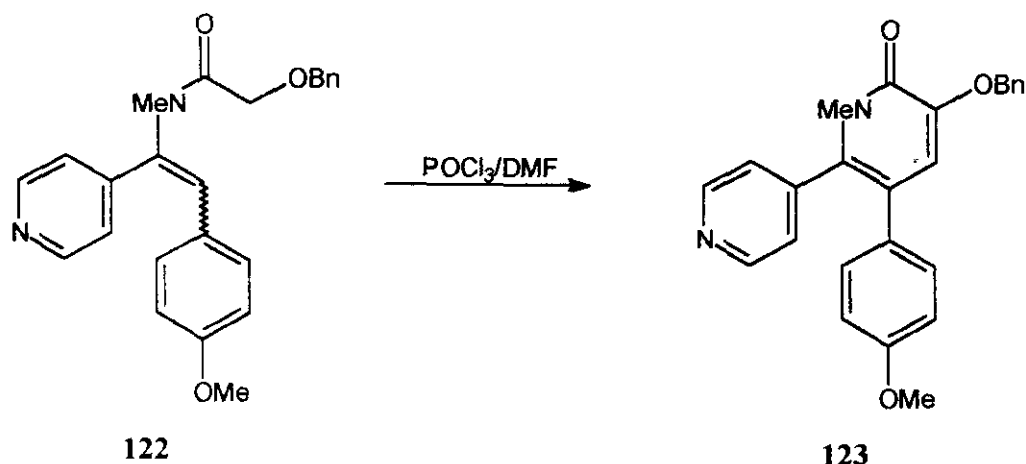
1.6 Iminium Salt Mediated Synthesis of Pyridines

Risch and co-workers developed a simple method for substituted pyridines by the condensation of enamines **119** with iminium salts. This method was further modified for the synthesis of unsymmetrically substituted derivatives by the condensation of Mannich base **120** with ketones (Scheme 46).⁵⁹



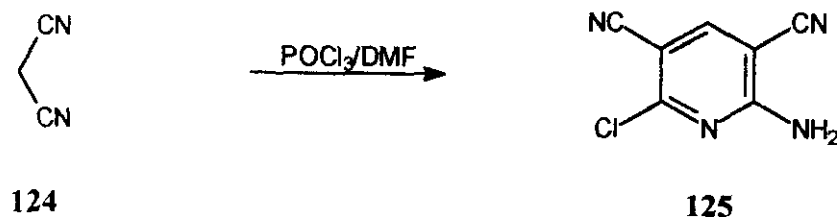
Scheme 46

A convenient synthesis of 3-trifluoromethanesulfonyloxy-2-pyridone **123** was achieved by Vilsmeier formylation and cyclization of the acyl enamine **122** (Scheme 47).⁶⁰



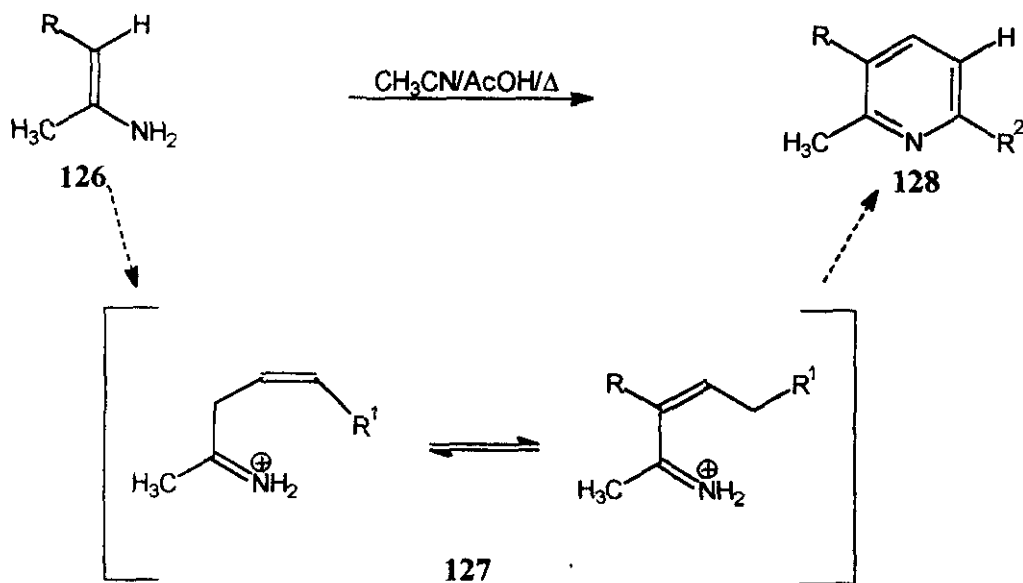
Scheme 47

Reaction of malononitrile **124** with Vilsmeier reagent generated from DMF and POCl_3 afforded 2-amino-6-chloro-3,5-pyridinedicarbonitrile **125** in good yield (Scheme 48).⁶¹



Scheme 48

Singh and co-workers have synthesized pyridine derivatives **128** via iminium salts **127**, thus β -ethoxycarbonyl enamine, β -acyl enamine and β -cyano enamine have been successfully transformed to ethyl 2-(5-ethoxycarbonyl-6-methylpyridyl)acetate, ethyl 2-(5-acetyl-6-methylpyridyl)acetate, and ethyl 2-(5-cyano-6-methylpyridyl)acetate respectively through an iminium salt by refluxing the enamines **126** in anhydrous acetonitrile : acetic acid mixture. (Scheme 49).⁶²



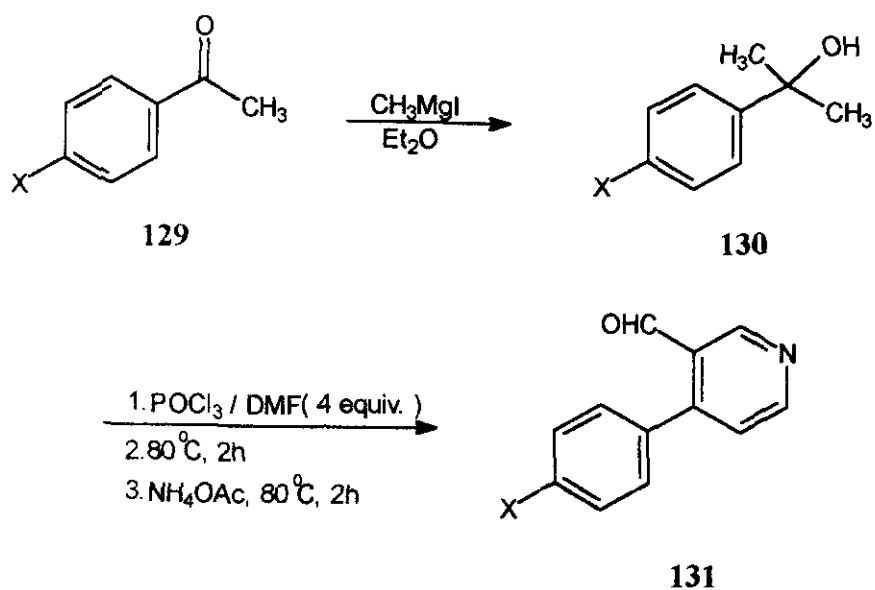
Scheme 49

1.7 Reactions of Tertiary Alcohols with Vilsmeier Reagent Followed by Ammonium Acetate: Synthesis of Functionalized Pyridines and Naphthyridines

Synthesis of functionalized pyridines and naphthyridines are important considering their potential applications as building blocks in the construction of several alkaloids of biological interest. In the course of our studies directed towards the utilization of chloromethyleneiminium salts in the synthesis of heterocyclic compounds, we have developed a convenient method for the synthesis of substituted pyridines and naphthyridines starting from aliphatic tertiary alcohols. Secondary or tertiary alcohols are known to give moderate to good yields of enaldehydes on treatment with chloromethyleneiminium salts, followed by hydrolysis.²⁵ Aliphatic alcohols can lead to multiple iminoalkylations in the presence of excess of Vilsmeier-Haack reagent. Thus, carbinols having at least two methyl groups or methylene groups in the α positions lead to the formation of conjugated polyenyl iminium salt intermediates which have been cyclized by the addition of ammonium acetate to afford substituted pyridines.

1.7.1 Reactions of 2-Aryl-2-propanols with Chloromethyleneiminium Salt Followed by Ammonium Acetate

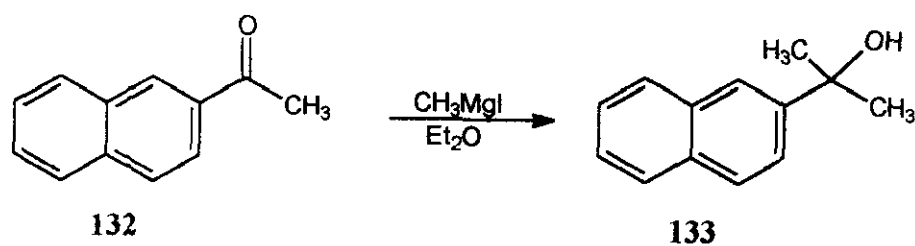
The tertiary alcohols **130** derived from substituted acetophenones **129** by the addition of methyl Grignard underwent multiple iminoalkylations on treatment with chloromethyleneiminium salt, followed by cyclization to afford substituted pyridines **131** on the addition of ammonium acetate (Scheme 50).

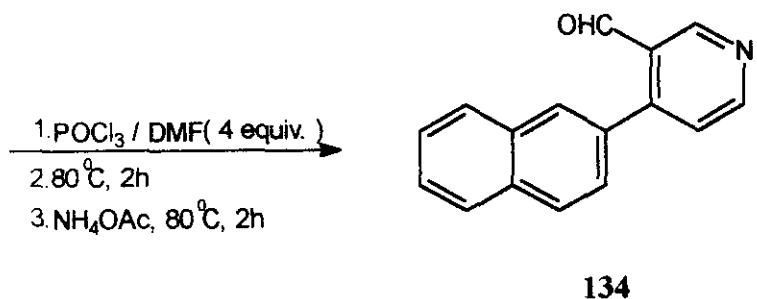


131	X	Yield (%)
a	H	60
b	OCH_3	66
c	CH_3	61
d	Cl	63
e	Br	60

Scheme 50

2-(2-naphthyl)propan-2-ol **133** derived from 2-acetyl naphthalene **132** underwent a similar reaction to afford corresponding 4-(2-naphthyl)nicotinaldehyde **134** in 43% yield (Scheme 51).

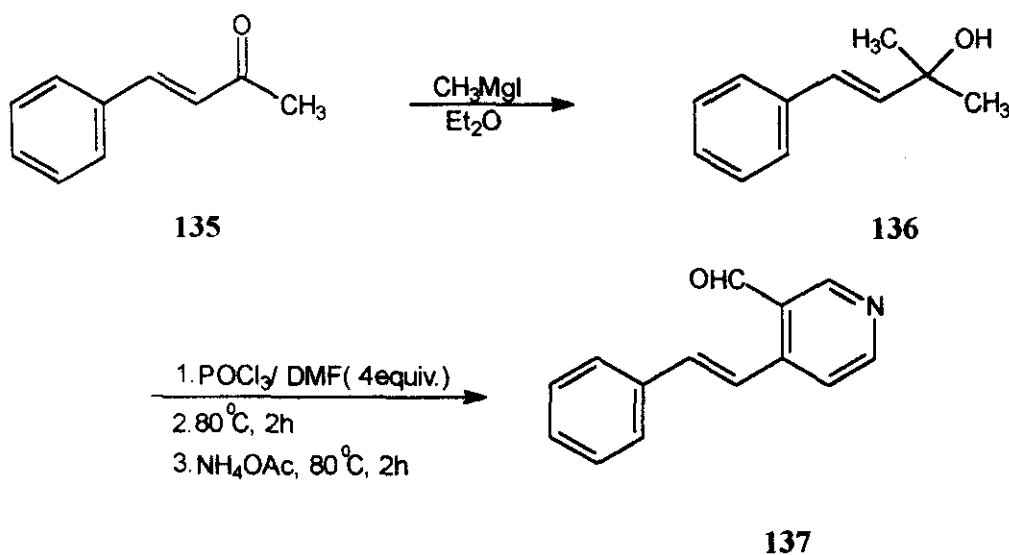




Scheme 51

1.7.2 Reaction of 2-Methyl-4-phenyl-3-buten-2-ol with Chloromethyleneiminium Salt Followed by Ammonium Acetate

We have next examined the reactivity of 2-methyl-4-phenyl-3-buten-2-ol **136** derived from benzalacetone **135** to Vilsmeier-Haack reagent. When the reaction was carried out with four equivalents of Vilsmeier reagent followed by treatment with ammonium acetate, 4-(phenylvinyl)nicotinaldehyde **137** was formed (Scheme 52).

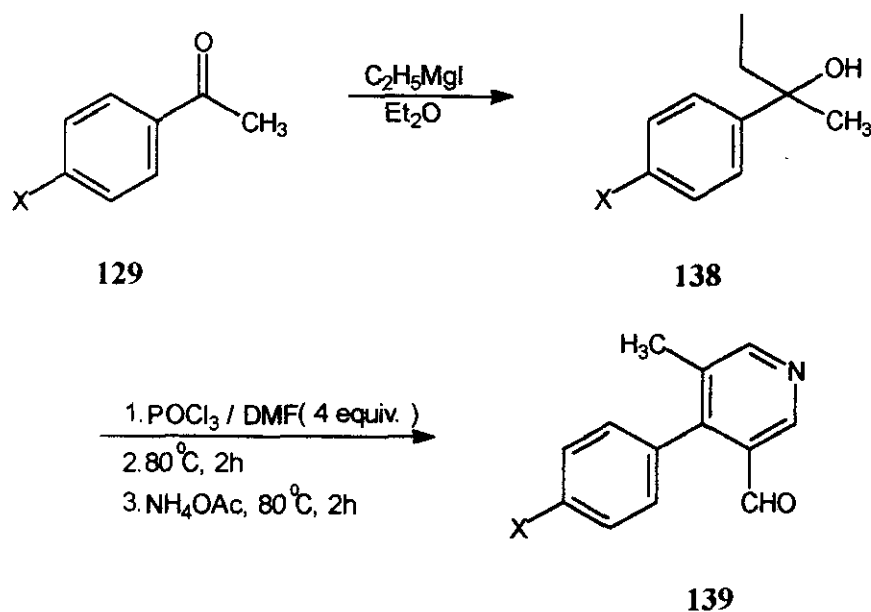


Scheme 52

1.7.3 Reactions of 2-Aryl-2-butanols with Chloromethyleneiminium Salt Followed by Ammonium Acetate

The reactivity of chloromethyleneiminium salts with 2-aryl-2-butanols was also studied. This would enable us to introduce a methyl group on the pyridine ring, in addition to the aryl and formyl groups. Thus the reaction of 2-aryl-2-butanols **138**, derived from acetophenones on the addition of ethyl magnesium bromide, with chloromethyleneiminium

salt followed by treatment with ammonium acetate gave 4-aryl-5-methylnicotinaldehydes **139** in good yields (Scheme 53).

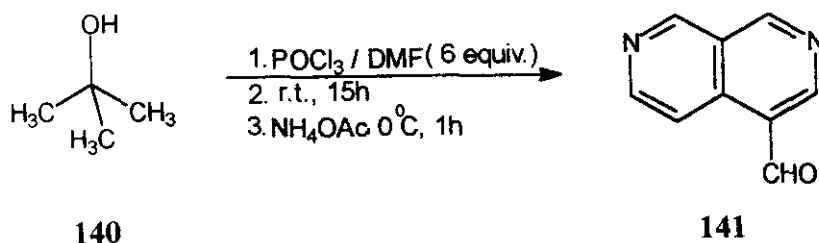


139	X	Yield(%)
a	H	55
b	MeO	57
c	Me	52
d	Cl	54

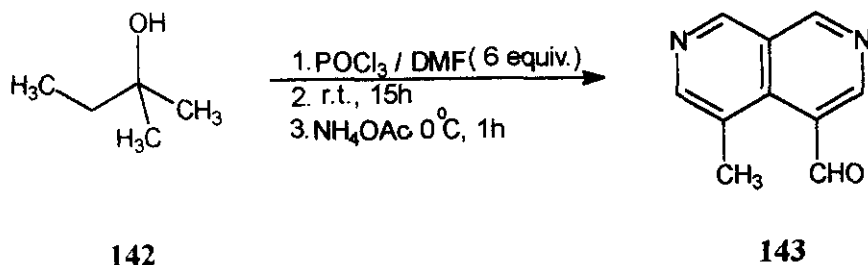
Scheme 53

1.7.4 Reactions of Aliphatic and Alicyclic Alcohols with Chloromethyleneiminium Salt Followed by Ammonium Acetate

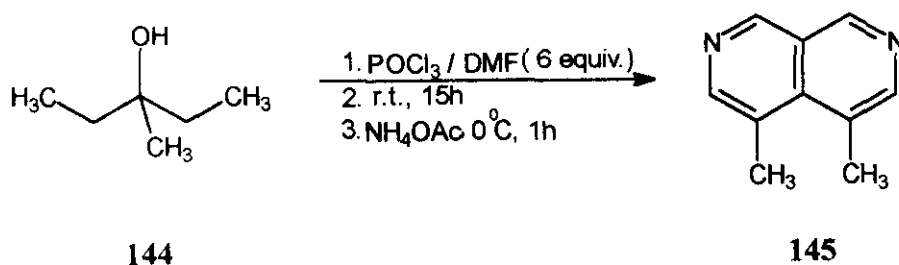
We have investigated the reactions of some aliphatic tertiary alcohols like *t*-butanol **140**, 2-methyl-2-butanol **142** and 3-methyl-3-pentanol **144** with Vilsmeier-Haack reagent and subsequent nucleophile assisted cyclization to [2,7]naphthyridine nuclei (Scheme 54, Scheme 55 and Scheme 56).



Scheme 54

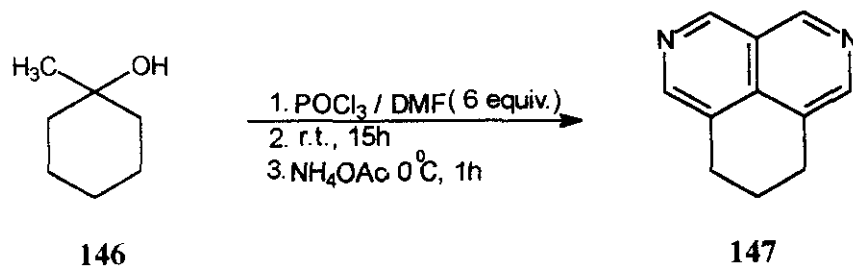


Scheme 55



Scheme 56

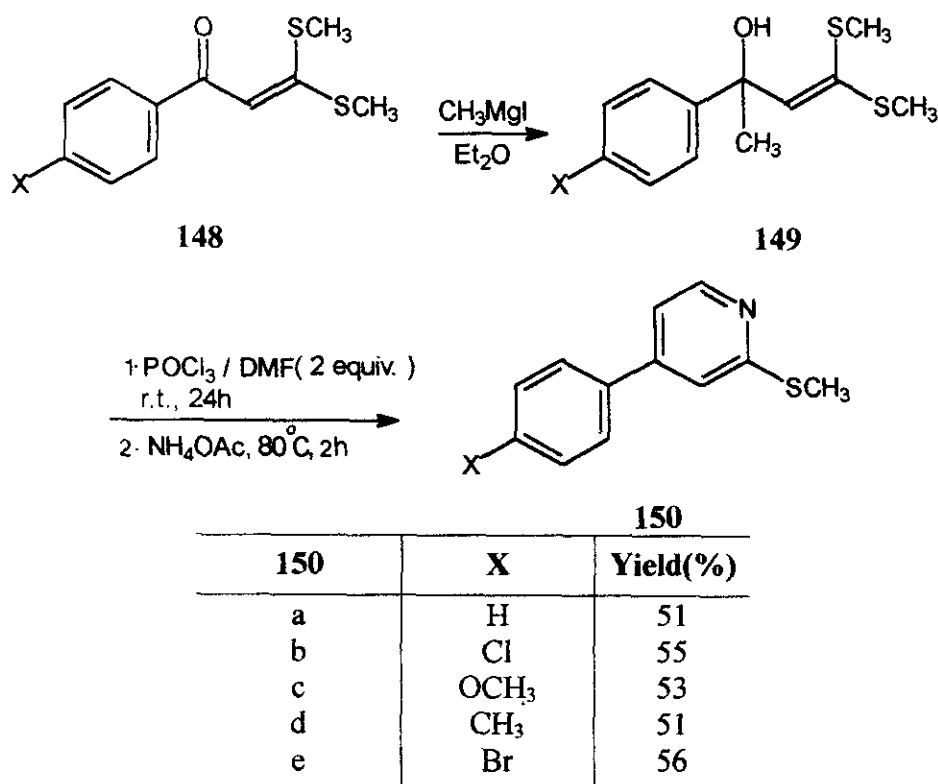
Among the tertiary alcohols derived from cyclic ketones, we have examined the reactivity of 1-methyl-1-cyclohexanol **146** with chloromethyleneiminium salt. Thus, the reaction of cyclohexanol **146** with six equivalents of Vilsmeier reagent followed by treatment with ammonium acetate gave the naphthyridine **147** (Scheme 57).



Scheme 57

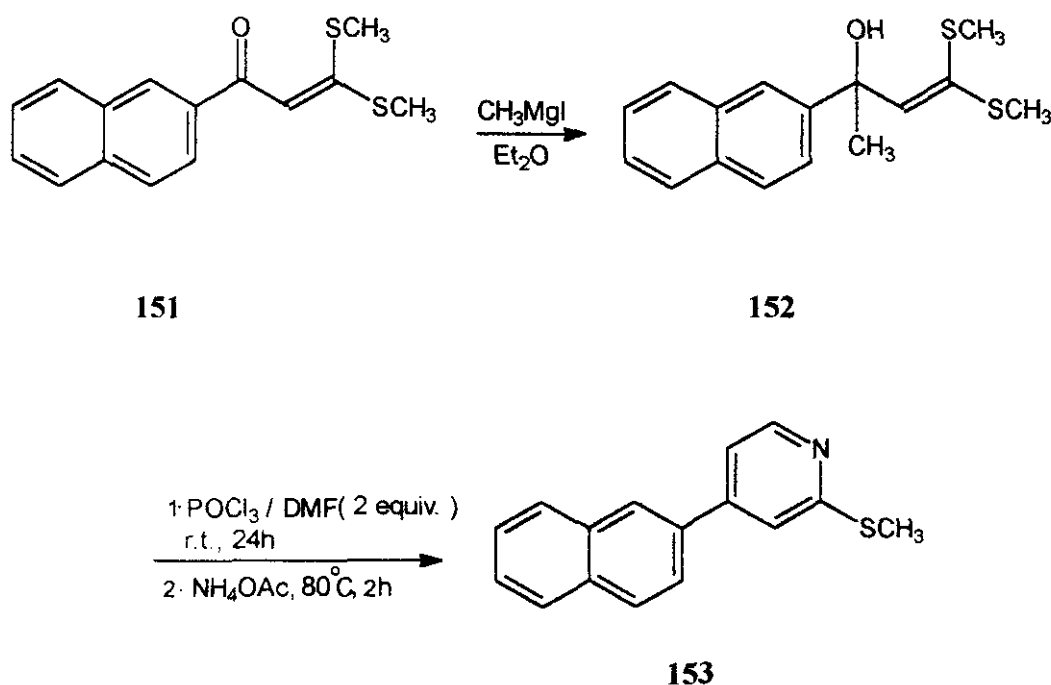
1.8 Reactions of α -Hydroxyketenedithioacetals with Chloromethyleneiminium Salt Followed by Ammonium Acetate: Synthesis of 4-Aryl-2-(methylsulfanyl)pyridines

The allylic carbinols obtained by the reduction of acyl ketene dithioacetals undergo reaction with the Vilsmeier reagent are known to afford the 2,4-pentadienaldehydes stereoselectively in good yields.³² We have contemplated on extending this reaction to allylic tertiary alcohols obtained by the addition of carbon nucleophiles to the carbonyl group of acyl ketenedithioacetal followed by reaction with chloromethyleneiminium salt and subsequent quenching of the resultant iminiumsalt intermediate by ammonium acetate. When we attempted the reaction of alkyl Grignard reagents with acyl ketenedithioacetals derived from aliphatic ketones, though the intermediate allylic alcohols were obtained in good yields, subsequent reaction with chloromethyleneiminium salt gave complex reaction mixtures. However, when the reaction was carried out on benzoyl ketenedithioacetals the resultant carbinol underwent a smooth reaction with the Vilsmeier reagent prepared from POCl₃ and DMF followed by cyclization using ammonium acetate to afford 4-aryl-2-(methylsulfanyl)pyridines **150** in good yields (Scheme 58).



Scheme 58

This protocol was extended to the α -hydroxyketenedithioacetal **152** derived from the α -oxoketenedithioacetal of 2-acetylnaphthalene **151** to obtain the corresponding 2-(methylsulfanyl)-4-(2-naphthyl)pyridine **153** in 41% yield (Scheme 59).



Scheme 59

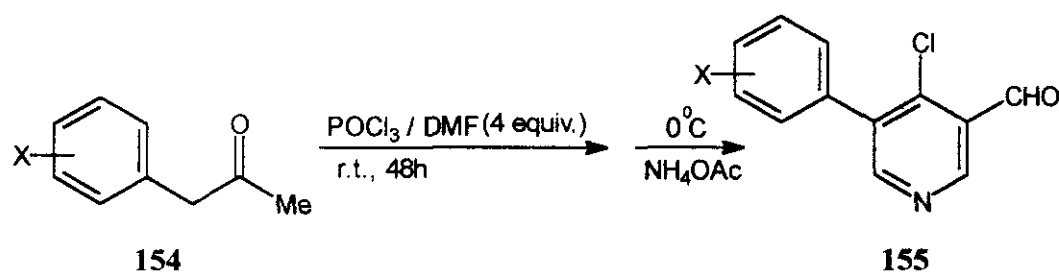
1.9 Reactions of Carbonyl Compounds with Chloromethylene iminium Salt Followed by Ammonium Acetate: Synthesis of Substituted Pyridines

The carbon-carbon bond forming reactions of aliphatic carbonyl compounds with chloromethyleneiminium salts are highly versatile. The reaction often leads to β -chlorovinyl aldehyde moieties. Ketones flanked by two methyl or methylene groups can undergo multiple iminoalkylation reactions. This is exemplified by the reaction of dibenzyl ketone with Vilsmeier-Haack reagent to give 3,5-diphenyl-4-pyrone. The reaction apparently proceeds by a double formylation and subsequent electrocyclic ring closure of the intermediate pentadienaldehyde to form a pyrylium salt.

Earlier reports from our laboratory on the reactivity of compounds having carbonyl group flanked by methylene or methyl groups like aryl acetones towards Vilsmeier-Haack reagent have described the synthesis of substituted pyrones in excellent

yields. So we have further explored the synthetic potential of iminium salt intermediates generated from α,α' -dimethylene ketones on treatment with Vilsmeier-Haack reagent in the synthesis of substituted pyridines. The reactions of substituted benzyl methyl ketones with the chloromethyleneiminium salt prepared from POCl_3 and DMF were examined. We have also studied the reactivity of other related carbonyl compounds such as benzyl ethyl ketone and dibenzyl ketone. Similar studies were also carried out on acyl ketenedithioacetals as well.

The aryl acetones **154** were treated with four equivalents of Vilsmeier reagent prepared by the addition of POCl_3 to DMF and the multiple iminoalkylated iminium salt intermediates generated were allowed to react with ammonium acetate. This reaction gave good yields of 5-aryl-4-chloronicotinaldehydes **155** (Scheme 60).



155	X	Yield (%)
a	H	76
b	<i>p</i> -OMe	73

Scheme 60

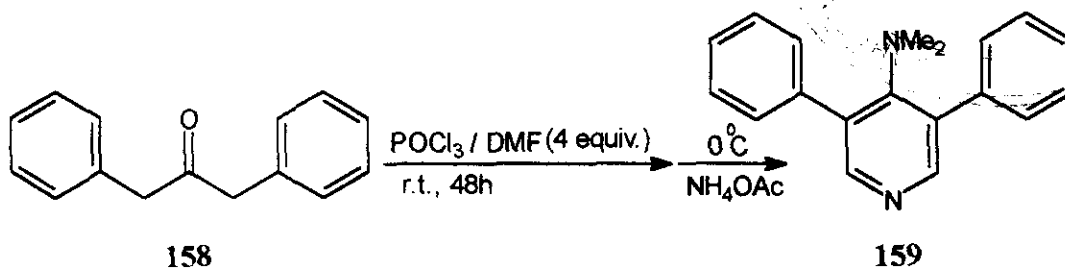
When benzyl ethyl ketone **156** under similar conditions gave the expected 4-chloro-3-methyl-5-phenyl pyridine **157**, dibenzyl ketone **158** gave the corresponding 3,5-diphenyl-4-(*N,N*-dimethylamino)pyridine **159** (Scheme 61 and 62).



Scheme 61

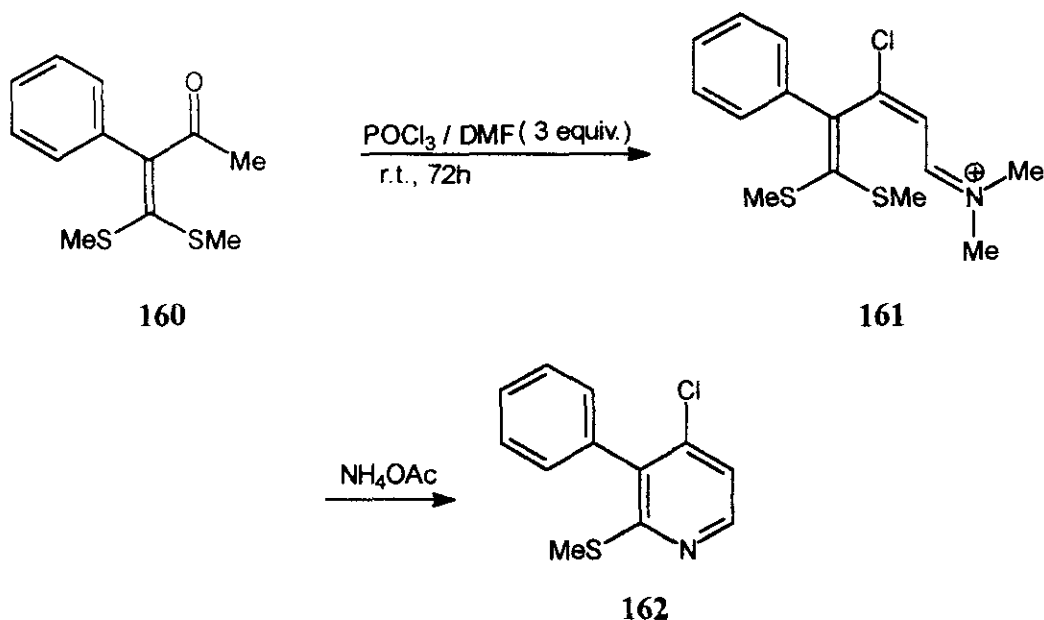
T1164

31



Scheme 62

The ketenedithioacetal **160** prepared from substituted phenyl acetone upon sequential Vilsmeier-Haack reaction and treatment with ammonium acetate afforded 4-chloro-2-(methylsulfanyl)-3-phenylpyridine **162** in good yield (Scheme 63).



Scheme 63

1.10 Conclusions

In this thesis we have explored the synthetic applications of the multiple iminoalkylation reactions of alcohols and carbonyl compounds using chloromethyleneiminium salt. The reactions of tertiary alcohols, α -hydroxy ketenedithioacetals and carbonyl compounds flanked by methylene groups have been studied. These substrates underwent facile sequential multiple iminoalkylations in the presence of Vilsmeier reagent. The multiple iminoalkylated intermediates have been then transformed to functionalized pyridines in the presence of ammonium acetate. Reactions of aliphatic tertiary alcohols under these conditions gave substituted naphthyridines.

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