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 $\text{POCl}_3$ with an $\text{N, N}$-disubstituted formamide such as $\text{DMF}$, are the reactive intermediates in the Vilsmeier-Haack reaction which is very useful in the formylation of electron rich aromatic compounds or olefins. Today it is well established that the reaction proceeds via the attack of the carbonyl oxygen of the amide to $\text{POCl}_3$ to form the adduct 2 at first, which reacts further to give the chloromethyleneiminium salt 3 (Scheme 1).

![Scheme 1](image)
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. 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. 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).
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 uvitraldehyde 7 (Scheme 3).\textsuperscript{16}

\[
\begin{array}{c}
\text{CHO} \\
\text{6} \quad \text{POCl}_3/\text{DMF} \quad \text{OHC} \\
\text{7}
\end{array}
\]

Scheme 3

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

\[
\begin{array}{c}
\text{Me}_2\text{Si}\text{Me}_2 \\
\text{TBDMSO} \\
\text{8} \quad \text{POCl}_3 / \text{DMF} \quad \text{OHC} \\
\text{9}
\end{array}
\]

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).\textsuperscript{18}

\[
\begin{array}{c}
\text{Me} \\
\text{10} \quad \text{CO}_2\text{Cl}_2 \quad \text{DMF} \quad \text{Me} \\
\text{11}
\end{array}
\]

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](image)

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](image)

![Scheme 8](image)
However when the rearrangements are restricted by the substituents at the α-position monofonylated products are obtained. This is demonstrated by the reaction of d,l-camphene 19 which underwent reaction with the reagent prepared from POCl₃ and DMF to give the monofonylated product 20 (Scheme 9).

\[ \text{19} \xrightarrow{\text{DMF, POCl₃}} \text{20} \]

Scheme 9

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

\[ \text{21} \rightarrow \text{22} \]

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).
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).
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

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

Vilsmeier-Haack formylations of alkenes conjugated with aromatic systems are simple and straightforward. 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.
1,2-Dihydronaphthalenes 38 ($X = CH_2$)\textsuperscript{26} and chromene 38 ($X = O$) derivatives\textsuperscript{27} also undergo similar formylation to afford the respective enaldehydes (Scheme 17).

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

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)nonapentenaldehyde 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 POCl₃, where DMF will be in excess and often serve as the solvent as well. The treatment of POCl₃ 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. 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).

![Diagram of reaction between chloromethyleneiminium salt and POCl₃](image)

Scheme 25
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).
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 quiet 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).\(^3\)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \xrightarrow{\text{DMF}, \text{POCl}_3} \\
\text{Cl} & \quad \text{Me} \quad \text{CHO} \\
71 & \quad 72
\end{align*}
\]

\textbf{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 \(N_2N\)-dimethylamino group, subsequent iminoalkylation can be performed conveniently to afford malonaldehyde 76 as the final product after basic hydrolysis (Scheme 29).\(^3\)

\[
\begin{align*}
\text{Me} & \quad \text{H} \quad \text{O} \\
\xrightarrow{1\text{-POCl}_3, \text{DMF}} \\
\text{Me} & \quad \text{NMe}_2 \\
73 & \quad 74
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{H} \quad \text{O} \\
\xrightarrow{\text{NaOAc, H}_2\text{O}} \\
\text{Me} & \quad \text{CHO} \\
75 & \quad 76
\end{align*}
\]

\textbf{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).

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.\(^{41}\)

Bodendorf and Mayer have found that 1-acetyl naphthalene and 2-acetyl naphthalene undergo Vilsmeier reaction with the reagent prepared from DMF and POCl\(_3\) 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).\(^{42}\)
Acetyl substituted pyrroles react with Vilsmeier reagent to afford the corresponding chlorovinyl pyrroles or acetylenic aldehydes.\textsuperscript{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\textsubscript{3} complex to synthesise bromo substituted cycloalkane carbaldehyde 85 (Scheme 33).\textsuperscript{45}

\begin{align*}
\text{Scheme 33}
\end{align*}

Similarly corresponding \(\beta\)-chloroacrylaldehydes 87 can be obtained by the reaction of POCl\textsubscript{3} and DMF (Scheme 34).\textsuperscript{46,47,48}

\begin{align*}
\text{Scheme 34}
\end{align*}
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 POCl₃ 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).

\[ \text{Cyclohexanone} \xrightarrow{\text{DMF, POCl}_3} \text{N,N-dimethylamino substituted pentadienaldehyde 90} \]

**Scheme 35**

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

Benzilidine acetone 91 (n=1) and cinnamylidine acetone 91 (n=2) were smoothly converted into their iminium salts 92 (Scheme 36).

\[ \text{Benzilidine acetone} \xrightarrow{\text{DMF, POCl}_3} \text{Iminium salt 92} \]

**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. 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).
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).

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).
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).
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).^1

![Scheme 41](image)

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](image)

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. The reagent is prepared from oxalyl chloride or bromide and DMF (Scheme 43).
1.3-Cyclohexanediene 113 affords a cross conjugated dialdehyde 115 along with dichlorosubstituted cyclohexadiene carbaldehyde 114 (Scheme 44). \(^5\)

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). \(^6\)

In 1,5-cyclooctadione the carbonyl groups reacted independently to afford the corresponding chloroformylated product. \(^7\)
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

A convenient synthesis of 3-trifluoromethanesulfonyloxy-2-pyridone 123 was achieved by Vilsmeier formylation and cyclization of the acyl enamine 122 (Scheme 47).60
Reaction of malononitrile 124 with Vilsmeier reagent generated from DMF and POCl₃ 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, ethyl2-(5-acetyl-6-methylpyridyl)acetate, and ethyl2-(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. 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).
1. POCl₃/DMF (4 equiv.)
2. 80°C, 2h
3. NH₄OAc, 80°C, 2h

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).
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 derived from benzalacetone 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 was formed (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, 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).

\[
\begin{align*}
\text{139} & \quad \text{138} \\
\text{H}_{3} \text{C} & \quad \text{CHO}
\end{align*}
\]

<table>
<thead>
<tr>
<th>139</th>
<th>X</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>55</td>
</tr>
<tr>
<td>b</td>
<td>MeO</td>
<td>57</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>52</td>
</tr>
<tr>
<td>d</td>
<td>Cl</td>
<td>54</td>
</tr>
</tbody>
</table>

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).
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).
1.8 Reactions of α-Hydroxyketenedithioacetals with Chloromethylene iminium 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. We have contemplated on extending this reaction to allylic tertiary alcohols obtained by the addition of carbon nucleophiles to the carbonyl group of acyl ketenedithioacetals followed by reaction with chloromethyleneiminium salt and subsequent quenching of the resultant iminium salt 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).

\[
\begin{array}{c}
\text{148} \\
\text{CH₃Mgl} \\
\text{Et₂O} \\
\text{149} \\
\end{array}
\]

\[
\text{X} \\
\text{H} \\
\text{Cl} \\
\text{OCH₃} \\
\text{CH₃} \\
\text{Br} \\
\text{Yield(%)} \\
\text{51} \\
\text{55} \\
\text{53} \\
\text{51} \\
\text{56} \\
\text{Scheme 58}
\]
This protocol was extended to the α-hydroxyketenedithioacetal 152 derived from the α-oxoketenedithioacetal of 2-acetyl napthalene 151 to obtain the corresponding 2-(methylsulfanyl)-4-(2-naphthyl)pyridine 153 in 41% yield (Scheme 59).

![Diagram](attachment:image.png)

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 iminooalkylation 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 \(\alpha,\alpha'-\)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 POCl₃ 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 keteneithioacetals as well.

The aryl acetones 154 were treated with four equivalents of Vilsmeier reagent prepared by the addition of POCl₃ 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).

\[
\text{Scheme 60}
\]

<table>
<thead>
<tr>
<th>155</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>76</td>
</tr>
<tr>
<td>b</td>
<td>p-OMe</td>
<td>73</td>
</tr>
</tbody>
</table>

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).

\[
\text{Scheme 61}
\]
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).

1.10 Conclusions

In this thesis we have explored the synthetic applications of the multiple iminoalkylation reactions of alcohols and carbonyl compounds using chloromethyleneimininium 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.
1.11 References

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