Chapter Two

The Vilsmeier-Haack Reaction

2.1 Introduction

The reaction of an N,N-disubstituted formamide, such as DMF or N-methyl formanilide, with acid chlorides, such as phosphoryl chloride or phosgene, leads to the formation of an adduct. This adduct, which is usually referred to as the Vilsmeier-Haack reagent, finds important applications in synthetic organic chemistry particularly in the formylation of electron rich aromatic compounds or olefins. Normally the reagent prepared in situ is sufficient to carry out the desired transformations effectively. However, the adducts formed from POCl₃ and DMF or N-methyl formanilide have been isolated and the structure and constitution determined. Today it is well established that the reaction proceeds via the attack of the carbonyl oxygen of the amide to form the adduct 2 at first which reacts further to give the chloromethylene iminium salt 3 (Scheme 1).

Scheme 1

\[
\begin{align*}
\text{R}_1^1 & \quad \text{N} \quad \text{O} \quad \text{C} \quad \text{H} \\
\text{R}_2^2 & \quad \text{N} \quad \text{C} \quad \text{H} \\
& \quad \text{POCl}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1^1 & \quad \text{N} \quad \text{C} \quad \text{H} \\
\text{R}_2^2 & \quad \text{N} \quad \text{C} \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1^1 & \quad \text{N} \quad \text{C} \quad \text{H} \\
\text{R}_2^2 & \quad \text{N} \quad \text{C} \quad \text{H} \\
& \quad \text{Cl} \quad \text{OPOCl}_2 \\
\end{align*}
\]
It is suggested that the initial adduct formed from POCl₃ and DMF 2 (R¹ = R² = Me) is more reactive than the adduct 3 (R¹ = R² = Me) which is formed subsequently. This argument is based on the fact that the chloromethylene iminium chloride 4 is less reactive compared to the iminium salt formed in situ from POCl₃ and DMF.

The conventional Vilsmeier-Haack reaction involves the reaction of the electron rich aromatic compounds or alkenes with the iminium salts obtained from formamides and acid chlorides. The initial step is an iminoalkylation which is essentially an electrophilic substitution where the iminium salt of the type 2 or 3 acts as the electrophile. The reaction leads to the formation of an aldehyde on alkaline hydrolysis. The reaction of p-N,N-dimethylanilinobenzene¹²,¹³ with the reagent prepared in situ from POCl₃ and DMF illustrates the reaction. The iminium salt 6 formed as the result of the iminoalkylation on hydrolysis with saturated sodium acetate solution provides p-N,N-dimethylanilinobenzaldehyde 7 (Scheme 2).

The Vilsmeier-Haack reaction is an important method for the synthesis of various aromatic aldehydes and α,β-unsaturated aldehydes. In addition to this the reactions of carbonyl compounds and its derivatives with Vilsmeier reagent are highly versatile and often lead to products of high synthetic potential. The reagent is also used in a variety of cyclization and cycloaromatization reactions.
Other than DMF and N-methyl formanilide, formamides such as benzyl methyl formamide, N-formyl piperidine and N-formyl morpholine are also employed in the Vilsmeier-Haack reaction. Thionyl chloride, phosgene and oxalyl chloride etc. are the acid chlorides used in addition to the most popular POCl₃. While DMF is used also as the solvent in most occasions, other solvents such as dichloromethane, chloroform etc. may also be used. The choice of solvent could be important to control the possibility of multiple iminoalkylations.

2.2 Reactions of aromatic compounds

Aromatic compounds substituted with electron donating substituents undergo Vilsmeier-Haack reaction leading to the formation of the corresponding formylated products. Selected examples which illustrates the formylation reactions of electron rich aromatic substrates are given in Table 1.

However simple aromatic compounds such as benzene or naphthalene do not react with the Vilsmeier-Haack reagent.
Heteroaromatic compounds also undergo formylations at the electron rich positions when treated with Vilsmeier-Haack reagents. Thus the reaction of pyrrole, furan, thiophene and selenophene derivatives undergo formylation at 2 or 5 position unless otherwise directed by substitution pattern.\textsuperscript{14-21} Benzo derivatives of these heterocycles also participate in the Vilsmeier-Haack reactions.\textsuperscript{27-32} A few selected examples of Vilsmeier reaction are given in Table 2.

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>4</td>
<td><img src="image7" alt="" /></td>
<td><img src="image8" alt="" /></td>
</tr>
</tbody>
</table>

Ref. 7,8

Ref. 9

Ref. 10

Ref. 11
2.3 Reactions of Carbonyl Compounds

The iminoalkylation of electron rich substrates with the Vilsmeier-Haack reagent prepared from N,N-disubstituted formamides and an acid chloride such as phosphorous oxychloride or oxalyl chloride lead to the formation of iminium salts which on alkaline hydrolysis provide the respective formylated products.

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
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<td><img src="chart3" alt="Substrate 2" /></td>
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<td><img src="chart5" alt="Substrate 3" /></td>
<td><img src="chart6" alt="Product 3" /></td>
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<tr>
<td>4</td>
<td><img src="chart7" alt="Substrate 4" /></td>
<td><img src="chart8" alt="Product 4" /></td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$X = S$ or $NH$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="chart9" alt="Substrate 5" /></td>
<td><img src="chart10" alt="Product 5" /></td>
<td>26</td>
</tr>
</tbody>
</table>
Though the Vilsmeier-Haack reaction in general involve iminoalkylation of electron rich substrates their applications in the synthesis of useful multifunctional synthetic intermediates particularly starting from carbonyl compounds are highly versatile.\textsuperscript{1,5,33} The Vilsmeier-Haack reaction of enolizable ketones lead to the formation of chlorovinyl iminium salts 9 which on basic hydrolysis give $\beta$-chloro substituted enaldehydes 10 (scheme 3).\textsuperscript{34,35} $\beta$-Alkoxy or alkylthioethylenic aldehydes may also be obtained directly by carrying out the reaction on acetals or dithio-acetals.\textsuperscript{36-38} It has also been shown that the Vilsmeier reagent, under mild conditions, is able to convert an enolizable carbonyl group to the corresponding chlorovinyl functionality, without undergoing subsequent imino-alkylation.\textsuperscript{39}

Scheme 3

![Scheme 3](image-url)
2.3.1 Aldehydes and Ketones

Arnold and Zemlicka were the first to report the reaction of enolizable ketones with the Vilsmeier-Haack reagent prepared from DMF and phosgene or POCI₃. Several enolizable ketones which they have converted to the respective β-chloroacroleins are given in Table 3.

Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
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<td>( \text{CH}_3\text{C} = \text{CH}_3 )</td>
<td>( \text{H}_3\text{C} - \text{C} = \text{Cl} - \text{CHO} )</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>( \text{CH}_3\text{C} = \text{CH}_3 )</td>
<td>( \text{H}_3\text{C} - \text{C} = \text{Cl} - \text{CHO} )</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>( \text{C}_6\text{H}_5\text{C} = \text{CH}_3 )</td>
<td>( \text{C}_6\text{H}_5 - \text{C} = \text{Cl} - \text{CHO} )</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>( (\text{CH}_3)_2\text{C} = \text{CH}_3 )</td>
<td>( (\text{CH}_3)_2\text{C} - \text{C} = \text{Cl} - \text{CHO} )</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>( \text{C}_6\text{H}_5\text{C} = \text{CH}_3 )</td>
<td>( \text{C}_6\text{H}_5 - \text{C} = \text{Cl} - \text{CHO} )</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>( (_)_n )</td>
<td>( (_)_n - \text{C} = \text{Cl} - \text{CHO} )</td>
<td>34</td>
</tr>
</tbody>
</table>

\( n = 1-3 \)
The reaction of methyl ketones with Vilsmeier reagent prepared from DMF and POCl₃ or phosgene on subsequent reaction with dimethyl amine leads to the formation of the iminium salts 12 which undergo further formylation with Vilsmeier reagent to give 13. Unstable acyl malonaldehydes could be obtained by the basic hydrolysis of iminium salts 13 (Scheme 4).³⁷

Scheme 4

Methyl ketones disubstituted at the α-position gave the chloro substituted iminium salts 16 which on basic hydrolysis directly gave the acyl malonaldehydes 17 (Scheme 5). The chlorovinyl iminium salt which could be obtained from acetophenone undergo substitution with dimethyl amine and on further reaction with the Vilsmeier reagent leads to the formation of the bis iminium salt 20 (Scheme 6) which on hydrolysis with base gives benzoyl malonaldehyde. α-Formyl vinylogous amide 23 could be prepared by treating the malonaldehyde with dimethyl amine (Scheme 7).
Other ketones such as 4-N,N-dimethylaminoacetophenone, t-butyl methyl ketone and isopropyl methyl ketone were also examined under similar reaction conditions. The acyl malonaldehydes obtained from Vilsmeier reaction on subsequent
treatment with dimethyl amine gave enaminoketones as the products. α-Formyl enaminoketones were formed when the reaction was carried out on the copper salt of the acyl malonaldehydes.

Scheme 7

\[
\begin{align*}
21 & \quad \rightarrow \quad 22 & \quad \rightarrow \quad 23
\end{align*}
\]

The dimethyl amino substituted vinyl iminium salt derived from acetone on further reaction with POCl\(_3\) and DMF gave dimethyl amino substituted iminium salt 25 (Scheme 8).

Scheme 8

\[
\begin{align*}
24 & \quad \rightarrow \quad 25
\end{align*}
\]

Subsequently several groups have reported reactions of carbonyl compounds under Vilsmeier-Haack conditions. The reaction of substituted \(\alpha\)-tetralones and 4-
chromanone on Vilsmeier reaction give the corresponding chloroenaldehydes 27 (Scheme 9). Reactions of α-tetralones having various substituents are given in Table 4.

Scheme 9

![Scheme 9](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
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<td><img src="image" alt="Substrate 3" /></td>
<td><img src="image" alt="Product 3" /></td>
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<tr>
<td>4</td>
<td><img src="image" alt="Substrate 4" /></td>
<td><img src="image" alt="Product 4" /></td>
<td>41</td>
</tr>
</tbody>
</table>
Krishna Rao and Anantha Reddy have also examined the reactions of β-tetralones under similar conditions. The reaction proceeds with bisformylation and subsequent oxidation leading to the formation of chlorobisformyl naphthalenes 29 (Scheme 10).

**Scheme 10**

\[
\begin{array}{c}
\text{Entry} \quad \text{Substrate} \quad \text{Product} \quad \text{Ref.} \\
5 & \begin{array}{c}
\text{CH}_3\text{O} \\
\text{H} \quad \text{CHO} \\
\text{R} \quad \text{R} \quad \text{CH}_3
\end{array} & \begin{array}{c}
\text{CH}_3\text{O} \\
\text{Cl} \quad \text{CHO} \\
\text{R}_1 \quad \text{R}_2 \quad \text{CHO}
\end{array} & 41 \\
6 & \begin{array}{c}
\text{CH}_3\text{O} \\
\text{H} \quad \text{CHO} \\
\text{R}_1 \quad \text{R}_2 \quad \text{CH}_3
\end{array} & \begin{array}{c}
\text{CH}_3\text{O} \\
\text{Cl} \quad \text{CHO} \\
\text{R}_1 \quad \text{R}_2 \quad \text{CHO}
\end{array} & 41 \\
\end{array}
\]

\[R^1 = \text{H}; R^2 = \text{OMe} \]
\[R^1 = \text{OMe}; R^2 = \text{H} \]
Giles and Marson have extended the chloroformylation reaction to cyclic ketones having heteroatoms. The Vilsmeier reaction of tetrahydropyranone and the tetrahydrothiopyranone affords the corresponding chloroformylated products 31 (Scheme 11).

Scheme 11

The dihydrothiopyranone under similar conditions also gave chloroformylation product though in low yields (30%). The reaction of chromanone gave the chlorovinyl aldehyde 33 when the reaction was carried out at 20°C. At higher temperature the 3-chloromethyl chromone 34 was obtained as the product.

The 3-formyl thiochromone 37 was also obtained along with the chloroformylated product 36 when the reaction was carried out with thiochromone.
Pallini and Sciaky have studied the reaction of steroids with Vilsmeier-Haack reagent. The 5-α androstan-17β-ol-3-one acetate on chloroformylation gave the product having the formyl group at the 2-position while the reaction of the 5-β isomer under similar conditions gave the product having the formyl group at the 4-position. (Table 5, Entry 1 and 2). The reaction dehydroisoandrosterone acetate also gave the chloroformylated product along with the vinyl chloride (Table 5, Entry 3).

Table 5
Chloroformylation of Steroid Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Substrate 1]</td>
<td>![Product 1]</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>![Substrate 2]</td>
<td>![Product 2]</td>
<td>48</td>
</tr>
</tbody>
</table>
The regioselectivity of the Vilsmeier-Haack chloroformylation has been compared with the acid catalyzed enol acetate formation. The reaction of cyclic ketones having a 3-methyl substituent with the Vilsmeier reagent in dichloroethane shows a high regioselectivity due to the steric influence of the methyl substituent except in the case of the 3-methyl cyclopentanone. Cycloheptanone with a methyl group at 4-position did not show any regioselectivity in chloroformylation.

Scheme 16

While the reaction of cyclic ketones with one or two equivalents of Vilsmeier reagent provide the chloroformylated product, reaction with excess reagent can lead to the formation of chlorosubstituted pentamethinium salts. This is exemplified by the reaction of cyclohexanone with excess of POCl₃ in DMF. The pentamethinium salt 41 could be isolated as its perchlorate salt. Hydrolysis of this iminium salt leads to the corresponding aldehyde (Scheme 17). Similarly the reaction of 2-indanone with
Vilsmeier reagent proceed with chloroformylation followed by incorporation of the N,N-dimethylaminomethylene group. The chlorosubstituent could be replaced by N,N-dimethylamino group and subsequent hydrolysis with saturated potassium carbonate solution gave the indene aldehyde 45.

Scheme 17

\[
\begin{align*}
\text{O} & \xrightarrow{\text{POCl}_3(\text{excess})} \\
40 & \xrightarrow{\text{DMF}} \\
\end{align*}
\]

Scheme 18

\[
\begin{align*}
\text{42} & \xrightarrow{\text{POCl}_3} \\
43 & \xrightarrow{\text{Me}_2\text{NH}} \\
44 & \xrightarrow{\text{B/H}_2\text{O}} \\
45 &
\end{align*}
\]
Katritzky, Marson and Wang have examined the reactions of several substituted cyclohexenones under Vilsmeier-Haack conditions. The reaction of cyclohexenones with Vilsmeier reagent undergo chloroformylation and subsequent iminoalkylation reactions leading to a variety of products. Often the reaction leads to aromatization of the ring. This is exemplified by the reaction of 4-isopropyl-2-cyclohexenone with Vilsmeier reagent prepared from N-formylmorpholine and POCI₃ which gave an aromatic dialdehyde. Formyl substituents are incorporated at the 2,4 and 6 positions of the incorporated chlorine, if other substituents are not already present there. This reaction provides an access to aromatic di and tri aldehydes. However 4,4-dimethyl substituted and 2-methyl substituted cyclohexenones did not lead to the formation of aromatized products under these conditions. (Table 6, Entry 2 and 3). 2-Cyclohexanone with a methyl group at the α-position gave the simple chloroformylated product along with the allyl alcohol (Table 6, Entry 3). However Raju and Krishna Rao have observed that when the mixture of methyl substituted cyclohexenones obtained by the Birch reduction of 2-methyl anisole, on Vilsmeier reaction gave the 6-methyl chlorobenzene 2,4-dicarbaldehyde 49 (Scheme 19).
Similar polyaldehydes were also obtained from other substituted cyclohexenones as well. The reaction of 2-cyclohexenones having a chloro or bromo substituent at the 3-position is similar to that of 1,3-cyclohexadiones and leads to the formation of cross conjugated dialdehydes (Entry Nos. 9 and 10, Table 6). When a methyl substituent is present at the β-carbon of the cyclohex-2-enone the Vilsmeier reaction proceeds with formylation on methyl group rather than the methylene group. (Table 6, Entry 6, 7 and 8). In the case of isophorone a pyran was also isolated in low yield.

\[
\text{ CHO} \\
\text{ Cl}
\]

50

Attempts to change the regio selectivity using silyl enol ethers instead of the ketones as such was not very successful. For instance, the silyl enol ethers derived from isophorone gave the usual chloro formylation product in 87% yield and the aldehyde was obtained only in low yield.

Table 6

<table>
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<td>44,45</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td>44</td>
</tr>
</tbody>
</table>

Chalcones 51 which cannot undergo chloroformylation cyclizes to chlorosubstituted indene derivatives 52 in moderate yields in the presence of Vilsmeier-Haack reagent (Scheme 20). 47

Scheme 20

2.3.2 1,3-Dicarbonyl Compounds

The reaction of acetyl acetone with the Vilsmeier reagent prepared from POCl3 and DMF provides exclusively the 2,4-dichlorobenzaldehyde 54 (Scheme 18). 57
When this reaction was performed with the reagent prepared from N-formyl morpholine, 4,6-dichloroisophthalaldehyde 55 was also obtained along with 2,4-dichlorobenzaldehyde 54 (Scheme 22).58

Scheme 21

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{O} \\
& \quad \text{H}_3\text{C} \quad \text{CH}_3 \\
\text{53} & \quad \xrightarrow{\text{POCl}_3, \text{DMF}} \\
& \quad \text{Cl} \quad \text{CHO} \\
\text{54} & 
\end{align*}
\]

Scheme 22

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{O} \\
& \quad \text{H}_3\text{C} \quad \text{CH}_3 \\
\text{53} & \quad \xrightarrow{\text{POCl}_3} \\
& \quad \text{Cl} \quad \text{CHO} \\
& \quad \text{CHO} \\
\text{54} & \quad + \\
\text{55} & 
\end{align*}
\]

The cyclization of the iminium salt 56 leads to the formation of the 2,4-dichlorobenzaldehyde while that of the bis-iminium salt 57 provides the isophthalaldehyde. The iminium salt 56b having morpholine moieties cyclize slowly compared to 56a with dimethyl amino groups. This results in further iminoalkylation of the iminium salt 56b to give 57b and thus the isophthalaldehyde 55.
The reaction of cyclohexane dione gives a cross conjugated dialdehyde 60 along with the dichlorosubstituted cyclohexadiene carbaldehyde 59 (Scheme 23).\(^5^9\)

Scheme 23

The reaction of 2-bromocyclohexane 1,3-dione proceeds with aromatization and results in the formation of 2,4-dichlorobenzaldehyde. Similarly cyclohexane 1,4-dione also leads to aminomethyl substituted chlorophenol (Table 7).

2.3.3 Enol ethers, Acetals and Enamines

The reaction of diethyl acetals of enolizable aldehydes 61 with Vilsmeier-Haack reagent prepared from DMF and phosgene gave the corresponding $\beta$-amino acroleins
A variety of substituted β-dimethylaminoacroleins (R = H, Me, Et, n-Pr, i-Pr, n-Bu, Pentyl, Phenyl, Benzyl) could be prepared by this method.

Table 7
Vilsmeier Reaction of Cyclohexanediones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
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<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>59</td>
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<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>59</td>
</tr>
</tbody>
</table>

Scheme 24

The reaction of ketals with Vilsmeier reagent was similar to that of their parent ketones which has been discussed already. Thus the reaction of ketals derived from methyl ketones on reaction with the reagent prepared from DMF and POCl₃ or phosgene on subsequent reaction with dimethyl amine leads to the formation of the iminium salts which undergo further formylation with Vilsmeier reagent to give 65.
Unstable acyl malonaldehydes could be obtained by the basic hydrolysis of 65 (Scheme 25).

Scheme 25

The diethyl acetal derived from acetophenone 67 underwent reaction with the chloromethylene iminium salt 4 to give the alkoxy substituted vinyl iminium salt 68.
which on hydrolysis with sodium acetate gave the \( \beta \)-ethoxy cinnamaldehyde 69 (Scheme 26).

The diethyl ketal of acetone 70 on Vilsmeier reaction with \( \text{POCl}_3 \) and DMF gave the ethoxy substituted iminium salt 71 (Scheme 27).

\[ \text{Scheme 27} \]

\[ \begin{align*} 
\text{EtO} & \quad \text{Me} \quad \text{Me} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*} \]

The enol acetate of acetone reacted with the chloromethylene iminium chloride also gave similar reaction leading to the formation of chlorosubstituted iminium salt 73 (scheme 28).

\[ \text{Scheme 28} \]

Sciaky and Pallini have studied the reactions of cyclic ketals derived from steroids. The reactions of ethylene ketals with the Vilsmeier reagent leads to the formation of chloroethoxy substituted enaldehydes. This exemplified the reaction of
ethylene ketal of progrenolone acetate 74 with the reagent prepared from DMF and 
POCl₃ in trichloroethylene which gave the chloroethoxy substituted enaldehyde 75 
(Scheme 29).

**Scheme 29**

The ethylene ketal derived from 16-dehydropregnenolone also gave the 
corresponding β-2-chloroethoxy substituted enaldehyde. The ketal derived form 
pregnenolone having a α-hydroxysubstituent cyclizes to the dihydro-spirofuranone 77 
in the presence of Vilsmeier reagent (Scheme 30).

**Scheme 30**
Similar spirofuranones having a β-chlorosubstituent were obtained when the reaction was carried out with epoxy ketals 78 (Scheme 31).

Scheme 31

![Scheme 31](image)

Several enol ethers prepared from steroids having a carbonyl group at 3-position could be conveniently transformed to the 6-formyl derivatives under the Vilsmeier-Haack conditions (Scheme 32).50-54

Scheme 32

![Scheme 32](image)

When the reaction was carried out with ethylene ketal 82 the chloroethoxy substituted aldehyde 83a (X = Cl) or the formate ester 83b (X = OCHO) was obtained as the product (Scheme 33). However, similar enamines are more reactive and leads to the formation of bis formylation products on Vilsmeir reaction (Scheme 34).46
Scheme 33

\[
\text{O} \quad \overset{\text{POCl}_3, \text{DMF}}{\text{1)}} \xrightarrow{\text{H}_2\text{O}, \text{NaOH}} \quad \text{XCH}_2\text{CH}_2\text{O} \quad \overset{\text{NaOH}}{\xrightarrow{\text{H}_2\text{O}}} \quad \text{X} = \text{Cl} \text{ or OCHO}
\]

82

83

Scheme 34

\[
\text{N,N-Dimethyl formamide acetal adds to indene to give the N,N-dimethylaminomethylene indene 86 which consumes an equivalent of chloromethylene iminium salt to give the iminium salt 87 which on hydrolysis with saturated potassium carbonate solution gives N,N-dimethylaminoindene aldehyde 88.}^{79}
\]

The reaction of methoxy substituted cyclohexadienes are similar to that of \(\alpha,\beta\)- or \(\beta,\gamma\)-unsaturated cyclohexenones towards the Vilsmeier reagent and leads to the formation of poly formylated aromatic compounds (Scheme 36 and Scheme 37).^{55}
Scheme 35

\[
\begin{align*}
\text{86} & \quad \rightarrow \quad \text{87} \quad \rightarrow \quad \text{88}
\end{align*}
\]

Scheme 36

\[
\begin{align*}
\text{89} & \quad \xrightarrow{\text{POCl}_3, \text{DMF}} \quad \text{90}
\end{align*}
\]

Scheme 37

\[
\begin{align*}
\text{91} & \quad \xrightarrow{\text{POCl}_3, \text{DMF}} \quad \text{92}
\end{align*}
\]
2.3.4 Dithioacetals

Enolizable ketones lead to chloroformylation under the Vilsmeier-Haack conditions. Replacement of the chlorine with sulfur nucleophiles in the presence of base provides β-alkylthio or arylthioethylenic aldehydes. Alternatively the β-alkylthioethylenic aldehydes can be directly prepared by the Vilsmeier reaction of dithioketals. Though the reactions of ketals, enol ethers and enamines are known to give β-alkylthio or β-amino acroleins, the easy hydrolysis of the enol ether or enamine functionality under the alkaline work up conditions of the Vilsmeier reaction often leads to the formation of the β-oxo aldehydes as the end products. Moreover the enamines undergo very facile imino alkylation so that it is difficult to stop the reaction at the mono iminoalkylation stage. An earlier report from this laboratory shows that the dithioketals derived from ketones leads to very facile and selective mono iminoalkylation and the resultant alkylthiovinyl iminium salt undergo regioselective hydrolysis to give high yields of β-alkylthioethylenic aldehydes (Scheme 38). The reaction proceeds with high stereoselectivity to afford the E-isomer as the major product. The β-alkylthioethylenic aldehydes could be prepared from aliphatic, alicyclic and aryl alkyl ketones. Table 8 shows examples of the butylthioethylenic aldehydes prepared according to this method.

Scheme 38

\[
\begin{align*}
\text{93} &\quad \text{BuSH, TiCl} &\quad \text{BuS, SBu} &\quad \text{POCl}_3, \text{DMF} &\quad \text{95}
\end{align*}
\]
Table 8

Vilsmeier Reaction of Dithioketals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{BuS}^\text{S} \text{Bu}$</td>
<td>$\text{BuS}^\text{CH}_3 \text{CH}_3$</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>$\text{BuS}^\text{S} \text{Bu}$</td>
<td>$\text{BuS}^\text{CHO}$</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>$\text{BuS}^\text{S} \text{Bu}$</td>
<td>$\text{BuS}^\text{CH}_3 \text{CHO}$</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>$\text{BuS}^\text{S} \text{Bu}$</td>
<td>$\text{BuS}^\text{CHO}$</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>$\text{BuS}^\text{S} \text{Bu}$</td>
<td>$\text{BuS}^\text{CHO}$</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>$\text{BuS}^\text{S} \text{Bu}$</td>
<td>$\text{BuS}^\text{CH}_3 \text{CHO}$</td>
<td>38</td>
</tr>
</tbody>
</table>
2.3.5 Amides and Lactams

The Vilsmeier-Haack reactions of amides and lactams have been studied extensively. The formation of quinoline from acetanilide derivatives was observed by Vilsmeier himself (Scheme 39). Later this reaction has been extensively explored particularly by Meth-Cohn and co-workers.

Scheme 39

The formation of quinoline derivatives may be exemplified by the Vilsmeier reaction of 2,5-dimethoxy anilides. The quinoline trione could be obtained by the acid catalyzed hydrolysis followed by the oxidation of initial product 99.

The chloroformylation of N-substituted succinimides leads to the formation of pyrrole-3,4-dicarboxaldehydes (Scheme 40).
Scheme 40

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[\text{101}\]

\[
\begin{align*}
\text{R} & \quad = \quad \text{Me, Et, i-Pr, Ph,} \\
\text{OHC} & \quad \text{CHO}
\end{align*}
\]

\[\text{102}\]

When the pyrrole carboxaldehydes 102 were refluxed in methanol in the presence of potassium hydroxide the hydroxymethylene derivatives 103 were formed which could be further converted to the aminomethylene pyrrolones 104.

Scheme 41

\[
\begin{align*}
\text{OHC} & \quad \text{CHO} \\
\text{Cl} & \quad \text{N} \\
\text{N} & \quad \text{Cl} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[\text{103}\]

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{Cl} & \quad \text{N} \\
\text{N} & \quad \text{Cl} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[\text{104}\]

The reaction of N-alkyl succinamidals 106 with the Vilsmeier-Haack reagent derived from POCI₃ and DMF afford the pyrrole carboxaldehyde 107 or the pyrrole dicarboxaldehyde 108 (Scheme 42). The formation of either of the products can be controlled by the molar ratio of the reagent and the temperature at which the reaction is carried out. N-Unsubstituted aldehydes could be obtained when N-\text{t-}butoxycarbonyl succinamidal 109 was used as the substrate.
Scheme 42

Alternatively pyrrole aldehydes also could be prepared by the Vilsmeier reaction of 2-chloropyrrole derivatives\textsuperscript{92} or 3-pyrrolin-2-one \textsuperscript{110}.\textsuperscript{93}

Similarly the N-substituted glutarimide \textsuperscript{111} also underwent chloroformylation of both the amide carbonyl groups when subjected to Vilsmeier-Haack conditions (Scheme 43).\textsuperscript{89}
Scheme 43

4-Aryl substituted glutarimides 113 on treatment with Vilsmeier-Haack reagent (POCl₃ and DMF) and subsequent hydrolysis with sodium acetate followed by acid hydrolysis gave the chlorosubstituted dicarboxaldehydes 114. They could be further oxidized to the corresponding pyridine derivatives 115 by ceric ammonium nitrate.

Scheme 44

Similarly 3,4-dihydro-2-pyridone 116 on treatment with the reagent prepared from oxalyl chloride and DMF provided 2-chloro-1,4-dihydropyridine-3,5-dicarboxaldehyde 117 which also could be oxidized to the corresponding pyridine derivative 118.
The sodium salt of ethane thiol could replace only one of the chlorosubstituents of the dicarboxaldehyde 119 while sodium thiophenolate could replace both the chlorosubstituents (Scheme 46).

This reaction has been further utilized in the synthesis of (-) coniine. A one pot hydrogenation of chlorosubstituted diene 126 obtained by the Vilsmeier reaction of the dihydro pyridone 125 gave the (-) conine 127. The dihydro pyridone 125 was prepared from the substituted pyridine 124.95

N-Acyl-2,3-dihydro-4-pyridones 122 react with one equivalent of Vilsmeier reagent to afford 1-acyl-4-chloro-1,2-dihydropyridines 123.
However the reaction of 4-piperidone 128 gave only the chloroformylation product 129 along with unreacted starting material.

Di-β-chlorovinyl aldehydes 131 also could be prepared by the Vilsmeier formylation of azepines (Scheme 47).
2.3.6 Carboxylic acids

The reactions of substituted acetic acids with Vilsmeier reagent leads to the formation of the α-substituted β-dimethylaminoacroleins 135. The iminium salt intermediates 134 leading to this products also have been isolated. The substituent at the α-position is usually aromatic or a heteroaromatic ring. Substrates having α-halosubstituents and carboxyl derivatives were also studied (Scheme 48).

The reaction of α-bromoacetic acid with the Vilsmeier reagent prepared from POCl₃ and DMF gave the bisiminium salt 137 a derivative of triformylmethane (Scheme 49). α-Chloroacetic acid also gives the same iminium salt 137 with three equivalents of the Vilsmeier reagent but at higher temperature (90°C). The reaction of substituted malonaldehydes in a similar fashion providing an alternative route for the synthesis of β-dimethylaminoacroleins. Vilsmeier reactions of aldehydes, carboxylic acids and substituted malonaldehydes give the same α-substituted β-aminoacroleins. Therefore any of these starting compounds may be used depending on their availability or ease of preparation (Scheme 50).

The Vilsmeier reaction of 1,4 benzene diacetic acid underwent double iminoalkylation accompanied by decarboxylation to give the iminium salt 142 which on basic hydrolysis gave the tetraldehyde 143 (Scheme 51).
Scheme 48

\[
R - \text{CO}_2\text{H} \quad \rightarrow \quad \begin{array}{c}
\text{Me} \\
X = \text{Cl}, \text{Br}
\end{array}
\]

132  

134  

135

\[
R
\]

| a | \[
\begin{array}{c}
\text{Ph}\\
\end{array}
\] |
|---|---|
| b | \[
\begin{array}{c}
\text{O}_2\text{N} \\
\end{array}
\] |
| c | \[
\begin{array}{c}
\text{CH}_3\text{O} \\
\end{array}
\] |
| d | 

Scheme 49

\[
X - \text{CO}_2\text{H} \quad \stackrel{\text{POCl}_3/\text{DMF}}{\longrightarrow} \quad \stackrel{\text{NaClO}_4}{\longrightarrow} \quad \begin{array}{c}
\text{Me} \\
\text{ClO}_4
\end{array}
\]

136  

137
Scheme 50

\[
\begin{align*}
R & \quad \text{CO}_2\text{H} \\
R & \quad \text{CO}_2\text{H} \\
138 & \\
\xrightarrow{\text{R}} & \\
\xrightarrow{\text{X}} & \\
\xrightarrow{\text{Me}} & \\
\xrightarrow{\text{NMMe}_2} & \\
139 & \\
\xrightarrow{\text{CHO}} & \\
\xrightarrow{\text{R}} & \\
\xrightarrow{\text{NMMe}_2} & \\
140 & \\
\hline
R & \\
a & \text{Bu}
\text{n}
\\nb & \text{PhCH}_2\\nc & \text{CH}_2=\text{CHCH}_2
\end{align*}
\]

Scheme 51

\[
\begin{align*}
\text{CH}_2\text{CO}_2\text{H} & \\
\text{CH}_2\text{CO}_2\text{H} & \\
141 & \\
\xrightarrow{\text{POCl}_3}
\quad \text{DMF} & \\
\xrightarrow{\text{X}} & \\
\xrightarrow{\text{Me}_2\text{N}} & \\
\xrightarrow{\text{NMMe}_2} & \\
142 & \\
\xrightarrow{\text{Base}}
\quad \text{H}_2\text{O} & \\
\xrightarrow{\text{X}} & \\
\xrightarrow{\text{Me}_2\text{N}} & \\
\xrightarrow{\text{NMMe}_2} & \\
143 & \\
\end{align*}
\]
Similarly the 1,3 benzene diacetic acid also gave decarboxylative double iminoalkylation which on subsequent basic hydrolysis gave the corresponding tetraldehyde. However the 1,2 benzene diacetic acid on Vilsmeier reaction gave complex product mixture of which only the indene derivative 145 has been isolated (Scheme 52).

Scheme 52

2.4 Reactions of Alkenes

The reactions of olefins substituted with electron donating substituents such as enamines and enol ethers have been already discussed. The reactions of simple alkenes possessing alkyl substituents are rather complex due to subsequent imino alkylations and migrations of carbon-carbon double bonds. Methylene cyclohexene underwent double iminoalkylation to produce 132 as its perchlorate (Scheme 53).
The reaction methylene bornane proceeded with multiple iminoalkylation to give the iminium salt 134 which could be converted to the pyridine 135 (Scheme 54).  

**Scheme 54**

![Reaction diagram](image)

Similar multiple iminocyclizations and subsequent conversions to 2,7-naphthyridine 138 or pyridine derivatives 141 have been observed in the cases of isobutene 136 (Scheme 56) and 2-phenyl propene 139 (Scheme 57) respectively.  

**Scheme 55**

![Reaction diagram](image)
However, if the migration of the double bond is restricted by the substituents at the α-position, monoformylated products are obtained. This is demonstrated by the reaction of d,l-camphene 142 which underwent reaction with the reagent prepared from $\text{PDC}_2 \text{POCl}_3$ and DMF to give the monoformylated product 143 (Scheme 57).

Similarly, the hexamethyl substituted 4-methylene cyclohexadiene 144 also underwent monoalkylation to give the corresponding α,β-unsaturated aldehyde (Scheme 58).
The steroid diene 146 having exocyclic methylene group, gave the dienaldehyde 147 though the 3-methyl-3,5-diene is thermodynamically much more stable. However when the reaction was carried out at higher temperature the dienaldehyde 149 derived from the more stable diene could be obtained (Scheme 59).69

Scheme 59

Steroids 150 having exomethylene group at C-17 also undergo monoformylation leading to the formation of the enaldehydes 151. However under more vigorous conditions multiple formylations do occur and the dialdehydes 152 have been isolated under such conditions (Scheme 60 and 61).72
Scheme 60

Limonene 153 undergo monoformylation under Vilsmeier-Haack conditions to give the enaldehyde 154 though the rearrangement product terpinolene 155 was also formed along with the aldehyde (Scheme 62).
Vinyl cyclopropanes also react with the chloromethylene iminium salt leading to the formation of the mono formylated products 157 in good yields (Scheme 63).  

Scheme 63

\[
\begin{align*}
\text{156} & \quad \rightarrow \quad \text{157}
\end{align*}
\]

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 64). 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. Here the Vilsmeier reagent assisted elimination of hydroxy group and subsequent iminoalkylation leads to the formation of the styryl methyleneiminium salts.

Scheme 64

\[
\begin{align*}
\text{158} & \quad \rightarrow \quad \text{159}
\end{align*}
\]
1,2-Dihydronaphthalenes 160 ($X = \text{CH}_2$)\(^75\) and chromene 160 ($X = \text{O}$) derivatives\(^76\) also undergo similar formylation to the respective formyl derivatives (Scheme 65).

**Scheme 65**

![Scheme 65](image)

Other substrates that are reported to undergo similar formylations are phenyl substituted butadiene 162 (Scheme 66)\(^77\) and hexatrienes 164 (Scheme 67)\(^78\), indene 166 (Scheme 68)\(^79\) and fulvene 168 (Scheme 69)\(^80\) derivatives.

**Scheme 66**

![Scheme 66](image)

**Scheme 67**

![Scheme 67](image)
The carbinols derived from 1,2-reduction of acyl ketenedithioacetics 170 undergo facile Vilsmeier-Haack reaction to give 5,5-bis(methylthio)substituted pentadienaldehydes 172 (Scheme 70).
Ketene dithioacetals derived from cyclic ketones also could be similarly transformed to the respective pentadienaldehydes.

ω,ω-Bis(methylthio)substituted polyenaldehydes could 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)nonapentaenaldehyde 175 (Scheme 71).

Scheme 71

Alternatively synthesis of similar polyenes could be also achieved by a combination of methyl Grignard addition and Vilsmeier-Haack formylation (Scheme 72).
The polyenaldehydes prepared by this method have been shown to be valuable intermediates in carbonyl group transposition reactions.

2.5 Cyclization and Cycloaromatization Reactions

Addition of allyl Grignard to methyl ketones and Vilsmeier reaction of the resulting allyl carbinols 177 provide a useful synthesis of biphenyl derivatives 178 (Scheme 73).\textsuperscript{82}

The Vilsmeier reaction of 2,4 dienoic acids leads to cycloaromatization to afford benzene tricarboxyaldehydes or dicarboxyaldehydes. Thus the reaction of 2,4
hexadienoic acid 179 gave a mixture of 1,3,5 benzene tricarboxaldehyde 180 and 2,4,6 chloro benzene tricarboxaldehyde 182 (Scheme 74). Similarly other substituted dienoic acids also gave corresponding cycloaromatised products.

Scheme 74

The Vilsmeier reaction of 3,5-dimethyl 2,4-hexadienoic acid gave a mixture of a phenolic aldehyde and a phenol.

Intramolecular attack of heteronucleophiles to the iminium salts formed under Vilsmeier-Haack reaction lead to the formation of heterocycles. For instance isoflavons 183 could be prepared by the Vilsmeier-Haack reaction of 2-phenyl-2',4'-dihydroxy acetophenone 182 (Scheme 75).

Scheme 75
Semicarbazones 184 and phenyl hydrazones 186 are converted to pyrazoles when treated with excess of Vilsmeier reagent (Schemes 76 and 77).

Scheme 76

\[
\begin{align*}
\text{CH}_3 \quad \text{CONH}_2 \\
\text{NH} \\
\text{N} \\
\text{NH} \\
\text{CH}_3 \\
\end{align*}
\]

184 →

\[
\begin{align*}
\text{NH} \\
\text{N} \\
\text{N} \\
\end{align*}
\]

185

Scheme 78

\[
\begin{align*}
\text{CH}_3 \\
\text{NH} \\
\text{N} \\
\text{Ph} \\
\end{align*}
\]

186 →

\[
\begin{align*}
\text{NH} \\
\text{N} \\
\text{N} \\
\text{Ph} \\
\end{align*}
\]

187

Seshadri and Padmanathan have reported formation of isoquinoline derivatives from the Vilsmeier reactions of benzimidazoles and benzoazoles\(^ {100}\) (Scheme 79).

Scheme 79

\[
\begin{align*}
\text{H} \\
\text{N} \\
\text{N} \\
\text{Ph} \\
\end{align*}
\]

188 → \[
\begin{align*}
\text{POCl}_3 \\
\text{DMF} \\
\end{align*}
\]

189
2.6 Miscellaneous Reactions

The Vilsmeier reaction of oximes prepared from o-hydroxy acetophenones 190 and 2-acetyl-1-napthol 191 gave the malonaldehyde derivatives of substituted benzoxazoles 193 (X=O) or naphthoxazole 194 respectively. The reaction proceeds, via a Beckmann rearrangement followed by cyclization and usual double iminomethylation.

![Chemical Structures](image)

The reaction of benzothiazole gave directly the corresponding malonaldehyde derivatives 193 (X=S). The malonaldehydes prepared were then converted various heterocycles such as pyrimidines 195, pyrazoles 197 and oxazoles 196. Conversion of the malonaldehydes to the corresponding cyanoacetaldehyde 198 and their further transformation to the aminopyrazoles 199 also have been reported.
2.7 The Synthetic Potential of the Vilsmeier-Haack Reaction Products

Arnold and Zemlicka have examined the reactions of β-chloroacroleins with secondary amines. The reaction of β-chlorocinnamaldehydes with dimethylamine gave the β-dimethylaminocinnamaldehyde 201 (Scheme 80). \(^{34}\)

**Scheme 80**

![](image)

Similar reaction of β-t-butyl β-chloroacrolein with dimethylamine gave the enamino ketone 203 (Scheme 81).
The chloroenaldehyde derived from cyclopentanone gave a mixture of dimethyl amino substituted enaldehyde 205 and the enamino ketone 207 (Scheme 82).

The reactions of β-chloroacroleins with sodium alkoxide in alcohols lead to the formation of hydroxymethylene ketones. The 3-chloro-4-formyl androstanol 207 could transformed to the hydroxymethylene derivative 208 in the presence of sodium ethoxide in refluxing ethanol (Scheme 83).
β-Chloroethoxy substituted enaldehyde 209 prepared from dehydroisoandrosterone also could be transformed to the hydroxymethylene ketones 210 on alkaline hydrolysis (Scheme 84).

Scheme 84

Solvolysis of β-alkoxy substituted enaldehydes 211 in the presence of sulfuric acid in methanol lead to the formation of β-oxoacetals 212 which could be converted into vinylogous esters 213 (Scheme 85).

Scheme 85
The di-β-chlorovinyl aldehydes were converted to the dipyrazolo azepines 214 and dithieno azepines 215. The reaction with phenyl hydrazine gave pyrazoles while the reaction with ethyl mercapto acetate in the presence of triethyl amine in pyridine gave the thiophene derivatives.90

Recently Powell and co-workers have synthesized several 2-chloropyridines using the β-chloro or dimethyl amino substituted enaldehydes obtained from the Vilsmeier reactions of a-methylene carboxylic acids or ketones.102 For instance the condensation of 2-aryl-3-(dimethyl amino)-2-propenals with cyano acetamide103 gave the 5-aryl-3-cyano pyridones 216 which on treatment with phosphorous oxychloride gave 5-aryl-3-chloro pyridines (Scheme 86).

Scheme 86

A variety of substituted 5-(dimethyl aminio)pentadienyl nitriles 217 underwent cyclization in the presence of hydrochloric acid to give 2-chloro substituted pyridines 218. Alternatively similar cyclizations in the presence of ammonia gave 2-amino substituted pyridines 219 (Scheme 87). Similar cyllizations with hydrobromic acid give corresponding 2-bromo pyridines.104
2.8 References


1955, 20, 668.
1946, 68, 1156.
33. For an excellent review on the Vilsmeier-Haack reaction of carbonyl compounds see C. M. Marson, Tetrahedron, 1992, 48, 3659.


M.A Alonso, J.I Ubeda, C. Avendano, J.C Menendez, M. Villacampa.

*Tetrahedron* 1993, 49, 10997


