Chapter 2

Vilsmeier-Haack reactions in Synthesis of Heterocycles: An Overview

2.1 Introduction

In 1927 Vilsmeier and Haack observed that N-methylformanilide can formylate aniline derivatives in the presence of POCl₃.¹ Later the reaction was extended using simple formamide derivatives like N,N-dimethylformamide, N-formylpiperidine, N-formylmorpholine etc. to formylate electron rich aromatic and aliphatic substrates, and these types of reactions are known as Vilsmeier-Haack reactions.² A Vilsmeier-Haack reagent 3 is produced when a disubstituted formamide or amide, typically N,N-dimethylformamide (DMF) 1 is treated with an acid halide, frequently phosphorous oxychloride, though to a lesser extent, oxalyl chloride (Scheme 2.1).

\[
\begin{align*}
1 & \xrightarrow{\text{POCl}_3} 2 & 2 & \xrightarrow{\text{HNO}_2} 3
\end{align*}
\]

Scheme 2.1

A large number of aromatic and aliphatic substrates, particularly the carbonyl compounds containing methyl or methylene groups adjacent to the carbonyl groups undergo iminoalkylation by the Vilsmeier-Haack reagent.² Hydrolysis of iminium salts formed in this reaction afford aldehyde derivatives. Usually the reactions of active methylene compounds with reagents of the Vilsmeier type afford β-chloromethyleneiminium salts or β-chlorovinylaldehydes, which have been recognized as useful intermediates
in heterocyclic synthesis. An overview of important Vilsmeier-Haack formylation reactions and Vilsmeier-Haack reactions leading to heterocycles is included in this chapter.

2.2 **The Vilsmeier-Haack reactions of aromatic compounds**

The Vilsmeier-Haack reactions of electron rich aromatic compounds, generally, afford aldehyde derivatives in good yields. For example, N,N-dimethylaniline 4 afford p-N,N-dimethylaminobenzaldehyde 6 (Scheme 2.2). Anthracenes, naphthalenes and other polycyclic aromatic compounds also undergo facile formylation.

![Scheme 2.2](image)

Heterocyclic compounds like pyrrole, furan, thiophene and selenophene derivatives also yield, aldehyde derivatives 8 in the Vilsmeier-Haack reaction (Scheme 2.3). Annulated heterocycles like indoles are also amenable to formylation reactions.

![Scheme 2.3](image)

Electrophilic substitution is sometimes followed by intramolecular cyclization. This is exemplified by the synthesis of 2-substituted benzo[b]furan derivative 11 from phenyl ethers 9 via an intermediate iminium salt 10 (Scheme 2.4).
A versatile synthesis of benzofurans 13 was accomplished by the Vilsmeier-Haack reaction of the phenoxyacetophenones 12 (Scheme 2.5). However the Vilsmeier-Haack reaction of simple phenoxyacetone affords N,N-dimethylamino substituted pentadienaldehydes in good yields.

Koyama et al reported the synthesis of thienopyridine derivative 16 from 3-cyanomethylthiophene 14 via an intermediate iminium salt 15 (Scheme 2.6).

Similarly Vilsmeier-Haack reaction of benzimidazole derivatives 17 leads to the synthesis of benzimidazo[1,2-b]isoquinoline derivatives 18 instead of the expected acenaphthalene derivatives (Scheme 2.7).
Scheme 2.7

Synthesis of 6-substituted-pyridazin-3(2H)-one 20 from Vilsmeier-Haack reaction of 3-methoxy-6-(6-methoxy-3-pyridyl)pyridazines 19 is reported.\(^8\)

Scheme 2.8

Several porphyrin derivatives participate in the Vilsmeier-Haack reaction giving products of substitution in either the pyrrole ring or at the methylene bridge position.\(^9\)

2.3 The Vilsmeier-Haack reactions of alkene derivatives

The reactions of simple alkenes possessing alkyl substituents are rather complex due to subsequent iminoalkylations and migrations of carbon-carbon bonds. For example, simple alkenes like isobutene on reaction with Vilsmeier-Haack reagent affords 2,7-naphthyridine 23 via a multiple iminoalkylated intermediate 22 (Scheme 2.9).\(^10\)
Similarly, 2-phenylpropene affords corresponding nicotinaldehydes 25 in good yields (Scheme 2.10).\textsuperscript{10}

It is interesting to note that the multiple iminoalkylation of simple alkenes are controlled by substituents on the allylic carbon atoms. For example, the Vilsmeier-Haack reaction of camphene 26 affords simple formylated product 27 (Scheme 2.11) while that of methylenebornane 28 undergoes multiple iminoalkylations to afford pyridine derivatives 30 (Scheme 2.12).\textsuperscript{11}
In the course of our studies directed towards the utilization of chloromethyleneiminium salts in the synthesis of heterocyclic compounds, we have developed convenient methods for the synthesis of substituted pyridines and naphthyridines. For example carbinols derived from acetophenones undergo multiple iminoalkylation reaction followed by reaction with ammonium acetate to afford substituted pyridines (Scheme 2.13). In this reaction the iminoalkylation is considered to occur on an alkene intermediate.

When the same protocol was extended to aliphatic or alicyclic carbinols, [2,7]naphthyridine derivatives were obtained (Scheme 2.14).

In the case of alkenes like methylenecyclohexene, the reaction affords as perchlorate salts (Scheme 2.15).
It has also been shown that the iminoalkylation is stereoselective and regioselective. Regioselectivity may result from either electronic factors or the steric hindrance resulting from bulky substituents and it has been well documented in the reactions of limonene 37 and steroid diene 39 having exocyclic methylene group with chloromethyleneiminium salts to afford corresponding formylated products 38, 40 and 42 (Scheme 2.16 and 2.17)\textsuperscript{13,14}
Vilsmeier-Haack reactions of steroids 43, having exocyclic methylene group at C-17 also have been reported. At mild conditions it afforded enaldehyde 44 while at vigorous condition it underwent multiple formylation reaction to afford enaldehyde 45 (Scheme 2.18).\textsuperscript{15}

\[ 
\text{\includegraphics[width=0.5\textwidth]{scheme218.png}} 
\]

\textbf{Scheme 2.18}

Alkenes conjugated with aromatic systems undergo simple monoformylation reactions. For example, the reaction of substituted styrenes 46 with the Vilsmeier-Haack reagent leads to the formation of cinnamaldehyde derivatives 47 on the hydrolysis of the intermediate iminium salts (Scheme 2.19).\textsuperscript{16} Alternatively carbinols obtained by carbonyl group reduction of substituted acetophenones or addition of Grignard reagent to benzaldehydes may be directly used for the preparation of cinnamaldehydes by their treatment with the Vilsmeier-Haack reagents.\textsuperscript{17}

\[ 
\text{\includegraphics[width=0.5\textwidth]{scheme219.png}} 
\]

\textbf{Scheme 2.19}
Similar to styrenes, vinylcyclopropane 48 also undergoes Vilsmeier-Haack reaction to afford monoformylated product 49 (Scheme 2.20).

![Scheme 2.20](image)

In the literature there are reports on the Vilsmeier-Haack reactions of 1,2-dihydronaphthalenes\textsuperscript{19} and chromene\textsuperscript{20} derivatives to afford corresponding enaldehydes 51 (Scheme 2.21).

![Scheme 2.21](image)

The formylation has been extended to several related alkene derivatives like indene 52, polene 54 and 56 and fulvene derivatives 58 to afford corresponding aldehydes (Schemes 2.22, 2.23, 2.24 \& 2.25)\textsuperscript{21,22,23}.

![Scheme 2.22](image)

![Scheme 2.23](image)
In several cases, the products of monosubstitution undergo polysubstitution reactions and afford in most cases, cyclized products. For example, the alcohol derivative 60 on Vilsmeier-Haack reaction afforded biphenyl derivatives 61 in 30-98% yield (Scheme 2.26). This is a useful method for the synthesis of a variety of biphenyls.

Numerous alkene derivatives like enamines, enamides, encarbasates, enol ethers, enol acetates etc. also undergo iminoalkylation under Vilsmeier-Haack reaction condition. Electrophilic substitution of these alkene derivatives occurs readily, yielding iminium salts that have found substantial use in synthesis. For example, enamine derivative 62, when treated with chloromethyleneiminium salt, gives alkyl substituted
iminium salt 63 which on treatment with hydrazine affords pyrazole derivative 64 in 18-64% yields (Scheme 2.27). 25a

Scheme 2.27

The dienamine 65 afford the corresponding iminium salts 67 resulting from disubstitution in the presence of Vilsmeier-Haack reagent. The iminium salt 67 on hydrolysis affords dialdehyde derivatives 68 while on treatment with aqueous ammonium chloride solution affords pyridine-3-carbaldehyde 66 (Scheme 2.28). 25b

Scheme 2.28

Similarly the dienamine 69 on reaction with iminium salts affords the dienedialdehyde 70 (Scheme 2.29). 25c
Scheme 2.29

A convenient iminium salt mediated synthesis of 2-pyridone derivative 72 was achieved by the Vilsmeier-Haack formylation followed by cyclization of the acylenamine 71 (Scheme 2.30).\textsuperscript{25d}

Scheme 2.30

Several enamides have been used as precursors for the synthesis of pyridone derivatives. The enamides 73 on reaction with iminium salt afford N-substituted 2-pyridone derivatives 74 and pyridine-3-carbaldehyde derivative 75 in 14-69% yield (Scheme 2.31).\textsuperscript{26a}

Scheme 2.31

Enecarbamates such as 76, give formylation products 77 on treatment with Vilsmeier-Haack reagent (Scheme 2.32).\textsuperscript{27b}
Enol ethers represented by the general structure 78 undergo iminoalkylation to give iminium salt 79, which on hydrolysis affords $\beta$-ethoxyacrolein derivatives 81 and on amination using dimethylamine affords synthetically useful vinylamidinium salts 80 (Scheme 2.33).28

An interesting transformation of 1-methoxycyclohexa-3,6-diene 82 to chlorobenzene-2,4,6-tricarbaldehyde 83 under Vilsmeier-Haack reaction condition also have been reported (Scheme 2.34).29
Recent studies on the applications of iminoalkylated intermediates have resulted in many heterocyclic syntheses. For example, 2-chloronicotinonitriles 86 and fused bicyclo-2-chloro-3-cyanopyridines 88 are obtained from alkylidenemalononitriles 84 and 87 respectively by the Vilsmeier reaction (Scheme 2.35 and 2.36).\textsuperscript{30} In these reactions the iminoalkylated intermediates undergo cyclization reaction to afford the corresponding nicotinonitriles.

\[ \text{Scheme 2.35} \]

Similar approach to synthesize fused tricyclo-2-chloro-3-cyanopyridine 90 from 2-[3,4-dihydro-1(2H)-napthalenyliden]malanonitrile 89, has been reported by Aadil et al (Scheme 2.37).\textsuperscript{31}

\[ \text{Scheme 2.36} \]

It is interesting to note that the Vilsmeier-Haack reaction of malononitrile affords simple nicotinonitrile derivative 93 \textit{via} an intermediate 92 (scheme 2.38).\textsuperscript{32}
2.4 The Vilsmeier-Haack reactions of 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 94 react with chloromethyleneiminium salts to afford the corresponding β-chloroethylenic aldehydes 95 (Scheme 2.39).  

It has been suggested that the ketone enolizes prior to its reaction with Vilsmeier-Haack reagent. The enolization is enhanced due to the presence of HCl that would be formed as a result of the iminoalkylation at the oxygen of the carbonyl group. The enol form 96 of the ketone reacts with the Vilsmeier reagent to afford the β-enaminoketone 97 which undergo further reaction with the reagent to afford the iminium salt 99, which on alkaline hydrolysis lead to the formation of β-chloroethylenic aldehydes 95 (Scheme 2.40).  

Scheme 2.38

Scheme 2.39
By replacing the chloro substituent of the intermediate iminium salt 99 by N,N-dimethylamino group, subsequent iminoalkylation can be performed conveniently to afford malonaldehyde derivative 102 (Scheme 2.41).44

Aliphatic α,β-unsaturated ketones or β-diketones undergo cycloaromatization reactions on treatment with chloromethyleneiminium salts. For example, β-methyl substituted α,β-unsaturated ketone 103 undergoes cycloaromatization to afford the aromatic dialdehyde 105 (Scheme 2.42).45
Similar aromatizations of alicyclic α,β-ketones also have been reported. Katritzky et al reported the reaction of cyclohexenone 106 to afford aromatic aldehyde 107 using N-formylmorpholine instead of DMF (Scheme 2.43). Related, aromatization reactions have been reported by Raju and Rao on cyclohexenones obtained by the Birch reduction of 2-methylanisole, as well. Perumal et al have shown that oximes of α,β-unsaturated ketones can be transformed to 3-pyridine-3-carboxaldehydes under the Vilsmeier-Haack reaction conditions.

The treatment of acetylacetone 108 with DMF-POCl₃ affords 2,4-dichlorobenzaldehyde 110 via a heptamethinium species 109, which undergoes ring closure, probably in a pericyclic process (Scheme 2.44). Katritzky and Marson showed that the course of the reaction depends on the nature of the dialkylformamide. They reported the formation of 4,6-dichloroisophthalaldehyde from acetyl acetone using N-formylmorpholine-POCl₃ as the reagent. In this reaction the relative bulk of the morpholino group presumably reduces the rate of ring closure of the cation, so that
further iminoalkylation can occur giving the dicationic species, which then yields a dialdehyde.

![Chemical structure](image1)

**Scheme 2.44**

The Vilsmeier cyclization of 2'-aminochalcones 111 provides a mild one pot synthesis of 2-aryl-4-chloro-N-formyl-1,2-dihydroquinolines 112 (Scheme 2.45). The scope of the reaction has been extended for the synthesis of quinolines themselves, by replacing 2'-aminochalcones with 2'-azidochalcones as the starting material.

![Chemical structure](image2)

**Scheme 2.45**

Like acyclic ketones, cyclic ketones can also be transformed to the haloformylated products. For example, cyclic ketones 113 can be effectively transformed into corresponding β-haloacrylaldehydes 114 on reaction with halomethyleneiminium salts (Scheme 2.46). Karlsson and Frejd have showed that substituents at 3-position of the ring have steric influences on the attack of the chloromethyleneimininium salt, in the cases of six, seven and eight membered rings. They reported that the larger rings, despite possessing more conformational mobility, exhibit greater regioselectivity.
Vilsmeier-Haack reaction of cyclobutanone also has been reported. Even when an excess of formylating agent was used, cyclobutanone afforded only monoformylated product 116 (Scheme 2.47).\textsuperscript{42}

Arnold \textit{et al} have treated cycloalkanones with a large excess of Vilsmeier-Haack reagent followed by sodium perchlorate solution to afford 3-chloropentamethinium salts 118, which in the case of the cyclohexanone derivative only hydrolyzed to aldehyde derivative 119 (Scheme 2.48).\textsuperscript{40c}

Benzo-fused cycloalkanones are usually converted by Vilsmeier reagent into the corresponding chlorovinylaldehydes in good yield under mild conditions.\textsuperscript{43} The resulting chlorovinylaldehydes have been used in the synthesis of a wide variety of polycondensed heterocycles.\textsuperscript{44} For example, 1-
indanone,$^{39}$ α-tetralone$^{39}$ and benzosuberone$^{45}$ afford the corresponding β-chlorovinylaldehydes 121 (Scheme 2.49).

![Scheme 2.49](image)

Derivatives of α-tetralone and β-tetralone with alkyl groups on either ring afford the expected β-chlorovinylaldehydes 123 and 125 respectively (Scheme 2.50 and 2.51).$^{46}$

![Scheme 2.50](image)

The Vilsmeier-Haack reaction of acenaphthenone 126 and anthrone 128 affords aldehyde derivative 127 and 10-chloro-9-anthracene carboxaldehyde 129 respectively (Scheme 2.52 and 2.53)$^{40a,47}$.
Similarly the Vilsmeier-Haack reactions of chroman-4-one 130 and thiochroman-4-one 133 afford corresponding β-chlorovinylaldehydes 131 and 134 at low temperature. At higher temperature 130 afforded 3-(chloromethyl)chromone 132 and 133 afforded 3-formylthiochromone 135 in moderate yields (Scheme 2.54 and 2.55). The Vilsmeier-Haack reactions of flavanones and related benzofused compounds have also been reported.
Using Vilsmeier methodology, the diketone 136 was converted into the dialdehyde 137, which afforded a convergent and unambiguous route to the intricate macrocyclic pyrilium salt 138 (Scheme 2.56).\(^{43a}\)

\[
\begin{align*}
\text{Scheme 2.56} \\
3\text{-Halo-2-methyl-2-cyclopenten-1-ones 140 can be prepared in excellent yield by the reaction of cycloalkene-1,3-diones 139 with Vilsmeier-Haack reagents prepared from DMF and (COCl)}_2 \text{ or (COBr)}_2 \text{ (Scheme 2.57).}^{49}\text{ The absence of formylated product is a notable feature in this reaction. The same reaction has been observed for the formation of 3-halo-2-cyclohexen-1-ones from cyclohexane-1,3-dione.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 2.57} \\
\end{align*}
\]

In the case of 1,4-diketones like 141, the Vilsmeier-Haack reagent induces aromatization reaction. For example, cyclohexane-1,4-dione reacts with N-formylmorpholine-POCl\(_3\) to give the phenol 142 (Scheme 2.58).\(^{36a}\) Similarly, the chloroformylation of cyclooctane-1,5-dione affords ketoaldehyde or dialdehyde according to the reaction conditions.\(^{50}\)
Scheme 2.58

The reaction of aryl alkyl ketone with Vilsmeier-Haack reagent is more selective. Arnold et al reported the reactions of substituted acetophenones 143 with chloromethyleneiminium salts to afford β-chlorocinnamaldehydes 144 in moderate to good yields (Scheme 2.59).45

Scheme 2.59

When electron-releasing substituents are present on the aromatic ring, cyclization of the intermediate chloromethyleneiminium salt is occurred. For example, substituted propeophenone 145 undergo cyclization to chlorosubstituted N,N-dimethylamino substituted indenes 146 (Scheme 2.60).51 Similarly, aryl benzyl ketones also afforded the corresponding chlorindenones.52

Scheme 2.60
By the attack of Vilsmeier-Haack reagent, $o$-hydroxyacetophenones 147 are cyclized to give the valuable intermediates 3-formylchromones 149 in good yield (Scheme 2.61).\textsuperscript{53} Similarly cyclization of 2-hydroxy-$\alpha$-phenoxyacetophenone derivatives by the Vilsmeier reagent, catalysed by BF$_3$.OEt$_2$ to 3-phenoxychromone derivatives has also been reported.\textsuperscript{54} The reaction mechanisms and kinetics of these reactions also have been well studied.\textsuperscript{55} Appropriately substituted naphthalenes and coumarins react similarly.

\[
\text{147} \quad \overset{\text{DMF, POCl}_3}{\longrightarrow} \quad \text{148} \quad \overset{\text{DMF, POCl}_3}{\longrightarrow} \quad \text{149}
\]

Scheme 2.61

Similarly, $o$-aminoacetophenones 150 react with the Vilsmeier-Haack reagent to afford the corresponding 4-chloroquinoline derivatives 151 (Scheme 2.62).\textsuperscript{56}

\[
\text{150} \quad \overset{\text{DMF, POCl}_3}{\longrightarrow} \quad \text{151}
\]

Scheme 2.62

A variation involves by the conversion of 1-acetyl-2-hydroxynaphthalene into a difluoro-1,3-dioxaborin 152 and subsequent formylation reaction by Vilsmeier-Haack reagent. In this case phenalenone 153 is the major product along with the expected chromone 154 (Scheme 2.63).\textsuperscript{57}
Scheme 2.63

During the chloroformylation of 1-acetonaphthone 155 migration of the acetyl group occurs, with formation of the same aldehyde 156 as that obtained from 2-acetonaphthone 157 (Scheme 2.64).58

Scheme 2.64

The Vilsmeier-Haack reaction of 1,5-diketones of the type 158 affords 3-formylpyran derivatives 159 (Scheme 2.65).59

Scheme 2.65

In our laboratory, various aryl-substituted acetones 160 were treated with three equivalents of Vilsmeier-Haack reagent, prepared by the addition of POCl₃ to DMF to afford 5-aryl-3-formyl-4-pyrones 161 in good yields (Scheme 2.66). In the case of 1-(3-methoxyphenyl)-2-propanone, the reaction afforded 2-chloronaphthalene-1,3-dicarbaldehyde 163 as the major product (Scheme 2.67).60
When benzyl ethyl ketone 164 was treated with Vilsmeier-Haack reagent under the same conditions, 3-methyl-5-phenylpyran-4-one 165 was obtained (Scheme 2.68).  

**Scheme 2.68**

Dibenzyl ketone 166 and phenoxyacetone 168 gave the corresponding N,N-dimethylamino substituted pentadienaldehydes 167 and 169 respectively (Scheme 2.69 and 2.70).
Similarly the reaction of benzylacetone 170 with the Vilsmeier-Haack reagent under the same condition gave substituted phenol 171 (Scheme 2.71).\(^6\)

Vilsmeier-Haack reactions of steroidal carbonyl groups also have been reported. The regioselectivity of formylation is markedly influenced by the relative configuration of the adjacent ring junction. For example, the steroids 172 and 175 afford 3-chloro-3,5,7-trienes 174 and aromatic dialdehydes 177 respectively, along with the corresponding chlorovinyl aldehydes 173 and 176 (Scheme 2.72 and 2.73).\(^6\)
Similarly the Vilsmeier-Haack reaction of 19-nortestosterone acetate 178 affords the aldehydes 179 and 180 (Scheme 2.74).^62

The Vilsmeier-Haack reactions of the synthetic equivalents of carbonyl compounds such as enol ethers, acetics and enamines also have been studied. For example, β-dimethylaminoacrolins 182 can be prepared by the treatment of diethylacetals 181 of aliphatic aldehydes with the reagent prepared from phosgene and DMF (Scheme 2.75).^63

Earlier reports from this laboratory describe a convenient synthesis of β-alkylthioethylenic aldehyde 185 starting from dithioketals 184. The
dithioketals undergo very selective monoiminooalkylation in the presence of the reagent prepared from POCl₃ and DMF (Scheme 2.76).⁶⁴

![Scheme 2.76](image)

However, similar reactions with ketals and vinyl acetates always lead to multiple iminoalkylation reactions. Interesting transformations have been reported by the reactions of α-hydroxy ketals. α-Hydroxy ketal 186 on reaction with Vilsmeier-Haack reagent afforded the dihydrospirofuranone 187 (Scheme 2.77).⁶⁵

![Scheme 2.77](image)

A one-pot synthesis of substituted pyridine-2(1H)-ones 189 and 190 through the Vilsmeier-Haack reaction of 1-acetyl, 1-carbamoyl cyclopropanes 188 is reported by Pan et al. The reaction proceeds through sequential ring-opening, haloformylation and intramolecular nucleophilic cyclization (Scheme 2.78).⁶⁶
Scheme 2.78

Another one-pot protocol for the synthesis of polysubstituted pyridine-2(1H)-ones 192 from β-oxo-amidines 191 under Vilsmeier conditions is reported by the same group (Scheme 2.79). 67

Scheme 2.79

Yet another protocol for the synthesis of polysubstituted pyridine-2-(1H)-ones 194 was developed by Dong, D and coworkers. Here 2-arylamino-3-acetyl-5,6-dihydro-4H-pyrans 193 undergoes Vilsmeier-Haack reaction resulting in the formation of 194 (Scheme 2.80). 68

Scheme 2.80

Synthesis of alkyl-3-aryl-4-formyl-5-(alkylsulfanyl)-1H-pyrrole-2-carboxylates 196 from Vilsmeier-Haack reaction of α-oxoketene-N,S-acetals 195 is reported by Asokan and coworkers (Scheme 2.81). 69
Recently, we have developed a new method for synthesizing α-formylketene dithioacetals 198 from arylketene dithioacetals 197 by treating them with well-known Vilsmeier-Haack reagent prepared from phosphorous oxychloride and N,N-dimethylformamide (Scheme 2.82). \(^{70}\)

We have explored the synthetic utility of this valuable synthon in synthesizing heterocycles like 2-pyridones 199 (Scheme 2.83), \(^{71}\) nicotinonitriles 200 & 201 (Scheme 2.84), \(^{72}\) isoxozoles 202 (Scheme 2.85) \(^{73}\) and pyrimidinecarbaldehydes 203 and 204 (Scheme 2.86). \(^{74}\)
2.5 The Vilsmeier-Haack reactions of carboxylic acids and their derivatives

The Vilsmeier-Haack reactions of carboxylic acids like 205 generally affords, synthetically important vinamidinium salts 206 which on hydrolysis affords corresponding acrylaldehydes 207 (Scheme 2.87).

Similarly, benzimidazole-2-propionic acid 208 is converted into the enaminketone 209 by the Vilsmeier-Haack reagent at room temperature.

Scheme 2.84

Scheme 2.85

Scheme 2.86

Scheme 2.87
(Scheme 2.88) \(^{76}\) and benzene-1,2-diacetic acid \(210\) affords the benzofulvene \(211\) in low yield (Scheme 2.89)\(^{20b}\).

\[
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{N} \\
\text{C} \quad \text{H}_3 \\
\text{D} \quad \text{M} \quad \text{F} \\
\text{P} \quad \text{O} \\
\text{C} \quad \text{H}_3 \\
\end{array}
\xleftarrow{\text{DMF}, \text{POCl}_3, 20 \, ^\circ\text{C}, 24 \text{ h}}
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{N} \\
\text{C} \quad \text{H}_3 \\
\end{array}
\]

Scheme 2.88

\[
\begin{array}{c}
\text{COOH} \\
\text{COOH} \\
\end{array}
\xleftarrow{\text{DMF}, \text{POCl}_3}
\begin{array}{c}
\text{O} \quad \text{H} \\
\text{Me}_2\text{N} \\
\end{array}
\]

Scheme 2.89

Generally ester groups are inert towards the Vilsmeier-Haack reagent, while lactonic carbonyl groups undergo chlorovinylation along with enamine formation. Thus the Vilsmeier-Haack reactions of benzazoles \(212\) afford the enamines \(213\) (Scheme 2.90).\(^{77}\)

\[
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{C} \quad \text{O}_2\text{Et} \\
\text{Et} \\
\text{X} \\
\text{N} \\
\text{C} \quad \text{O}_2\text{Et} \\
\text{Et} \\
\end{array}
\xleftarrow{\text{DMF}, \text{POCl}_3}
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{C} \quad \text{O}_2\text{Et} \\
\text{Et} \\
\text{X} \\
\text{Me}_2\text{N} \\
\end{array}
\]

Scheme 2.90

The treatment of 2-coumaranone \(214\) with the Vilsmeier-Haack reagent afforded the products \(215, 216\) and \(217\) (Scheme 2.91).\(^{78}\)
On reaction with Vilsmeier reagent, 5(4H)-isoxazolones 218 affords dichloromethylisoxazolones 219 (Scheme 2.92).\(^\text{79}\)

An interesting, chloromethyleneiminium salt mediated transformations of isoxazolinones to 1,3-oxazin-6-ones under Vilsmeier-Haack conditions also have been reported. In this reaction 1,3-oxazin-6-ones 223 were prepared by the reaction of Vilsmeier-Haack reagent on isoxazolin-5-one 220 via the intermediates 221 and 222 (Scheme 2.93).\(^\text{80}\)

The greater basicity of the carbonyl oxygen atom in carbonamides as compared with ketones suggests that the chloromethyleneiminium cation will usually initially attack on the carbonyl carbon atom to form intermediates 225 and 226 and they rapidly react to give the stable...
intermediates 227 and 228 which on hydrolysis affords an amide 229 (Scheme 2.94).\textsuperscript{2a}

Scheme 2.94

For example, N,N-dimethylacetamide 230 is converted into highly functionalized amide 232 by the Vilsmeier-Haack reagent (Scheme 2.95).\textsuperscript{2a}

Scheme 2.95

2-Acetylbenzamide derivatives 233 undergo iminium salt mediated dehydration of tautomers, which on further reaction with iminium salt affords aldehyde derivative 235 (Scheme 2.96).\textsuperscript{2b}
In the literature there are a number of reports on the synthesis of quinolines and their derivatives using the chloromethyleneimininium salts prepared from anilides. The Vilsmeier-Haack reaction of acylanilides afforded the functionalized quinoline in good yields (Scheme 2.97).

In the case of N-phenylacetanilides Vilsmeier-Haack reaction afforded 1-phenyl-2-quinolones such as (Scheme 2.98).

A variety of N-acetyl derivatives of amino acids like and have been subjected to Vilsmeier-Haack reaction to obtain 2,4-dichloro-3,5-diformyl pyrroles and 2-formylmethylene-4-substituted oxazolidin-5-ones (Scheme 2.99 and 2.100).
Similarly N-acetylhomocysteine thiolactone 246 give 5-chloro-3-formylthieno[2,3-b]pyridine 247 (Scheme 2.101).\(^{85}\)

While Vilsmeier-Haack reactions of monocyclic lactams like \(\alpha\)-pyrrolones, N-methyl-\(\delta\)-valerolactam, N-methyl-\(\epsilon\)-caprolactam etc. afford corresponding dimethylaminomethylene derivatives and benzofused lactams afford corresponding chlorovinylaldehydes. For example, oxindole 248 was converted by DMF-POCl\(_3\) into the 2-chloro-3-formylindole 250 (Scheme 2.102).\(^{86}\)
However, the Vilsmeier-Haack reaction of 1-acyloxindoles resulted in the 3-dimethylaminomethylidene derivatives 252 (Scheme 2.103). In this case the corresponding chlorovinylaldehydes are prepared not by chloromethylation, but due to the acylation of 2-chloro-3-formyloxindole.

\[
\begin{align*}
\text{Scheme 2.103} \\
\end{align*}
\]

Vilsmeier-Haack reaction of oxindoles, substituted with chlorine in the benzene ring, afforded corresponding aldehyde derivatives and dimethylaminomethylene derivatives depending on the reaction temperature. For example, the chlorosubstituted oxindole 253 reacted with chloromethyleneiminium salt at 35 °C to afford the aldehyde 254, while the reaction on heating afforded N-formyldimethylaminomethylene derivative 255 in excellent yields (Scheme 2.104). Vilsmeier-Haack reactions of lactams with two or more heteroatoms also have been reported.

\[
\begin{align*}
\text{Scheme 2.104} \\
\end{align*}
\]

2-Phenyliminothiazolidin-4-ones 256 are converted, by a Vilsmeier reagent, into versatile derivatives 257 from which several 5,5-fused heterocycles have been made (Scheme 2.105).
Scheme 2.105

An oxazine derivative 259, which is a useful fungicide and analgesic, was prepared by the Vilsmeier-Haack reaction of an amide 258 (Scheme 2.106).\(^9^1\)

Scheme 2.106

Unactivated pyrimidines do not usually react with Vilsmeier-Haack reagents. However, the unsubstituted 5-position of derivatives of barbituric acid, uracils and 4-hydroxy-6-oxo-dihydropyrimidines undergoes formylation in accordance with its reactivity as a $\beta$-enamide. For example barbituric acid derivatives 260 afforded either 261 or 262, depending on the solvent employed (Scheme 2.107).\(^9^2\)

Scheme 2.107

In the case of barbituric acid 263, the Vilsmeier-Haack reaction afforded corresponding chlorovinylaldehyde 264 (Scheme 2.108).\(^9^3\)
Imides of five, six, and seven membered ring react with excess DMF-POCl₃ to give useful di-β-chlorovinylaldehydes 267 (Scheme 2.109).

The Vilsmeier-Haack reaction on 4-hydroxyquinaldines 270 which is obtained from aniline 268 and ethyl acetate 269 is reported by Nandhakumar and coworkers. The reaction yielded 4-chloro-3-formyl-2-(2-hydroxyethene-1-yl)quinolines 271 was reported to be a valuable intermediate for biologically active diazepinoquinoline derivatives (Scheme 2.110).
In all the above reactions the Vilsmeier reagent acts as a formylating agent or an equivalent to this. However when the reaction is directed adjacent to tertiary amino groups it can lead to cyclization of the intermediate iminium salt instead of formylation resulting quaternized 1,3-diazone ring formation. For example the attempts to formylate 4-dimethylaminotoluene using POCl₃ in DMF or N-formylmorpholine give the quinazolinium salts (Scheme 2.111).

\[
\begin{align*}
\text{H}_3\text{C} & \text{H}_3\text{C} \\
\text{N} & \text{N} \\
\text{O} & \text{O} \\
\text{N} & \text{N} \\
\text{H}_3\text{C} & \text{H}_3\text{C} \\
\text{N} & \text{N} \\
\text{H}_3\text{C} & \text{H}_3\text{C} \\
\text{N} & \text{N} \\
\text{O} & \text{O} \\
\text{N} & \text{N} \\
\text{H}_3\text{C} & \text{H}_3\text{C} \\
\end{align*}
\]

Scheme 2.111

In conclusion, the Vilsmeier-Haack reaction is synthetically versatile and mechanically interesting and is known to proceed beyond introduction of formyl or equivalent groups, to the annulations of a variety of ring systems. The varying trends in organic chemistry has explored the synthetic potential of this reagent in the heterocyclic syntheses and in the functionalization of a variety of compounds having different functional groups as well as biologically important molecules like steroids, amino acids, carbohydrates, porphyrins, corroles etc. Still it is considered that many more reactions and their mechanistic pathways utilizing the chloromethyleneiminium salt remain to be explored.
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