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Introduction

The Vilsmeier (or Vilsmeier-Haack) reaction has historically been a topic of great interest to organic chemists, and it continues to attract considerable attention. Since its discovery in 1927,1 it has been developed into a powerful synthetic tool in organic chemistry. The Vilsmeier reaction was used initially for the introduction of the formyl group in activated aromatic and heteroaromatic compounds.2 Subsequently, it has been utilized in chlorination,3 chloroformylation,4 chloroformylation,4 aromatization,5 cyclizations,6 among others. In recent years, the Vilsmeier reaction has also found growing application in the domino synthesis of heteroaromatic compounds.7 The wide scope of the Vilsmeier reaction renders it an extremely useful tool in organic synthesis.

It is well known that inorganic acid halides react with disubstituted amides to form active complexes, halomethyleniminium salts, referred to as Vilsmeier reagents.1,8 N,N-dimethylformamide (DMF) is the most commonly employed disubstituted amide. N,N-dimethylacetamide,9 N,N-dimethylbenzamide,9,10 N-methylformanilide, 4-formylimorpholine, 1,4-dicarboxy piperazine11 and morpholino(phenyl)methanone.12 have also found application as disubstituted amides occasionally. The temperature used in the formation of the Vilsmeier reagent with DMF and an inorganic acid chloride is generally in the range of 0–25°C.

The inorganic acid halide used in the Vilsmeier complex is commonly phosphoryl chloride,13 though the use of other acid halides such as phosphorus trichloride,14 thionyl chloride,15 oxaly chloride,16 phosgene,17 2,4,6-trichloro[1,3,5]triazine,18 and bis-(trichloromethyl) carbonate (BTC, triphosgene)19 has also been reported. Recently, the
Vilsmeier reagent derived from BTC and DMF has attracted considerable attention since it avoids the formation of inorganic phosphoric acid salts encountered with the POCl₃/DMF complex, and shows great potential in industrial processes.

The generally accepted representation of the Vilsmeier reagent derived from N,N-dimethylformamide and phosphorus chloride corresponds to structures 1 or 2. The mechanism for formation of 1 or 2 is depicted in Scheme 1.

![Scheme 1](image)

Substrates used in Vilsmeier reactions include alkenes, active methyl or methylene groups, hydrazones, azines, aliphatic diazo compounds and activated aromatic or heteroaromatic compounds. Recently, substrates containing cyclopropyl or ketene dithioacetal groups have been utilized in Vilsmeier reactions. In some of these reactions, different products are formed under different reaction conditions (e.g. temperature, equiv.). With this strategy, a large number of heterocyclic compounds such as pyridines, quinolines and indoles were synthesized successfully.

In recent years, Vilsmeier reagents supported on solid phase have also been applied in organic synthesis. This reagent offers many benefits compared with the traditional Vilsmeier complexes, such as inherent time saving, reasonable purity of the final products without significant purification steps, as is necessary in most solution phase procedures and ease of recovery and activation for further use. Vilsmeier reaction under microwave irradiation has also been reported. The latter can be conducted rapidly and provides pure products in higher yield without the use of organic solvents and thus is environment friendly.

Until now, there have been two reviews about the Vilsmeier reaction. This review covers the developments in the Vilsmeier reaction mainly since 2000.

I. Vilsmeier-Haack Type Acylations

1. Formylation

The Vilsmeier reaction is primarily a mild method for formylating a wide variety of substrates. The Vilsmeier reagent is an often employed, well-suited electrophilic formylation reagent. Substrates which participate in Vilsmeier formylations include activated aromatic or heteroaromatic compounds, alkenes (including enamines and enol derivatives), and active methyl or methylene groups in general.
a. Formylation of Heterocycles

Formylation of pyrrole, thiophene, furan, and their derivatives usually occurs in the α-position. For example, Vilsmeier formylation of dipyrromethane 3 under standard conditions (room temperature, work-up with 10 M aqueous NaOH) gave the desired diformyldipyrromethane 4 (Scheme 2). Treatment of compound 4 with excess propylamine in THF quantitatively afforded the 1,9-bis(propyliminomethyl)dipyrromethane, which is the key intermediate for the 4-nitrophenyl-substituted swallowtail-porphyrin.

Scheme 2

In 2006, two methods for the synthesis of 1-formyldipyrromethanes 6 were investigated by Ptaszek’s group.34 One route to the compounds 6 is outlined in Scheme 3, wherein, treatment of dipyrromethanes 5 with the Vilsmeier reagent afforded the expected mixture of the 1-formyldipyrromethanes 6 and 1,9-diformyldipyrromethanes. To facilitate separation of the formyldipyrromethane species, the mixture was treated with Bu₂SnCl₂ and triethylamine (TEA) in CH₂Cl₂ at room temperature. The tin-complexation process was selective for the 1,9-diformyl species, yielding hydrophobic 1,9-diformyldipyrromethane-dibutyltin complexes 7 and 1-formyldipyrromethanes 6. The mixture was separated by flash chromatography to afford the desired 1-formyldipyrromethanes 6.

Scheme 3

Dihexylquaterthiophenedialdehyde 9 is one of the important intermediates in the synthesis of many classic π-conjugated thiophene-based oligomers, which can be produced from easily available dihexylquaterthiophene 8 by Vilsmeier-Haack formylation.35 Control
of the amount of Vilsmeier reagent led to formylation can occur at one of the terminal positions. Thus, Kanato et al.\textsuperscript{36} provided a method with POCl$_3$/DMF in 1,2-dichloroethane at 40°C to give the corresponding monoformyl derivate 10 in 40% yield (Scheme 4).

\begin{center}
\textbf{Scheme 4}
\end{center}

Electrophilic substitution reactions of thienylpyrroles were found to be very selective. Pyrrole is considerably more reactive towards electrophilic substitution than thiophene (Scheme 5),\textsuperscript{37} since the pyrrole nitrogen atom has a greater ability to delocalize the positive charge of $\sigma$-complexes than the sulfur atom in thiophene.

\begin{center}
\textbf{Scheme 5}
\end{center}

Meth-Cohn et al.\textsuperscript{38} examined the regioselective formylation of 3-methylthiophene (11) using the disubstituted amides, such as N-formylpyrrolidine. 3-Methylthiophene-2-carbaldehyde (12) was the major product and, when the disubstituted amide employed was dicyclohexylformamide, 4-methylthiophene-2-carbaldehyde (13) was the major product (Scheme 6).

\begin{center}
\textbf{Scheme 6}
\end{center}
In general, the regiochemistry of the Vilsmeier reaction of indoles is quite predictable, occurring at the 3-position, unless this position is occupied. For instance, the synthesis of 1-methoxy-6-(methylsulfonyl)-1H-indole-3-carbaldehyde (15) was achieved via the Vilsmeier formylation of 1-methoxy-6-(methylsulfonyl)-1H-indole (14) in good yield (Scheme 7).39

\[
\text{POCl}_3/\text{DMF} \quad 0^\circ C \text{ to r.t.}
\]

Scheme 7

The Vilsmeier formylation of protected indoles 16 with POCl₃ in DMF afforded the corresponding aldehydes 17 in moderate to excellent yields. Apparently, in the course of this reaction with substrate 16b, some hydrolysis of the protective group occurred, resulting in the formation of alkyl chloride 18 (Scheme 8).40

\[
\text{16a: } \text{PG} = \text{Benzyl} \quad \text{16b: } \text{PG} = \text{p-Methoxybenzyl}
\]

Scheme 8

When 6,7-dihydro-pyrazolo[1,5-a]pyrimidines 19 were treated with the Vilsmeier reagent (POCl₃/DMF), a double formylation at positions 3 and 6 of the pyrazolopyrimidine system occurred yielding pyrazolo[1,5-a]pyrimidine-3,6-dicarbaldehydes 20. On the other hand, the Vilsmeier reaction of pyrazolopyrimidines 21 took place only at position 3 of the pyrazole ring, leading to the formation of the pyrazolopyrimidine-3-carbaldehydes 22 (Scheme 9).41

Porphyrins play an important role in biological processes such as oxygen transport, electron transfer and photosynthesis.42 One functional group, which allows asymmetric modification and is widely used in porphyrin chemistry, is the formyl group. Dahms and co-workers43 provided a wonderful method which used Vilsmeier reagent to give the desired formylporphyrins 24 (Scheme 10) using compounds 23 as substrates. The yield was between 13% (for 24b) and 97% (for 24i), as summarized in Table 1.

Over the past ten years, some novel techniques have been developed for the Vilsmeier process. For instance, Nagarajan et al.44 reported the synthesis of carbazole aldehydes 26 from carbazole 25 through Vilsmeier reaction under microwave irradiation (Scheme 11). The method has several advantages including high yields, short reaction times, and simple work up procedure.
Scheme 9

\[ \text{R} = \text{H, C}_6\text{H}_5 \]
\[ \text{R'} = \text{H, Br, Cl, NO}_2, \text{OCH}_3, \]

Scheme 10

\[ \text{M} = \text{Ni}^{II}, \text{Cu}^{II} \]
\[ \text{R}^1 = \text{Ph, 3-MeOC}_6\text{H}_4, \text{Hexyl, i-Bu, 1-Ethylpropyl} \]
\[ \text{R}^2 = \text{H or CHO} \]

Scheme 11

\[ \text{a: R}^1 = \text{CH}_3, \text{R}^2 = \text{H}; \text{b: R}^1 = \text{C}_2\text{H}_5, \text{R}^2 = \text{H} \]
\[ \text{c: R}^1 = \text{C}_2\text{H}_5, \text{R}^2 = \text{CH}_3; \text{d: R}^1 = \text{C}_2\text{H}_5, \text{R}^2 = \text{Br} \]
Table 1

Facile Synthesis of Formylporphyrins 24

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24a</td>
<td>Ni²⁺</td>
<td>Ph</td>
<td>H</td>
<td>59</td>
</tr>
<tr>
<td>24b</td>
<td>Cu²⁺</td>
<td>3-MeOC₆H₄</td>
<td>H</td>
<td>13</td>
</tr>
<tr>
<td>24c</td>
<td>Cu²⁺</td>
<td>3-MeOC₆H₄</td>
<td>CHO</td>
<td>20</td>
</tr>
<tr>
<td>24d</td>
<td>Ni²⁺</td>
<td>3-MeOC₆H₄</td>
<td>CHO</td>
<td>48</td>
</tr>
<tr>
<td>24e</td>
<td>Ni²⁺</td>
<td>Hexyl</td>
<td>H</td>
<td>60</td>
</tr>
<tr>
<td>24f</td>
<td>Ni²⁺</td>
<td>Hexyl</td>
<td>CHO</td>
<td>42</td>
</tr>
<tr>
<td>24g</td>
<td>Cu²⁺</td>
<td>Hexyl</td>
<td>CHO</td>
<td>18</td>
</tr>
<tr>
<td>24h</td>
<td>Cu²⁺</td>
<td>i-Bu</td>
<td>H</td>
<td>47</td>
</tr>
<tr>
<td>24i</td>
<td>Cu²⁺</td>
<td>1-Ethylpropyl</td>
<td>H</td>
<td>97</td>
</tr>
</tbody>
</table>

9-Ethylcarbazole-3-aldehyde (26b). Typical Procedure.⁴⁴ To a stirred ice cold solution of 9-ethylcarbazole in DMF was added POCl₃. When the addition was over, the reaction was brought to room temperature and irradiated in a microwave oven under low power (30%) for 1.5 min (with time intervals of 30 sec). After work up, the crude product was purified by column chromatography and eluted with ethyl acetate–petroleum ether to give 9-ethylcarbazole-3-aldehyde in 89% yield.

b. Formylation of Arenes

The electron-donating effect of methoxy and methyl groups has a beneficial influence on the Vilsmeier-Haack reaction. Thus, 1,2,3-trimethoxy-5-methylbenzene (27), upon treatment with POCl₃ and DMF at 65 °C for 5 h, gave aldehyde 28, a key material for synthesis of coenzyme Q₁₀, in 95% yield (Scheme 12).⁴⁵

![Scheme 12](image)

Brenna et al.⁴⁶ found also that the formyl group was added regioselectively to the aromatic ring of (15,4S)-1-isopropyl-6-methoxy-4-methyl-1,2,3,4-tetrahydronaphthalene (29) by the Vilsmeier reaction, giving the corresponding aldehyde 30 (Scheme 13).

Azulene dicarbaldehydes are important intermediates for the preparation of azuliporphyrins. The substituted azulenes can be converted into dialdehydes under Vilsmeier-Haack
When the substituent at position 6 was a phenyl, a mixture of dialdehyde 32b and monoaldehyde 32c was obtained, while treatment of 6-tert-butylnazulene (31a) gave the related dialdehyde 32a (Scheme 14).

Dye-sensitized solar cells (DSCs) have attracted considerable interest for the conversion of sunlight into electricity.48,49 There are four main factors that affect the performance of the DSCs: anode,50,51 cathode,52 electrolyte,53–55 and photosensitive dyes.56 Among the metal-free organic dyes, triphenylamine (33) and its derivatives, such as 4-(diphenylamino)benzaldehyde (34) have displayed promising properties in the development of photovoltaic devices.57–59 Substituted triphenylamines 34, 35, 36 were synthesized via Vilsmeier-Haack reaction with different ratios of Vilsmeier reagent and substrate 33 (Scheme 15).60,61

Resveratrol has been suggested as a possible cancer chemopreventive agent on the basis of its inhibitory effects on tumor initiation, promotion, and progression.62 In order to discover novel anti-tumor agents with high efficiency, broad-spectrum activity and safety, Huang’s group63 designed and synthesized 4,6-dihydroxy-6-[2-(4-hydroxyphenyl) vinyl]benzaldehyde (38) and 4,6-dihydroxy-2-[2-(4-hydroxyphenyl)vinyl]benzene-1,3-dicarbalddehyde (39) by the reaction of resveratrol 37 with DMF and POCl3 in CH3CN as shown in Scheme 16. The results of cytotoxicity assays demonstrated that compounds 38 and 39 showed remarkable antitumor activity in vitro.

c. Formylation of C=O or C=C bonds

In 2006, Anabha et al.64 developed a valuable synthetic method, which used the Vilsmeier reagent to prepare 2-aryloyl-3,3-bis(alkylsulfonyl)acrylaldehydes 41 from aroylketene dithioacetals 40 in excellent yields (Scheme 17).
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Scheme 15

Scheme 16

Scheme 17
2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes 41. General Procedure.\textsuperscript{64} The Vilsmeier–Haack reagent was prepared by adding POCl\(_3\) (0.67 mL, 7 mmol) to DMF (6 mL, 70 mmol) at 0°C and stirring the mixture for 20 min at room temperature. The appropriate \(\alpha\)-oxoketene dithioacetal 40 (4.7 mmol) was added to this mixture, and the solution was stirred well for 10–16 h (monitored by TLC). The reaction mixture was poured into cold sat. K\(_2\)CO\(_3\) solution (70 mL) and was extracted with Et\(_2\)O (3 x 25 mL). The combined organic layers were washed with H\(_2\)O then dried, and the solvent was evaporated. The crude product obtained was filtered through a column of silica gel (EtOAc–hexane, 1:50).

Unsaturated \(\delta\)-lactones are found in a variety of biologically important natural products\textsuperscript{65–69} and are widely used as intermediates in organic synthesis.\textsuperscript{70–75} Liu \textit{et al.}\textsuperscript{76} have developed a useful method by which a formyl group was selectively introduced at the 5-position of the lactone ring of \(\delta\)-lactones 42 to give the polyfunctionalized unsaturated \(\delta\)-lactones 43 in high yields (Scheme 18).

Scheme 18

\[ \text{Scheme 18} \]

\textit{\(\alpha,\beta\)}-Unsaturated aldehydes 45 are key intermediates of indenols which have many biologically activities. In 2006, Singh and co-workers\textsuperscript{77} reported a new method for the synthesis of \(\alpha,\beta\)-unsaturated aldehydes 45 from alkenes 44 by Vilsmeier formylation in high yields (Scheme 19).

2-Phenylglyoxal hydrazones 47 were synthesized in a two-step sequence by Vilsmeier formylation of benzaldehyde \(N,\text{N}\)-dimethylhydrazones 46 followed by hydrolysis in aqueous NaHCO\(_3\) (Scheme 20).\textsuperscript{78,79}

Scheme 19

\[ \text{Scheme 19} \]
d. Formylation of Methylene Groups

Reger et al. developed a new and practical procedure for the formylation of active methylene groups (Scheme 21). The reaction between diethylacetals and the Vilsmeier reagent occurred smoothly at or below 80°C to give a mixture of ethoxyacroleins and dimethylaminoacroleins. The temperature at which the Vilsmeier reaction was carried out was found to be critical to the success of the reactions; when the reactions were performed above 80°C extensive decomposition occurred.

$N,N$-Dimethylaminomethylene-substituted cephems are functional intermediates which can be used in the synthesis of cephalosporin analogs. Vorona and co-workers reported an effective method for the preparation of these compounds based on introduction of the $N,N$-dimethylaminomethylene group at position 2 of the cephem nucleus of compounds as shown in Scheme 22.
e. Formylation of Amines

Formylation of amines usually provided N-formyl products. For example, 7-amino-2-substituted-[1,2,4]triazolo[1,5-c]pyrimidine-5(6H)-thiones 53 were subjected to Vilsmeier reaction to prepare amides 54 (Scheme 23).82

![Scheme 23]

Formylpyrazoles are very important intermediates and building blocks widely employed in the synthesis of diverse useful pyrazole derivatives in some fields of agrochemistry and biomedical chemistry.83 Luo’s group84 designed and synthesized two species of N-arylpyrazoles containing active amino group as shown in Scheme 24. Formylation at the 4-position of the N-arylpyrazoles 55 afforded pyrazole intermediates 56 in higher yield, but required more time than formylation at the 3-position of N-arylpyrazoles 57, as the electron-density at the 4-position of compounds 55 is greater than at the 3-position of compounds 57. However, because of the hindering effect of the imino group, formation of the formylation intermediate requires more time at the 4-position than at the 3-position.

![Scheme 24]
f. Formylation of Alcohols or Phenols

Generally, during a multistep synthesis of a natural product, several groups are first protected and then deprotected after the completion of the desired reactions. Formylation of alcohols is one of the most useful and versatile reactions for the protection of the hydroxy group in organic chemistry. Srivastava et al.\textsuperscript{85} provided a simple, mild, chemoselective method for the formylation of sec-sterols \textsuperscript{59} to esters \textsuperscript{60} by treatment with the Vilsmeier reagent (Scheme 25).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme25.png}
\end{center}

Scheme 25

The reaction of phenol derivatives with the Vilsmeier reagent affords the corresponding formic esters. Thus, in 1977, Morimura et al.\textsuperscript{86} developed a new and practical procedure for the preparation of esters \textsuperscript{62} from substituted phenols \textsuperscript{61} via the Vilsmeier reaction (Scheme 26).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme26.png}
\end{center}

Scheme 26

g. Other Formylations

Silyl ethers RO-SiR'\textsubscript{3} \textsuperscript{63} have become the most popular protecting groups for hydroxyl functions during complex multistep synthesis, especially when orthogonal protective/deprotective steps are required. In 2001, Lellouche’s group\textsuperscript{87} provided a powerful method, which transformed silyl ethers \textsuperscript{63} into formates \textsuperscript{66}. A likely mechanism is the addition of the Vilsmeier reagent to the silyl ethers \textsuperscript{63} to afford the intermediate oxonium cations \textsuperscript{64} (mixture of Cl\textsuperscript{-} and/or Cl\textsubscript{2}P(O)O- counteranions). Due to the formation of the thermodynamically strong Si-Cl/Si-O bonds (111.0 and 128.2 kcal, respectively), the
elimination of the neutral species $R'_{3}Si-X_{1}$ ($X_{1} = \text{Cl and/or } O(O)\text{PCl}_2$) generates *in situ* the related salts 65 (mixture of same counteranions), whose subsequent smooth hydrolysis affords the corresponding formates 66 (Scheme 27).

\[
\begin{align*}
\text{RO-SiR'_{3}} & \xrightarrow{\text{POCl}_3/DMF} \begin{array}{c}
\text{X'} \text{Si} \text{NMe}_2 \\
\text{X' = -Cl, Cl}_2\text{P(O)O or Cl}_2\text{P(O)O-}, \text{Cl}
\end{array} \\
\text{X'} & \xrightarrow{\text{Hydrolysis}} \begin{array}{c}
\text{RO-CHO} \\
\text{X'} = \text{Cl or Cl}_2\text{P(O)O}
\end{array}
\end{align*}
\]

**Scheme 27**

Andrade *et al.* reported a simple method for the preparation of formic esters 68 from the corresponding silyl ethers. Thus the monosaccharides 67 underwent formylation with 1.1 equiv. of the Vilsmeier reagent affording the 6-formic esters 68 in good yields (Scheme 28).

\[
\begin{align*}
\text{AcO} & \xrightarrow{\text{1. POCl}_3/DMF, 0^\circ \text{C to } 20^\circ \text{C}} \begin{array}{c}
\text{AcO} \\
\text{AcO} \\
\text{OMe}
\end{array} \\
\text{H} & \xrightarrow{\text{2. NaHCO}_3} \begin{array}{c}
\text{AcO} \\
\text{AcO} \\
\text{OMe}
\end{array}
\end{align*}
\]

**Scheme 28**

Shoji *et al.* found that the Vilsmeier formylation of the 1,1′-biazulene derivative 69 gave 3,3′-formyl-1,1′-biazulene (70) in 90% yield. This was the first example where the methylmercapto group behaved as a leaving group in electrophilic *ipso*-substitution in azulene chemistry (Scheme 29).

2. Other Acylations

Kreisberg *et al.* reported a simple, high-yield method for preparing of 2-(2-(4-(2-substituted)-1H-indol-3-yl)-2-oxoethyl)isoindoline-1,3-diones 72 using the Vilsmeier reagent. Thus, Vilsmeier formylation of 4-(2-substituted)-1H-indoles 71 at 95°C for 3 h,
followed by work-up with 2.5 M aqueous NaOH, gave the desired 2-(2-(4-(2-substituted)-1H-indol-3-yl)-2-oxoethylisoindoline-1,3-diones 72 (Scheme 30).

Pedras et al. synthesized 1-(1H-indol-3-yl)propan-1-one (74) by the reaction of indole (73) with N,N-dimethylpropionamide and POCl₃ as shown in Scheme 31.

Su and co-workers developed a new and practical procedure for the preparation of phenyl(1H-pyrrol-2-yl)methanone (76) from pyrrole (75) via Vilsmeier formylation (Scheme 32). Compared with POCl₃, bis-(trichloromethyl) carbonate (BTC) is safer and more convenient to handle and the yields of this reaction were also very good.

Photodynamic therapy is a relatively new modality for treatment of diseases that involve uncontrollable cell proliferation. In this regard, Nickel complexes 78
are important intermediates in the synthesis of chlorin-based photosensitizers. The 2-formylvinylation of nickel complexes 77 was performed by the Vilsmeier reaction with 3-dimethylaminoacrolein (3-DMA) in the presence of phosphoryl chloride followed by basic hydrolysis with saturated aqueous sodium carbonate solution to afford compounds 78 (Scheme 33).  

Enaminones are important intermediates in the synthesis of pyrazoles and pyrimidines. Kanishchev et al.\textsuperscript{95} described an effective method for the preparation of 1-dimethylamino-2- (p-tolylsulfonyl)polyfluoro-1-alken-3-ones 80 by the Vilsmeier-Haack-Arnold reaction from 1-tosyl-1,1 -dihydropolyfluoro-2-alkanone hydrates 79 (Scheme 34).
II. Chlorination Reactions

1. Reaction with Hydroxy Groups

The enantioselectivity achieved using transition metal catalysts can be strongly influenced by chiral bisoxazoline ligands. Catalysts such as 86, which utilize pyridine bisoxazoline ligands, have been employed in the preparation of chiral catalysts for asymmetric transformations. Totleben et al. reported an improved and safer method to prepare catalysts 86 on a near kilogram scale with good purity (Scheme 35). Thus, 2,6-pyridinedicarbonyl chloride (82) was prepared by treatment of inexpensive 2,6-pyridinedicarboxylic acid (81) with excess Vilsmeier reagent in CH₂Cl₂, affording 82 in yields of >94% as determined by in-process quantization. Subsequently, addition of a THF slurry of 83 to the Vilsmeier reagent in THF at 20–25°C gave 84 as the major product after 10–12 h. During the process, treatment of 83 with methanesulfonyl chloride and a variety of amine bases produced mixtures containing a number of unidentified impurities and small amounts of 85. The intermediate product 84, which is chlorinated using the Vilsmeier reagent, plays a key role in this process.

Oxalyl chloride is known to react with DMF under mild conditions to generate the corresponding Vilsmeier salt, which is the actual halogenating reagent. Encinas et al. reported a route that used oxalyl chloride as a chlorinating reagent for the preparation of glycosyl chlorides 88 from sugar hemiacetals 87 in the presence of DMF. Glycosyl
chlorides 88 (Scheme 36) were employed in order to synthesize complex O-glycosides in the presence of heavy metal salts or halide ions as promoters.

![Scheme 36](image)

Sucralose-6-acetate (90) is employed to synthesize sucralose as a key intermediate. Chen et al.\textsuperscript{98} reported a method to prepare sucralose-6-acetate (90) through chlorination of sucrose-6-acetate (89) using the Vilsmeier reagent, which was prepared through reaction of DMF with BTC (Scheme 37).

![Scheme 37](image)

Racemization of the amine-protected amino acid partner is the predominant problem in coupling two amino acids. Jass et al.\textsuperscript{99} reported that the temperature was the major factor in controlling racemization, and rapid formation of the N-trifluoroacetyl-protected amino acid chloride 92 at low temperature could be achieved conveniently from amino acid 91 by Vilsmeier chlorination (Scheme 38). In this reaction, the use of Vilsmeier reagent at or below $-10^\circ\text{C}$ led to a reasonably rapid reaction while providing excellent control over racemization.

![Scheme 38](image)
Lipshutz et al.\textsuperscript{100} described a concise series of reactions beginning with inexpensive trimethoxytoluene \textit{93} that very efficiently leads to chloromethylated \textit{para}-quinone \textit{95}, a key intermediate to Coenzyme \textit{Q}\textsubscript{10}. The final step in this sequence employed a modified Vilsmeier chlorination to convert the quinine alcohol \textit{94} into the corresponding chloride coupling partner \textit{95} (Scheme 39).

![Scheme 39](image)

Acyl azides are widely applied in heterocyclic synthesis. Sridhar et al.\textsuperscript{101} reported an efficient route wherein the Vilsmeier reagent and NaN\textsubscript{3} were used as reagents for the conversion of carboxylic acids \textit{96} to carboxylic acid azides \textit{97} (Scheme 40). The strength of this method lay in the \textit{in situ} acyl chloride generation by DMF/POCl\textsubscript{3} and the carboxylic acids \textit{96}, which then reacted with sodium azide to give the corresponding carboxylic acid azides \textit{97}.

![Scheme 40](image)

Amino-substituted pyrido[2,3-\textit{d}]pyrimidinediones have been found previously to bind to adenosine \textit{A}_1 and \textit{A}_2\textsubscript{A} receptors in micromolar concentrations. Bulicz and co-workers\textsuperscript{102} reported that most of the compounds investigated bore polar substituents (such as ethoxy-carbonyl groups) and basic amino functions, in order to improve their water-solubility. In this reaction, treatment of compound \textit{98} with POCl\textsubscript{3} in DMF under Vilsmeier conditions provided the desired 5-chloro derivative \textit{99}, while treatment of \textit{98} with phosphorus oxychloride without any solvent failed to give compound \textit{99} (Scheme 41).

2. Chlorination of Carbonyl Compounds

The formation of chloroalkenes \textit{102} as by-products or as main products in the Vilsmeier chloroformylation process has been reported occasionally.\textsuperscript{103,104} Lilienkampf et al.\textsuperscript{105}
described that these chloroalkenes arise from a nucleophilic substitution by chloride ion at the vinyl ether carbon of the iminium species 101 formed by electrophilic attack of the Vilsmeier reagent at the carbonyl group of the starting ketones 100. The formation of iminium species 101 liberates HCl which catalyzes the required enolization (Scheme 42).

Functionalized chromenes are important intermediates in the synthesis of several natural products and medicinal agents. Perumal et al. presented an effective method for the one-pot preparation of 2H-4-chlorochromenes 104 from 2′-hydroxychalcones 103 (Scheme 43). In this reaction, different ratios of POCl₃ in DMF were explored and it was found that 6 equiv. of POCl₃ in DMF was suitable for the preparation of 104. No chlorochromenes were obtained when the reaction was carried out in POCl₃ alone.

Tetrathiafulvalene (TTF) and its derivatives (TTFs) have been widely explored in both materials and supramolecular chemistry. Recently, Zhao and co-workers described their synthetic applications (Scheme 44). A series of α-chloro-vinylketene-(S,S)-acetals 106 was prepared in high yields from the corresponding α-acetylketene-(S,S)-acetals 105 via a Vilsmeier-Haack reaction under mild conditions. Subsequently, compounds 106 underwent
Recent Progress in the Use of Vilsmeier-Type Reagents

Scheme 44

**dehydrochlorination to give α-ethynylketene-(S,S)-acetals 107, which, through sequential oxidative coupling, afforded the desired products 108.**

Thioacetalization is a popular tool to protect carbonyl groups of aldehydes and/or ketones. Liu and co-workers\textsuperscript{111} reported the preparation of 2-[2-chloro-1-(1-chlorovinyl)allylidene]-1,3-dithiane (110) and its application in a thioacetalization reaction as a novel non-thiolic, odorless substitute for 1,3-propanedithiol. Through the Vilsmeier-Haack reaction, compound 110 was synthesized from 3-(1,3)-dithian-2-ylidenepentane-2,4-dione (109) in 99\% yield (Scheme 45).

Scheme 45

3. Chlorination of Amides

\( N \)-Heterocyclic compounds play an important role in the pesticide and pharmaceutical fields.\textsuperscript{112–115} Su \textit{et al.}\textsuperscript{116} reported the preparation of 2,3,5-substituted-[1,2,4]-thiadiazoles. In this reaction, the key intermediates, chlorimides 112, were synthesized from benzamides 111 by reaction with the Vilsmeier reagent (BTC/DMF). Therein, BTC reacts with DMF under mild conditions to generate the corresponding Vilsmeier salt as a chlorinating reagent (Scheme 46).
III. Chloroformylation Reactions

1. Reaction with Aryl Ketones

Pyrazole derivatives have been reported as pharmaceuticals for the treatment of cerebrovascular disorders\textsuperscript{117} and for their antiarrhythmic, sedative, and platelet anti-aggregating activities.\textsuperscript{118} Meesala \textit{et al}.\textsuperscript{119} reported an effective method to synthesize 3,6-di(pyrazol-4-yl)carbazoles from 3,6-diacetylcarbazoles. Thus, treatment of 9-methyl-3,6-diacetylcarbazole (113) with DMF/POCl\textsubscript{3} gave carbazolyl-bis-\(\beta\)-chloroacrolein (114) in 72\% yield. Condensation, followed by cyclization with hydrazine hydrate in acetic acid at reflux for 1h, gave dipyrazolylcarbazole 115 in 76\% yield (Scheme 47).
Acetylenes and ferrocenylacetylenes are highly versatile species.\textsuperscript{120} Schottenberger \textit{et al.}\textsuperscript{121} described a method for the synthesis of 4-ferrocenylphenylchloroacrolein (117) by chloroformylation of 4-ferrocenylacetophenone (116) with the Vilsmeier reagent; 116 is a key intermediate for the conversion to ferrocenylphenylacetylene (118) (Scheme 48).

Thieno[2,3-d]imidazolones 121 have an interesting fused heterocyclic species which can replace the benzimidazole moiety in pharmaceutical drugs.\textsuperscript{122–124} Kirsch \textit{et al.}\textsuperscript{125} developed a method that allows the preparation of functionalized thiophenes starting from the $\beta$-chloroacrolein moiety, as outlined in Scheme 49. Therein, it was found that only when 1,3-dibenzyl-2,4-imidazolidine (119) was heated for five hours at 90$^\circ$C with a 10-fold excess of the Vilsmeier-Haack reagent that the $\alpha$,$\beta$-di-substituted $\beta$-chloroacrolein 120 was formed in high yield.

Naphthalene derivatives are widely used in the synthesis of dyes, pesticides, and drugs.\textsuperscript{126} One of the convenient routes to naphthalene functionalized derivatives is by introduction of the ethynyl group into the side-chain of the naphthalene system,\textsuperscript{127} followed by the synthesis of highly reactive metal acetylides.\textsuperscript{128,129} Under Vilsmeier conditions, ketone 122 could be converted to (Z)-3-(2-naphthyl)-3-chloropropenal (124), which proved to be an important intermediate for the synthesis of copper, mercury and silver 2-naphthylacetylenides.\textsuperscript{130} The naphthylchloropropenal (124) was obtained upon treatment of the intermediate 123 with sodium acetate in aqueous solution (Scheme 50).
Thiophene and its benzo analogues find wide applications in pharmaceuticals, pesticides, polymers, liquid crystals and dyes. The utilization of benzo[b]thiophene3(2H)-one-1,1-dioxide (125) as an intermediate for the synthesis of a range of disperse dyes was explored. In this reaction, the active methylene next to the α-carbonyl and sulfone groups of 125 was subjected to the Vilsmeier-Haack reaction with the aim of generating the chloroformyl derivative 126 (Scheme 51). Because of the high lability of the chlorine atom in the intermediate 126, the ultimate product was hydroxyaldehyde 127.

2. Reaction with Alkyl Ketones

Kanomata and co-workers reported that (E)-2-chloro-cycloalk-1-enecarbaldehydes 129 could be used as intermediates for the synthesis of (vinylimino)phosphoranes 130 (Scheme 52). Vilsmeier-Haack formylation of cycloalkanones 128 afforded compounds 129 in good
yields; it was found that even milder reaction conditions worked very well for the synthesis of 129 where the reaction with excess amounts of DMF and POCl₃ at the 70°C led to the predominant formation of (Z)-129 in good to moderate isolated yields.

Diterpene heterocycles are key intermediates for heterocyclization. Tret'yakova et al.¹³⁸ reported a method for the synthesis of aldehyde 132, prepared according to Vilsmeier-Haack conditions, by reaction of ketone 131 with phosphoryl chloride in DMF (Scheme 53).

IV. Aromatization

1. Reaction with Lactams

The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. Therein, Park et al.¹³⁹ reported systematic replacement with a wide range of substituents within the pyrazole moiety. Thus, the pyrazolones 133 were subjected to Vilsmeier-Haack chloroformylation using DMF and excess POCl₃ to yield the corresponding 5-chloro-4-formylpyrazoles 134, which were key intermediates for the preparation of pyrazole oxime ethers. The latter were found to have promising antiproliferative properties against several kinds of human tumor cell lines (Scheme 54).

2. Reaction with α,β-Unsaturated Ketones

Aldehydes and ketones have played a primary role in perfumery and continue to be some of the leading choices in perfume composition.¹⁴⁰ Recently, Anzaldi et al.¹⁴¹ reported that the Vilsmeier reagent derived from N,N-dimethylformamide and phosphorus oxychloride reacted with carvone (135) to produce aldehydes in a one-step procedure.
(Scheme 55). In this reaction, the Vilsmeier formylation of carvone (135) afforded a mixture of the expected formylcyclohexadiene 137 together with indene derivative 136 and the 2-chlorobenzaldehyde 138 (Scheme 55). The formation of 136 can be understood as arising from further iminoalkylation on the inactivated double bond of the isopropenyl group, whereas benzaldehyde 138 arises presumably from the oxidative aromatization of 137.

3. Reaction with Diketones

The utilization of Vilsmeier salts derived from bis-(trichloromethyl) carbonate (triphosgene, BTC) and N,N-dimethylformamide (DMF) has been explored extensively.\textsuperscript{142,143}
Su et al.\textsuperscript{144} reported the aromatization of substituted 3-benzoylpentane-2,4-diones 139 with the Vilsmeier reagent derived from BTC/DMF to give substituted 3-benzoyl-2,4-dichlorobenzaldehydes 140 in moderate yields (25–66\%) (Scheme 56). It was found that the yields were affected strongly by the substituents on the aromatic ring. Thus, substrates with strong electron-donating groups provided higher yields than those with electron-withdrawing groups.

\[
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{O} \\
\text{O} \\
\text{BTC/DMF (3.0 equiv)} \\
\text{CH}_2\text{Cl}_2, \text{reflux, 6h} \\
\text{O} \\
\text{Cl} \\
\text{CHO} \\
\end{array}
\]

\textit{Scheme 56}

V. Cyclization

The Vilsmeier-Haack reaction provides a facile entry into large numbers of aromatic and heteroaromatic systems. The reaction of aromatic substrates and aliphatic substrates with chloromethyleneiminium salts is highly versatile. The broad synthetic utility of the halomethyleniminium salts leads to multiple iminoalkylations in the presence of excess reagent followed by cyclization to afford aromatic or heterocyclic compounds.

1. Intramolecular Cyclization

a. Cyclization of Ketones

Recently Tang and co-workers\textsuperscript{145} reported a convenient and efficient method for the synthesis of substituted pyran-4-ones 142 and naphthaldehydes 143, when 1-cyclopropyl-2-arylethanones 141 were treated with the Vilsmeier reagent at different temperatures. Substrates bearing electron-withdrawing groups on the benzene ring required higher reaction temperatures (Scheme 57).

A plausible mechanism involving sequential enolization, ring-opening, haloformylation, and intramolecular nucleophilic cyclization or Friedel-Crafts alkylation reactions was proposed in the original text.

Vilsmeier-Haack reaction of substituted phenylacetones 144 led to the formation of conjugated iminium salts 145 which, upon aqueous basic work-up, afforded 3-formyl-4-pyrones 146 or, on ammonium acetate-induced cyclization, provided 5-aryl-4-chloronicotinaldehydes 147 in good yields (Scheme 58).\textsuperscript{146} The tentative mechanism indicated that substrates 144 were easily transformed into their enol intermediates 145 with the hydrochloric acid produced by the Vilsmeier reagent at first.

Nohara and co-workers\textsuperscript{147,148} reported that 3-cyano-4-benzopyrones 151 were generally synthesized in three steps starting from 2-hydroxyacetophenones 148 (Scheme 59). However, this method suffered from several disadvantages such as the necessity for
isolating the intermediate 3-formylbenzopyrones 149 and the corresponding oximes 150, long reaction periods, and low overall yields.

Reddy’s group reported an efficient one-pot synthesis of 3-cyano-4-benzopyrones employing 2-hydroxyacetophenones as substrates under Vilsmeier conditions. This procedure, owing to its considerable synthetic versatility and generality of preparation, is worthy of note (Scheme 60).

Scheme 57

Scheme 58
Mathew and co-workers\textsuperscript{150} presented a facile and high-yield regioselective method for the synthesis of annulated pyrrole \textsuperscript{153} by iminoalkylation of ketene-\textit{N,S}-acetal \textsuperscript{152}, followed by intramolecular cyclization in the presence of the Vilsmeier-Haack reagent (Scheme 61). Compared with the classical method using DBU as reagent to obtain the annulated pyrrole \textsuperscript{153} (56\%), the protocol employing the Vilsmeier reagent provided higher yields.

Akila \textit{et al.}\textsuperscript{151} conducted a systematic investigation of the one-pot conversion of 2′-aminochalcones \textsuperscript{154} into quinoline derivatives \textsuperscript{156} in 68–85\% yields under Vilsmeier conditions. The reaction proceeded through \textit{N}-formylation followed by cyclization to give intermediates \textsuperscript{155}, which, upon hydrolysis, furnished the corresponding dihydroquinolines \textsuperscript{156} as shown in Scheme 62. The scope of the reaction has been extended to the synthesis of quinolines \textsuperscript{158} themselves by replacing 2-aminochalcones \textsuperscript{154} with 2-azidochalcones \textsuperscript{157}. The reaction may be proceeding through initial cyclization followed by reductive elimination of nitrogen as proposed in Scheme 63.
Scheme 62

Scheme 63

Scheme 64

Scheme 65
Table 2
Synthesis of Amino-substituted pyrido[2,3-d]pyrimidinediones 161

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Y</th>
</tr>
</thead>
</table>
| 161a  | \(\begin{array}{c}
\text{NH} \\
\text{苯基}
\end{array}\) | H  |
| 161b  | \(\begin{array}{c}
\text{N} \\
\text{CH}_3
\end{array}\) | H  |
| 161c  | \(\begin{array}{c}
\text{NH}
\end{array}\) | H  |
| 161d  | \(\begin{array}{c}
\text{N}
\end{array}\) | H  |
| 161e  | \(\begin{array}{c}
\text{NH}_2
\end{array}\) | H  |
| 161f  | \(\begin{array}{c}
\text{N}
\end{array}\) | H  |
| 161g  | \(\begin{array}{c}
\text{N}
\end{array}\) | H  |

Bulicz's group\(^{152}\) carried out the introduction of the keto function into substrate 159 followed by ring closure using the Vilsmeier reagent. The desired products, amino-substituted pyrido[2,3-d]pyrimidinediones 161, were obtained by reaction of amines with intermediate 160 (Scheme 64). Amino-substituted pyrido[2,3-d]pyrimidinediones 161 have been found previously to bind to adenosine A\(_1\) and A\(_{2A}\) receptors in micromolar concentrations (Table 2).

b. Cyclization of Amides

The case of oxazolines 163 as chiral ligands for the development of asymmetric catalysis has attracted widespread attention.\(^{153}\) Wuts et al.\(^{154}\) reported that the Vilsmeier-Haack reagent could be used to cyclize amido alcohols 162 to afford oxazolines 163 as well as the chloro by-products 164. The chlorides 164 were readily converted into oxazolines 163 upon treatment with DBU (Scheme 65). This methodology also has great benefits due to the low cost of the Vilsmeier reagent and the ease with which the reaction by-products are removed by extraction.

N-Acetylglycine (165) also can be converted by the Vilsmeier reagent into the poly-functional pyrrole (166), as shown in Scheme 66.\(^{155}\)

Halogenated pyridin-2(1H)-ones are useful intermediates for the synthesis of organic compounds with diverse bio-, physio-, and pharmacological activities in numerous natural products.\(^{156,157}\)
During the course of Dong et al.’s study of the Vilsmeier reactions, he developed a facile, one-pot synthesis of halogenated pyridin-2(1H)-ones from cyclopropyl amides 167,24 enaminones 168,158 cyclic enaminones 169159 and β-oxo amides 170160 under Vilsmeier conditions (Schemes 67–70). A mechanism involving sequential halogenation, formylation and intramolecular nucleophilic cyclization has been proposed. These protocols are very attractive due to simple execution, inexpensive reagents, and high yields.

Scheme 67

Scheme 68

Scheme 69

Scheme 70

\[ \text{R}^1 = \text{aryl, alkyl; } \text{R}^2 = \text{alkyl, H; } \text{X} = \text{Br, Cl} \]
Subsequently, Chen et al.\textsuperscript{25} developed a novel and efficient route for the preparation of 4-halogenated \textit{N}-substituted 2(1\textit{H})-pyridinones 172 via a one-pot domino process using readily available \textit{\alpha}-acetyl-\textit{\alpha}-carbamoyl ketene dithioacetals 171 with Vilsmeier reagents (Scheme 71). Pyrido[2,3-\textit{d}]pyrimidines are a type of annulated uracil, which have received considerable attention because of a wide range of biological activities.\textsuperscript{161,162} Treatment of Vilsmeier reagent with 2-amino-3-carbamoyl-5,6-dihydro-4-pyridones 173 provided highly functionalized dihydropyrido[2,3-\textit{d}]pyrimidines 174 and 175, respectively, via a [5 + 1] annulation strategy (Scheme 72). Compounds 174 were generated through a series of transformations, including acid-catalyzed elimination of dimethylamine, chlorovinylation and formylation. Formation of compounds 175 occurred by \textit{N}-formylation, dehydration, nucleophilic attack of dimethylamine at the carbon atom and subsequent aromatization.

Microwave irradiation resulted in compounds 177 with good yields (90–95\%). A similar reaction was reported by Aghera’s group.\textsuperscript{168} Thus, the pharmacologically active quinolines 179 (SDQ-1 to SDQ-3) were synthesized in good yields through the cyclization reaction of symmetric double acetamides 178 (SDA-1 to SDA-3) with POCl\textsubscript{3}/DMF (Scheme 74).
The Vilsmeier-Haack formylation has become one of the most common methods of cyclization of iminium species to aromatic compounds or heterocycles and the Vilsmeier-Haack acetylation also can produce aromatic compounds or heterocycles via cyclization of iminium species.\textsuperscript{23,169}

Rajanna’s group\textsuperscript{170} reported the Vilsmeier-Haack acetylation of aromatic compounds by employing POCl\textsubscript{3}/N,N-dimethylacetamide (DMA) as acetylating reagent in the presence of micelles (Scheme 75). They applied this methodology to one-pot synthesis of 2-chloro-3-acetyl-quinolines \textsuperscript{181} from acetanilides \textsuperscript{180}. There was a remarkable improvement in the yields of products formed via cyclization in the presence of micelles, \textit{i.e.} CTAB (cetyltrimethylammonium bromide), SDS (sodium dodecylsulfate) and TX (Triton-X-100), under reflux conditions.

In some cases, the protocol employing BTC/DMF as Vilsmeier reagent provides mild reaction conditions and higher yields than other methods employing POCl\textsubscript{3}/DMF. For example, Gangadasu’s group\textsuperscript{171} reported that chloronicotinaldehyde \textsuperscript{183} was prepared in higher yields by the cyclization of enamide \textsuperscript{182} when treated with 7.0 equiv. BTC/DMF.
compared with the classical method of using POCl₃ for the formation of Vilsmeier reagent. The use of 2.5 equiv. of the Vilsmeier reagent led to a lower yield of chloronicotinaldehyde 183, and 2-chloro-5-methylpyridine (184) was the major product (Scheme 76).

c. Cyclization of Aromatic Hydrazones

Pyrazole derivatives have been reported as pharmaceuticals for the treatment of cerebrovascular disorders¹⁷² and for their antiarrhythmic, sedative and platelet anti-aggregating activities.¹⁷³ Hydrazones are easily accessible starting materials yielding pyrazoles upon treatment with the Vilsmeier reagent.

Thus, Sridhar et al.¹⁷⁴ reported that 1-¹⁴H-pyrazole-4-carboxylic acid esters 186 could be synthesized via ring closure of 2,4-dinitrophenylhydrazones of β-ketoesters 185 using the Vilsmeier reagent (POCl₃/DMF) both in conventional and microwave methods (Scheme 77). Compared with conventional methods, the main advantages of the microwave approaches were good yields and relatively by short reaction times. When the reaction mixture was subjected to microwave irradiation on a SiO₂ support, even better yields were obtained. The chloromethyleniminium ion was responsible for the cyclization, furnishing the pyrazole
when it reacted selectively with hydrazones containing an active methylene carbon groups. No further addition of the Vilsmeier complex occurred even if an excess of reagent was employed.

**1H-Pyrazole-4-carboxylic Acid Esters 186. General Procedure (Method III).** After dropwise addition of POCl₃ (0.003 mol) to an ice-cold solution of 0.001 mol of hydrazone in 4 ml of dry DMF, the reaction mixture was slurried with SiO₂ (60–120 mesh). The slurry was subjected to microwave irradiation in a domestic microwave oven (BPL microwave cooking system model BMO-7007) for about 3 min with a pulse of 20 s each at 70% power corresponding to 210 Watts. Finally, the slurry was washed with ice-cold water, allowed to settle and the supernatant washings were collected. The process was repeated 3 to 4 times and the combined water washings were filtered to obtain the crude pyrazole which was recrystallized with chloroform to yield the pure product.

Chornous et al. reported a method for the synthesis of 1-aryl-4-formylpyrazoles via formylation with subsequent intramolecular cyclocondensation of acetaldehyde N-arylhydrazones using the Vilsmeier reagent generated in situ from POCl₃ and DMF (Scheme 78). When the chloromethyleniminium ion reacted selectively with hydrazones containing an active methyl group, 4-formylpyrazoles were obtained via double formylation.

In a similar manner, a practical procedure for the preparation of steroidal pyrazoles from the Vilsmeier reagent and semicarbazones is shown in Scheme 79. The steroidal pyrazoles were found to possess antimicrobial, antiinflammatory, hypotensive, hypocholesterolemic and diuretic activities.
d. Cyclization of Oximes

The pyrazole motif makes up the core structure of numerous biologically active compounds that find a wide range of applications in the pharmaceutical and agrochemical industries. Substituted 1H-pyrazoles 192 were obtained by ring closure of cyclopropyl oximes 191 with the Vilsmeier reagent (POCl₃/DMF) in 38–56% yields (Scheme 80). A plausible mechanism involving sequential ring-opening, chlorovinylation, and intramolecular azacyclization has been proposed.

![Scheme 80]

\[
\begin{align*}
\text{191} & \xrightarrow{\text{POCl}_3/\text{DMF}} \text{192} \\
\text{191} & \xrightarrow{\text{DMF}} \text{192}
\end{align*}
\]

(38-56%)

e. Cyclization of Nitriles

Cuccia and co-workers studied focused on the reaction of acetophenone cyanoimines 193 with the Vilsmeier reagent to target 4-phenyl-2-chloropyrimidines 195 in acceptable yields (Scheme 81). The reaction presumably proceeds by addition of the Vilsmeier reagent to the active methyl group and HCl to the nitrile to afford the intermediates 194, followed by intramolecular cyclization. Substrates containing electron-donating groups enhance the reaction rate.

![Scheme 81]

\[
\begin{align*}
\text{193} & \xrightarrow{\text{POCl}_3/\text{DMF}} \text{194} \\
\text{194} & \xrightarrow{} \text{195}
\end{align*}
\]

(22-58%)

The Vilsmeier-Haack cyclization is one of the most useful, general methods employed for the synthesis of substituted 2-chloro-3-cyanopyridines 197 from 2-propylidenemalonitriles 196, however, the yields of the reaction are low (Scheme 82).
Substituted 2-chloro-3-cyanopyridines 197. General Procedure.\textsuperscript{185} To a flask containing 10 mmol of alkene 196 and 20 mmol (3.0 g) of POCl\textsubscript{3} in DMF (10 ml), phosphate catalyst (NP or KF/NP, 0.1 g) was added and the mixture was stirred at room temperature for 30 min and the bath temperature was slowly raised to 70–80°C. The reaction mixture was heated during 3 h and then washed with water. The solid was filtered off and the catalyst washed with dichloromethane. After concentration of the filtrate under reduced pressure the residue was subjected to chromatography or recrystallisation (n-hexane/ethyl acetate) leading to the Vilsmeier–Haack adduct as a solid.

f. Other Cyclizations

Lyakhovnenko \textit{et al}.\textsuperscript{186} have reported that the reaction of the amines 198 with DMF or with diethylamides of other carboxylic acids in the presence of POCl\textsubscript{3} gives high yields (82–88\%) of 2,3\textsuperscript{′}-biquinolines 199 (Scheme 83). Comparing this method with the alternative approach involving reaction of the amines 198 with acid chlorides and subsequently treatment with POCl\textsubscript{3}, this protocol provided higher yields of compounds 199.

The trans-DOTTAD aldehydes 201 were formed by Vilsmeier formylation (followed by cyclization and N-demethylation) of 2,5-dimethyl-3,6-dicarboxypyrazine (200) (Scheme 84).\textsuperscript{187} The reaction was conducted with preformed reagents derived from the corresponding dialkylformamides using POCl\textsubscript{3} as a solvent.
The bis-Vilsmeier reagent derived from \(N,N'\)-dimethyl-\(N,N'\)-diformyl-\(p\)-phenylene-diamine (202) reacts with 4-substituted \(N,N\)-dimethylanilines 203 to yield dibenzo[b,b']benzo[1,2-f:4,5-f']bis[1,5]diazocines 204 in a single step (Scheme 85). Due to the incomplete conversion of compound 202 into the bis-Vilsmeier reagent, in some cases the half-cyclized products 205 were also obtained.\(^{188}\)

5-Deazaflavins 207 have attracted great interest because of their biological activities and high activity toward tumor cells.\(^{189}\) Various novel 10-alkyl-2-deoxo-2-methylthio-5-deazaflavins 207 were synthesized in 71–99% yield from 6-(\(N\)-monoalkylanilino)-2-methylthiopyrimidin-4(3\(H\))-ones 206 using the Vilsmeier reagent (Scheme 86).\(^{190}\)
2. Intermolecular Cyclization

Many compounds containing the β-lactam nucleus have high antibiotic activity.191–193 A widely used method for the construction of the β-lactam ring is via the [2+2] cyclocondensation of ketenes to imines, a process known as the Staudinger reaction.194

Jarrahpour and co-workers195 described the first example using the Vilsmeier reagent for the one-step Staudinger reaction of substituted acetic acids 209 and imines 208 (Scheme 87). In this method, the ketenes were formed from the carboxylic acids, which proved quite practical, since the starting carboxylic acids could be easily handled and stored.

Thomas et al.196 have demonstrated that the cyclization of the α-hydroxyketenedithioacetals 211 (obtained by 1,2-nucleophilic addition to α-oxoketenedithioacetals 210) in the presence of the Vilsmeier reagent and ammonium acetate leads to the formation of substituted 2-methylsulfanyl-4-arylpyridines 212 (Scheme 88). A probable mechanistic pathway leading to the formation of 212 involves the dehydration and iminoalkylations of α-hydroxy ketenedithioacetals induced by the presence of the Vilsmeier reagent.

Asokan et al.197 have reported an example of the Vilsmeier-Haack reaction as a three-component reaction for the synthesis of nicotinonitriles 215 from acetophenones and benzylacetones 213. The mechanism for the formation of pyridines is presumed to involve one-pot iminoalkylation of the enolizable ketones followed by sequential condensation with malononitrile (214), cyclization and aromatization under Vilsmeier-Haack reaction conditions (Scheme 89).

A novel one-pot route to 2(3H)-benzimidazolones 217, 2(3H)-benzoxazolones 218 and 2(3H)-benzothiazolones 219 was developed via rearrangement and cyclization of ortho-substituted benzoic acids 216 by the addition of ammonium azide and the Vilsmeier complex (Scheme 90).198

VI. Rearrangements

Su and coworkers reported the synthesis of amides or nitriles via the Beckmann rearrangement reaction initiated by BTC/DMF, as shown in Scheme 91.199 A possible mechanism
indicated that the adducts 221 afforded amides 222 upon hydrolytic work-up in the case of ketoximes and afforded the nitriles 223 directly in the case of aldoximes. Experimental results have shown that aryl ketoximes are more reactive than alkyl ketoximes because electron-donating groups on the aromatic ring facilitate the reaction while electron-withdrawing groups retard it. Moreover, aromatic aldoximes provided the corresponding nitriles in excellent yields.

### VII. Dehydration

Andersson et al.\textsuperscript{200} reported an effective method for the formation of dienal oximes 225 derived from pyridine N-oxides 224 and a mild \textit{in situ} transformation to conjugated nitriles 226 (Scheme 92). They found that the corresponding nitriles 226a–c were accessible in 74\%, 49\% and 64\% yields, respectively, \textit{via} a mild \textit{in situ} transformation of the oxime using the Vilsmeier-Haack salt.


VIII. Other Reactions

Dimethylformamidrazones 228 have been employed for the construction of various heterocycles.\textsuperscript{201–205} A simple, direct method for preparation of dimethylformamidrazones starting from the corresponding hydrazines 227 has been developed in 69–99\% yields (Scheme 93).\textsuperscript{206} In this reaction, a novel, versatile reagent 229 was utilized as a stable Vilsmeier reagent analogue. When the scope of substrate was extended to hydrazides 230, 1,3,4-oxadiazoles 231 were obtained as pure compounds in 95–98\% yields (Scheme 94).
\[ \alpha\text{-Methylene carboxylic acid derivatives } 232 \text{ are converted by the Vilsmeier reagent (POCl}_3/\text{DMF) into vinamidinium chloride salts } 233, \text{ which are water sensitive and difficult to purify from the reaction mixture. In the work of Davies’s group, vinamidinium hexafluorophosphate salts } 234 \text{ were prepared in moderate to excellent yields by adding aqueous hexafluorophosphoric acid to the reaction mixture containing the vinamidinium chloride salts (Scheme 95).} \text{ To our knowledge, the utilization of vinamidinium hexafluorophosphate salts has not been reported previously, and such salts may prove to be a potential substitute for the perchlorates that frequently have undesirable thermal and shock-sensitive properties.} \]

**IX. Conclusions and Outlook**

As a classical synthetic reagent, the Vilsmeier reagent has found very wide application in organic synthesis. Over the past ten years, the Vilsmeier reagent has been used in organic synthesis in concert with new techniques such as microwave irradiation, and reaction in...
the solid state. Because of its potential for phosphorus pollution, the Vilsmeier reagent has
been improved also to a more environmentally friendly species by employing BTC instead
of inorganic acid halides. Our laboratory is contributing to those advances. Extensive
application of Vilsmeier reagent-based chemistry to industrial production can be expected
in the near future.

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