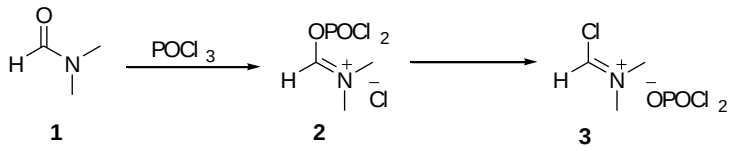
Chapter 2

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 $POCl_3$.[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).



1 **2** **3**

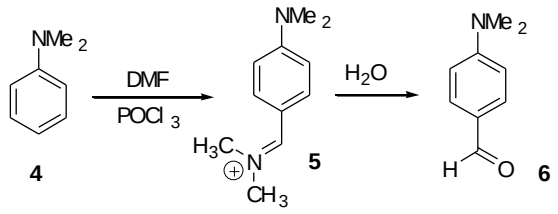
Scheme 2.1

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.

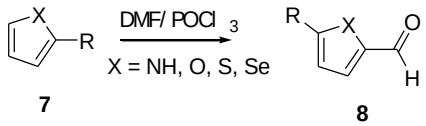
2.2 The Vilsmeier-Haack reactions of aromatic compounds

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).[2a] Anthracenes, naphthalenes and other polycyclic aromatic compounds also undergo facile formylation.



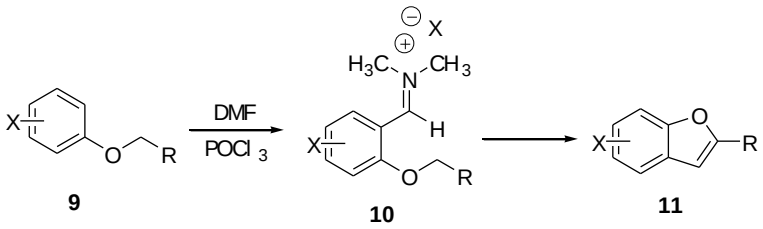
Scheme 2.2

Heterocyclic compounds like pyrrole, furan, thiophene and selenophene derivatives also yield, aldehyde derivatives **8** in the Vilsmeier-Haack reaction (Scheme 2.3).[3] Annulated heterocycles like indoles are also amenable to formylation reactions.[3c]



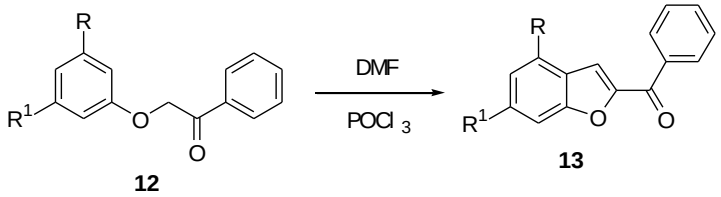
Scheme 2.3

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).[4]



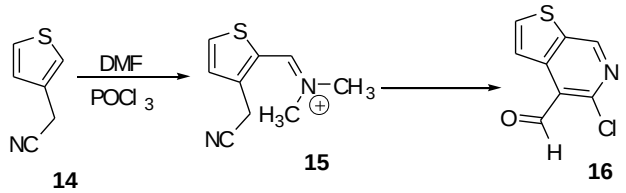
Scheme 2.4

A versatile synthesis of benzofurans **13** was accomplished by the Vilsmeier-Haack reaction of the phenoxyacetophenones **12** (Scheme 2.5).[5] However the Vilsmeier-Haack reaction of simple phenoxyacetone affords N,N-dimethylamino substituted pentadienaldehydes in good yields.



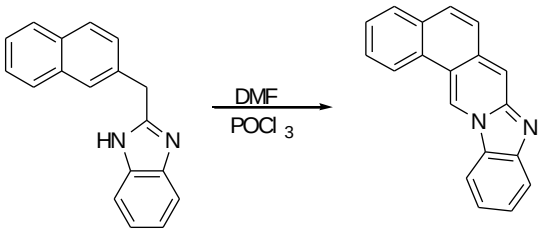
Scheme 2.5

Koyama *et al* reported the synthesis of thienopyridine derivative **16** from 3-cyanomethylthiophene **14** *via* an intermediate iminium salt **15** (Scheme 2.6).[6]



Scheme 2.6

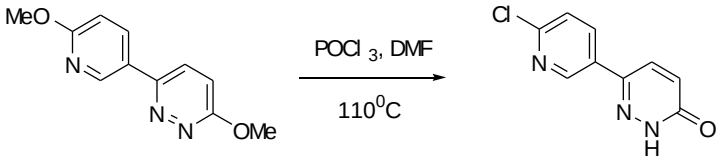
Similarly Vilsmeier-Haack reaction of benzimidazole derivatives **17** leads to the synthesis of benzimidazo[1,2-b]isoquinoline derivatives **18** instead of the expected acenaphthalene derivatives (Scheme 2.7).[7]



17 18

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]



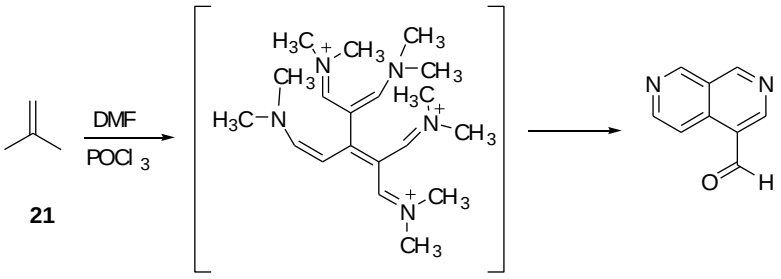
19 20

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]

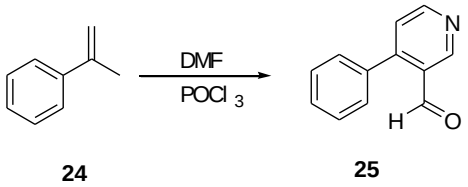
2.3 The Vilsmeier-Haack reactions of alkene derivatives

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]



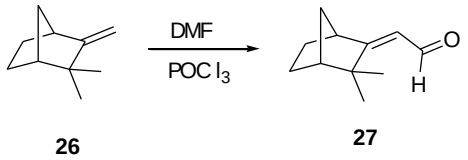
Scheme 2.9

Similarly, 2-phenylpropene affords corresponding nicotinaldehydes **25** in good yields (Scheme 2.10).[10]

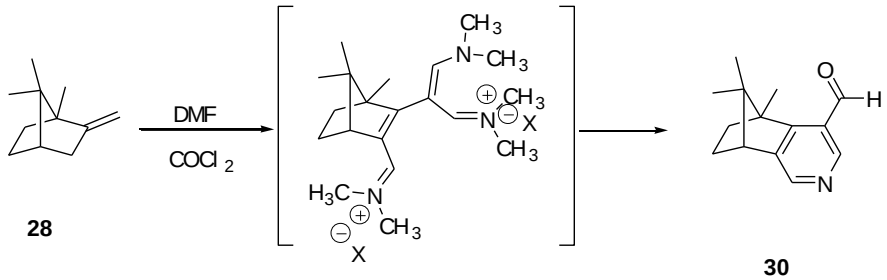


Scheme 2.10

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).[11]

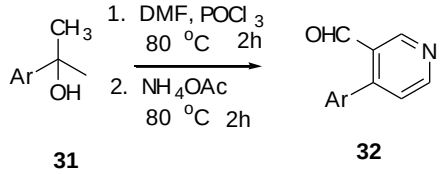


Scheme 2.11



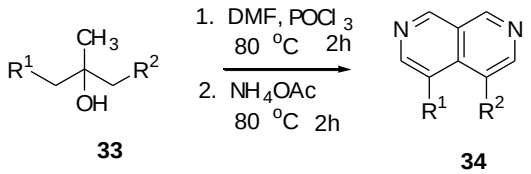
Scheme 2.12

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 **31** derived from acetophenones undergo multiple iminoalkylation reaction followed by reaction with ammonium acetate to afford substituted pyridines **32** (Scheme 2.13).[12] In this reaction the iminoalkylation is considered to occur on an alkene intermediate.



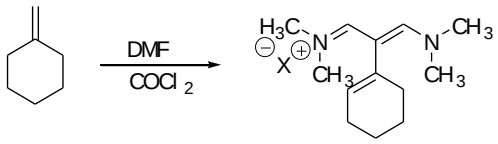
Scheme 2.13

When the same protocol was extended to aliphatic or alicyclic carbinols **33**, [2,7]naphthyridine derivatives **34** were obtained (Scheme 2.14).[12]



Scheme 2.14

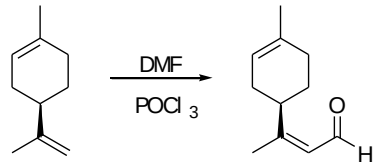
In the case of alkenes like methylenecyclohexene **35**, the reaction affords **36** as perchlorate salts (Scheme 2.15).[11]



35 36

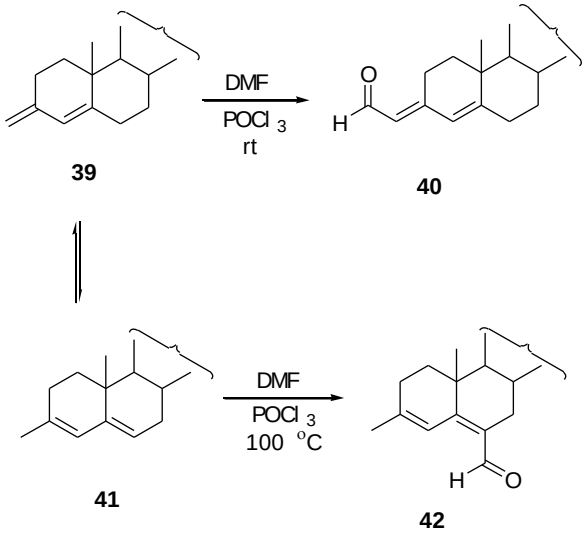
Scheme 2.15

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) [13,14]



37 38

Scheme 2.16

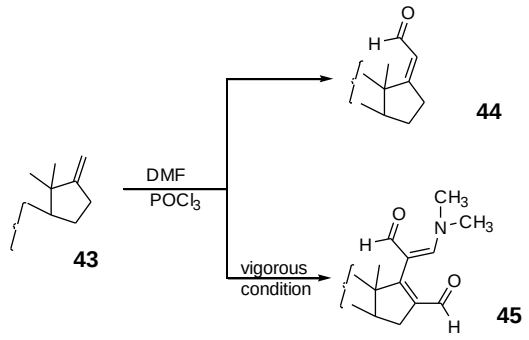


39 40

41 42

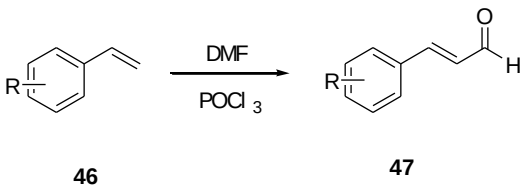
Scheme 2.17

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).[15]



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).[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.[17]



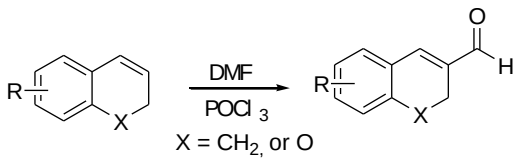
Scheme 2.19

Similar to styrenes, vinylcyclopropane **48** also undergoes Vilsmeier-Haack reaction to afford monoformylated product **49** (Scheme 2.20).[18]

48 **49**

Scheme 2.20

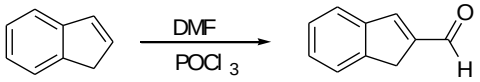
In the literature there are reports on the Vilsmeier-Haack reactions of 1,2-dihydronaphthalenes[19] and chromene[20] derivatives to afford corresponding enaldehydes **51** (Scheme 2.21).



50 **51**

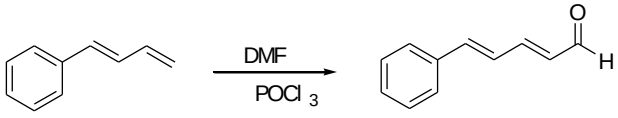
Scheme 2.21

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) [21, 22, 23].



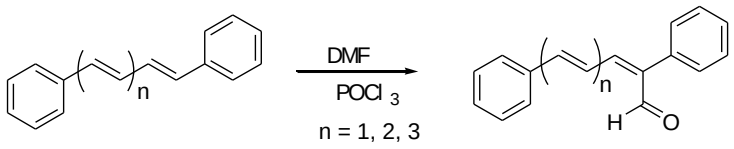
52 **53**

Scheme 2.22



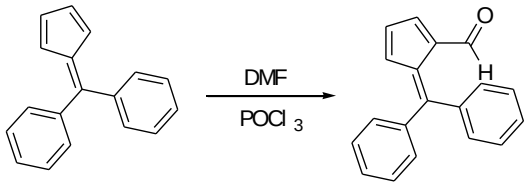
54 **55**

Scheme 2.23



56 **57**

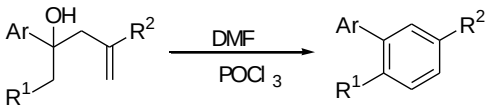
Scheme 2.24



58 **59**

Scheme 2.25

In several cases, the products of monosubstitution undergo polysubstitution reactions and afford in most cases, cyclized products.[24] For example, the alcohol derivative **60** on Vilsmeier-Haack reaction afforded biphenyl derivatives **61** in 30-98% yield (Scheme 2.26).[24b] This is a useful method for the synthesis of a variety of biphenyls.

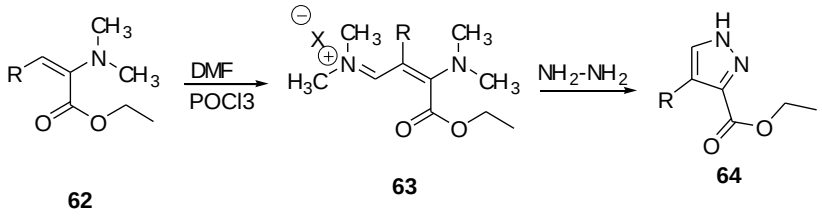


60 **61**

Scheme 2.26

Numerous alkene derivatives like enamines,[25] enamides,[26] encarbamates,[27] enol ethers,[28] enol acetates *etc.* also undergo iminoalkylation under Vilsmeier-Haack reaction condition. Electrophilic substitution of these alkene derivatives occurs readily, yielding iminiuim salts that have found substantial use in synthesis. For example, enamine derivative **62**, when treated with chloromethyleneiminium salt, gives alkyl substituted

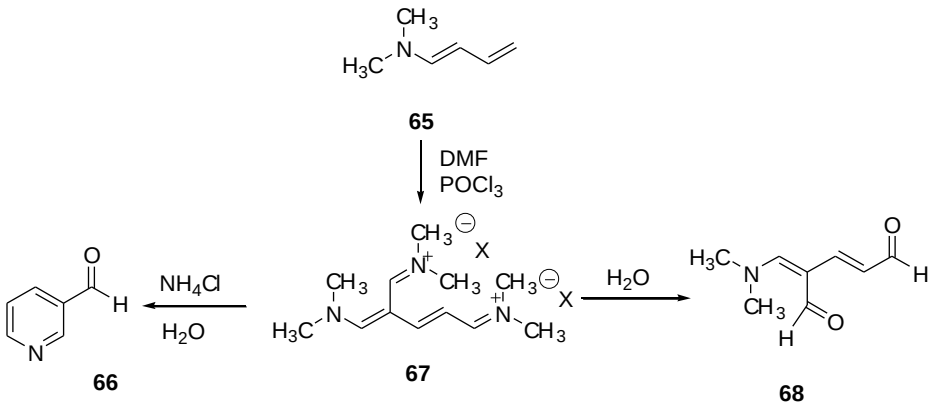
iminium salt **63** which on treatment with hydrazine affords pyrazole derivative **64** in 18-64% yields (Scheme 2.27).[25a]



62 **63** **64**

Scheme 2.27

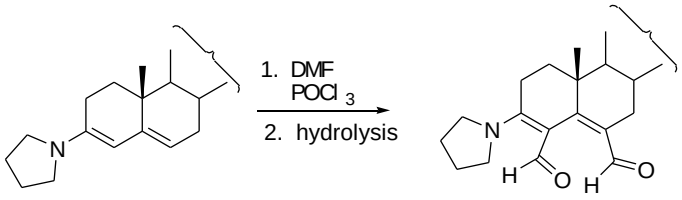
The dienamine **65** afford the corresponding iminium salts **67** resulting from disubstitution in the presence of Vilsmeier-Haack reagent. The iminium salt **67** on hydrolysis affords dialdehyde derivatives **68** while on treatment with aqueous ammonium chloride solution affords pyridine-3-carbaldehyde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



65 **66** **67** **68**

Scheme 2.28

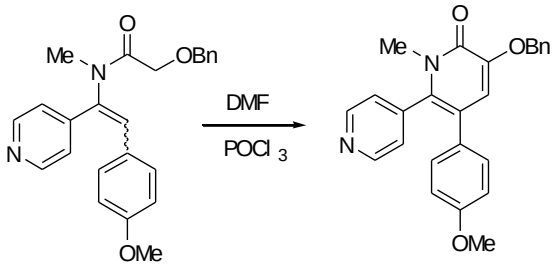
Similarly the dienamine **69** on reaction with iminium salts affords the dienedialdehyde **70** (Scheme 2.29).[25c]



69 **70**

Scheme 2.29

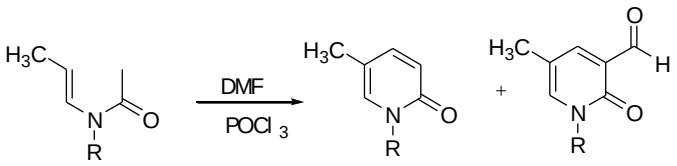
A convenient iminium salt mediated synthesis of 2-pyridone derivative **72** was achieved by the Vilsmeier-Haack formylation followed by cyclization of the acylenamine **71** (Scheme 2.30).[25d]



71 **72**

Scheme 2.30

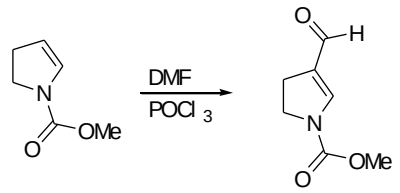
Several enamides have been used as precursors for the synthesis of pyridone derivatives. The enamides **73** on reaction with iminium salt afford N-substituted 2-pyridone derivatives **74** and pyridine-3-carbaldehyde derivative **75** in 14-69% yield (Scheme 2.31).[26a]



73 **74** **75**

Scheme 2.31

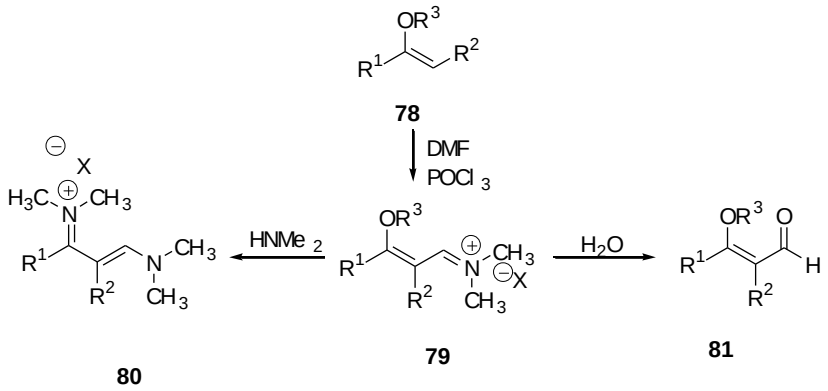
Enecarbamates such as **76**, give formylation products **77** on treatment with Vilsmeier-Haack reagent (Scheme 2.32).[27b]



76 **77**

Scheme 2.32

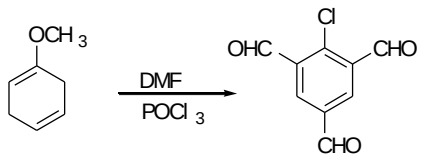
Enol ethers represented by the general structure **78** undergo iminoalkylation to give iminium salt **79**, which on hydrolysis affords β-ethoxyacrolein derivatives **81** and on amination using dimethylamine affords synthetically useful vinylamidinium salts **80** (Scheme 2.33).[28]



78 **80** **79** **81**

Scheme 2.33

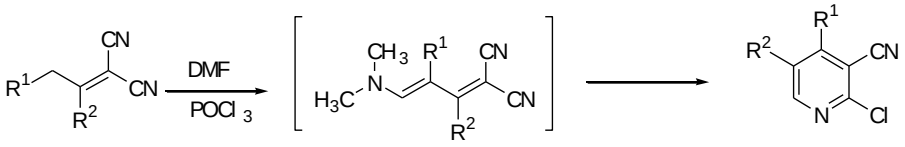
An interesting transformation of 1-methoxycyclohexa-3,6-diene **82** to chlorobenzene-2,4,6-tricarbaldehyde **83** under Vilsmeier-Haack reaction condition also have been reported (Scheme 2.34).[29]



82 **83**

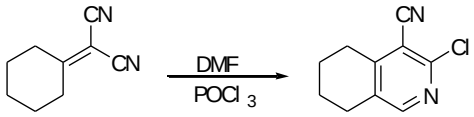
Scheme 2.34

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).[30] In these reactions the iminoalkylated intermediates undergo cyclization reaction to afford the corresponding nicotinonitriles.



84 **85** **86**

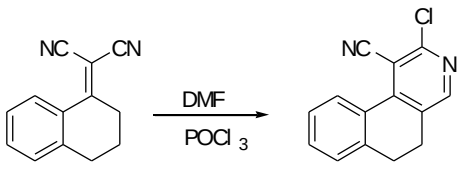
Scheme 2.35



87 **88**

Scheme 2.36

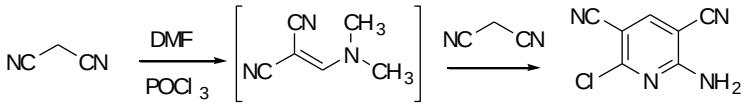
Similar approach to synthesize fused tricyclo-2-chloro-3-cyanopyridine **90** from 2-[3,4-dihydro-1(*2H*)-napthalenyliden]malanonitrile **89**, has been reported by Aadil *et al* (Scheme 2.37).[31]



89 **90**

Scheme 2.37

It is interesting to note that the Vilsmeier-Haack reaction of malononitrile affords simple nicotinonitrile derivative **93** *via* an intermediate **92** (scheme 2.38).[32]

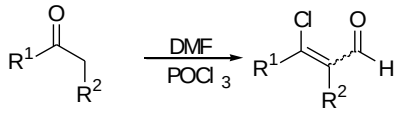


91 **92** **93**

Scheme 2.38

2.4 The Vilsmeier-Haack reactions of carbonyl compounds

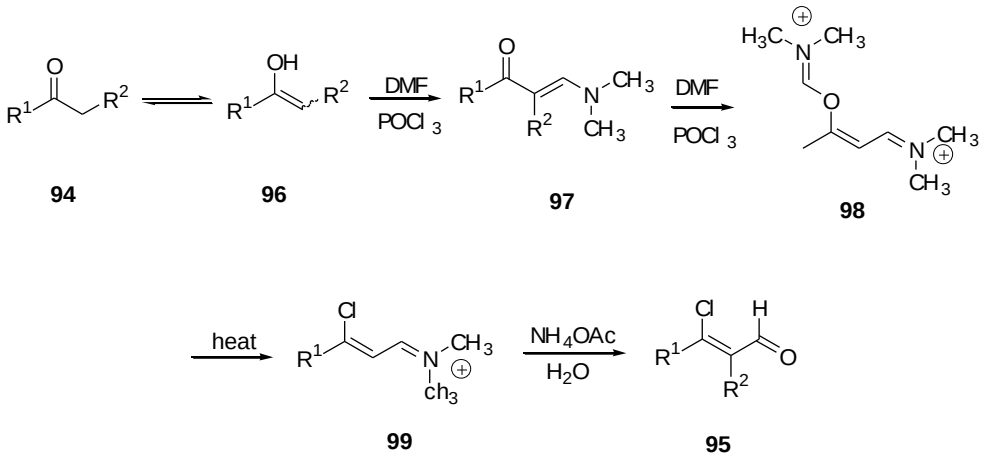
The reactions of chloromethyleneiminium salts with carbonyl compounds and their derivatives are highly versatile. On treatment with chloromethyleneiminium salts they provide multifunctional synthons, having potential for further application in synthesis, as products. Simple enolizable carbonyl compounds **94** react with chloromethyleneiminium salts to afford the corresponding β-chloroethylenic aldehydes **95** (Scheme 2.39).[33]



94 **95**

Scheme 2.39

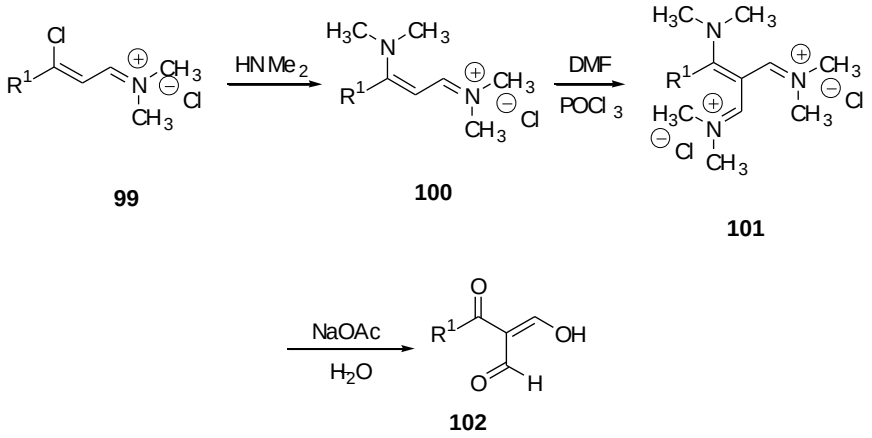
It has been suggested that the ketone enolizes prior to its reaction with Vilsmeier-Haack reagent. The enolization is enhanced due to the presence of HCl that would be formed as a result of the iminoalkylation at the oxygen of the carbonyl group. The enol form **96** of the ketone reacts with the Vilsmeier 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).[33a]



94 96 97 98 99 95

Scheme 2.40

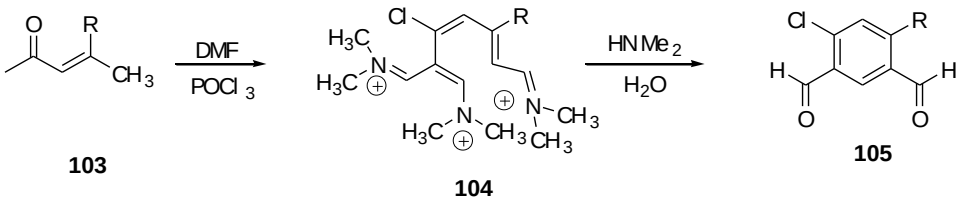
By replacing the chloro substituent of the intermediate iminium salt **99** by N,N-dimethylamino group, subsequent iminoalkylation can be performed conveniently to afford malonaldehyde derivative **102** (Scheme 2.41).[34]



99 100 101 102

Scheme 2.41

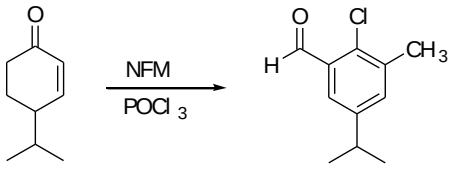
Aliphatic α,β-unsaturated ketones or β-diketones undergo cycloaromatization reactions on treatment with chloromethyleneiminium salts. For example, β-methyl substituted α,β-unsaturated ketone **103** undergoes cycloaromatization to afford the aromatic dialdehyde **105** (Scheme 2.42).[35]



103 **104** **105**

Scheme 2.42

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)[36] Related, aromatization reactions have been reported by Raju and Rao on cyclohexenones obtained by the Birch reduction of 2-methylanisole, as well.[37] 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.[38]

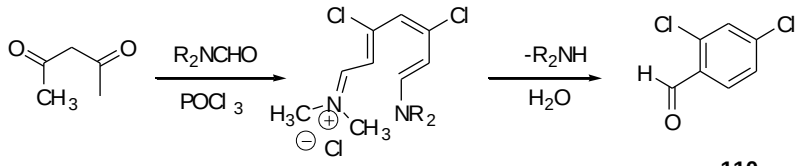


106 **107**

Scheme 2.43

The treatment of acetylacetone **108** with DMF-$POCl_3$ affords 2,4-dichlorobenzaldehyde **110** *via* a heptamethinium species **109**, which undergoes ring closure, probably in a pericyclic process (Scheme 2.44).[36a] 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-$POCl_3$ 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

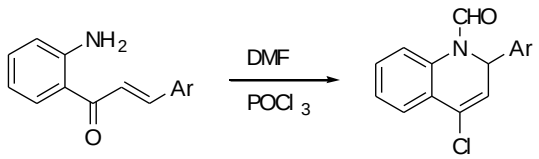
further iminoalkylation can occur giving the dicationic species, which then yields a dialdehyde.



108 **109** **110**

Scheme 2.44

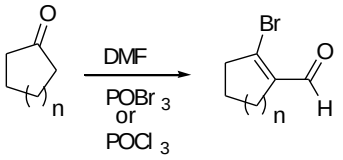
The Vilsmeier cyclization of 2'-aminochalcones **111** provides a mild one pot synthesis of 2-aryl-4-chloro-N-formyl-1,2-dihydroquinolines **112** (Scheme 2.45).[39] The scope of the reaction has been extended for the synthesis of quinolines themselves, by replacing 2'-aminochalcones with 2'-azidochalcones as the starting material.



111 **112**

Scheme 2.45

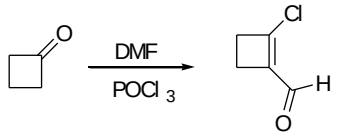
Like acyclic ketones, cyclic ketones can also be transformed to the haloformylated products. For example, cyclic ketones **113** can be effectively transformed into corresponding β-haloacryladehydes **114** on reaction with halomethyleneiminium salts (Scheme 2.46).[40] Karlsson and Frejd have showed that substituents at 3-position of the ring have steric influences on the attack of the chloromethyleneiminium 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.[41]



113 **114**

Scheme 2.46

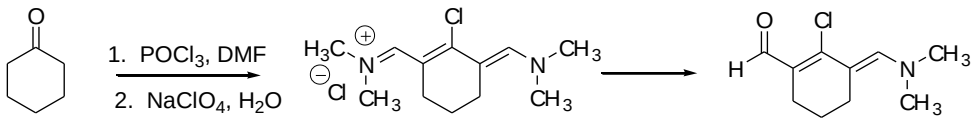
Vilsmeier-Haack reaction of cyclobutanone also has been reported. Even when an excess of formylating agent was used, cyclobutanone afforded only monoformylated product **116** (Scheme 2.47).[42]



115 **116**

Scheme 2.47

Arnold *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).[40c]

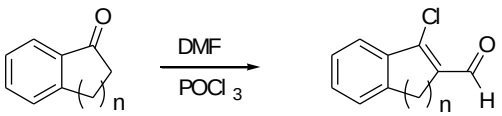


117 **118** **119**

Scheme 2.48

Benzo-fused cycloalkanones are usually converted by Vilsmeier reagent into the corresponding chlorovinylaldehydes in good yield under mild conditions.[43] The resulting chlorovinylaldehydes have been used in the synthesis of a wide variety of polycondensed heterocycles.[44] For example, 1-

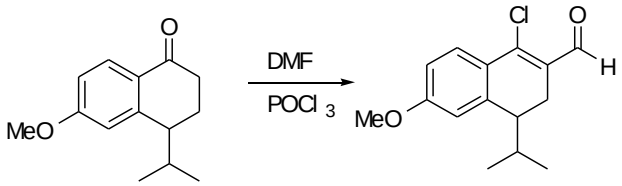
indanone,[39] α-tetralone[39] and benzosuberone[45] afford the corresponding β-chlorovinylaldehydes **121** (Scheme 2.49).



120 **121**

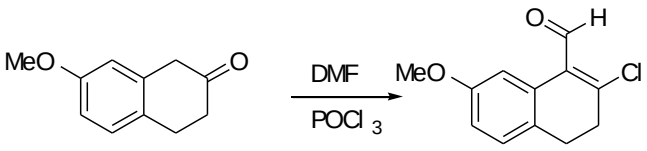
Scheme 2.49

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]



122 **123**

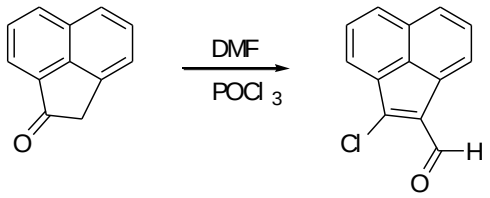
Scheme 2.50



124 **125**

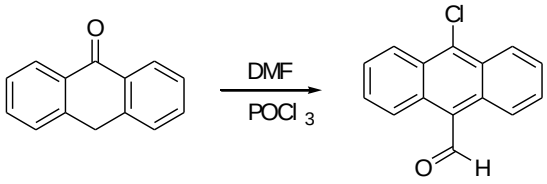
Scheme 2.51

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] .



126 **127**

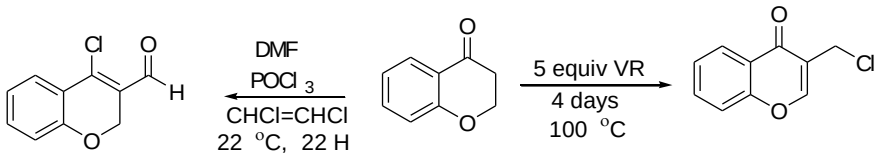
Scheme 2.52



128 **129**

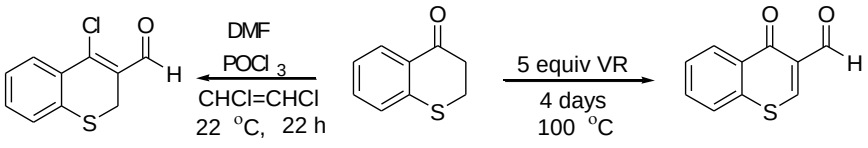
Scheme 2.53

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).[48] The Vilsmeier-Haack reactions of flavanones and related benzofused compounds have also been reported.



131 **130** **132**

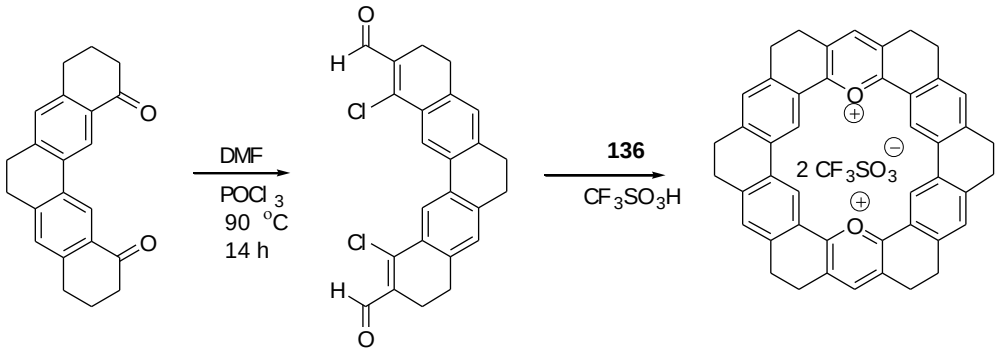
Scheme 2.54



134 **133** **135**

Scheme 2.55

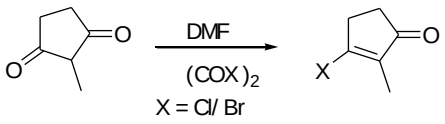
Using Vilsmeier methodology, the diketone **136** was converted into the dialdehyde **137**, which afforded a convergent and unambiguous route to the intricate macrocyclic pyrilium salt **138** (Scheme 2.56).[43a]



136 **137** **138**

Scheme 2.56

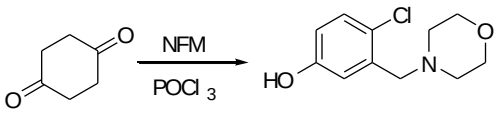
3-Halo-2-methyl-2-cyclopenten-1-ones **140** can be prepared in excellent yield by the reaction of cycloalkene-1,3-diones **139** with Vilsmeier-Haack reagents prepared from DMF and $(COCl)_2$ or $(COBr)_2$ (Scheme 2.57).[49] The absence of formylated product is a notable feature in this reaction. The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



139 **140**

Scheme 2.57

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]



141 **142**

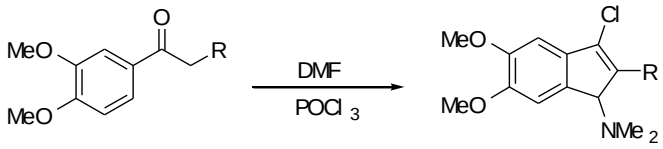
Scheme 2.58

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]

143 **144**

Scheme 2.59

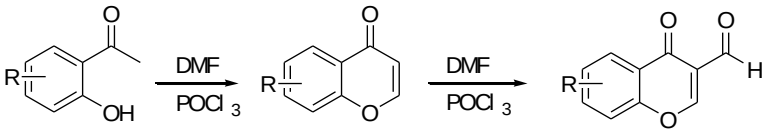
When electron-releasing substituents are present on the aromatic ring, cyclization of the intermediate chloromethyleneiminium salt is occurred. For example, substituted propeophenone **145** undergo cyclization to chlorosubstituted N,N-dimethylamino substituted indenes **146** (Scheme 2.60).[51] Similarly,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



145 **146**

Scheme 2.60

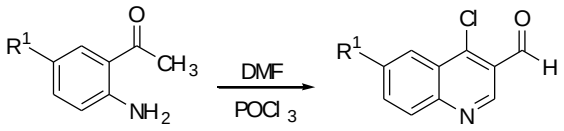
By the attack of Vilsmeier-Haack reagent, *o*-hydroxyacetophenones **147** are cyclized to, give the valuable intermediates 3-formylchromones **149** in good yield (Scheme 2.61).[53] Similarly cyclization of 2-hydroxy-α-phenoxyacetophenone derivatives by the Vilsmeier reagent, catalysed by $BF_3.OEt_2$ to 3-phenoxychromone derivatives has also been reported.[54] The reaction mechanisms and kinetics of these reactions also have been well studied.[55] Appropriately substituted naphthalenes and coumarins react similarly.



147 **148** **149**

Scheme 2.61

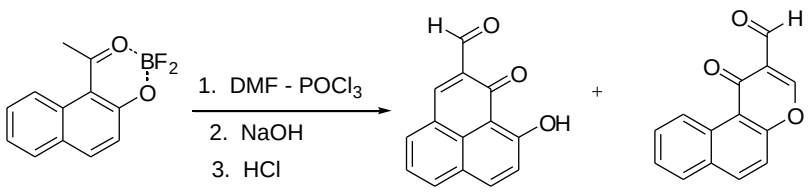
Similarly, *o*-aminoacetophenones **150** react with the Vilsmeier-Haack reagent to afford the corresponding 4-chloroquinoline derivatives **151** (Scheme 2.62).[56]



150 **151**

Scheme 2.62

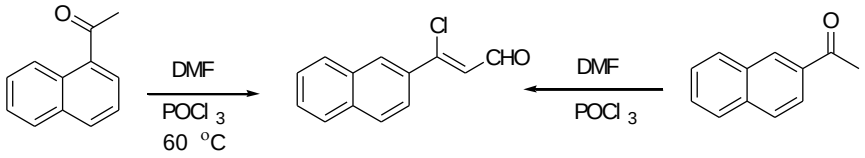
A variation involves by the conversion of 1-acetyl-2-hydroxynaphthalene into a difluoro-1,3-dioxaborin **152** and subsequent formylation reaction by Vilsmeier-Haack reagent. In this case phenalenone **153** is the major product along with the expected chromone **154** (Scheme 2.63).[57]



152 **153** **154**

Scheme 2.63

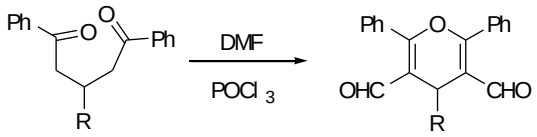
During the chloroformylation of 1-acetonaphthone **155** migration of the acetyl group occurs, with formation of the same aldehyde **156** as that obtained from 2-acetonaphthone **157** (Scheme 2.64).[58]



155 **156** **157**

Scheme 2.64

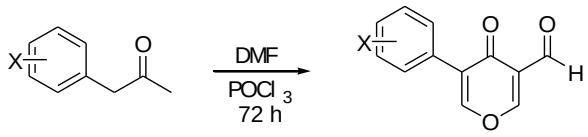
The Vilsmeier-Haack reaction of 1,5-diketones of the type **158** affords 3-formylpyran derivatives **159** (Scheme 2.65). [59]



158 **159**

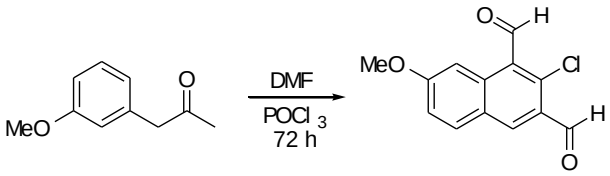
Scheme 2.65

In our laboratory, various aryl-substituted acetones **160** were treated with three equivalents of Vilsmeier-Haack reagent, prepared by the addition of $POCl_3$ 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]



160 **161**

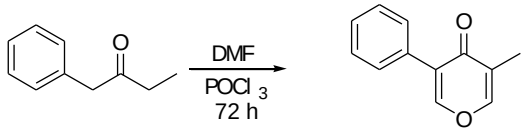
Scheme 2.66



162 **163**

Scheme 2.67

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).[60]



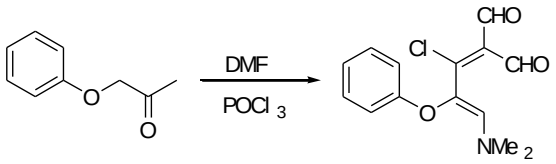
164 **165**

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).[60]

166 **167**

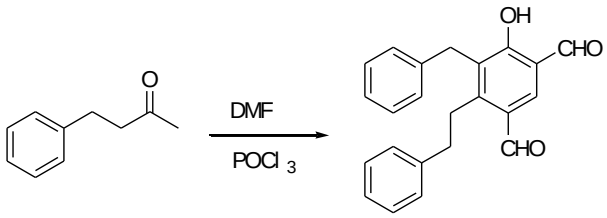
Scheme 2.69



168 **169**

Scheme 2.70

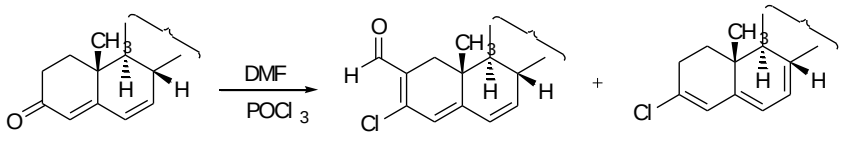
Similarly the reaction of benzylacetone **170** with the Vilsmeier-Haack reagent under the same condition gave substituted phenol **171** (Scheme 2.71). [60]



170 **171**

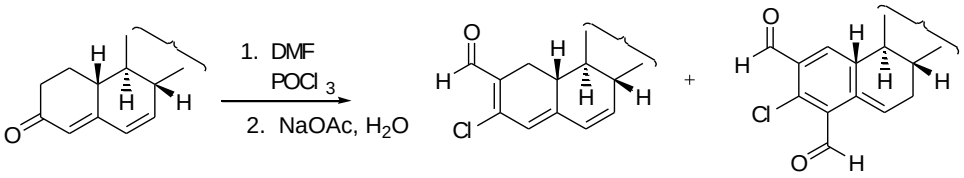
Scheme 2.71

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).[61]



172 **173** **174**

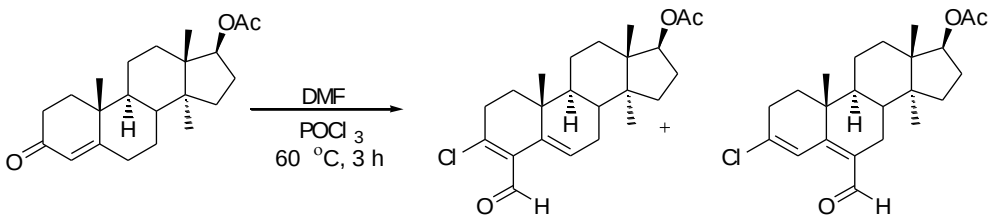
Scheme 2.72



175 **176** **177**

Scheme 2.73

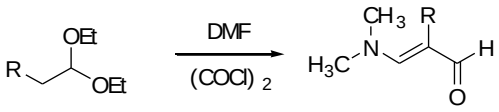
Similarly the Vilsmeier-Haack reaction of 19-nortestosterone acetate **178** affords the aldehydes **179** and **180** (Scheme 2.74).[62]



178 **179** **180**

Scheme 2.74

The Vilsmeier-Haack reactions of the synthetic equivalents of carbonyl compounds such as enol ethers, acetals 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]

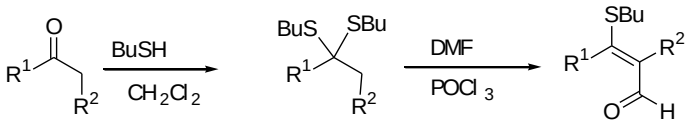


181 **182**

Scheme 2.75

Earlier reports from this laboratory describe a convenient synthesis of β-alkylthioethylenic aldehyde **185** starting from dithioketals **184**. The

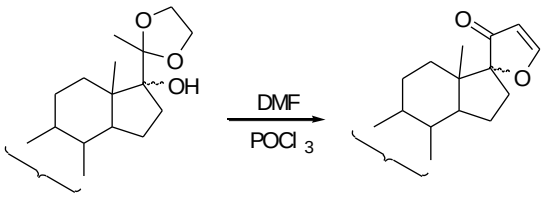
dithioketals undergo very selective monoiminoalkylation in the presence of the reagent prepared from $POCl_3$ and DMF (Scheme 2.76).[64]



183 **184** **185**

Scheme 2.76

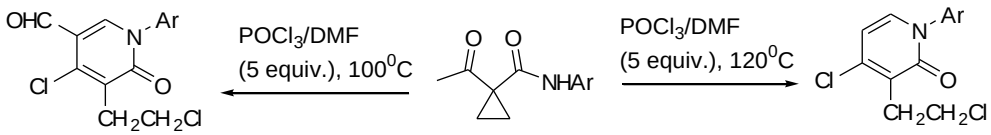
However, similar reactions with ketals and vinyl acetates always lead to multiple iminoalkylation reactions. Interesting transformations have been reported by the reactions of α-hydroxy ketals. α-Hydroxy ketal **186** on reaction with Vilsmeier-Haack reagent afforded the dihydrospirofuranone **187**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



186 **187**

Scheme 2.77

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 neucleophilic cyclization (Scheme 2.78).[66]



189 **188** **190**

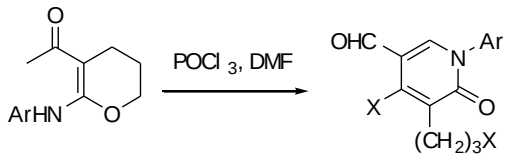
Scheme 2.78

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]

191 **192**

Scheme 2.79

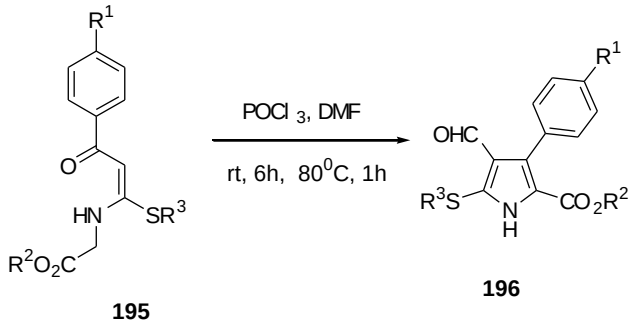
Yet another protocol for the synthesis of polysubstituted pyridine-2-(1H)-ones **194** was developed by Dong, D and coworkers. Here 2-arylamino-3-acetyl-5,6-dihydro-4H-pyrans **193** undergoes Vilsmeier-Haack reaction resulting in the formation of **194** (Scheme 2.80). [68]



193 **194**

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]



195 **196**

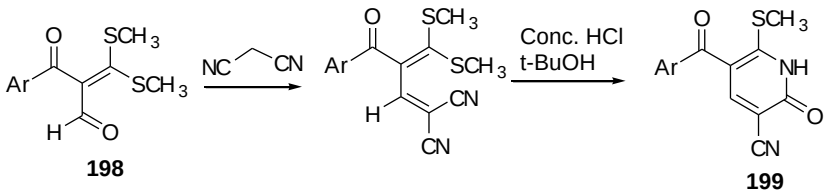
Scheme 2.81

Recently, we have developed new method for synthesizing α-formylketene dithioacetals **198** from aroylketene dithioacetals **197** by treating them with well-known Vilsmeier-Haack reagent prepared from phosphorous oxychloride and N,N-dimethylformamide (Scheme 2.82).[70]

197 **198**

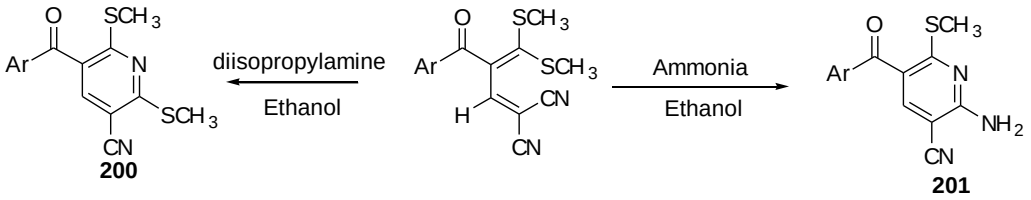
Scheme 2.82

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].



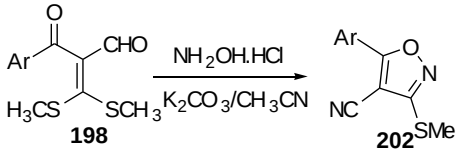
198 **199**

Scheme 2.83



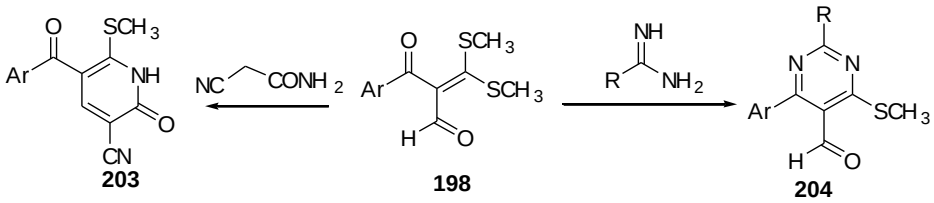
200 **201**

Scheme 2.84



198 **202**

Scheme 2.85

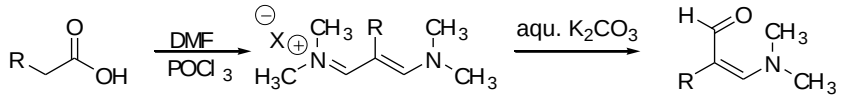


203 **198** **204**

Scheme 2.86

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).[75]

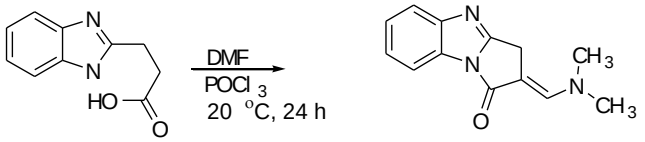


205 **206** **207**

Scheme 2.87

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

(Scheme 2.88) [76] and benzene-1,2-diacetic acid **210** affords the benzofulvene **211** in low yield (Scheme 2.89)[20b]



208 **209**

Scheme 2.88

210 **211**

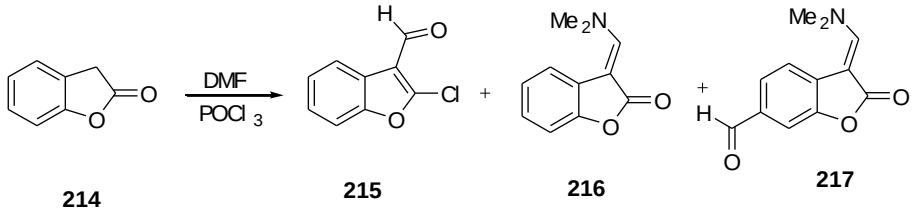
Scheme 2.89

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]

212 **213**

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]



214 **215** **216** **217**

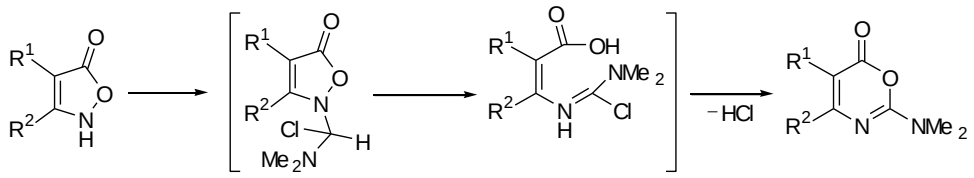
Scheme 2.91

On reaction with Vilsmeier reagent, 5(4H)-isoxazolones **218** affords dichloromethylisoxazolones **219** (Scheme 2.92).[79]

218 **219**

Scheme 2.92

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).[80]

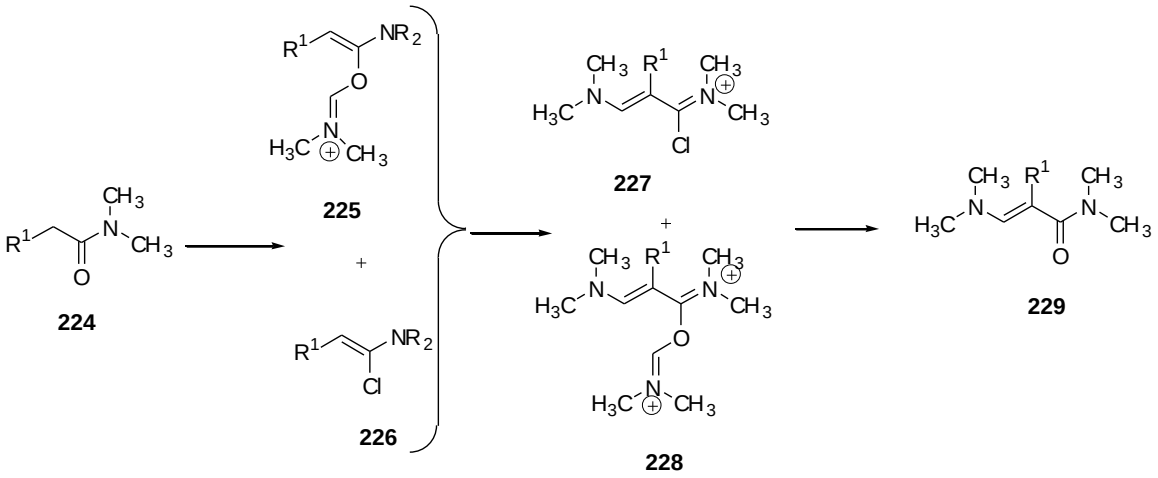


220 **221** **222** **223**

Scheme 2.93

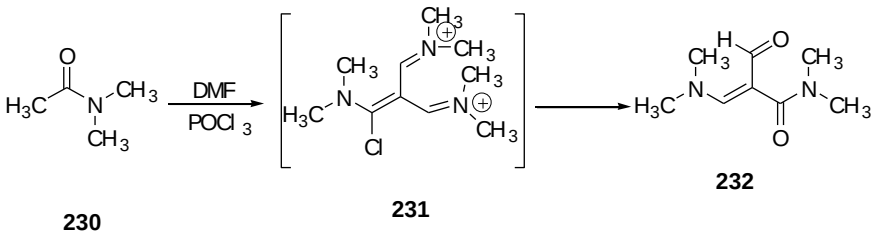
The greater basicity of the carbonyl oxygen atom in carbonamides as compared with ketones suggests that the chloromethyleneiminium cation will usually initially attack on the carbonyl carbon atom to form intermediates **225** and **226** and they rapidly react to give the stable

intermediates **227** and **228** which on hydrolysis affords an amide **229** (Scheme 2.94).[2a]



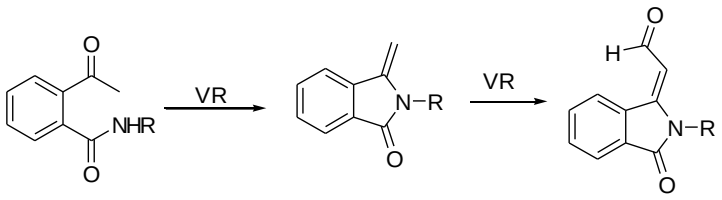
Scheme 2.94

For example, N,N-dimethylacetamide **230** is converted into highly functionalized amide **232** by the Vilsmeier-Haack reagent (Scheme 2.95).[2a]



Scheme 2.95

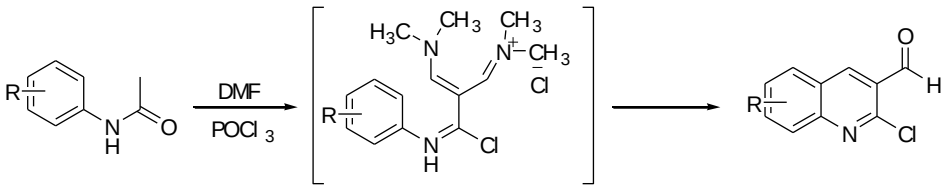
2-Acetylbenzamide derivatives **233** undergo iminium salt mediated dehydration of tautomers, which on further reaction with iminium salt affords aldehyde derivative **235** (Scheme 2.96).[26b]



233 **234** **235**

Scheme 2.96

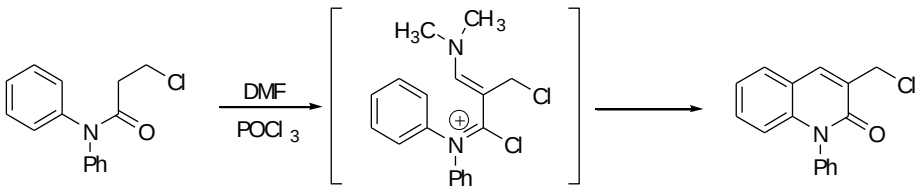
In the literature there are a number of reports on the synthesis of quinolines and their derivatives using the chloromethyleneiminium salts prepared from anilides.[81] The Vilsmeier-Haack reaction of acylanilides **236** afforded the functionalized quinoline **238** in good yields (Scheme 2.97).[82]



236 **237** **238**

Scheme 2.97

In the case of N-phenylacetanilides **239** Vilsmeier-Haack reaction afforded 1-phenyl-2-quinolones such as **241** (Scheme 2.98).[83]



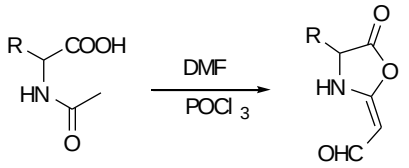
239 **240** **241**

Scheme 2.98

A variety of N-acetyl derivatives of amino acids like **242** and **244** have been subjected to Vilsmeier-Haack reaction to obtain 2,4-dichloro-3,5-diformyl pyrroles **243** and 2-formylmethylene-4-substituted oxazolidin-5-ones **245** (Scheme 2.99 and 2.100).[84]

242 243

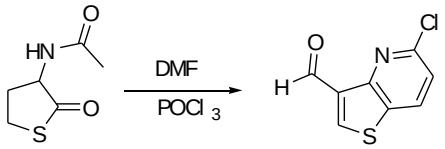
Scheme 2.99



244 245

Scheme 2.100

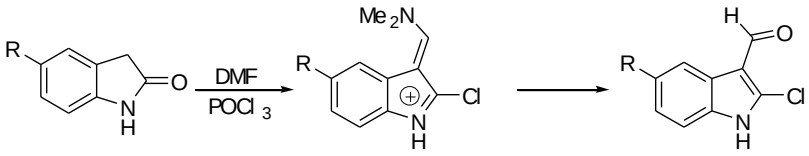
Similarly N-acetylhomocysteine thiolactone **246** give 5-chloro-3-formylthieno[2,3-b]pyridine **247** (Scheme 2.101).[85]



246 247

Scheme 2.101

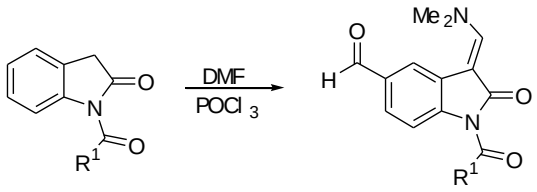
While Vilsmeier-Haack reactions of monocyclic lactams like α-pyrrolones, N-methyl-δ-valerolactam, N-methyl-ε-caprolactam *etc.* afford corresponding dimethylaminomethylene derivatives and benzofused lactams afford corresponding chlorovinylaldehydes. For example, oxindole **248** was converted by DMF-$POCl_3$ into the 2-chloro-3-formylindole **250** (Scheme 2.102).[86]



248 249 250

Scheme 2.102

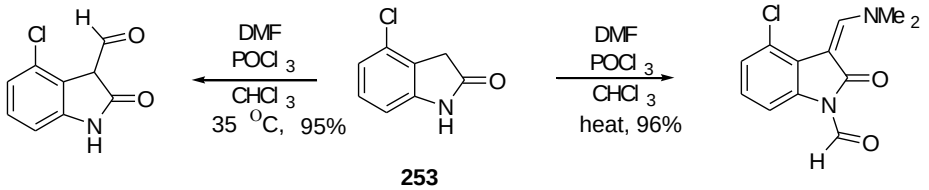
However, the Vilsmeier-Haack reaction of 1-acyloxindoles resulted in the 3-dimethylaminomethylidene derivatives **252** (Scheme 2.103).[87] In this case the corresponding chlorovinylaldehydes are prepared not by chloromethylation, but due to the acylation of 2-chloro-3-formylindole.



251 **252**

Scheme 2.103

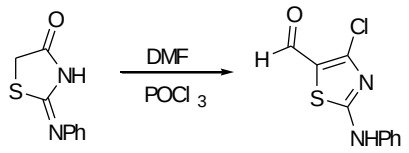
Vilsmeier-Haack reaction of oxindoles, substituted with chlorine in the benzene ring, afforded corresponding aldehyde derivatives and dimethylaminomethylene derivatives depending on the reaction temperature. For example, the chlorosubstituted oxindole **253** reacted with chloromethyleneiminium salt at 35 °C to afford the aldehyde **254**, while the reaction on heating afforded N-formyldimethylaminomethylene derivative **255** in excellent yields (Scheme 2.104).[88] Vilsmeier-Haack reactions of lactams with two or more hetroatoms also have been reported.[89]



254 **253** **255**

Scheme 2.104

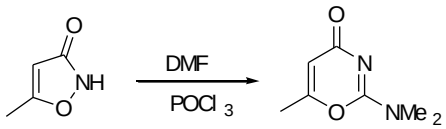
2-Phenyliminothiazolidin-4-ones **256** are converted, by a Vilsmeier reagent, into versatile derivatives **257** from which several 5,5-fused heterocycles have been made (Scheme 2.105).[90]



256 **257**

Scheme 2.105

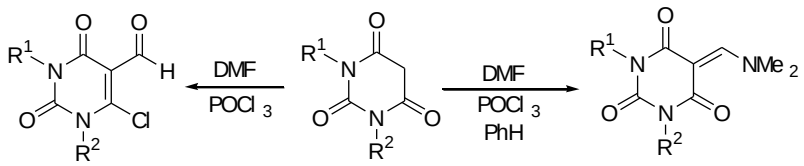
An oxazine derivative **259**, which is a useful fungicide and analgesic, was prepared by the Vilsmeier-Haack reaction of an amide **258** (Scheme 2.106).[91]



258 **259**

Scheme 2.106

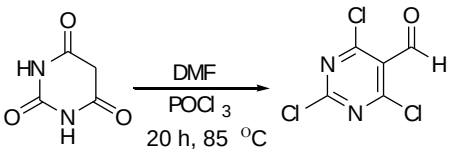
Unactivated pyrimidines do not usually react with Vilsmeier-Haack reagents. However, the unsubstituted 5-position of derivatives of barbituric acid, uracils and 4-hydroxy-6-oxo-dihydropyrimidines undergoes formylation in accordance with its reactivity as a β-enamide. For example barbituric acid derivatives **260** afforded either **261** or **262**, depending on the solvent employed (Scheme 2.107).[92]



261 **260** **262**

Scheme 2.107

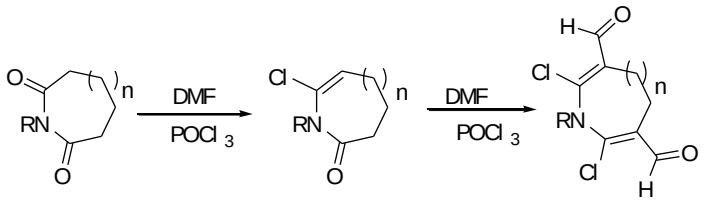
In the case of barbituric acid **263**, the Vilsmeier-Haack reaction afforded corresponding chlorovinylaldehyde **264** (Scheme 2.108).[93]



263 264

Scheme 2.108

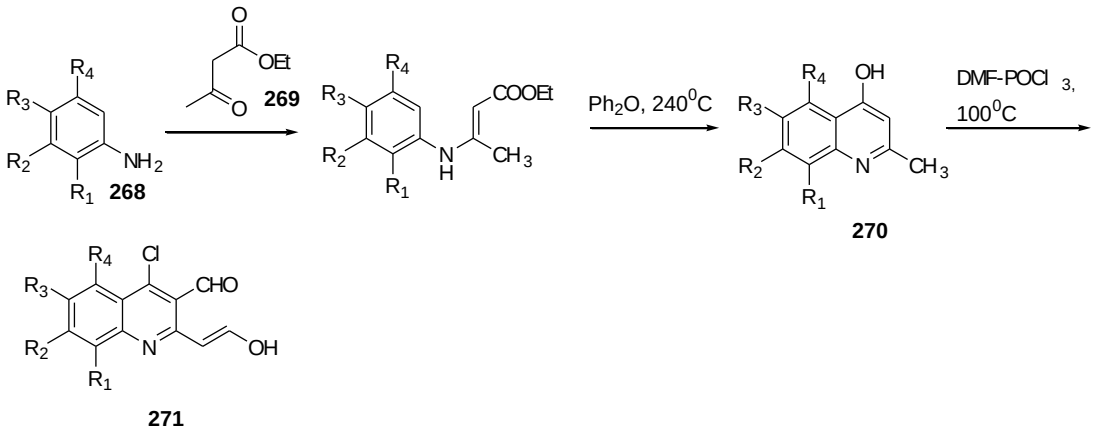
Imides of five, six, and seven membered ring react with excess DMF-$POCl_3$ to give useful di-β-chlorovinylaldehydes **267** (Scheme 2.109).[94]



265 266 267

Scheme 2.109

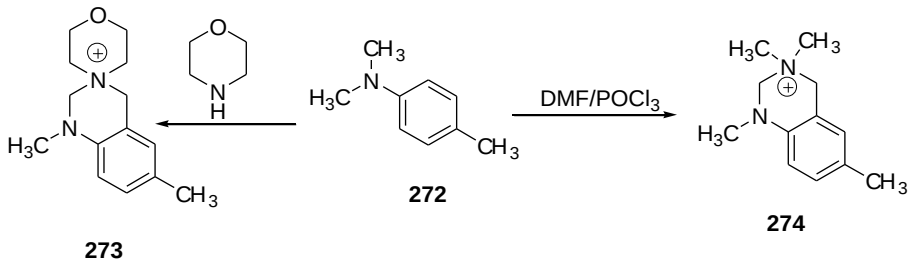
The Vilsmeier-Haack reaction on 4-hydroxyquinaldines **270** which is obtained from aniline **268** and ethyl acetate **269** is reported by Nandhakumar and coworkers. The reaction yielded 4-chloro-3-formyl-2-(2-hydroxy-ethene-1-yl)quinolines **271** was reported to be a valuable intermediate for biologically active diazepinoquinoline derivatives **(**Scheme 2.110**)**.



268 270 271

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-diazine ring formation.[95] For example the attempts to formylate 4-dimethylaminotoluene using $POCl_3$ in DMF or N-formylmorpholine give the quinazolinium salts (Scheme 2.111).



273 **272** **274**

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,[96] porphyrins, corroles[97] *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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