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REACTIONS OF CARBONYL COMPOUNDS WITH (MONOHALO) METHYLENIMINIUM SALTS (VILSMEIER REAGENTS)

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Contents

1. INTRODUCTION

1.1 Scope

Halomethyleniminium salts,[1] *e.g. N,N*-dimethylchloromethylenammonium chloride,[2] $[Me_2NCHCl]^+ Cl^-$, are perhaps best known as reagents for, or intermediates generated in, the Vilsmeier-Haack reaction,[3] one of the most common methods of formylating activated aromatic rings. A Vilsmeier reagent is produced when a disubstituted amide, typically *N,N*-dimethylformamide[4] (DMF), is treated with an acid halide, frequently phosphorus oxychloride, though to a lesser extent, phosgene.

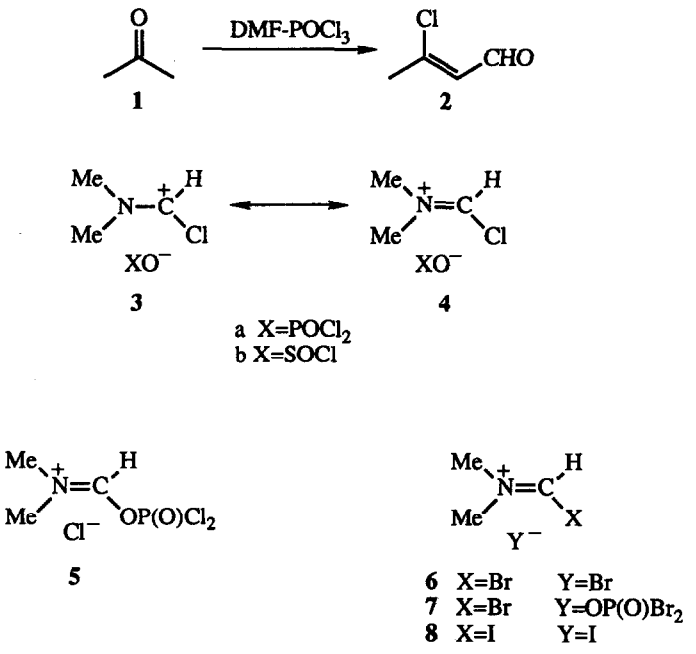
The potential for carbon-carbon bond-forming reactions[5,6] of halomethyleniminium salts in organic synthesis is by no means confined to Vilsmeier-Haack-Arnold 'formylation' of activated aromatic nuclei. The synthetic value of halomethyleniminium salts is well-illustrated in their reactions with compounds containing a C=O linkage *e.g.* acetone **1**, by virtue of the number of varied, and otherwise inaccessible compounds which have been prepared. The carbonyl compounds surveyed in this Report are chiefly those for which enolisation is possible, and often essential, during the Vilsmeier reaction.

The reaction of Vilsmeier reagents with ketones containing methyl or methylene groups adjacent to the carbonyl group, reported in the late 1950's by Arnold and co-workers,[7,8] affords substituted β-chloroacrylaldehydes, such as **2** (Scheme 1). This Report emphasises the wide-ranging reactivity[5] of Vilsmeier reagents which extends far beyond the formylation of an activated aromatic nucleus. The reagents allow carbon-carbon bonds to be formed in many other contexts. Recent work has shown that the course of such reactions can often be controlled by substrate, conditions, or temperature. Although Vilsmeier reagents are known to be capable of a variety of somewhat unexpected transformations, considerable rationalisation of the products is now possible.

The scope of this Report is confined to the reaction of organic compounds containing a C=O double bond with reagents of the Vilsmeier type. The following topics, having been discussed and reviewed elsewhere, will not be considered in any detail here: (i) Vilsmeier-Haack-Arnold formylation of activated aromatic rings[3] (ii) electrophilic formylating agents in general[9] (iii) the chemistry of β-chlorovinylaldehydes[10] (common products of the reaction of Vilsmeier reagents with ketones) (iv) cyclisations under Vilsmeier conditions[11] (although such cyclisations involving carbonyl compounds will be considered). The importance of β-chlorovinylaldehydes, owing to their considerable synthetic versatility and generality of preparation is worthy of note.

1.2 Formation and Structure of Halomethyleniminium Salts (Vilsmeier Reagents)

It is well-known that inorganic acid halides (*e.g.* $SOCl_2$, $COCl_2$ and $POCl_3$) react with *N,N*-dimethylformamide (DMF) to form active complexes, referred to as Vilsmeier-Haack reagents[12-15] which have found extensive use as formylating, halogenating and dehydroxylating reagents.[16] DMF has been shown to react with $SOCl_2$ at room



Scheme 1

temperature giving a 1:1 complex $[Me_2NCHOS(O)Cl]^+ Cl^-$ which loses SO_2 reversibly to give the crystalline complex $[Me_2NCHCl]^+ Cl^-$; both salts have been characterised,[12] and the latter has been used frequently in organic synthesis.

The generally accepted representation[17-20] of the Vilsmeier reagent derived from *N,N*-dimethylformamide and phosphorus oxychloride or thionyl chloride corresponds to the respective structures **3a/4a** and **3b/4b**. However, the β-phosphoryliminium chloride **5** has been suggested[21] as being *more* reactive than the β-chloroiminium phosphate **4a**, an equilibrium mixture of those salts being generated. Raman spectra have been held[22] to establish the structure **5**, formed in the reaction of DMF with $POCl_3$. The alternative structure **4a** (formed from DMF and $COCl_2$) was not Raman active. However, this claim for structures other than **4** has been considered to be erroneous.[11]

The mechanism of formation and the structures of the Vilsmeier reagents (derived from DMF and $POCl_3$, $SOCl_2$ or $COCl_2$) have been studied by ^1H NMR[23-25] and ^{31}P NMR[23,24] spectroscopy. Rate constants and activation parameters have been determined for formylation by the complex $HCONMe_2$-$COCl_2$ in $CHCl_3$ of furan, thiophen, selenophen and tellurophen.[26]

For the generation of halomethyleniminium salts, DMF is the amide most commonly used; the acid chloride employed is usually phosphorus oxychloride, although phosgene and thionyl chloride also find use. As with the Vilsmeier-Haack-Arnold reaction, a number of dialkyl or aryldialkyl amides may be used, including *N*-phenyl-*N*-methylformamide. Advantages of DMF[27] over *N*-methylformanilide include the cost and weight of formylating agent required. Solvents commonly employed[11] are DMF, a chloroalkane or chloroalkene (*e.g.* CH_2Cl_2, $CHCl_3$ or $CH_2Cl.CH_2Cl$), or $POCl_3$. Temperatures used are normally in the range 0-100°C, 70-80°C being a satisfactory general working temperature.[11]

Bromoformylation and iodoformylation procedures are usually similar to those for chloroformylation. DMF does not react with carbonyl bromide; the desired bromomethylenedimethyliminium bromide **6** and the analogous iodo compound **8** are usually prepared by treating the chloromethyleniminium salt in chloroform with gaseous HBr or HI, respectively. Salt **8** exhibits the same properties as the adducts of DMF with either $POBr_3$ or PBr_3,[28,29] the structure **7** having been proposed for the latter adduct.[28]

2. REACTIONS OF ALDEHYDES WITH HALOMETHYLENIMINIUM SALTS

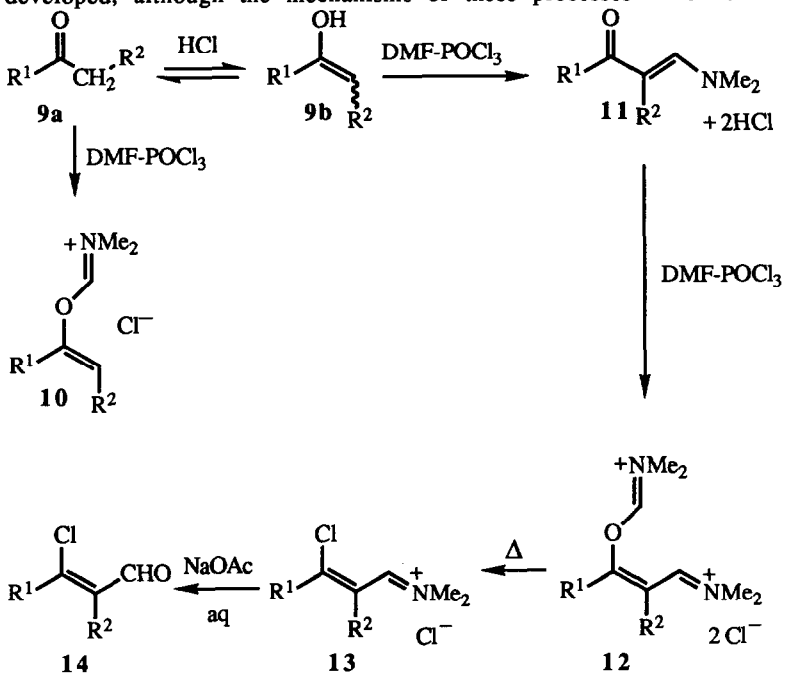
The literature concerning the reaction of aldehydes with Vilsmeier reagents is not extensive. Arnold and Zemlicka[7,30,31] described the preparation of 2-(dimethylaminomethylene)butanal from DMF-$POCl_3$ and butanal; Barton and co-workers[32] described an improved procedure (51% yield) using 1,1-diethoxybutane.

Aminoformylation of 1-formylcyclohexene proceeds with less than 10% conversion, although acetals react rapidly with iminium salts.[33] β-Dimethylaminoacrylaldehyde reacts with DMF-$COCl_2$ in chloroform giving triformylmethane (84%).[34] Aliphatic dialdehydes, upon reaction with Vilsmeier reagents, hydrolysis of the intermediates, and reaction with arylamines, lead to malondialdehyde anils.[35a] Phenylacetaldehydes usually afford predominantly the *(E)*-β-chlorovinylaldehydes.[35b]

3. REACTIONS OF KETONES WITH HALOMETHYLENIMINIUM SALTS

3.1 General Remarks and Mechanistic Considerations

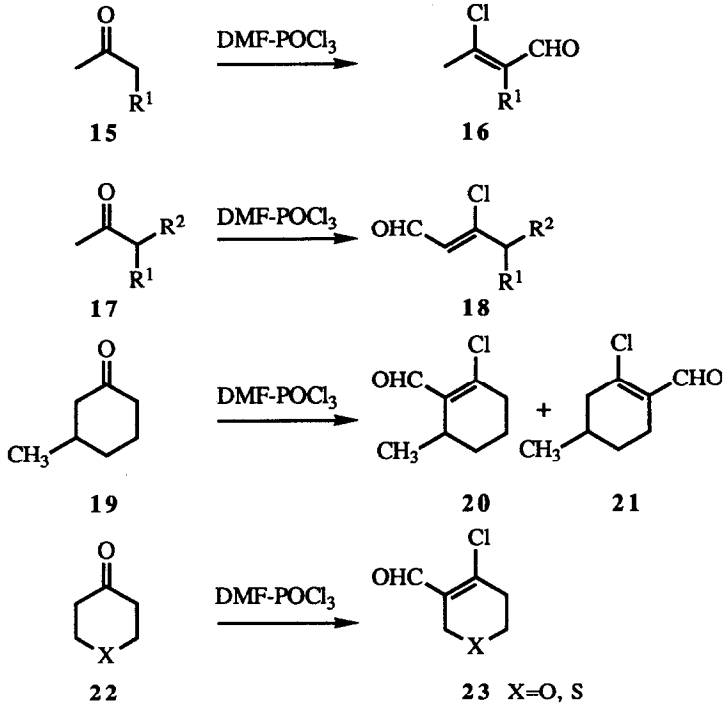
The reaction of Vilsmeier reagents with simple enolisable ketones has been extensively explored, unlike the action of Vilsmeier reagents on α-hydroxyketones.[36] No unambiguous mechanistic course for the reaction of ketones with Vilsmeier reagents has been developed, although the mechanisms of these processes which usually involve



Scheme 2

chloroformylation have been the source of much speculation. Arnold[7] suggested that the ketone enolises prior to reaction with the Vilsmeier reagent; this is consistent with the fact that only sufficiently nucleophilic alkenes are formylated by this reagent. Scheme 2 outlines a currently accepted reaction mechanism.[1]

Electrophilic attack by the Vilsmeier reagent on the weakly basic carbonyl oxygen atom of ketone **9a** slowly forms salt **10** and HCl (Scheme 2). Further substitution of salt **10** by the Vilsmeier reagent to give the dication **12** is improbable. The key role in this reaction is thought to be the liberation of HCl during the conversion of ketone **9a** into salt **10**. HCl catalyses the equilibrium between tautomers **9a** and **9b**; the latter undergoes rapid substitution by the Vilsmeier reagent giving the β-*N*,*N*-dimethylaminovinylketone **11** which is isolable in certain cases. Additionally, salt **10** may formylate the enol **9b** giving ketone **11**. With increasing concentration of HCl, autocatalytic acceleration of the reaction is observed. Reaction of ketone **11** with the Vilsmeier reagent gives the labile bisiminium chloride **12** which readily collapses to the iminium precursor **13** of the β-chloroacrylaldehyde **14**. The perchlorate analogues of salts **13** have been isolated in very high yield.[37] In the chloroformylation of enolisable



Scheme 3

ketones, molar ratios of iminium species to ketone are frequently between 4:1 and 5:1, with or without a solvent. A period of induction is frequently observed prior to an exothermic reaction.

Chlorotrienes[38-41] (obtained during the chloroformylation of some steroidal dienones) can be converted by the Vilsmeier reagent into the same chloroformyltrienes which are derived from the steroidal dienones themselves. However, it appears unlikely that chloroalkenes are the primary intermediates in the process of chloroformylation; Arnold showed that α-chlorostyrene does not react with Vilsmeier reagents.[7]

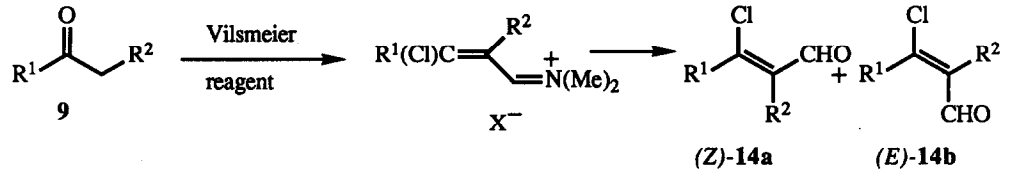
Typical patterns of regioselectivity for ketones are illustrated in Scheme 3. For acyclic ketones, monosubstitution generally favours[10] the regioisomer **16**, a course predominantly governed by the relative thermodynamic stability of the two possible enol intermediates. However, α,α-disubstitution is found to block formylation at the α-site so that only the aldehyde **18** can be formed, and that is usually the sole product. Karlsson and Frejd[42] have shown that the methyl group of 3-methylcyclohexanone has only a moderate effect on the regioselectivity (**20**:**21**=10:90).

The usual product of monoformylation of ketones is the salt **13** [7,37](Scheme 2); further formylation can arise only if deprotonation, involving the R^1 group of the cation, is possible. Polyformylation is sometimes observed (*e.g.* as for cyclopentanone, section 3.3.1).

3.2 ACYCLIC KETONES

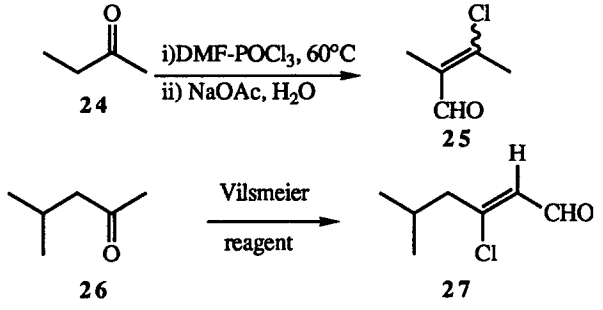
3.2.1 Acyclic Ketones with Two sp^3 Carbon Atoms adjacent to the Carbonyl Group.

Many methyl ketones, as well as acyclic and cyclic methylene ketones, are converted by Vilsmeier reagents into 3-haloacrylaldehydes (Scheme 4); these reactions are well-covered in previous reviews.[1,4,10] The usual procedure involves slow addition of the ketone to the Vilsmeier reagent (2.5-5 eq.), with cooling. Solvent is usually employed to control the exothermic, and sometimes violent reaction. After the initial reaction has subsided, the mixture may be heated, prior to being quenched with ice and neutralised by cold aqueous sodium acetate or sodium carbonate. β-Haloacrylaldehydes of low molecular mass are lachrymatory oils which decompose spontaneously within a few hours, sometimes violently. Acyclic β-bromoacrylaldehydes[29] are generally preparable from complexes of DMF-$POBr_3$.

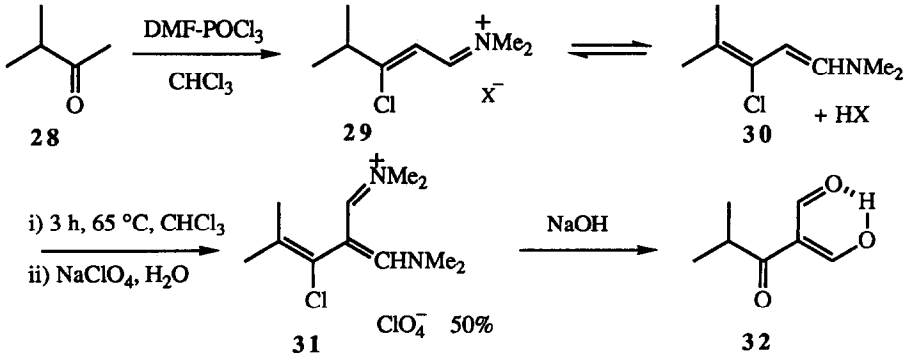


Scheme 4

In the simplest cases, monochloroformylation occurs, and usually with the formation of a mixture of the *(Z)*-isomer **14a** and the *(E)*-isomer **14b**. Acetone afforded 3-chlorobut-2-enal in 39% yield.[7] However, acetone and methyl ethyl ketone, with the DMF-$COCl_2$ or DMF-$POCl_3$ complex, can give triformyl derivatives.[43] Formylation usually occurs at the more substituted α-carbon atom, giving, for example, the aldehyde **25** (Scheme 5).[7] However, 4-methylpentan-2-one gives chiefly 3-chloro-5-methylhex-2-enal **27** predominantly as the *(Z)*-isomer[44] owing to the steric bulk of



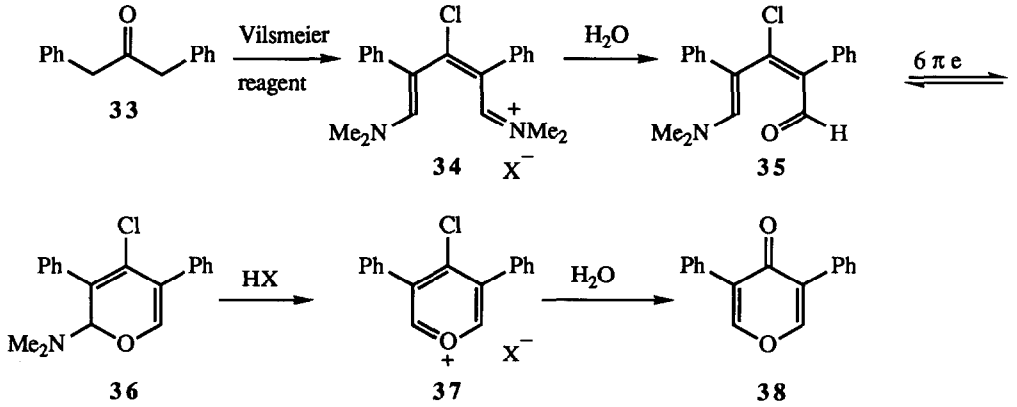
Scheme 5



Scheme 6

the isopropyl group. Isopropyl methyl ketone **28** reacts at the methyl carbon atom, but subsequent deprotonation at the methine carbon atom allows further attack by the iminium species giving the trimethinium salt **31** (Scheme 6). Methyl acetoacetate gives only one isomer, apparently the *(Z)*-form, **14a** (R^1=Me; R^2=CO_2Me).[45]

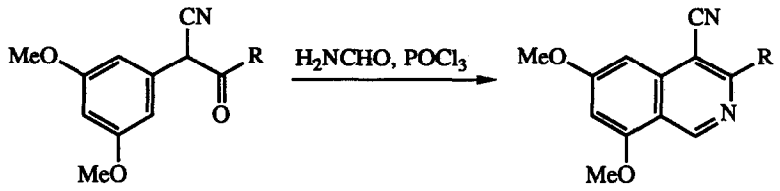
Dibenzyl ketone **33** undergoes only a double formylation, the product 3,5-diphenyl-4-pyrone **38** being considered to be formed by a 6π-electrocyclic ring-closure of the pentadienal **35** and subsequent hydrolysis of the pyrylium salt **37** (Scheme 7).[46] Related ketones can afford either isoquinolines or pyrimidines, depending upon the substitution, and hence the reactivity of the benzene ring. Phenylacetone itself gives a mixture of substituted pyrimidines (derived from chloromethyleniminium units) and a tetrasubstituted benzene; 3-methoxyphenylacetone gives a mixture of 6-methoxy-3-methylisoquinoline and three compounds containing a pyrimidine ring.[47]



33 **34** **35** **36** **37** **38**

Scheme 7

In 1968, Koyama and co-workers reported a synthesis of isoquinolines **40** from α-acyl-α-arylacetonitriles **39** and formamide-$POCl_3$ (modified Vilsmeier reaction; Scheme 8).[48] The formation of isoquinolines *versus* pyrimidines was further studied,[49] revealing that $MeCONH_2$-$POCl_3$ can afford 4-(3*H*)-pyrimidinones. However, the same Vilsmeier reagent was shown[49] to convert certain alkoxy-substituted acetophenones into either isoquinolines or naphthalenes, depending upon the substitution.



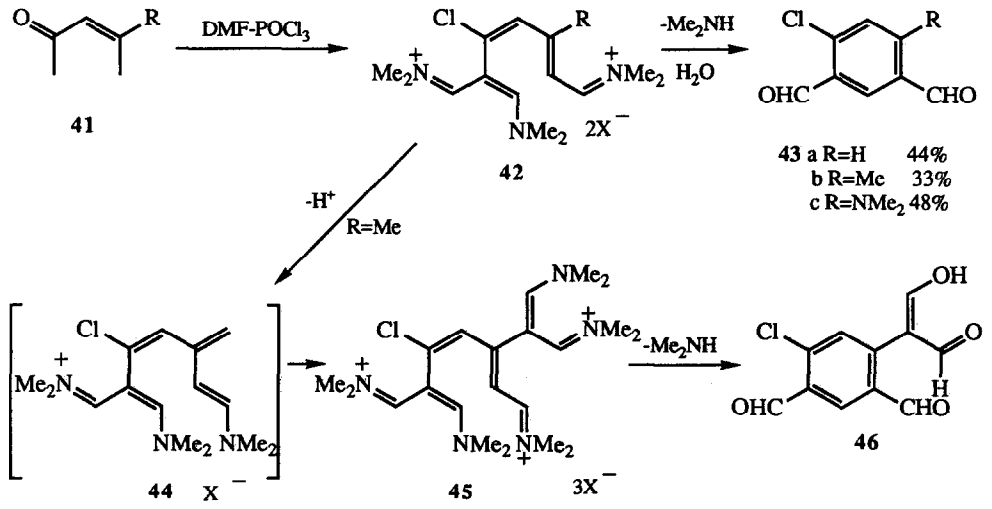
39 40

R=H, Me, Et, Ph

Scheme 8

3.2.2 Acyclic Alkyl Vinyl Ketones

Methyl propenyl ketones including 3-penten-2-one, mesityl oxide and 4-dimethylamino-3-penten-2-one afford the respective isophthaldialdehydes **43a**, **43b** and **43c**.[50,51] For the related reaction of the methyl ether of acetylacetone, the formation of 3-chloroanisole (42%) can be rationalised by assuming a 6π electrocyclic ring-closure. The simplest explanation of the formation of arenes from acyclic α,β-unsaturated ketones is a ring-closure of a 1,3,5-triene, which, depending on its reactivity, and the steric demands associated with its substituents, may contain from one to five carbon atoms derived from the Vilsmeier reagent, of which zero to three may be formally represented as iminium moieties (Scheme 9).



41 42

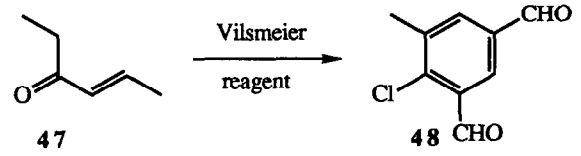
43 a R=H 44%
b R=Me 33%
c R=NMe2 48%

44 X− 45 3X− 46

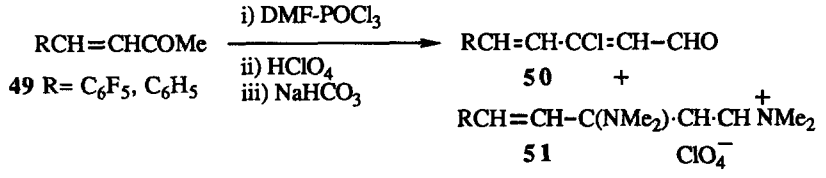
Scheme 9

Extensions to the above ring-closures have been reported. Several α,β-unsaturated alkenones have been converted by Vilsmeier reagents into chlorobenzene mono-, di-, and tri-carboxaldehyde. Conversion of 2-hexen-4-one **47** into **48** is illustrative.[52] Benzalacetophenones **49** reacted giving **50** and **51** (Scheme 10).[53]

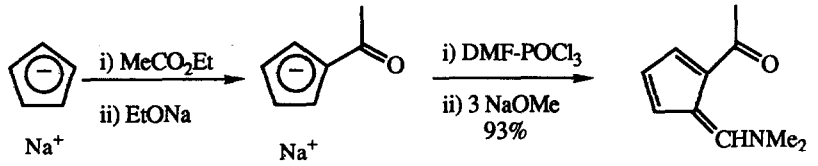
2-Acyl-6-aminofulvenes **54** are formed[54] by the action of DMF-$POCl_3$ on the salt **53** of acetylcyclopentadiene; the lack of introduction of a formyl group at the methyl carbon atom is notable. Acetylferrocenes react with Vilsmeier reagents at 0°C giving high yields of 2-formyl-1-chlorovinylferrocenes.[55,56] Benzylideneacetone and cinnamylideneacetone are smoothly converted into the respective coloured, crystalline iminium salts **55** and **56**.[57] The reaction of DMF-$POCl_3$ with crotonophenone affords, after treatment with aqueous perchlorate, the salt **57** (65%) (Scheme 11).[58]

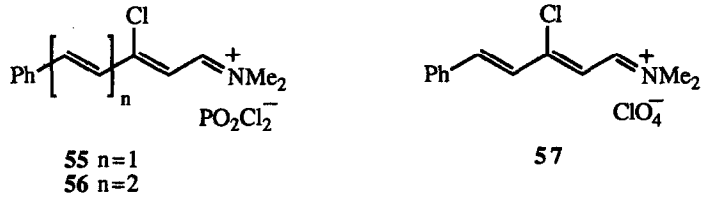


47 **48**



Scheme 10

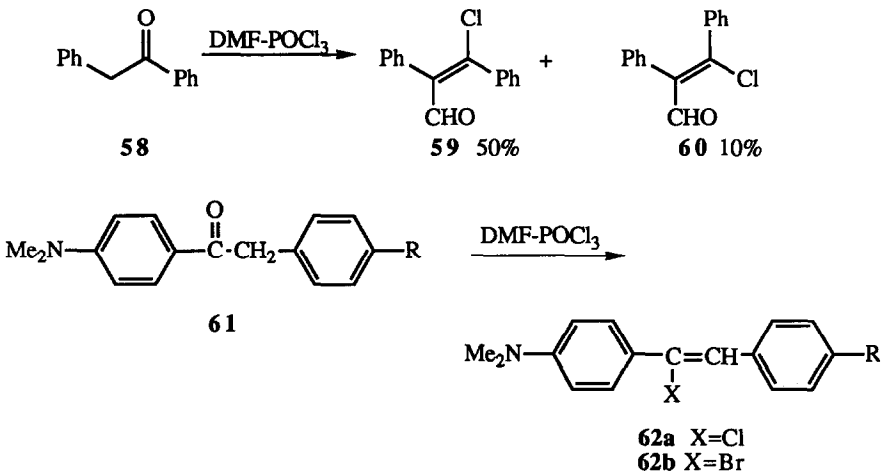




Scheme 11

3.2.3 *Aryl Alkyl Ketones*

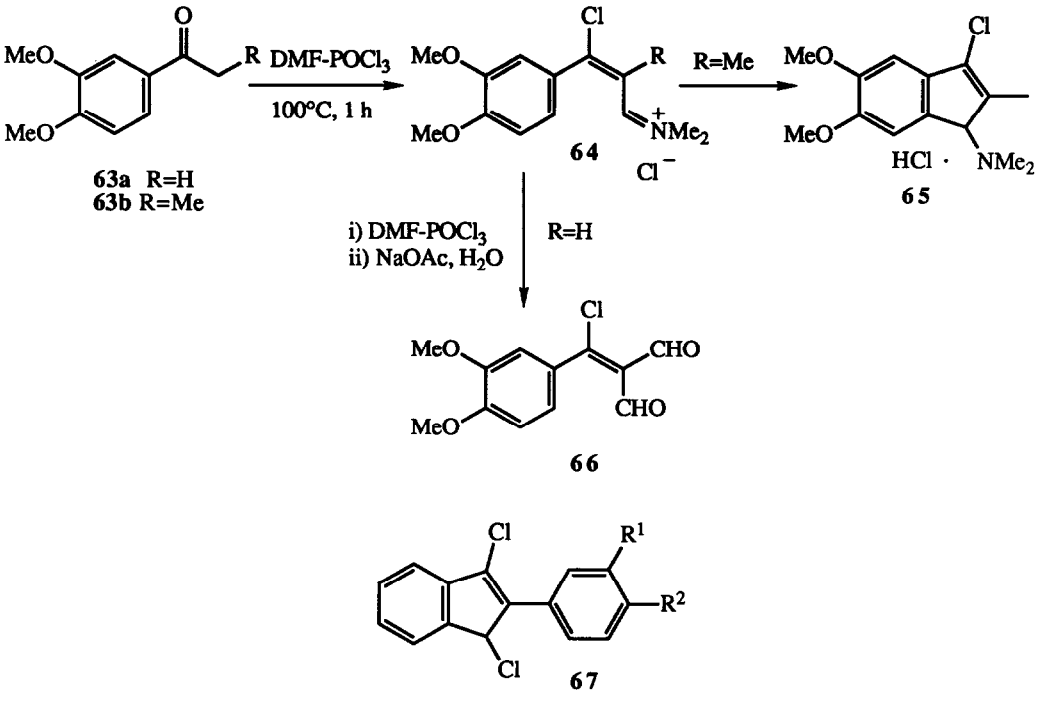
Simple aryl alkyl ketones usually give the chloroformylalkene in good yield: acetophenone and propiophenone afford the β-chlorocinnamaldehydes (47% and 90% respectively).[7,8] However, yields from *p*-substituted acetophenones are typically below 30%.[59] A recent procedure for the preparation of substituted dihydrocinnamaldehydes[60] from aryl ketones involves addition at 70-80°C to a mixture of DMF-$POCl_3$, followed by cooling and treatment with aqueous NaOH. Desoxybenzoin affords a mixture of diastereoisomeric β-chlorovinylaldehydes upon treatment with DMF-$POCl_3$ (Scheme 12).[61] However, a Vilsmeier-Haack reaction using β-4-(dimethylamino)-desoxybenzoins **61** did not give the anticipated chloroformylstilbenes, but instead 4-(dimethylamino)-α-halostilbenes **62**.[62]



Scheme 12

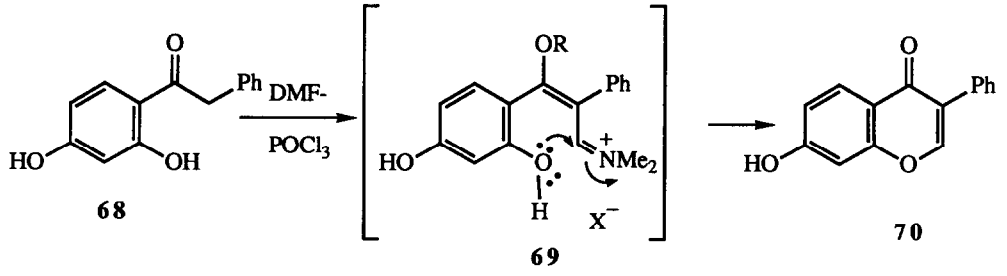
Diacetylbenzenes undergo diformylation: when DMF-$COCl_2$ is used as the Vilsmeier reagent, a mixture of $CHCl_3$ and CH_2Cl_2 as solvent gave excellent yields of β,β'-dichloro-*m*-benzenediacrylaldehyde.[63] Bis- and tris-(β-chlorovinylaldehydes) were formed from 1,4-diacetylbenzene and 1,3,5-triacetylbenzene respectively.[52]

3,4-Dimethoxyacetophenone **63a** can undergo both mono- and di-formylation,[64] whereas the indene **65** is formed[65] from propioveratrone **63b** (Scheme 13). Other chloroindenes **67** have been prepared[66] by the action of Vilsmeier reagents on aryl benzyl ketones.



R^1=R^2=OMe, R^1=H, R^2=OMe, F, Br, Cl

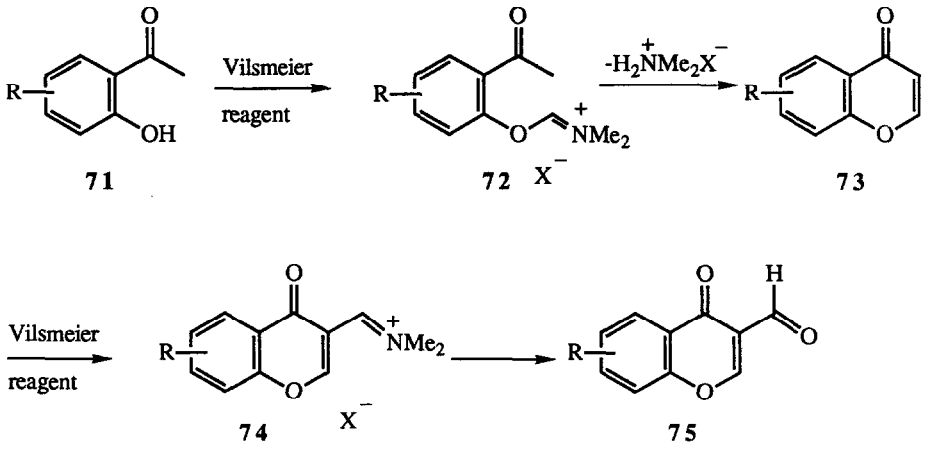
Scheme 13



Scheme 14

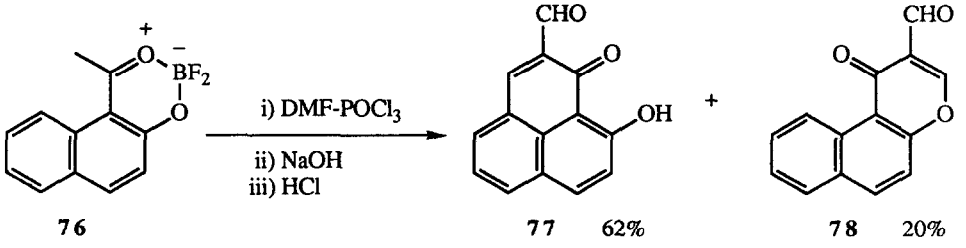
In Scheme 14, initial attack on oxygen cannot be excluded, although attack by the Vilsmeier reagent on the enolised methylene group to give intermediate **69** is presumed to occur, prior to cyclisation with loss of methylamine. *o*-Hydroxyacetophenones cyclise in good yield giving the valuable intermediates, 3-

formylchromones.[67-69] Related cyclisation of acetophenone derivatives giving 3-phenoxychromones are catalysed by $BF_3.OEt_2$.[70] Cyclisation of 2-hydroxy-α-phenoxyacetophenone derivatives by the Vilsmeier reagent, catalysed by $BF_3.OEt_2$, to 3-phenoxychromone derivatives has been reported.[70,71] In these cases, initial attack on the hydroxyl group has been considered more likely (cf. **72**; Scheme 15).

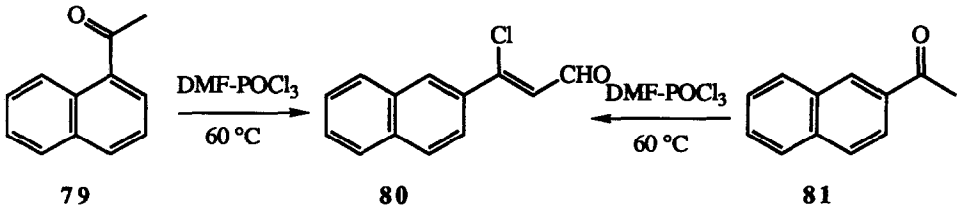


Scheme 15

Appropriately substituted naphthalenes and coumarins react similarly.[67-69] A variation involves conversion of the 1-acetyl-2-hydroxynaphthalene into a difluoro-1,3,2-dioxaborin with $BF_3.OEt_2$, and subsequent formylation, by which the phenalenone **77** can be generated, as well as the expected chromone **78** (Scheme 16).[72,73] During the chloroformylation of 1-acetonaphthone **79**, migration of the acetyl group occurs, with formation of the same aldehyde **80** as that obtained from 2-acetonaphthone **81** (Scheme 17).[74]

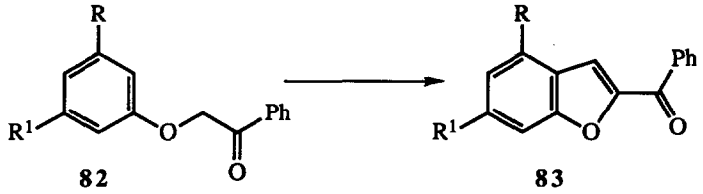


Scheme 16



79 80 81

Scheme 17



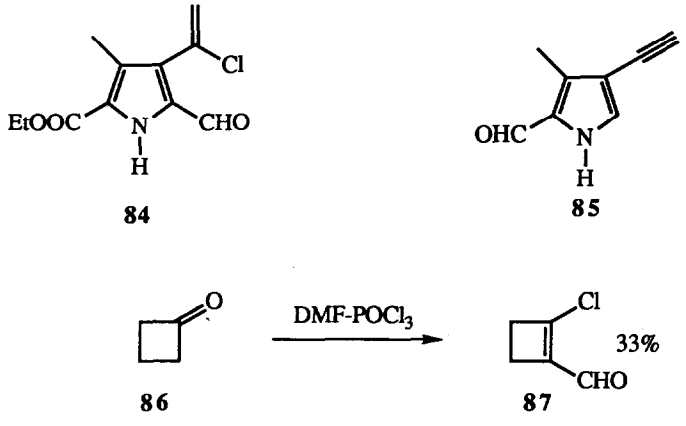
82 83

R=R[1]=OMe

R=H, R[1]=OMe, OEt, NEt_2

Scheme 18

A versatile synthesis of benzofurans **83** was accomplished by the Vilsmeier reaction of the phenoxyacetophenones **82** (Scheme 18).[75] Treatment of polysubstituted 3-acetylpyrroles under Vilsmeier-Haack reaction conditions afforded the corresponding chlorovinylpyrroles such as **84** (Scheme 19).[76] Vilsmeier formylation of 3-acetyl-4-methylpyrrole gave the acetylenic aldehyde **85** (34%).[77]



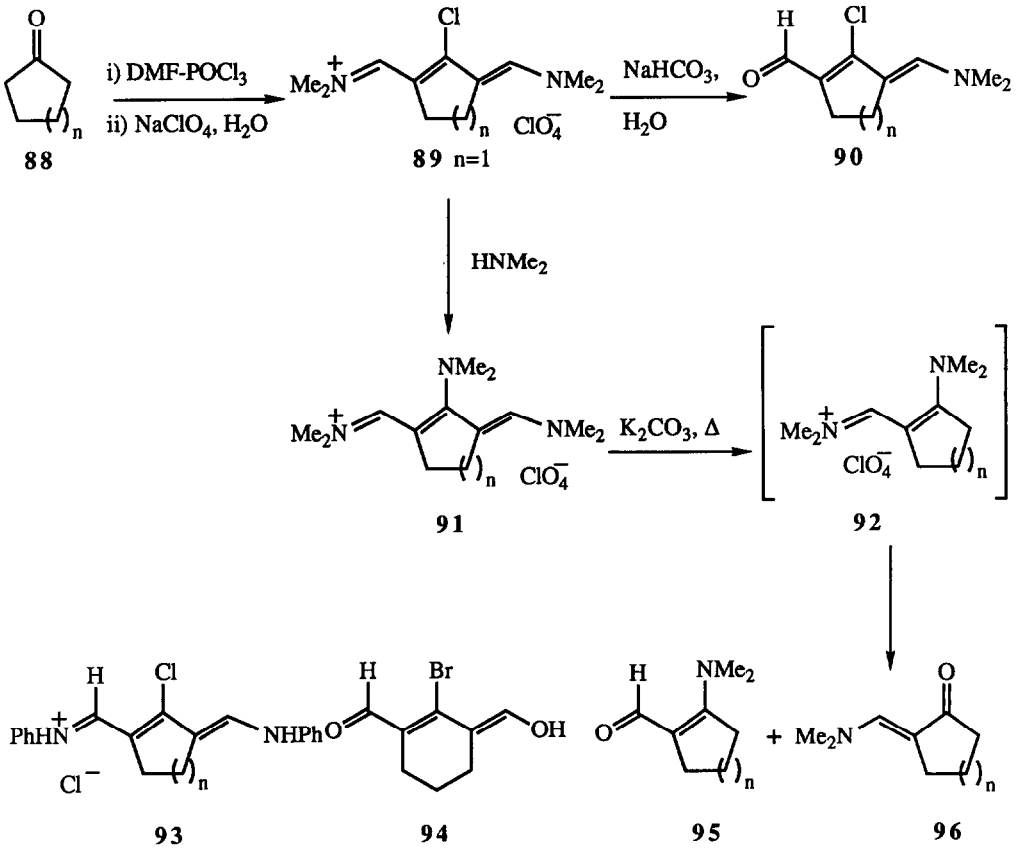
84 85 86 87

Scheme 19

3.3 *Saturated Monocarbocyclic Ketones*

3.3.1 *Unsubstituted Cycloalkanones*

β-Chlorovinylaldehydes are the most abundant of the β-halovinylaldehydes prepared using Vilsmeier reagents, although Arnold and Holy[78] showed that cycloalkanones of five- to eight-membered rings are converted into the corresponding β-bromoacrylaldehydes by DMF-PBr_3 complexes. The corresponding β-chloroacrylaldehydes were reported by Ziegenbein and Lang.[79]

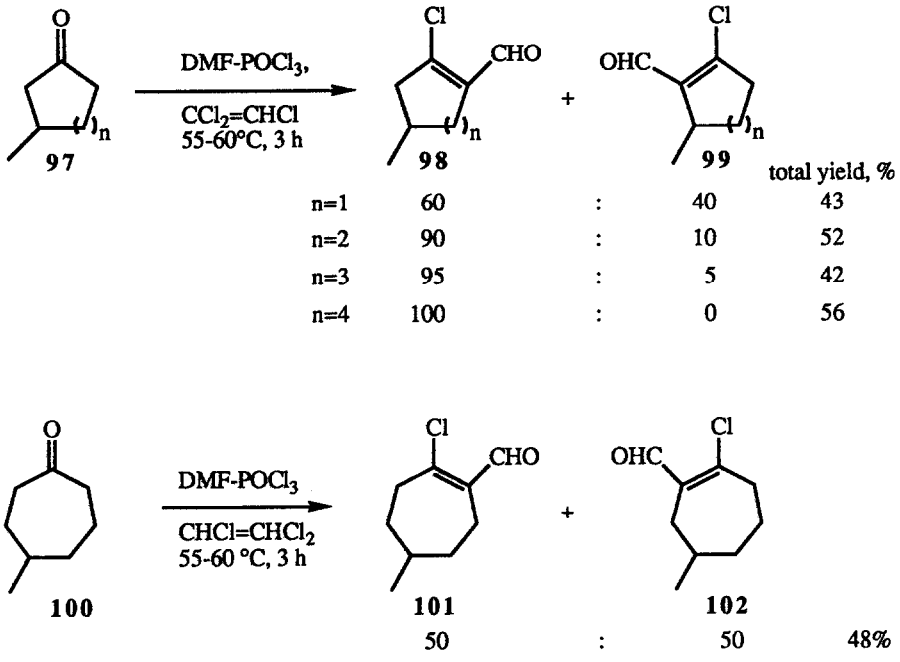


Scheme 20

Cyclobutanone **86** affords the β-chlorovinylaldehyde **87** (Scheme 19).[37] No other product was reported, even when an excess of formylating agent was used. With DMF-$POCl_3$, cyclopentanone was converted into 2-chlorocyclopentene-1-carboxaldehyde (54%),[80] the reaction for cyclohexanone proceeding analogously.[79,81] A large excess of the Vilsmeier reagent, followed by addition of sodium perchlorate solution, afforded the 3-chloropentamethinium salts **89** (n=1), which in the case of the cyclohexanone derivative could be hydrolysed to **90** (n=2; Scheme 20). Work-up of the reaction mixture from cyclopentanone with aqueous potassium carbonate afforded the salt **91**, which with hot aqueous potassium carbonate is evidently hydrolysed to **92** and DMF, since a mixture of the amino aldehyde **95** and the amino ketone **96** is obtained.[37] The conversion of **91** into **96** illustrates the important observations of effectively thermal deformylations of intermediates obtained from certain Vilsmeier reactions. The reaction of cyclohexanone using the bromomethyleniminium salt afforded a small quantity of the doubly substituted aldehyde **94**.[29] The conjugated salts **93** are formed when cyclopentanone and cyclohexanone react with formanilide-$POCl_3$.[33] The formation of pentamethinium salts is controlled by the number of alkyl groups present. No other sites of the pentamethinium unit are available for formylation, and its stability evidently prevents isomerisation into compounds which might undergo deprotonation and hence further reaction with the Vilsmeier reagent.

3.3.2 Monosubstituted Cycloalkanones

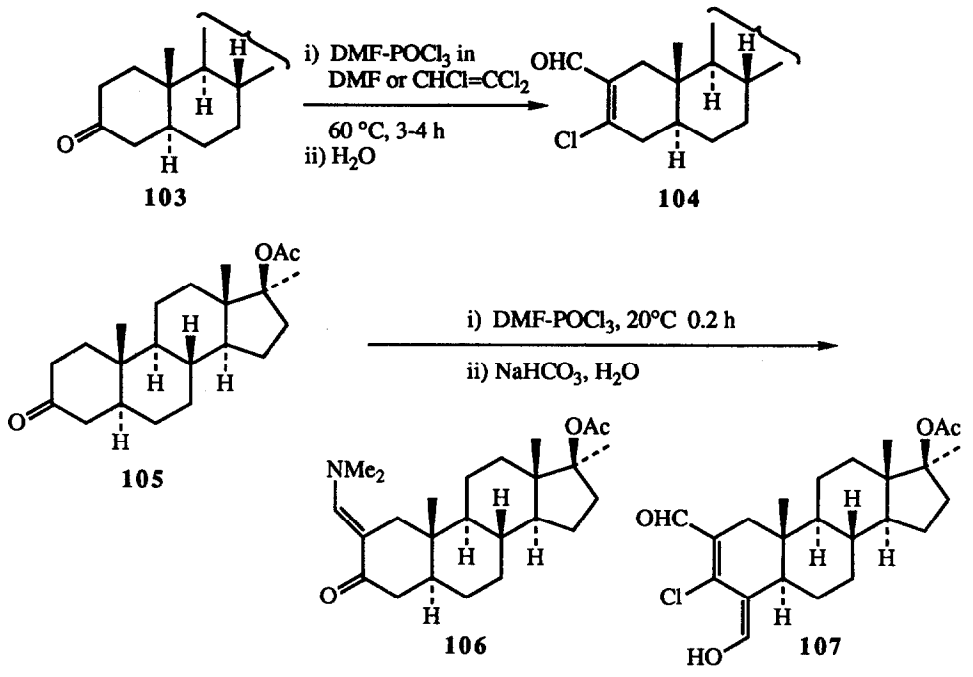
The regiochemistry in the reaction of unsymmetrical monosubstituted cycloalkanones has been little explored. Karlsson and Frejd[42] showed that a relatively small group, a 3-methyl substituent has a large steric influence on the attack of the Vilsmeier reagent, in the cases of six-, seven-, and eight-membered rings, although not for the five-membered case (Scheme 21). An equilibrium mixture of enols was proposed as being present under Vilsmeier-Haack conditions. Interestingly, the larger rings, despite possessing more conformational mobility, exhibit greater regioselectivity. However, 4-methylcycloheptanone gave a 1:1 mixture of the regioisomers **101** and **102**, showing that the 4-methyl group has little influence on the regiochemistry of the reaction.



Scheme 21

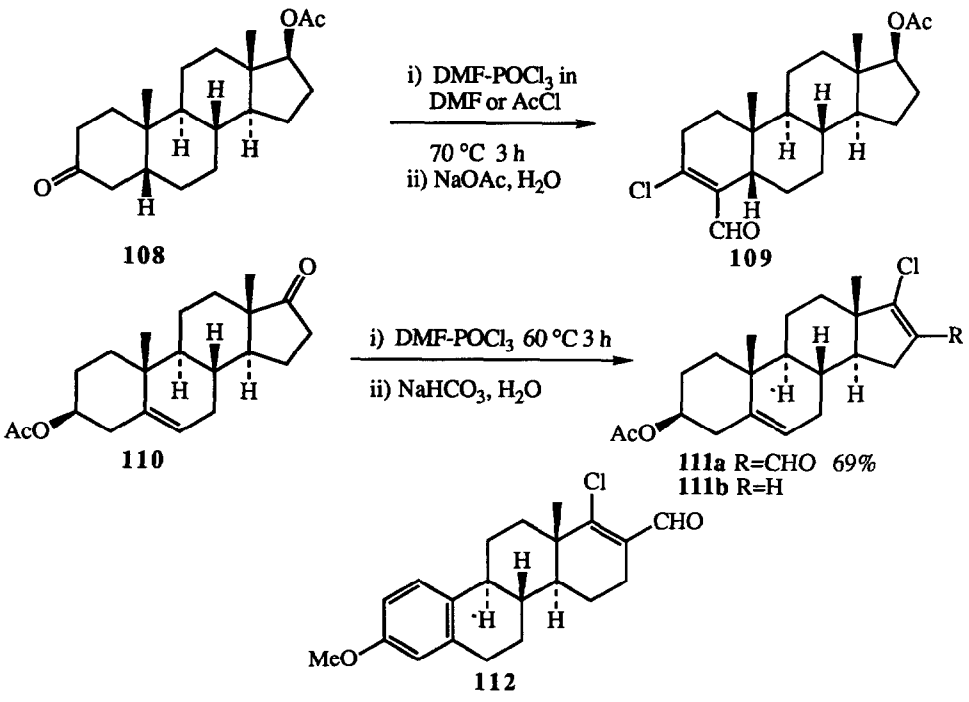
3.3.3 Steroidal Cycloalkanones

3-Keto-5α-steroids afford the 3-chloro-2-formyl-2-ene derivatives with DMF-POCl3; thus 17-acetoxy-5α-androstan-3-one,[82] 17β-acetoxy-17α-methyl-5α-androstan-3-one,[83] and 5α-pregnan-3,20-dione[84] give the corresponding 3-chloro-2-formyl derivatives **104** (22-27%) (Scheme 22). The reaction proceeds with 4,4-disubstituted precursors: 17β-acetoxy-4,4-dimethylandrost-5-en-3-one affords 17β-acetoxy-3-chloro-2-formyl-4,4-dimethylandrosta-2,5-diene (62%) from a reaction with DMF-POCl3 at 50-60°C for 4 hours.



Scheme 22

The regioselectivity of formylation in ring A is markedly influenced by the relative configuration of the A-B ring junction. Thus, the 5β-androst-3-ene **108** is converted into the 3-chloro-4-formyl derivative **109**;[28,82] the use of acetyl chloride as the solvent is unusual. Chloroformylation of a steroidal ketone having the carbonyl group at a position other than C-3 usually affords the corresponding β-chlorovinylaldehyde. Thus, 3β-hydroxyandrost-5-en-17-one 3-acetate **110** is chiefly converted into the aldehyde **111a**, with the chloroalkene **111b** being formed as a by-product (Scheme 23). A *D*-homosteroidal ketone has been converted by DMF-POCl3 into the chlorovinylaldehyde **112**.[85]

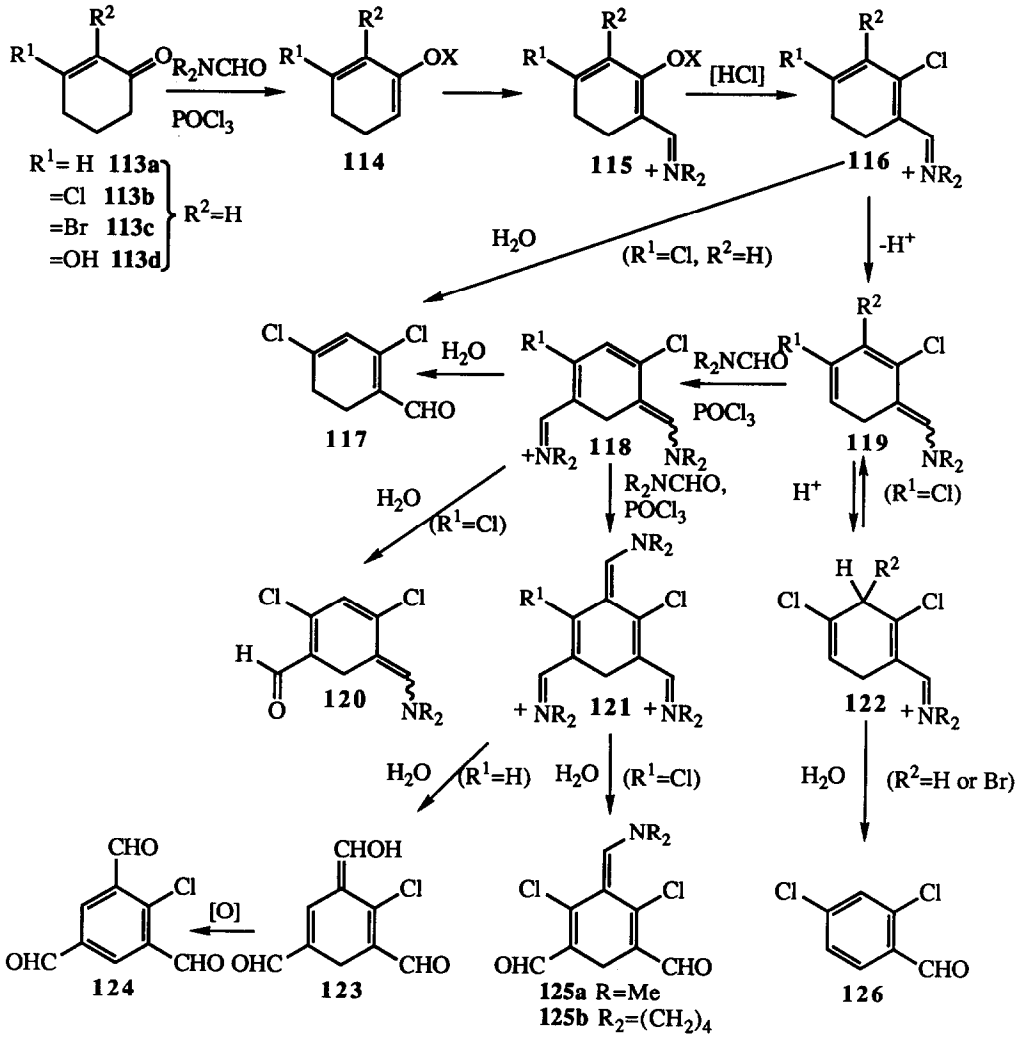


Scheme 23

3.4. α,β-Unsaturated Carbocyclic Ketones.

3.4.1. 2-Cycloalken-1-ones

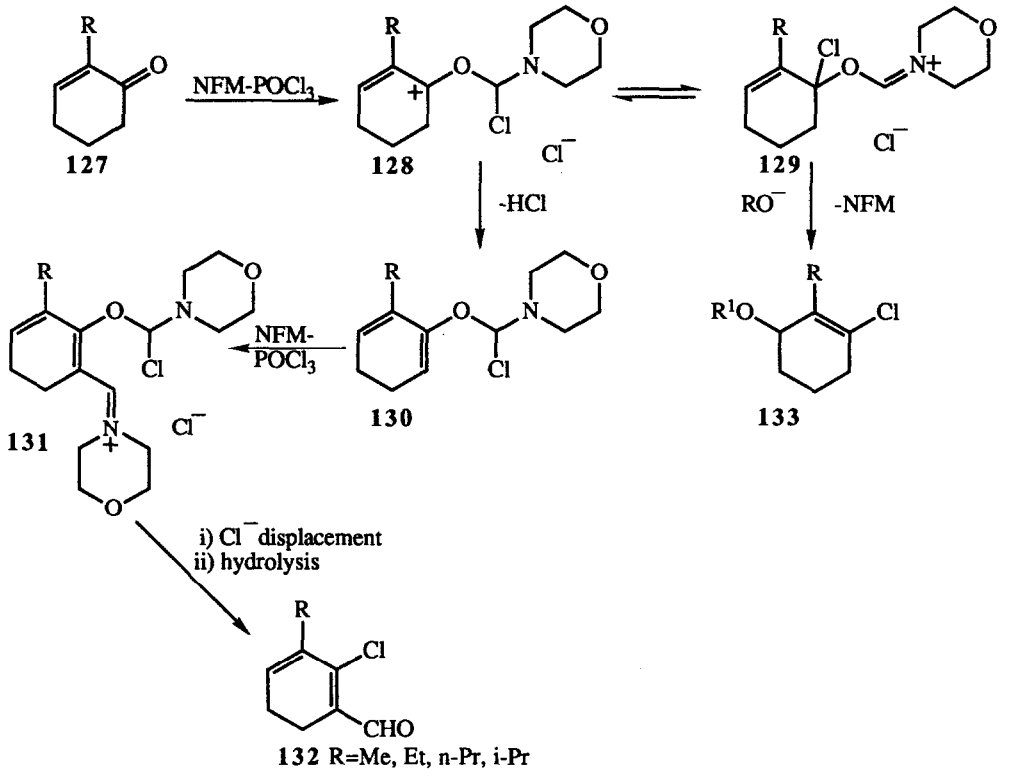
Of the 2-cycloalken-1-ones reacted with Vilsmeier reagents, 2-cyclohexen-1-ones are the most common. The exothermic reaction of 2-cyclohexen-1-one with *N*-formylmorpholine (NFM)-POCl3 in trichloroethylene at 20°C afforded a deep red mixture which upon hydrolysis gave the somewhat unstable dialdehyde **123**;[86] upon keeping at 25°C for several weeks, aerial oxidation afforded the trialdehyde **124**.



Scheme 24

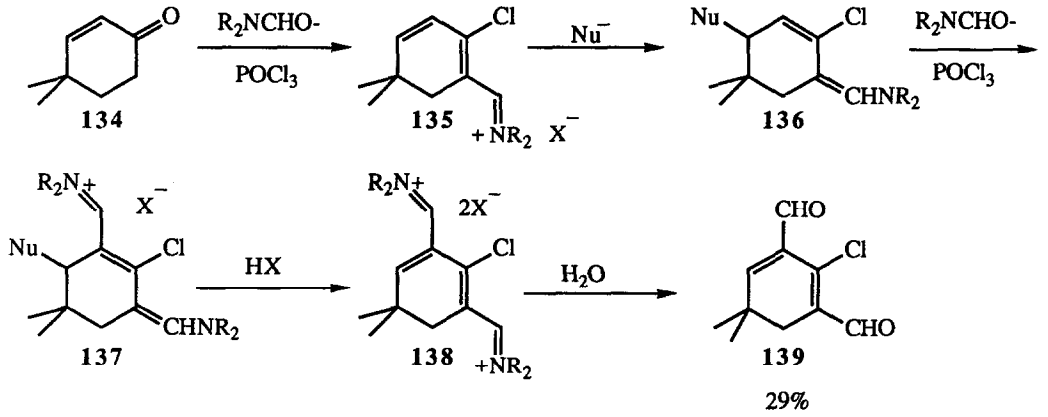
Scheme 24 provides a pathway which unifies the experimental observations or the reaction of the 3-substituted-2-cycloalken-1-ones **113a-113c** with Vilsmeier reagents; cyclohexane-1,3-dione **113d** is discussed in section 3.6.2. There is substantial evidence

for the involvement of an enolic intermediate **114** (in which X may be $CH(Cl)NR_2$ rather than the enol, X=H, or a phosphate derivative). For ketones **113a-113c**, the early stages of the reaction apparently do not involve the C=C double bond. A common intermediate of the form **121**, stabilised by extensive delocalisation, is considered to be present prior to hydrolytic work-up. For the ketones **113b** and **113d**, partial hydrolysis affords the dialdehydes **125** (section 3.6.2), whereas for 2-cyclohexen-1-one, the intermediate **121** (R^1=H) is more susceptible to nucleophilic attack, and the enolic dialdehyde **123** is formed, which is remarkable for its stability over the benzenoid tautomer.



Scheme 25

For 2-alkyl-2-cyclohexen-1-ones, intermediates of the form **116** (R^1=H) are evidently involved because hydrolytic work-up affords the aldehydes **132**. The allylic alcohols **133** (R≠H) are also formed. Scheme 25 shows a pathway consistent with current observations. The presence of a cationic allylic species, possibly **128** or its equivalent, was confirmed by quenching the Vilsmeier reaction mixture with alkoxide, whereby the corresponding alkoxy ethers **133** (R^1=alkyl) were obtained.[87] The above mechanistic features are compatible with the formation of the dialdehyde **139** from 4,4-dimethyl-2-cyclohexen-1-one **134** and NFM-$POCl_3$ (Scheme 26).[87,88]

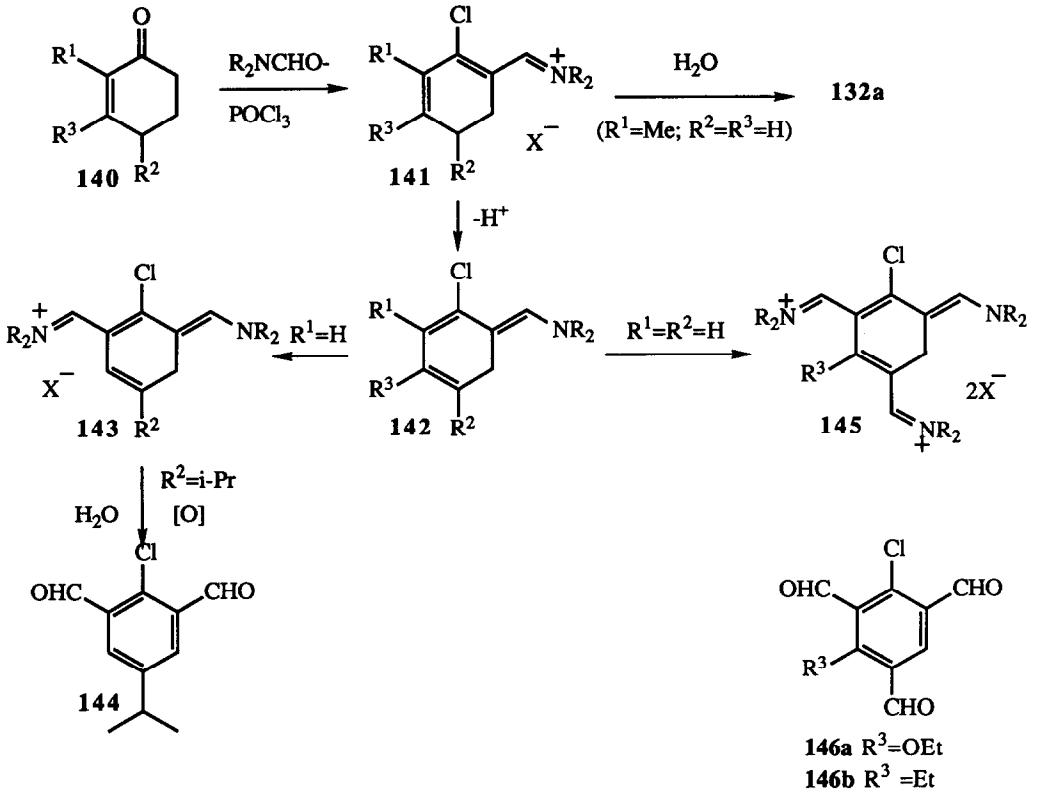


Scheme 26

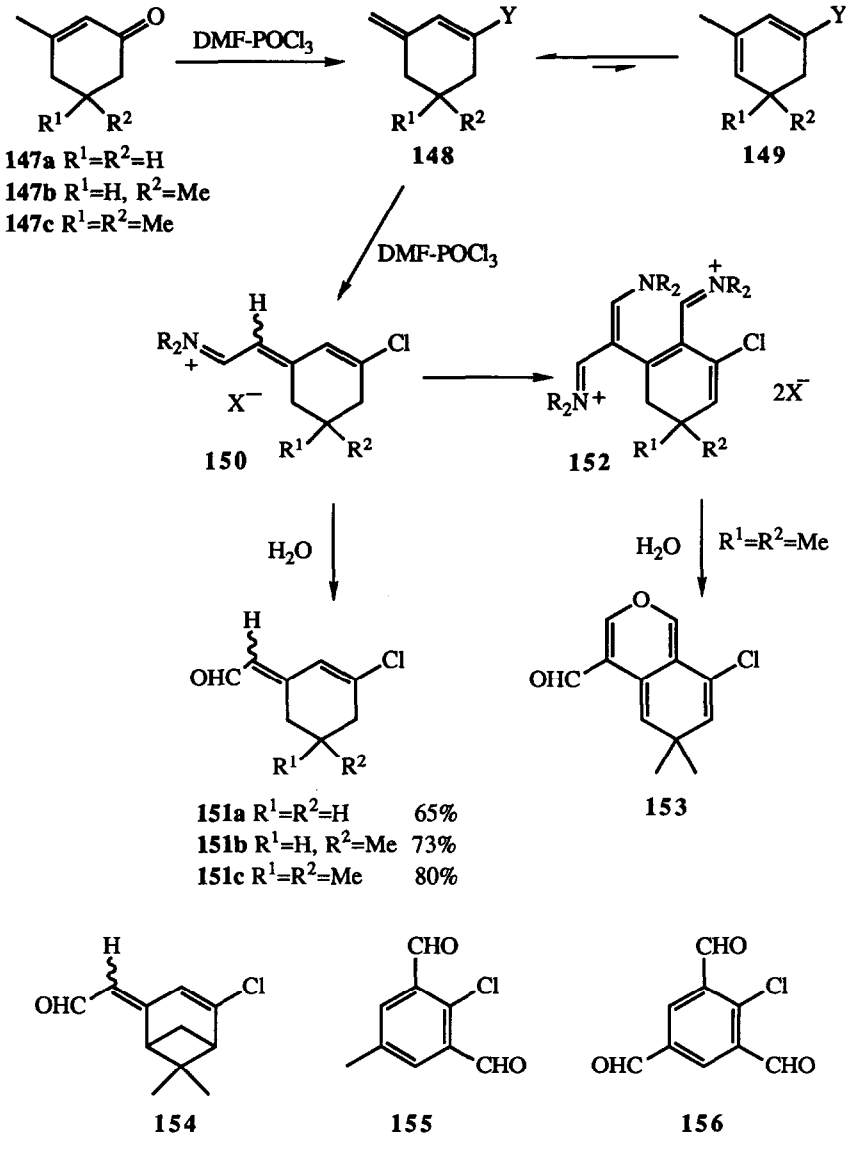
A unified pathway[87] illustrating typical processes involving 2-cyclohexen-1-ones lacking a methyl group at C-3 is given in Scheme 27. For 3-methyl-2-cyclohexen-1-one and its 5-substituted derivatives **147** an entirely different course is followed[87-89] (Scheme 28). Although it is uncertain whether Y=Cl or an oxygenated moiety in the exocyclic alkene **148**, several exocyclic alkenes analogous to **148** are known to be thermodynamically favoured over their endocyclic isomers **149**.

Isophorone **147c** affords **151c**[90] with 2 equiv. of the Vilsmeier reagent, but with a large excess of the reagent undergoes iminoalkylation to give the polymethinium species **152**, which is converted, during hydrolysis into the 4*H*-pyran **153** (Scheme 28).[87,88] If the reaction of isophorone **151c** with DMF-$POCl_3$ (2 equiv.) is quenched after 15 minutes an 80% yield of a mixture of three chloro-dienes is obtained.[88] From the aldehydes **151a-151c**, a mixture of *(E)*- and *(Z)*-isomers was obtained. *(1S)*-(-)-Verbenone afforded the chlorinated aldehyde **154**.

Trialdehydes **146** have been obtained by the Vilsmeier reaction of cyclohexenones prepared by Birch reduction. The trialdehyde **156** was formed from cyclohexenone in a Vilsmeier reaction, and the dialdehyde **155** from 4-methyl-2-cyclohexen-1-one.[91]



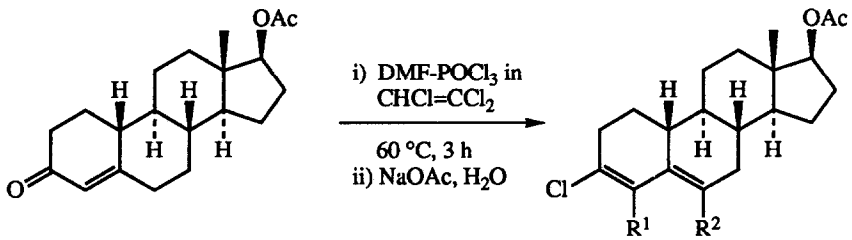
Scheme 27


DMF-POCl3
147a R1=R2=H
147b R1=H, R2=Me
147c R1=R2=Me
148
149
DMF-POCl3
150
152
2X−
H2O
H2O
R1=R2=Me
151a R1=R2=H 65%
151b R1=H, R2=Me 73%
151c R1=R2=Me 80%
153
154
155
156

Scheme 28

3.4.2 α,β-Unsaturated Steroidal Ketones

There have been few papers in this area since it was last reviewed.[1,7] α,β-Unsaturated steroidal ketones usually afford a mixture of products of which the halo-diene is the major component. Thus, 3-oxo-4-ene steroids when heated with DMF-$POCl_3$ in an inert solvent afforded the corresponding 3-chloro-3,5-dienes; 3-oxo-1,4,6-trienes gave the 3-chloro-1,3,5,7-tetraenes.[92] However, 19-nortestosterone acetate **157** gave the aldehydes **158b** and **158c** in equal amounts, in addition to the chlorodiene **158a** (Scheme 29).[93] Whereas enolisation of the 3-oxo group was postulated as the first step,[93] both for the 19-methyl-3-oxo-enes and for the 19-nor-compounds, only in the latter series was the Vilsmeier reagent able to attack the C-4 and C-6 positions, prior to subsequent displacement of the 3-oxygenated function by chloride. The steric hindrance of the 19-methyl group prevents further reaction of the 3-halo-3,5-dienes with the Vilsmeier reagent.



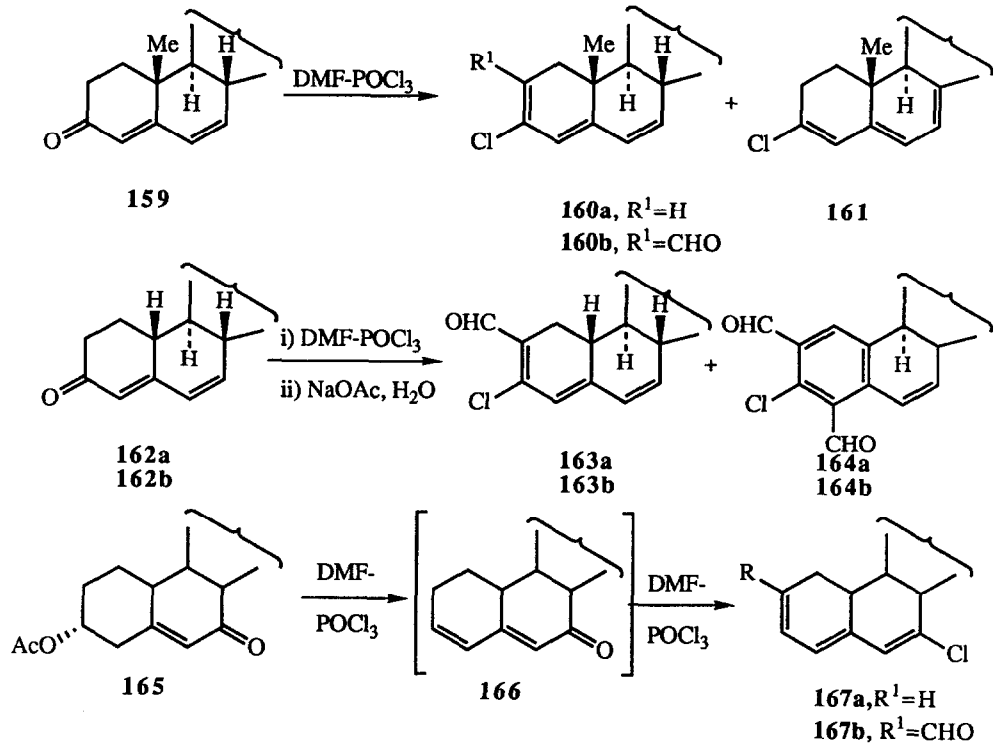
157

158a $R^1=R^2=H$
158b $R^1=H$, $R^2=CHO$
158c $R^1=CHO$, $R^2=H$

Scheme 29

A series of steroidal 4,6-dien-3-ones afforded with DMF-$POCl_3$ a mixture of 3-chloro-2,4,6-trienes **160a**, 3-chloro-2-formyl-2,4,6-trienes **160b**, and 3-chloro-3,5,7-trienes **161** (Scheme 30). The steroid **160a** is implicated as an intermediate since it was converted by DMF-$POCl_3$ into the aldehyde **160b**.[39] In the cases of 17β-acetoxyoestra-4,6-dien-3-one **162a** and 17-acetoxy-19-norpregna-4,6-dien-3,20-dione **162b**, the expected aldehydes **163a** and **163b**, respectively, are accompanied by the aromatic dialdehydes **164a** and **164b**, formed by oxidation.[39] 3β-Acetoxy-5-ene-7-ketosteroids **165** eliminate acetic acid under Vilsmeier conditions giving the 3,5-dien-7-ones **166**

which are then converted into a mixture of chlorinated steroids **167a** and **167b**. Formylation of triene **167a** gives the aldehyde **167b**.[38] 3-Alkoxy-3,5-dienes undergo attack by Vilsmeier reagents at C-6 only.[94]

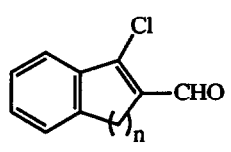


Scheme 30

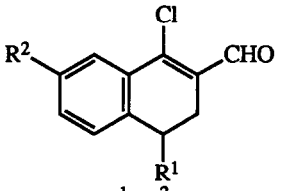
3.4.3 Benzo-Fused Cycloalkanones

Benzo-fused cycloalkanones are usually converted by Vilsmeier reagents into the corresponding chlorovinylaldehydes in good yield and under mild conditions (Scheme 31). Under normal conditions, formylation of the aromatic ring does not occur. The resulting chlorovinylaldehydes have been used in the synthesis of a wide variety of polycondensed heterocycles.[95-98]

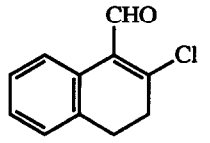
1-Indanone, α-tetralone and benzosuberone afford the corresponding β-chlorovinylaldehydes **168a**, **168b** (77%)[78] and **168c** (75%)[59] respectively. Derivatives of α-tetralone with alkyl groups on either ring afford the expected β-chlorovinylaldehydes **169**.[97] No aromatic formylation is observed even when 6- or 7-methoxy groups are present. β-Tetralones usually give the 2-chloro-3,4-dihydro-1-naphthalene-carboxaldehyde derivatives [*e.g.* **170** is formed[99] (44%)], although these decompose much more readily than the isomers such as **169**.[100] Some β-tetralones afford the corresponding 2-chloro-1,3-naphthalenedicarboxaldehydes. The reaction of β-tetralone with $HCONH_2$-$POCl_3$ afforded 5,6-dihydrobenzo[*f*]quinazoline[101] in very low yield.



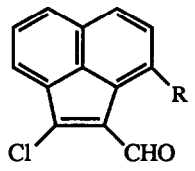
168a n=1
168b n=2
168c n=3



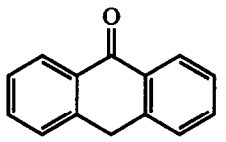
169a R^1=R^2=H
169b R^1=Me, R^2=H
169c R^1=H, R^2=Me



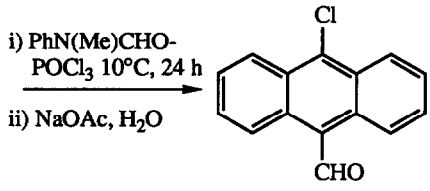
170



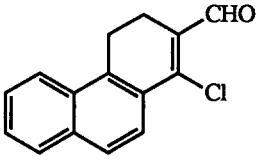
171a R=H
171b R=Me



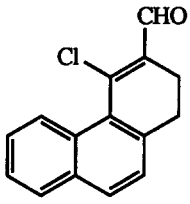
172



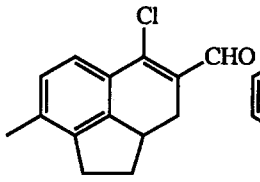
173 98%



174



175



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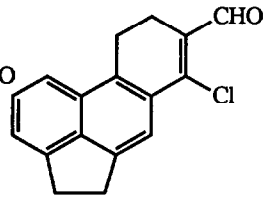
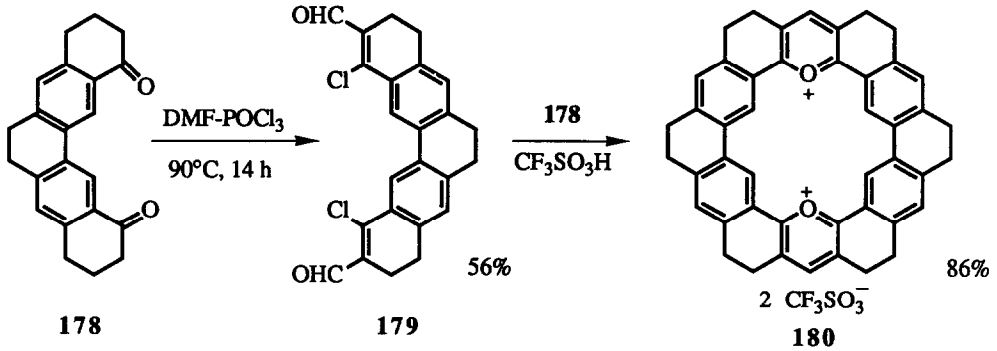


177

Scheme 31

Acenaphthenone with DMF-$POCl_3$ in trichloroethylene affords the aldehyde **171a** (80%) (50°C, 3 h);[79] the methyl derivative **171b** was similarly obtained.[97] Other ketones of the α-tetralone type have been converted into the corresponding aldehydes **174-177**. The conversion of anthrone **172** into 10-chloro-9-anthracenecarboxaldehyde **173** is probably the earliest reported example of a 'chloroformylation' of a methylene ketone.[102] Using Vilsmeier methodolgy, the diketone **178** was converted into the dialdehyde **179** which afforded a convergent and unambiguous route to the intricate macrocyclic pyrylium salt **180** (Scheme 32).[95]



178 **179** **180**

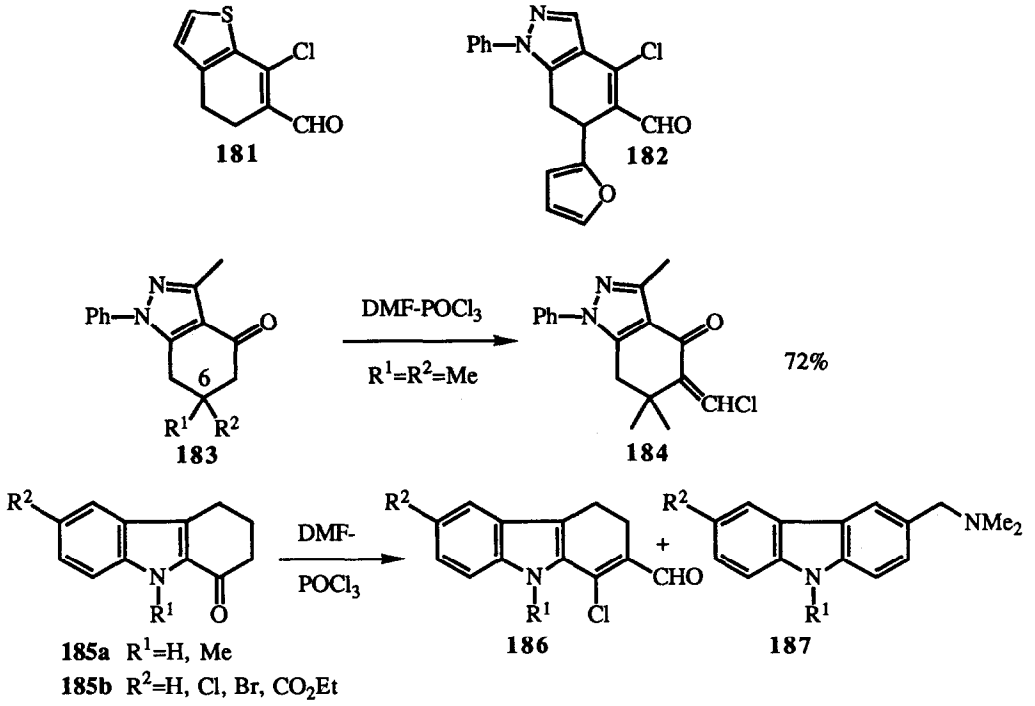
Scheme 32

3.4.4 Cycloalkanones fused to Heteroaromatic Rings

The aldehyde **181** was prepared from the corresponding ketone.[97] The indazolecarboxaldehyde **182** was also directly prepared by the action of a Vilsmeier reagent on the corresponding ketone.[103] A number of other 4-oxo-4,5,6,7-tetrahydroindazoles **183** were investigated. Aldehydes were obtained when C-6 was not disubstituted, but the chlorovinyl ketone **184** was formed from the 6,6-*gem*-dimethyl ketone **183** (Scheme 33).[104]

The Vilsmeier formylation of 1-ketotetrahydrocarbazoles **185** gave appreciable quantities of aromatised products **187**, in addition to the chlorovinylaldehydes **186** as the major products (Scheme 33).[105]

The benzo[*b*]thiophen-4-one **188** reacts with the Vilsmeier-Haack reagent giving four products **189-192**, which demonstrates competition between formylation of the carbonyl group and the thiophene ring (Scheme 34).[106]

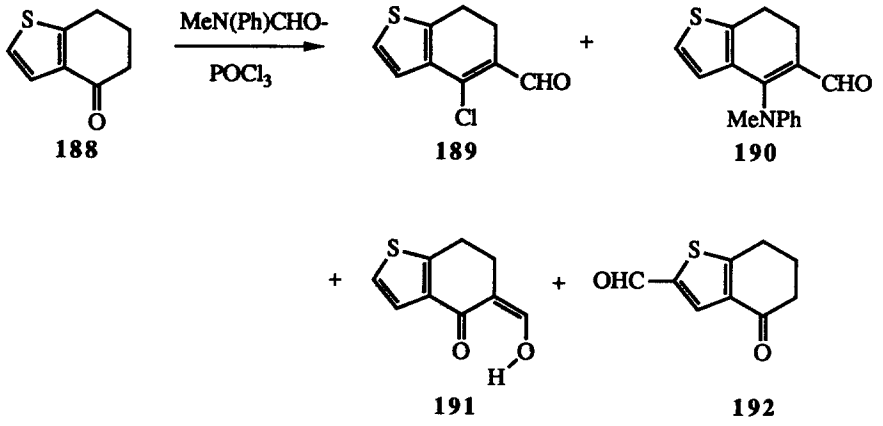


Scheme 33

3.5 Cyclic Ketones with One or More Heteroatoms in the Ketone Ring

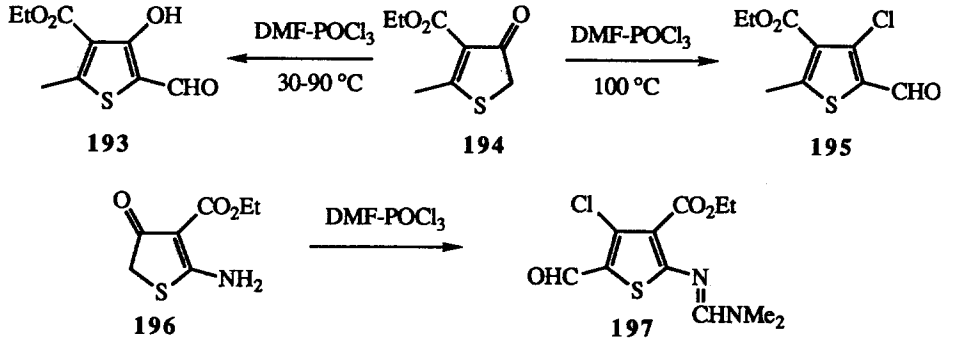
3.5.1 Monocyclic Systems

The principal reactions are of five- and six-membered heterocyclic ketones containing either a sulphur or an oxygen atom in the ring. Aromatisation to formylthiophenes is typical. Vilsmeier reaction of the keto-ester **194** is temperature-dependent.[107] Some 4-oxo-4,5-dihydrothiophenes **196** have been converted[108] by Vilsmeier reagents into 4-chloro-5-formylthiophene derivatives **197** which are key intermediates in the preparation of thiophene azo dyes (Scheme 35).



188 189 190 191 192

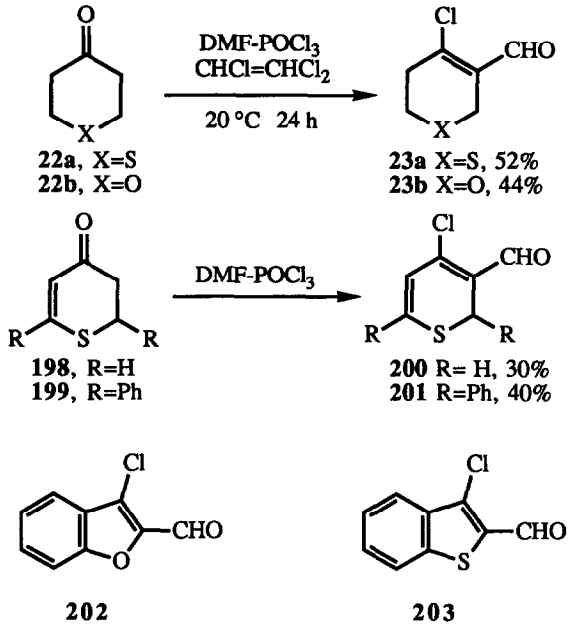
Scheme 34



193 194 195 196 197

Scheme 35

Tetrahydro-4*H*-thiopyran-4-one **22a** and tetrahydro-4*H*-pyran-4-one **22b** are converted at ambient temperatures by DMF-POCl3 into the respective chlorovinylaldehydes **23a** and **23b**[109] which are suitable for further functionalisation. Two 2,3-dihydro-4*H*-thiopyran-4-ones afforded the 4-chloro-2*H*-thiopyran-3-carboxaldehydes **200a**[109] and **201** (Scheme 36).[110]

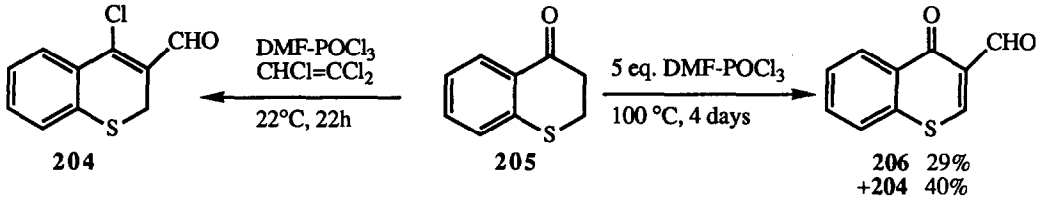


Scheme 36

3.5.2 Bicyclic Systems

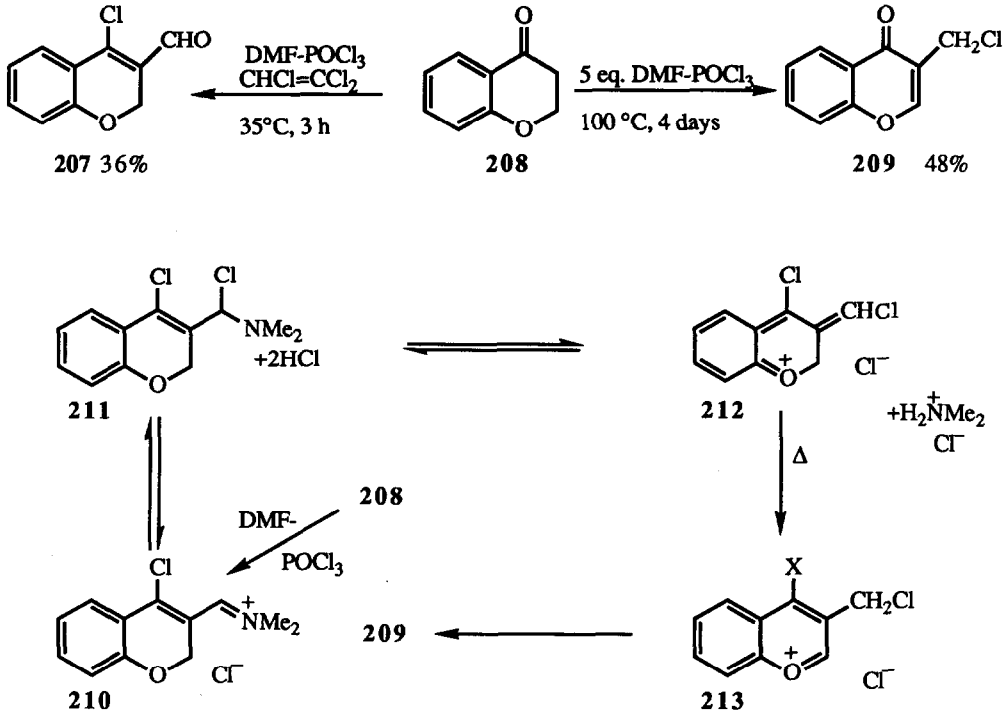
The reaction of 3-coumaranone with DMF-POCl3 gave 3-chloro-2-formylbenzo[*b*]furan **202**.[111] The aldehyde **203** is efficiently prepared[112] by reacting 3-methoxybenzo[*b*]thiophene with DMF-POCl3.

The action of DMF-POCl3 on thiochroman-4-one **205** was shown[59,109] to afford the β-chlorovinylaldehyde exclusively at temperatures below 50°C, but at 100°C, 3-formylthiachromone **206** was formed in appreciable quantity.[109] A mechanism involving oxidation by the Vilsmeier reagent was tentatively proposed (Scheme 37).



Scheme 37

The reaction of chroman-4-one **208** is also temperature-dependent,[109] the expected aldehyde **207** [59,109] being obtained at 35°C. The formation[109] of 3-(chloromethyl)chromone **209** at 100°C is thought to proceed by isomerisation to a 3-(chloromethyl)benzo[*b*]pyrylium cation **213** (Scheme 38).

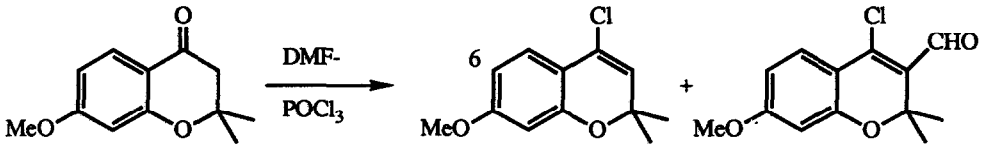


Scheme 38

The reaction of substituted chroman-4-ones with Vilsmeier reagents illustrates the importance of intricate steric effects in Vilsmeier reactions with ketones. 4-Chloro-3-carboxaldehydes can be obtained from many C-2 unsubstituted chroman-4-ones,[59,113] but a single 2-methyl group is sufficient to block 3-formylation. 7-Methoxy-2-methylchroman-4-one[114] affords the 4-chlorochromene in high yield.[115] The Vilsmeier formylation of chromenes is also usually prevented by substitution at C-2,[116,117] although the electronic effect of a 7-methoxy group, if introduced into 2,2-dimethyl-2*H*-chromene is sufficient to promote 6-formylation.[117] The interplay of steric and electronic effects operating during the Vilsmeier formylation of 2,2-dimethylchroman-4-one derivatives has been studied.[115] The high degree of solvation

of the Vilsmeier reagent in the mildly polar solvents normally employed[1] renders the reaction particularly susceptible to steric effects.

2,2-Dimethylchroman-4-one derivatives **214** gave high yields of the corresponding 4-chloro-2*H*-chromenes **215** and only a small quantity (or none) of the chlorocarboxaldehydes **216** (Scheme 39). Prolonged reaction times did not increase the yield of the latter; instead, formylation at C-6 of **215** occurred. The results indicate that the chlorocarboxaldehydes **216** arise not by formylation of **215**, but presumably by formylation of an enolic precursor.

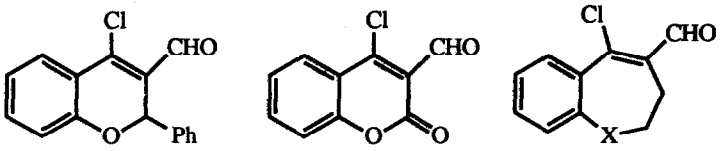


214 **215** **216**

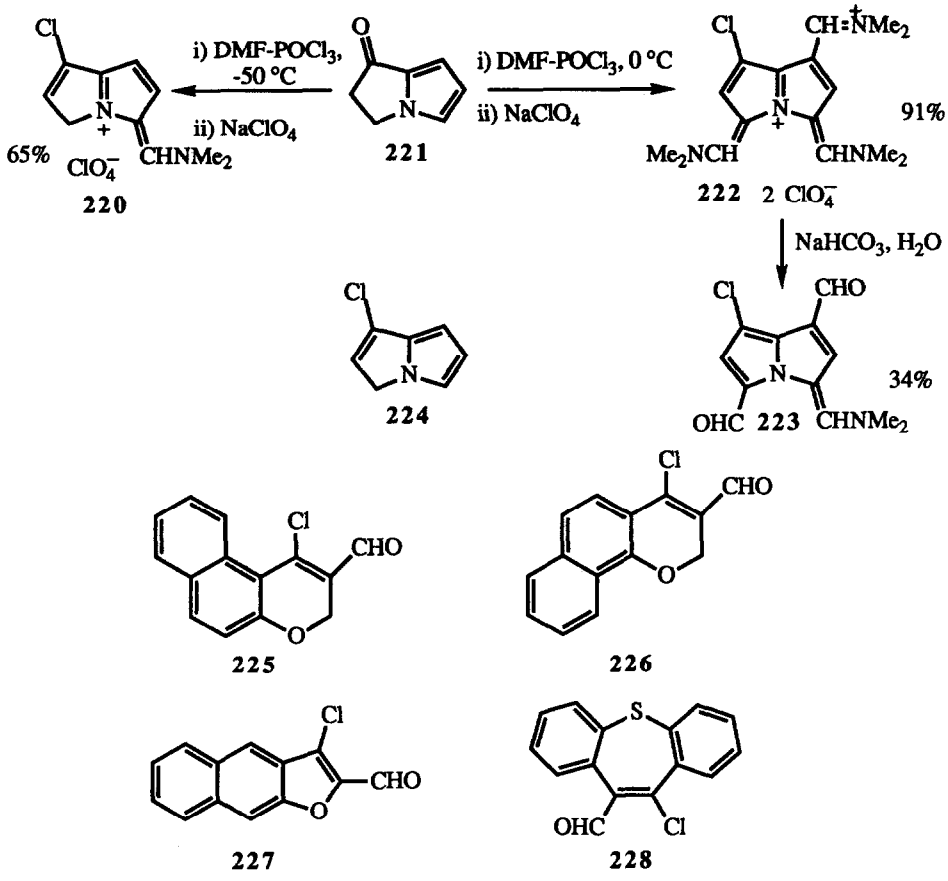
Scheme 39

Flavanone affords the aldehyde **217**[118] when treated with DMF-$POCl_3$. 4-Chloro-3-formylcoumarin **218** has also been prepared[119] by a Vilsmeier reaction. The heterocyclic aldehydes **219a** and **219b** have been prepared.[59] Reaction of heterocycles containing a carbonyl group and a nitrogen atom in the same ring with Vilsmeier reagents are rare.

2,3-Dihydro-1*H*-pyrrolizin-1-one **221** is converted by DMF-$POCl_3$ into **220** and **222**, depending on the reaction conditions (Scheme 40).[120] The chloroalkene **224** was detected, and it is surmised that enolisable C=O groups of acylated pyrroles are first converted into chloroalkenes, formylation occurring subsequently.



217 **218** **219a** X=S 54 %
219b X=O 70 %



Scheme 40

3.5.3 Polycyclic Systems

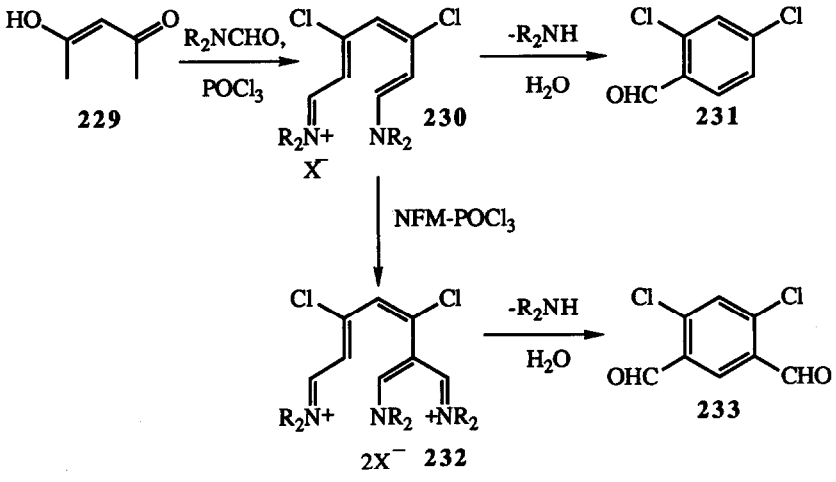
Angularly annellated derivatives of chroman-4-one are also converted into the corresponding β-chlorovinylaldehydes **225**[121,122] and **226**.[121] The formylated naphtho[2,3-*b*]furan **227** was similarly prepared from the corresponding naphtho[*b*]furanone.

Vilsmeier reaction of 10,11-dihydrobenzo[*b*,*f*]thiepin-10-one with DMF-POCl3 in trichloroethylene at 80°C gave the carboxaldehyde **228** (52%).[123]

3.6 Diketones

3.6.1 Acyclic 1,3-Diketones

Holy and Arnold showed[50] that treatment of acetylacetone **229** with DMF-$POCl_3$ afforded 2,4-dichlorobenzaldehyde **231** (84%; Scheme 41). The route involves the heptamethinium species **230** which undergoes ring-closure, probably in a pericyclic process, although a closure of the Enamine-Exo-6-Exo-Trig type cannot be excluded. Katritzky and Marson showed[86] that the course of the reaction depends on the nature of the dialkylformamide; 4,6-dichloroisophthalaldehyde **233** was the major product when the Vilsmeier complex derived from *N*-formylmorpholine-$POCl_3$ was used. The relative bulk of the R group when R_2N = morpholino presumably reduces the rate of ring-closure of the cation **230**, so that further iminoalkylation can occur giving the dicationic species **232** which then yields the dialdehyde **233**.

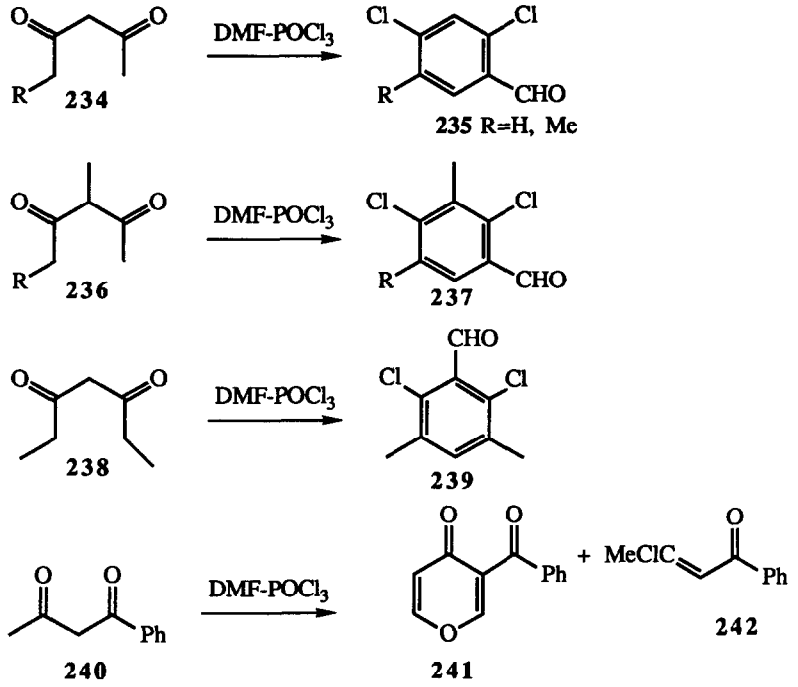


Scheme 41

A seminal study[51] of the action of Vilsmeier reagents with acyclic β-diketones showed that dichlorobenzaldehydes (*e.g.* **235**, **237**, and **239**) were formed, although steric hindrance markedly decreased the yields when the pentasubstituted benzene **239** was formed (Scheme 42). A terminal acetyl group appears to be necessary for cyclisation

to 2,4-dichlorobenzaldehydes. Replacement of one of the alkyl groups by phenyl necessarily prevented the formation of a substituted benzene and in the case of benzoylacetone **240** gave the products **241** and **242**.

A comparative study[124] of the ligand reactivity at the 3-position of trisacetylacetonates of Cr(III) and Co(III) by means of Vilsmeier-Haack reactions has been made.

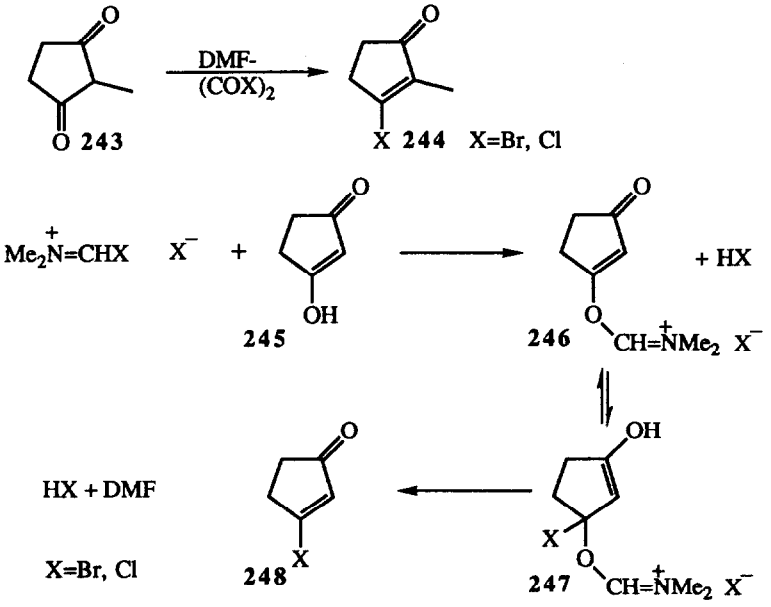


Scheme 42

3.6.2 Cyclic 1,3-Diketones

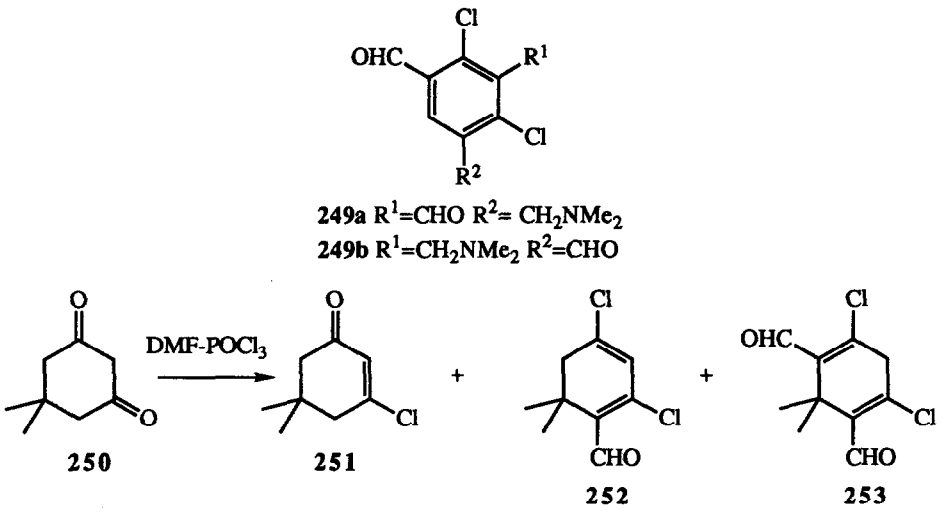
3-Halo-2-cycloalken-1-ones **244** can be prepared[125] in excellent yield by the reaction of cycloalkane-1,3-diones with Vilsmeier reagents prepared from DMF and $(COCl)_2$ or $(COBr)_2$. A mechanism involving initial attack at oxygen is proposed (Scheme 43). The absence of formylated products is a notable feature since β-chlorovinylaldehyde moieties are usually introduced. Thus, the cross-conjugated dialdehyde **125a** (Scheme 24,

section 3.4.1) was formed (24%) by treating cyclohexane-1,3-dione **113d** with DMF-$POCl_3$ at 20°C.[126] The same reaction was also observed for the 3-halo-2-cyclohexen-1-ones **113b** and **113c**. The pathway by which dialdehydes **125** are formed is outlined in Scheme 24. The methinium species is thought to be the final product of the reaction prior to hydrolysis. The stability of alkenes **121** and **125** towards aromatisation has been investigated;[127] heating the reaction mixture under reflux afforded the pentasubstituted benzene **249a** (20%) yield. MNDO calculations indicated an energy difference between **125a** and **249b** of 13 kcal mol^{-1} in favour of the arene **249b**. Reaction of cyclohexane-1,3-dione with DMF-$POCl_3$ in chloroform at 50°C afforded 2,4-dichloro-1-formylcyclohexa-1,3-diene **117**. This formation of a less substituted aldehyde at higher temperatures suggests that thermal decomposition of **121** (known to be formed at 20°C) can occur (presumably by nucleophilic attack, probably involving addition of HCl to the dication **121**) to give **118**, and hence the aldehyde, **117**. A related thermal deformylation was referred to in section 3.3.1.



Scheme 43

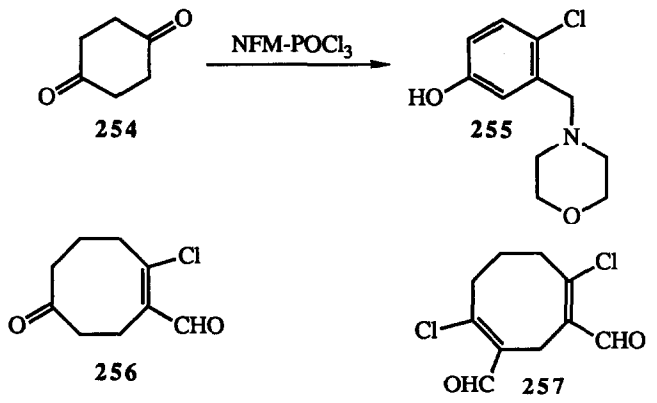
The general pathways depicted in Scheme 24 are consistent with the products formed by the action of DMF-$POCl_3$ on dimedone **250** (Scheme 44).[128] The dialdehyde **253** could be derived from the *gem*-dimethyl analogue of the dication **121** by nucleophilic attack leading to dealkylation; alternatively, the reaction might not proceed beyond the formation of the *gem*-dimethyl analogue of the cation **118**.



Scheme 44

3.6.3 1,4- and 1,5-Diketones

Few examples have been reported. Cyclohexane-1,4-dione **254** reacts with *N*-formylmorpholine-$POCl_3$ to give the phenol **255** (Scheme 45).[86] The probable intermediates are not stabilised by strongly electron-withdrawing groups, as are the methinium species depicted in Scheme 24, so that pathways leading to aromatisation are favoured. Chloroformylation of cyclooctane-1,5-dione under mild conditions gave the keto-aldehyde **256**. The dialdehyde **257** is formed[129] from cyclooctane-1,5-dione and DMF-$POCl_3$.



Scheme 45

4. REACTIONS OF AMIDIC CARBONYL COMPOUNDS

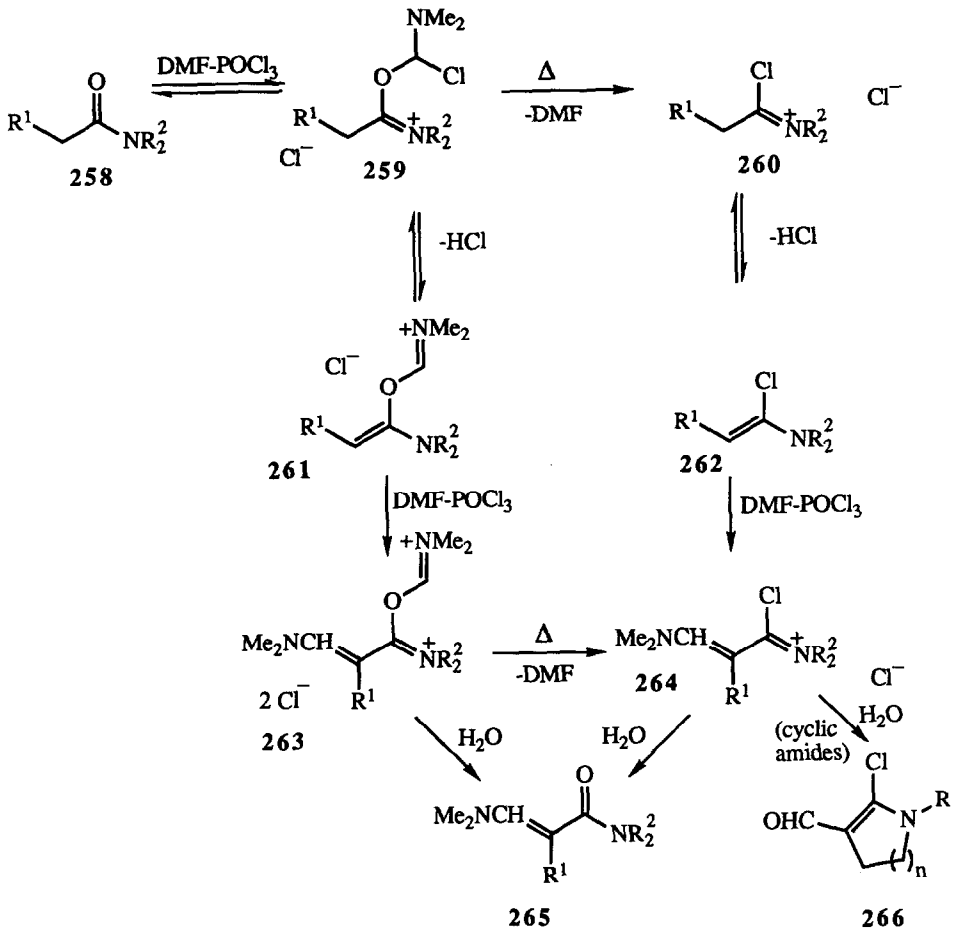
Similar mechanistic features apply to the reaction of carbonamides with Vilsmeier reagents as apply to ketones. The greater basicity of the carbonyl oxygen atom in carbonamides as compared with ketones suggests that the chloromethyleniminium cation will usually initially attack the carbonyl oxygen atom in the former cases (which may also apply to ketones). Since the last reviews,[1,8] the area has grown substantially, particularly in the reaction of lactams with Vilsmeier reagents. In this Section are emphasised reactions in which the amide group undergoes transformation into other functionalities. However, Bischler-Napieralski-type cyclisations, extensively reviewed elsewhere, are not considered in this Report.

4.1 Amides

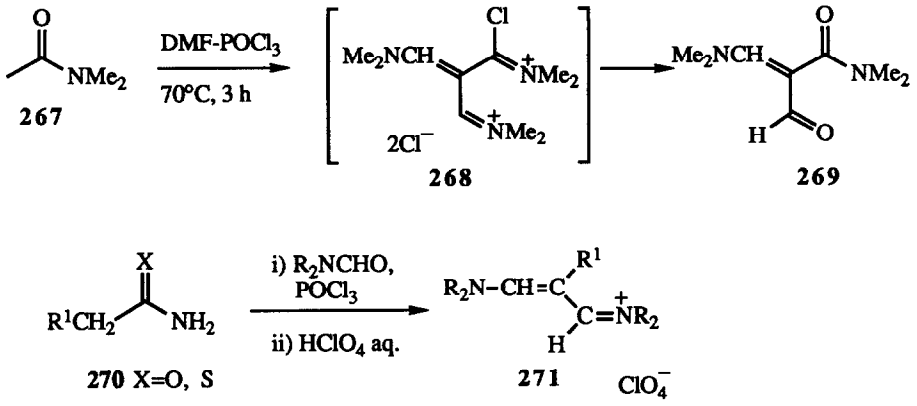
Scheme 46 outlines the general pathways[1] involved when amides or lactams react with Vilsmeier reagents. Chlorinated products are derived by initial *O*-acylation, followed by nucleophilic attack by chloride ion to give an enamine **262** which rapidly reacts to give the stable intermediates **264**; hydrolysis can afford either an amide **265** or the enaminoaldehyde **266**. For some simple amides, chlorinated products are not observed, so that the iminium species **259** may be deprotonated to give **261** followed by

subsequent acylation. Thus, *N,N*-dimethylacetamide **267** is converted into the highly functionalised amide **269** (Scheme 47). The dehydrating properties of Vilsmeier reagents may lead to nitriles, presumably *via* the iminium species **260**.

Synthesis of the trimethinium salts **271** using Vilsmeier reagents has been extended from carboxylic acids to acetamides and thioamides.[130]

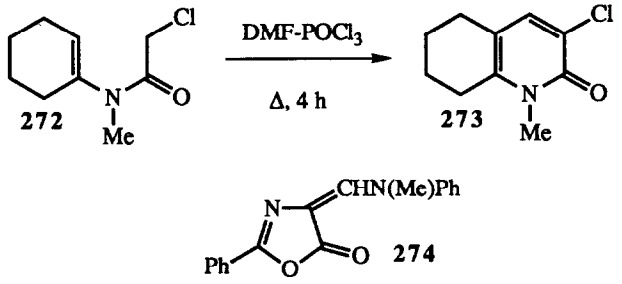


Scheme 46



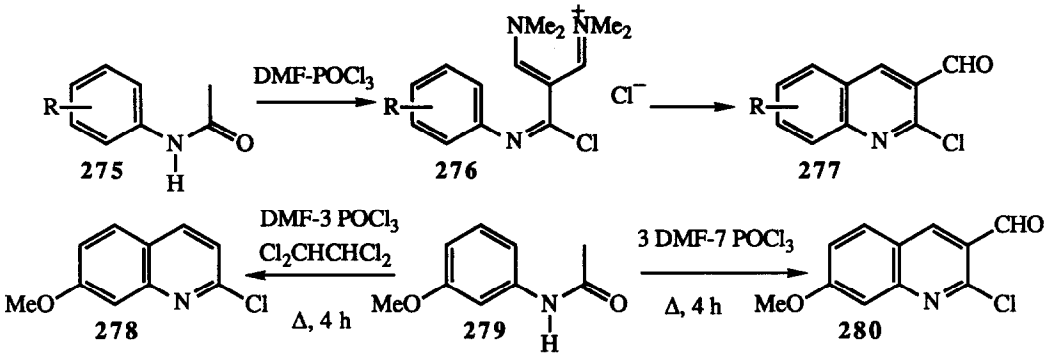
Scheme 47

Fused pyridin-2-ones **273** are formed in low yields by the cyclisation of enamides (Scheme 48).[131] Hippuric acid is converted[132] into the oxazole **274** by NMF-POCl3.



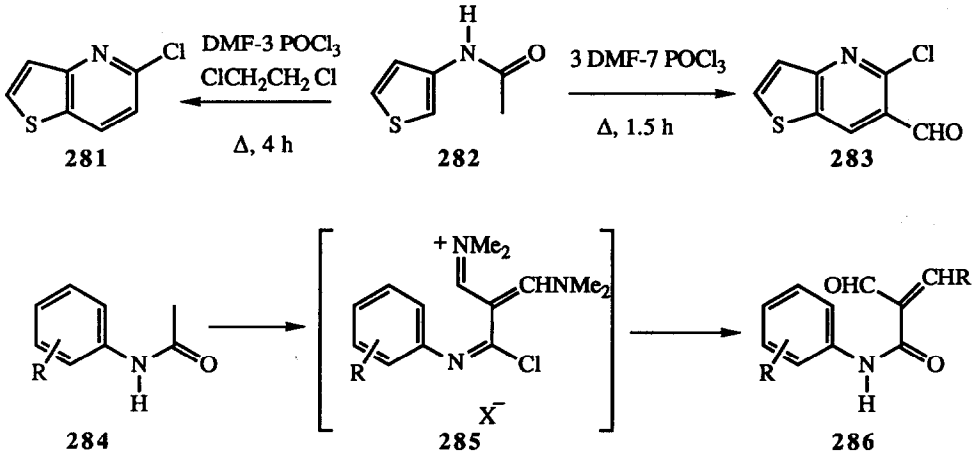
Scheme 48

Since the pioneering work of Fischer, Mueller and Vilsmeier,[133] numerous quinolines have been prepared by Vilsmeier reactions of acylanilides; these include 2-chloro-3-cyanoquinolines, prepared[134] by the action of hydroxylamine hydrochloride on the Vilsmeier reaction mixture. Other 2-chloro-3-substituted quinolines have also been prepared.[135] In certain cases, the uncyclised intermediate was identified as the salt **276** (Scheme 49).[136]



Scheme 49

In versatile syntheses of quinolines, thienopyridines, and related fused pyridines, by the use of the Vilsmeier reagent under controlled conditions afforded high yields of chlorinated heterocycles (Scheme 50).[137] Intermediates **286**, derived from **285**, can be isolated in cases where quinoline formation is slow.[138]

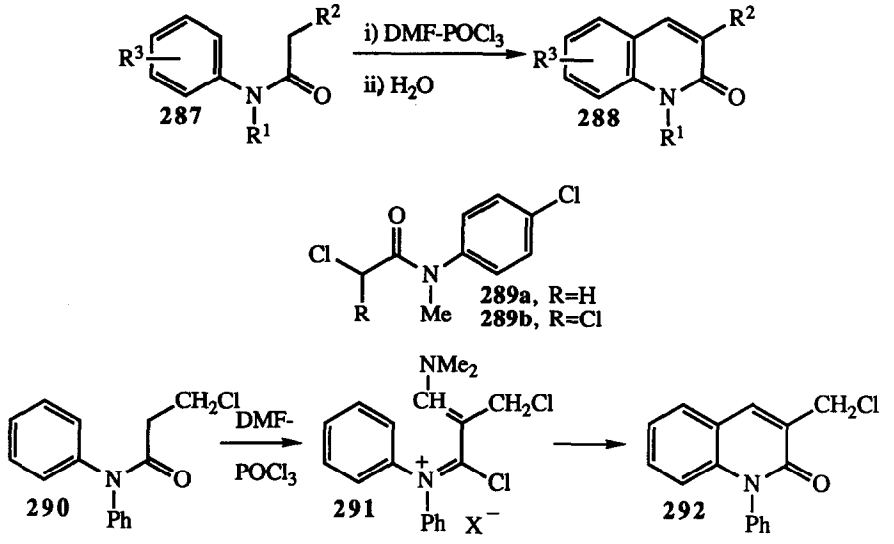


Scheme 50

Carbostyrils **288** generally result from the action of the Vilsmeier reagent on α-substituted acetanilides (Scheme 51). Electron-donating groups placed *meta* or *para* assist

the cyclisation whereas the same groups placed *ortho* hinder the reaction. A *p*-chloro group deactivates the ring sufficiently to prevent cyclisation; the acetanilide **289a** is converted by the Vilsmeier reagent into the anilide **289b**.[131]

The formylation of *N*-phenylacetanilides **290** was initially misinterpreted,[139] but has been shown to provide an excellent route[140,141] to 1-phenyl-2-quinolones such as **292**.



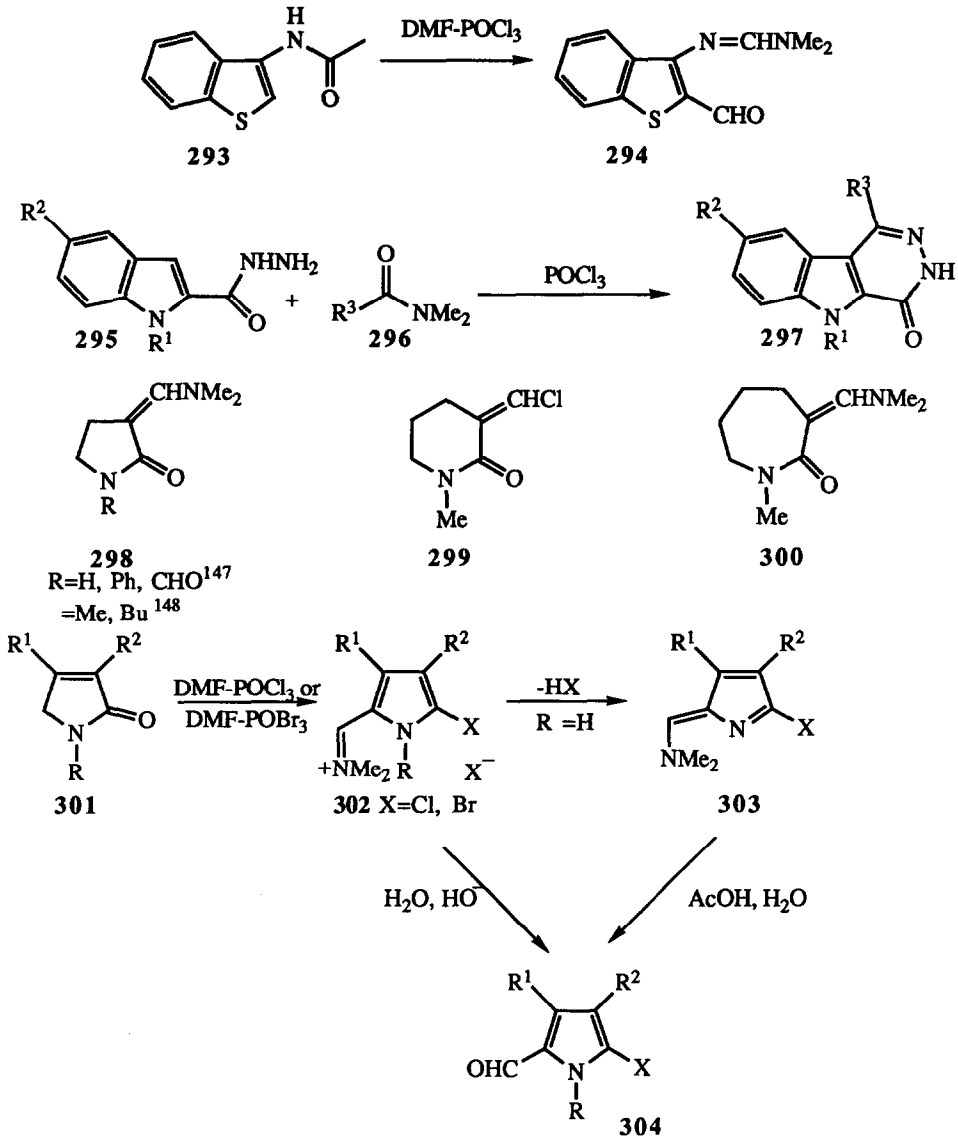
Scheme 51

3-Acetamidothiophene, when heated with DMF-$POCl_3$, and then treated with $HONH_2$.HCl, afforded 5-chlorothieno[3,2-*b*]pyridine-6-carbonitrile.[142] The amidine **294**, rather than the expected 2-formyl derivative of 3-(acetylamino)benzo[*b*]thiophene **293**, was obtained upon Vilsmeier formylation (Scheme 52).[143]

4-Oxo-3,4-dihydro-5*H*-pyridazino[4,5-*b*]indoles **297** have been prepared in excellent yield by a one-pot procedure from 2-indolecarbohydrazides **295**.[144]

4.2 Monocyclic Lactams

α-Pyrrolones are converted by Vilsmeier reagents into either the 2-chloro-3-formyl derivatives[145] or the 2-halo-5-formyl derivatives,[146] depending on the substitution in the ring. In some cases, the intermediate enamines can be isolated. The 2-bromopyrrole-


DMF-POCl3
N=CHNMe2
CHO
293
294
NHNH2
POCl3
295
296
297
CHNMe2
CHCl
298
R=H, Ph, CHO147
=Me, Bu 148
299
300
DMF-POCl3 or
DMF-POBr3
-HX
R =H
301
302 X=Cl, Br
303
H2O, HO−
AcOH, H2O
304

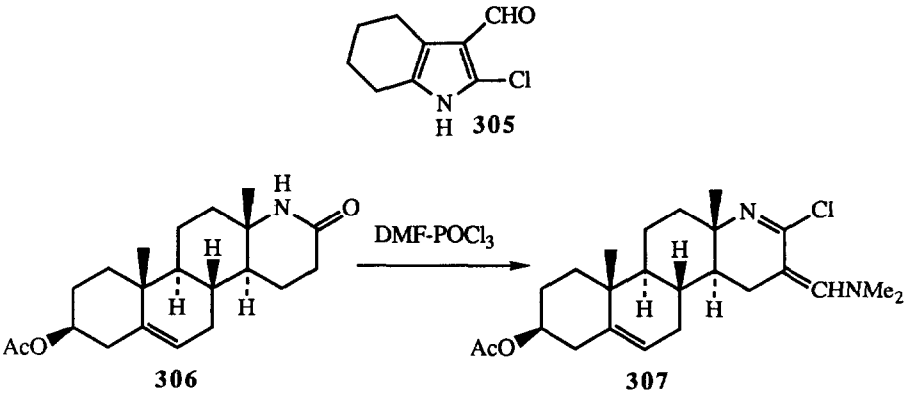
Scheme 52

-5-aldehydes so obtained are useful compounds for the synthesis of pyrromethenes. In other cases,[147,148] α-pyrrolones afford the dimethylaminomethylene derivatives **298**. The lactams **299** and **300** were obtained[148] from *N*-methyl-δ-valerolactam and *N*-methyl-ε-caprolactam, respectively, but were accompanied by other products.

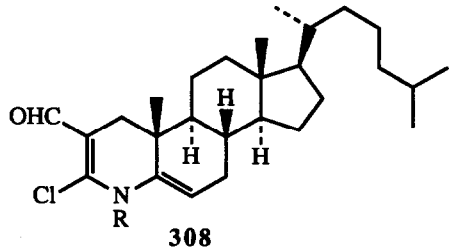
2-Chloropyrrole-3-carboxaldehydes have been prepared by treating Δ^4-pyrrolidin-2-ones with DMF-$POCl_3$ in chloroform.[145,149] The reaction of 4-methoxycarbonyl-5-methyl-Δ^4-pyrrolin-2-one with chlorinated and brominated Vilsmeier reagents has been studied.[150] A wide variety of Δ^3-pyrrolin-2-ones **301** are smoothly converted into the functionalised pyrroles **304** (Scheme 52).[150,151]

4.3 Lactams Fused to Carbocyclic Rings

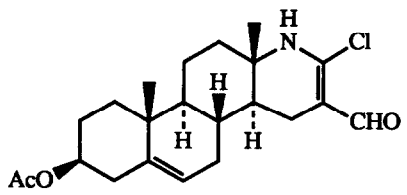
The enamino-aldehyde **305** has been prepared[145] from the corresponding pyrrolone and DMF-$POCl_3$. Vinylogous amidines, *e.g.* **307** have been prepared[152,153] from steroidal lactams such as **306** (Scheme 53). In general, the vinylogous amidines have tolerable stability to acids unless aromatisation can occur. The chloroformylated steroid derivatives **308** and **309** are formed[153] by treating the appropriate aza-cholestanone and aza-homoandrostenone derivatives with DMF-$POCl_3$ in refluxing $CHCl_3$.



Scheme 53



308

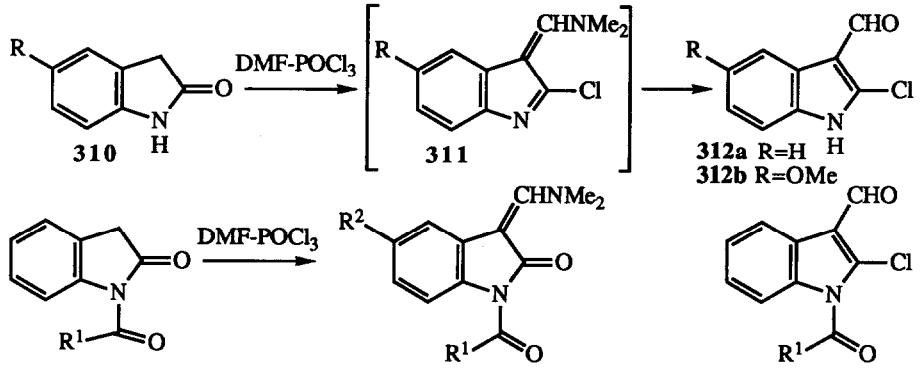


309

4.4 Lactams with Benzo-Fusion

Early work showed that oxindole **310** (R=H) was converted by DMF-$POCl_3$ into the 2-chloro-3-formylindole **312a** (Scheme 54).[154] The reaction also proceeds with a variety of 1-substituted oxindoles.[155]. The remarkable conversion of 1-methyloxindole into 3-chloro-1-methyl-2-quinolinone (79%) has been reported.[156]

The Vilsmeier reagent converted 1-acyloxindoles **313** into the 3-dimethylaminomethylidene derivatives **314a** and **314b**. The products **315** had to be prepared by acylation of 2-chloro-3-formylindole.[157] Some oxindoles substituted at either the 5- or 7-position were converted into the corresponding 2-chloro-3-formylindoles;[158] however, other substituted oxindoles reacted differently (Scheme 55).[154]



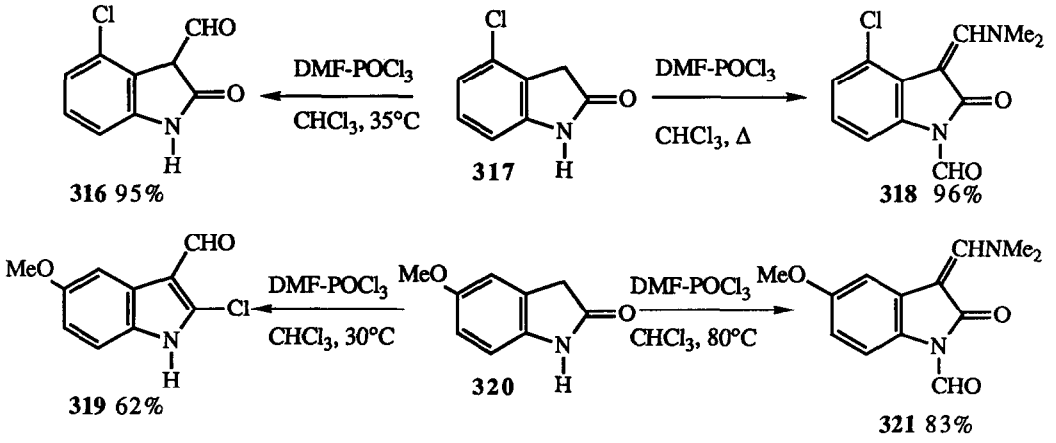
313 R^1=Me, Et, Pr

314a R^2=H
314b R^2=CHO

315

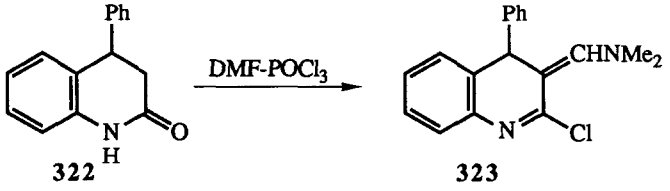
Scheme 54

Isatin β-oxime was converted by DMF-POCl3 into *N*,*N*-dimethyl-*N*-(*o*-cyanophenyl)formamidine.[159]



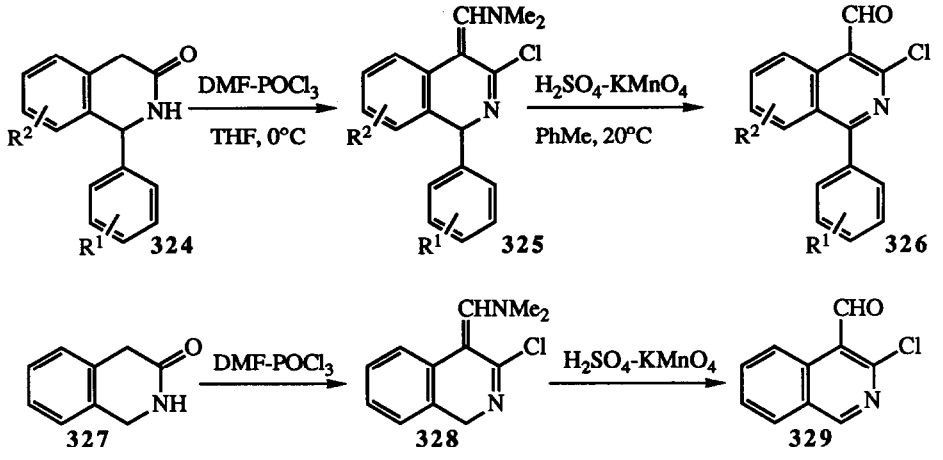
Scheme 55

Stable vinylogous amidines such as **323** can be obtained from lactams in a Vilsmeier reaction (Scheme 56).[152,160]

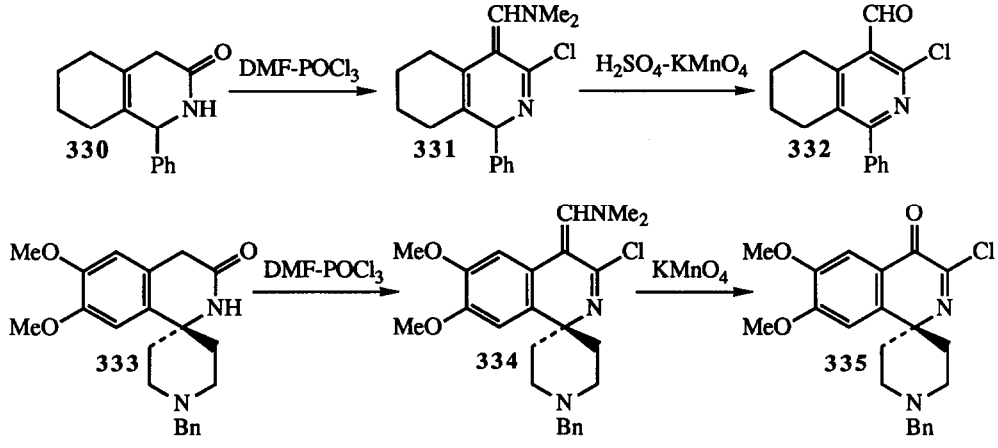


Scheme 56

Dihydroisoquinolin-3-ones **324** have been converted into 3-chloro-4-formylisoquinolines **326** by the action of Vilsmeier reagents followed by oxidation (Scheme 57).[161] The sequence of the Vilsmeier-Haack reaction followed by oxidation can also be applied to other dihydroisoquinolinone derivatives including **327** and **330** (Scheme 58); blocking the nitrogen atom afforded 3-chloro-1,2-dihydro-1-phenylisoquinoline-4-aldehyde (25%). Blocking the 1-position of the isoquinolone enabled the spirocyclic chloroketone **335** to be obtained.[161]



Scheme 57



Scheme 58

Benzazepin-2-ones **336** react with Vilsmeier reagents to afford the corresponding chloroformyl derivatives.[59,162] Related benzazepin-2-thiones also react analogously.[162]

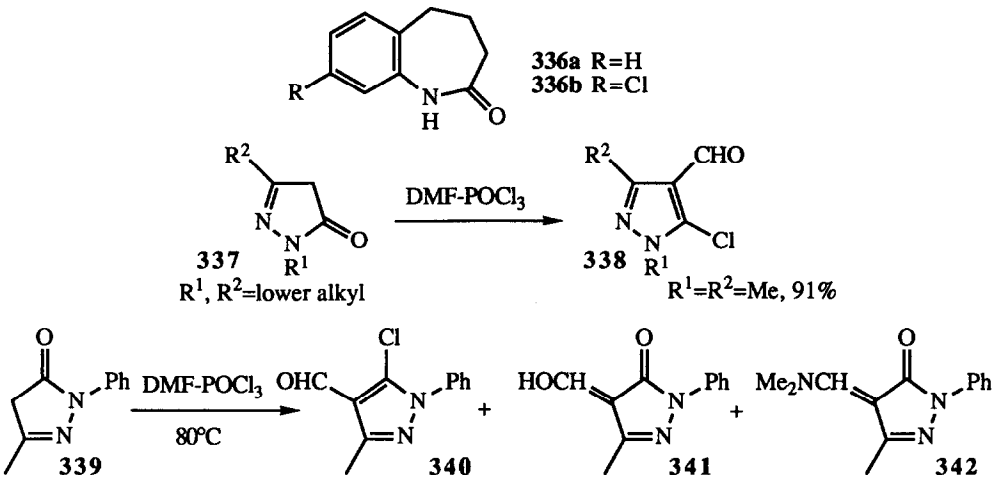
4.5 Lactams with Two or More Heteroatoms

4.5.1 Five-membered Heterocycles

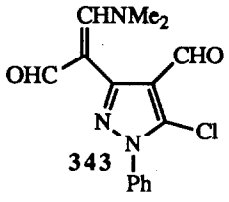
5-Pyrazolones usually react with Vilsmeier reagents to give formylated pyrazoles.[163] A variety of other functionalities may be produced, depending upon the substrate and reaction conditions. Formylpyrazole derivatives **338** have been prepared by treating 5-pyrazolones **337** with DMF-$POCl_3$ (Scheme 59).

1-Phenyl-3-methyl-5-pyrazolone **339** afforded the pyrazole carboxaldehyde **340**[164] when the reaction mixture was added to water and slowly neutralised. However, when the mixture was poured into aqueous K_2CO_3, some of the hydroxymethylene derivative **341** was also obtained. Working at lower temperatures, the formation of the aminomethylenepyrazolone **342** has been observed.

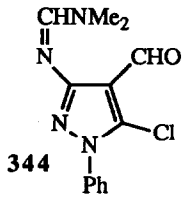
3-Methyl-1-phenyl-5-pyrazolone is converted by a Vilsmeier reagent into the dialdehyde **343**,[165] although simple chloroformylation of the pyrazole has also been observed. 3-Amino-1-phenyl-5-pyrazolone was converted by a Vilsmeier reagent into the aldehyde **344**.[166]



Scheme 59



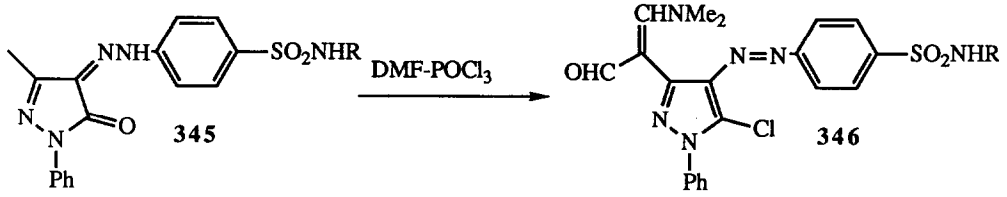
343



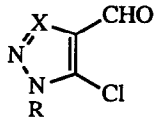
344

Chlorination of a 5-oxopyrazolone system **345**, in addition to an effectively diformylated 3-methyl group, has been observed using Vilsmeier reagents (Scheme 60).[167] When the product derived from a Vilsmeier reaction on 3-methyl-5-pyrazolone is treated with NH_4Cl, 3-chloro-7-formyl-1*H*-pyrazolo[4,3-*c*]pyridine is obtained.[168]

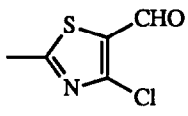
The five-membered heterocyclic chloro-aldehydes **347** and **348** were prepared by Vilsmeier-Haack reactions on the appropriate heterocyclic amides (Scheme 60).[169]



345 346



347 X=N, CMe

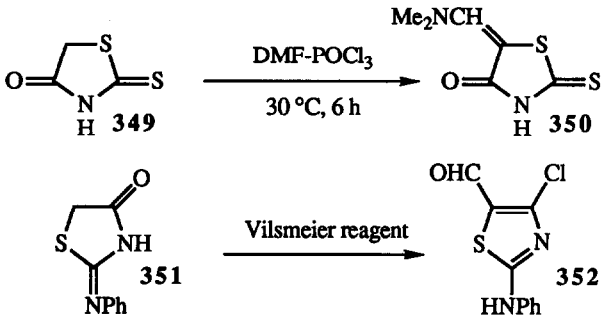


348

Scheme 60

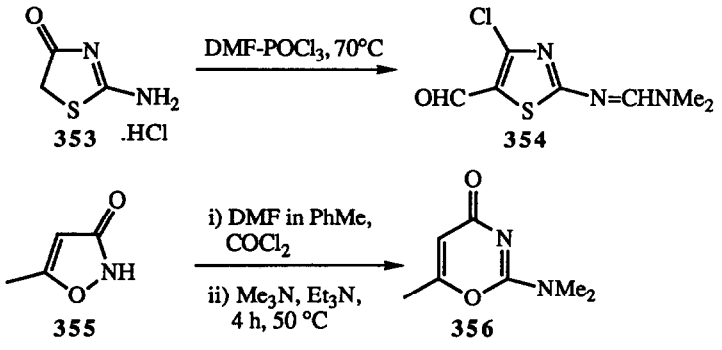
Rhodanine **349** was converted into 4-dimethylaminoformylidene rhodanine **350**. 2-Phenyliminothiazolidin-4-one **351** is converted by a Vilsmeier reagent into the versatile derivatives **352** (Scheme 61) from which several 5,5-fused heterocycles have been made.[170]

2-Amino-4-thiazolinones are transformed into 4-chloro-5-formylthiazole derivatives by Vilsmeier reagents (Scheme 62).[171] Oxazine derivatives **356**, useful as



Scheme 61

fungicides and analgesics, were prepared by a Vilsmeier reaction on the amide **355**;[172] the thiazine analogues of **355** reacted similarly.

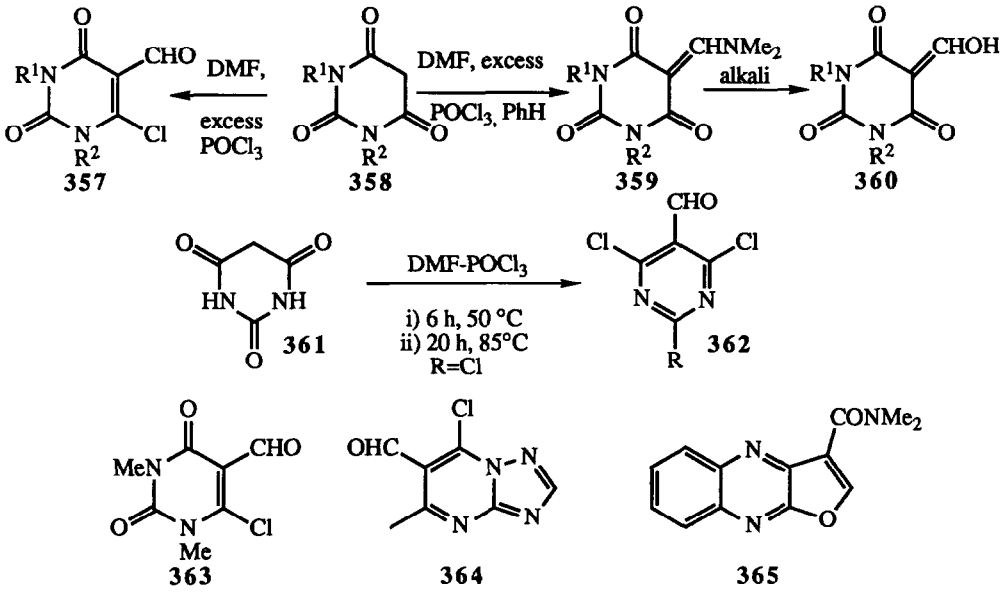


Scheme 62

4.5.2 Six-membered Heterocycles

Unactivated pyrimidines (*e.g.* 4,6-dichloropyrimidine) do not usually react with Vilsmeier reagents. However, the unsubstituted 5-position of derivatives of barbituric acid, uracils,[173] and 4-hydroxy-6-oxodihydropyrimidines undergoes formylation, in accordance with its reactivity as a β-enamide. Barbituric acid derivatives **358** afforded either **357** or **359**, depending on the solvent employed (Scheme 63). The 5-

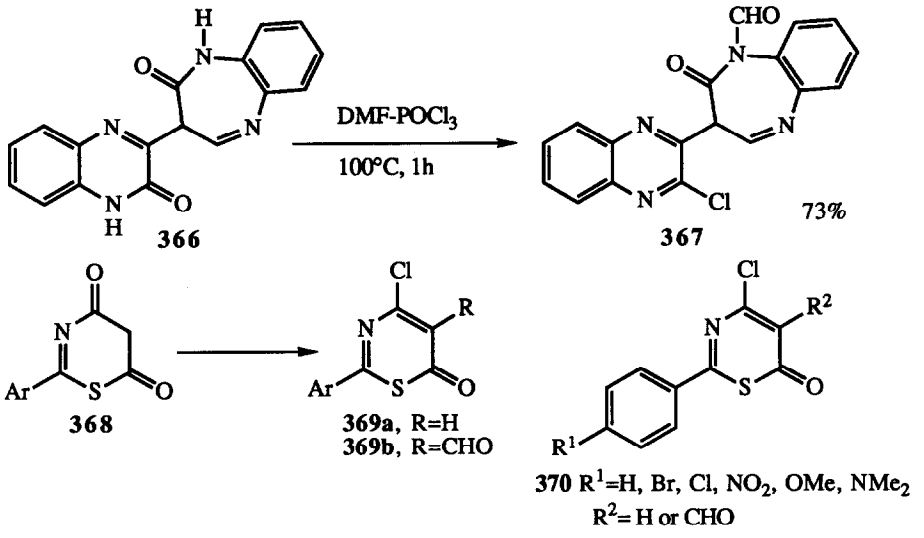
dimethylaminomethylenebarbituric acid derivatives **359** were hydrolysed by alkali to the 5-formylbarbituric acids **360**. The Vilsmeier reaction of 1,3-disubstituted uracil derivatives afforded 1,3-disubstituted 5-formyluracil derivatives.[173,174] Reactive intermediates **362** (R=Cl, Ph, NMe_2, NEt_2) for dyes have been prepared[175] by Vilsmeier reactions; barbituric acid **361** afforded the aldehyde **362** (R=Cl). Aldehyde **363** was obtained from the corresponding barbituric acid and DMF-$POCl_3$.[176]



Scheme 63

Hydroxytriazolopyrimidines have been converted by Vilsmeier-Haack reagents into chlorovinylaldehydes such as **364** (3 h; 70-80°C; 85%).[177] The amide **365** was prepared by the Vilsmeier reaction of 2-ethoxycarbonylmethylene-3-oxo-1,2,3,4-tetrahydroquinoxaline.[178]

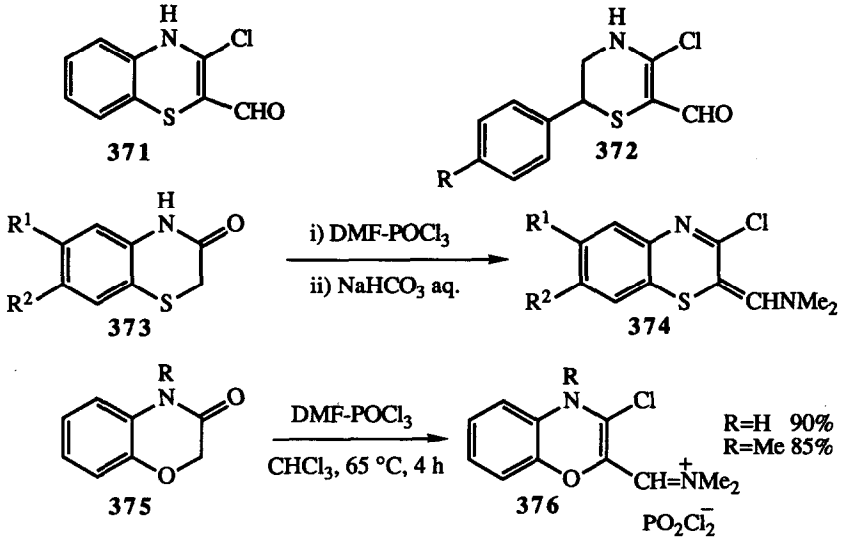
Substituted 1-formyl-1,5-benzodiazepines were prepared in improved yield by decreasing the amount of Vilsmeier reagent used (*e.g.* 10 g of amide **366**, 50 ml DMF, and 50 ml $POCl_3$; Scheme 64).[179]



Scheme 64

Several thiazinones have been reacted with Vilsmeier reagents. A variety of 2-arylthiazine derivatives **368** afforded mixtures of the chlorinated thiazinones **369a** and **369b** in ratios depending on the electronegativity of the *p*-substituents in the aryl ring; electron-donating substituents (*e.g.* NMe_2) favoured **369b**, whereas electron-withdrawing ones (*e.g.* *p*-NO_2) favoured **369a**.[180] Vilsmeier reactions of 2-aryl-4-hydroxy-1,3-thiazin-6-ones **368** were analysed by CNDO/2 and MNDO/3 MO methods, and by photoelectron spectroscopy; the product ratios (R=H or CHO in **369**) are chiefly determined by the energetic and structural parameters of the HOMO.[181] The chloroformyl derivatives **371** and **372** were formed by the action of DMF-$POCl_3$ on the corresponding lactams.[162] A similar reaction using 4*H*-1,4-benzothiazin-3-ones **373** enabled the corresponding enamines **374** to be isolated, but they decomposed during a period of two days (Scheme 65).[164]

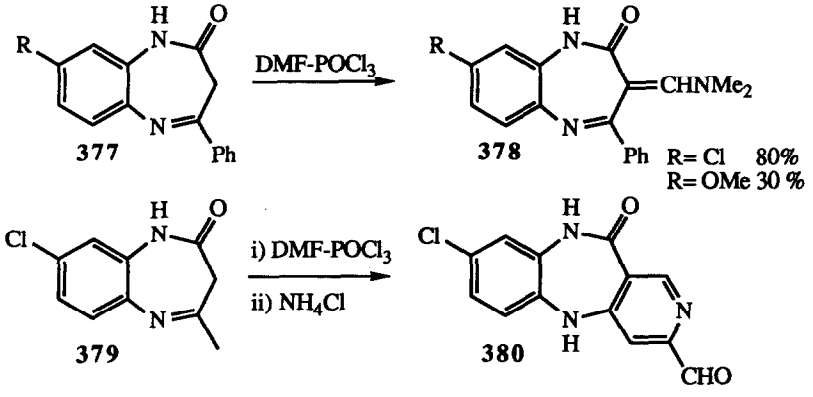
2*H*-1,4-Benzoxazin-3-one and its derivatives react with DMF-$POCl_3$ to give iminium salts **376** which form a variety of products with alkali, some lacking chloro-substituents (Scheme 65).[182]



Scheme 65

4.5.3 Seven-membered Heterocycles

The action of Vilsmeier reagents on benzazepin-2-ones was described in Section 4.4. Several benzo-fused 1,4-diazepinones (Scheme 66) have also been subjected to

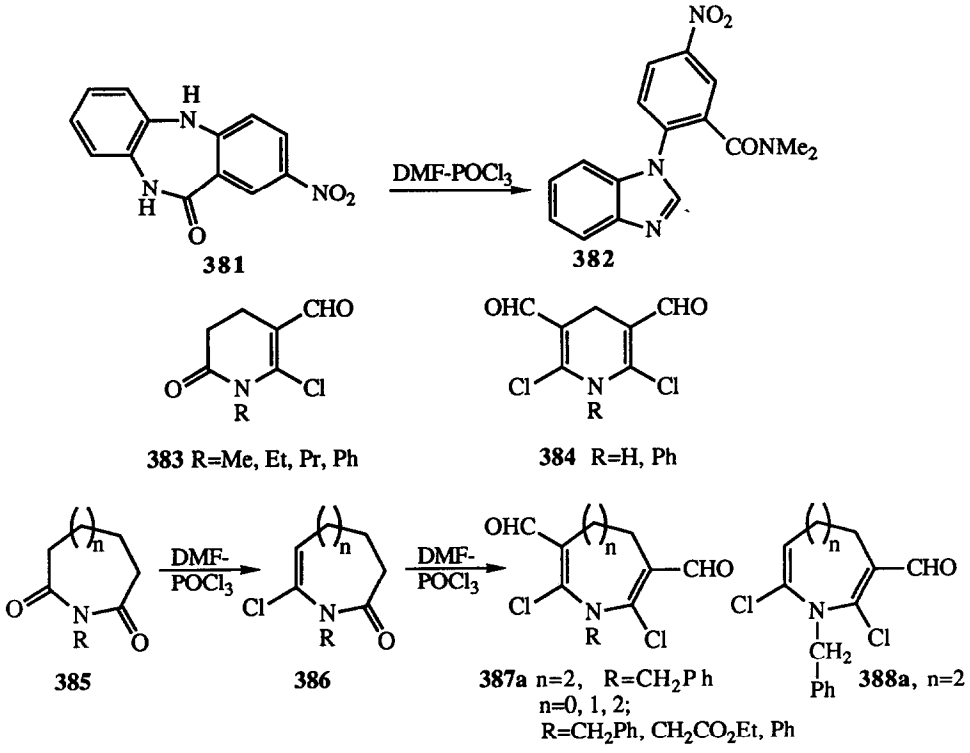


Scheme 66

Vilsmeier reactions. The benzodiazepin-2-ones **377** were converted into the aminomethylene derivatives **378**, rather than the corresponding chloroformylated compounds.[183] The pyrido-fused benzodiazepin-2-one **380** was produced *via* a Vilsmeier reaction on the benzodiazepin-2-one **379**.[184] Ring contraction of the dibenzodiazepinone **381** to the benzimidazole **382** occurred under Vilsmeier conditions (Scheme 67).[185]

4.6 Imides

Glutarimides are converted by DMF-$POCl_3$ into the lactams **383**;[186] the diformyldihydropyridines **384** can also be obtained.[187] Imides of five-, six-, and seven-membered rings react with excess DMF-$POCl_3$ to give the useful di-β-chlorovinylaldehydes **387** (Scheme 67).[188]



Scheme 67

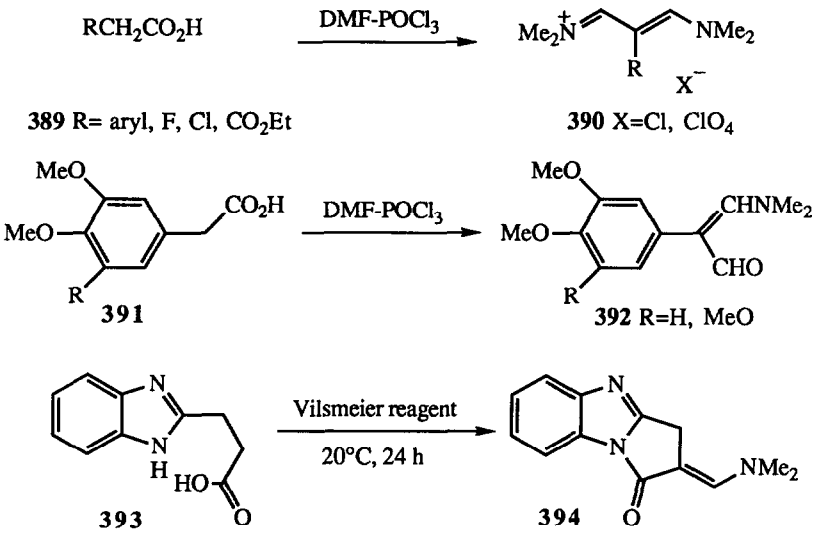
The azepines **386** are converted by excess DMF-$POCl_3$ into the aldehydes **387**; 4 equiv. of the Vilsmeier reagent diluted with $CHCl_3$ afforded a mixture of azepines **387a** (10%) and **388a** (35%).

5. REACTIONS OF CARBOXYLIC ACIDS

A general method for the preparation of vinamidinium salts **390**[189-192] is the reaction of derivatives of acetic acid with Vilsmeier reagents (Scheme 68). Malonic acids,[193] cyanoacetic acid,[194] and substituted derivatives of glycine[195] also afford vinamidinium salts. The action of DMF-$POCl_3$ on sodium trifluoroacetate, followed by addition of Et_3N, affords 2-fluoro-3-dimethylaminoacrylaldehyde which can be converted into fluoromalondialdehyde.[196]

The acrylaldehydes **392** were prepared by Vilsmeier reaction of the corresponding acetic acids **391** (Scheme 68).[197]

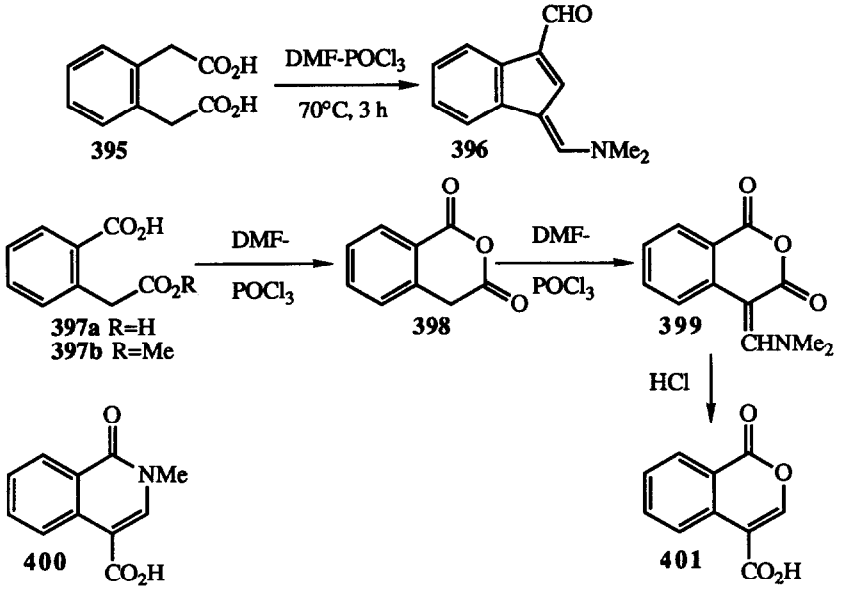
Formylation of 2,4-dienoic acids under Vilsmeier conditions gave low yields of isophthalaldehyde derivatives, with poor selectivity. However, 3,5-xylenol was prepared in 45% yield from 3-methylhexa-2,4-dienoic acid.[198]



Scheme 68

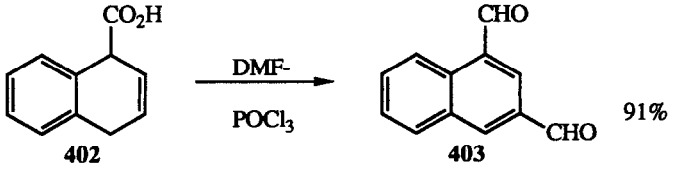
Benzimidazole-2-propionic acid **393** is converted into the enamino–ketone **394** by the Vilsmeier reagent at room temperature.[199] Benzene-1,2-diacetic acid **395** affords the benzofulvene **396** in low yield (Scheme 69).[200] Benzene-1,3-

diacetic acid and benzene-1,4-diacetic acid afford the corresponding bistrimethinium salts in respective yields of 65 and 82%. Homophthalic acid **397a**, its methyl ester **397b**, and homophthalic anhydride **398** all reacted with the Vilsmeier reagent to give the isochroman-1,3-dione **399** in excellent yield. The latter underwent ring-opening and ring-closure with acid or $POCl_3$ to give the carboxyisoquinolone **400**.[201] Upon treatment of the Vilsmeier product **399** with HCl, isocoumarin-4-carboxylic acid **401** is obtained.[202]



Scheme 69

1,4-Dihydrobenzoic acids react with DMF-$POCl_3$ to give benzene mono-, di-, and tri-carboxaldehydes. This procedure also afforded naphthalene-1,3-dicarboxaldehyde **403** (Scheme 70).[203]

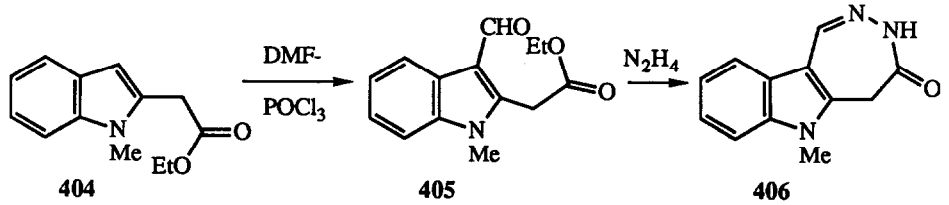


Scheme 70

6. REACTIONS OF ESTERS AND LACTONIC CARBONYL COMPOUNDS

A two-step route to diazepinoindoles **406** depends on the inertness of an ester group towards Vilsmeier reagents (Scheme 71).[204] The 2-methyl group of a 2,6-dimethyl-1,4-dihydropyridine was formylated by a Vilsmeier reagent, leaving intact the ester groups at the 3- and 5-positions.[205]

Vilsmeier reactions of benzazoles **407** generated the enamines **408** (Scheme 71).[206] Ethyl 2-pyridineacetate **409** reacted analogously (Scheme 72).

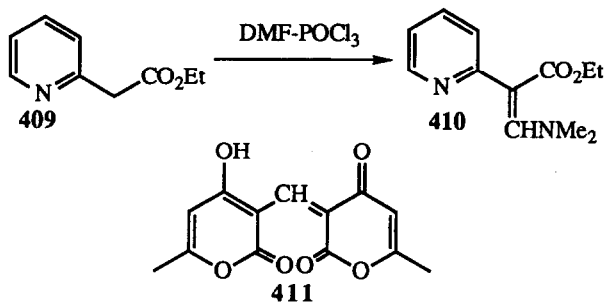


404 **405** **406**

407 **408** X=NH, S, O

Scheme 71

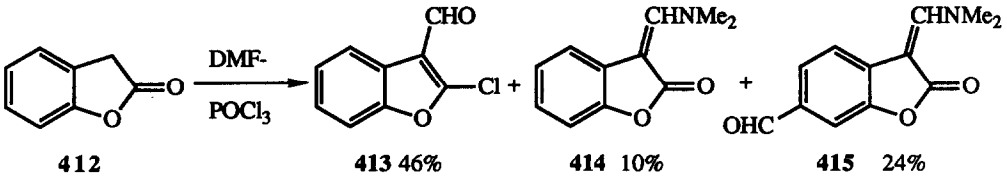
The pyran-2,4-dione **411**, a useful intermediate in the preparation of dyes and pharmacologically active compounds, was prepared by treating triacetic acid lactone with DMF and $POCl_3$ under cooling.[207]



409 **410** **411**

Scheme 72

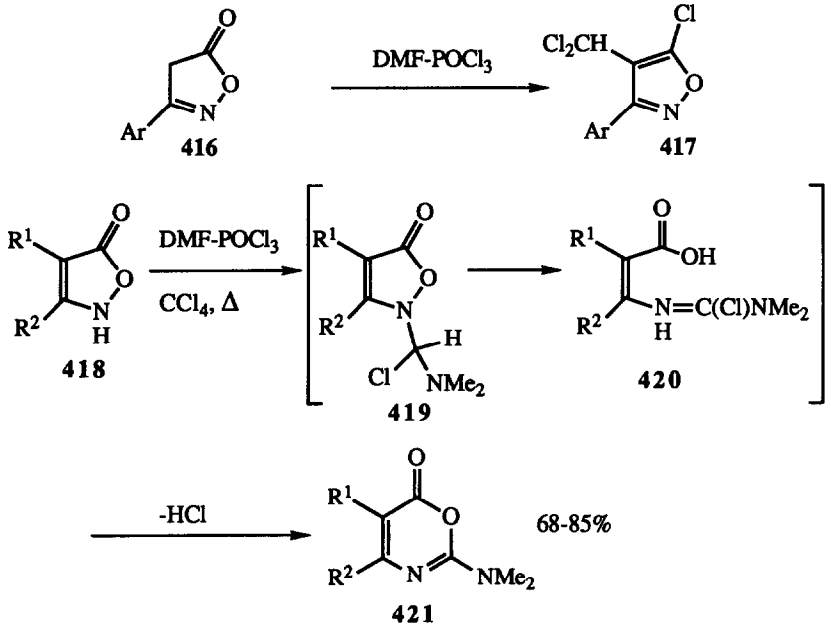
Treatment of 2-coumaranone **412** with the Vilsmeier reagent afforded the three products **413**, **414**, and **415**, the latter two as mixtures of *(E)*- and *(Z)*-isomers (Scheme 73).[208]



412 **413** 46% **414** 10% **415** 24%

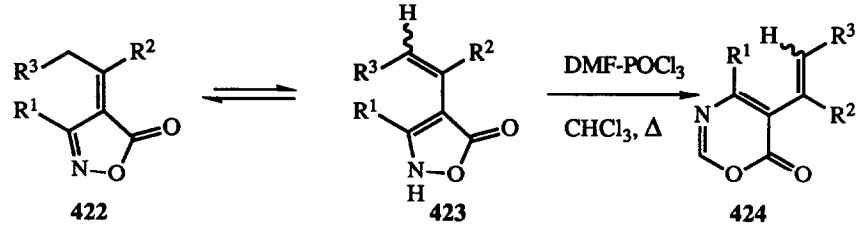
Scheme 73

Vilsmeier-Haack reactions on 5(4*H*)-isoxazolones **416** led to dichloromethyl-isoxazolones **417**.[209] Recently, new routes to 1,3-oxazin-6-ones by the Vilsmeier reaction on isoxazolin-5-ones **418** have been developed (Scheme 74).[210]



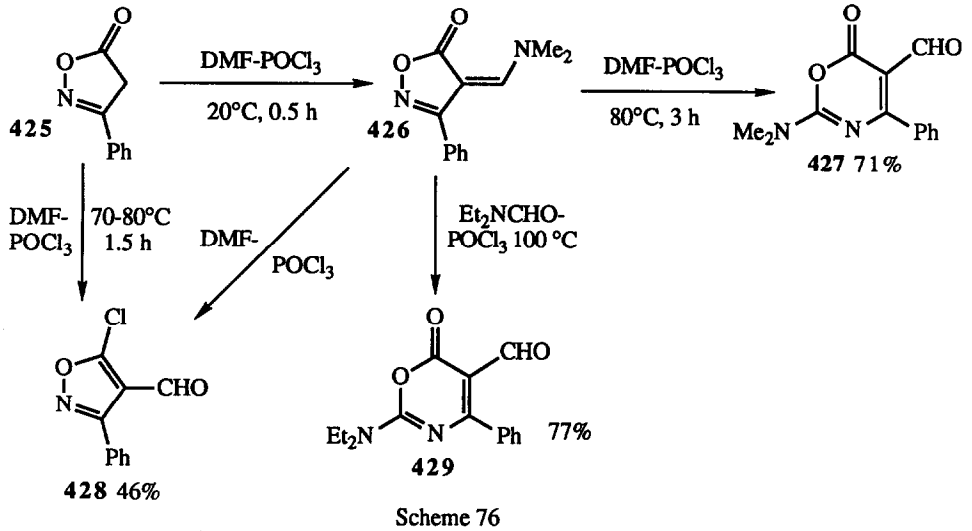
Scheme 74

The Vilsmeier-Haack reaction on 4-alkylideneisoxazolin-5-ones **422** gives 1,3-oxazin-6-ones **424** which are useful precursors of α-pyrones, 2-pyridones and pyridines (Scheme 75).[211]



422 **423** **424**

Scheme 75

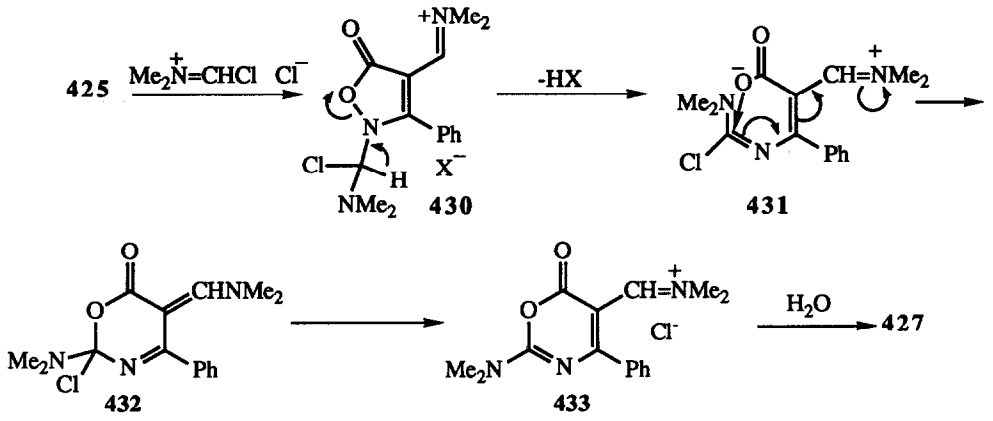


425 **426** **427** 71% **428** 46% **429**

Scheme 76

A reinvestigation[212] of the reaction of 3-phenyl-5-isoxazolinone **425** with excess Vilsmeier reagents revealed a ring-expansion at temperatures around 80°C, to give 1,3-oxazin-6-ones (Scheme 76). The following rationale has been proposed: the isoxazolone **425** reacts *via* its enol form with the chloromethyleniminium species to give, after loss of HCl, the dimethylamino-derivative **426**, which under more forcing conditions reacts with excess Vilsmeier reagent at the ring nitrogen atom (Scheme 77). Ring-opening, subsequent ring-closure, and lastly hydrolysis affords the 1,3-

oxazin-6-one **427**. Formation of the 5-chloro-4-formylisoxazole **428** evidently proceeds *via* phosphorylation of the exocyclic oxygen atom of **426**.[212]



Scheme 77

7. CONCLUSION

In the last decade, both the synthetic potential and the understanding of the reaction of halomethyleniminium salts with carbonyl compounds has grown significantly. Reactions have been extended, among other classes, to α,β-unsaturated ketones, diketones, lactones, lactams, and β-haloenones. Recent mechanistic insights have led to the development of new reactions and compounds. The variety of more or less unexpected transformations by Vilsmeier reagents referred to by Burn[5a] is rapidly gaining both intelligibility and predictability. The inexpensive reagents, usually employed under mild conditions, and the ease of scaling up Vilsmeier reactions ensure the continued academic and industrial importance of Vilsmeier reagents. The products are often β-chlorovinylaldehydes, versatile intermediates in synthesis,[10,213] and deserving of further study.

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