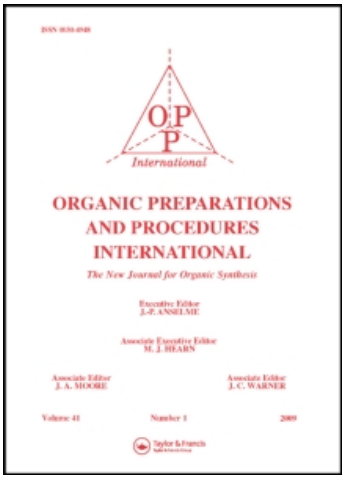

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Recent Progress in the Use of Vilsmeier-Type Reagents

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Introduction

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

It is well known that inorganic acid halides react with disubstituted amides to form active complexes, halomethyleniminium salts, referred to as Vilsmeier reagents.[1,8] N,N-dimethylformamide (DMF) is the most commonly employed disubstituted amide. N,N-dimethylacetamide,[9] N,N-dimethylbenzamide,[9,10] N-methylformanilide, 4-formylmorpholine, 1,4-dicarboxy piperazine[11] and morpholino(phenyl)methanone.[12] have also found application as disubstituted amides occasionally. The temperature used in the formation of the Vilsmeier reagent with DMF and an inorganic acid chloride is generally in the range of 0–25°C.

The inorganic acid halide used in the Vilsmeier complex is commonly phosphoryl chloride,[13] though the use of other acid halides such as phosphorus trichloride,[14] thionyl chloride,[15] oxalyl chloride,[16] phosgene,[17] 2,4,6-trichloro[1,3,5]triazine,[18] and *bis*-(trichloromethyl) carbonate (BTC, triphosgene)[19] has also been reported. Recently, the

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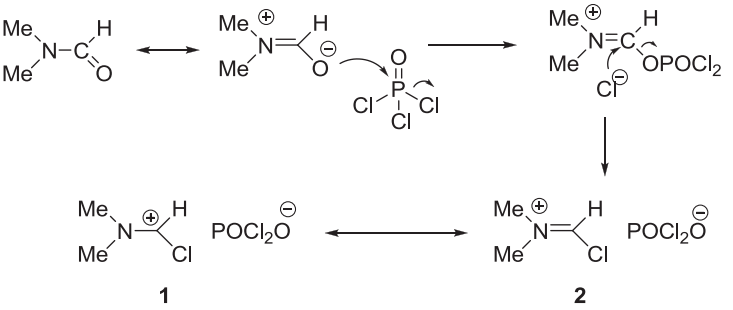
Vilsmeier reagent derived from BTC and DMF has attracted considerable attention since it avoids the formation of inorganic phosphoric acid salts encountered with the $POCl_3$/DMF complex, and shows great potential in industrial processes.

The generally accepted representation of the Vilsmeier reagent derived from N,N-dimethylformamide and phosphorus chloride corresponds to structures **1** or **2**.[20] The mechanism for formation of **1** or **2** is depicted in *Scheme 1*.



Scheme 1

Substrates used in Vilsmeier reactions include alkenes, active methyl or methylene groups, hydrazones, azines, aliphatic diazo compounds and activated aromatic or heteroaromatic compounds.[21–23] Recently, substrates containing cyclopropyl[24] or ketene dithioacetal[25] groups have been utilized in Vilsmeier reactions. In some of these reactions, different products are formed under different reaction conditions (*e.g.* temperature, equiv.).[24] With this strategy, a large number of heterocyclic compounds such as pyridines,[26] quinolines[27] and indoles[28] were synthesized successfully.

In recent years, Vilsmeier reagents supported on solid phase have also been applied in organic synthesis.[11,29] This reagent offers many benefits compared with the traditional Vilsmeier complexes, such as inherent time saving, reasonable purity of the final products without significant purification steps, as is necessary in most solution phase procedures and ease of recovery and activation for further use. Vilsmeier reaction under microwave irradiation has also been reported.[30] The latter can be conducted rapidly and provides pure products in higher yield without the use of organic solvents and thus is environment friendly.

Until now, there have been two reviews[31,32] about the Vilsmeier reaction. This review covers the developments in the Vilsmeier reaction mainly since 2000.

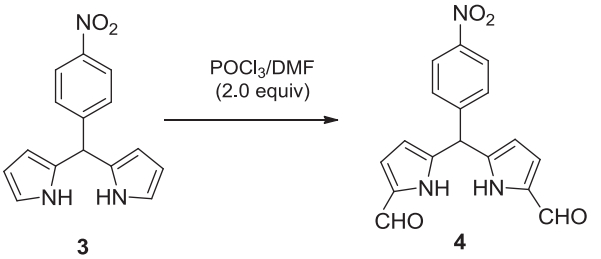
I. Vilsmeier-Haack Type Acylations

1. Formylation

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

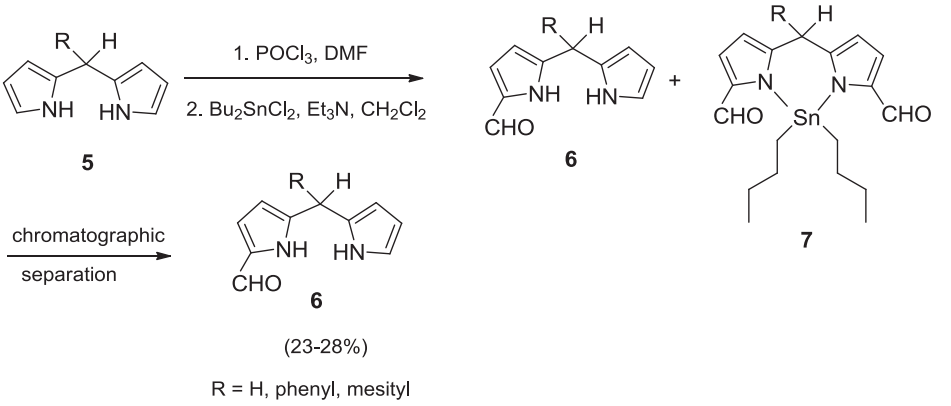
a. Formylation of Heterocycles

Formylation of pyrrole, thiophene, furan, and their derivatives usually occurs in the α-position. For example, Vilsmeier formylation of dipyrromethane **3** under standard conditions (room temperature, work-up with 10 M aqueous NaOH) gave the desired diformyldipyrromethane **4** (*Scheme 2*).[33] Treatment of compound **4** with excess propylamine in THF quantitatively afforded the 1,9-*bis*(propyliminomethyl)dipyrromethane, which is the key intermediate for the 4-nitrophenyl -substituted swallowtail-porphyrin.



Scheme 2

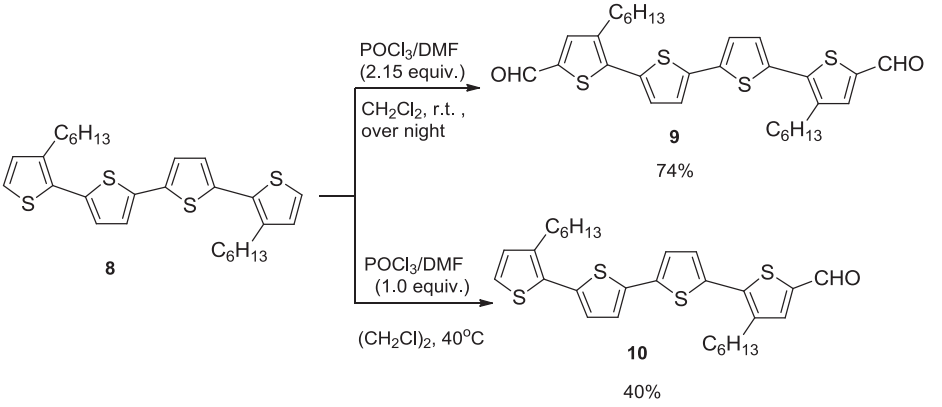
In 2006, two methods for the synthesis of 1-formyldipyrromethanes **6** were investigated by Ptaszek's group.[34] One route to the compounds **6** is outlined in *Scheme 3*, wherein, treatment of dipyrromethanes **5** with the Vilsmeier reagent afforded the expected mixture of the 1-formyldipyrromethanes **6** and 1,9-diformyldipyrromethanes. To facilitate separation of the formyldipyrromethane species, the mixture was treated with Bu_2SnCl_2 and triethylamine (TEA) in CH_2Cl_2 at room temperature. The tin-complexation process was selective for the 1,9-diformyl species, yielding hydrophobic 1,9-diformyldipyrromethane-dibutyltin complexes **7** and 1-formyldipyrromethanes **6**. The mixture was separated by flash chromatography to afford the desired 1-formyldipyrromethanes **6**.



Scheme 3

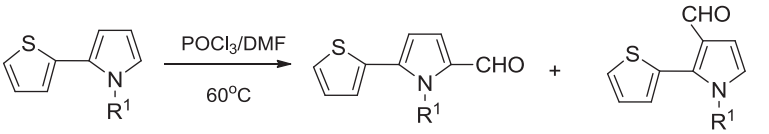
Dihexylquaterthiophenedialdehyde **9** is one of the important intermediates in the synthesis of many classic π-conjugated thiophene-based oligomers, which can be produced from easily available dihexylquaterthiophene **8** by Vilsmeier-Haack formylation.[35] Control

of the amount of Vilsmeier reagent led to formylation can occur at one of the terminal positions. Thus, Kanato *et al.*[36] provided a method with $POCl_3$/DMF in 1,2-dichloroethane at 40°C to give the corresponding monoformyl derivate **10** in 40% yield (*Scheme 4*).



Scheme 4

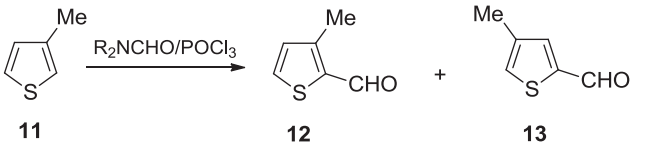
Electrophilic substitution reactions of thienylpyrroles were found to be very selective. Pyrrole is considerably more reactive towards electrophilic substitution than thiophene (*Scheme 5*),[37] since the pyrrole nitrogen atom has a greater ability to delocalize the positive charge of σ-complexes than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



R^1 = *n*-Propyl, Phenyl, 4-MeOPhenyl

Scheme 5

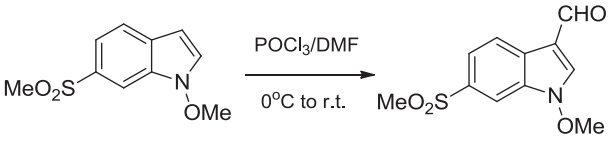
Meth-Cohn *et al.*[38] examined the regioselective formylation of 3-methylthiophene (**11**) using the disubstituted amides, such as N-formylpyrrolidine. 3-Methylthiophene-2-carbaldehyde (**12**) was the major product and, when the disubstituted amide employed was dicyclohexylformamide, 4-methylthiophene-2-carbaldehyde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



R_2NCHO = DMF, *N*,*N*-diisopropylformamide, pyrrolidine-1-carbaldehyde, *N*,*N*-dicyclohexylformamide

Scheme 6

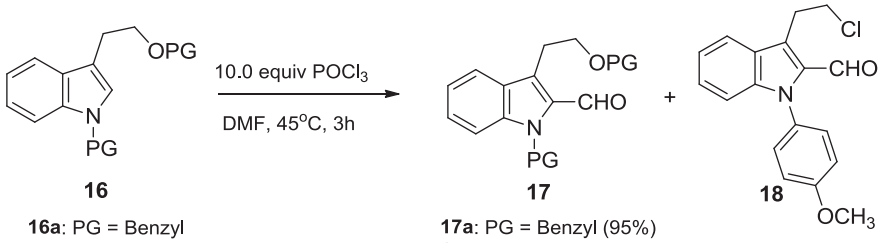
In general, the regiochemistry of the Vilsmeier reaction of indoles is quite predictable, occurring at the 3-position, unless this position is occupied. For instance, the synthesis of 1-methoxy-6-(methylsulfonyl)-1*H*-indole-3-carbaldehyde (**15**) was achieved *via* the Vilsmeier formylation of 1-methoxy-6-(methylsulfonyl)-1*H*-indole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



14 **15**

Scheme 7

The Vilsmeier formylation of protected indoles **16** with $POCl_3$ in DMF afforded the corresponding aldehydes **17** in moderate to excellent yields. Apparently, in the course of this reaction with substrate **16b**, some hydrolysis of the protective group occurred, resulting in the formation of alkyl chloride **18** (*Scheme 8*).[40]



16
16a: PG = Benzyl
16b: PG = *p*-Methoxybenzyl

17
17a: PG = Benzyl (95%)
17b: PG = *p*-Methoxybenzyl (62%)

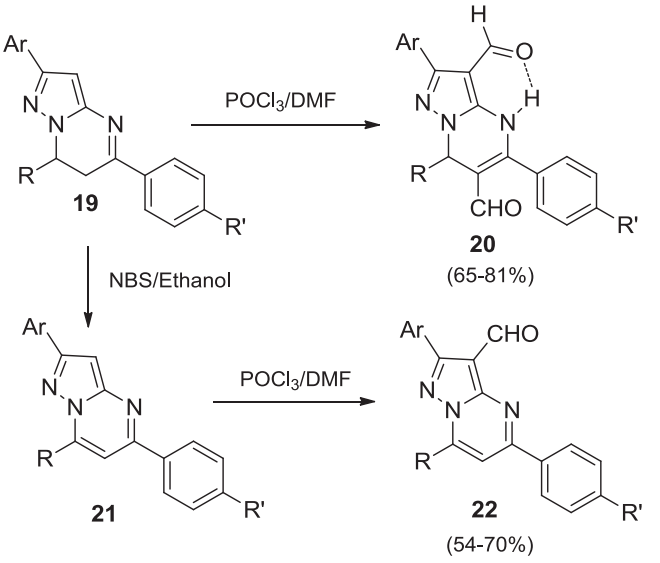
18
23%

Scheme 8

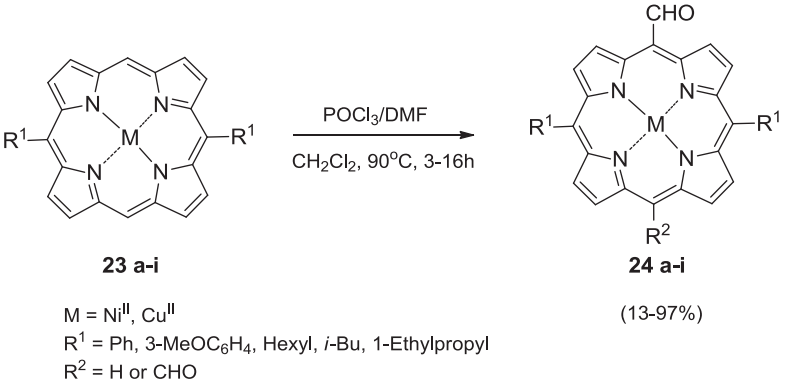
When 6,7-dihydro-pyrazolo[1,5-a]pyrimidines **19** were treated with the Vilsmeier reagent ($POCl_3$/DMF), a double formylation at positions 3 and 6 of the pyrazolopyrimidine system occurred yielding pyrazolo[1,5-a]pyrimidine-3,6-dicarbaldehydes **20**. On the other hand, the Vilsmeier reaction of pyrazolopyrimidines **21** took place only at position 3 of the pyrazole ring, leading to the formation of the pyrazolopyrimidine-3-carbaldehydes **22** (*Scheme 9*).[41]

Porphyrins play an important role in biological processes such as oxygen transport, electron transfer and photosynthesis.[42] One functional group, which allows asymmetric modification and is widely used in porphyrin chemistry, is the formyl group. Dahms and co-workers[43] provided a wonderful method which used Vilsmeier reagent to give the desired formylporphyrins **24** (*Scheme 10*) using compounds **23** as substrates. The yield was between 13% (for **24b**) and 97% (for **24i**), as summarized in Table 1.

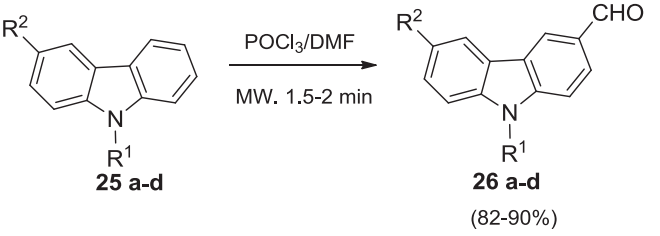
Over the past ten years, some novel techniques have been developed for the Vilsmeier process. For instance, Nagarajan *et al.*[44] reported the synthesis of carbazole aldehydes **26** from carbazole **25** through Vilsmeier reaction under microwave irradiation (*Scheme 11*). The method has several advantages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



Scheme 9



Scheme 10



Scheme 11

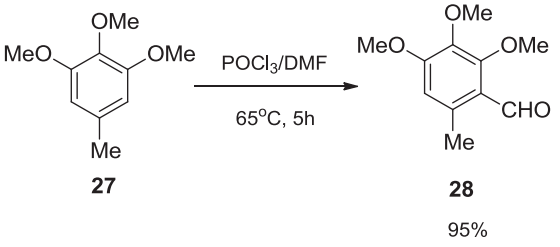
Table 1
Facile Synthesis of Formylporphyrins **24**

Entry	M	R^1	R^2	Yield (%)
24a	Ni^{2+}	Ph	H	59
24b	Cu^{2+}	3-$MeOC_6H_4$	H	13
24c	Cu^{2+}	3-$MeOC_6H_4$	CHO	20
24d	Ni^{2+}	3-$MeOC_6H_4$	CHO	48
24e	Ni^{2+}	Hexyl	H	60
24f	Ni^{2+}	Hexyl	CHO	42
24g	Cu^{2+}	Hexyl	CHO	18
24h	Cu^{2+}	*i*-Bu	H	47
24i	Cu^{2+}	1-Ethylpropyl	H	97

9-Ethylcarbazole-3-aldehyde (26b). Typical Procedure.[44] *To a stirred ice cold solution of 9-ethylcarbazole in DMF was added $POCl_3$. When the addition was over, the reaction was brought to room temperature and irradiated in a microwave oven under low power (30%) for 1.5 min (with time intervals of 30 sec). After work up, the crude product was purified by column chromatography and eluted with ethyl acetate–petroleum ether to give 9-ethylcarbazole-3-aldehyde in 89% yield.*

b. Formylation of Arenes

The electron-donating effect of methoxy and methyl groups has a beneficial influence on the Vilsmeier-Haack reaction. Thus, 1,2,3-trimethoxy-5-methylbenzene (**27**), upon treatment with $POCl_3$ and DMF at 65 °C for 5 h, gave aldehyde **28**, a key material for synthesis of coenzyme $Q_{10,}$ in 95% yield (*Scheme 12*).[45]

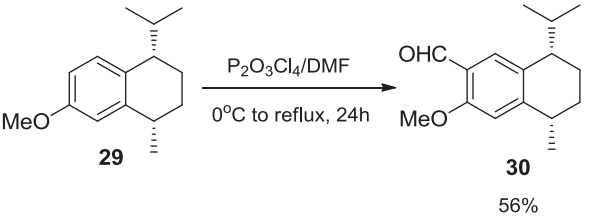


27 **28**
95%

Scheme 12

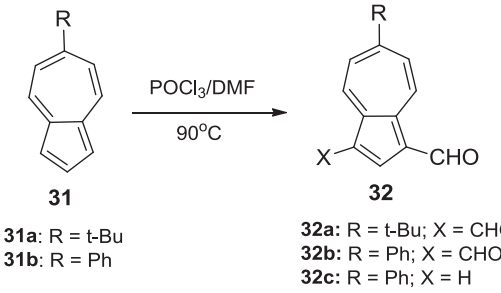
Brenna *et al.*[46] found also that the formyl group was added regioselectively to the aromatic ring of (1*S*,4*S*)-1-*iso*propyl-6-methoxy-4-methyl-1,2,3,4-tetrahydronaphthalene (**29**) by the Vilsmeier reaction, giving the corresponding aldehyde **30** (*Scheme 13*).

Azulene dicarbaldehydes are important intermediates for the preparation of azuliporphyrins. The substituted azulenes can be converted into dialdehydes under Vilsmeier-Haack



Scheme 13

conditions.[47] When the substituent at position 6 was a phenyl, a mixture of dialdehyde **32b** and monoaldehyde **32c** was obtained, while treatment of 6-*tert*-butylazulene (**31a**) gave the related dialdehyde **32a** (*Scheme 14*).



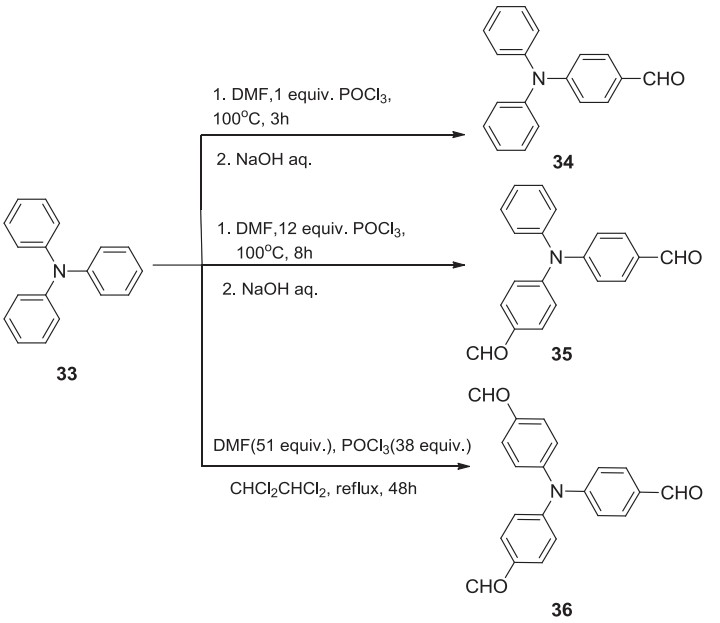
Scheme 14

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

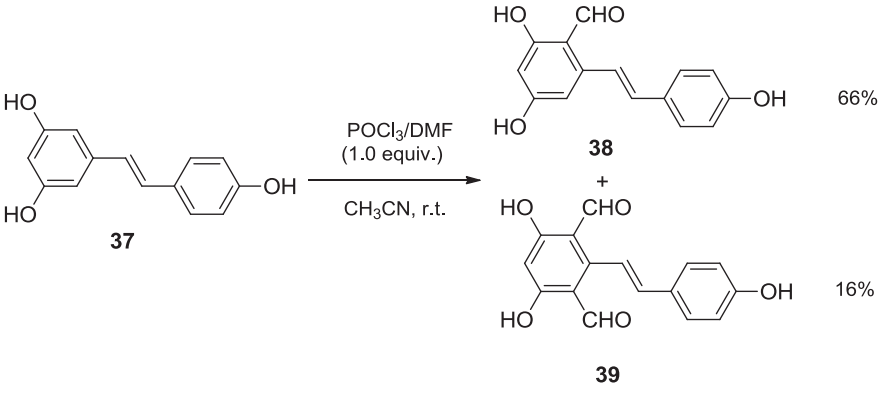
Resveratrol has been suggested as a possible cancer chemopreventive agent on the basis of its inhibitory effects on tumor initiation, promotion, and progression.[62] In order to discover novel anti-tumor agents with high efficiency, broad-spectrum activity and safety, Huang's group[63] designed and synthesized 4,6-dihydroxy-6-[2-(4-hydroxyphenyl) vinyl]benzaldehyde (**38**) and 4,6-dihydroxy-2-[2-(4-hydroxyphenyl)vinyl]benzene-1,3-dicarbaldehyde (**39**) by the reaction of resveratrol **37** with DMF and $POCl_3$ in CH_3CN as shown in *Scheme 16*. The results of cytotoxicity assays demonstrated that compounds **38** and **39** showed remarkable antitumor activity *in vitro*.

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

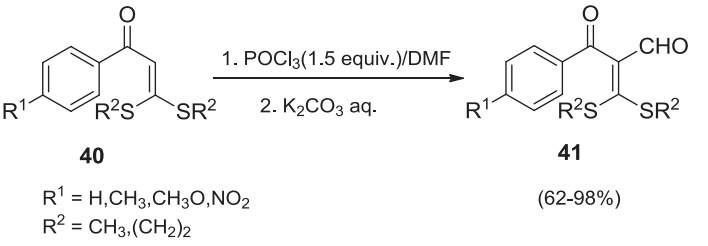
In 2006, Anabha *et al.*[64] developed a valuable synthetic method, which used the Vilsmeier reagent to prepare 2-aroyl-3,3-*bis*(alkylsulfanyl)acrylaldehydes **41** from aroylketene dithioacetals **40** in excellent yields (*Scheme 17*).



Scheme 15



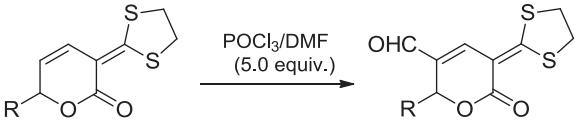
Scheme 16



Scheme 17

2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes 41. General Procedure.[64] *The Vilsmeier–Haack reagent was prepared by adding $POCl_3$ (0.67 mL, 7 mmol) to DMF (6 mL, 70 mmol) at 0°C and stirring the mixture for 20 min at room temperature. The appropriate α-oxoketene dithioacetal* ***40*** *(4.7 mmol) was added to this mixture, and the solution was stirred well for 10–16 h (monitored by TLC). The reaction mixture was poured into cold sat. K_2CO_3 solution (70 mL) and was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O then dried, and the solvent was evaporated. The crude product obtained was filtered through a column of silica gel (EtOAc–hexane, 1:50).*

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



42

42a: R = C_6H_5
42b: R = 4-ClC_6H_4
42c: R = 4-$CH_3C_6H_4$

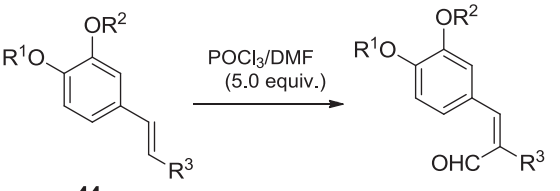
43

(76-81%)

Scheme 18

α,β-Unsaturated aldehydes **45** are key intermediates of indenols which have many biologically activities. In 2006, Singh and co-workers[77] reported a new method for the synthesis of α,β-unsaturated aldehydes **45** from alkenes **44** by Vilsmeier formylation in high yields (*Scheme 19*).

2-Phenylglyoxal hydrazones **47** were synthesized in a two-step sequence by Vilsmeier formylation of benzaldehyde *N*,*N*-dimethylhydrazones **46** followed by hydrolysis in aqueous $NaHCO_3$ (*Scheme 20*).[78,79]



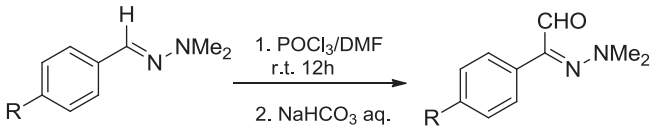
44

R^1 = OMe, OC_2H_5
R^2 = H, OMe, OC_2H_5
R^3 = C_6H_5, *p*-MeC_6H_4, C_2H_5, C_9H_{19}, $C_{11}H_{23}$

45

(72-91%)

Scheme 19



46

46a: R = H
46b: R= NO_2

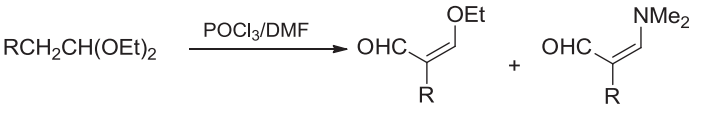
47

47a: 70%
47b: 84%

Scheme 20

d. Formylation of Methylene Groups

Reger *et al.*[80] developed a new and practical procedure for the formylation of active methylene groups (*Scheme 21*). The reaction between diethylacetals **48** and the Vilsmeier reagent occurred smoothly at or below 80°C to give a mixture of ethoxyacroleins **49** and dimethylaminoacroleins **50**. The temperature at which the Vilsmeier reaction was carried out was found to be critical to the success of the reactions; when the reactions were performed above 80 °C extensive decomposition occurred.



48

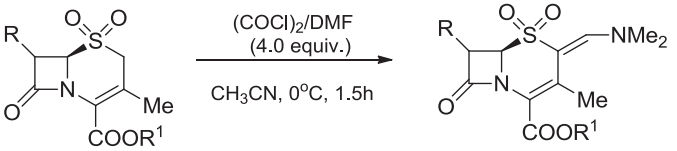
R = alkyl,aryl

49

50

Scheme 21

N,N-Dimethylaminomethylene-substituted cephems **52** are functional intermediates which can be used in the synthesis of cephalosporin analogs. Vorona and co-workers[81] reported an effective method for the preparation of these compounds based on introduction of the *N,N*-dimethylaminomethylene group at position 2 of the cephem nucleus of compounds **51** as shown in *Scheme 22*.



51

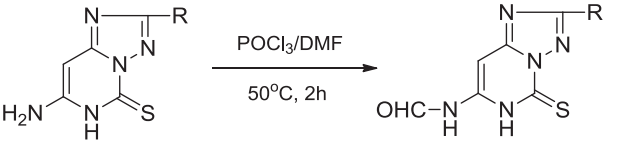
51a: R = (S)Cl, R^1 = *t*-Bu
51b: R = (R)$PhOCH_2CONH$, R^1 = $CH_2CH{=}CH_2$

52

Scheme 22

e. Formylation of Amines

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



53

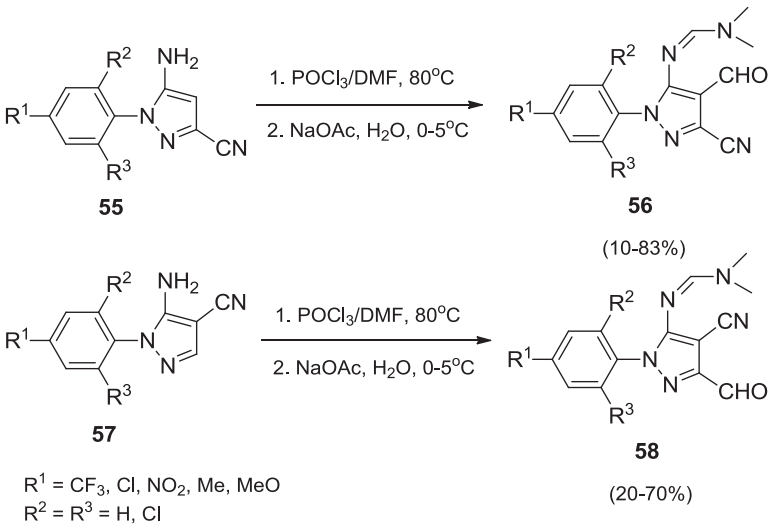
53a: R = H,
53b: R = CH_3

54

54a: 43%
54b: 34%

Scheme 23

Formylpyrazoles are very important intermediates and building blocks widely employed in the synthesis of diverse useful pyrazole derivatives in some fields of agrochemistry and biomedical chemistry.[83] Luo's group[84] designed and synthesized two species of *N*-arylpyrazoles containing active amino group as shown in *Scheme 24*. Formylation at the 4-position of the *N*-arylpyrazoles **55** afforded pyrazole intermediates **56** in higher yield, but required more time than formylation at the 3-position of *N*-arylpyrazoles **57,** as the electron-density at the 4-position of compounds **55** is greater than at the 3-position of compounds **57**. However, because of the hindering effect of the imino group, formation of the formylation intermediate requires more time at the 4-position than at the 3-position.



55

56

(10-83%)

57

R^1 = CF_3, Cl, NO_2, Me, MeO
R^2 = R^3 = H, Cl

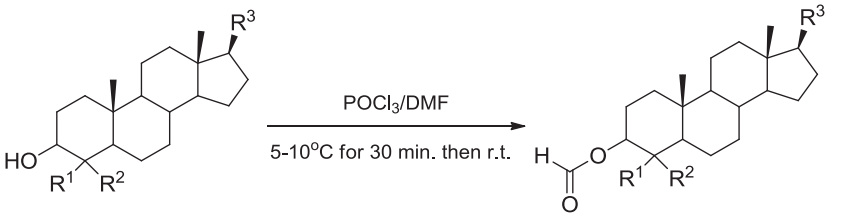
58

(20-70%)

Scheme 24

f. Formylation of Alcohols or Phenols

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



R^1, R^2 = H/Me
R^3 = different alkyl/alkenyl chains

59 **60** (48-91%)

Scheme 25

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

61 **62**

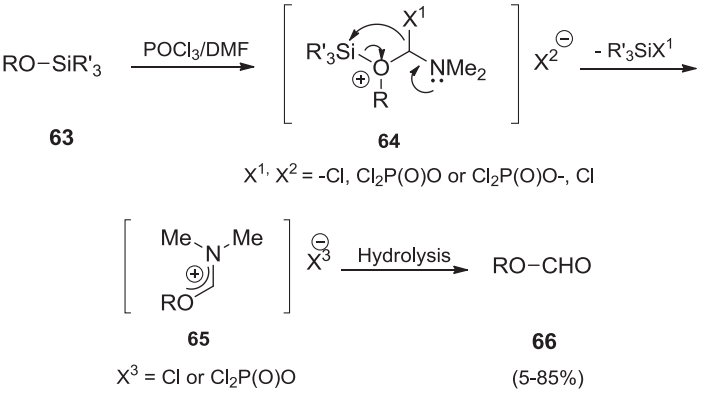
R^1, R^2, R^3 = H, t-Bu (58-83%)

Scheme 26

g. Other Formylations

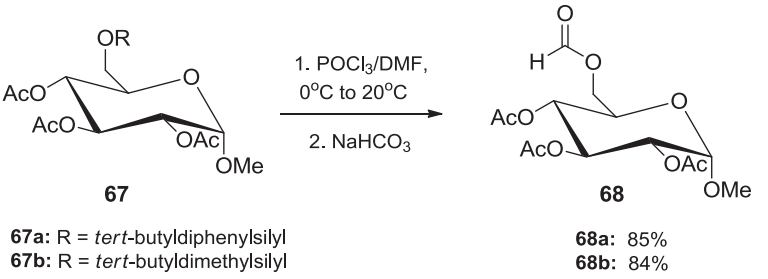
Silyl ethers RO-SiR'$_3$ **63** have become the most popular protecting groups for hydroxyl functions during complex multistep synthesis, especially when orthogonal protective/deprotective steps are required. In 2001, Lellouche's group[87] provided a powerful method, which transformed silyl ethers **63** into formates **66**. A likely mechanism is the addition of the Vilsmeier reagent to the silyl ethers **63** to afford the intermediate oxonium cations **64** (mixture of Cl^- and/or $Cl_2P(O)O$- counteranions). Due to the formation of the thermodynamically strong Si-Cl/Si-O bonds (111.0 and 128.2 kcal, respectively), the

elimination of the neutral species $R'_3Si\text{-}X_1$ (X_1 = Cl and/or $O(O)PCl_2$) generates *in situ* the related salts **65** (mixture of same counteranions), whose subsequent smooth hydrolysis affords the corresponding formates **66** (*Scheme 27*).



Scheme 27

Andrade *et al.*[88] reported a simple method for the preparation of formic esters **68** from the corresponding silyl ethers. Thus the monosaccharides **67** underwent formylation with 1.1 equiv. of the Vilsmeier reagent affording the 6-formic esters **68** in good yields (*Scheme 28*).

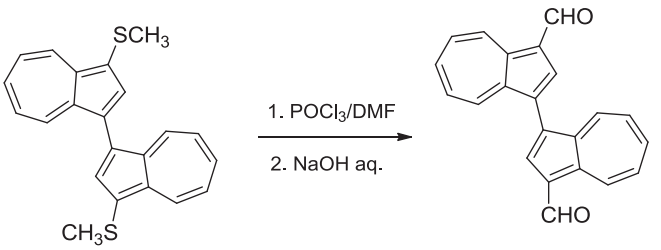


Scheme 28

Shoji *et al.*[89] found that the Vilsmeier formylation of the 1,1′-biazulene derivative **69** gave 3,3′-formyl-1,1′-biazulene (**70**) in 90% yield. This was the first example where the methylmercapto group behaved as a leaving group in electrophilic *ipso*-substitution in azulene chemistry (*Scheme 29*).

2. Other Acylations

Kreisberg *et al.*[90] reported a simple, high-yield method for preparaing of 2-(2-(4-(2-substituted)-1H-indol-3-yl)-2-oxoethyl)isoindoline-1,3-diones **72** using the Vilsmeier reagent. Thus, Vilsmeier formylation of 4-(2-substituted)-1H-indoles **71** at 95°C for 3 h,

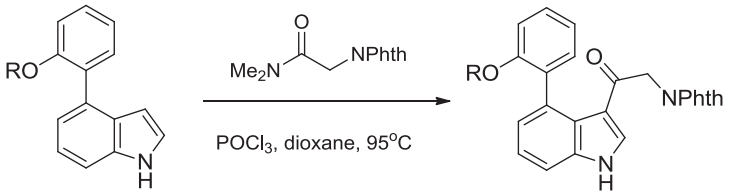


69 **70**

90%

Scheme 29

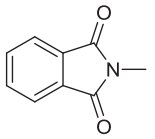
followed by work-up with 2.5 M aqueous NaOH, gave the desired 2-(2-(4-(2-substituted)-1H-indol-3-yl) -2-oxoethyl)isoindoline-1,3-diones **72** (*Scheme 30*).



71a: R = Me
71b: R = Bn

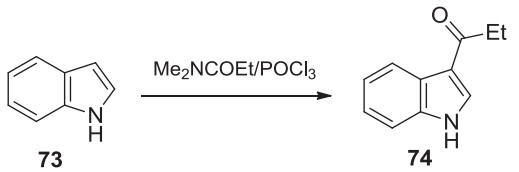
72a: 80%
72b: 95%

NPhth =



Scheme 30

Pedras *et al.*[91] synthesized 1-(*1H*-indol-3-yl)propan-1-one (**74**) by the reaction of indole (**73**) with N,N-dimethylpropionamide and $POCl_3$ as shown in *Scheme 31*.



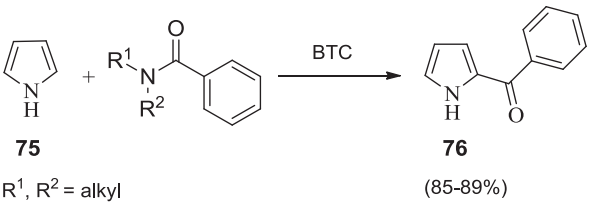
73 **74**

86%

Scheme 31

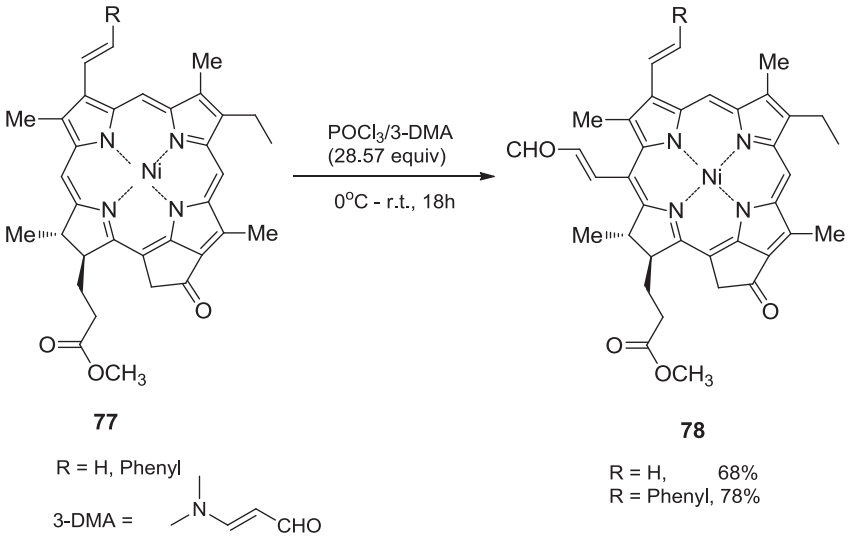
Su and co-workers[92] developed a new and practical procedure for the preparation of phenyl(1H-pyrrol-2-yl)methanone (**76**) from pyrrole (**75**) *via* Vilsmeier formylation (*Scheme 32*). Compared with $POCl_3$, *bis*-(trichloromethyl) carbonate (BTC) is safer and more convenient to handle and the yields of this reaction were also very good.

Photodynamic therapy is a relatively new modality for treatment of diseases that involve uncontrollable cell proliferation.[93] In this regard, Nickel complexes **78**



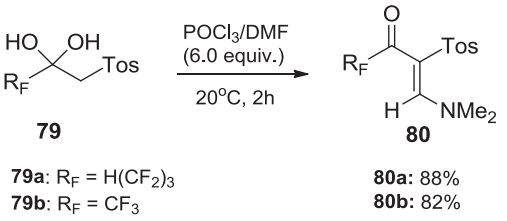
Scheme 32

are important intermediates in the synthesis of chlorin-based photosensitizers. The 2-formylvinylation of nickel complexes **77** was performed by the Vilsmeier reaction with 3-dimethylaminoacrolein (3-DMA) in the presence of phosphoryl chloride followed by basic hydrolysis with saturated aqueous sodium carbonate solution to afford compounds **78** (*Scheme 33*). [94]



Scheme 33

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

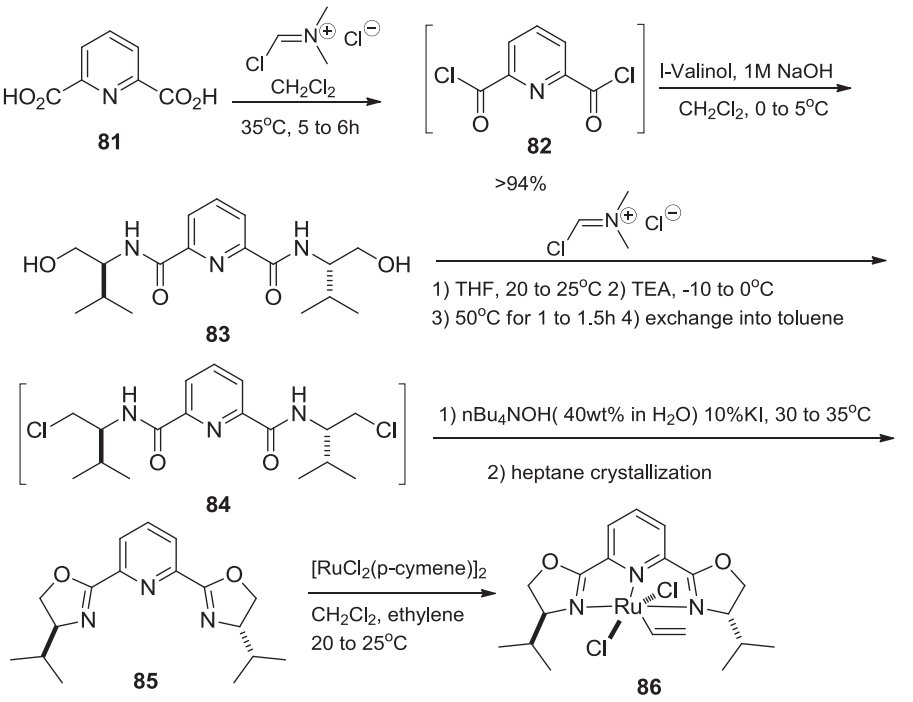


Scheme 34

II. Chlorination Reactions

1. Reaction with Hydroxy Groups

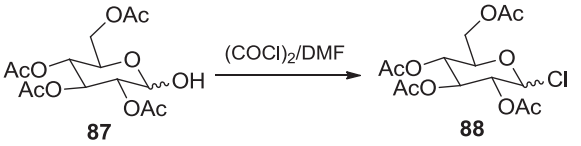
The enantioselectivity achieved using transition metal catalysts can be strongly influenced by chiral bisoxazoline ligands.[96] Catalysts such as **86**, which utilize pyridine bisoxazoline ligands, have been employed in the preparation of chiral catalysts for asymmetric transformations. Totleben *et al.*[97] reported an improved and safer method to prepare catalysts **86** on a near kilogram scale with good purity (*Scheme 35*). Thus, 2,6-pyridinedicarbonyl chloride (**82**) was prepared by treatment of inexpensive 2,6-pyridinedicarboxylic acid (**81**) with excess Vilsmeier reagent in CH_2Cl_2, affording **82** in yields of >94% as determined by in-process quantization. Subsequently, addition of a THF slurry of **83** to the Vilsmeier reagent in THF at 20–25°C gave **84** as the major product after 10–12h. During the process, treatment of **83** with methanesulfonyl chloride and a variety of amine bases produced mixtures containing a number of unidentified impurities and small amounts of **85**. The intermediate product **84,** which is chlorinated using the Vilsmeier reagent, plays a key role in this process.



Scheme 35

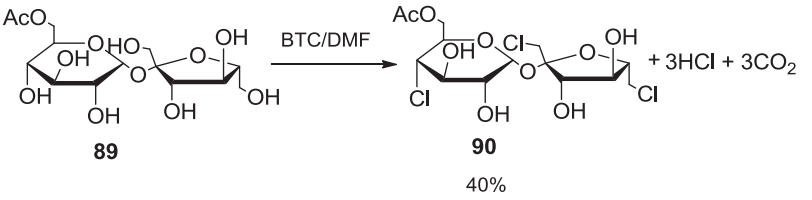
Oxalyl chloride is known to react with DMF under mild conditions to generate the corresponding Vilsmeier salt, which is the actual halogenating reagent. Encinas *et al.*[29] reported a route that used oxalyl chloride as a chlorinating reagent for the preparation of glycosyl chlorides **88** from sugar hemiacetals **87** in the presence of DMF. Glycosyl

chlorides **88** (*Scheme 36*) were employed in order to synthesize complex *O*-glycosides in the presence of heavy metal salts or halide ions as promoters.



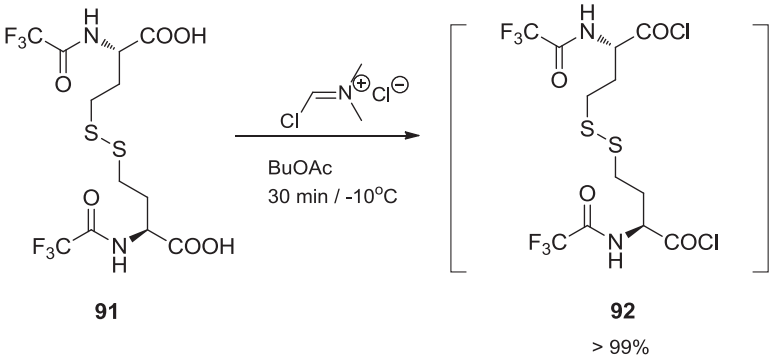
Scheme 36

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



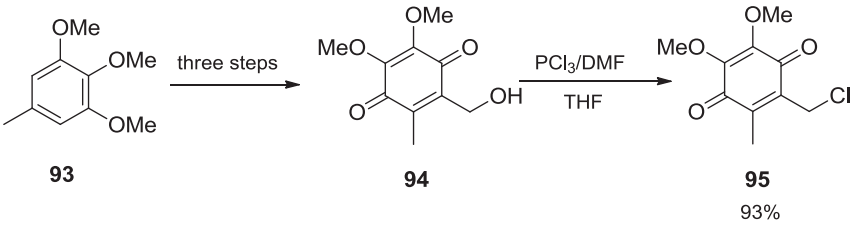
Scheme 37

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



Scheme 38

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

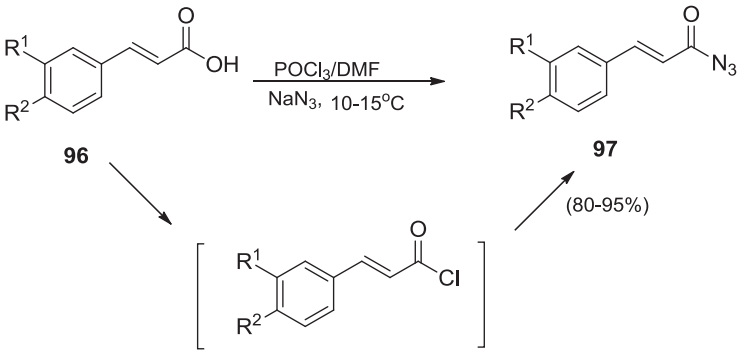


93 **94** **95**

93%

Scheme 39

Acyl azides are widely applied in heterocyclic synthesis. Sridhar *et al.*[101] reported an efficient route wherein the Vilsmeier reagent and NaN_3 were used as reagents for the conversion of carboxylic acids **96** to carboxylic acid azides **97** (*Scheme 40*). The strength of this method lay in the *in situ* acyl chloride generation by DMF/$POCl_3$ and the carboxylic acids **96**, which then reacted with sodium azide to give the corresponding carboxylic acid azides **97**.



Scheme 40

Amino-substituted pyrido[2,3-*d*]pyrimidinediones have been found previously to bind to adenosine A_1 and A_{2A} receptors in micromolar concentrations. Bulicz and co-workers[102] reported that most of the compounds investigated bore polar substituents (such as ethoxycarbonyl groups) and basic amino functions, in order to improve their water-solubility. In this reaction, treatment of compound **98** with $POCl_3$ in DMF under Vilsmeier conditions provided the desired 5-chloro derivative **99,** while treatment of **98** with phosphorus oxychloride without any solvent failed to give compound **99** (*Scheme 41*).

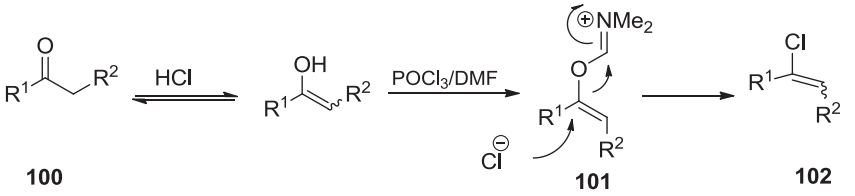
2. Chlorination of Carbonyl Compounds

The formation of chloroalkenes **102** as by-products or as main products in the Vilsmeier chloroformylation process has been reported occasionally.[103,104] Lilienkampf *et al.*[105]

98 **99**

Scheme 41

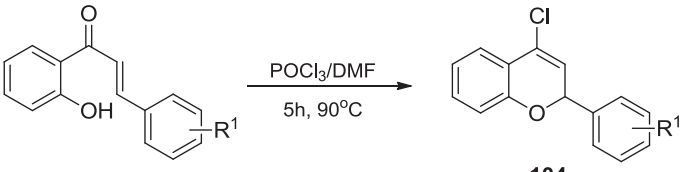
described that these chloroalkenes arise from a nucleophilic substitution by chloride ion at the vinyl ether carbon of the iminium species **101** formed by electrophilic attack of the Vilsmeier reagent at the carbonyl group of the starting ketones **100**. The formation of iminium species **101** liberates HCl which catalyzes the required enolization (*Scheme 42*).



100 **101** **102**

Scheme 42

Functionalized chromenes are important intermediates in the synthesis of several natural products and medicinal agents.[106] Perumal *et al.*[107] presented an effective method for the one-pot preparation of 2*H*-4-chlorochromenes **104** from 2′-hydroxychalcones **103** (*Scheme 43*). In this reaction, different ratios of $POCl_3$ in DMF were explored and it was found that 6 equiv. of $POCl_3$ in DMF was suitable for the preparation of **104**. No chlorochromenes were obtained when the reaction was carried out in $POCl_3$ alone.



103

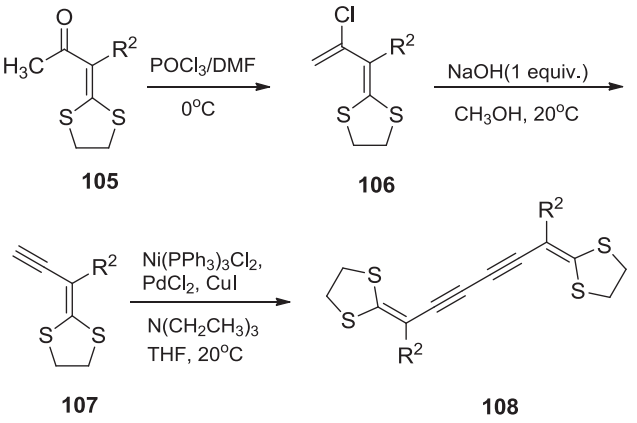
103a: R^1 = *p*-Cl;
103b: R^1 = *p*-OMe
103c: R^1 = *m*-NO_2;
103d: R^1 = *p*-Me

104

104a: 66%
104b: 68%
104c: 30%
104d: 65%

Scheme 43

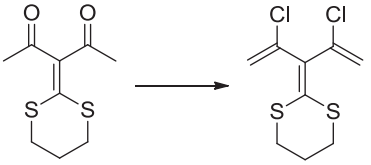
Tetrathiafulvalene (TTF) and its derivatives (TTFs) have been widely explored in both materials and supramolecular chemistry.[108,109] Recently, Zhao and co-workers.[110] described their synthetic applications (*Scheme 44*). A series of α-chloro-vinylketene-(S,S)-acetals **106** was prepared in high yields from the corresponding α-acetylketene-(S,S)-acetals **105** *via* a Vilsmeier-Haack reaction under mild conditions. Subsequently, compounds **106** underwent



Scheme 44

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

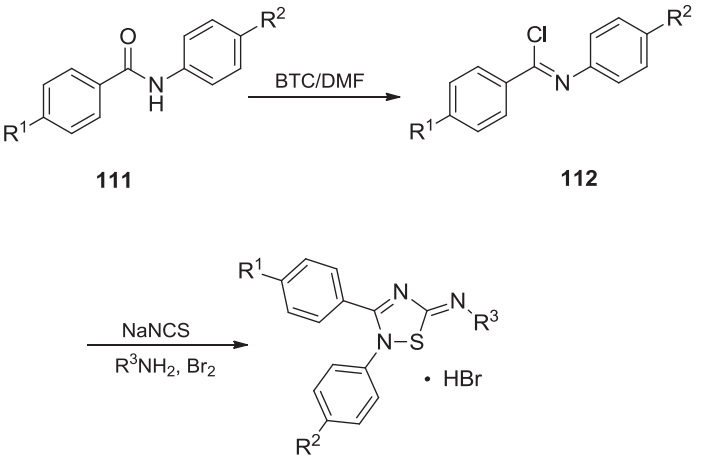
Thioacetalization is a popular tool to protect carbonyl groups of aldehydes and/or ketones. Liu and co-workers[111] reported the preparation of 2-[2-chloro-1-(1-chlorovinyl)allylidene]-1,3-dithiane (**110**) and its application in a thioacetalization reaction as a novel non-thiolic, odorless substitute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



Scheme 45

3. Chlorination of Amides

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

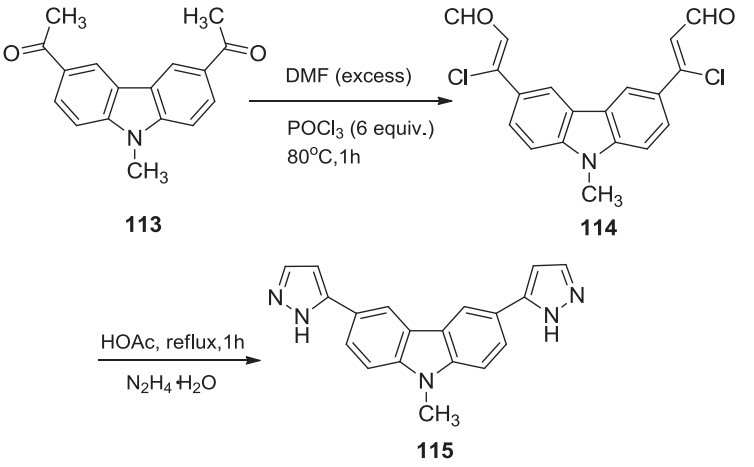


Scheme 46

III. Chloroformylation Reactions

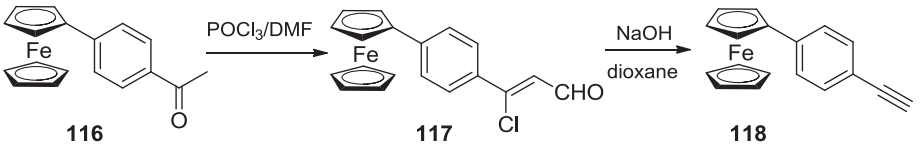
1. Reaction with Aryl Ketones

Pyrazole derivatives have been reported as pharmaceuticals for the treatment of cerebrovascular disorders[117] and for their antiarrhythmic, sedative, and platelet anti-aggregating activities.[118] Meesala *et al.*[119] reported an effective method to synthesize 3,6-di(pyrazol-4-yl)carbazoles from 3,6-diacetylcarbazoles. Thus, treatment of 9-methyl-3,6-diacetylcarbazole (**113**) with DMF/$POCl_3$ gave carbazolyl-bis-β-chloroacrolein (**114**) in 72% yield. Condensation, followed by cyclization with hydrazine hydrate in acetic acid at reflux for 1h, gave dipyrazolylcarbazole **115** in 76% yield (*Scheme 47*).



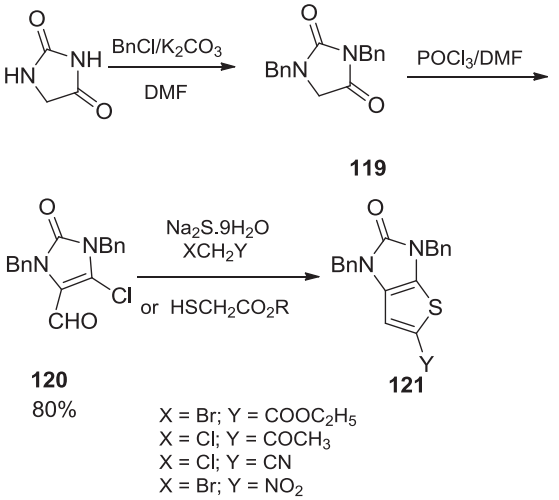
Scheme 47

Acetylenes and ferrocenylacetylenes are highly versatile species.[120] Schottenberger *et al.*[121] described a method for the synthesis of 4-ferrocenylphenylchloroacrolein (**117**) by chloroformylation of 4-ferrocenylacetophenone (**116**) with the Vilsmeier reagent; **116** is a key intermediate for the conversion to ferrocenylphenylacetylene (**118**) (*Scheme 48*).



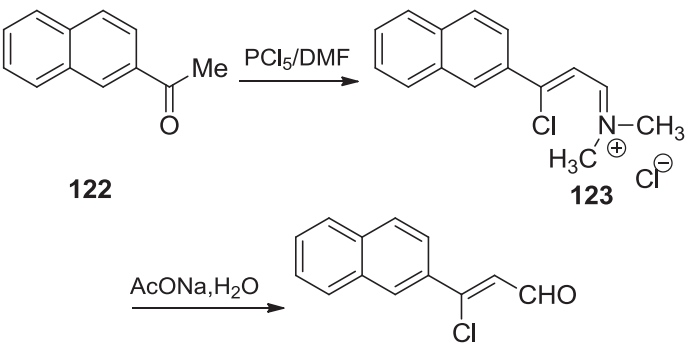
Scheme 48

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



Scheme 49

Naphthalene derivatives are widely used in the synthesis of dyes, pesticides, and drugs.[126] One of the convenient routes to naphthalene functionalized derivatives is by introduction of the ethynyl group into the side-chain of the naphthalene system,[127] followed by the synthesis of highly reactive metal acetylenides.[128,129] Under Vilsmeier conditions, ketone **122** could be converted to (*Z*)-3-(2-naphthyl)-3-chloropropenal (**124**), which proved to be an important intermediate for the synthesis of copper, mercury and silver 2-naphthylacetylenides.[130] The naphthylchloropropenal (**124**) was obtained upon treatment of the intermediate **123** with sodium acetate in aqueous solution (*Scheme 50*).

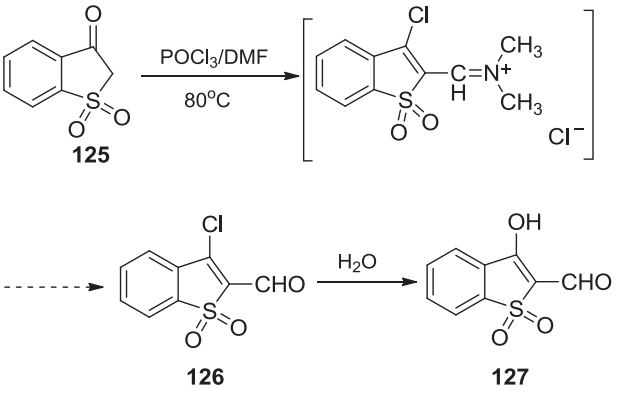


122 **123** **124**

72%

Scheme 50

Thiophene and its benzo analogues find wide applications in pharmaceuticals,[131] pesticides,[132] polymers,[133] liquid crystals[134] and dyes.[135] The utilization of benzo[b]thiophene3(2*H*)-one-1,1-dioxide (**125**) as an intermediate for the synthesis of a range of disperse dyes was explored.[136] In this reaction, the active methylene next to the α-carbonyl and sulfone groups of **125** was subjected to the Vilsmeier-Haack reaction with the aim of generating the chloroformyl derivative **126** (*Scheme 51*). Because of the high lability of the chlorine atom in the intermediate **126**, the ultimate product was hydroxyaldehyde **127**.

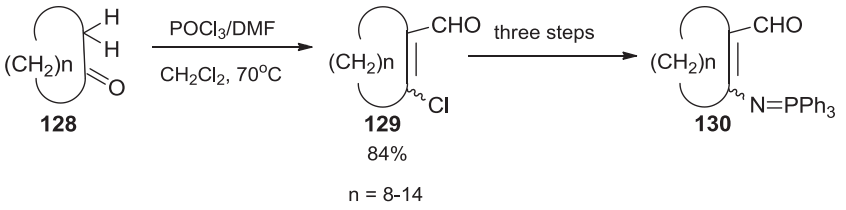


125 **126** **127**

Scheme 51

2. Reaction with Alkyl Ketones

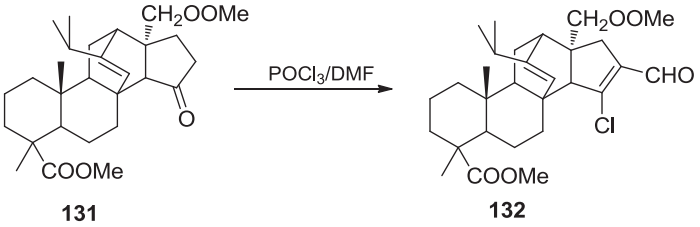
Kanomata and co-workers[137] reported that *(E)*-2-chloro-cycloalk-1- enecarbaldehydes **129** could be used as intermediates for the synthesis of (vinylimino)phosphoranes **130** (*Scheme 52*). Vilsmeier-Haack formylation of cycloalkanones **128** afforded compounds **129** in good



Scheme 52

yields; it was found that even milder reaction conditions worked very well for the synthesis of **129** where the reaction with excess amounts of DMF and $POCl_3$ at the 70°C led to the predominant formation of (*Z*)**-129** in good to moderate isolated yields.

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



Scheme 53

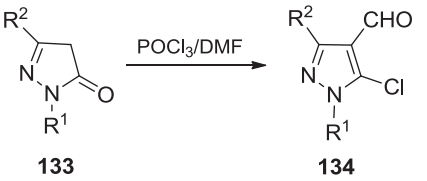
IV. Aromatization

1. Reaction with Lactams

The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. Therein, Park *et al.*[139] reported systematic replacement with a wide range of substituents within the pyrazole moiety. Thus, the pyrazolones **133** were subjected to Vilsmeier-Haack chloroformylation using DMF and excess $POCl_3$ to yield the corresponding 5-chloro-4-formylpyrazoles **134**, which were key intermediates for the preparation of pyrazole oxime ethers. The latter were found to have promising antiproliferative properties against several kinds of human tumor cell lines (*Scheme 54*).

2. Reaction with α,β-Unsaturated Ketones

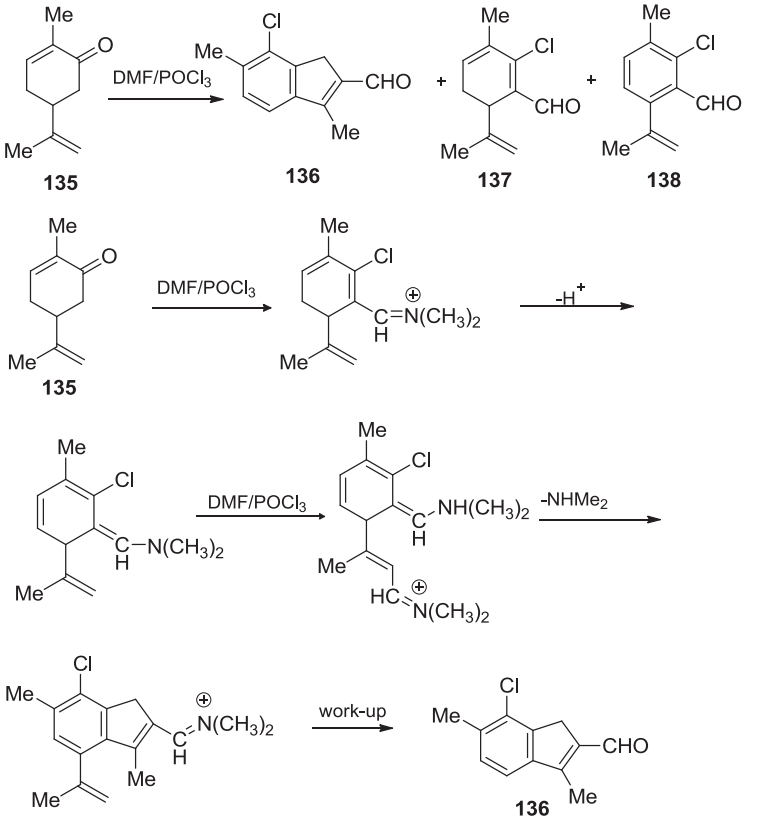
Aldehydes and ketones have played a primary role in perfumery and continue to be some of the leading choices in perfume composition.[140] Recently, Anzaldi *et al.*[141] reported that the Vilsmeier reagent derived from *N,N*-dimethylformamide and phosphorus oxychloride reacted with carvone (**135**) to produce aldehydes in a one-step procedure



133 134

Scheme 54

(*Scheme 55*). In this reaction, the Vilsmeier formylation of carvone (**135**) afforded a mixture of the expected formylcyclohexadiene **137** together with indene derivative **136** and the 2-chlorobenzaldehyde **138** (*Scheme 55*). The formation of **136** can be understood as arising from further iminoalkylation on the inactivated double bond of the isopropenyl group, whereas benzaldehyde **138** arises presumably from the oxidative aromatization of **137**.

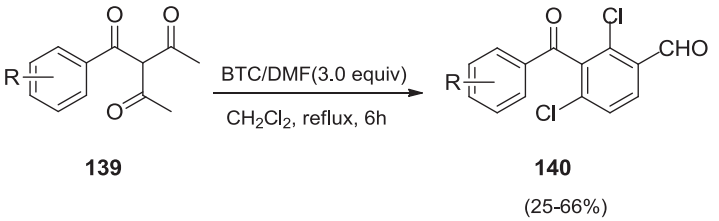


Scheme 55

3. Reaction with Diketones

The utilization of Vilsmeier salts derived from *bis*-(trichloromethyl) carbonate (triphosgene, BTC) and N,N-dimethylformamide (DMF) has been explored extensively.[142,143]

Su *et al.*[144] reported the aromatization of substituted 3-benzoylpentane-2,4-diones **139** with the Vilsmeier reagent derived from BTC/DMF to give substituted 3-benzoyl-2,4-dichlorobenzaldehydes **140** in moderate yields (25–66%) (*Scheme 56*). It was found that the yields were affected strongly by the substituents on the aromatic ring. Thus, substrates with strong electron-donating groups provided higher yields than those with electron-withdrawing groups.



139 **140** (25-66%)

Scheme 56

V. Cyclization

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

1. Intramolecular Cyclization

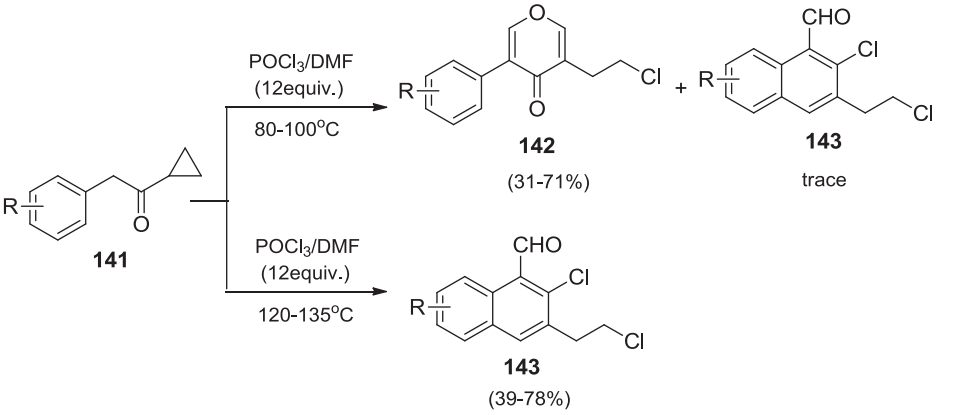
a. Cyclization of Ketones

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

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

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

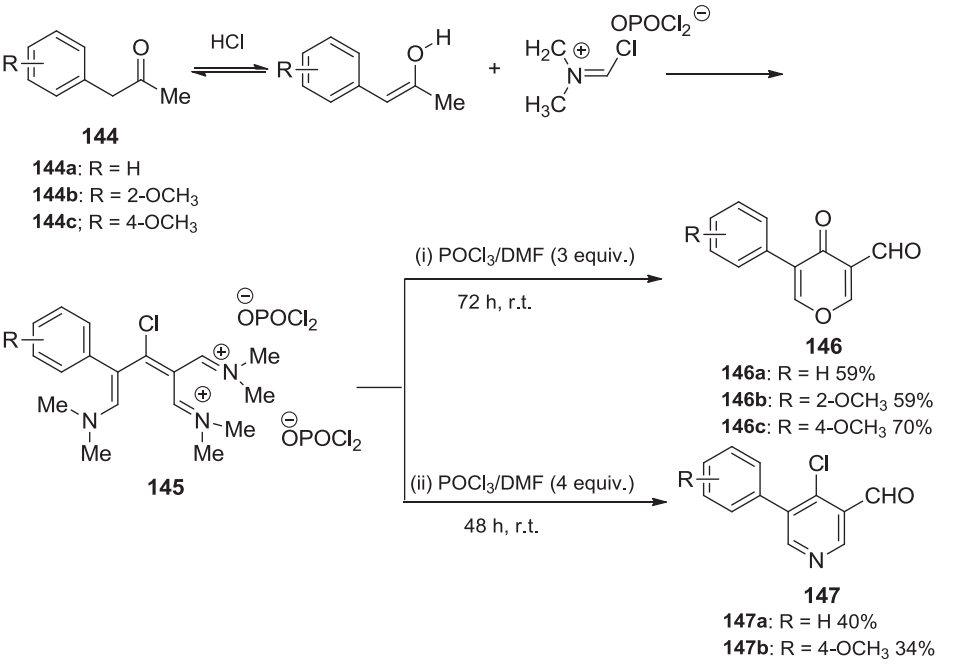
Nohara and co-workers[147,148] reported that 3-cyano-4-benzopyrones **151** were generally synthesized in three steps starting from 2-hydroxyacetophenones **148** (*Scheme 59*). However, this method suffered from several disadvantages such as the necessity for



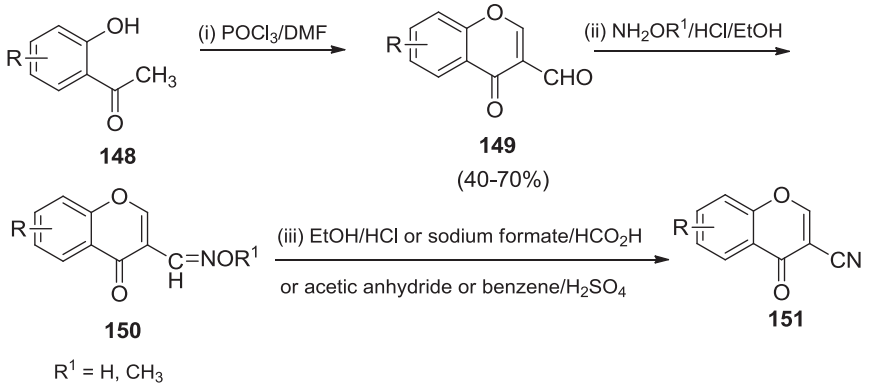
Scheme 57

isolating the intermediate 3-formylbenzopyrones **149** and the corresponding oximes **150**, long reaction periods, and low overall yields.

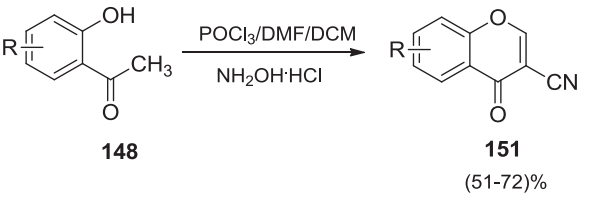
Reddy's group[149] reported an efficient one-pot synthesis of 3-cyano-4-benzopyrones **151** employing 2-hydroxyacetophenones **148** as substrates under Vilsmeier conditions. This procedure, owing to its considerable synthetic versatility and generality of preparation, is worthy of note (*Scheme 60*).



Scheme 58

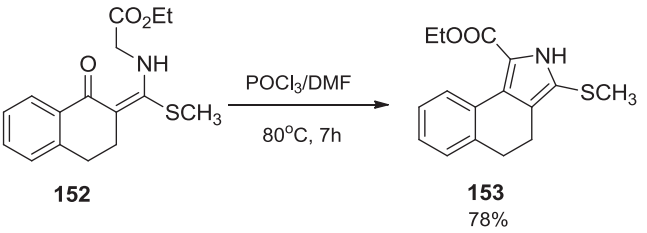


Scheme 59



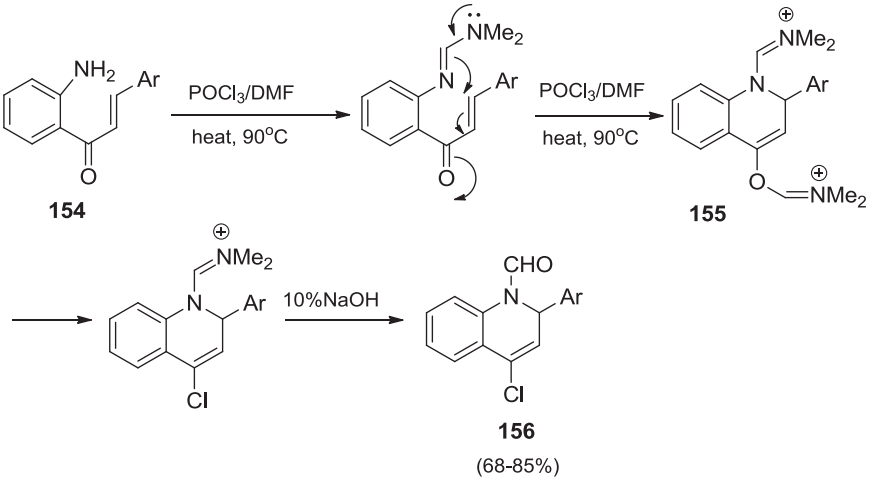
Scheme 60

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



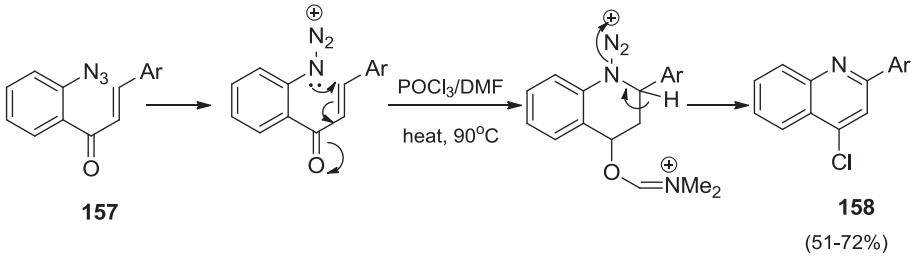
Scheme 61

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



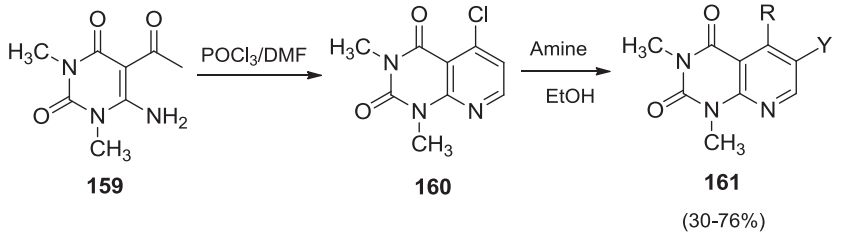
154 155 156 (68-85%)

Scheme 62



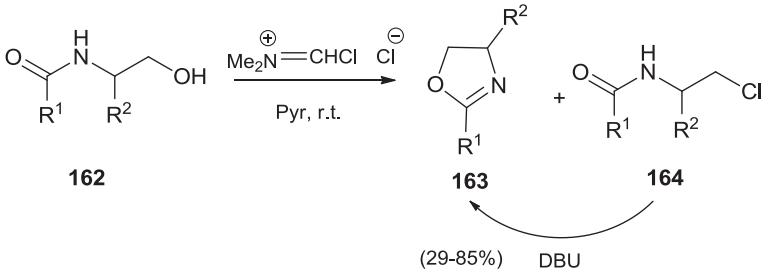
157 158 (51-72%)

Scheme 63



159 160 161 (30-76%)

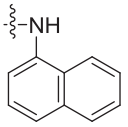
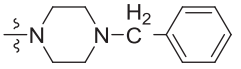
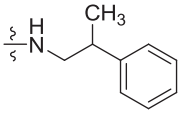
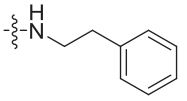
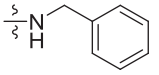
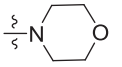
Scheme 64



162 163 164 (29-85%) DBU

Scheme 65

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

Entry	R	Y
161a		H
161b		H
161c		H
161d		H
161e		H
161f		H
161g		H

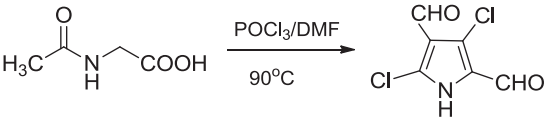
Bulicz' s group[152] carried out the introduction of the keto function into substrate **159** followed by ring closure using the Vilsmeier reagent. The desired products, amino-substituted pyrido[2,3-d]pyrimidinediones **161**, were obtained by reaction of amines with intermediate **160** (*Scheme 64*). Amino-substituted pyrido[2,3-d]pyrimidinediones **161** have been found previously to bind to adenosine A_1 and A_{2A} receptors in micromolar concentrations (*Table 2*).

b. Cyclization of Amides

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

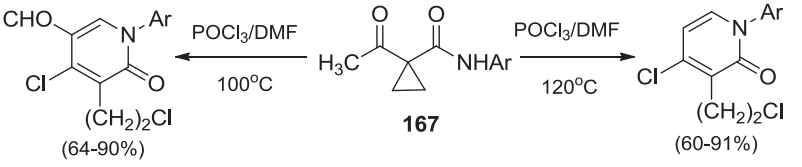
N-Acetylglycine (**165**) also can be converted by the Vilsmeier reagent into the poly-functional pyrrrole (**166**), as shown in *Scheme 66*.[155]

Halogenated pyridin-2(1*H*)-ones are useful intermediates for the synthesis of organic compounds with diverse bio-, physio-, and pharmacological activities in numerous natural products.[156,157]

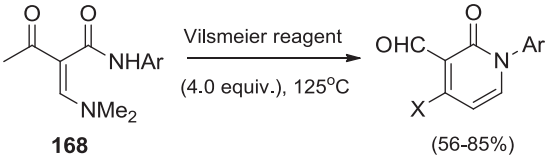


Scheme 66

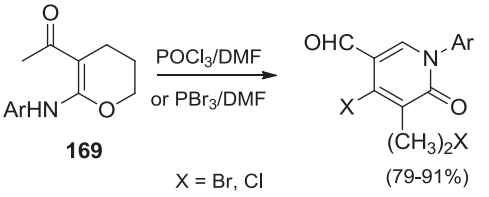
During the course of Dong *et al.*'s study of the Vilsmeier reactions, he developed a facile, one-pot synthesis of halogenated pyridin-2(1*H*)-ones from cyclopropyl amides **167**,[24] enaminones **168**,[158] cyclic enaminones **169**[159] and β-oxo amides **170**[160] under Vilsmeier conditions (*Schemes 67–70*). A mechanism involving sequential halogenation, formylation and intramolecular nucleophilic cyclization has been proposed. These protocols are very attractive due to simple execution, inexpensive reagents, and high yields.



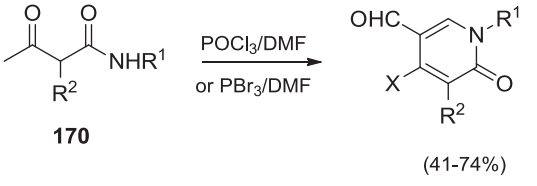
Scheme 67



Scheme 68

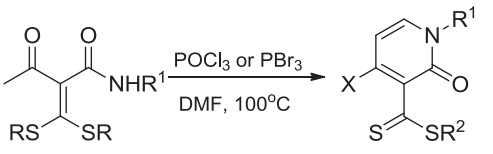


Scheme 69



R^1 = aryl, alkyl; R^2 = alkyl, H; X = Br, Cl

Scheme 70



171 **172**

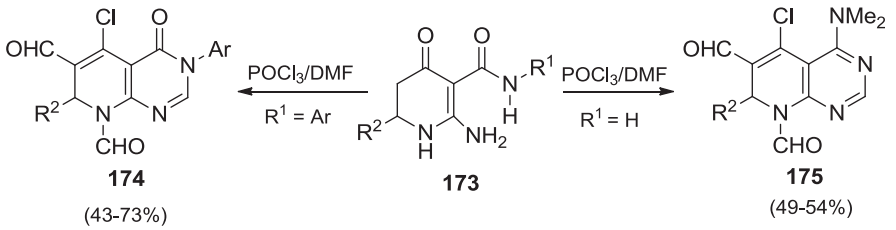
(50-92%)

R = -$(CH_2)_3$- , R =Et; R^1 = 4-Cl-C_6H_4, R^1 = C_6H_5,
R^1 = 4-CH_3O-C_6H_4, R^1 = 2-CH_3-C_6H_4, R^1 = 2-$(CH_3)_2$-C_6H_3,
R^1 = 2-Cl-C_6H_4, R^1 = 2-CH_3O-C_6H_4, R^1 = CH_3;
R^2 = $(CH_2)_2CH_2X$, R^2 = Et; X = Cl, Br

Scheme 71

Subsequently, Chen *et al.*[25] developed a novel and efficient route for the preparation of 4-halogenated *N*-substituted 2(1*H*)-pyridinones **172** *via* a one-pot domino process using readily available α-acetyl-α-carbamoyl ketene dithioacetals **171** with Vilsmeier reagents (*Scheme 71*).

Pyrido[2,3-*d*]pyrimidines are a type of annulated uracil, which have received considerable attention because of a wide range of biological activities.[161,162] Treatment of Vilsmeier reagent with 2-amino-3-carbamoyl-5,6-dihydro-4-pyridones **173** provided highly functionalized dihydropyrido[2,3-*d*]pyrimidines **174** and **175**, respectively, *via* a [5 +1] annulation strategy (*Scheme 72*).[163] Compounds **174** were generated through a series of transformations, including acid-catalyzed elimination of dimethylamine, chlorovinylation and formylation. Formation of compounds **175** occurred by *N*-formylation, dehydration, nucleophilic attack of dimethylamine at the carbon atom and subsequent aromatization.

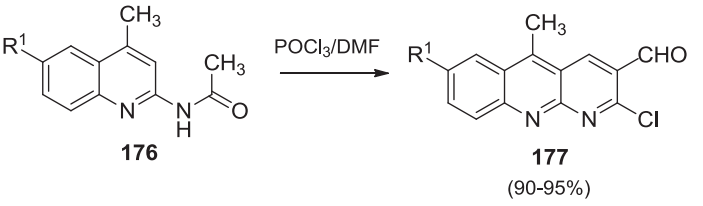


174 (43-73%) **173** **175** (49-54%)

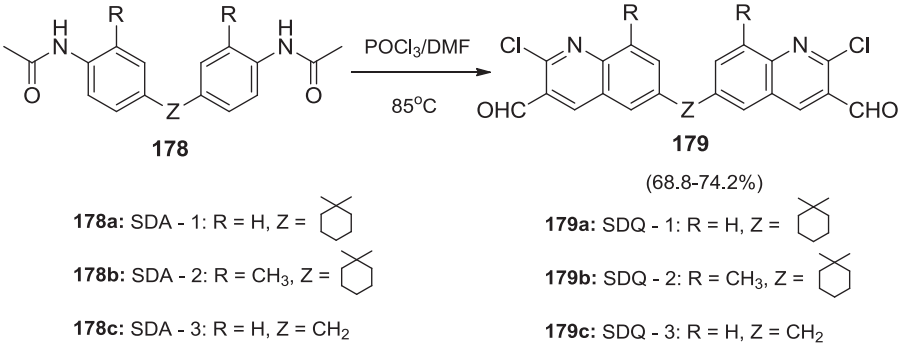
Scheme 72

Naphthyridine derivatives have been widely used for the diagnosis and chemotherapy of infectious diseases of humans, including AIDS.[164–166] Reaction of the Vilsmeier reagent with the amido *N*-(4-methylquinolin-2-yl) acetamides **176** has been shown to be an effective tactic for the formation of 2-chloro-3-formylbenzo[1,8]naphthyridines **177** (*Scheme 73*).[167] Microwave irradiation resulted in compounds **177** with good yields (90–95%).

A similar reaction was reported by Aghera's group.[168] Thus, the pharmacologically active quinolines **179** (SDQ-1 to SDQ-3) were synthesized in good yields through the cyclization reaction of symmetric double acetamides **178** (SDA-1 to SDA-3) with $POCl_3$/DMF (*Scheme 74*).



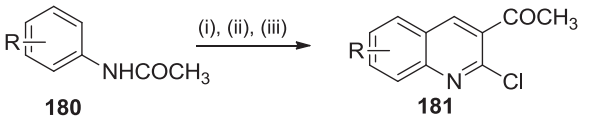
Scheme 73



Scheme 74

The Vilsmeier-Haack formylation has become one of the most common methods of cyclization of iminium species to aromatic compounds or heterocycles and the Vilsmeier-Haack acetylation also can produce aromatic compounds or heterocycles *via* cyclization of iminium species.[23,169]

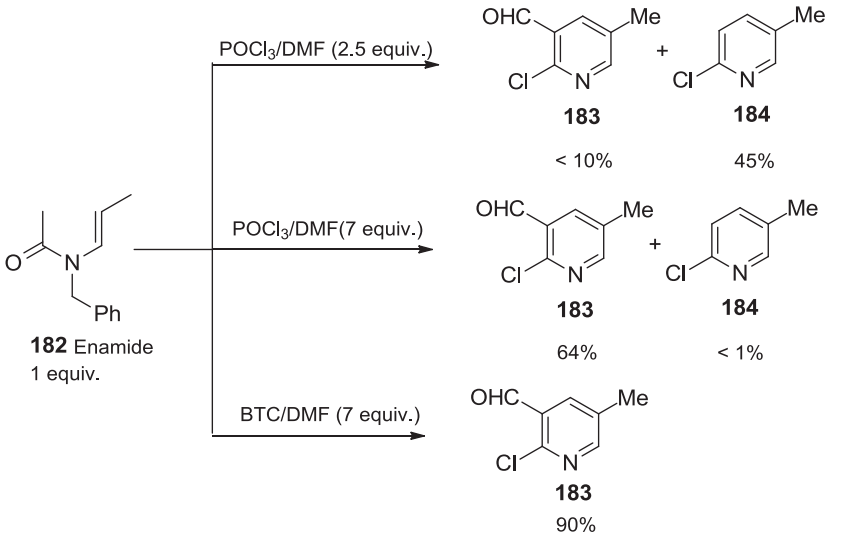
Rajanna's group[170] reported the Vilsmeier-Haack acetylation of aromatic compounds by employing $POCl_3$/N,N-dimethylacetamide (DMA) as acetylating reagent in the presence of micelles (*Scheme 75*). They applied this methodology to one-pot synthesis of 2-chloro-3-acetyl- quinolines **181** from acetanilides **180**. There was a remarkable improvement in the yields of products formed *via* cyclization in the presence of micelles, *i.e*. CTAB (cetyltrimethylammonium bromide), SDS (sodium dodecylsulfate) and TX (Triton-X-100), under reflux conditions.



(i) $POCl_3$/DMA, CTAB, CH_3CN, reflux, 45-90 min; (72-90%)
(ii) $POCl_3$/DMA, SDS, CH_3CN, reflux, 45-90 min; (74-90%)
(iii) $POCl_3$/DMA, TX-100, CH_3CN, reflux, 45-90 min; (74-90%)

Scheme 75

In some cases, the protocol employing BTC/DMF as Vilsmeier reagent provides mild reaction conditions and higher yields than other methods employing $POCl_3$/DMF. For example, Gangadasu's group[171] reported that chloronicotinaldehyde **183** was prepared in higher yields by the cyclization of enamide **182** when treated with 7.0 equiv. BTC/DMF



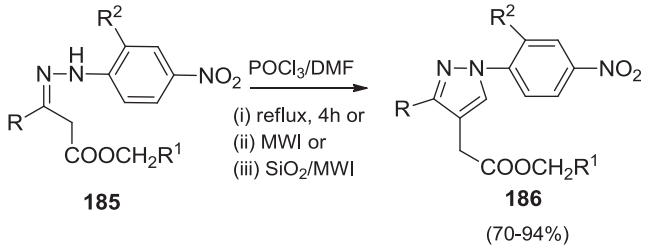
Scheme 76

compared with the classical method of using $POCl_3$ for the formation of Vilsmeier reagent. The use of 2.5 equiv. of the Vilsmeier reagent led to a lower yield of chloronicotinaldehyde **183**, and 2-chloro-5-methylpyridine (**184**) was the major product (*Scheme 76*).

c. Cyclization of Aromatic Hydrazones

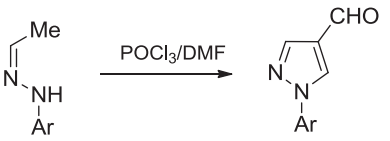
Pyrazole derivatives have been reported as pharmaceuticals for the treatment of cerebrovascular disorders[172] and for their antiarrhythmic, sedative and platelet anti-aggregating activities.[173] Hydrazones are easily accessible starting materials yielding pyrazoles upon treatment with the Vilsmeier reagent.

Thus, Sridhar *et al.*[174] reported that 1-*H*-pyrazole-4-carboxylic acid esters **186** could be synthesized *via* ring closure of 2,4-dinitrophenylhydrazones of β-ketoesters **185** using the Vilsmeier reagent ($POCl_3$/DMF) both in conventional and microwave methods (*Scheme 77*). Compared with conventional methods, the main advantages of the microwave approaches were good yields and relatively by short reaction times. When the reaction mixture was subjected to microwave irradiation on a SiO_2 support, even better yields were obtained. The chloromethyleniminium ion was responsible for the cyclization, furnishing the pyrazole



R = CH_3, C_6H_5, p-chlorophenyl; R^1 = H, CH_3 and R^2 = H, NO_2

Scheme 77



187a: Ar = Ph, **187b:** Ar = 4-ClC_6H_4, **187c:** Ar = 4-MeC_6H_4

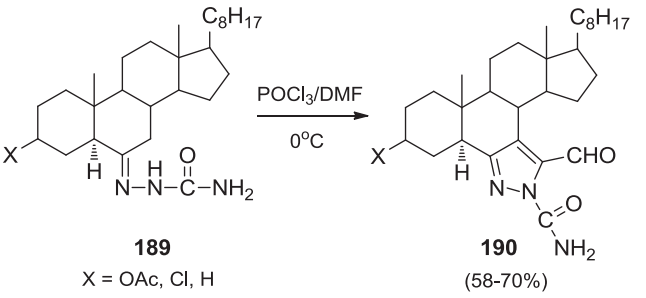
Scheme 78

when it reacted selectively with hydrazones containing an active methylene carbon groups. No further addition of the Vilsmeier complex occurred even if an excess of reagent was employed.

1H-Pyrazole-4-carboxylic Acid Esters 186. General Procedure (Method III).[174] *After dropwise addition of $POCl_3$ (0.003 mol) to an ice-cold solution of 0.001 mol of hydrazone* ***185*** *in 4ml of dry DMF, the reaction mixture was slurried with SiO_2 (60–120 mesh). The slurry was subjected to microwave irradiation in a domestic microwave oven (BPL microwave cooking system model BMO-7007) for about 3 min with a pulse of 20 s each at 70% power corresponding to 210 Watts. Finally, the slurry was washed with ice-cold water, allowed to settle and the supernatant washings were collected. The process was repeated 3 to 4 times and the combined water washings were filtered to obtain the crude pyrazole which was recrystallized with chloroform to yield the pure product.*

Chornous *et al.*[175] reported a method for the synthesis of 1-aryl-4-formylpyrazoles **188** *via* formylation with subsequent intramolecular cyclocondensation of acetaldehyde N-arylhydrazones **187** using the Vilsmeier reagent generated *in situ* from $POCl_3$ and DMF (*Scheme 78*). When the chloromethyleniminium ion reacted selectively with hydrazones **187** containing an active methyl group, 4-formylpyrazoles **188** were obtained *via* double formylation.

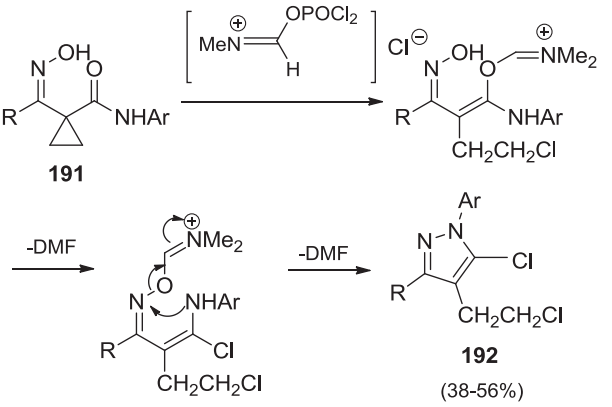
In a similar manner, a practical procedure for the preparation of steroidal pyrazoles **190** from the Vilsmeier reagent and semicarbazones **189** is shown in *Scheme 79*.[176] The steroidal pyrazoles **190** were found to possess antimicrobial, antiinflammatory, hypotensive, hypocholesterolemic and diuretic activities.[177–181]



Scheme 79

d. Cyclization of Oximes

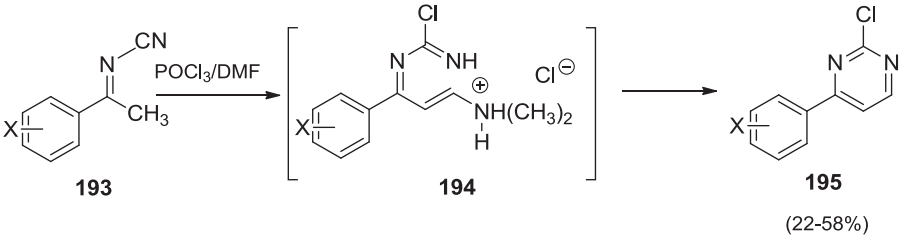
The pyrazole motif makes up the core structure of numerous biologically active compounds that find a wide a wide range of applications in the pharmaceutical and agrochemical industries.[182] Substituted 1*H*-pyrazoles **192** were obtained by ring closure of cyclopropyl oximes **191** with the Vilsmeier reagent ($POCl_3$/DMF) in 38–56% yields (*Scheme 80*).[183] A plausible mechanism involving sequential ring-opening, chlorovinylation, and intramolecular azacyclization has been proposed.



Scheme 80

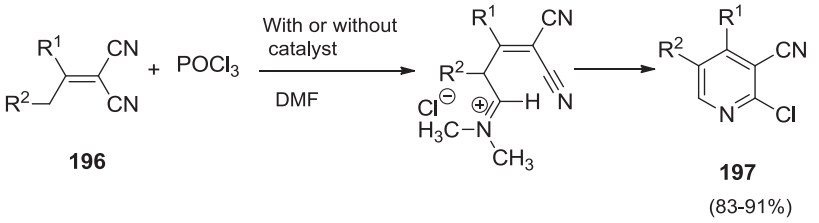
e. Cyclization of Nitriles

Cuccia and co-workers studied focused on the reaction of acetophenone cyanoimines **193** with the Vilsmeier reagent, to target 4-phenyl-2-chloropyrimidines **195** in acceptable yields (*Scheme 81*).[184] The reaction presumably proceeds by addition of the Vilsmeier reagent to the active methyl group and HCl to the nitrile to afford the intermediates **194**, followed by intramolecular cyclization. Substrates containing electron-donating groups enhance the reaction rate.



Scheme 81

The Vilsmeier-Haack cyclization is one of the most useful, general methods employed for the synthesis of substituted 2-chloro-3-cyanopyridines **197** from 2-propylidenemalonitriles **196**, however, the yields of the reaction are low (*Scheme 82*).



Scheme 82

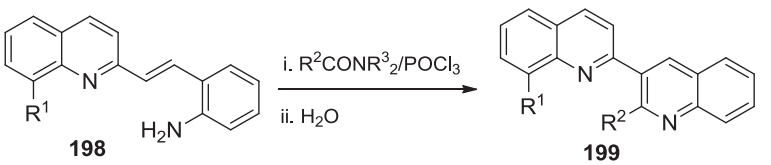
Zahouily *et al.*[185] have designed and carried out the introduction of catalytic amounts of natural phosphate (NP) alone or KF/NP as new efficient solid catalysts in the Vilsmeier-Haack reaction, in order to enhance the yields. Addition of NP to the usual Vilsmeier-Haack reagent mixture led to remarkable improvements in yields of **197**, which increased from 12–56% to 62–80%. NP could be regenerated by calcination at 500°C for 15 min. The protocol employing KF/NP as catalyst provided higher yields (83–91%).

Substituted 2-chloro-3-cyanopyridines 197. General Procedure.[185] *To a flask containing 10 mmol of alkene* ***196*** *and 20 mmol (3.0 g) of $POCl_3$ in DMF (10 ml), phosphate catalyst (NP or KF/NP, 0.1 g) was added and the mixture was stirred at room temperature for 30 min and the bath temperature was slowly raised to 70–80°C. The reaction mixture was heated during 3 h and then washed with water. The solid was filtered off and the catalyst washed with dichloromethane. After concentration of the filtrate under reduced pressure the residue was subjected to chromatography or recrystallisation (n-hexane/ethyl acetate) leading to the Vilsmeier–Haack adduct as a solid.*

f. Other Cyclizations

Lyakhovnenko *et al.*[186] have reported that the reaction of the amines **198** with DMF or with diethylamides of other carboxylic acids in the presence of $POCl_3$ gives high yields (82–88%) of 2,3′-biquinolines **199** (*Scheme 83*). Comparing this method with the alternative approach involving reaction of the amines **198** with acid chlorides and subsequently treatment with $POCl_3$, this protocol provided higher yields of compounds **199**.

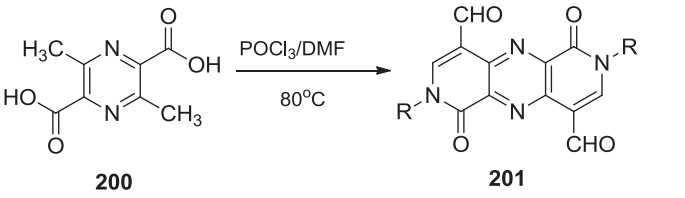
The *trans*-DOTTAD aldehydes **201** were formed by Vilsmeier formylation (followed by cyclization and *N*-demethylation) of 2,5-dimethyl-3,6-dicarboxypyrazine (**200**) (*Scheme 84*).[187] The reaction was conducted with preformed reagents derived from the corresponding dialkylformamides using $POCl_3$ as a solvent.



198 a: R^1 = H, **b:** R^1 = NO_2;

199 a-e: R^1 = H; **a:** R^2 = H, **b:** R^2 = Me, **c:** R^2 = Pr, **d:** R^2 = Bu, **e:** R^2 = Ph; **f:** R^1 = NO_2, R^2 = H,

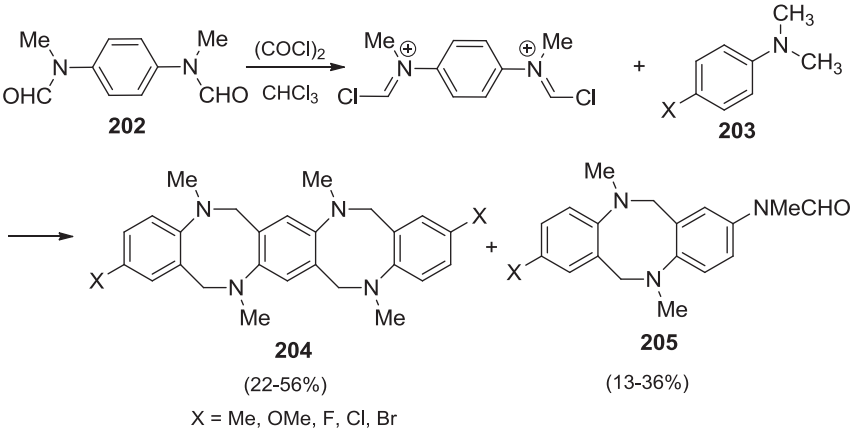
Scheme 83



200 **201**

201a: R = CH_3 (25%)
201b: R = CH_3CH_2 (35%)
201c: R = CH_2 = CH-CH_2 (32%)

Scheme 84



202 **203** **204** **205**

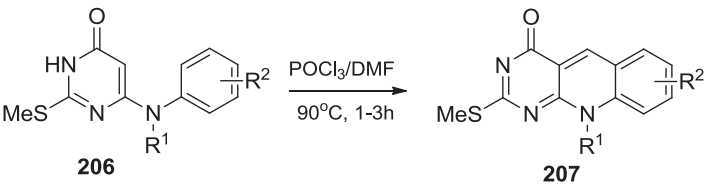
(22-56%) (13-36%)

X = Me, OMe, F, Cl, Br

Scheme 85

The *bis*-Vilsmeier reagent derived from *N,N′*-dimethyl-*N,N′*-diformyl-*p*- phenylenediamine (**202**) reacts with 4-substituted *N,N*-dimethylanilines **203** to yield dibenzo[b,b′] benzo[1,2-f:4,5-f′]*bis*[1,5]diazocines **204** in a single step (*Scheme 85*). Due to the incomplete conversion of compound **202** into the *bis*-Vilsmeier reagent, in some cases the half-cyclized products **205** were also obtained.[188]

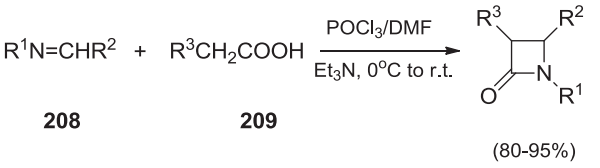
5-Deazaflavins **207** have attracted great interest because of their biological activities and high activity toward tumor cells.[189] Various novel 10-alkyl-2-deoxo-2-methylthio-5-deazaflavins **207** were synthesized in 71–99% yield from 6-(N-monoalkylanilino)-2-methylthiopyrimidin-4(*3H*)-ones **206**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



206 **207**

(71-99%)

Scheme 86



Scheme 87

2. Intermolecular Cyclization

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

Jarrahpour and co-workers[195] described the first example using the Vilsmeier reagent for the one-step Staudinger reaction of substituted acetic acids **209** and imines **208** (*Scheme 87*). In this method, the ketenes were formed from the carboxylic acids, which proved quite practical, since the starting carboxylic acids could be easily handled and stored.

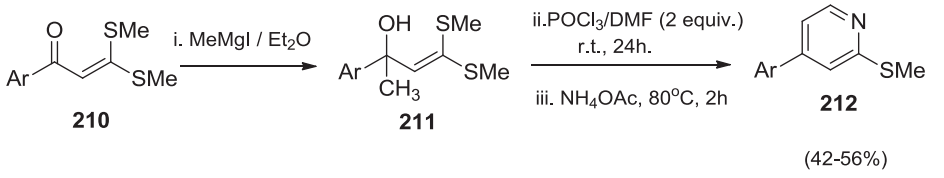
Thomas *et al.*[196] have demonstrated that the cyclization of the α-hydroxyketenedithioacetals **211** (obtained by 1,2-nucleophilic addition to α-oxoketenedithioacetals **210**) in the presence of the Vilsmeier reagent and ammonium acetate leads to the formation of substituted 2-methylsulfanyl-4-arylpyridines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

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

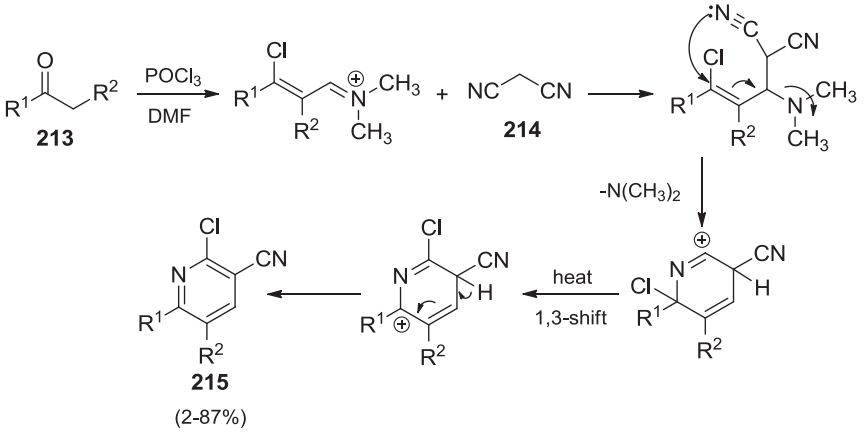
A novel one-pot route to 2(*3H*)-benzimidazolones **217**, 2(*3H*)-benzoxazolones **218** and 2(3*H*)-benzothiazolones **219** was developed *via* rearrangement and cyclization of *ortho*-substituted benzoic acids **216** by the addition of ammonium azide and the Vilsmeier complex (*Scheme 90*).[198]

VI. Rearrangements

Su and coworkers reported the synthesis of amides or nitriles *via* the Beckmann rearrangement reaction initiated by BTC/DMF, as shown in *Scheme 91*.[199] A possible mechanism

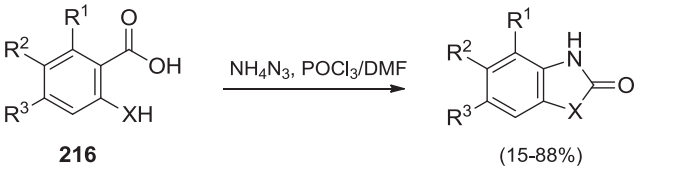


Scheme 88



a) $R^1 = C_6H_5$-, R^2 = H; b) R^1 = 4-CH_3-C_6H_4-, R^2 = H; c) R^1 = 4-$CH_3OC_6H_4$-, R^2 = H;
d) R^1 = 4-Br-C_6H_4-, R^2 = H; e) R^1 = 4-Cl-C_6H_5-, R^2 = H; f) R^1 = 3-$CH_3OC_6H_4$-,R^2 = H;
g) $R^1 = C_6H_5$-, $R^2 = CH_3$; h) R^1 = 2-thienyl, R^2 = H; i) R^1 = 2-C_3H_7-C_6H_4-, R^2 = H;
j) R^1 = Ph-C_3H_5-, R^2 = H; k) R^1 = (4-Cl)PhC_3H_5-, R^2 = H; l) R^1 =(4-OMe)PhC_3H_5-, R^2 = H.

Scheme 89



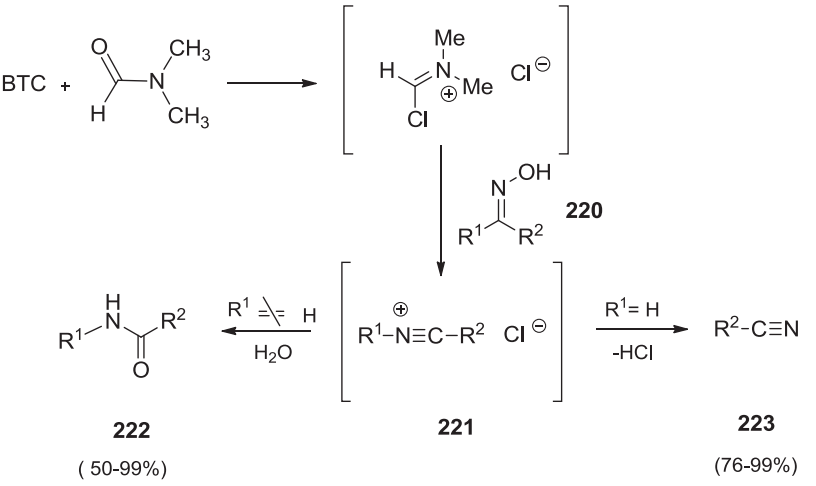
217: X = NH, **218:** X = O, **219:** X = S

Scheme 90

indicated that the adducts **221** afforded amides **222** upon hydrolytic work-up in the case of ketoximes and afforded the nitriles **223** directly in the case of aldoximes. Experimental results have shown that aryl ketoximes are more reactive than alkyl ketoximes because electron-donating groups on the aromatic ring facilitate the reaction while electron-withdrawing groups retard it. Moreover, aromatic aldoximes provided the corresponding nitriles in excellent yields.

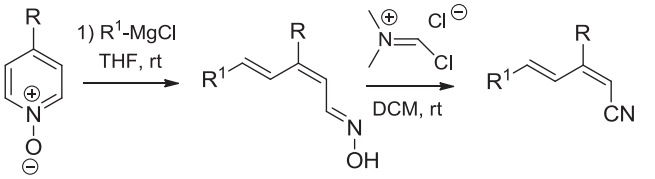
VII. Dehydration

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



a) $R^1 = C_6H_5$, $R^2 = CH_3$; b) R^1 =3-$O_2NC_6H_4$, $R^2 = CH_3$; c) R^1 = 4-$CH_3OC_6H_4$, $R^2 = CH_3$; d) R^1 =3-O_2N-4-CH_3-C_6H_3, $R^2 = CH_3$; e) R^1 = 2,5-Cl_2-4-F- C_6H_2, $R^2 = CH_3$; f) R^1 = 3-$MeCONHC_6H_4$, $R^2 = CH_3$; g) $R^1 = C_6H_5$, $R^2 = C_6H_5$; h) R^1 = 3-ClC_6H_4, $R^2 = C_2H_5$; i) R^1-R^2 = $(CH_2)_6$; j) R^1-R^2 = 1,2,3,4-tetrahydronaphthalen -1-yl; k) R^1 = 2-thienyl, $R^2 = CH_3$; l) R^1 = 2-furyl, $R^2 = CH_3$; m) R^1 = 4-$CH_3OC_6H_4$, R^2 = 4-ClC_6H_4; n) R^1 = iso-butyl, $R^2 = CH_3$; o) $R^1 = CH_3CH_2$, $R^2 = CH_3$; p) R^1 = H, R^2 =C_6H_5; q) R^1 = H, R^2 =3-$O_2NC_6H_4$; r) R^1 = H, R^2 =4-$MeOC_6H_4$; s) R^1 = H, R^2 = 4-ClC_6H_4; t) R^1 = H, R^2 = 4-$Me_2NC_6H_4$; u) R^1 = H, R^2 =2-Cl-6-F-C_6H_3; v) R^1 = H, R^2 =tert-amyl; w) R^1 = H, R^2 = cyclohexyl.

Scheme 91

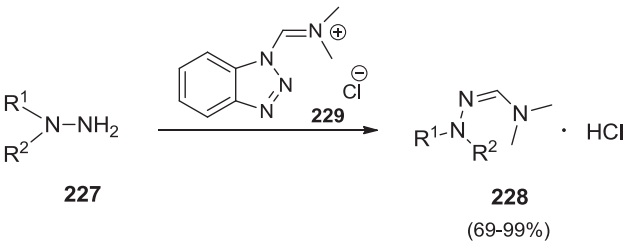


224a: R = H	**225a:** R = H, R^1 = Ph	85%	**226a:** 74%
	225b: R = H, R^1 = $CH(Me)_2$	trace	**226b:** 49%
224b: R = Ph	**225c:** R = Ph, R^1 = Me	trace	**226c:** 64%

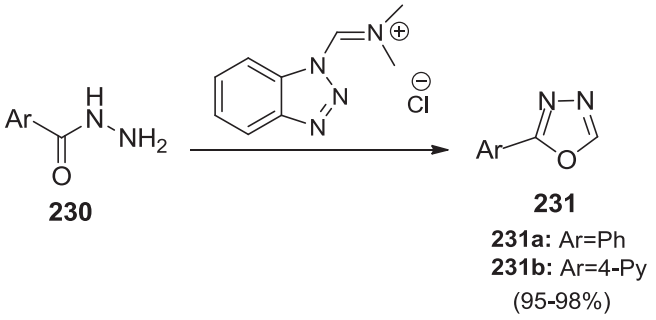
Scheme 92

VIII. Other Reactions

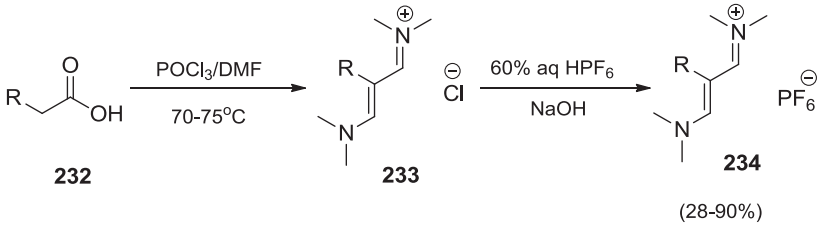
Dimethylformamidrazones **228** have been employed for the construction of various heterocycles.[201–205] A simple, direct method for preparation of dimethylformamidrazones starting from the corresponding hydrazines **227** has been developed in 69–99% yields (*Scheme 93*).[206] In this reaction, a novel, versatile reagent **229** was utilized as a stable Vilsmeier reagent analogue. When the scope of substrate was extended to hydrazides **230**, 1,3,4-oxadiazoles **231** were obtained as pure compounds in 95–98% yields (*Scheme 94*).



Scheme 93



Scheme 94



Scheme 95

α-Methylene carboxylic acid derivatives **232** are converted by the Vilsmeier reagent ($POCl_3$/DMF) into vinamidinium chloride salts **233**, which are water sensitive and difficult to purify from the reaction mixture. In the work of Davies's group, vinamidinium hexafluorophosphate salts **234** were prepared in moderate to excellent yields by adding aqueous hexafluorophosphoric acid to the reaction mixture containing the vinamidinium chloride salts (*Scheme 95*).[207] To our knowledge, the utilization of vinamidinium hexafluorophosphate salts has not been reported previously, and such salts may prove to be a potential substitute for the perchlorates that frequently have undesirable thermal and shock-sensitive properties.

IX. Conclusions and Outlook

As a classical synthetic reagent, the Vilsmeier reagent has found very wide application in organic synthesis. Over the past ten years, the Vilsmeier reagent has been used in organic synthesis in concert with new techniques such as microwave irradiation, and reaction in

the solid state. Because of its potential for phosphorus pollution, the Vilsmeier reagent has been improved also to a more environmentally friendly species by employing BTC instead of inorganic acid halides. Our laboratory is contributing to those advances. Extensive application of Vilsmeier reagent-based chemistry to industrial production can be expected in the near future.

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