THE SYNTHESIS OF PYRIDINES, QUINOLINES AND OTHER RELATED SYSTEMS BY THE VILSMEIER AND THE REVERSE VILSMEIER METHOD

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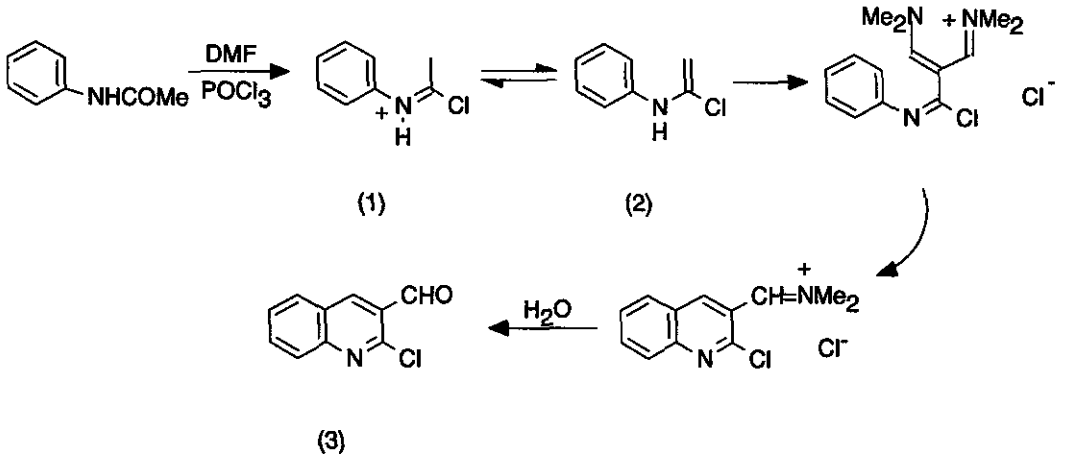
Dedicated to the ever youthful Ted Taylor on his 70th birthday

Abstract *- Quinolines, pyridines, thienopyridines, quinolones, isoquinolones, naphthyridines and related systems can be made efficiently from acylamides under Vilsmeier conditions. This review focusses on the application of both the Vilsmeier and the Reverse Vilsmeier approach. In the former method the acylamide becomes a nucleophile and is the source of the nitrogen and the 2,3-carbons of the resulting heterocycle while in the latter the acylamide reacts as an electrophile which yields the product heterocycle by reaction with an electron-rich alkene or its equivalent. This 'alkene' can be an enamine, a vinyl ester, an amide, or a masked nucleophilic alkene such as a ketone or an 'active' methyl or methylene group as in an α–substituted acetic acid .*

The synthesis of pyridines and condensed pyridines using Vilsmeier reagents has become an important synthetic tool particularly to the pharmaceutical industry. In this review the method is shown to follow two distinct pathways: In the Vilsmeier approach the reagent behaves as a normal electrophilic Vilsmeier formylating agent, usually contributing the 4-carbon of the pyridine ring. In what we call the Reverse Vilsmeier approach the reagent contributes the ring nitrogen and may behave either as an electrophile or (more commonly) may be transformed into a nucleophile prior to reaction. These two approaches are illustrated below

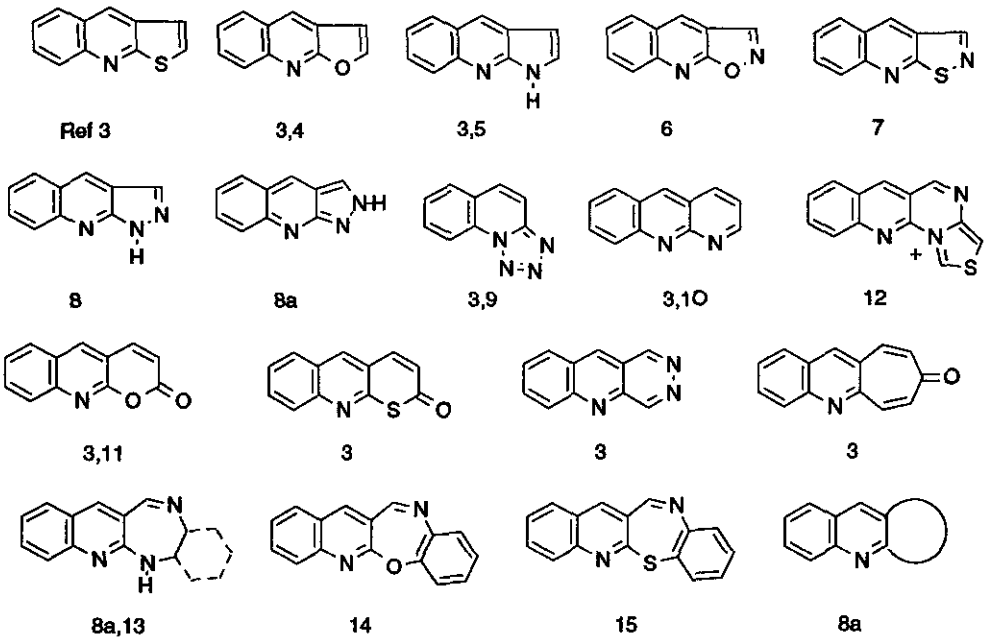
The Vilsmeier approach to quinolines, pyridines and related heterocycles



Scheme 1

In 1978 my group described a new versatile synthesis of quinolines and related fused heterocycles.[1] Typically an acylanilide was treated with a Vilsmeier reagent (e.g. dimethylformamide [DMF] and phosphoryl chloride) as exemplified in Scheme 1. This reaction involves conversion of the acyl goup into a nucleophilic enamine(2) by way of the corresponding imine(1), diformylation and cyclisation. Yields are generally good particularly with anilides bearing electron-donating groups. The 2-chloroquinoline-3-aldehydes are superb substrates for further [*b*]-annelation of a wide variety of rings (Scheme 2).

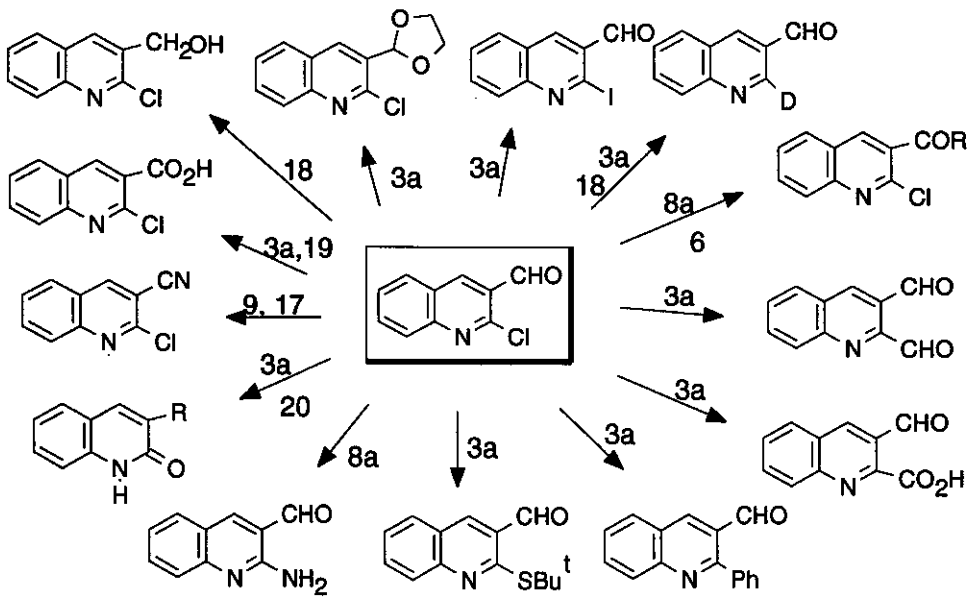
Examples of [*b*]-fusion of thieno-, furano-, pyrrolo-, isoxazolo-, isothiazolo-, pyrazolo-, pyrido-, pyrono-, thiopyrano-, pyrimidino-, pyridazino-, tropono-, diazepino-, oxazepino-, thiazepino- and macrocyclic rings have all been achieved in good yields. Furthermore [*a*]-fusion of a tetrazolo-ring has also been reported.



Heterocyclic systems synthesised from 2-chloroquinoline-3-aldehydes

Scheme 2

Diverse functional group interconversions have been conducted as illustrated in (Scheme 3). When *N*-substituted acylanilides are treated under the same Vilsmeier conditions, the corresponding *N*-substituted 2-quinolones are isolated in high yield.[16] A useful variant for the formation of 2-chloro-3-cyanoquinolines is to treat the reaction mixture containing the iminium salt with hydroxylamine hydrochloride, the $POCl_3$ transforming the oxime into the nitrile.[22] Bhaduri and his co-workers have produced more examples of many of these transformations and has summarised this work in a review.[21a]

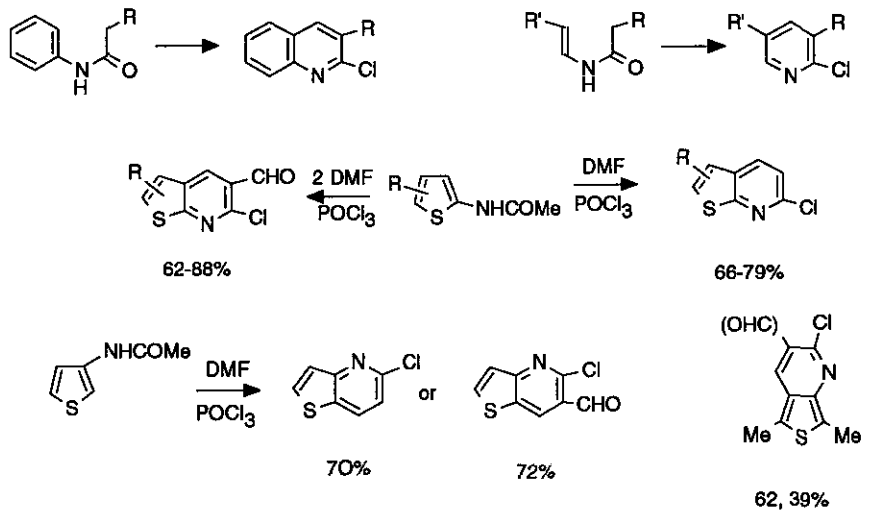


Functional group interconversions of 2-chloroquinoline-3-aldehyde

Scheme 3

The reactions have been carried out on multi-kilo scale and can be readily extended to higher anilides (where only monoformylation is observed),[23] and to enamides (which yield pyridines).[24] Acetamidothiophenes similarly give thienopyridines.[2,25] However in this case ring formylation occurs first, allowing selective mono- or diformylation and thus the chlorothienopyridine or the chlorothienopyridine-3-aldehyde may be formed at will. The reaction is equally applicable to 2-acetamido- or 3-acetamidothiophene; when the thiophene α-positions are blocked, a [3,4-*b*]-thienopyridine is formed . A similar fusion of a pyridine ring onto a pyrazole has also been reported.[26] All these variants are illustrated in Scheme 4. If an acylanilide is treated with *N*-nitrosodimethylamine (the nitrogen analogue of DMF) and $POCl_3$, a quinoxaline is produced, albeit in low yield.[23]

Earlier work on this reaction has already been reviewed[27] and only a summary and more recent aspects will be treated in this paper. Products have been patented as dyestuffs,[12] anti-ulcer compounds,[20b] anti-allergics,[9,20a] antiviral agents,[8b] vasodilators and bronchodilators,[22a,22b,22d] antifertility,[21a] anthelmintic,[21a]antimalarial,[21a] ion-channel interference agents[21a] and drugs for the treatment of baldness.[22a,22b,22d]

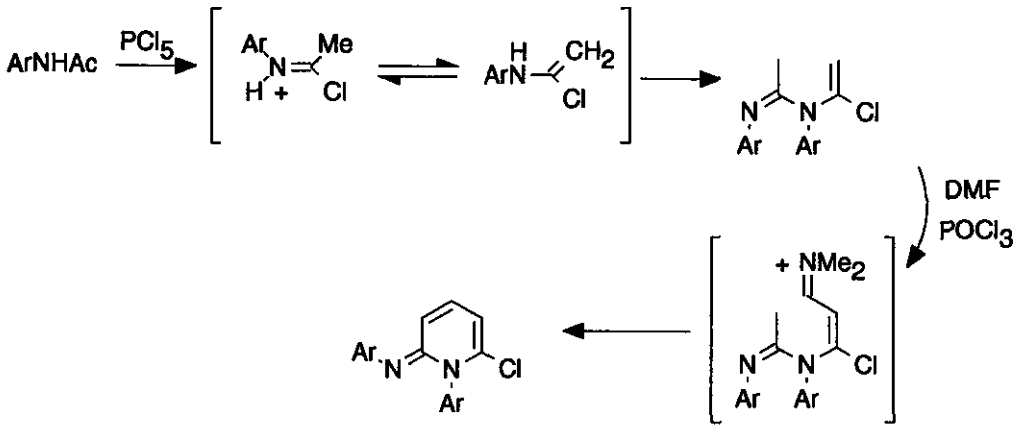


Scheme 4

In another approach to pyridines we have utilised an old reaction of von Braun who noted that some acetanilides dimerised on treatment with PCl_5 to give enamidines, which are of course reactive nucleophilic enamine analogues.[28] These enamidines are converted efficiently (54-88%) into iminopyridines by the action of DMF/$POCl_3$. A one-pot pyridine synthesis gives the products in somewhat reduced yield (Scheme 5). When an α-chloroacetanilide or propionanilide is used instead of an acetanilide, the corresponding 3,5-disubstituted iminopyridine is obtained.

The Reverse Vilsmeier approach

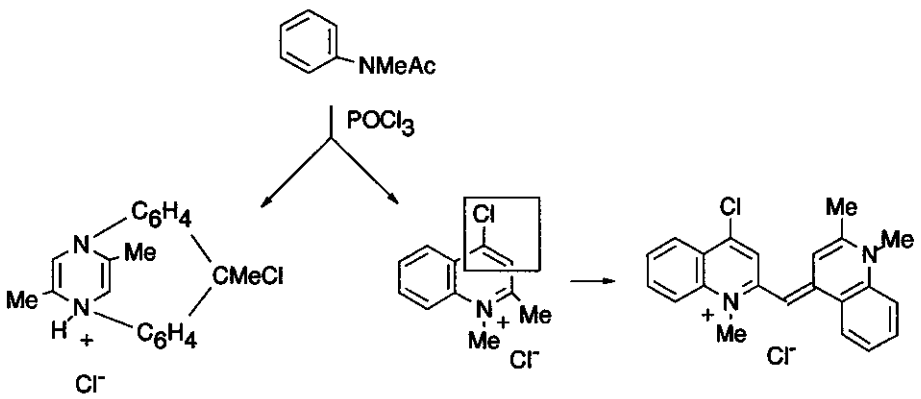
It is not generally appreciated that the discovery of the Vilsmeier reaction stemmed from a quinoline synthesis. In 1896 Friedel noted that the action of $POCl_3$ on N-methylacetanilide gave very low yield of a red dye to



Scheme 5

which he assigned the unbelievable structure (4).[29] In 1925 Otto Fischer and his two young colleagues Müller and Vilsmeier corrected this problematic structure, showing that the product was the cyanine dye (5), formed from the quinolinium salt (6).[30] Vilsmeier recognised that the formation of the intermediate salt (5) involved an acetylation of the *N*-methylacetanilide to account for the 3,4-carbons of the quinoline ring (boxed in the formula). Clearly the acetylating agent must have derived from another molecule of *N*-methylacetanilide.

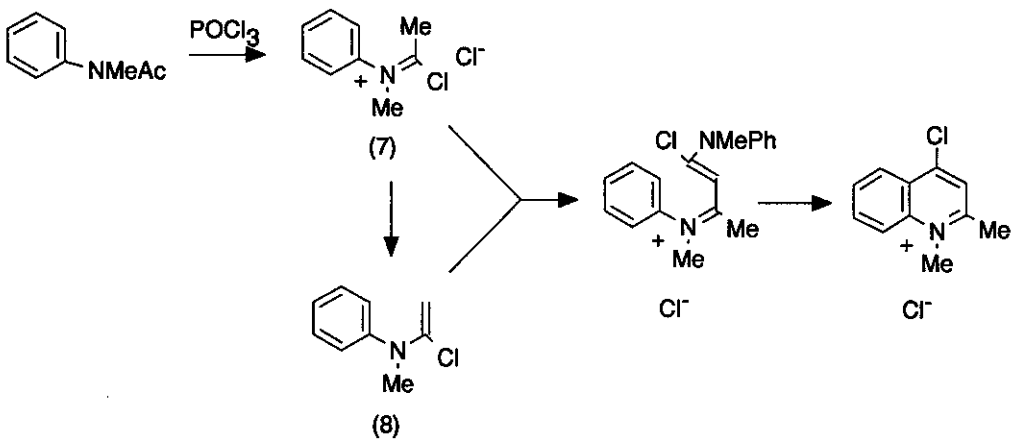
Although he incorrectly postulated that ortho-acetylation of the *N*-methylacetanilide had occurred prior to cyclisation (and was unable to use the *N*-methylacetanilide as an acetylating agent, not surprisingly since we now know that it tends to dimerise by self-acetylation), he showed with Haack, that *N*-methylformanilide (NMF) was an excellent para-formylating agent of reactive aromatics such as *N,N*-dimethylaniline.[31] Having made this seminal contribution to chemistry he disappeared into the chemical industry, his further publications being dyestuff patents! We interpret Friedels reaction to proceed as indicated in Scheme 6 , the Vilsmeier reagent (7) being the acylating agent of its tautomer, the enamine (8).



(4) (6) (5)

Friedel's incorrect structure

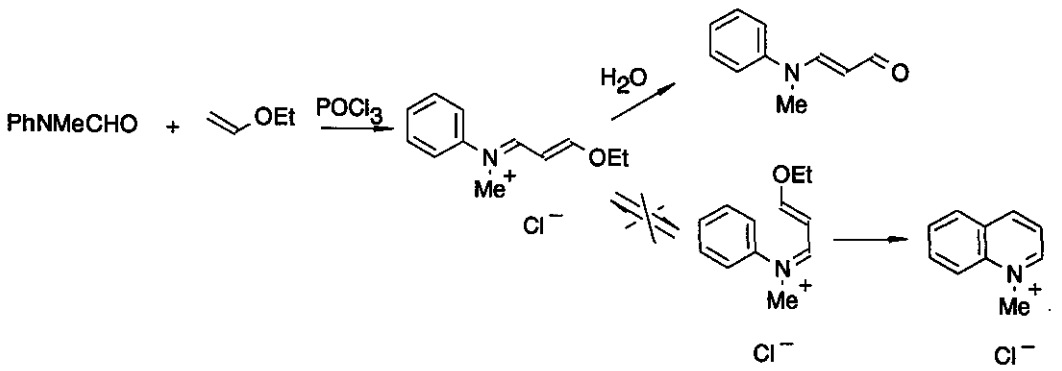
Correct structure for Friedel's cyanine dye



Scheme 6

The quinoline nitrogen derives from the iminium salt (7). This reaction is quite different from the preceeding Vilsmeier cyclisations in which the enamine component (e.g. acetanilide) forms the substrate from which the major portion of the quinoline derives by addition of a nucleophilic two-carbon unit. Hence we refer to this proccess as the *reverse* Vilsmeier cyclisation. Surprisingly this excellent reaction lay undeveloped for almost 60 years! However we believe that many chemists have unwittingly reproduced this proccess on attempted use of MFA as a formylating agent, not realising that the lower than expected yield of their desired product stemmed from the formation of a water-soluble quinolinium salt!

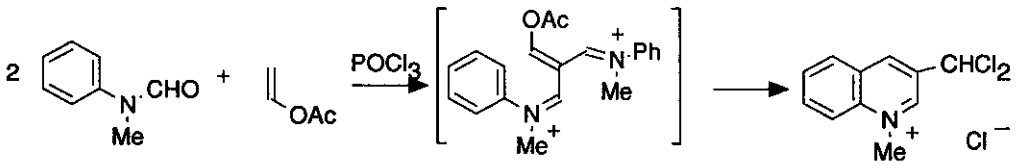
A good example of this dichotomy was revealed recently in an interesting paper[32] reporting the synthesis and use of vinylogous Vilsmeier reagents such as $PhN^{+}Me{=}CHCH{=}CHX\ {}^{-}OPOCl_2$ (X= OEt or Cl) by treatment of a vinyl ether with MFA and $POCl_3$. The vinylogous amide (PhNMeCH=CHCHO)) was formed from this reagent on aqueous workup. The authors were able to produce such reagents in yields in the high 80's% in kilo amounts. The conditions involved heating at up to 55°C for 1.5 hours with apparently no serious effect on the yields (Scheme 7).



Scheme 7

It seems evident that the geometry for cyclisation to occur in this case is not achieved. We had earlier observed that vinyl acetate undergoes bis-formylation and cyclisation very readily to give the unexpected

3-dichloromethylquinolinium salt in good yield under mild conditions (Scheme 8).[33] We were not able to monoformylate or isolate any intermediate in this case. (The dichloromethyl group behaves very much like an aldehyde in subsequent reactions). *In virtually all the cyclisations of this type that we have observed proceeding by the Reverse Vilsmeier approach, the presence of a 3-substituent in the quinolinium salt appears essential for success.* It would seem probable that the known[33] bis-formylated analogue of ethyl vinyl ether should cyclise to give a quinoline derivative.



Scheme 8

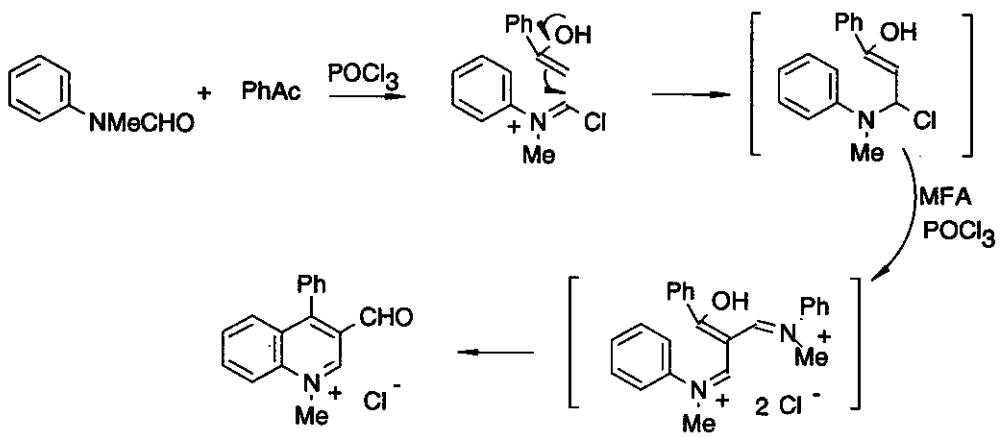
The two-carbon electron-rich alkene required to form the 3,4-carbons of the quinolinium salt can be derived in a wide variety of ways and those studied to date will be delineated below.

Ketones as sources of the quinoline 3,4-carbons

An enolisable ketone proves to be an excellent source of an electron-rich alkene, (by way of the enol tautomer) on reaction with $POCl_3$. Thus acetophenone undergoes bis-formylation and cyclisation to give 1-methyl-4-phenylquinolinium-3-aldehyde (Scheme 9).[33] In a similar way 2-acetylthiophene gives the corresponding 4-(2-thienyl) analogue (63%) but the reaction remains to be fully exploited.[33]

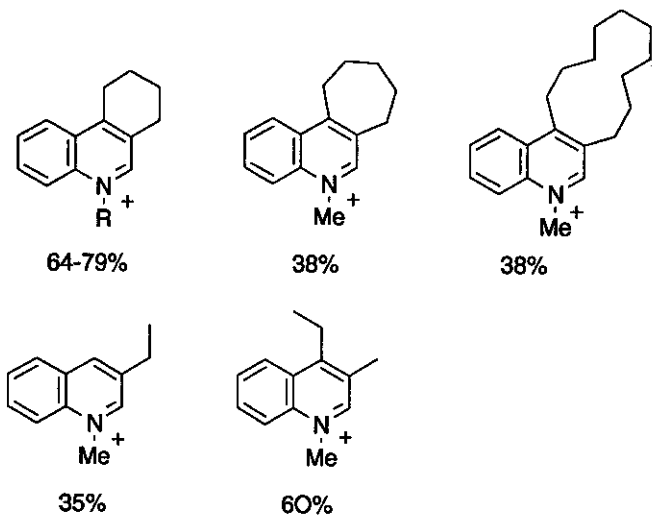
Aldehyde and ketone enamines as sources of the quinoline 3,4-carbons

Since enamines have been postulated as being involved in the 'Friedel dye' formation, it is not surprising that they are highly reactive in the Reverse Vilsmeier reaction. Generally pyrrolidine enamines give somewhat better yields than others though the convenience of using the more stable morpholine analogues makes them



Scheme 9

generally preferable.[33b] Thus while cyclohexanone enamines yield 7,8,9,10-tetrahydrophenanthridines,[33a] higher analogous cyclic ketone enamines gave related fused quinolines albeit in lower yields (Scheme 10).[33b]

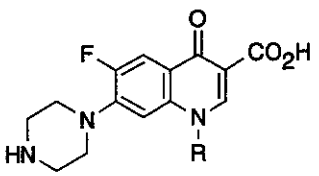


Scheme 10

The *N*-substituent can be varied by use of appropriate *N*-substituted formanilides.[33] We have so far only used one aldehyde enamine to demonstrate their application; thus butyraldehyde morpholine enamine gave the 3-ethylquinolinium salt in moderate yield.[33a] Dialkyl ketone enamines can also be used and the morpholine enamine of diethyl ketone yields the 1,3-dimethyl-4-ethylquinolinium salt (60%). [33a]

Acetic acid derivatives as sources of the quinoline 3,4-carbon

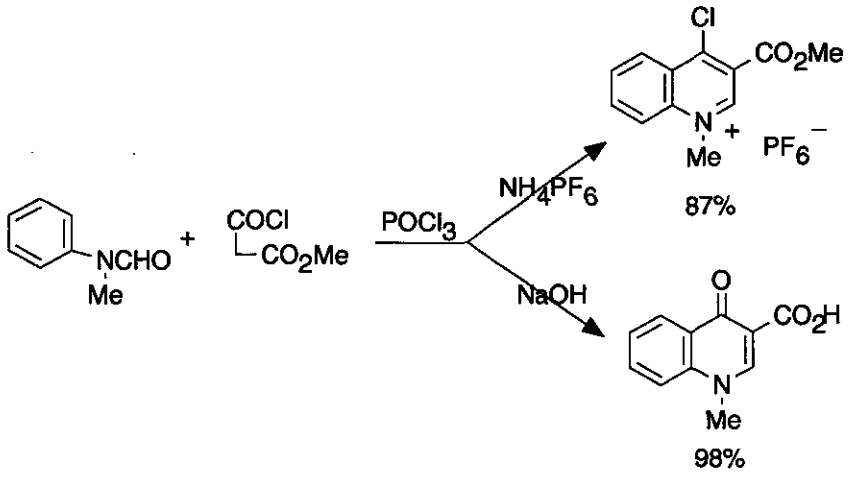
Arnold and coworkers demonstrated that acetic acids were effective substrates for Vilsmeier formylation yielding for example malonaldehydes, dimethylaminoacroleins or trimethinium salts in appropriate cases.[34] We find that using MFA and an 'activated' acetic acid derivative, a ready synthesis of valuable 3-substituted 4-quinolones is observed.[35] Since an important group of antibiotics (two important examples of many are shown in Scheme 11) are based on 4-quinolone-3-carboxylic acids, this approach allows a short synthesis of the key intermediates to this class of compounds.



R = Et, Norfloxacin
R = cyclopropyl, Ciprofloxacin

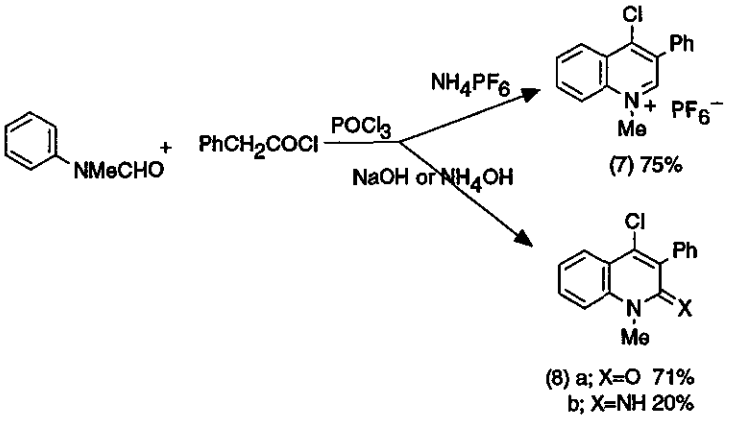
Scheme 11

Thus treatment of methyl malonyl chloride with MFA in $POCl_3$ yields on aqueous alkaline workup the 1-methyl-4-quinolone-3-carboxylic acid in almost quantitative yield while workup with water and NH_4PF_6 allowed isolation of the intermediate methyl 4-chloroquinolinium-3-carboxylate (Scheme 12) .

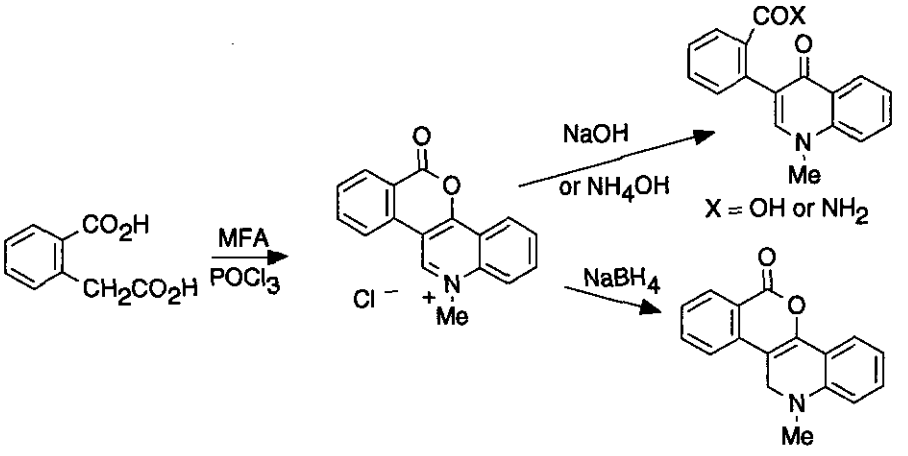


Scheme 12

In a similar way cyanoacetyl chloride yielded the corresponding quinolone-3-carboxamide (60%). Curiously phenylacetyl chloride on aqueous workup gave the expected 3-phenyl-4-chloroquinolinium salt (7, 75%) which on treatment with sodium hydroxide gave the 2-quinolone (8a) . Similarly with ammonia the corresponding imine (8b) was isolated. The attack of the base at the 2-position in this case is probably caused by the steric bulk of the phenyl ring.



When homophthalic acid or anhydride were treated with MFA/$POCl_3$ an isocoumarin-fused quinolinium salt is formed in 94% yield.[35] This salt with aqueous alkali gave a 3-aryl-4-quinolone while with sodium borohydride a fused 2,3-dihydroquinoline was formed (Scheme 13).In all these cyclisations the preferred method of

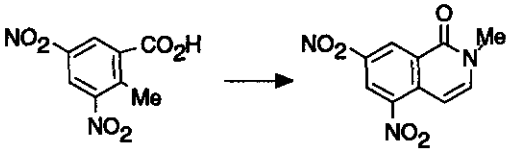


Scheme 13

formylation/cyclisation is to use $POCl_3$ as the solvent for the reaction. This also allows the reaction to be readily followed by nmr spectroscopy to allow optimisation. It is probable that in this medium we create the more reactive iminium chlorophosphate rather than the iminium chloride Vilsmeier reagent. Heaney and co-workers have recently demonstrated the improved yields of formylated products by utilising the former reagent (made by use of pyrophosphoryl chloride in place of $POCl_3$).[36]

The synthesis of isoquinolines and other [*c*]-fused pyridines

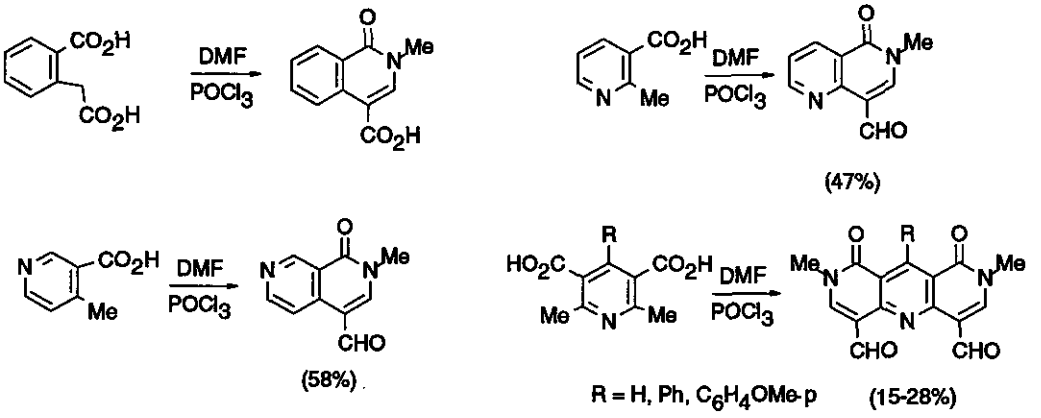
When an aromatic ring containing an 'active' methyl or methylene *ortho* to a carboxylic acid group is treated with a Vilsmeier reagent, a cyclisation ensues to give a [*c*]-fused pyridine.[37] Thus 3,5-dinitrotoluic acid is transformed into 2-methyl-5,7-dinitroisoquinol-1-one on treatment with DMF/$POCl_3$ (Scheme 14).[37a] In a similar way homophthalic acid and its heteroaromatic analogues yield *N*-methylisoquinol-1-one-4- carboxylic



Scheme 14

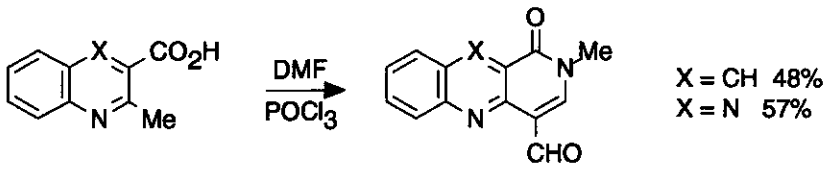
acid or the related analogue in good yield.[37b,c]

Naphthyridines are easily made by treating methylpyridinecarboxylic acids with DMF/$POCl_3$, while dimethylpyridinedicarboxylic acids similarly give triazaanthracenes (Scheme 15).[37c]



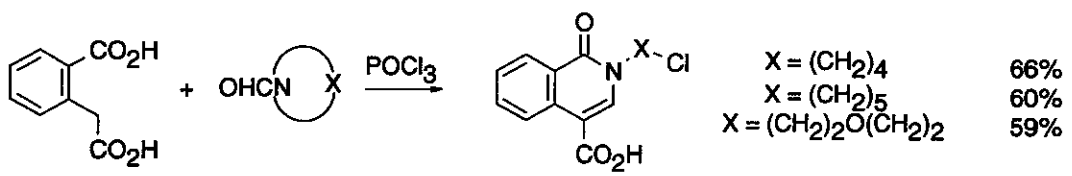
Scheme 15

Whenever a methyl rather than a methylene derivative is employed the product is derived *via* bis-formylation to give a useful aldehyde derivative. Use of methylquinoline- or methylquinoxalinecarboxylic acids are also effective in yielding [*c*]-fused pyridone derivatives (Scheme 16).[37c]



Scheme 16

In a simple extension of this methodology the use of amides other than dimethylformamide have been investigated with some fascinating developments when an *N*-formylated cyclic amine is used.[38] Thus homophthalic acid reacts with *N*-formylpyrrolidine in $POCl_3$ to give an *N*-(5-chlorobutyl)isoquinolone in 66% yield. In a similar way piperidine and morpholine derivatives are ring opened (Scheme 17). This variation can be applied successfully to other systems to give useful intermediates containing *N*-chloroalkyl functions for further derivatisation.



Scheme 17

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