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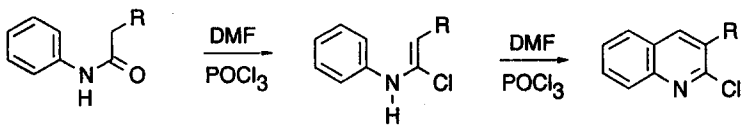
A NOVEL ONE-STEP SYNTHESIS OF QUINOLINIUM SALTS AND 4-QUINOLONES FROM FORMANILIDES

Otto Meth-Cohn* and David L Taylor

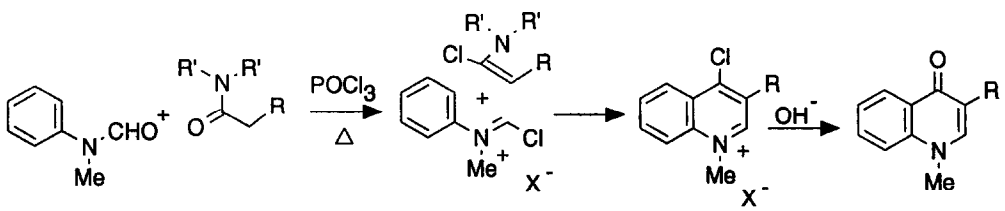
Chemistry Department, University of Sunderland, Sunderland SR1 3SD, England

Abstract: N-Methylformanilide in $POCl_3$ reacts readily at 80^0C with alkanoamides($RCH_2CONR'_2$) to give 3-R-4-chloroquinolinium salts in good yields. The arylamide reacts as its Vilsmeier salt and the alkanoamide as an α-chloroenamine. High yields of 4-quinolones are easily obtained by base treatment.

We have demonstrated elsewhere that Vilsmeier reagents are superb for the synthesis of quinolines[1]. Thus for example, acylanilides react with Vilsmeier reagents to give 2-chloro-3-substituted quinolines in high yield by way of a nucleophilic enamine (Scheme 1). We now disclose an alternative approach in which the quinoline framework is constructed largely from an electrophilic iminium salt, the Vilsmeier reagent, by interaction with an α-chloroenamine which supplies the 3-4 carbons. The enamine is produced *in situ* from an alkanoamide (Scheme 2) and we refer to this process as the 'Reverse Vilsmeier Approach' to quinolines.



Scheme 1



Scheme 2

The former method is excellent for the generation of [b]-fused quinolines[1] while the present method produces quinolines ideal for the synthesis of [c] fused derivatives and of 4-quinolones. A number of examples are shown in the Table.

Table

Quinolinium salts(1) and 4-Quinolones(2) from the Reaction of N-Methylformanilide (10mmol) $POCl_3$ (5cc) and an Alkanoamide (10mmol)

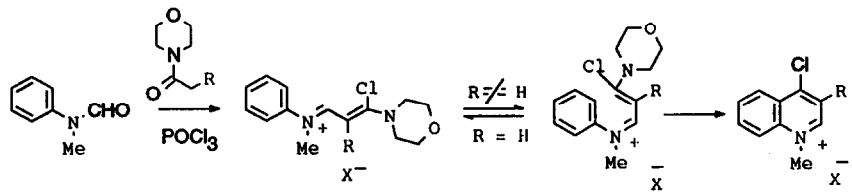
Amide[b] $RCH_2CONR'_2$ R	R'$_2$	Temp (°C)	Time (h)	Quinolinium Salt (1) X = PF_6 R	M.p. (°C)	%	Quinolone (2) M.p. (°C)	% (recryst)
H	Me_2	50	20	-		-[c]		
H	Me_2	110	17	-		-[c]		
Me	Me_2	80	2.5	Me	222	72	159[e]	88
Me	$(CH_2)_4$	80	2.5	Me	222	56		
Me	$(CH_2)_2O(CH_2)_2$	80	2.5	Me	222	79		
Cl	$(CH_2)_2O(CH_2)_2$	80	4.5	Cl	249	76	236	74
Et	$(CH_2)_2O(CH_2)_2$	80	1.5	Et	171	73	132	67
i-Pr	$(CH_2)_2O(CH_2)_2$	80	2.25	i-Pr	191	78	105	89
$PhCH_2$	$(CH_2)_2O(CH_2)_2$	80	2	$PhCH_2$	211	93	123	91
CH_2Cl	$(CH_2)_2O(CH_2)_2$	80	1.5	CH_2Cl	185	60		
t-Bu	$(CH_2)_2O(CH_2)_2$	80	2	t-Bu	274-276	7 (32[d])		
t-Bu	$(CH_2)_2O(CH_2)_2$	80	10	t-Bu	274-276	30 (9[d])		
CH_2CH_2OH	$(CH_2)_2O(CH_2)_2$	80	2	CH_2CH_2Cl	232	63		

[a] The reactions are conveniently followed by NMR spectroscopy, $POCl_3$ being an excellent NMR solvent. All new compounds gave satisfactory spectra and CHN analyses. [b]The amides were made by reaction of the appropriate acid chloride with the amine; N-(4-hydroxybutyryl) morpholine was made by heating γ-butyrolactone with morpholine at 110°C for 2h (92%). [c] No cyclised product was isolated; Under similar conditions Lee and co-workers[2] isolated (N-methyl-N-phenylamino) acrolein in 88% yield. [d] The yield in parentheses is that of the 4-morpholino-derivative (3). [e] Lit[4] m.p. 152-153°C.

Some features of the reaction deserve further comment:

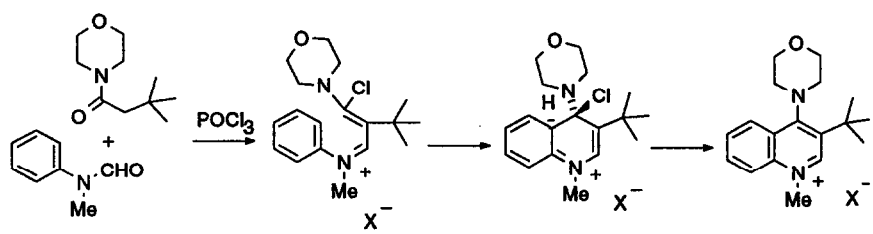
- Morpholine amides proved to be the most effective.

- The reactions generally proceed in good yield. However acetamides did not give quinolinium salts but gave solely uncyclised product (see footnote c) in accord with the reported literature[2]. We believe that the substituent that ends up in the quinolinium 3-position allows ready transformation of the intermediate to the geometry necessary for cyclisation (Scheme 3).



Scheme 3

- When a t-butyl substituent is generated in the 3-position of the quinolinium salt , the reaction is anomalous in that the 4-morpholino derivative (3) is initially formed. This compound is slowly transformed into the 4-chloro-derivative on prolonged heating of the reaction mixture. We explain this process in Scheme 4. The intermediate iminodiene (2) will tend to form with the bulky t-butyl and morpholino groups *trans* to each other, which upon $_{\pi}6_{s}$ electrocyclisation will give an intermediate that by *anti*-elimination of HCl will generate the

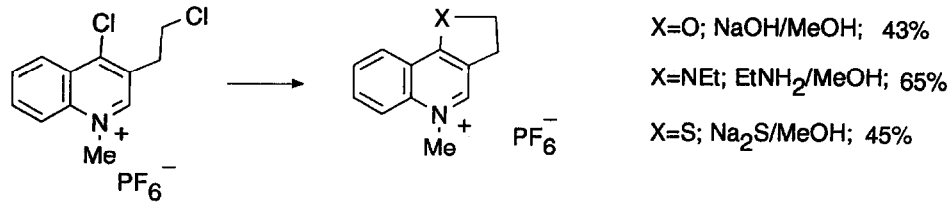


Scheme 4

4-morpholino quinolinium salt (3).

- The products are easily isolated as the insoluble PF_6^- salts, which may be easily transformed into 4-quinolones by brief treatment with aqueous sodium hydroxide. Other nucleophiles

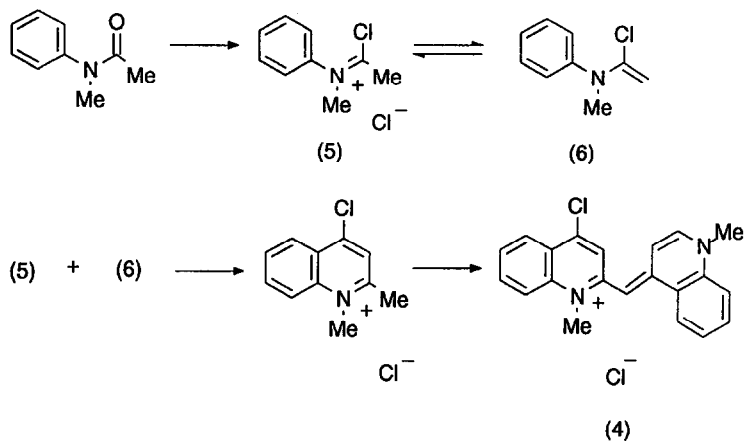
can be introduced into the 4-position allowing further annelated quinolines to be synthesised given an appropriate 3-substituent (e.g. CH_2Cl, CH_2CH_2Cl).



Scheme 5

- A typical application of [c]-annelation is outlined in Scheme 5.

The discovery of the Vilsmeier reaction stemmed from the reinvestigation of the effect of $POCl_3$ on N-methylacetanilide by Fischer, Müller and Vilsmeier[3] who showed that the low yield of dyestuff produced was a quinolinium salt (4). We interpret this reaction as shown in Scheme 6 - the interaction of a Vilsmeier reagent (5) with an enamine (6), both being derived from N-methylacetanilide. This



Scheme 6

reaction is the prototype of our present quinoline synthesis.

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