

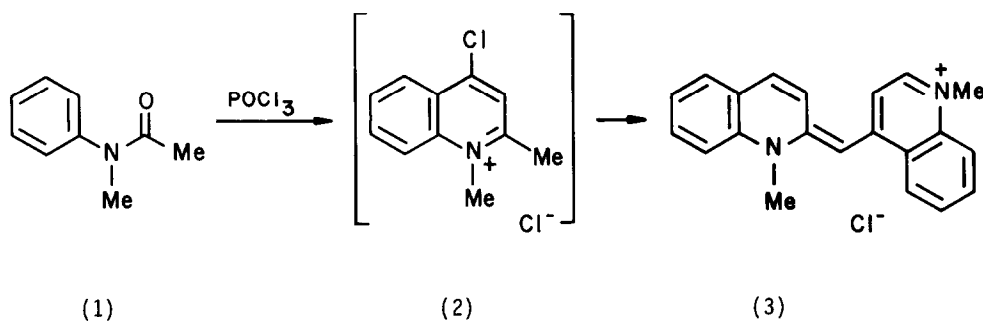
## THE SYNTHESIS OF QUINOLINES FROM N-ALKYLFORMANILIDES AND ELECTRON-RICH ALKENES<sup>1</sup>

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**Summary:** N-Methylformanilide in phosphoryl chloride reacts with ketones, aldehyde and ketone enamines or enol acetates to give N-methylquinolinium salts in good yields.

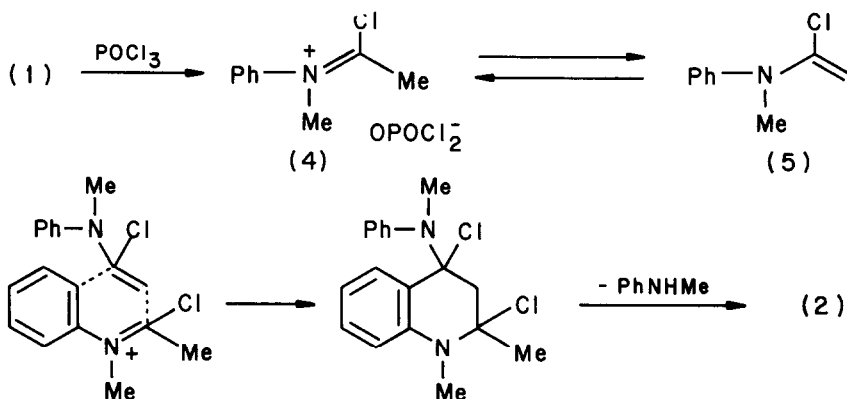
In 1925, Otto Fischer<sup>2a</sup> solved the long-standing riddle<sup>2b</sup> of the action of  $\text{POCl}_3$  on N-methylacetanilide (1) which gave a red dye (3), by way of an isolable quinolinium salt (2).



The reaction may be rationalised by attack of the  $\alpha$ -chloroenamine (5) on its tautomeric iminium ion (4) followed by cyclisation and loss of N-methylanilinium hydrochloride to give the salt (2) (Scheme 1).

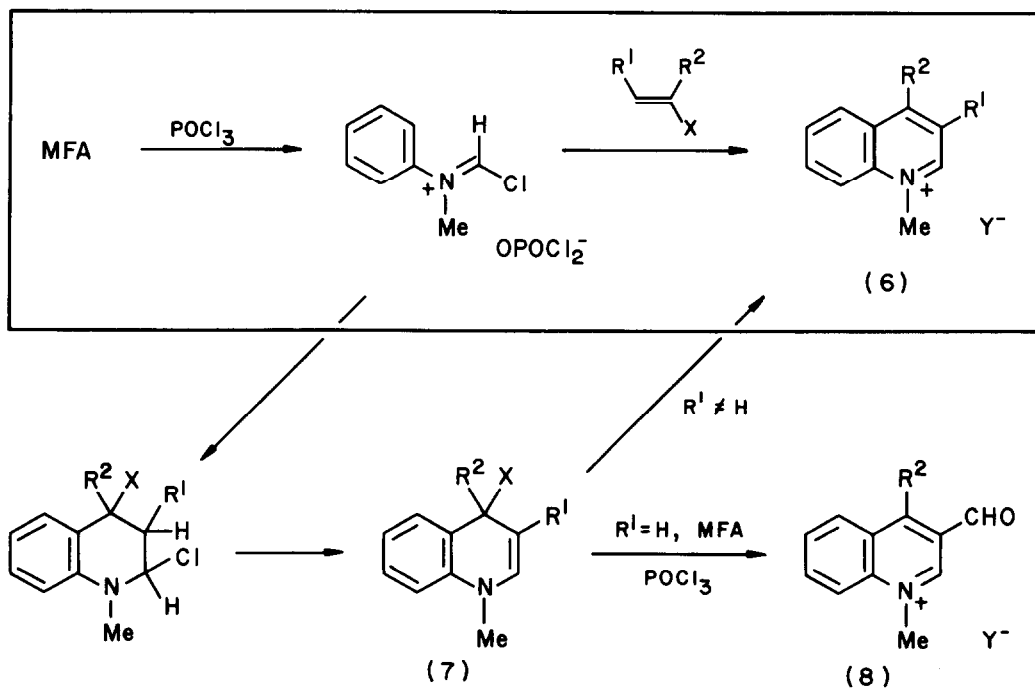
It was the unravelling of this problem that led to Vilsmeier's discovery<sup>3</sup> of the formylation method named after him, since he mistakenly assumed that ortho-acylation of the anilide ring had occurred to account for the quinolinium salt (2) formation. Surprisingly, this approach to quinoline synthesis has lain dormant for 60 years. I herein

describe the application of this process which opens up a versatile approach to useful quinolines.



Scheme 1

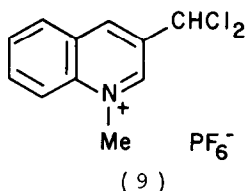
Using *N*-methylformanilide (MFA) in POCl<sub>3</sub> as the acylating agent a variety of electron rich alkenes (CH=C X, where X is an oxygen or nitrogen function) react readily to yield quinolines (6), a process rationalised in Scheme 2<sup>4</sup>.



Scheme 2

That the dihydro-compound (7), (itself an enamine) or the 3,4-dihydro- isomer is involved is indicated by the fact that when  $R^1$  is hydrogen, further formylation occurs to give the 3-formylquinoline (8)<sup>5</sup>.

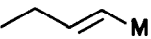

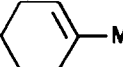
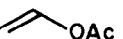
In this way aryl methyl ketones give the quinolinium salts (8) in reasonable yields (Table, expts. 1-3) while aldehyde and ketone enamines (added to the other two premixed reagents dropwise below 10°) give the salts (6) (Table, expts. 4-6). Vinyl acetate reacts smoothly and efficiently to give the diacylated quinolinium salt (9) containing a  $\text{CHCl}_2$



instead of the expected 3-aldehyde; albeit the compound reacts as for the aldehyde (e.g. phenylhydrazone derivative, m.p. 221-2°). N-Vinylpyrrolidone was ineffective in this reaction.

The full scope of this simple reaction is under active investigation.

TABLE  
Formation of quinolinium salts (6, 8 or 9) from MFA,  $\text{POCl}_3$  and activated alkenes

Expt.	Reagent <sup>a</sup>			Conditions <sup>b</sup>		Salt ( $\text{Y} = \text{PF}_6$ ) <sup>c</sup>			Yield %	M.p. °C
	Alkene (10 mmol)	MFA mmol	$\text{POCl}_3$ ml	Time min.	Temp. °C	No	$R^1$	$R^2$		
1	PhAc	40	5	10	60	8	-	Ph	69	223-6
2	p-MeC <sub>6</sub> H <sub>4</sub> Ac	40	5	10	55	8	-	p-MeC <sub>6</sub> H <sub>4</sub>	32	215-6
3	2-ThAc	22	5	150	20	8	-	2-Th	63	263
4		10	4	10	20	6	Et	H	35	156-8
5		10	4	10	60	6	Me	Et	60	166-7
6		10	4	10	70	6	-(CH <sub>2</sub> ) <sub>4</sub>	-	79	199-200
7		10	4	10	60	9	-	-	93	193-6

a M = morpholino, Th = thienyl. b After reaction the mixture was poured into ice water, 10-15 mls EtOAc and then 1.5 g  $\text{NH}_4\text{PF}_6$  added. After 0.5 h stirring at RT the solution was filtered, washed with water and a little EtOAc and the residue recrystallised from MeCN/EtOAc. c All new compounds gave correct CHN, IR and  $^1\text{H}$  NMR data.

#### References and Footnotes

1. Part 13 in the series 'A Versatile New Synthesis of Quinolines and Related Fused Pyridines'. Part 12: O. Meth-Cohn and K.T. Westwood, J. Chem. Soc., Perkin Trans. 1, 1984, 1173.
2. (a) O. Fischer, A. Müller, and A. Vilsmeier, J. Prakt. Chem., 1925, 109, 69. (b) M.C. Friedel, Bull. Soc. Chim. Fr., 1896, 11, 1028.
3. A. Vilsmeier and A. Haack, Chem. Ber., 1927, B6Q, 119.
4. The interaction of the alkene with the Vilsmeier reagent (6) may be viewed either as a concerted [4+2] cycloaddition or as a stepwise acylation and ring-closure.
5. It is also conceivable that diacylation of the substrate precedes cyclisation.

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