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A VERSATILE NEW SYNTHESIS OF QUINOLINES AND RELATED FUSED PYRIDINES. PART II.[1]

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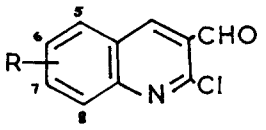
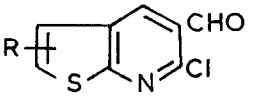
The conversion of acetanilides to 2-chloroquinoline-3-aldehydes by Vilsmeier reagent proceeds efficiently in $POCl_3$ solution at 75°. The intermediate, in which the acetyl group has been diformylated, may in some cases be isolated and separately cyclised.

We have recently discovered a remarkably versatile and simple route to fused pyridines (e.g. 1-3), by subjecting N-arylacetamides to Vilsmeier formylating conditions (Scheme 1).[1]



(1)



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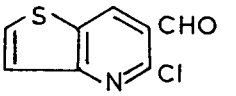

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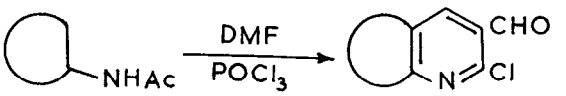
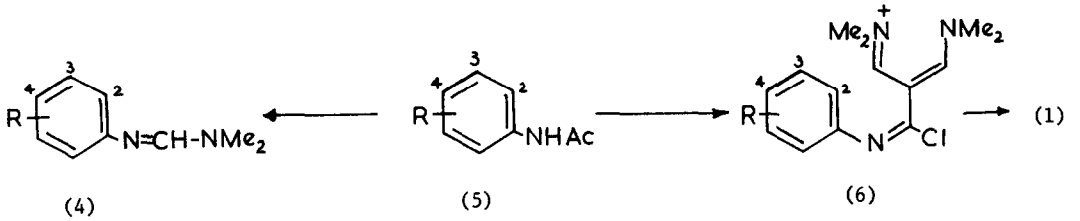


Scheme 1

Our published method,[1] however, was only effective with acetamidothiophens or with anilides which contained at least one activating substituent, such as the m-methoxy-, m-methyl-, 3,4-dimethoxy- or 3,4,5-trimethoxy-derivative. However, it failed with o- or p-methoxy-, o- or p-methyl unsubstituted or halo-acetanilides, yielding only the corresponding formamidines (4). We have now fully explored this reaction making it of considerably wider scope and mechanistically clear.

A careful study of the reaction indicates two formylation pathways are open to the

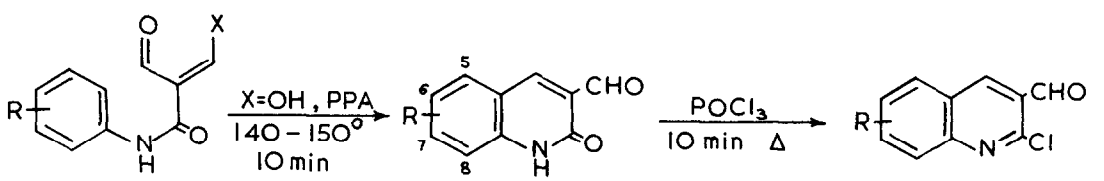
acetanilides (5) (Scheme 2). Under vigorous conditions (1M ArNHAc, 2-3M DMF, 7M $POCl_3$,



(4) (5) (6)

Scheme 2

reflux), the lesser reactive acetanilides (e.g. R=H, o- or p-OMe, Cl, Br, etc) rapidly yield the formamidine (4), an irreversible process. However, under controlled conditions the 2-chloroquinoline-3-aldehyde (1) may be formed in good yield (Table) by way of bis-formylation of the side-chain (6). Indeed, the intermediates (7), derived from (6) may be isolated in good yield in those cases where quinoline formation is slow. These useful dialdehydes (7b) may then be rapidly cyclised with PPA to give the quinolone-aldehydes (8) in high yield, and may if required, be further converted into the chloroaldehydes (1) quantitatively with $POCl_3$ (Scheme 3 and Table).



(7) (8) (1)

a; X = NMe_2
b; X = OH

R=8-Cl, 91%; R=7-Cl, 98%
R=6-Cl, 100%; R=6-Br, 97%

Scheme 3

The best methods for direct chloroquinoline aldehyde formation from an acetanilide are as follows: (A) Reaction at lower temperature. By heating the acetanilides (5) with dimethylformamide (2.5M) and phosphoryl chloride (7M) at 75°, the chloroquinoline aldehydes (1; R=H, 6-, 7- or 8-Me and 6- or 7-OMe) are all obtained in good yield (Table).

TABLE

Products from the acetanilides (5) with DMF (2.5-3M) and $POCl_3$ (7M)

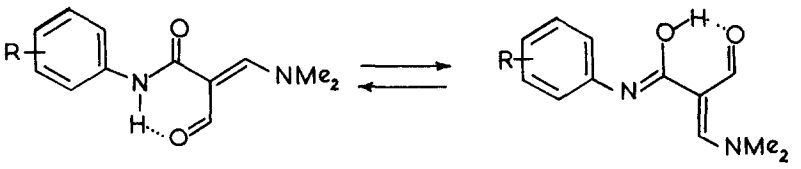
ArNHAc (5) R	Product No	Product R	Yield (%)* A	A'	B	C	M.p. (°C)	Other Products
H	1	H	68	0	78	-	148-9	A' gave (4; R=H) 96%
2-Me	1	8-Me	67	28	63	-	137-8	
3-Me	1	7-Me	66	64	66	-	144-5	
4-Me	1	6-Me	70	28	74	-	124-5	
2-OMe	1	8-OMe	5	-	-	14	191-2	C gave (7b) 28%
3-OMe	1	7-OMe	66	89	-	-	197-8	
4-OMe	1	6-OMe	56	-	10	55	146-7	
3-SMe	1	7-SMe	-	92	-	-	195-6	
$2,4-Me_2$	1	$6,8-Me_2$	-	32	-	-	110-1	
$3,4-OMe_2$	1	$6,7-OMe_2$	-	72	-	-	215	
$3,4,5-OMe_3$	1	$5,6,7-OMe_3$	-	92	-	-	149	
2-Cl	7b	2-Cl	53†	-	0	-	104-5	B gave (4; R=2-Cl) 90%
3-Cl	1	7-Cl	25	-	35	-	159-160	A also gave (7b; R=3-Cl) 39%
4-Cl	7b	4-Cl	69	-	0	-	134-5	B gave (1; R=7-Cl) 13% m.p. 191-2°
4-Br	1	7-Br	23	-	30	-	188-9	A also gave (7b; R=7.Br) 30%
$2-NO_2$	7b	$2-NO_2$	14	-	0	-	120.1	B gave (4; R=$2-NO_2$) 64%
$3-NO_2$	7b	$3-NO_2$	61	-	13	-	180d	B also gave (4; R=$3-NO_2$) 66%
$4-NO_2$	7b	$4-NO_2$	53	-	16	-	232-3d	B also gave (4; R=$4-NO_2$) 72%

* A-- reaction at 75° for 1.5-18 h; A' - reaction at reflux for 1.5-6 h; B - reaction in a sealed tube at 80-115° for 1-4 h; C - reaction as for B but with added PCl_5 (1M).

† Reaction done at 20° for best results.

(B) Use of a sealed tube. Similar good results may be obtained more rapidly at higher temperatures by use of the same reagents in a sealed tube. (C) Addition of PCl_5. Occasionally, addition of one molar ratio of PCl_5 results in improved yields (Table).

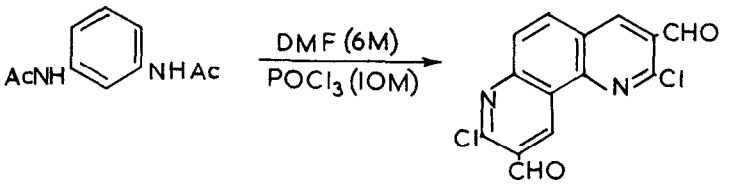
The anilinoacylmalonaldehyde imines (7a) exhibit an interesting amide-hydroxyimine tautomerism (Scheme 4) showing a 2:1 ratio by n.m.r. spectroscopy.



(7a) (7a')

Scheme 4

The formation of 2-chloroquinoline-3-aldehydes (1) is remarkably specific. In no case where two cyclisation pathways are possible have we encountered two products. Even diacetyl m-phenylenediamine (9) gives solely the 1,5-phenanthroline (10) in almost



(9) (10) 92%, m.p. 274°(d)

quantitative yield. We attribute this remarkable specificity to the large steric demand and dipolar nature of the intermediates.

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Reference

1. Part I; B. Narine and O. Meth-Cohn, Tetrahedron Letters, 1978, 2045.

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