Tetrahedron Letters No. 23, pp 2045 - 2048, 1978. 0040-4039/78/0601-2045$02.00/0

A VERSATILE NEW SYNTHESIS OF QUINOLINES, THIENOPYRIDINES AND RELATED FUSED PYRIDINES

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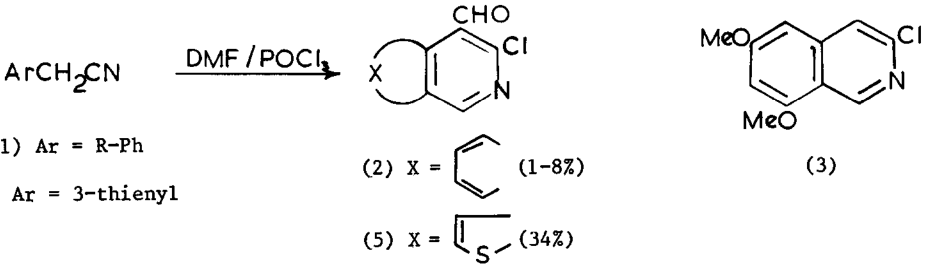
(Received in UK 31 March 1978; accepted for publication 13 April 1978)

The Vilsmeier-Haack reaction is a mild but efficient method for the formylation of reactive aromatic substrates. Occasionally, unexpected cyclisations are noted accompanying or following such formylations. Thus recently, Japanese workers[1] noted the formation of very low yields of isoquinolines (2) (in one case admixed with a good yield of the isoquinoline (3)) during attempts to formylate the phenylacetonitriles (1). This method was applied[2] to the corresponding thiophen (4) giving the thienopyridine (5), but attempts to extend the reaction to 3-acetamidothiophen led to a mixture of 5 products (Scheme 1).



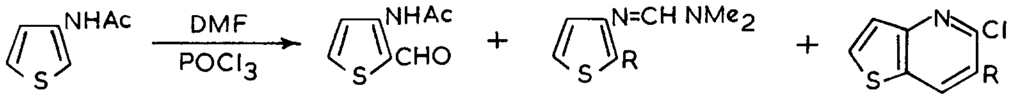
(1) Ar = R-Ph

(4) Ar = 3-thienyl

(2) X = (1-8%)

(5) X = (34%)

(3)



(6)

(7) (4%)

8a; R=H (7%)

8b; R=CHO (15%)

9a; R=H (23%)

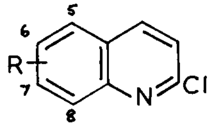
9b; R=CHO (5%)

Scheme 1

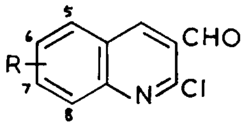
Russian workers[3] had earlier formylated 2-acetamido-5-substituted thiophens at the 3-position, apparently without by-products.[4]

We herein report an important new route to the title compounds and define specific conditions for the formation of 2-chloro- or 2-chloro-3-formyl fused pyridines in high yield.

p-Methoxyacetanilide is not formylated under Vilsmeier conditions.[5] However, m-methoxy-, m-methyl-, 3,4-dimethoxy-, and 3,4,5-trimethoxy-acetanilide give high yields of quinolines (10) and (11) (Table). Use of the usual Vilsmeier conditions[1-3] gives mixtures but under the controlled conditions (Table) either of the products may be formed at will.



(10)



(11)

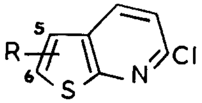
a; R=7-OMe

b; R=7-Me

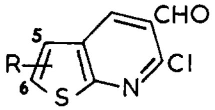
c; R=6,7-$(OMe)_2$

d; R=5,6,7-$(OMe)_3$

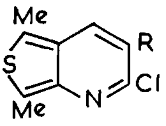
Using the same approach, thieno(2,3-b)pyridines (12) and (13) are also readily available, as are the isomeric thieno(3,2-b)- (9a and 9b), and thieno(3,4-c)pyridine (14) (Table) all in good yield,[6] starting with the appropriate acetamidothiophen[7] (Table).



(12)



(13)



(14)

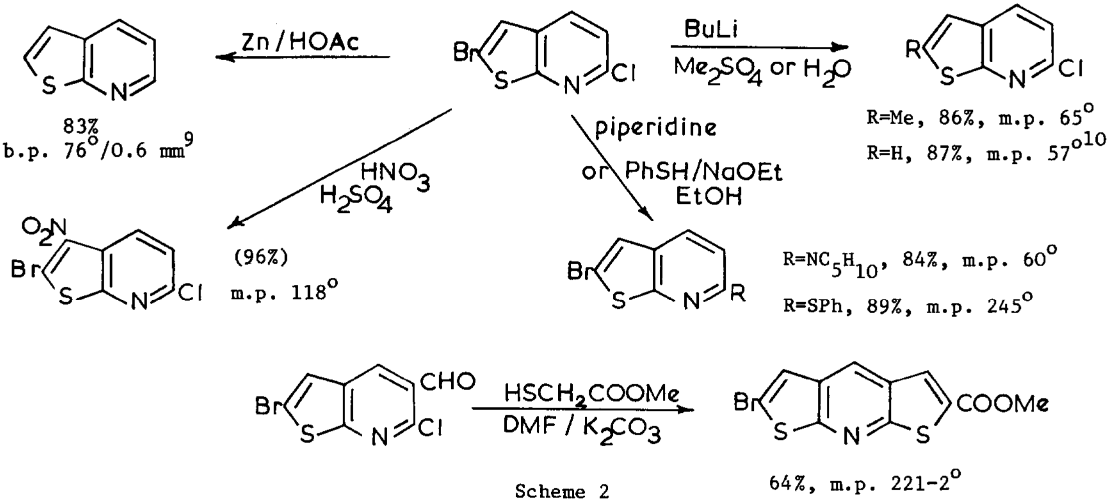
a; R=6-Br; b; R=6-Me; c; R=5,6-Me_2

d; R=5,6-$(CH_2)_4$

a; R=H

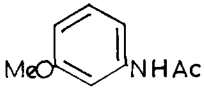
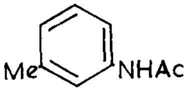
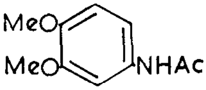
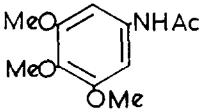
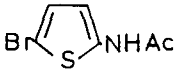
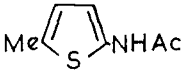
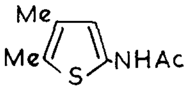
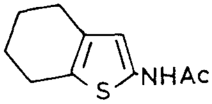
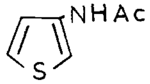
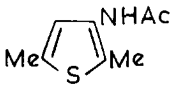
b; R=CHO

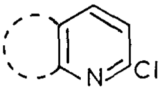
The importance of these fused pyridines is emphasised by some typical conversions exemplified in Scheme 2.

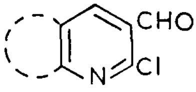


Scheme 2

TABLE

Starting Amide	DMF Moles	$POCl_3$ Moles	Solvent	Reflux Time (h)	Product*	Yield (%)	M.p.** or b.p./mm
	1 3	3 7	t -	4 4	a b	73 89	145/0.6[¶] 190
	1 3	3 7	t -	6 6	a b	59 64	120/0.5[¶] 142
	1 3	3 7	t -	4 2	a b	69 72	72-74[¶] 215
	1 3	3 7	t -	6 1.5	a b	71 92	92-93 149.5
	1 3	3 7	t -	12 4	a b	66 66	115-116 170
	1 3	3 7	d -	6 3	a b	79 62	65 127
	1 3	3 7	d -	5 2	a b	72 73	91 157
	1 3	3 7	d -	4 2	a b	79 88	64.5 145
	1 3	3 7	d -	4 1.5	a b	70 72	63-64[†] 122[†]
	1 3	3 7	d -	6 2.5	a b	52 39	158 146

* a = 

b = 

t = $Cl_2CHCHCl_2$

d = $ClCH_2CH_2Cl$

** All new compounds gave correct analytical and spectral data (I.R., P.M.R., C.M.R., M.S.).

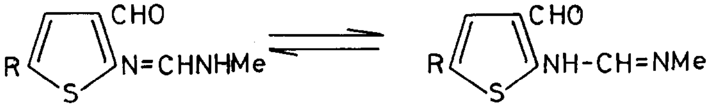
[†] Ref. 1 gives m.p. a=64°, b=122°.

[¶] Mixture of 2 isomers produced.

Clearly the chloroformylquinolines are ideal vehicles for elaborating important furoquinoline alkaloids. Preliminary studies indicate that variations in the acyl group of both substrate and reagent (DMF) lead to useful analogues of the above reaction while other systems such as acetamido-selenophens, -naphthalenes, -benzothiophens, -indoles, etc, all seem good candidates for this widely applicable synthesis. Further details will appear elsewhere as will our mechanistic studies.[8]

References and Footnotes

1. T. Koyama, T. Hirota, Y. Shinohara, M. Yamato and S. Ohmori, Chem. and Pharm. Bull. (Japan), 1975, 23, 497.
2. C. Paulmier and F. Outurquin, J. Chem. Research (S), 1977, 318; J. Chem. Research (M), 1977, 3660.
3. V.I. Shvedov, I.A. Kharizomenova and A.N. Grinev, Chem. Heterocyclic Compounds, 1974, 10, 50.
4. We found that repeating Shvedov's work[3] gave mixtures of the reported aldehyde together with the compounds (12) and (13).
5. The amidine, $MeOC_6H_4{=}CHNMe_2$, a light yellow oil, b.p. 190° at 1.5 mm is formed.
6. By use of 3 moles DMF and 3 moles $POCl_3$ in $ClCH_2CH_2Cl$, red oils, which we tentatively assign as tautomers (15) are the major products.



(15a) (15b)

7. The acetamidothiophens were obtained in high yield (62-84%) by a modified Beckmann reaction similar to that reported by Cymerman-Craig (J. Cymerman-Craig and D. Willis, J. Chem. Soc., 1955, 1071).
8. This work and our modification of the Beckmann reaction (Ref. 7) are the subjects of recently filed provisional patents.
9. L.H. Klemm, C.E. Klopfenstein, R. Zell, D.R. McCoy and R.A. Klemm, J. Org. Chem., 1969, 34, 347, report b.p. 61-2°/0.2 mm.
10. L.H. Klemm and R. Hartling, J. Heterocyclic Chem., 1976, 13, 1197, report m.p. 56.5°.

We thank Croda Synthetic Chemicals for a maintenance grant and gift of chemicals.