One-step Synthesis of 8-Chloroflavins by the Cyclization of 5-Nitro-6-(*N*-substituted-anilino)uracils with the Vilsmeier Reagent. Vilsmeier Reagent as a Reducing Agent

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Summary Treatment of 5-nitro-6-(*N*-substituted-anilino)-uracils with the Vilsmeier reagent (dimethylformamide–phosphorus trichloride oxide) gave the corresponding 8-chloroflavins; the Vilsmeier reagent acted as a reducing agent as well as a dehydrating and chlorinating agent.

WE report a new approach to flavins which is widely applicable and especially convenient for the synthesis of 8-chloroflavins. This route consists of treatment of 5-nitro-6-(*N*-substituted-anilino)uracils[1,2] with the Vilsmeier reagent [dimethylformamide (DMF)–$POCl_3$].

For example, heating the uracil (Ia) (2 mmol) with dimethylformamide (30 mmol) and $POCl_3$ (4 mmol) at 90 °C for 1 h, followed by dilution with water, caused the separation of the isoalloxazine (IIa) in 73% yield and in a high state of purity. The product was identical in all respects with an authentic sample prepared by the condensation of 6-methylamino-3-methyluracil with 4-chloronitrosobenzene in acetic anhydride.[3] Similarly, heating other uracils (Ib—e) with DMF–$POCl_3$ led to the formation of the respective 8-chloroflavins (IIb—e) (Table).

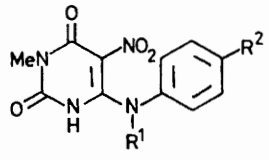
TABLE. 8-Chloroflavin formation by the reaction of 5-nitro-6-(*N*-substituted-anilino)uracils with the Vilsmeier reagent

Starting material	8-Chloroflavin	M.p./°C	Yield/%
(Ia)	(IIa)[a]	>330	73
(Ib)	(IIb)	321	71
(Ic)	(IIc)	279	72
(Id)	(IId)	267	56
(Ie)	(IIe)	>330	88

[a] Ref. 3.

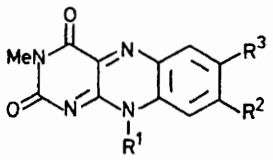
The conversion of (I) into (II) probably involves the initial formation of the flavin 5-oxides (III)[3] by dehydrative cyclization of (I), followed by subsequent chlorination on the 8-position of (III) and loss of the *N*-oxide group. In fact, treatment of (IIIa and b), prepared alternatively,[3] with DMF–$POCl_3$ gave (IIa and b) in 80 and 78% yields respectively, while the flavins (IIi and j) themselves did not react, starting materials being recovered. Nucleophilic chlorinations of aromatic *N*-oxides with loss of the *N*-oxide group have been reviewed;[4] many heterocyclic *N*-oxides have been converted into the corresponding chloro-heterocycles, mainly using $POCl_3$. However, the conversion of (I) or (III) into (II) required the Vilsmeier reagent; $POCl_3$ alone was not effective even under more drastic conditions, starting materials being recovered.

When the anilino-group of the starting materials (I) possessed a *para*-substituent, chlorination of the initially formed (III) was prevented because of steric hindrance and only loss of the *N*-oxide group took place. For example, treatment of the *N*-ethyl-*p*-toluidino-compound (If) with



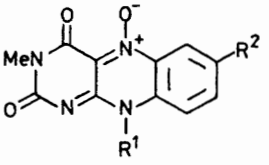
(I)

a; R^1 = Me, R^2 = H
b; R^1 = Et, R^2 = H
c; R^1 = Pr^n, R^2 = H
d; R^1 = Bu^n, R^2 = H
e; R^1 = Ph, R^2 = H
f; R^1 = Et, R^2 = Me



(II)

a; R^1 = Me, R^2 = Cl, R^3 = H
b; R^1 = Et, R^2 = Cl, R^3 = H
c; R^1 = Pr^n, R^2 = Cl, R^3 = H
d; R^1 = Bu^n, R^2 = Cl, R^3 = H
e; R^1 = Ph, R^2 = Cl, R^3 = H
f; R^1 = Me, R^2 = H, R^3 = Br
g; R^1 = Et, R^2 = H, R^3 = Br
h; R^1 = Et, R^2 = H, R^3 = Me
i; R^1 = Me, R^2 = R^3 = H
j; R^1 = Et, R^2 = R^3 = H



(III)

a; R^1 = Me, R^2 = H
b; R^1 = Et, R^2 = H
c; R^1 = Me, R^2 = Br
d; R^1 = Et, R^2 = Br
e; R^1 = Et, R^2 = Me

DMF–$POCl_3$ under the same conditions gave the isoalloxazine (IIh). Furthermore, treatment of the 7-substituted flavin 5-oxides (IIIc—e)† with DMF–$POCl_3$ at 90 °C for 10 min gave the corresponding flavins (IIf) (m.p. 314 °C, 91%), (IIg) (m.p. 288 °C, 80%), and (IIh) (m.p. 270 °C, 82%). It is interesting that the Vilsmeier reagent acts as a reducing agent.

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† These were prepared by the nitrosative cyclization of the corresponding 6-(*N*-substituted-anilino)uracils with sodium nitrite in acetic acid.

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