A New, General, and Convenient Synthesis of 5-Deazaflavins (5-Deazaisoalloxazines)

Tomohisa Nagamatsu, Yuko Hashiguchi, Masatsugu Higuchi, and Fumio Yoneda*

Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

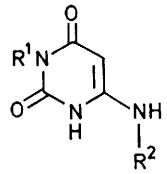
The condensation of 6-substituted-aminouracils with *o*-halogenobenzaldehydes in dimethylformamide led to the formation of the corresponding 5-deazaflavins in a single step.

5-Deazaflavins (5-deazaisoalloxazines) have been studied extensively in both enzymatic[1] and model systems[2] to provide mechanistic insight into flavin-catalysed reactions. They have aroused further interest because of the recent discovery that coenzyme F_{420} from methanogenic bacteria possesses the 8-hydroxy-5-deazaflavin moiety.[3] Moreover, our findings that the oxidation of alcohols under alkaline conditions by 5-deazaflavins yields the corresponding carbonyl compounds[4] and that the reduction of carbonyl compounds by 1,5-dihydro-5-deazaflavins yields the corresponding alcohols in the presence of strong proton sources[5] have prompted us to prepare a great variety of 5-deazaflavins in order to pick out the more efficient oxidizing or reducing agents.

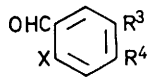
5-Deazaflavins have previously been prepared by (a) the condensation of anthranilaldehydes with barbituric acid,[6] (b) the cyclization of 6-(*N*-alkylanilino)uracils with one-carbon reagents including the Vilsmeier reagent,[7] (c) the condensation of 6-chloro-5-formylpyrimidines with *N*-alkylanilines,[7] and (d) the oxidative cyclization of arylbis(6-substituted-amino-3-methyluracil-5-yl)methanes with diethyl azodicarboxylate (DAD).[8,9] However we encountered difficulties when attempting to prepare the 10-aryl-5-deazaflavin derivatives (**1**) by the methods (b) and (c), because the intermediate 6-(*N*-arylanilino)-uracils were not available by the usual condensation of 6-chlorouracils with diphenylamines and because the 6-chloro-5-formylpyrimidines and diphenylamines were unreactive under conventional conditions. Furthermore, the synthetic method (d), consisting of the oxidative coupling of arylbis-(6-anilinouracil-5-yl)methanes (**2**), gave the corresponding 5-deazaflavins (**1**) in overall low yields based on the starting 6-anilinouracils (**3**).

We now report a new, general, and convenient synthesis of the 5-deazaflavin derivatives (**6**), which consists of the condensation of 6-substituted-aminouracils (**4**) with *o*-halogeno-benzaldehydes (**5**). This method is noteworthy owing to the availability of all kinds of 5-deazaflavins, the simplicity of the procedure, and the very high yield of products.

A mixture of 6-*N*-alkyl- or 6-*N*-aryl-aminouracils (**4**)[10] (2.5 mmol) and the appropriate *o*-chloro- or *o*-bromo-benzaldehydes (**5**) (3.0 mmol) in dimethylformamide (DMF, 20 ml) was heated under reflux for 3—5 h. Concentration of

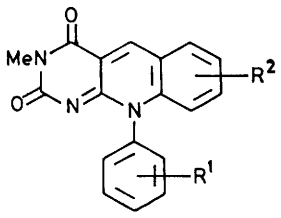


(**4**) **a**; R^1 = H, R^2 = Bu^n
b; R^1 = H, R^2 = Ph
c; R^1 = H, R^2 = 3,4-$Me_2C_6H_3$
d; R^1 = R^2 = Me
e; R^1 = Me, R^2 = Pr^n
f; R^1 = Me, R^2 = Bu^n
g; R^1 = Me, R^2 = CH_2Ph
h; R^1 = Me, R^2 = Ph
i; R^1 = Me, R^2 = 3-MeC_6H_4
j; R^1 = Me, R^2 = 4-MeC_6H_4
k; R^1 = Me, R^2 = 3,4-$Me_2C_6H_3$
l; R^1 = Ph, R^2 = Me
m; R^1 = R^2 = Ph

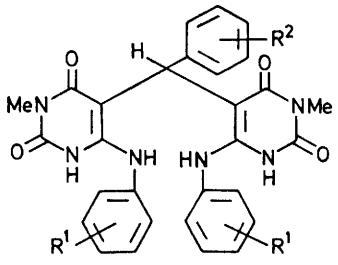


X = halogen

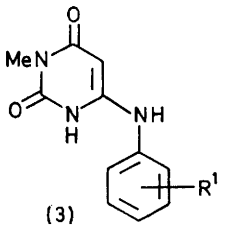
(**5**) **a**; R^3 = R^4 = H
b; R^3 = NO_2, R^4 = H
c; R^3 = H, R^4 = Cl
d; R^3 = H, R^4 = OH



(1)



(2)

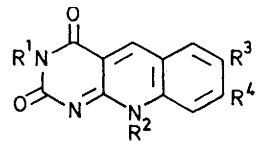


(3)

Table 1. Formation of 5-deazaflavins (**6**) and their C-5 proton chemical shifts.

Starting materials	Product	Yield (%)	M.p.[a] /°C	Recrystn. solvent	δ (CF_3CO_2H)
(**4a**) + (**5b**)	(**6a**)	80	290	EtOH	9.96
(**4b**) + (**5a**)	(**6b**)	82	>330	DMF	9.91
(**4b**) + (**5b**)	(**6c**)	90	>330	DMF–EtOH	10.05
(**4b**) + (**5c**)	(**6d**)	95	>330	DMF	9.87
(**4b**) + (**5d**)	(**6e**)	79	>330	EtOH	9.66
(**4c**) + (**5a**)	(**6f**)	80	>330	EtOH	9.86
(**4d**) + (**5d**)	(**6g**)[8]	83	>330	AcOH	9.56
(**4e**) + (**5a**)	(**6h**)[8]	78	267	EtOH	9.80
(**4f**) + (**5d**)	(**6i**)	92	>330	DMF	9.61
(**4g**) + (**5a**)	(**6j**)	73	>330	EtOH	9.94
(**4h**) + (**5a**)	(**6k**)[9]	95	>330	DMF	9.92
(**4h**) + (**5c**)	(**6l**)[9]	92	>330	DMF	9.93
(**4i**) + (**5a**)	(**6m**)	82	>330	EtOH	9.96
(**4j**) + (**5a**)	(**6n**)[9]	89	>330	DMF	9.97
(**4k**) + (**5b**)	(**6o**)	73	>330	DMF–EtOH	9.97
(**4l**) + (**5d**)	(**6p**)	74	>330	DMF	9.60
(**4m**) + (**5a**)	(**6q**)	81	>330	DMF	10.00
(**4m**) + (**5c**)	(**6r**)	87	>330	DMF–EtOH	9.90

[a]All compounds were obtained as yellow needles or prisms.



(6) **a**; $R^1 = R^4 = H$, $R^2 = Bu^n$, $R^3 = NO_2$
b; $R^1 = R^3 = R^4 = H$, $R^2 = Ph$
c; $R^1 = R^4 = H$, $R^2 = Ph$, $R^3 = NO_2$
d; $R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = Cl$
e; $R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = OH$
f; $R^1 = R^3 = R^4 = H$, $R^2 = 3,4\text{-}Me_2C_6H_3$
g; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OH$
h; $R^1 = Me$, $R^2 = Pr^n$, $R^3 = R^4 = H$
i; $R^1 = Me$, $R^2 = Bu^n$, $R^3 = H$, $R^4 = OH$
j; $R^1 = Me$, $R^2 = CH_2Ph$, $R^3 = R^4 = H$
k; $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = H$
l; $R^1 = Me$, $R^2 = Ph$, $R^3 = H$, $R^4 = Cl$
m; $R^1 = Me$, $R^2 = 3\text{-}MeC_6H_4$, $R^3 = R^4 = H$
n; $R^1 = Me$, $R^2 = 4\text{-}MeC_6H_4$, $R^3 = R^4 = H$
o; $R^1 = Me$, $R^2 = 3,4\text{-}Me_2C_6H_3$, $R^3 = NO_2$, $R^4 = H$
p; $R^1 = Ph$, $R^2 = Me$, $R^3 = H$, $R^4 = OH$
q; $R^1 = R^2 = Ph$, $R^3 = R^4 = H$
r; $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = Cl$

the solution under reduced pressure and recrystallization of the residue from appropriate solvents (indicated in Table 1) gave the corresponding 5-deazaflavins (**6**) *via* dehydration and dehydrochlorination. The structures of the products (**6**) were established from satisfactory analytical and spectral data, and in particular, by the presence of the characteristic C-5 proton resonance at δ 9.6—10.1 in the ^1H n.m.r. spectra for compounds (**6**) (see Table 1).

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