A New and Versatile Synthesis of Isoalloxazines

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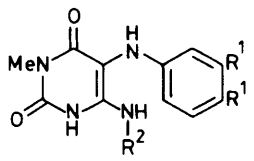
Isoalloxazines (**2**) were prepared easily by heating of the corresponding 5-anilino-6-(alkyl or aryl amino)pyrimidine-2,4(1*H*,3*H*)-diones (**1**) in dimethylformamide under oxygen.

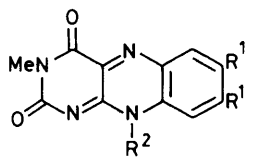
The use of isoalloxazines as flavin mimics has aided the development of chemical insight into flavin-catalysed redox reactions,[1] and various methods for the preparation of the isoalloxazine ring systems have been developed.

We now report here a new and versatile method for the synthesis of isoalloxazines, which involves a novel oxidative cyclisation, starting from the readily available 5-anilino-6-(alkyl or aryl amino)pyrimidine-2,4(1*H*,3*H*)-diones (**1**). The method is in principle applicable to the synthesis of isoalloxazines possessing a variety of substituents at the *N*(10)-position and on the benzene ring.

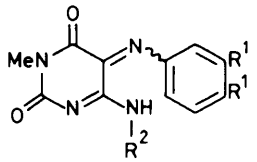
The pyrimidinediones (**1a—f**) were prepared easily in high yields by the reactions of the appropriate 5-bromo-6-(alkyl or aryl amino)pyrimidinediones with the corresponding anilines.[3] A solution of compound (**1a**) (1.0 mmol) in dimethylformamide (10 ml) was heated at 120 °C for 1 h under oxygen.†



(**1**)



(**2**)



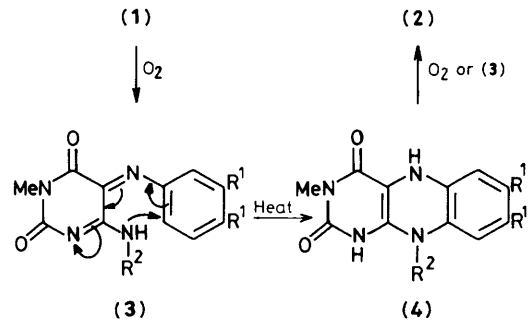
(**3**)

a; R^1 = H, R^2 = Me
b; R^1 = H, R^2 = Et
c; R^1 = H, R^2 = Ph
d; R^1 = H, R^2 = 2,6-$Me_2C_6H_3$
e; R^1 = R^2 = Me
f; R^1 = Me, R^2 = Ph

Dilution with diethyl ether followed by filtration led to the pure 3,10-dimethylisoalloxazine (**2a**).‡ Hexamethylphosphoric triamide or lutidine could also be used as solvent. Similarly, the isoalloxazines (**2b—f**)‡ were obtained in high yields from the diones (**1b—f**), respectively. The 7,8-dimethylisoalloxazines (**2e** and **f**) were formed exclusively without contamination from the isomeric 8,9-dimethylisoalloxazines in the thermal reactions of (**1e** and **f**). The results are summarised in Table 1.

When a solution of (**1a**) (1.0 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 2 h under oxygen, the imino compound (**3a**),§ m.p. 190—191 °C, was isolated in 55% yield, together with unchanged (**1a**) and a small amount of (**2a**). The structure of (**3a**) was assigned from microanalytical and spectral data [$\nu_{max.}$(KBr) 3290 (NH), 1710 (C=O), and 1665 (C=O) cm^{-1}; $\lambda_{max.}$ (MeCN) 460 (ε 2.34 × 10^3), 277 (8.91 × 10^3), and 228 nm (2.13 × 10^4); δ_H(60 MHz, CD_3SOCD_3) 2.94 (3 H, d, *J* 5.0 Hz, 6-NH*Me*; singlet on addition of D_2O), 3.02 (3 H, s, 3-Me), 6.80—7.60 (5 H, m, Ph), and 8.90 (1 H, br. d, *J* 5.0 Hz, D_2O-exchangeable 6-N*H*Me); *m/z* 244 $(M)^+$]. On heating as for (**1a**) the product (**3a**) was converted into (**2a**) almost quantitatively,¶ clearly indicating that compound (**3**) is an intermediate in the present isoalloxazine synthesis.

Taking these facts into consideration, a plausible mechanism is shown in Scheme 1.



Scheme 1

Table 1. Formation of the isoalloxazines (**2**).

Isoalloxazine	M.p. (*t*/°C)(lit.)	Yield (%)
(**2a**)	>300 (323)[a]	88
(**2b**)	287 (299)[b]	85
(**2c**)	>300 (360)[c]	90
(**2d**)	299 (297)[d]	95
(**2e**)	>300 (326)[e]	85
(**2f**)	>300	93

[a] R. Kuhn and F. Weygand, *Chem. Ber.*, 1934, **67**, 1459. [b] Ref. 2. [c] R. Kuhn and F. Weygand, *Chem. Ber.*, 1935, **68**, 1282. [d] L. Main, G. J. Kasperek, and T. C. Bruice, *Biochemistry*, 1972, **11**, 3991. [e] R. Kuhn and H. Rudy, *Chem. Ber.*, 1934, **67**, 1125.

† The reaction was completely inhibited by degassing.

‡ The products (**2a—e**) were identical with authentic samples. The product (**2f**) gave satisfactory microanalytical results and spectral data consistent with the structure.

§ Compound (**3**) has been proposed as an intermediate in the thermal condensation of 6-(monosubstituted amino)pyrimidinediones with nitrosobenzenes leading to the isoalloxazines: *cf.* F. Yoneda, K. Shinozuka, K. Tsukuda, and A. Koshiro, *J. Heterocycl. Chem.*, 1979, **16**, 1365. The product (**3a**) is a mixture of geometrical isomers with respect to the C(5)-imino function in solution. These isomers were detectable by n.m.r. spectroscopy.

¶ Treatment of (**3a**) under argon afforded (**1a**) and (**2a**) in 40 and 45% yields, respectively. The formation of (**1a**) in this reaction may be explained in terms of the oxidation of the intermediate 1,5-dihydroisoalloxazine (**4a**) by (**3a**). Recently, we have demonstrated that (**3**) possesses oxidative ability; *cf.* ref. 3.

The reaction could be initiated by autoxidation of (**1**) to give (**3**). In a basic polar solvent, the C(6)-amino group of (**3**) attacks the *ortho*-position of the electron-deficient phenyl ring to give the dihydroisoalloxazine (**4**). Subsequent oxidation of (**4**) by oxygen or the intermediate (**3**)¶ results in the formation of the isoalloxazines (**2**).

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References

1 For recent reviews concerning mechanism of flavin catalysis, see C. Walsh, *Acc. Chem. Res.*, 1980, **13**, 148; T. C. Bruice, *ibid.*, 1980, **13**, 256; H. Dugus and C. Penny, 'Bioorganic Chemistry. A Chemical Approach to Enzyme Action,' Springer-Verlag, New York, 1981, p. 460.
2 F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, *J. Am. Chem. Soc.*, 1976, **98**, 830, and references cited therein.
3 M. Sako, Y. Kojima, K. Hirota, and Y. Maki, *Heterocycles*, 1984, **22**, 1021.