NOVEL RING-CONTRACTION OF 5-ANILIDENE-6-(N-METHYLANILINO)PYRIMIDINE-2,4(3H,5H)-DIONE

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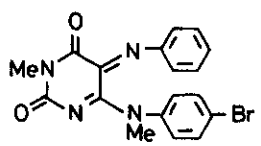
Abstract —— Treatment of 5-anilidene-6-(N-methylanilino)pyrimidine-2,4(3H,5H)-dione (1) with primary alcohols without any catalyst causes smooth ring-contraction leading to 4-alkoxycarbonyl-4-anilino-5-(N-methylanilino)imidazol-2(3H,4H)-ones (2) in high yields.

Recently, we have reported a facile preparation of 5-anilidene-6-(N-methylanilino)pyrimidine-2,4(3H,5H)-dione (1) which involves the reaction of 5-bromo-6-(N-methylanilino)uracils with aniline followed by oxidation.[1] The reactivity of 1 toward various substrates is of special interest in connection with the flavin chemistry, since 1 is regarded as a ring-opened analogue of 3,10-dimethylisoalloxazine (3) which is a simple flavin model compound.[2]

During the course of our investigation on the chemical reactivity of 1, we found that the treatment of 1 with primary alcohols under mild conditions without any catalyst caused a novel ring-contraction to give the corresponding imidazolones (2) in high yields. Contrary to the case of 1, 3 is stable under the conditions employed. Thus, the conjugated system in 1 showed the chemical reactivity



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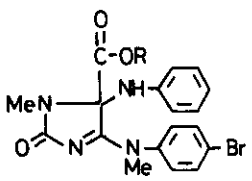

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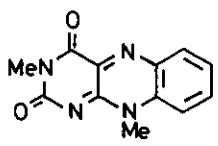
a: R= Me, b: R= Et
c: R= Pr^n, d: R=-CH_2Ph



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different from that of 3.

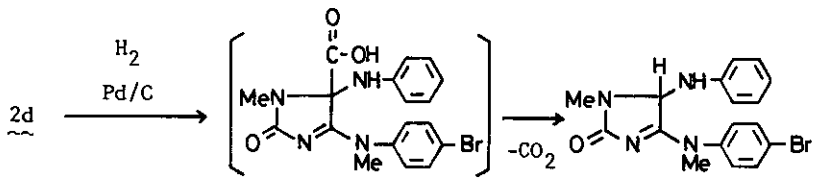
When 1 was dissolved in methanol at room temperature, the reddish-orange color of the solution faded gradually. TLC analysis of the reaction mixture showed the formation of a sole product. The UV spectral change during the reaction showed four isosbestic points at 213, 238, 265, and 278 nm. The reaction was significantly accelerated by heating of the solution or by addition of a catalytic amount of sodium methoxide. After removal of the solvent under reduced pressure, the residue was recrystallized from methanol to isolate 4-anilino-4-methoxycarbonyl-5-(N-methylanilino)imidazol-2(3H,4H)-one (2a) as colorless crystals in an almost quantitative yield. The structure of 2a was fully supported by its microanalytical results and spectral data [MS m/e 431 (M^+), 372 (M^+-59); IR(KBr) 3340 (NH), 1750 (C=O), 1720 (C=O)cm^{-1}; UV(MeCN) 255 (sh, 1.3 x 10^4), 232 (1.7 x 10^4)nm; NMR($CDCl_3$,δ) 2.63 (3H, s, NMe), 3.43 (3H, s, NMe), 3.89 (3H, s, COOMe), 4.63 (1H, b, deuterium exchangeable NH), 6.30-7.60 (9H, m, phenyl ring protons)]. The product 2a was stable in refluxing ethylene glycol for 7 h. Analogous smooth ring-contraction of 1 was also observed when ethanol or n-propanol was employed as a solvent, though prolonged reaction time was required for the completion of the reaction. Although the reaction of 1 with benzyl alcohol did not proceed smoothly under mild conditions, heating of a solution of 1 (0.5 mmol) in benzyl alcohol (20 ml) at 120°C for 4 h under an argon atmosphere and subsequent chromatographic separation of the reaction mixture allowed isolation of the corresponding imidazolone derivative (2d) in 33% yield, together with 5-

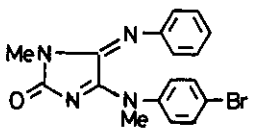
Table 1 Reaction of 5-Anilidene-6-(N-methylanilino)pyrimidinedione (1) with Primary Alcohols

Alcohol	Pseudo-first order rate constant $10^4 \cdot K'$ (S^{-1}) [a]	Product (Mp, °C)
MeOH	2.35	(2a) (159)
EtOH	1.91	(2b) (133)
n-PrOH	1.72	(2c) (140)
$PhCH_2OH$ [b]	-	(2d) (182)

a) at 25°C, [1] = 6.26 x 10^{-6}M. b) at 120°C for 4 h.

anilino-3-methyl-6-(N-methyl-p-bromoanilino)uracil (49%).[3] The latter product was identical with a sample prepared by the reaction of 5-bromo-3-methyl-6-(N-methyl-p-bromoanilino)uracil with aniline. On the other hand, the reaction of 1 with i-propanol or t-butanol recovered the unchanged starting material even under severe conditions (reflux for 2 days). The results of these reactions of 1 with primary alcohols are summarized in Table 1.





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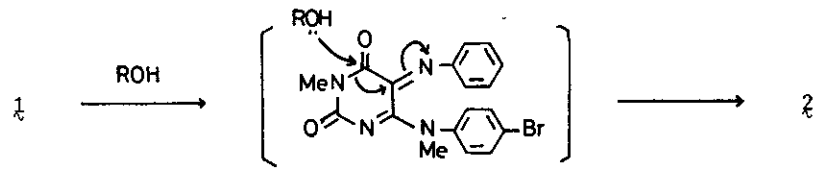
Catalytic reduction of the benzyl ester (2d) using 5% palladium-carbon afforded 4-anilino-5-(N-methylanilino)imidazol-2(3H,4H)-one (5),[4] mp 169°C, in 80% yield. The structure of 5 was confirmed by its microanalytical results and spectral data [MS m/e 373 (M^+), 371; IR(KBr) 3200 (NH), 1760 (C=O), 1660 (C=N)cm^{-1}; UV (MeCN) 257 (1.7×10^4), 232 (1.8×10^4)nm; NMR($CDCl_3$, δ) 2.48 (3H, s, NMe), 3.15 (3H, s, NMe), 5.98 (1H, broad d, J= 1 Hz, coalesced to a singlet by deuterium exchange, C_4-H), 6.20 (1H, b, deuterium exchangeable NH), 6.10-7.35 (9H, m, phenyl ring protons)] and by its oxidation using 2,3-dichloro-5,6-dicyanobenzoquinone to give 4-anilidene-5-(N-methylanilino)imidazol-2(3H)-one (6).[5] The NMR spectrum of 5 is similar to that of 2a, except for the presence of a methine proton signal at δ5.98 instead of a methoxy signal (δ 3.89) in 2a. The UV spectrum of 5 also shows a close similarity to that of 2a. The formation of 5 in the reduction of 2d could be reasonably explained in terms of decarboxylation of the initially formed 4-anilino-4-carboxy-5-(N-methylanilino)imidazolone (4) under the conditions employed. Thus, the conversion of 2d into 5 provides a chemical evidence in support of the structures of the products 2 in the reaction of 1 with primary alcohols.

We suggest that 2 is formed from 1 by the mechanism outlined below, in which the ring-contraction step is a benzylic acid type rearrangement similar to that firmly established for the conversion of alloxan to alloxanic acid.[6] The unique feature of the rearrangement in the present case is that the ring-contraction takes place even under neutral conditions, although the reaction can be accelerated by a base catalyst.



REFERENCES AND FOOTNOTES

1 M. Sako, Y. Kojima, K. Hirota, and Y. Maki, Heterocycles, 1984, 22, 1021.

2 For recent reviews concerning mechanisms of flavin catalysis, see C. Walsh, Acc. Chem. Res., 1980, 13, 148; T. C. Bruice, ibid., 1980, 13, 256; H. Dugas, and C. Penney, ' Bioorganic Chemistry. A Chemical Approach to Enzyme Action ' Springer-Verlag, New York, 1981, p 400.

3 Significant amounts of benzaldehyde was detected by GC analysis of this reaction mixture. The formation of the 5-anilino-6-(N-methylanilino)uracil and benzaldehyde in this reaction apparently shows occurrence of redox reaction between 1 and benzyl alcohol under the thermal conditions. Thus, the oxidation capacity of 1 was substantiated in this thermal reaction with benzyl alcohol. Recently, oxidation of benzyl alcohol by 2H-chromeno[2,3-d]pyrimidine-2,4(3H)-diones, which is a deazaflavin analogue, under the thermal conditions similar to our case (at 90°C for 10 h) has been reported. Cf. F. Yoneda, R. Hirayama, and M. Yamashita, Chem. Lett., 1980, 1157.

4 The imidazolone (5) was also obtained by treatment of 1 (0.5 mmol) with MeCN-H_2O containing a trace amount of 1N-NaOH at room temperature for 10 min. The intermediary carboxylic acid (4), however, was not isolated in a pure state.

5 Mp 140°C (from diethyl ether); MS m/e 371(M^+), 356(M^+-15); IR(KBr) 1755 (C=O), 1690 (C=N)cm^{-1}; UV(MeCN) 323 (6.2 x 10^3), 250 (1.7 x 10^4), 237 (1.7 x 10^4)nm; NMR($CDCl_3$,δ) 2.68 (3H, s, NMe), 3.74 (3H, broad s, NMe), 6.45-7.65 (9H, m, phenyl ring protons).

6 H. Kwart and I. M. Sarasohn, J. Am. Chem. Soc., 1961, 83, 909.

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