

STUDIES ON PYRIMIDINE-ANNULATED HETEROCYCLES: SYNTHESIS AND FUNCTION OF NOVEL 9-SUBSTITUTED CYCLOHEPTA[*b*]PYRIMIDO[5,4-*d*]FURAN-8,10(9H)-DIONES¹

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Abstract-A new short synthesis of 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9H)-diones has been accomplished by the reaction of 3-methyl-, 3-butyl-, and 3-phenylbarbituric acids with 2-chlorotropone in an enolate-substitution process and subsequent dehydrative cyclization by using CF₃CO₂H. These novel compounds exhibited a strong function in oxidizing some alcohols under neutral and aerobic conditions to give an aldehyde or ketones in an autorecycling process, while they are hydrogenated to mixtures of 5,7-, 1,7-, and 3,7-dihydrocyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9H)-dione derivatives.

The importance of fused pyrimidines, which are common sources for the development of new potential therapeutic agents,^{2,3} is well known. Among these, 5-deazaflavin (**1**) (5-deazaisoalloxazine) has been studied extensively in both enzymatic^{4,5} and model systems^{5,6} in the hope of providing mechanistic insight into flavin-catalyzed reactions. Previously, we studied a convenient preparation of 6,9-disubstituted

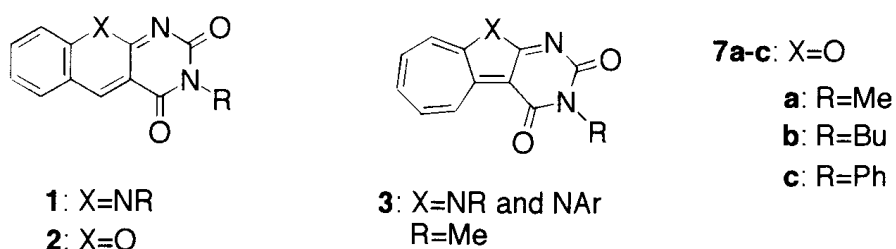
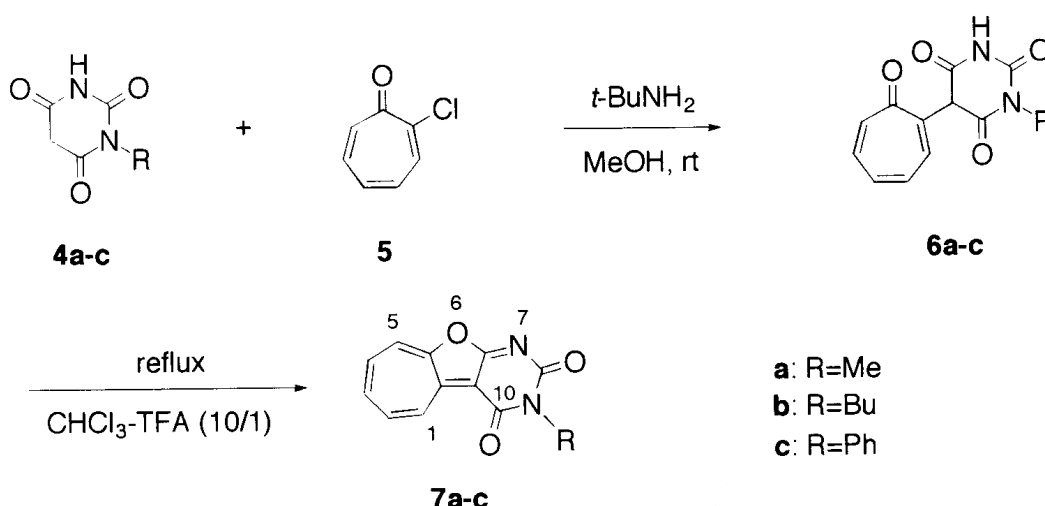


Figure 1

cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8,10(6*H*,9*H*)-diones (**3**), which are isomers of 5-deazaflavin (**1**), and their strong function in oxidizing benzyl alcohol to give benzaldehyde.⁷ On the other hand, 5-deaza-10-oxaflavin (**2**) (2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione), in which the nitrogen atom of the 5-deazaflavin (**1**) is replaced by an oxygen, has been synthesized and found to possess a strong function to oxidize alcohols to carbonyl compounds.⁸ On the basis of the above observations, we investigated a synthesis of 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-dione (**7**), which is a structural isomer of 5-deaza-10-oxaflavin (**2**) and has an isoelectronic structure with compound (**3**), and a preliminary study of its function in oxidizing some alcohols.

Since a reaction of 2-chlorotropone (**5**) with diethyl malonate or ethyl acetoacetate in the presence of NaOEt gives 3-ethoxycarbonylcyclohepta[*b*]furan-2-one,^{9,10} the method was applied to a synthesis of 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-dione derivatives (**7a-c**) by using barbituric acid (**4a-c**). Appropriate barbituric acid derivatives (**4a-c**) were prepared as described in the literature.¹¹ Reaction of barbituric acids (**4a-c**) (10 mmol) with 2-chlorotropone (**5**) (10 mmol) was performed in MeOH (10 mL) in the presence of *t*-BuNH₂ (25 mmol) at room temperature for 24 h. After evaporation of the MeOH and excess *t*-BuNH₂, the resulting residue was filtered and washed with Et₂O to give 5-(tropon-2-yl)barbituric acids (**6a-c**) as yellow crystals, which exhibited satisfactory ¹H NMR spectra and were contaminated with *t*-BuNH₃Cl. Since the compounds (**6a-c**) are very polar and sparingly



Scheme 1

soluble in the usual solvents and removal of *t*-BuNH₃Cl seemed to be difficult, the crystals (**6a-c**) were subsequently treated with CHCl₃-TFA (10/1) under reflux for 8 h. After the solvent was removed *in vacuo*, the residual solid was collected by filtration and washed with MeOH to give 9-substituted

cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-dione derivatives (**7a-c**) in 82, 89, and 84% yields, respectively. The structures of compounds (**7a-c**) were assigned on the basis of their spectral data and elemental analyses. In particular, the presence of the characteristic H-1 signal appearing at around δ 8.8 in their ^1H NMR and the carbonyl absorption of the pyrimidinedione moiety^{7,12} and the ether absorption in their IR spectra are in good agreement with the proposed structures (Table 2).¹³

Table 1. Selected physical data of new compounds (**7a-c**)

7a: yellow powder; mp 261-262 °C (AcOH); ^1H NMR (400 MHz, CDCl_3) δ 3.45 (3H, s, Me), 7.70 (1H, dd, $J=10.4$, 9.0, H-3), 7.80 (1H, dd, $J=10.4$, 9.5, H-4), 7.94 (1H, d, $J=10.7$, 9.0, H-2), 7.99 (1H, d, $J=9.5$, H-5), 8.89 (1H, d, $J=10.7$, H-1); IR (KBr)/ cm^{-1} 1685, 1635, 1266.

7b: yellow powder; mp 188-189 °C (AcOH); ^1H NMR (400 MHz, CDCl_3) δ 0.96 (3H, t, $J=7.2$, CH_3), 1.41 (2H, sext, $J=7.2$, CH_2), 1.67 (2H, quint, $J=7.2$, CH_2), 4.04 (2H, t, $J=7.2$, CH_2), 7.67 (1H, dd, $J=9.2$, 10.4, H-3), 7.77 (1H, dd, $J=10.4$, 9.4, H-4), 7.91 (1H, dd, $J=10.8$, 9.2, H-2), 7.96 (1H, d, $J=9.4$, H-H-5), 8.87 (1H, d, $J=10.8$, H-1); IR (KBr)/ cm^{-1} 1702, 1632, 1267.

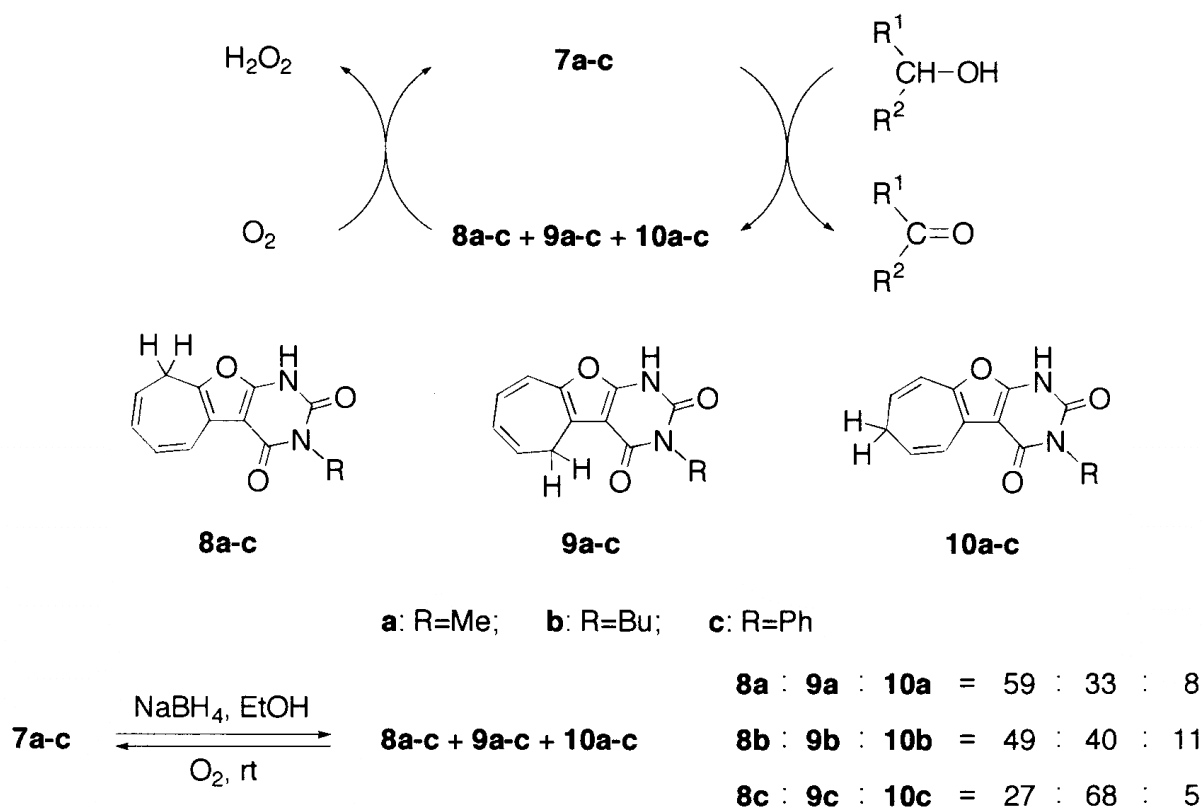
7c: yellow powder; mp 272-274 °C (AcOH); ^1H NMR (400 MHz, CDCl_3) δ 7.28 (2H, d, $J=9.0$, Ph), 7.43 (1H, t, $J=9.0$, Ph), 7.51 (2H, t, $J=9.0$, Ph), 7.72 (1H, dd, $J=10.0$, 9.3, H-3), 7.83 (1H, dd, $J=10.0$, 9.6, H-4), 7.95 (1H, dd, $J=10.5$, 9.3, H-2), 8.04 (1H, d, $J=9.6$, H-5), 8.85 (1H, d, $J=10.5$, H-1); IR (KBr)/ cm^{-1} 1698, 1627, 1263.

Since compounds (**1**)^{5,6} and (**2**)⁸ as well as compound (**3**)⁷ were clarified to possess an oxidizing function of alcohols, thus, we turned our attention to the oxidation of some alcohols to determine the ability of **7a-c** as efficient organic oxidants. The compounds (**7a-c**) (0.05 mmol) were added to alcohols (1 mL), and the mixtures were heated at 90 °C for the periods indicated in Table 2 under neutral and aerobic conditions. The reaction mixture was diluted with ether and filtered; the filtrate was treated with 2,4-dinitrophenylhydrazine in 2N HCl to give 2,4-dinitrophenylhydrazones. The results are summarized in Table 2. Thus, we have found that compounds (**7a-c**) have remarkable ability to oxidize some alcohols, benzyl alcohol, 1-phenylethanol, and cyclohexanol, to give benzaldehyde, acetophenone, and cyclohexanone, while the compounds (**7a-c**) themselves are reduced to mixtures of 5,7-, 1,7-, and 3,7-dihydrocyclohepta[*b*]pyrimido[5,4-*d*]furan-2-ones (**8a-c**), (**9a-c**), and (**10a-c**), respectively (Scheme 2).

Table 2. Oxidation of alcohols by compounds (**7a-c**) under aerobic conditions at 90 °C

Compd	Alcohol	Reaction Time / h	Product ^a	Yield ^b %
7a	PhCH ₂ OH	120 ^c	PhCHO	367
7a	PhCHMeOH	40	PhCOMe	280
7a	Cyclohexanol	40	Cyclohexanone	220
7b	PhCH ₂ OH	120 ^c	PhCHO	313
7b	PhCHMeOH	48	PhCOMe	515
7c	PhCH ₂ OH	120 ^c	PhCHO	395
7c	PhCHMeOH	48	PhCOMe	403

a. Isolated as 2,4-dinitrophenylhydrazone. b. Based on compounds (**7a-c**). c. Compounds (**7a-c**) disappeared.



Scheme 2

The reduction of **7a-c** with NaBH₄ in EtOH afforded mixture of dihydrogenated compounds, (**8a-c**), (**9a-c**), and (**10a-c**), in a similar ratio, and the mixture is oxidized by air at room temperature to give **7a-c**, respectively (Scheme 2). Thus, it is remarkable that an autorecycling oxidation was observed to yield

more than 100% of ketones [based on compounds (**7a-c**)].

In conclusion, the present study demonstrates that the synthesis of 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-2-ones (**7a-c**) is practical and convenient, and the compounds (**7a-c**), which contain an oxaazulene nucleus, are found for the first time to possess an excellent function as an organic oxidant like 5-deazaflavin and 5-deaza-10-oxaflavin. Further studies of the redox-reaction of compounds (**7a-c**), including the mechanistic aspect, are now underway.

ACKNOWLEDGMENT

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REFERENCES

1. This paper is dedicated to Professor Sho Itô on the occasion of his 77th birthday.
2. D. J. Brown, In *Comprehensive Heterocyclic Chemistry*, Vol. 3, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, pp. 57-155.
3. H. Wamhoff, J. Dzenis, and K. Hirota, *Adv. Heterocycl. Chem.*, 1992, **55**, 129.
4. C. Walsh, *Acc. Chem. Res.*, 1986, **19**, 216.
5. F. Yoneda and K. Tanaka, *Med. Res. Rev.* 1987, **7**, 477.
6. F. Yoneda and B. Kokel, In *Chemistry and Biochemistry of Flavoenzymes*, Vol. 1, ed. by F. Müller, CRC Press, Boca Raton, 1991, pp. 121-169.
7. M. Nitta and Y. Tajima, *Synthesis*, 2000, 651.
7. F. Yoneda, R. Hirayama, and M. Yamashita, *Chem. Lett.*, 1980, 1157; X. Chen, K. Tanaka, and F. Yoneda, *Chem. Pharm. Bull.*, 1990, **38**, 307.
9. T. Nozoe, K. Takase, T. Nakazawa, and S. Fukuda, *Tetrahedron*, 1971, **27**, 3357.
10. T. Nozoe, S. Seto, and S. Matsumura, *Proc. Japan Acad.*, 1952, **28**, 483; S. Seto, *Sci. Repts, Tohoku Univ.*, 1953, I, **37**, 367.
11. A. Stein, H. P. Gregor, and P. E. Spoerri, *J. Am. Chem. Soc.*, 1956, **78**, 6185; A. K. Macbeth, T. H. Nuhan, and D. Trail, *J. Chem. Soc.*, 1926, 1248.
12. M. Nitta and Y. Tajima, *J. Chem. Res. (S)*, 1999, 372; N. Abe, H. Matsuda, and Y. Sugihara, *J.*

Heterocycl. Chem., 1996, **33**, 1323.

13. Elemental analyses and mass spectral data are satisfactory for new compounds (**7a-c**) and mixtures of compounds (**8a-c**), (**9a-c**), and (**10a-c**)..