HETEROCYCLES, Vol. 54, No. 2, pp.601-606, Received, 17th July, 2000

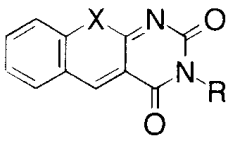
STUDIES ON PYRIMIDINE-ANNULATED HETEROCYCLES: SYNTHESIS AND FUNCTION OF NOVEL 9-SUBSTITUTED CYCLOHEPTA[b]PYRIMIDO[5,4-d]FURAN-8,10(9H)-DIONES[1]

Tohru Takayasu,[a] Yutaka Mizuta,[b] and Makoto Nitta*[b]

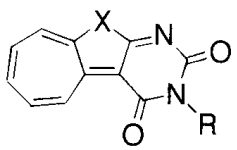
[a]Department of Chemistry, Faculty of Education, Fukushima University, Kanayagawa, Fukushima, 960-1296 Japan; [b]Department of Chemistry, School of Science and Engineering, Materials Research Laboratory for Bioscience and Photonics, Waseda University, Shinjuku-ku, Tokyo 169-8555, Japan

Abstract-A new short synthesis of 9-substituted cyclohepta[*b*]pyrimido[5,4-*d*]furan-8,10(9*H*)-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 CF_3CO_2H. 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(9*H*)-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



1: X=NR
2: X=O



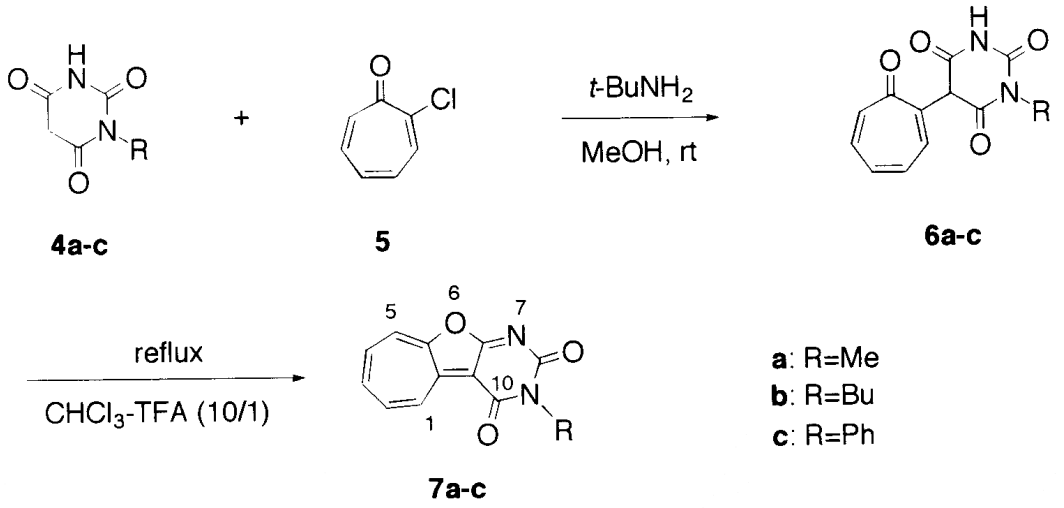
3: X=NR and NAr
R=Me

7a-c: X=O
a: R=Me
b: R=Bu
c: R=Ph

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*-$BuNH_2$ (25 mmol) at room temperature for 24 h. After evaporation of the MeOH and excess *t*-$BuNH_2$, the resulting residue was filtered and washed with Et_2O to give 5-(tropon-2-yl)barbituric acids (**7a-c**) as yellow crystals, which exhibited satisfactory ^1H NMR spectra and were contaminated with *t*-$BuNH_3Cl$. Since the compounds (**6a-c**) are very polar and sparingly



4a-c **5** **6a-c** **7a-c**

Scheme 1

soluble in the usual solvents and removal of *t*-$BuNH_3Cl$ seemed to be difficult, the crystals (**6a-c**) were subsequently treated with $CHCl_3$-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 ^{1}H 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); ^{1}H 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); ^{1}H 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.

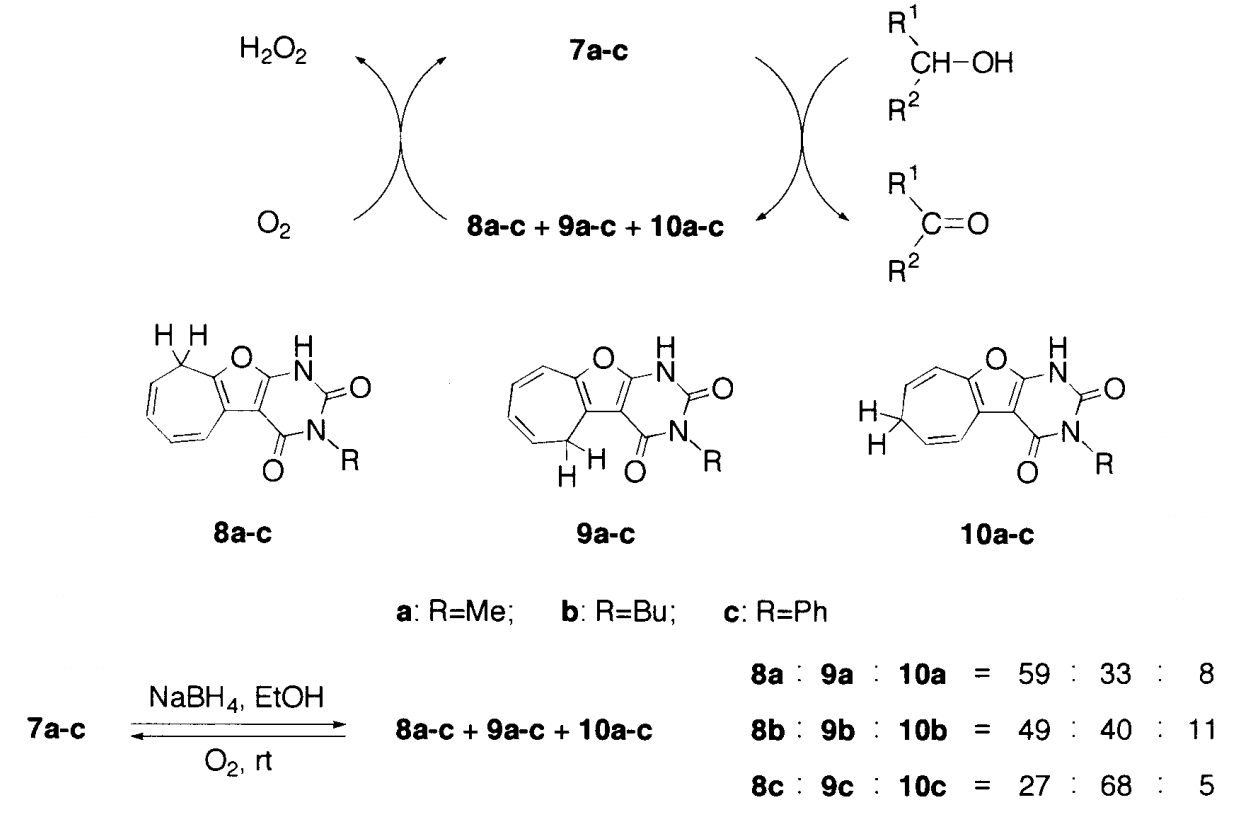
7c: yellow powder; mp 272-274 °C (AcOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J*=9.0, Ph), 7.43 (1H, t, *J*=9.0, Ph), 7.51 (2H, t, *J*=9.0, Ph), 7.72 (1H, dd, *J*=10.0, 9.3, H-3), 7.83 (1H, dd, *J*=10.0, 9.6, H-4), 7.95 (1H, dd, *J*=10.5, 9.3, H-2), 8.04 (1H, d, *J*=9.6, H-5), 8.85 (1H, d, *J*=10.5, 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	$PhCH_2OH$	120[c]	PhCHO	367
7a	PhCHMeOH	40	PhCOMe	280
7a	Cyclohexanol	40	Cyclohexanone	220
7b	$PhCH_2OH$	120[c]	PhCHO	313
7b	PhCHMeOH	48	PhCOMe	515
7c	$PhCH_2OH$	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 $NaBH_4$ 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

Financial support from a Waseda University Grant for a Special Research Project is gratefully acknowledged. The authors also thank Materials Characterization Central Laboratory, Waseda University, for technical assistance with spectral data and elemental analyses.

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**)..