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

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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

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
cyclohepta[b]pyrimido[5,4-d]pyrrole-8,10(6H,9H)-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\(_2\)O to give 5-(tropon-2-yl)barbituric acids (7a-c) as yellow crystals, which exhibited satisfactory \(^1\)H NMR spectra and were contaminated with \(t\)-BuNH\(_3\)Cl. Since the compounds (6a-c) are very polar and sparingly soluble in the usual solvents and removal of \(t\)-BuNH\(_3\)Cl 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(9H)-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).

<table>
<thead>
<tr>
<th>Table 1. Selected physical data of new compounds (7a-c)</th>
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<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
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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

<table>
<thead>
<tr>
<th>Compd</th>
<th>Alcohol</th>
<th>Reaction Time / h</th>
<th>Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; %</th>
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</thead>
<tbody>
<tr>
<td>7a</td>
<td>PhCH₂OH</td>
<td>120&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PhCHO</td>
<td>367</td>
</tr>
<tr>
<td>7a</td>
<td>PhCHMeOH</td>
<td>40</td>
<td>PhCOMe</td>
<td>280</td>
</tr>
<tr>
<td>7a</td>
<td>Cyclohexanol</td>
<td>40</td>
<td>Cyclohexanone</td>
<td>220</td>
</tr>
<tr>
<td>7b</td>
<td>PhCH₂OH</td>
<td>120&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PhCHO</td>
<td>313</td>
</tr>
<tr>
<td>7b</td>
<td>PhCHMeOH</td>
<td>48</td>
<td>PhCOMe</td>
<td>515</td>
</tr>
<tr>
<td>7c</td>
<td>PhCH₂OH</td>
<td>120&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PhCHO</td>
<td>395</td>
</tr>
<tr>
<td>7c</td>
<td>PhCHMeOH</td>
<td>48</td>
<td>PhCOMe</td>
<td>403</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated as 2,4-dinitrophenylhydrazone.  
<sup>b</sup> Based on compounds (7a-c).  
<sup>c</sup> Compounds (7a-c) disappeared.

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

![Scheme 2](image-url)
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.
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).