A ONE-STEP SYNTHESIS OF PYRIMIDO[4',5'-c]ISOQUINOLINE RING SYSTEM BY
REACTION OF 6-(N-METHYLFFURFURYLAMINO)URACILS WITH DMAD¹

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Abstract—Several pyrimido[4,5-c]isoquinoline derivatives were obtained
from the reaction of 6-(N-methylfurfurylamino)uracils 1 and DMAD in
refluxing ethanol. The formation of the pyrimidoisoquinoline system was
due to a sequence of the initial Diels-Alder reaction of the furan moiety of
1 and DMAD, and the successive intramolecular Michael addition.

Synthesis of the derivatives containing a pyrido[2,3-d]pyrimidine ring system and their
potentialities for antitumor² and antibacterial agents³ have attracted our attention, because this
ring system is widely found in biologically active compounds.⁴

Previously, we reported a facile synthetic approach to pyrazolopyridopyrimidine derivatives by an
intramolecular 1,3-dipolar addition reaction of pyrimidine system¹ In the course of our
synthetic study of pyrido[2,3-d]pyrimidines, which is made of a pyridine ring construction onto
pyrimidine system, we wish to communicate here the reaction of 6-(N-methylfurfurylamino)uracils
1 with dimethyl acetylenedicarboxylate (DMAD) giving pyrimido[4,5-c]isoquinoline derivatives.
Thus, the Diels-Alder reaction between a furan moiety of 1 and DMAD took place to afford an
oxanorbornadiene system, and the successive Michael addition of enamine part onto the
oxanorbornadiene system resulted in a pyrimido[4,5-c]isoquinoline system formation.

When 1,3-dimethyl derivative 1a was allowed to react with DMAD (1.1 mol equiv.) in refluxing
ethanol for 2 days, two isomeric 1:1 adducts 2a and 3a were obtained in both 19% yields together
with the starting materials. From their analytical⁵ and spectral data⁶, the structures of 2a and
3a were deduced to be 5,6,6a,9,10,10a-hexahydro-6a,9-epoxy-2,4-dimethyl-10,10a-bis(methoxy-
carbonyl)pyrimido[4,5-c]isoquinolone-1,3(2H,4H)-dione.

Although their configurations of the 10a-position were obscure, the two were corresponding to the
stereoisomers about the 10-position, which were assigned on the basis of the values of the
coupling constant between 9- and 10-H.
Table 1. Reaction of 1a with DMAD in Several Solvents

<table>
<thead>
<tr>
<th>Solvents</th>
<th>1a/DMAD</th>
<th>2a</th>
<th>3a</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Recovered 1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanol</td>
<td>1/1</td>
<td>19</td>
<td>19</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>48</td>
</tr>
<tr>
<td>1-pentanol</td>
<td>1/1</td>
<td>17</td>
<td>13</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>59</td>
</tr>
<tr>
<td>acetonitrile</td>
<td>1/1</td>
<td>4</td>
<td>--</td>
<td>14</td>
<td>10</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>dioxane</td>
<td>1/1</td>
<td>4</td>
<td>--</td>
<td>14</td>
<td>21</td>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td>dioxane</td>
<td>1/2</td>
<td>4</td>
<td>--</td>
<td>9</td>
<td>35</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>toluene</td>
<td>1/1</td>
<td>2</td>
<td>--</td>
<td>11</td>
<td>44</td>
<td>--</td>
<td>26</td>
</tr>
</tbody>
</table>

It turned out that the reaction of 1a with DMAD was sensitive to the solvents employed. The reaction proceeded in a more complicated manner in other solvents than alcohols: heating of 1a and DMAD in acetonitrile or dioxane afforded the Diels-Alder adduct 47, 1:2 adduct 58, and 5-(2-propioyloxy)uracil derivative 69 together with 2a as a minor product (Table 1).

In an attempt to obtain a better understanding for the pathway and solvent dependency of the reaction, the chemical conversions of 4 were investigated. The results revealed that 4 was a key intermediate in this reaction. Heating of 4 in ethanol gave a mixture (molar ratio: 12/1) of 2a and 1a10, in which the Michael addition of the C-5 of 4 onto the electron-deficient ene moiety in the oxanorbornadiene system and the retro Diels-Alder reaction took place, respectively. On the contrary, the heating in dioxane gave only 1a together with the unreacted 4. The pathway leading to 5 was also investigated. Treatment of 2a with DMAD in refluxing dioxane or ethanol gave a complex mixture of products, including another type of 1:2 adduct of 1a and DMAD.
other hand, the reaction of 4 with DMAD in refluxing dioxane afforded 5 in 83% yield, whereas the reaction in refluxing ethanol gave 2a predominantly (Scheme 1).

As evident from these findings, the formation of pyrimido[4,5-g]isoquinolines from 1a and DMAD was ascribed to be a sequence of two reactions, the Diels-Alder and Michael addition reactions. The reaction proceeded efficiently in protic solvents such as ethanol. Therefore, we next performed Scheme 2.
the reaction of 3-methyl-(lb) and 3-phenyluracil derivative (lc) with DMAD in ethanol to afford the expected 2'' and 3'1 in high total yields (Scheme 2).

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REFERENCES AND NOTES


5. All new compounds in this communication gave satisfactory analytical values.

6. 2a: mp 173-174 °C; ir(KBr): 1720, 1700, 1680 cm⁻¹ (CO); ¹H nmr(CDCl₃) δ: 2.98(s, 3H, N-CH₃), 3.32(d, 1H, 10-H, J=4 Hz), 3.35, 3.42(2s, 3H each, N-CH₃), 3.60, 3.77(2s, 3H each, OCH₃), 3.49, 3.96(2d, 1H each, 6-H, J=15 Hz), 5.08(dd, 1H, 9-H, J=4, 2 Hz), 6.18(1H, d, 7-H, J=6 Hz), 6.96(dd, 1H, 8-H, J=6, 2 Hz); ¹³C nmr(CDCl₃) δ: 28.1, 34.5, 43.6(N-CH₃), 49.9 (6-C), 52.2, 52.7(OCH₃), 56.6(10-C), 58.1(10a-C), 80.6(9-C), 89.6(8a-C), 99.4(10b-C), 132.2, 140.8(7- and 8-C), 152.8, 154.6, 162.3, 171.2, 171.4(C=O and 4a-C); ms m/z: 391(M⁺).

3a: mp 174-176 °C; ir(KBr): 1720, 1700, 1680 cm⁻¹ (CO); ¹H nmr(CDCl₃) δ: 3.00, 3.20, 3.41(3s, 3H each, N-CH₃), 3.52, 3.60(2s, 3H each, OCH₃), 3.90(br s, 1H, 10-H), 3.80, 3.96(2d, 1H each, 6-H, J=15 Hz), 5.00(br s, 1H, 9-H), 6.10(d, 1H, 7-H, J=6 Hz), 6.60(br d, 1H, 8-H, J=6 Hz); ms m/z: 391(M⁺).

7. 4: mp 162-164 °C; ir(KBr): 1710, 1700, 1630 cm⁻¹ (CO); ¹H nmr(CDCl₃) δ: 2.78, 3.34, 3.38(3s, 3H each, N-CH₃), 3.77, 3.80(2s, 3H each, OCH₃), 3.70, 3.92(2d, 1H each, -CH₂-, J=15 Hz), 5.33(s, 1H, 5-H), 5.71(d, 1H, 4'-H, J=2 Hz), 7.00(d, 1H, 2'-H, J=6 Hz), 7.23(dd, 1H, 3'-H, J=2, 6 Hz); ¹³C nmr(CDCl₃) δ: 27.9, 32.8, 42.5(N-CH₃), 51.6(-CH₂-), 52.3, 52.4(OCH₃), 84.3 (4'-C), 89.3(1'-C), 97.6(5-C), 143.5, 144.9(2'- and 3'-C), 153.0, 153.2(5'- and 6'-C), 160.5, 162.8, 163.0, 163.2, 164.1(C=O and 4a-C); ms m/z: 391(M⁺).
8. 5: mp 248-250 °C; ir(KBr): 1740, 1660 cm⁻¹ (CO); ¹H nmr(CF₃COOD) δ: 3.28, 3.34(2s, 9H total), \(>\text{N-CH₃}\), 3.50(d, 1H, 7-H, J=4 Hz), 3.72, 3.78, 3.84(3s, 12H total, OCH₃), 3.90, 4.42(2d, 1H each, 11-H, J=4 Hz), 5.27(dd, 1H, 8-H, J=4, 2 Hz), 6.18(d, 1H, 10-H, J=6 Hz), 7.09(dd, 1H, 9-H, J=2, 6 Hz); ¹³C nmr(CF₃COOD) δ: 30.6, 41.5, 43.8(N-CH₃), 49.8(11-C), 55.2, 55.8, 56.0, 56.2(OCH₃), 60.6(7-C), 77.3(6a-C), 82.0(8-C), 88.0(10a-C), 91.9(4a-C), 106.4(6-C), 144.2, 147.2(9- and 10-C), 159.5(5-C), 160.7(12a-C), 166.1, 167.2, 168.4, 168.8, 170.6, 172.7(C=O).

9. 6: mp 203-204 °C; ir(KBr): 1740, 1720, 1670 cm⁻¹ (CO); ¹H nmr(CDC13) δ: 3.25, 3.28, 3.37(3s, 3H each, \(>\text{N-CH₃}\), 3.97(s, 3H, OCH₃), 5.10(s, 1H, -CH₂-), 6.4, 7.4(m, 3H total, furan ring protons); ms m/z: 359(M⁺).

A formation of products similar to 6 was reported in the reaction of 6-aminouracils with DMAD.¹³

10. The accurate pathway leading to 3a is not attained so far. However, we suppose that the conversion of 4 to 2a or 3a would be highly dependent upon the conditions.

11. 2b: mp 204-205 °C; ir(KBr): 3200(NH), 1730, 1700, 1640 cm⁻¹ (CO); ¹H nmr(CDCl₃) δ: 3.15, 3.24(2s, 3H each, \(>\text{N-CH₃}\), 3.57, 3.73(2s, 3H each, OCH₃), 3.80(d, 1H, 10-H, J=4.5 Hz), 3.59, 4.18(2d, 1H each, 6-H, J=14 Hz), 5.05(dd, 1H, 9-H, J=4.5, 1.5 Hz), 6.04(d, 1H, 7-H, J=6 Hz), 6.65(dd, 1H, 8-H, J=6, 1.5 Hz), 9.7(br s, 1H, >NH).

Product 2c was not isolated as a pure form. However, the structure was confirmed by ¹H nmr spectrum in CDCl₃ δ: 1.96(s, 3H, \(>\text{N-CH₃}\), 3.62, 3.67(2s, 3H each, OCH₃), 3.63, 4.06(2d, 1H each, 6-H, J=14 Hz), 3.82(d, 1H, 10-H, J=4 Hz), 5.06(dd, 1H, 9-H, J=4, 1.5 Hz), 6.36(d, 1H, 7-H, J=6 Hz), 6.77(dd, 1H, 8-H, J=6, 1.5 Hz), 7.0-7.6(m, 5H, phenyl), 10.2(br, 1H, >NH).

12. 3b: mp 215-217 °C; ir(KBr): 3250-2950(NH), 1760, 1720, 1640 cm⁻¹ (CO); ¹H nmr(CDCl₃) δ: 2.97(s, 3H, \(>\text{N-CH₃}\), 3.54, 3.62(2s, 3H each, OCH₃), 3.51, 4.17(2d, 1H each, 6-H, J=14 Hz), 3.79(s, 1H, 10-H), 3.60, 4.19(2d, 1H each, 6-H, J=14 Hz), 4.94(d, 1H, 9-H, J=1.5 Hz), 6.18(d, 1H, 7-H, J=6 Hz), 6.78(dd, 1H, 8-H, J=6, 1.5 Hz), 10.3(br, 1H, >NH).

3c: mp 243-245 °C(dec.); ir(KBr): 3200-3000(NH), 1730, 1700, 1640 cm⁻¹ (CO); ¹H nmr(CDCl₃) δ: 2.97(s, 3H, \(>\text{N-CH₃}\), 3.54, 3.62(2s, 3H each, OCH₃), 3.51, 4.17(2d, 1H each, 6-H, J=14 Hz), 3.79(s, 1H, 10-H), 4.95(d, 1H, 9-H, J=1.5 Hz), 6.02(dd, 1H, 8-H, J=6, 1.5 Hz), 7.0-7.5(m, 5H, phenyl), 10.3(br, 1H, >NH).


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