A ONE-STEP SYNTHESIS OF PYRIMIDO[4,5-c]ISOQUINOLINE RING SYSTEM BY REACTION OF 6-(N-METHYLFURFURYLAMINO)URACILS WITH DMAD[1]

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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 antitumor[2] and antibacterial agents[3] have attracted our attention, because this ring system is widely found in biologically active compounds.[4]

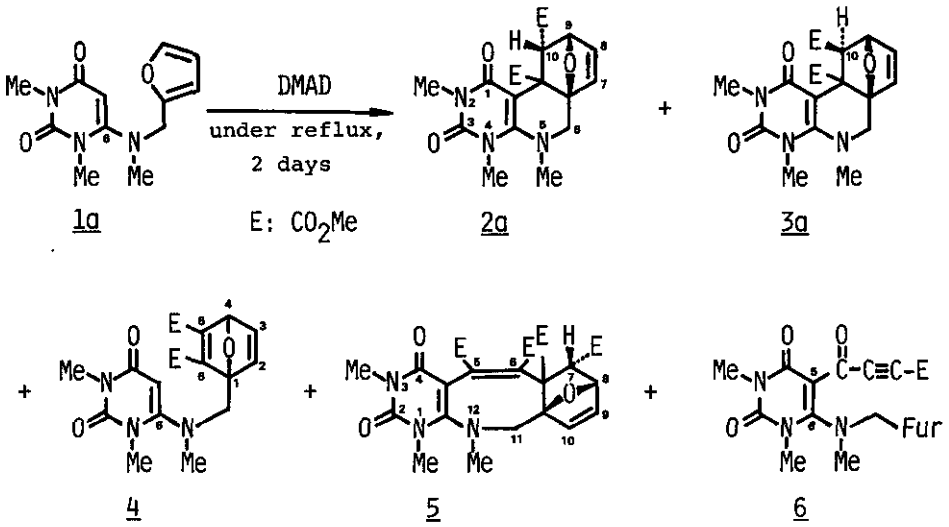
Previously, we reported a facile synthetic approarch to pyrazolopyridopyrimidine derivatives by an intramolecular 1,3-dipolar addition reaction of pyrimidine system.[1] In the course of our synthetic study of pyrido[2,3-d]pyrimidines, which is made of a pyridine ring construction onto pyrimidine system, 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 analytical[5] and spectral data[6], 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(methoxycarbonyl)pyrimido[4,5-c]isoquinoline-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



1a 2a 3a

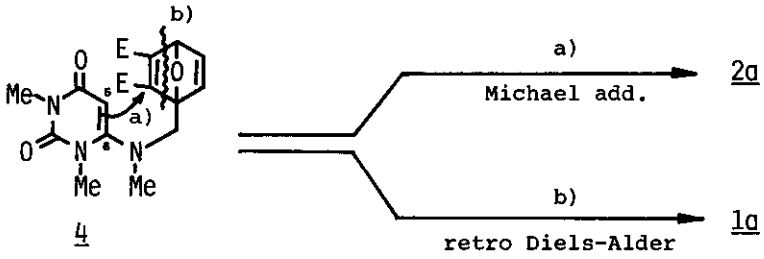
4 5 6

Solvents	1a/DMAD	Yields (%) 2a	3a	4	5	6	Recovered 1a
ethanol	1/1	19	19	—	—	—	48
1-pentanol	1/1	17	13	—	—	—	59
acetonitrile	1/1	4	—	14	10	8	20
dioxane	1/1	4	—	14	21	8	37
dioxane	1/2	4	—	9	35	14	21
toluene	1/1	2	—	11	44	—	26

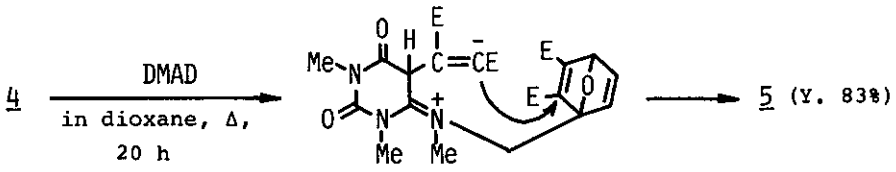
It turned out that the reaction of **1a** with DMAD was sensitive to the solvents employed. The reaction proceeded in a more complicated manner in other solvents than alcohols: heating of **1a** and DMAD in acetonitrile or dioxane afforded the Diels-Alder adduct **4**[7], 1:2 adduct **5**[8], and 5-(2-propioloyl)uracil derivative **6**[9] 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 **1a**[10], in which the Michael addition of the C-5 of **4** onto the electron-deficient ene moiety in the oxanorbonadiene 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 adductof **1a** and DMAD. On the

Scheme 1



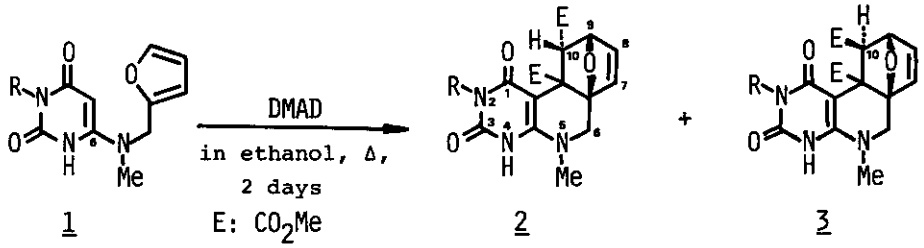
Reaction Conditions	Molar Ratio 2a	1a	4
ethanol, reflux, 20 h	12	1	—
dioxane, reflux, 20 h	trace	5	7



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-c]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



	R	Product/Yield (%)	
b)	Me	**2b** (34)	**3b** (54)
c)	Ph	**2c** (27)	**3c** (42)

the reaction of 3-methyl- (**1b**) and 3-phenyluracil derivative (**1c**) with DMAD in ethanol to afford the expected **2**[11] and **3**[12] in high total yields (Scheme 2).

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2. G. L. Anderson, J. L. Shim, and A. D. Broom, J. Org. Chem., 1976, **41**, 1095; E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch, and C. A. Nichol, J. Med. Chem., 1980, **23**, 327
3. J. Matsumoto and S. Minami, J. Med. Chem., 1975, **18**, 74; N. Suzuki, Chem. Pharm. Bull., 1980, **28**, 761.
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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); ^{1}H nmr($CDCl_3$) δ: 2.98(s, 3H, $\rangle N-CH_3$), 3.32(d, 1H, 10-H, J=4 Hz), 3.35, 3.42(2s, 3H each, $\rangle N-CH_3$), 3.60, 3.77(2s, 3H each, OCH_3), 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); ^{13}C nmr($CDCl_3$) δ: 28.1, 34.8, 43.6($N-CH_3$), 49.9 (6-C), 52.2, 52.7(OCH_3), 56.6(10-C), 58.1(10a-C), 80.6(9-C), 89.0(6a-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): 1760, 1730, 1650 cm^{-1} (CO); ^{1}H nmr($CDCl_3$) δ: 3.00, 3.20, 3.41(3s, 3H each, $\rangle N-CH_3$), 3.52, 3.60(2s, 3H each, OCH_3), 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, 1680, 1630 cm^{-1} (CO); ^{1}H nmr($CDCl_3$) δ: 2.78, 3.34, 3.38(3s, 3H each, $\rangle N-CH_3$), 3.77, 3.80(2s, 3H each, OCH_3), 3.70, 3.92(2d, 1H each, $-CH_2-$, 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); ^{13}C nmr($CDCl_3$) δ: 27.9, 32.8, 42.5($N-CH_3$), 51.6($-CH_2-$), 52.3, 52.4(OCH_3), 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(CF_3COOD)δ : 3.28, 3.34(2s, 9H total), >N-CH_3), 3.50(d, 1H, 7-H, J=4 Hz), 3.72, 3.78, 3.84(3s, 12H total, OCH_3), 3.90, 4.42(2d, 1H each, 11-H, J=14 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); ^{13}C nmr(CF_3COOD) δ: 30.6, 41.5, 43.8(N-CH_3), 49.8(11-C), 55.2, 55.8, 56.0, 56.2(OCH_3), 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($CDCl_3$) δ: 3.25, 3.28, 3.37(3s, 3H each, >N-CH_3), 3.97(s, 3H, OCH_3), 5.10(s, 2H, -CH_2-), 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($CDCl_3$) δ: 3.15, 3.24(2s, 3H each, >N-CH_3), 3.57, 3.73(2s, 3H each, OCH_3), 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 $CDCl_3$; δ: 1.96(s, 3H, >N-CH_3), 3.62, 3.67(2s, 3H each, OCH_3), 3.63, 4.06(2d, 1H each, 6-H, J=14 Hz), 3.82(d, 1H, 10-H, J=4 Hz), 5.06(br 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($CDCl_3$) δ : 2.97 (s, 3H, >N-CH_3), 3.54, 3.62(2s, 3H each, OCH_3), 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($CDCl_3$) δ : 2.97(s, 3H, >N-CH_3), 3.54, 3.62(2s, 3H each, OCH_3), 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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