Regioselective Synthesis of 6-Alkylated Lumazine Derivatives

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The regiospecific synthesis of alkylated lumazines is achieved by hetero Diels-Alder addition between an oxadiazinone **2** and enamine. The reactions proceed stepwise by cycloaddition, decarboxylation and deamination to produce the 6-alkylated lumazines.

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Most pteridines are synthesized by the Gabriel-Isay reaction [1] which consists of the condensation of 5,6-diaminopyrimidines with α-dicarbonyl compounds. The regioselectivity during this condensation of the pyrimidines and unsymmetrical α-dicarbonyl compounds is not high and both 6- and 7-substituted pteridines are obtained. Many natural products containing a pteridine ring have an alkyl side chain at the 6-position [2], and the regioselective synthesis of substituted pteridines is in demand. In this paper, we report a convenient method for the syntheses of 6-alkylated lumazines.

A reversed electron-demanding Diels-Alder reaction is a facile one in many cases [3], and we were interested in the pyrazine formation using a hetero Diels-Alder reaction with an enamine as the electron-rich dienophile and oxadiazinone as the diene counterpart [4].

Guarneri *et al.* reported the hetero Diels-Alder reaction of this type between oxadiazinones and the enolate from 1,3-dicarbonyl compounds [5]. We expected that similar types of cycloadditions between oxadiazinone and enamines derived from aldehydes would give 6-alkylated lumazines.

The enamines were prepared from pyrrolidine and aldehydes as reported by Mannich and Davidsen [6]. An oxadiazinone, 3,6,8-trioxo-5,7-dimethyl-5,6,7,8-tetrahydro-3*H*-pyrimido[5,4-*c*][1,2,5]oxadiazine (**2**), was synthesized according to the reported method with minor modification, using bis(trichloromethyl)carbonate instead of phosgene [7a] or trichloromethyl chlorocarbonate [7b] (Scheme I).

A 1:2 mixture of oxadiazinone **2** and an enamine, **3a-h** in tetrahydrofuran was stirred under nitrogen. The reaction conditions and the yields are shown in Table 1.

All the reactions gave a single product, **4a-h**. Structures of the products were determined by ^{1}H-nmr, ^{13}C-nmr, mass spectra, and elemental analyses. Particularly, the position of the alkyl substituent in the products **4a-h** was determined by evaluating the ^{13}C-nmr spectra shown in Table 2, and by comparison of the data with those of 1,3-dimethyllumazine (**4i**, R = H) [8]. The ^{13}C-nmr signal of C-6 moves to a lower field and weakens the intensity due to alkylation at the C-6 position, whereas the signal of C-7 remains essentially unchanged [8].

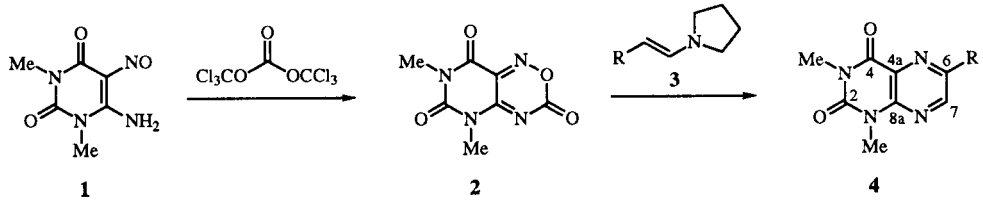
The reactions are considered to proceed *via* the mech-

Table 1
Reaction of Oxadiazinone **2** with Enamines **3a-h**

Entry	R	Method	Product	Yield (%)
1	Me	A[a]	**4a**	34
2	Me	B[b]	**4a**	35
3	Et	A[a]	**4b**	63
4	Et	B[b]	**4b**	64
5	*n*-Pr	A[a]	**4c**	22
6	*n*-Pr	B[b]	**4c**	16
7	*i*-Pr	A[a]	**4d**	42
8	*i*-Pr	B[b]	**4d**	27
9	*c*-Hex	A[a]	**4e**	22
10	*c*-Hex	B[b]	**4e**	44
11	*t*-Bu	A[a]	**4f**	50
12	*t*-Bu	B[b]	**4f**	70
13	Ph	A[a]	**4g**	79
14	Ph	B[b]	**4g**	72
15	Bn	A[a]	**4h**	31
16	Bn	B[b]	**4h**	42

[a] Method A: Oxadiazinone **2** and enamine **3** were mixed in tetrahydrofuran at -78°, then the solution was warmed to room temperature over a period of 12 hours under stirring. [b] Method B: The solution was refluxed for 3 hours after the reaction by method A.

Scheme I

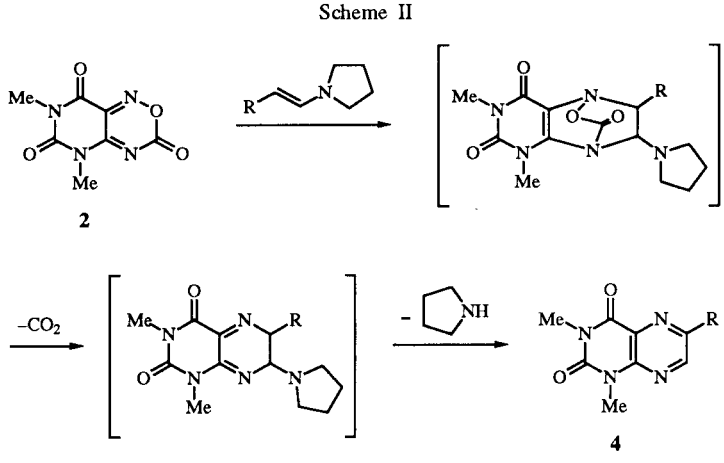


1 2 4

Table 2
^{13}C-NMR Chemical Shifts of Reaction Products

Compound	C-6	C-7	C-2	C-4	C-4a	C-8a	N-Me	R
4a	149.9	147.6	160.3	150.6	126.5	146.3	29.0, 29.3	21.0
4b	154.8	146.9	160.3	150.6	126.6	146.4	29.0, 29.3	13.9, 28.2
4c	153.7	147.3	160.3	150.6	126.8	146.5	29.0, 29.3	13.7, 23.1, 36.8
4d	158.4	145.8	160.3	150.5	127.9	146.5	29.0, 29.3	22.2, 33.9
4e	157.6	146.1	160.3	150.7	126.5	146.5	29.0, 29.3	25.6, 26.2, 32.5, 43.7
4f	160.2	144.5	160.1	150.7	125.9	146.0	28.8, 29.1	29.8, 36.5
4g	148.6	144.9	160.3	150.6	126.7	146.8	29.1, 29.5	126.9, 129.1 130.1, 134.9
4h	152.4	147.9	160.2	150.6	126.3	146.5	29.0, 29.3	41.4, 127.0, 128.9, 129.0, 137.6
4i	140.1	147.5	160.0	150.5	127.9	148.2	29.0, 29.3	

Scheme II



anism shown in Scheme II. However, no intermediates were obtained and the yields were not much improved by heating the reaction mixture (method B, see Table 1). The highest yield was obtained in the reaction with enamine **3g** (R = Ph) using method A rather than method B.

The present reactions are explained by the hetero Diels-Alder reaction (Scheme II) of reverse electron demand which was proposed by Ganesan and Heathcock [4]. Thus, the oxadiazinone **2** regioselectively adds to the enamine which is an electron rich alkene. The loss of carbon dioxide followed by the aromatization due to deamination produces **4**. Overall, this type of cycloaddition has analogies in the Diels-Alder reaction of pyrones with enamines [9].

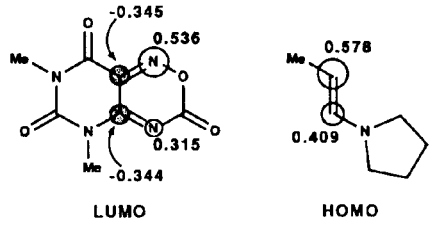


Figure 1. Frontier orbitals of oxadiazinone **2** and enamine **3a**.

The MNDO calculation [10] (MOPAC [11]) supported the observed regiospecificity (Figure 1). Frontier orbitals, the HOMO of the enamine **3a** and the LUMO of the oxadiazinone **2** predict the preferred interaction between the reaction centers of both components in the observed regiospecificity.

In conclusion, the present reaction provides a convenient route for the preparation of 6-alkylated lumazine derivatives.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Hitachi R-90 (90 MHz), JEOL EX-270 (270 MHz) and JEOL GSX-400 (400 MHz) spectrometers in deuteriochloroform. The ^{13}C-nmr spectra were recorded on a JEOL EX-270 (68 MHz) and JEOL GSX-400 (100 MHz) spectrometers in deuteriochloroform. Chemical shifts were given in δ (ppm) relative to the internal tetramethylsilane standard and coupling constants were recorded in Hz. The ir spectra were measured by a Perkin-Elmer 1640 FT-IR spectrophotometer. Mass spectra were measured using a Shimadzu GCMS QP-1000 spectrometer. Melting points were recorded on a Yamato apparatus model MP-21 and are uncorrected. Elemental analyses were performed at the Materials Characterization Central Laboratory in Waseda University.

Preparation of 3,6,8-Trioxo-5,7-dimethyl-5,6,7,8-tetrahydro-3*H*-pyrimido[5,4-*c*][1,2,5]oxadiazine (**2**).

The mixture of 1,3-dimethyl-4-amino-5-nitrosouracil (**1**) [12] (3.68 g, 20 mmoles) and bis(trichloromethyl)carbonate (6.51 g, 22 mmoles) in anhydrous tetrahydrofuran (100 ml) was stirred at room temperature for 12 hours. The solution was evaporated *in vacuo* and the residue was washed with water and methanol to give 3.78 g (90%) of **2**. Compound **2** melted at 216.0-217.0° (lit [7b] 218-220°); ^{1}H-nmr (90 MHz): δ 3.50 (3H, s), 3.62 (3H, s); ms: (20 eV) m/s (relative intensity) = 210 (M^+, 38%), 153 (29%), 83 (100%).

General Procedure for the Preparation of Enamines **3a-h**.

The mixture of one of the aldehydes (40 mmoles), pyrrolidine (80 mmoles) and potassium carbonate (5.5 g, 40 mmoles) was stirred at 0°, then warmed to room temperature over a period of 12 hours. The reaction mixture was then centrifuged to remove the solid residue and the supernatant was distilled under reduced pressure to obtain the enamine in 30-70% yield.

1-(1-Propenyl)pyrrolidine (**3a**) [13], 1-(1-butenyl)pyrrolidine (**3b**) [14], 1-(3-methyl-1-butenyl)pyrrolidine (**3d**) [15], 1-styrylpyrrolidine (**3g**) [16] and 1-(3-phenyl-1-propenyl)pyrrolidine (**3h**) [17] were identified by comparison of the boiling points and spectral data. Unknown enamines, **3c**, **3e**, and **3f**, were characterized using the following ^{1}H-nmr and ir spectra.

1-(1-Hexenyl)pyrrolidine (**3c**) was distilled at 72°/22 mm Hg; ^{1}H-nmr (90 MHz): δ 0.89 (3H, t, J = 7.3), 1.05-2.16 (8H, m), 2.42-3.27 (4H, m), 4.13 (1H, td, J = 6.7, 13.5), 6.17 (1H, d, J = 13.5); ir (neat): 2961, 2915, 2870, 2815, 1655 cm^{-1}.

1-(2-cyclohexyl-1-ethenyl)pyrrolidine (**3e**) was distilled at 142°/24 mm Hg; ^{1}H-nmr (90 MHz): δ 0.85-2.03 (15H, m), 2.69-3.10 (4H, m), 4.12 (1H, dd, J = 6.7, 13.6), 6.11 (1H, d, J = 13.6); ir (neat): 2965, 2883, 1650 cm^{-1}.

1-(3,3-Dimethyl-1-buthenyl)pyrrolidine (**3f**) was distilled at 90°/26 mm Hg; ^{1}H-nmr (90 MHz): δ 0.99 (9H, s), 1.55-2.04 (4H, m), 2.68-3.10 (4H, m), 4.17 (1H, d, J = 13.5), 6.05 (1H, d, J = 13.5); ir (neat): 2955, 2905, 2870, 2815, 1650 cm^{-1}.

Reaction of **2** with Enamines **3a-h**.

(1) Method A.

Oxadiazinone **2** (63 mg, 0.3 mmole) in 1.5 ml of anhydrous tetrahydrofuran and one of the enamines (0.6 mmole) in 0.5 ml of anhydrous tetrahydrofuran were mixed at -78°. The solution was then warmed to room temperature over a period of 12 hours with stirring.

(2) Method B.

The reaction mixture was refluxed for 3 hours after treatment of the reaction mixture using method A.

The reaction mixture was concentrated, except for the case of the reaction of enamine **3g** and the product was isolated by preparative tlc on a silica gel plate (20 x 20 cm, 2 mm thickness) using chloroform-ethyl acetate (1:1) and then recrystallized from ethanol or benzene/hexane. In case of the enamine **3g**, the reaction mixture was filtered to collect the residual powder which was washed with ethanol and recrystallized from benzene.

Compound **4a** was recrystallized from ethanol and melted at 197.0-198.5° (lit [18] 201-203°); ^{1}H-nmr (90 MHz): δ 2.70 (3H, s), 3.54 (3H, s), 3.70 (3H, s), 8.51 (1H, s); ^{13}C-nmr (100 MHz): δ 21.0, 29.0, 29.3, 126.5, 146.3, 147.6, 149.9, 150.6, 160.3.

Compound **4b** was recrystallized from ethanol and melted at 141.0-143.0° (lit [19] 139-141°); ^{1}H-nmr (90 MHz): δ 1.37 (3H, t, J = 7.5), 3.00 (2H, q, J = 7.5), 3.54 (3H, s), 3.70 (3H, s), 8.52 (1H, s); ^{13}C-nmr (100 MHz): δ 13.9, 28.2, 29.0, 29.3, 126.6, 146.4, 146.9, 150.6, 154.8, 160.3.

Compound **4c** was recrystallized from ethanol and melted at 113.5-114.0°; ^{1}H-nmr (270 MHz): δ 1.00 (3H, t, J = 7.3), 1.81 (2H, six, J = 7.3), 2.94 (2H, q, J = 7.3), 3.55 (3H, s), 3.71 (3H, s), 8.51 (1H, s); ^{13}C-nmr (68 MHz): δ 13.7, 23.1, 29.0, 29.3, 36.8, 126.5, 146.5, 147.3, 150.6, 153.7, 160.3; ir (chloroform): 2964, 2934, 2875, 1720, 1672, 1548, 1497 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 234 (M^+, 19%), 206 (100%).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.36; H, 5.88; N, 23.72.

Compound **4d** was recrystallized from ethanol and melted at 119.0-119.3°; ^{1}H-nmr (400 MHz): δ 1.40 (6H, d, J = 7.0), 3.32 (1H, sept, J = 7.0), 3.54 (3H, s), 3.71 (3H, s), 8.57 (1H, s); ^{13}C-nmr (68 MHz): δ 22.2, 29.0, 29.3, 33.9, 127.9, 145.8, 146.5, 150.5, 158.4, 160.3; ir (chloroform): 2969, 2874, 1720, 1671, 1548, 1498 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 234 (M^+, 37%), 219 (100%).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.31; H, 5.98; N, 24.00.

Compound **4e** was recrystallized from ethanol and melted at 157.5-158.2°; ^{1}H-nmr (400 MHz): δ 1.31 (1H, qt, J = 12.5, 3.3), 1.44 (2H, qt, J = 12.5, 3.3), 1.62 (2H, qt, J = 12.5, 3.3), 1.74-1.82 (1H, m), 1.85-1.93 (2H, m), 1.93-2.04 (2H, m), 2.99 (1H, tt, J = 12.5, 3.3) 3.54 (3H, s), 3.71 (3H, s), 8.53 (1H, s); ^{13}C-nmr (100 MHz): δ 25.6, 26.2, 29.0, 29.3, 32.5, 43.7, 126.5, 146.1, 146.5, 150.7, 157.6, 160.3; ir (chloroform): 2932, 2856, 1720, 1672, 1548, 1496 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 274 (M^+, 33%), 219 (60%), 206 (100%).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.13; H, 6.56; N, 20.20.

Compound **4f** was recrystallized from ethanol and melted at 138.0-139.2° (lit [8] 142-143°); ^{1}H-nmr (90 MHz): δ 1.42 (9H, s), 3.48 (3H, s), 3.65 (3H, s), 8.66 (1H, s); ^{13}C-nmr (100 MHz): δ 28.8, 29.1, 29.8, 36.5, 125.9, 144.5, 146.0, 150.7, 160.1, 160.2.

Compound **4g** was recrystallized from benzene and melted at 248.6-249.2° (lit [20] 251-253°); ^{1}H-nmr (90 MHz): δ 3.57 (3H, s), 3.75 (3H, s), 7.38-7.65 (3H, m), 7.95-8.19 (2H, m), 9.06 (1H, s); ^{13}C-nmr (100 MHz): δ 29.1, 29.5, 126.7, 126.9, 129.1, 130.1, 134.9, 144.9, 146.8, 148.6, 150.6, 160.3.

Compound **4h** was recrystallized from benzene-hexane and melted at 130.0-130.7°; ^{1}H-nmr (90 MHz): δ 3.54 (3H, s), 3.66 (3H, s), 4.33 (2H, s), 6.86-7.67 (5H, m), 8.44 (1H, s); ^{13}C-nmr (100 MHz): δ 29.0, 29.3, 41.4, 126.3, 127.0, 128.9, 129.0, 137.6, 146.5, 147.9, 150.6, 152.4, 160.2; ir (chloroform): 3065, 3024, 2959, 1720, 1673, 1548, 1496 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 282 (M^+, 68%), 281 (100%).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.52; H, 4.88; N, 19.76.

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