Studies on Pyrazines. 36 [1]. A Novel Synthesis of 6-(2-Hydroxyethyl)-1,3-dimethyllumazine

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Received July 2, 1999

The titled compound was synthesized by cycloaddition of 5,6,7,8-tetrahydro-5,7-dimethyl-3,6,8-trioxo-3*H*-pyrimido[5,4-*c*][1,2,5]oxadiazine (**1**) with 2,3-dihydrofuran (**2a**).

J. Heterocyclic Chem., **37**, 419 (2000).

Intermolecular cyclization of oxadiazinone with dienophiles is a useful methodology for the construction of pyrazine rings. For example, reaction of 5,6,7,8-tetrahydro-5,7-dimethyl-3,6,8-trioxo-3*H*-pyrimido[5,4-*c*][1,2,5]-oxadiazine (**1**) with the enolate of 1,3-dicarbonyl compounds led to the formation of 6,7-disubstituted pteridine-2,4-diones [2]. The oxadiazinone **1** also undergoes cycloaddition with electron-rich dienophiles such as enamines [3] and silylenol ethers [4] affording 6-substituted 1,3-dimethyllumazines, which are of the same class of compounds as many natural pteridines of biological importance. In this paper, we report a successful hetero Diels-Alder reaction of oxadiazinone **1** with 2,3-dihydrofuran (**2a**) leading to 6-(2-hydroxyethyl)-1,3-dimethyllumazine (**3a**).

The oxadiazinone **1**, easily prepared by reaction of 1,3-dimethyl-6-amino-5-nitrosouracil with bis(trichloromethyl) carbonate [3], was refluxed in dihydrofuran **2a** for 4 hours providing β-lumazinylethanol **3a** in 74% yield together with its tetrahydrofuran derivative **4** (5%) as shown in Scheme 1. When a 1:2 mixture of **1** and **2a** was refluxed in 1,2-dichloroethane for 6 hours, the combined yields of lumazine products **3a** and **4** were reduced to 37% (entry 2 in Table 1) and 27% of the starting material was recovered. In analogy with dihydrofuran **2a**, 2,3-dihydropyrans **2b** and **c** were expected to be effective dienophiles but the expected lumazines were formed only in low yields (entries 3-6 in Table 1). Other furan derivatives, furan, 2-methylfuran, furfural and 2,2-dimethyl-3(2*H*)-furanone, gave no cycloaddition products. Thus, the hetero Diels-Alder reaction of oxadiazinone **1** with cyclic vinyl ether was found to proceed uniquely using dihydrofuran **2a**.

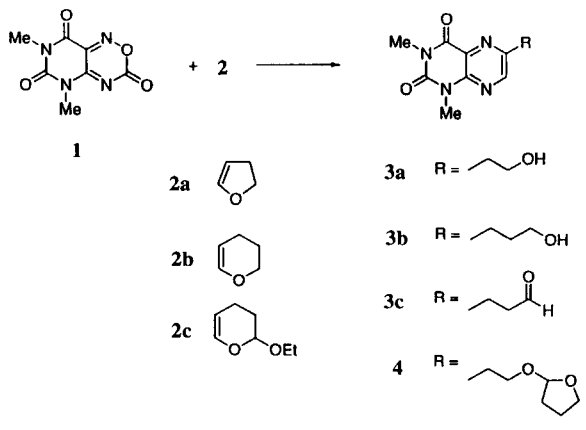
Table 1
Reaction of Oxadiazine **1** with Cyclic Vinyl Ethers **2**

Entry	Vinyl Ether	Method [1]	Product	Yield (%)	Starting Material Recovered (%)
1	**2a**	A	**3a**	74	0
			4	5	
2	**2a**	B	**3a**	20	27
			4	17	
3	**2b**	A	**3b**	18	24
4	**2b**	B	**3b**	0	17
5	**2c**	A	**3c**	13	32
6	**2c**	B	**3c**	1	50

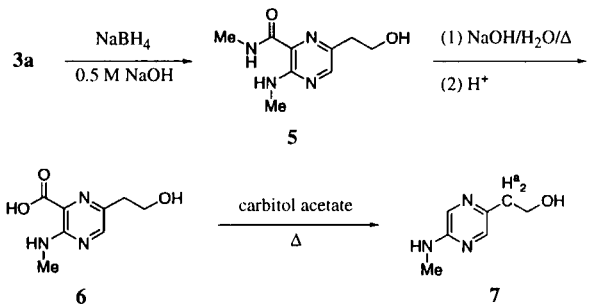
[1] A: The oxadiazine **1** was refluxed in dihydrofuran **2** for 4 hours. B: A 1:2 mixture of **1** and **2** was refluxed in 1,2-dichloroethane for 6 hours.

The position of 2-hydroxyethyl group at C-6 of lumazine **3a** was confirmed by degradation of **3a** to 2,5-disubstituted pyrazine **7**, and the reaction sequence is illustrated in Scheme 2. The pyrimidinedione ring of **3a** was readily cleaved by treatment with sodium borohydride in aqueous sodium hydroxide to give amide **5** [5], the hydrolysis of which to carboxylic acid **6** was achieved with alkali in a sealed vessel at 120-150°. Decarboxylation of **6** was completed by heating in carbitol acetate to furnish a hygroscopic product **7** in 39% overall yield.

Scheme 1



Scheme 2



2,5-Disubstitution of **7** is characterized by the ^{1}H nmr signal of the pyrazine ring at δ 7.82 (d, J = 1.3 Hz) and 7.91 (diffused singlet). The latter became a doublet (J = 1.3 Hz) by the decoupling with the methylene to the pyrazine ring. Pyrazine derivatives show the coupling constants of J_{para} = 1.2-1.8 Hz whereas J_{meta} = 0-0.6 Hz [6]. The signal at δ 7.91 became a diffused singlet by the weak coupling with the methylene and the para-hydrogen [6a,7].

EXPERIMENTAL

All melting points were determined using a Büchi 535 apparatus and are uncorrected. The nmr spectra were obtained with a JEOL JNM EX270 and a BRUKER AVANCE 400 spectrometers in deuteriochloroform containing tetramethylsilane as the internal standard. The ms spectra were obtained with a JEOL JMS-700 spectrometer.

Reaction of 5,6,7,8-tetrahydro-5,7-dimethyl-3,6,8-trioxo-3*H*-pyrimido[5,4-*c*][1,2,5]oxadiazine (**1**) with 2,3-Dihydrofuran (**2a**).

The oxadiazinone **1** (0.209 g, 0.99 mmole), prepared by the reported procedure [3], was added with dihydrofuran **2a** (5 ml) *via* a syringe in argon. The mixture was refluxed for 4 hours and then concentrated *in vacuo*. The residue was chromatographed on silica gel (14 g). The first fraction eluted with hexane-ethyl acetate (1:1) gave tetrahydrofuran derivative **4** (16 mg, 5%), which was recrystallized from hexane as colorless needles, mp 78°; ^{1}H nmr: 1.88 (4H, m), 3.22 (2H, t, J = 6.1 Hz), 3.55 (3H, s), 3.72 (3H, s), 3.80 (3H, m), 4.03 (1H, m), 5.09 (1H, d, J = 3.0 Hz), 8.58 (1H, s); ^{13}C nmr: 23.2, 28.8, 29.1, 32.1, 35.2, 65.5, 66.8, 103.7, 126.4, 146.4, 148.1, 150.4, 151.1, 160.0.

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.86; H, 5.92; N, 18.03.

Further elution with ethyl acetate afforded 6-(2-hydroxyethyl)-1,3-dimethyllumazine **3a** (0.174 g, 74%), which was recrystallized from ethanol providing colorless needles, mp 180.5-181.5°; ^{1}H nmr: 3.20 (2H, t, J = 5.8 Hz), 3.54 (3H, s), 3.71 (3H, s), 4.10 (2H, t, J = 5.8 Hz), 8.59 (1H, s); ^{13}C nmr: 28.9, 29.3, 37.1, 61.0, 126.4, 146.7, 148.2, 150.5, 151.2, 160.1; ms: (FAB) m/z (MH^+). Calcd. for $C_{10}H_{13}N_4O_3$: 237.0988. Found: 237.0977.

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.87; H, 5.21; N, 22.92.

The following compounds were prepared by the same procedure as for **3a**.

6-(3-Hydroxypropyl)-1,3-dimethyllumazine (**3b**).

This compound was obtained as pale yellow tiny needles, mp 158.5-159.5° (from ethanol); ^{1}H nmr: 2.06 (2H, m), 3.10 (2H, t, J = 7.4 Hz), 3.54 (3H, s), 3.71 (3H, s), 3.74 (2H, t, J = 6.6 Hz), 8.56 (1H, s); ^{13}C nmr: 29.0, 29.3, 31.2, 32.0, 61.6, 126.4, 146.5, 147.6, 150.5, 153.1, 160.2.

Anal. Calcd. for $C_{11}H_{14}H_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.89; H, 5.73; N, 21.92.

6-(2-Formylethyl)-1,3-dimethyllumazine (**3c**).

This compound was obtained as a tan oil, ^{1}H nmr: 3.14 (2H, t, J = 5.9 Hz), 3.24 (2H, t, J = 5.9 Hz), 3.53 (3H, s), 3.71 (3H, s), 8.63 (1H, s), 9.84 (1H, s); ^{13}C nmr: 21.0, 26.7, 29.0, 29.3, 42.4, 126.5, 146.6, 148.0, 150.5, 151.5, 160.1, 200.5; ms: (FAB) m/z (MH^+). Calcd. for $C_{11}H_{13}N_4O_3$: 249.0988. Found: 249.0984. This product was not submitted for elemental analysis because the Kugelrohr distillation resulted in decomposition.

Degradation of 6-(2-Hydroxyethyl)-1,3-dimethyllumazine (**3a**) to 2-(*N*-Methylamino)-5-(2-hydroxyethyl)pyrazine (**7**).

A mixture of **3a** (0.221 g, 0.94 mmole), sodium borohydride (0.039 g, 1.03 mmoles) in 0.5 M sodium hydroxide (10 ml) was stirred at room temperature for 1 hour and then acidified with 1*M* hydrochloric acid. The solution was then adjusted to *p*H 8 with sodium hydrogencarbonate and extracted with ethyl acetate (3 x 30 ml). The extract was dried over magnesium sulfate and concentrated *in vacuo* to give *N*-methyl-3-(*N'*-methylamino)-6-(2-hydroxyethyl)pyrazinecarboxamide (**5**) (0.145 g, 73%); ^{1}H nmr: 2.88 (2H, t, J = 6.1 Hz), 2.96 (3H, d, J = 4.9 Hz), 3.01 (3H, d, J = 5.0 Hz), 3.95 (2H, t, J = 6.1 Hz), 7.86 (1H, br s), 8.11 (1H, s), 8.43 (1H, br s); ^{13}C nmr: 25.7, 27.2, 36.6, 61.7, 125.4, 138.1, 146.0, 153.7, 166.9.

A mixture of **5** (0.120 g, 0.57 mmole) and aqueous sodium hydroxide (0.051 g, 1.28 mmoles in 8 ml of water) was heated in a sealed vessel at 120-150° for 2 hours. After cooling to room temperature, the solution was treated with Amberlite IR-120B (acid form, 0.2 ml) and concentrated *in vacuo*. The residual carboxylic acid **6** was dissolved in carbitol acetate (2 ml), and the solution was refluxed for 15 minutes and then concentrated *in vacuo*. The residue was chromatographed on silica gel (12.5 g), eluted with hexane-ethyl acetate (1:1), to afford **7** (0.050 g, 53%) as tan crystals, mp 85.5°; ^{1}H nmr: 2.88 (2H, t, J = 5.8 Hz), 2.97 (3H, d, J = 5.3 Hz), 3.95 (2H, t, J = 5.8 Hz), 4.55 (1H, br s), 7.82 (1H, d, J = 1.3 Hz), 7.91 (1H, s); ^{13}C nmr: 28.5, 35.6, 62.2, 130.0, 141.2, 142.5, 154.0. Spin decoupling by irradiation at δ 2.88 split the peak at δ 7.91 to a doublet (J = 1.3 Hz); ms: (EI) m/z (M^+). Calcd. for $C_7H_{11}N_3O$: 153.0902. Found: 153.0894. Due to its hygroscopicity, this product was not submitted for elemental analysis.

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