Regiospecific Synthesis of 6-Alkylated Lumazine Derivatives Using Silylenol Ethers

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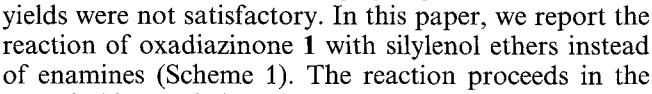
The reaction of oxadiazinone with silylenol ethers gave regiospecifically 6-substituted lumazines by an hetero Diels–Alder addition followed by decarboxylation and silanol elimination.

Most pteridines are synthesized by the Gabriel-Isay reaction[1] in which the easily available 5,6-diaminopyrimidines are condensed with α-dicarbonyl compounds. The condensation of pyrimidines with unsymmetrical α-dicarbonyl compounds, however, occurs non-regiospecifically giving a mixture of 6- and 7-substituted pteridines. Many natural products of biological importance (e.g. folic acid and biopterin) contain the pteridine ring having an alkyl side-chain at the 6-position,[2] and hence a versatile and regiospecific synthesis of 6-substituted pteridines is desirable.

We have recently reported the regioselective synthesis of 6-alkylated lumazine derivatives using 5,6,7,8-tetrahydro-5,7-dimethyl-3,6,8-trioxo-3*H*-pyrimido[5,4-*c*][1,2,5]oxadiazine (**1**) and the enamines derived from aldehydes.[3] This reaction is highly regioselective, but the yields were not satisfactory. In this paper, we report the reaction of oxadiazinone **1** with silylenol ethers instead of enamines (Scheme 1). The reaction proceeds in the same fashion and gives the same products as the reaction of oxadiazinone **1** with enamines. The yields of 6-alkylated lumazine derivatives were much improved by the new procedure.



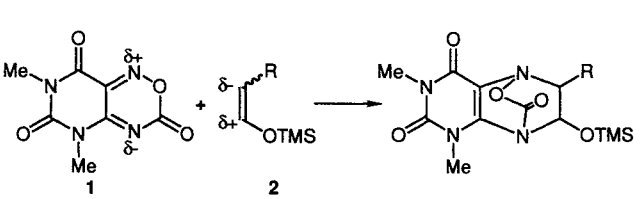
Scheme 1

The starting silylenol ethers (ca. 1:1 mixture of *E*- and *Z*-isomers) were prepared from the corresponding aldehydes by the procedure described by House et al.[4] A mixture of oxadiazinone **1** and one of the silylenol ethers **2a–h** was reacted under nitrogen under the reaction conditions shown in the Table to give the products **3a–h**, which were identified by comparison with the authentic samples of **3a–h** obtained in the reaction of **1** with enamines.[3]

As compared to the reaction of oxadiazinone **1** and enamines, the present method using silylenol ethers gave much improved yields of the products **3**. Particularly, Method C gave satisfactory yields with almost all silylenol ethers used.

In the case of silylenol ether **2a** (R = Me), heating was required to obtain a reasonable yield (Table), but all other reactions proceeded smoothly at room temperature giving high yields of the products.

The present reaction is initiated by an hetero Diels-Alder reaction of reversed electron demand[5] as in the reaction



Scheme 2

Table. Reaction of Oxadiazinone **1** with Silylenol Ethers **2a–h**

Product[a]	R	Yield (%)			mp (°C)	
		Method A[b]	Method B[c]	Method C[d]	found	reported
3a	Me	18	20	15 (53[e])	197.0–198.5	201.0–203.0[7]
3b	Et	30	35	82	141.0–143.0	139.0–141.0[8]
3c	Pr	51	57	78	113.5–114.0	113.5–114.0[3]
3d	*i*-Pr	50	46	90	119.0–119.3	119.0–119.3[3]
3e	*c*-C_6H_{11}	47	34	93	157.5–158.2	157.5–158.2[3]
3f	*t*-Bu	79	70	93	138.0–139.2	142.0–143.0[9]
3g	Ph	74	70	85	248.6–249.2	251.0–253.0[10]
3h	Bn	31	32	65	130.0–130.7	130.0–130.7[3]

[a] The spectral data (IR, NMR, MS) were identical with the authentic sample of **3a–h** reported in Ref. 3.
[b] A 1:2 mixture of oxadiazinone **1** (0.2 mmol) and silylenol ether **2** (0.4 mmol) in THF was stirred at r.t. for 12 h.
[c] A 1:2 mixture of oxadiazinone **1** (0.2 mmol) and silylenol ether **2** (0.4 mmol) was refluxed in THF for 12 h.
[d] A 1:5 mixture of oxadiazinone **1** and silylenol ether **2** was stirred at r.t. for 12 h without solvent.
[e] The reaction mixture was heated at 80 °C for 12 h.

of oxadiazinone **1** with enamines.[3] Thus, the electron rich silylenol ether adds regioselectively to the electron poor oxadiazinone **1**. The loss of carbon dioxide from the adduct followed by aromatization due to the elimination of trimethylsilanol produces the products **3** (Scheme 2). Polarities of oxadiazinone **1**[3] and the silylenol ether as shown in Scheme 2 define the regiospecificity of the first cycloaddition and therefore the final products.

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

Melting points were recorded on a Yamato apparatus model MP-21 and are uncorrected. The ^{1}H NMR spectra were recorded on a Hitachi R-90, JEOL EX-270 and JEOL GSX-400 spectrometers in $CDCl_3$. The ^{13}C NMR spectra were recorded on a JEOL EX-270 and JEOL GSX-400 spectrometers in $CDCl_3$.

Diazinone **1** was prepared by the reaction of 1,3-dimethyl-4-amino-5-nitrosouracil with bis(trichloromethyl) carbonate[3] by modification of the original procedure.[6] Silylenol ethers **(2a–h)** were prepared from the corresponding aldehydes by reaction with Me_3SiCl as reported by House et al.[4] All the starting materials gave correct spectral data.

Reaction of Diazinone 1 with Silylenol Ethers 2; General Procedure: An appropriate amount (see Table) of diazinone **1** and one of the silylenol ethers **2a–h** was dissolved in THF (1 mL) and the mixture was stirred under N_2 for the period recorded in the Table. The mixture was condensed in vacuo and the product was separated by preparative TLC on silica gel plate (20 × 20 × 0.2 cm) developed by EtOAc/$CHCl_3$ (1:1). The spectral data of products thus obtained were identical in every respect with the authentic samples reported in Ref. 3.

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