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Stereoselective synthesis of 4a-fluoro-5,10-ethenobenzo[*f*]quinazolines via photo-Diels–Alder reaction of 5-fluoro-1,3-dimethyluracil with naphthalenes

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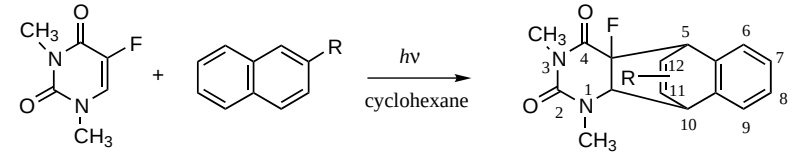
Abstract—UV-irradiation of a solution of 5-fluoro-1,3-dimethyluracil (5-FDMU) in aprotic media effected a stereoselective 1,4-cycloaddition reaction to give a barrelene derivative in high yield. In direct contrast, irradiation of a solution of 5-FDMU and naphthalene in a protic medium afforded 5-(1-naphthyl)uracil as the major product.

The chemical modification of nucleic bases is recognized as one of the most promising approaches for developing bioactive substances such as anticancer and antiviral agents.[1] During the course of our continuing studies on the photochemical modification of the pyrimidine ring, we have previously reported that UV-irradiation of 6-chloro-1,3-dimethyluracil (6-ClDMU) in benzene resulted in substitution at C6 to give 6-aryl-DMU (6-ArDMU), whereas the analogous photoreaction in the presence of TFA induced a 1,2-cycloaddition to give cyclooctapyrimidines at room temperature,[2] or pentalenopyrimidines at low temperature.[3] Certain cyclooctapyrimidines were further converted into various novel valence isomers, including bond-switching isomers,[4] cyclobutaquinazoline derivatives,[5] and pentalenoquinazolines[6] by way of a variety of electrocyclic pathways depending on the reaction conditions and substituents on the cycloadducts.

Thus, photocycloaddition of 6-ClDMU with benzene derivatives is demonstrated herein to be a useful method for the modification of the pyrimidine ring.

This finding is novel since photoreaction of 5-chloro-DMU (5-ClDMU) with benzene derivatives proceeds by way of the conventional substitution reaction to give 5-ArDMU. The addition of TFA serves only to improve the yield of the corresponding 5-ArDMU. Similar photosubstitution reactions with 5-fluoro-DMU (5-FDMU) have been shown to proceed only in the presence of TFA.[7a,b] However, no cycloaddition reaction products were observed under these conditions.[7a]



5-FDMU

1a, R = H
1b, R = CO_2CH_3
1c, R = CN

2a, R = H
2b, R = 12-CO_2CH_3
2ci, R = 12-CN
2cii, R = 11-CN

Scheme 1.

Abbreviations: Nuclear Overhauser effect (NOE); 1,3-dimethyluracil (DMU); trifluoroacetic acid (TFA); pyrimidine-2,4-dione (Uracil); fast atom bombardment mass spectrometry (FAB-MS); doublet of double doublets (ddd).

Keywords: photoreaction; photocycloaddition; 1,4-cycloaddition; 5-fluoro-1,3-dimethyluracil; naphthalene.

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Meanwhile, 5-FDMU is known to undergo cycloaddition with certain simple alkenes to give cyclobutapyrimidines.[8] In addition, naphthalene and its derivatives have previously been reported to add to alkenes in different manners including 1,2-,[9] 1,4-,[9] 1,8-[10] and/or [4+4] cycloadditions[9,11] to give various new ring systems. These findings have encouraged us to extend our work to the photoreaction of 5-FDMU with naphthalenes.

In the present paper, we wish to describe our finding that the photoreaction of 5-FDMU and naphthalene (**1a**) gives predominantly the novel 1,4-cycloadduct (**2a**), while this photoreaction in the presence of TFA yields 1,3-dimethyl-5-(1-naphthyl)uracil (**3**) as the major product.

A solution of 5-FDMU and naphthalene (**1a**) in cyclohexane was irradiated externally with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ >300 nm) for 1 h to furnish the novel 1,4 (*para*)-cycloadduct, benzopyrimidobarrelene (**2a**) in 91% yield as the sole product (Scheme 1).

The structural assignment of **2a**[12] was made on the basis of detailed MS and the NMR spectroscopic studies: the FAB-MS showed the expected molecular ion peak $[M+H]^+$ at m/z 287, along with fragment ions ascribable to the starting materials, 5-FDMU and naphthalene at m/z 159 and 128, respectively. The ^1H NMR ($CDCl_3$) spectrum showed signals due to N3-CH_3 and N1-CH_3 at δ 2.71 and 3.10 ppm, respectively. Two signals ascribable to the H-10 and H-5 methine protons appeared at δ 4.29 (ddd, $J=1.5$, 2.6, 6.2 Hz) and 4.64 (ddd, $J=1.5$, 1.7, 5.4 Hz) ppm, respectively. Two signals due to the H-12 and H-11 vinyl protons appeared at δ 6.68 (ddd, $J=1.5$, 5.4, 7.2 Hz) and 6.74 (ddd, $J=1.7$, 6.2, 7.2 Hz), respectively. The aromatic protons were observed in the region between δ 7.11 and 7.23.

The stereochemistry of **2a** was determined with the aid of NOE experiments. Irradiation of the H-10a proton significantly affected the H-11 vinyl proton, as well as H-10 and N1-CH_3. Additional NOE results confirmed the structure assigned to **2a** (Fig. 1).[13]

The present reaction was subsequently applied to methyl 2-naphthoate (**1b**) and 2-naphthonitrile (**1c**) (Scheme 1). Photoreaction with **1b** gave 1,4-adduct (**2b**, R = 12-CO_2CH_3)[14] in high regio- and stereoselectivity in fair yield (49%).

Under these same conditions, photoreaction of 5-FDMU with **1c** afforded the regioisomeric 1,4-adduct **2ci**[15] (12-CN) (34%) preferentially, together with **2cii**[16] (11-CN) (7%) as a minor product.

Interestingly, the stereochemistry of the resulting 1,4-cycloadduct (**2**) is consistent with that expected from a thermal [4+2] cycloaddition, i.e. Diels–Alder reaction. Hence, the thermal process for the formation of **2a** was examined. The formation of **2a**, however, could not be detected when a mixture of 5-FDMU and **1a** was heated in the dark in a degassed sealed tube at 150°C for 1 h.

In order to obtain more insight into the photochemical behavior of the present reaction, we have examined the solvent effects on the photoreaction (Table 1). The reaction in the aprotic solvents cyclohexane, benzene, and acetonitrile gave **2a** as the sole product, though the reaction proceeded less efficiently as the polarity of the solvent was increased. In contrast, the reaction in methanol predominantly afforded 5-naphthyluracil (**3**).[17] The photoreaction in cyclohexane in the presence of TFA (2 molar equivalents) gave the substitution product **3** as the major product, indicating that a substitution reaction was induced in protic media, while in aprotic solvents, the reaction proceeded by way of 1,4-cycloaddition (Scheme 2).[18]

Thus, the photoreaction of 5-FDMU with naphthalenes in an aprotic solvent was shown to furnish a 1,4-cycloadduct (**2**) in high stereoselectivity, with 10a–H and 4a–F remaining intact at the original position of the pyrimidine ring, in contrast to the photoreaction of 6-ClDMU and benzenes in the presence of TFA, wherein 1,2-cycloaddition accompanied by dehydrochlorination predominated. In addition, from a synthetic point of view, it is important to note that the present photocycloaddition does not require the addi-

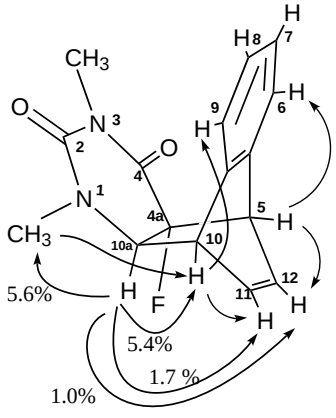
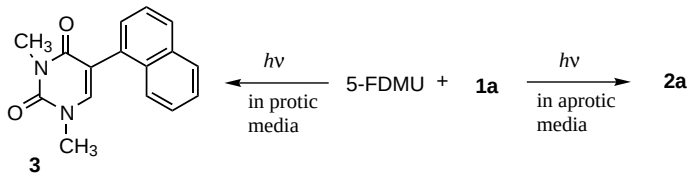


Figure 1. NOE correlations for **2a**.

Table 1. Photoreaction of 5-FDMU and naphthalene (**1a**) in various solvents[a]

Solvent	Yields (%) of		5-FDMU recovered
	2a	**3**	
Cyclohexane	82	0	10
Benzene	55	0	42
CH_3CN	21	0	72
CH_3OH	0	23	58
Cyclohexane + TFA	9	26	35

[a] Reaction conditions: an equivalent molar solution of 5-FDMU and **1a** (0.03 mmol) in a solvent (20 mL) was irradiated for 1 h, and the yields of the products were determined by means of ^1H NMR spectroscopy.



Scheme 2.

tion of acid, or excess amounts of naphthalene over 5-FDMU, and thus represents a novel method for the skeletal modification of the pyrimidine ring.

Further work on the scope of this photoreaction is now in progress.

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12. 4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-5,10-ethenobenzo[*f*]quinazoline-2,4-dione (**2a**): Colorless crystals, mp 163–164°C. ^{1}H NMR ($CDCl_3$) δ 2.71 (3H, d, J=0.7 Hz, N3-CH_3), 3.10 (3H, s, N1-CH_3), 3.58 (1H, dd, J=2.6, 31.3 Hz, H-10a), 4.29 (1H, ddd, J=2.6, 1.5, 6.2 Hz, H-10), 4.64 (1H, J=1.5, 1.7, 5.4 Hz, H-5), 6.68 (1H, ddd, J=5.4, 1.5, 7.2 Hz, H-12), 6.74 (1H, ddd, J=1.7, 6.2, 7.2 Hz, H-11), 7.11–7.23 (4H, m, aromatic-H). FAB-MS m/z (glycerol): 287 $[M+H]^+$, 267, 159, 128.
13. The optimized structure was obtained by the AM1 method with MOPAC on CAChe Work-system (Release 3.7; Cache Scientific, Inc.) and the results were traced by using 'CS ChemDraw ProI'.
14. Methyl 4a-fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-2,4-dioxo-5,10-ethenobenzo[*f*]quinazoline-12-carboxylate (**2b**): ^{1}H NMR ($CDCl_3$); 2.74 (3H, s, N^3-C$\underline{H}_3$), 3.11 (3H, S, N^1-C$\underline{H}_3$), 3.68 (1H, dd, J=2.4, 31.5, H-10a), 3.82 (3H, s, J=2.6, 1.5, 6.2, COOC$\underline{H}_3$), 4.44 (1H, dd, J=6.7, 2.4 Hz, H-10), 5.21 (1H, dd, J=5.1, 1.8 Hz, H-5), 7.15–7.29 (4H, m, H-6–H-9), 7.66 (1H, dd, J=6.7, 1.8, H-11). Ms m/z (%): 345 (M^++1, 100), 325 (18), 159 (98). HRS: calcd for $C_{18}H_{18}O_4N_2F$: 345.1250. Found $C_{18}H_{18}O_4N_2F$: 345.1281.
15. 4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-2,4-dioxo-5,10-ethenobenzo[*f*]quinazoline-12-carbonitrile (**2ci**): ^{1}H NMR (C_6D_6); 2.34 (3H, s, N^1-C$\underline{H}_3$), 2.59 (3H, d, J=0.8, N^3-C$\underline{H}_3$), 2.75 (1H, dd, J=31.1, 2.6 Hz, H-10a), 3.18 (1H, dd, J=6.6, 2.6 Hz, H-10), 4.77 (1H, dd, J=4.9, 2.0 Hz, H-5), 6.31 (1H, dd, J=6.6, 2.0 Hz, H-11), 6.54–6.60 (2H, m, H-6+H-9), 6.64–6.75 (2H, m, H-7+H-8). MS m/z (%): 312 (M^++1, 42), 292 (15), 159 (100). HRMS: calcd for $C_{17}H_{14}O_3N_2F$: 312.1148. Found $C_{17}H_{15}O_3N_2F$: 312.1136.
16. 4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-2,4-dioxo-5,10-ethenobenzo[*f*]quinazoline-11-carbonitrile (**2cii**): ^{1}H NMR (C_6D_6); 2.26 (3H, s, N^1-C$\underline{H}_3$), 2.57 (3H, d, J=0.9 Hz, N^3-C$\underline{H}_3$), 3.00 (1H, dd, J=31.0, 2.8 Hz, H-10a), 3.70 (1H, br d, J=2.8, 1.3 Hz, H-10), 4.40 (1H, br t, J=5.0, 6.0 Hz, H-5), 6.39 (1H, dd, J=6.0, 1.3 Hz, H-12), 6.53–6.71 (4H, m, H-6–H-9). Ms m/z (%): 312 (M^++1, 52), 292 (14), 159 (100), 154 (21). HRMS: calcd for $C_{17}H_{14}O_3N_2F$: 312.1148. Found $C_{17}H_{15}O_3N_2F$: 312.1144.
17. 1,3-Dimethyl-5-(1-naphthyl)pyrimidine-2,4-dione (**3**): Colorless crystals, mp 202–204°C (recrystallized from methanol). ^{1}H NMR (C_6D_6) δ: 2.54 (3H, s, N3-CH_3), 3.39 (3H, s, N1-CH_3), 6.05 (1H, s, H-4), 7.20–7.32 (4H, m, aromatic H), 7.64–7.77 (3H, m, aromatic H).
18. Addition of a triplet quencher, piperylene, to a solution of 5-FDMU and **1a** in cyclohexane suppressed the formation of **2a** significantly, suggesting that the present 1,4-cycloaddition may proceed via the excited triplet states.