Synthesis of Highly Conjugated Arylpropenylidene-1,3-diazin-2-ones via Paterno–Büchi Reaction by Photoreaction of 5-Fluoro-1,3-dimethyluracil with 1-Methoxynaphthalenes

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In contrast to photoreactions of 5-fluoro-1,3-dimethyluracil (5-FDMU) with various naphthalenes including 2-methoxynaphthalenes that proceeds in a manner to give ethenoquinazolines through 1,4-cycloaddition, UV-irradiation of a mixture of 5-FDMU and naphthalenes with a methoxy group at C-1 gave rise to the formation of novel cycloadducts, methyl 2-[(1*E*)-3-(5-fluoro-1,3-dimethyl-2-oxo-1,3-dihydropyrimidin-4-ylidene)-prop-1-enyl]benzoates, derived from the novel aromatic Paterno–Büchi type cycloaddition, followed by a concomitant disruption of the initially formed oxetane moiety.

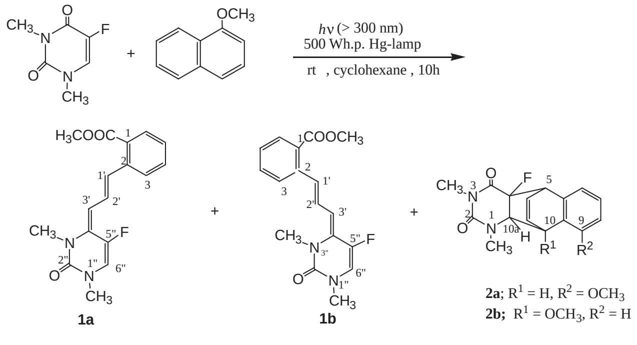
The photochemistry and photobiology of pyrimidine bases in DNA have been studied extensively, owing to their diverse reactivity based on both carbonyl groups and an olefinic double bond. The formation of thymine–adenine photoadducts[1] or of pyrimidine–pyrimidine cyclobutane dimers and bipyrimidine (6-4) photoadducts[2] between adjacent pyrimidine bases plays an important role in the direct induction of DNA damage. The former two reactions result through [2 + 2]-addition of olefinic double bonds while the (6-4) photoadducts derive from oxetane or azetidine intermediates formed by photoaddition of the C4-carbonyl of thymine or the C4-imino tautomer of cytosine[3] across the C5–C6 double bond of the adjacent base. From a synthetic view point, photochemical coupling reactions involving C=C or C=O double bonds have attracted our attention, since the chemical modification of nucleic bases has been recognized as one of the most promising approaches for developing bioactive substances such as anticancer and antiviral agents.[4] In this context, we have intensively studied the photochemical modification of halogenated and non-halogenated pyrimidines that occurs when they are irradiated in the presence of aromatic hydrocarbons such as benzene and naphthalene derivatives. We have thus successfully demonstrated that upon UV-irradiation pyrimidine derivatives undergo a variety of photocycloaddition reactions with benzene derivatives[5] and naphthalenes,[6] to give a structurally diverse range of photoproducts. The cycloadditions with aromatic hydrocarbons hitherto reported, however, are limited only to the couplings or substitutions on the C5=C6 double bond of the pyrimidine ring. No cycloaddition involving the carbonyl group has yet been discovered although the occurrence of the Paterno–Büchi type reaction would provide new possibilities for the photochemical modification of pyrimidine rings with aromatic compounds. We have recently reported that UV-irradiation of 5-FDMU with naphthalene and its derivatives substituted with electron-withdrawing groups, or electron-donating methyl or 2-methoxy groups, proceeded selectively by 1,2- and 1,4-cycloaddition, to afford naphthocyclobutapyrimidines and ethenobenzoquinazolines (barrelene), respectively.[7] In order to investigate the scope and limitations of the above photoreaction, we decided to extend our work to the photoreaction of 5-FDMU with naphthalenes having an electron-donating methoxy group at C-1.

In the present paper, we describe our finding that, UV-irradiation of a mixture of 5-FDMU and 1-methoxynaphthalene leads to the Paterno–Büchi type reaction yielding novel and highly conjugated propenylidene derivatives **1**.

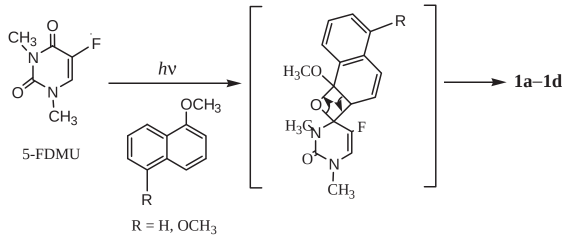
A degassed solution of 5-FDMU and 1-methoxynaphthalene in cyclohexane was irradiated externally with a 500-W high-pressure mercury lamp in a Pyrex tube ($\lambda > 300$ nm) for 10 h (Scheme 1). In contrast to the reaction with 2-methoxynaphthalene, whereby 1,4-cycloadducts are produced exclusively,[7b] the present reaction furnished the novel products, methyl 2-[(1*E*)-3-(5-fluoro-1,3-dimethyl-2-oxo-1,3-dihydropyrimidin-4-ylidene)prop-1-enyl]benzoate as a mixture of the 1′E,3′E isomer **1a**[8] (24%) and the 1′E,3′Z stereoisomer **1b**[9] (14%), together with the conventional regioisomeric 1,4-cycloadducts **2a**[10] and **2b**[11] in 5% and 4% yield respectively (yields are given based on 47% of 5-FDMU consumed).

The structural assignment of **1a** was made on the basis of detailed MS and the NMR spectroscopic studies.[8]

The stereochemistry of **1a** was determined with the aid of NOE experiments. Irradiation of the H-3′ proton significantly affected the H-1′ vinyl proton, as well as N3″–CH_3. Also irradiation at N3″–CH_3 showed enhancement of signal for H-3′ vinyl proton. On the other hand, the 1E,3Z isomer **1b** showed no NOE correlation for H-3′–N3″–CH_3, while significant correlation was observed between N3″–CH_3–H-2′. These differences in the NOE's conclusively determined the stereochemistry of **1a** as 1E,3E and **1b** to be 1E,3Z, respectively. The formation of **1** is rationally explained in terms of [2 + 2]-addition of the uracil C4=O carbonyl group with the C-1=C-2 double bond of the naphthalene ring, to give an oxetane intermediate (Paterno–Büchi reaction). Subsequent ring opening of the highly



Scheme 1.



Scheme 2.

strained oxetane moiety in the manner shown in Scheme 2 leads to cleavage of the naphthalene ring system as observed in compounds **1a**–**1d**.

Similar irradiation of equimolar amounts of 5-FDMU and 1,5-dimethoxynaphthalene in benzene furnished methyl 2-[(1*E*,3*E*)-3-(5-fluoro-1,3-dimethyl-2-oxo-1,3-dihydropyrimidin-4-ylidene)prop-1-enyl]-3-methoxybenzoate (**1c**)[12] in high yield (64%) together with small amounts of the 1E,3Z isomer **1d**[13] (9%) (at the stage where 44% of the 5-FDMU was consumed).

Although the precise factors responsible for the dramatically different outcomes of cycloaddition between 5-FDMU and 1-methoxy- or 2-methoxynaphthalene remain to be clarified, we consider that the reactivity of the intermediate oxetane plays a key role. In the former case, where the methoxy group is incorporated as a ketal function on the oxetane ring, we surmise that the rearrangement leading to ring fission and formation of a stable carbomethoxy function is favored energetically. With the oxetane derived from 2-methoxynaphthalene, where there is no such driving force, ring fission simply regenerates the original 5-FDMU and 2-methoxynaphthalene components.

Thus, the present study demonstrates the first aromatic Paterno–Büchi photocycloaddition involving 5-FDMU. Its reaction with naphthalene bearing a methoxy group at C-1 yields highly conjugated (phenylpropenylidene)-1,3-diazin-2-ones. A striking feature of this reaction, which entails oxetane formation between an aromatic hydrocarbon moiety and a carbonyl group, is that it leads to ring fission of the original aromatic nucleus. Further studies on the scope and the limitation of the present photoreaction are now in progress.

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8 Methyl 2-[(1*E*,3*E*)-3-(5-fluoro-1,3-dimethyl-2-oxo-1,3-dihydropyrimidin-4-ylidene)prop-1-enyl]benzoate (**1a**): ^{1}H NMR (C_6D_6): δ 2.43 (3H, s, N1″–CH_3), 2.76 (3H, s, N3″–CH_3), 3.50 (3H, s, C1-$COOCH_3$), 5.25 (1H, d, $J = 8.6$ Hz, H-6″), 5.38 (1H, d, $J = 11$ Hz, H-3′), 6.90 (1H, dd, $J = 7.4$, 8.0 Hz, H-5), 7.07 (1H, dd, $J = 7.4$, 8.0 Hz, H-4), 7.73 (1H, d, $J = 8.0$ Hz, H-3), 7.82 (1H, dd, $J = 11$, 15 Hz, H-2′), 7.90 (1H, d, $J = 8.0$ Hz, H-6), 7.92 (1H, dd, $J = 4.4$, 15 Hz, H-1′). NOE: H-3′ with N3″–CH_3 (14.1%), H-1′ (6.4%), H-6″ with N1″–CH_3 (7.1%), H-2′ with H-3 (2.5%), H-3′ (2.0%), H-3 with H-2′ (3.2%), H-4 (5.8%), N1″–CH_3 with H-6″ (3.3%). ^{13}C NMR (C_6D_6): δ 31.1 (N3″–CH_3), 35.3 (N1″–CH_3), 51.3 (OCH_3), 103.1 (d, $J = 7.2$ Hz, 3′), 116.4 (d, $J = 39.4$ Hz, 6″), 125.8 (5), 126.0 (3), 127.2 (1′), 127.6 (2′), 130.9 (6), 131.8 (4), 140.3 (2), 143.3 (d, $J = 231.3$ Hz, 5″), 149.8 (2″), 167.7 (C1-CO). FAB-MS *m*/*z*: 317 $[M + H]^+$. HRFABMS: Calcd for $C_{17}H_{18}N_2O_3F$: 317.1301. Found: 317.1316. IR ν_{max} (neat) cm^{-1}: 1719, 1670. UV λ_{max} ($CHCl_3$) nm (ε/$M^{-1}\,cm^{-1}$): 376 (21290).

9 Methyl 2-[(1*E*,3*Z*)-3-(5-fluoro-1,3-dimethyl-2-oxo-1,3-dihydropyrimidin-4-ylidene)prop-1-enyl]benzoate (**1b**): ^{1}H NMR (C_6D_6): δ 2.44 (3H, s, N1″–CH_3), 3.20 (3H, s, N3″–CH_3), 3.46 (3H, s C1-$COOCH_3$), 5.25 (1H, d, $J = 6.9$ Hz, H-6″), 5.86 (1H, d, $J = 12$ Hz, H-3′), 6.94 (1H, dd, $J = 7.4$, 8.0 Hz, H-5), 7.12 (1H, dd, $J = 7.4$, 8.0 Hz, H-4), 7.12 (1H, dd, $J = 12$, 15 Hz, H-2′), 7.43 (1H, d, $J = 8.0$ Hz, H-3), 7.71 (1H, d, $J = 15$ Hz, H-1′), 7.90 (1H, d, $J = 8.0$ Hz, H-6). NOE: H-3′ with H-1′ (20.4%), H-2′ (5.4%), H-6″ with N1″–CH_3 (7.1%), H-2′ with N3″–CH_3 (3.2%), H-3 (3.5%), H-3′ (1.2%). HRFABMS: Calcd for $C_{17}H_{18}N_2O_3F$: 317.1301. Found: 317.1296.

10 4a-Fluoro-4a,5,10,10a-tetrahydro-9-methoxy-1,3-dimethyl-*cis*-5,10-ethenobenzo[*f*]quinazoline-2,4-dione (**2a**): Colorless crystals, mp 149–151 °C (hexane). HRFABMS: Calcd for $C_{17}H_{18}N_2O_3F$: 317.1301. Found: 317.1328.

11 4a-Fluoro-4a,5,10,10a-tetrahydro-10-methoxy-1,3-dimethyl-*cis*-5,10-ethenobenzo[*f*]quinazoline-2,4-dione (**2b**): Colorless crystals, mp 134–135 °C (hexane). HRFABMS: Calcd for $C_{17}H_{18}N_2O_3F$: 317.1301. Found: 317.1324.

12 Methyl 2-[(1*E*,3*E*)-3-(5-fluoro-1,3-dimethyl-2-oxo-1,3-dihydropyrimidin-4-ylidene)prop-1-enyl]-3-methoxybenzoate (**1c**): yellow oil. FABMS *m*/*z*: 347 $[M + H]^+$. HRFABMS: Calcd for $C_{18}H_{20}N_2O_4F$: 347.1407. Found: 347.1390.

13 Methyl 2-[(1*E*,3*Z*)-3-(5-fluoro-1,3-dimethyl-2-oxo-1,3-dihydropyrimidin-4-ylidene)prop-1-enyl]-3-methoxybenzoate (**1d**): FABMS *m*/*z*: 347 $[M + H]^+$. HRFABMS: Calcd for $C_{18}H_{20}N_2O_4F$: 347.1407. Found: 347.1394.