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MODE SWITCHING DURING THE CYCLOADDITION OF 5-FLUORO-1,3-DIMETHYLURACIL WITH NAPHTHALENE FROM 1,4- TO 1,2-ADDITION

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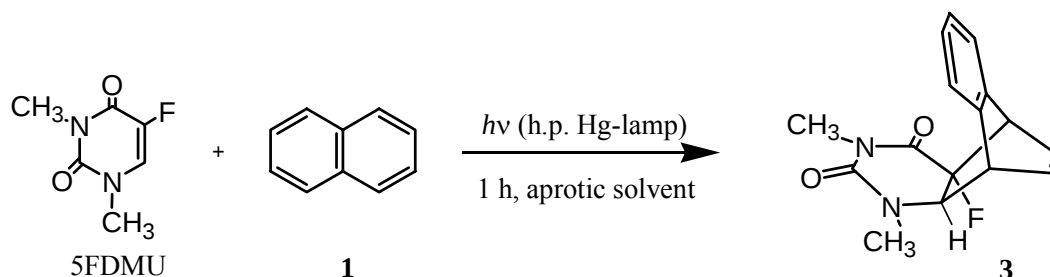
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Abstract – UV-irradiation of a solution of 5-fluoro-1,3-dimethyluracil (5-FDMU) and naphthalene (**1**) in acetonitrile effected both 1,2- and 1,4-cycloaddition. The 1,2-cycloaddition proceeds more smoothly than the alternative 1,4-cycloaddition. The 1,2-cycloadduct (**2**), however, is labile to the UV-light used for the reaction, and is rapidly converted to 5-FDMU and naphthalene, while the 1,4-adduct (**3**) is insensitive to UV-light. Thus, **2** is obtained as the major product by short-period irradiation, while **3** is produced predominantly when the irradiation duration is prolonged. Mode-selective 1,2-cycloaddition is achieved when UV-irradiation is performed in the presence of piperylene.

The photocycloaddition of naphthalenes with alkenes is well recognized as one of the useful procedures for constructing certain unique ring systems by way of 1,2-,¹ 1,4-,¹ and 1,8-additions.² The mode of the cycloaddition depends mainly on the substituents on the naphthalene ring and alkenes. In our continuing studies on the photochemical modification of the pyrimidine ring with arenes or alkenes,³ we have previously reported that UV-irradiation of a solution of 6-chloro-1,3-dimethyluracil (6-CIDMU) and naphthalene in polar media effected a 1,2-cycloaddition reaction to give naphthocyclobutapyrimidine in fair yield,⁴ while UV-irradiation of 5-fluoro-1,3-dimethyluracil (5-FDMU) with naphthalene (**1**) and its substituted derivatives in aprotic medium preferentially underwent 1,4-cycloaddition to give ethenoquinazoline (barrelene) derivative (**3**).⁵ Döpp *et al.* observed a time dependent mode-selectivity in the photocycloaddition of 1-acetonaphthone with captodative olefins; that is, 1,2-adduct was the major

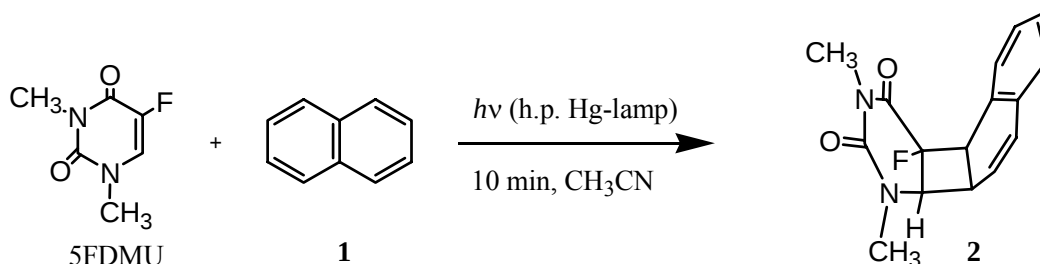
product formed at the beginning of the reaction, while the 1,4-adduct became the major product as the duration of irradiation was prolonged.⁶ These findings encouraged us to investigate the possibility of 1,2-cycloaddition in the photoreaction of 5-FDMU and **1**. In the present paper, we report our findings that UV-irradiation of a solution of 5-FDMU and naphthalene in acetonitrile effected both 1,2- and 1,4-cycloaddition. The 1,2-cycloaddition proceeds more smoothly than the alternative 1,4-cycloaddition. Thus, the 1,2-cycloadduct (**2**) is formed as the major product upon short-period irradiation. Cycloadduct (**2**) however, is quite labile to the UV-light used for the reaction, and rapidly reverts back to 5-FDMU and **1**, while the photochemically insensitive 1,4-adduct (**3**) accumulates in the reaction mixture as the irradiation time is prolonged. Photoreaction of a mixture of 5-FDMU and **1** in the presence of piperylene proceeds *via* 1,2-addition mode-selectively.

Previously, we reported that 1 h irradiation of a solution of 5-FDMU (1.5 mM) and naphthalene (**1**) (1.5 mM) in an aprotic solvent (cyclohexane, benzene, acetonitrile) at room temperature furnished 1,4-cycloadduct, benzopyrimidobarrelene (**3**) in high yield (Scheme 1).⁵



Scheme 1

Therefore, we first investigated the features of this photoreaction at the early reaction stage. A solution of 5-FDMU (4.5 mM) and **1** (4.5 mM) in acetonitrile irradiated with a 500 W high-pressure mercury lamp for 10 min in a degassed Pyrex test tube at room temperature furnished the novel cycloadduct (**2**) as the major product in 72% yield at the stage where 12.5% of **1** consumed, while the 1,4-adduct (**3**) was formed only in sparing yield (5%)(Scheme 2).



Scheme 2

The structure of the new compound (**2**) was assigned to be a 1,2-adduct of 5-FDMU and **1** on the basis

of ^1H -NMR and MS studies.⁷ The stereochemistry of **2** was determined to be *cis* (*endo*) on the basis of NOE experiments.⁷

The time course for the photoreaction of 5-FDMU with **1** in acetonitrile was investigated under the same conditions employed above, and the reaction was followed by ^1H -NMR spectroscopy (Figure 1).

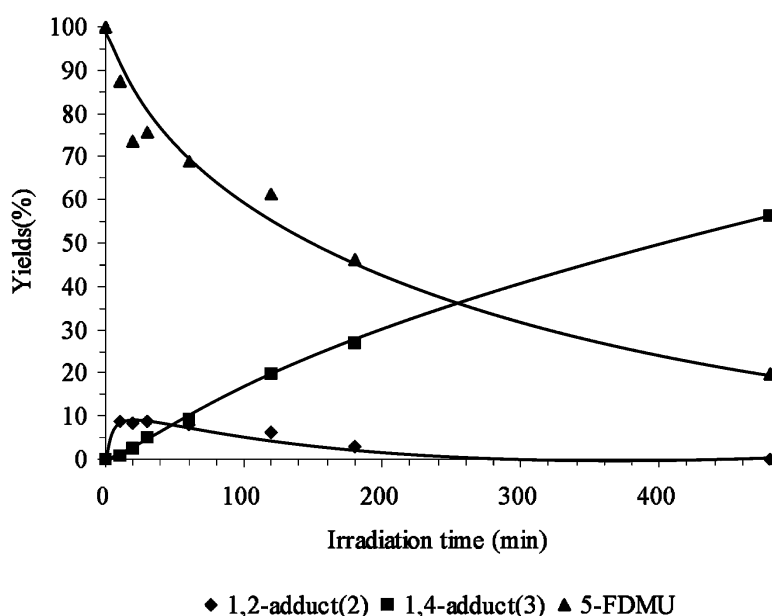


Figure 1

As shown in Figure 1, prompt formation of **2** occurred first, while the formation 1,4-adduct (**3**) was barely detectable at the initial stage. The formation of 1,2-adduct (**2**) reached maximum in 5 min, and gradually decreased after 30 min of irradiation. With the decrease of **2**, formation of **3** began to increase. Finally after 7 h of irradiation, the adduct (**2**) was no longer detected and **3** became the predominant photoproduct.

These results imply that initially produced **2** may be converted to **3** during the irradiation. In order to examine whether the 1,2-adduct (**2**) may be the precursor for **3**, **2** was exposed to UV-light, only to restore the starting 5-FDMU and **1** in high efficiency (63 % of **2** was converted in 10 min), while no formation of **3** was detected.

Similarly, the photochemical behavior of 1,4-adduct (**3**) was examined under the analogous conditions employed above, and starting **3** was recovered unchanged.

These findings indicate that although formation of **3** is less efficient than **2**, this adduct is insensitive to UV-light and accumulates in the solution during the photoreaction until it becomes the predominant product after 7 h irradiation. On the other hand **2**, once formed, is photo-labile under the irradiation conditions, and is rapidly converted back to the starting 5-FDMU and naphthalene through

cycloreversion.

Our present study has demonstrated that **3** is not a rearrangement product of **2**, but an independent product formed directly from the cycloaddition of 5-FDMU and naphthalene. These results are in accordance with those reported for the cycloaddition of acylnaphthalenes with some aminopropenenitriles (captodative olefins).⁶ In the paper, on the basis of quenching experiments, the 1,4-addition of acetophenone with aminopropenenitrile was demonstrated to be originating from the lowest excited triplet state of acylnaphthalene. Therefore the effect of triplet quencher piperylene on the present reaction was examined. Addition of piperylene to the above solution predominantly afforded **2** after 25 min irradiation (80% yield at the stage of 17% 5-FDMU consumed), and suppressed the formation of **3** completely, suggesting that excited triplet states may participate in the formation of **3**, while excited singlet states may be involved in the formation of **2**. It is noteworthy from a synthetic point of view that the photoreaction of 5-FDMU and naphthalene undergoes 1,2- and 1,4-cycloaddition mode selectively to give 1,2- and 1,4-adducts, respectively either in the presence or absence of piperylene.

Further study on the mechanism of this reaction is now in progress.

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7. *rel*-(6aR,6bS,10aS,10bR)-10a-Fluoro-7,9-dimethyl-6a,6b,10a,10b-tetrahydronaphtho[1',2':3,4]cyclobuta[1,2-d]pyrimidine-8,10(7H,9H)-dione (**2**): Colorless crystals, mp, 145.0-146.0 °C (from dichloromethane). ¹H-NMR (CDCl₃) δ: 2.98 (3H, s, N7-CH₃), 3.14 (3H, s, N9-CH₃), 3.81 (1H, m, H-6a), 4.03 (1H, dd, *J*=18.7, 11.4 Hz, H-10b), 4.45 (1H, dd, *J*=20.7, 8.6 Hz, H-6b), 5.57 (1H, dd, *J*=10.1, 3.6 Hz, H-6), 6.45 (1H, d, *J*=10.1 Hz, H-5), 7.01 (1H, d, *J*=7.0 Hz, H-4), 7.19 (1H, d, *J*=7.5 Hz, H-1), 7.24-7.30 (2H, m, H-2 and H-3). NOE: H-6a with H-6b, H-10b, H-6; H-6b with H-6a, H-10b, N7-CH₃. FAB-MS *m/z*: 287 [M+H]⁺.