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DIRECT C-C BOND FORMATION BETWEEN THYMINE DERIVATIVES AND NAPHTHALENE THROUGH [2+2]-PHOTO-CYCLOADDITION

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Abstract – In contrast to our previous findings that UV-irradiation of 1,3-dimethylthymine (**1a**) with naphthalene (**2**) underwent 1,4-cycloaddition to give an ethenobenzoquinazoline derivative, UV-irradiation of a mixture of **1a** and **2** in the presence of piperylene preferentially underwent 1,2-cycloaddition to give *cis*-tetrahydronaphthocyclobutapyrimidine in high stereoselectivity. Similar irradiation of 1,3-dimethyluracil and its derivatives (**1**) with substituents at C-5 gave the corresponding *cis*-1,2-adducts (**3**) in fair yields.

Photo-induced C-C bond formation of pyrimidine bases with alkenes, aromatic compounds or alcoholic compounds, including modified nucleic bases or amino acids, has been investigated intensively from biological, photochemical and synthetic points of view.[1] The photoproducts have been used as a tool for studying DNA repair,[2] probing protein-DNA interactions,[3] or arresting transcriptions.[4] Above all, the photochemistry of the cyclobutane ring system formed by [2+2]-cycloaddition has been extensively studied from the point of view of DNA damage and repair.

In continuation of our studies on the photochemistry of halogenated 1,3-dimethyluracil (XDMU) with aromatic compounds, we previously reported that photoreaction of 6-ClDMU with naphthalene in the presence of TFA furnished naphthocyclobutapyrimidines by way of [2+2]-cycloaddition (1,2-cycloaddition) accompanied by elimination of hydrogen chloride (HCl).[5] In contrast, we found that UV-irradiation of a solution of 5-fluoro-1,3-dimethyluracil (5-FDMU) and naphthalenes in aprotic media

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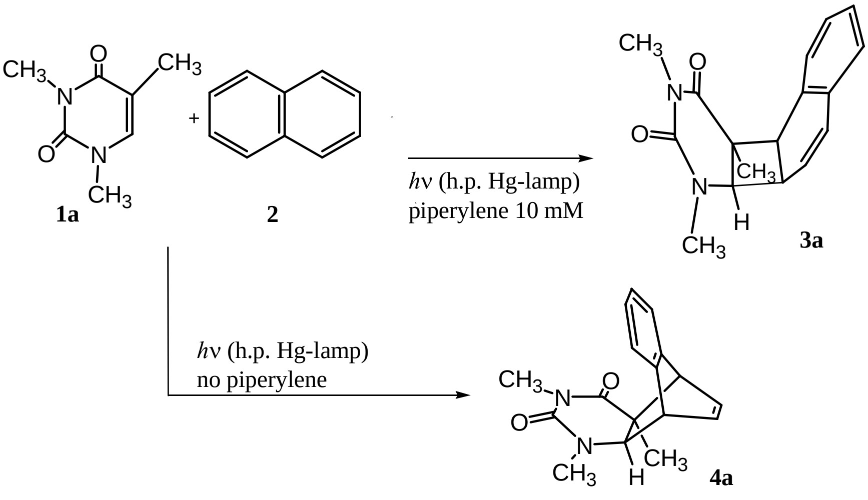
This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

underwent [4+2]-cycloaddition (1,4-cycloaddition) to give ethenobenzoquinazoline derivatives without eliminating hydrogen fluoride from the adduct in high yields.[6] Application of this photoreaction to 1,3-dimethylthymine and its related 5-subsituted uracils also furnished the corresponding 1,4-adducts in fair yields.[7] On further study, we recently found that the [4+2]-mode of cycloaddition observed for the above photoreaction with 5-FDMU and naphthalene was markedly changed to the alternative [2+2]-mode by performing the reaction in the presence of piperylene.[8]

These results have encouraged us to investigate an alternative C-C bond formation between thymine and naphthalene by way of 1,2-cycloaddition that would lead to the construction of a naphthocyclobutapyrimidine system. Herein we report that thymine couples with naphthalene to form a cyclobutapyrimidine through 1,2-cycloaddition when the photoreaction is performed in the presence of piperylene. UV-Irradiation of an equivalent molar solution (1.5 mM) of 1,3-dimethylthymine (**1a**) and naphthalene (**2**) in acetonitrile in the presence of piperylene (10 mM) with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ>300 nm) for 2 h at ambient temperature initiated 1,2-cycloaddition to give 6a,6b,10a,10b-tetrahydro-7,9,10a-trimethylnaphtho[1’,2’:3,4]cyclobuta[1,2-*d*]pyrimidine-8,10-dione (**3a**)[9] in the *cis*-geometry (*endo*-orientation) in 57% yield (based on 14% **1a** consumed).



Scheme1

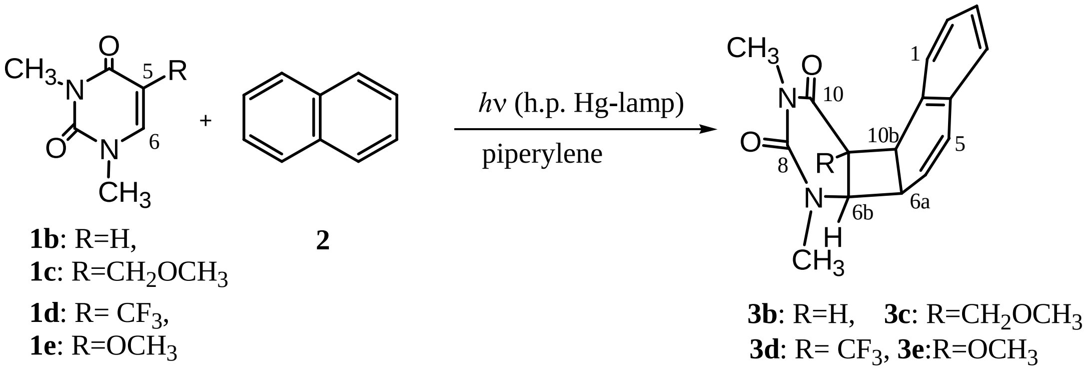
Alternatively, in the absence of piperylene, photoreaction proceeded very slowly but afforded the 1,4-adduct (**4a**) [7] exclusively (Scheme 1).

The structural assignment of **3a** was made on the basis of detailed MS and the NMR spectroscopic studies: The FAB-MS spectrum showed the expected molecular ion peak $[M+H]^+$ at *m/z* 283, and the ^{1}H-NMR ($CDCl_3$) spectrum showed signals due to C10a-CH_3, N^9-CH_3, and N^7-CH_3 at δ 1.57, 2.92, and

3.04 ppm (each 3H, s), respectively. Three signals ascribable to the H-6a, H-6b and H-10b methine protons appeared at δ3.68 (1H, m, H-6a), 3.92 (1H, d, J=7.5 Hz, H-6b), and δ3.50 ppm (1H, d, J=9.8 Hz, H-10b), respectively. Two signals due to the H-5 and H-6 vinyl protons appeared at δ6.39 (1H, dd, J = 10.3, 2.3 Hz) and 5.55 (1H, dd, J=10.3, 4.0 Hz) ppm respectively. The four aromatic protons were observed in the region between δ6.9 and 7.2 ppm.

The stereochemistry of **3a** was determined to be *cis* with the aid of NOE experiments. Irradiation of the H-10b proton significantly affected the H-1, H-6a, and H-6b protons. Irradiation of the H-6b proton significantly affected N7-CH_3, H-6a, H-10b, and C10a-CH_3. Additional NOE studies confirmed the structure assigned to **3a**.

Similarly, we further examined the photoreaction with uracil derivative (**1b**) and found that the corresponding 1,2-adduct (**3b**)[9] was formed in 24% yield (based on 32% **1b** consumed) (Scheme 2).



1b: R=H,
1c: R=CH_2OCH_3
1d: R= CF_3,
1e: R=OCH_3

2

3b: R=H, **3c**: R=CH_2OCH_3
3d: R= CF_3, **3e**:R=OCH_3

Scheme 2

Photoreaction of the methoxy derivative of 1,3-dimethylthymine (**1c**: R=CH_2OCH_3) for 2 h afforded the corresponding 1,2-adduct (**3c**)[9] as the sole product in moderate yield (36% based on 26% **1c** consummed). Similar photoreaction with trifluoromethyl derivative (**1d**: R=CF_3) afforded the corresponding 1,2-adduct (**3d**)[9] as the sole product in fair yield (42% based on **1d** 26% consumed) under analogous conditions. UV-Irradiation of 5-methoxy-1,3-dimethyluracil (**1e**) furnished the corresponding *cis*-cyclobutapyrimidine derivative (**3e**)[9] in 29% yield (based on 23% **1e** consumed).

Photo-induced cycloaddition of naphthalene has been studied from the mechanistic and synthetic view points, but so far unfortunately there has been hardly any change of addition modes in the same combination of reactants.[10] In this regard, it may be noteworthy that the mode of cycloaddition of 1,3-dimethyluracils with naphthalene can be switched perfectly from 1,4-addition to 1,2-addition by the addition of piperylene. In addition, the present study demonstrates the first photochemical cyclobutane ring formation of 1,3-dimethyluracils with naphthalene providing novel and unique skeletons. The C-C bond-formation between pyrimidines and naphthalene through cycloaddition may be of interest in relevance to nucleotide base recognition of small molecules.[11]

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9. Selected data for **3a**: Colorless crystals, mp 142-142.5 °C. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.12; H, 6.42; N, 9.77. **3b**: Colorless crystals, mp 162.5-165 °C. Anal. Calcd for $C_{16}H_{16}N_2O_2 \cdot 1/2H_2O$: C, 69.29; H, 6.18; N, 10.10. Found: C, 69.58; H, 5.90; N, 9.77. **3c**: Colorless oil, HRFAB-MS; Calcd for $C_{18}H_{21}N_2O_3$: 313.1552. Found: 313.1571. **3d**: Colorless crystals, mp 193.5-194.5 °C. Anal. Calcd for $C_{17}H_{15}N_2O_2F_3$: C, 60.53; H, 4.78; N, 8.31. Found: C, 60.26; H, 4.62; N, 8.44. **3e**: Colorless oil, HRFAB-MS; Calcd for $C_{17}H_{19}N_2O_3$: 299.1396. Found: 299.1401.
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