

PHOTO-INDUCED C-C BOND FORMATION OF 1,3-DIMETHYL- THYMINE AND ITS RELATED COMPOUNDS WITH NAPHTHALENE

Kazue Ohkura,^a Tetsuya Ishihara,^a Yasunobu Nakata,^a and Koh-ichi Seki*^{a,b}

^a Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

^b Central Institute of Radio Isotope Science, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-0815, Japan

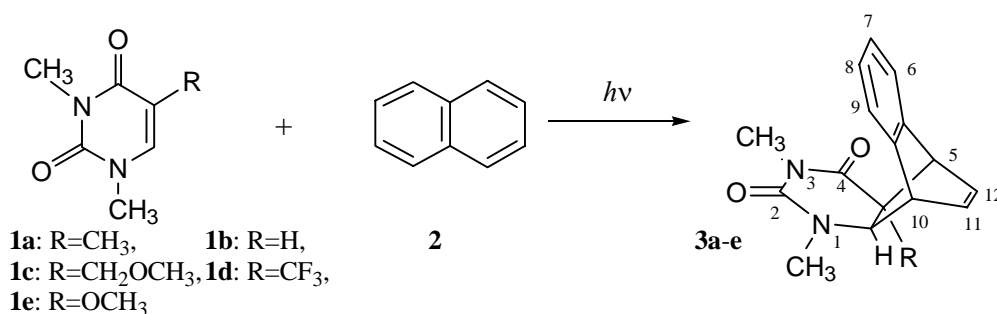
*To whom correspondence should be addressed: E-mail: seki@ric.hokudai.ac.jp

Abstract – UV-Irradiation of 1,3-dimethylthymine (**1a**) and naphthalene (**2**) resulted in C-C bond formation through 1,4-cycloaddition to give *cis*-ethenobenzoquinazoline (**3**) in high stereoselectivity and in fair yield. Similar irradiation of 1,3-dimethyluracil and its derivatives with a substituent at C-5 underwent cycloaddition to give the corresponding barrelene derivatives in fair yields.

C-C Bond formation of pyrimidine bases with aromatic compounds, alkenes or alcoholic compounds, including modified nucleic bases or amino acids have been studied intensively not only from synthetic but also from biological points of view.¹ Meanwhile nucleotide base recognition of small molecules attracted great interest for gene targeted drugs.² In relevance to molecular recognition, it is reported that simple aromatic hydrocarbon groups including a naphthalene moiety interact with thymine derivatives through electrostatic or π - π interactions.^{3,4} However, no C-C bond formation between aromatic hydrocarbons and non-halogenated nucleic bases has been reported. In our continuing studies on the photochemistry of halogenated 1,3-dimethyluracil (XDMU) with aromatic compounds, we have previously reported that photoreaction of 6-CIDMU with naphthalene in the presence of TFA furnished naphthocyclobutapyrimidines by way of 1,2-cycloaddition accompanied by elimination of hydrogen chloride (HCl).⁵ In contrast, we recently found that UV-irradiation of a solution of 5-fluoro-1,3-dimethyluracil (5-FDMU) and naphthalenes in aprotic media underwent 1,4-cycloaddition

in high yields to give ethenobenzoquinazoline derivatives with the fluoride atom remaining intact at the original positions in the adducts.⁶ This observation suggested that the presence of a halogen atom on the pyrimidine ring may not always be essential for the C-C bonding, and that pyrimidine bases could likewise undergo cross-linking with the naphthalene moiety through the cycloaddition with naphthalene. Hence our attention was focused on the possible photochemical cross-coupling between non-halogenated pyrimidine bases and naphthalene.

In the present paper, we report that UV-irradiation of an equivalent mixture of 1,3-dimethylthymine (**1a**) or its related compounds with naphthalene (**2**) provides benzopyrimidobarrelelene derivatives (**3**) through 1,4-cycloaddition.



Scheme 1.

UV-Irradiation of an equivalent molar solution (1.5 mM) of 1,3-dimethylthymine (**1a**) and naphthalene (**2**) in cyclohexane with a 500 W high-pressure mercury lamp in a degassed Pyrex tube ($\lambda > 300$ nm) for 15 h at ambient temperature initiated 1,4-cycloaddition to give 4a-methyl-5,10-ethenobenzo[*f*]-quinazolines (**3a**) in the *cis*-geometry (*endo*-orientation) in 72 % yield (at the stage where 46 % of **1a** has been consumed).

The structural assignment of **3a**⁷ 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 283, The ¹H-NMR (C₆D₆) spectrum showed signals due to C4a-CH₃, N¹-CH₃, and N³-CH₃ at δ 1.21, 2.68, and 2.80 (each 3H, s), respectively. Three signals ascribable to the H-10a, H-10 and H-5 methine protons appeared at δ 2.55 (1H, d, $J=2.3$ Hz), 3.51 (1H, ddd, $J=6.3, 2.3, 1.2$ Hz, H-10), and δ 4.10 ppm (1H, dd, $J=6.3, 1.8$ Hz, H-5), respectively. Two signals due to the H-11 and H-12 vinyl protons appeared at δ 6.05 (1H, ddd, $J=7.5, 6.3, 1.8$ Hz), and 6.14 (1H, ddd, $J=7.5, 6.3, 1.2$ Hz), respectively. The four aromatic protons were observed in the region between δ 6.8 and 7.1 ppm.

The stereochemistry of **3a** 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, C4a-CH₃, and N¹-CH₃. Additional NOE results confirmed the structure assigned to **3a** (Figure 1).

We then examined the photoreaction of 1,3-dimethyluracil (**1b**) (20 h) and found that the corresponding barrelene derivative (**3b**)⁷ was formed in high yield (68% at the stage where 44 % of **1b** consumed).

The present reaction may be the first report of photochemical C-C bond formation between non-halogenated pyrimidine bases and an aromatic ring.

These results encouraged us to further investigate the scope of the cross-linking of non-halogenated pyrimidine derivatives having various substituents at C-5 with naphthalene.

Photoreaction of methoxy derivative of 1,3-dimethylthymine (**1c**: R=CH₂OCH₃) for 15 h afforded the corresponding 1,4-adducts (**3c**)⁷ as the sole product in moderate yield (40% at the stage where 36 % of **1c** consumed).

Similarly trifluoromethyl derivative (**1d**: R = CF₃) afforded the corresponding 1,4-adducts (**3d**)⁶ as the sole products in moderate yields (38% based on **1d** 47% consumed) after 15 h irradiation.

UV-Irradiation of 5-methoxy-1,3-dimethyluracil (**1e**) furnished the corresponding *cis*-barrelene derivative (**3e**)⁶ in 38% yield (based on 85% **1e** consumed). In this case, photoreaction was performed in benzene, since **1e** is sparingly soluble in cyclohexane.

Similar photoreaction of either 5-cyano- (**1f**) or 5-nitro-1,3-dimethyluracil (**1g**) only recovered the starting materials and failed to give a cycloaddition product.

The present study demonstrates the first C-C bond formation between non-halogenated pyrimidine and naphthalene. In light of the report that 1-butylthymine forms a strong complex with naphthalene derivatives through stacking, and whose geometry in molecular recognition is controlled by electronic characteristics of the naphthalene moiety,³ the present findings may be of interest with respect to developing an analytical probe.

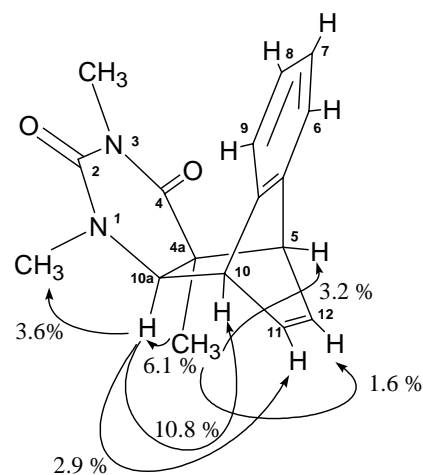


Figure 1. NOE Correlations for **3a**

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7. Selected data for; **3a**: Colorless crystals; mp 153.5-156.5 °C (hexane).
3b: Colorless crystals; mp 116.0-118.0 °C (hexane). ¹H-NMR (CDCl₃) : 2.70 (3H, s, N³-CH₃), 3.07 (3H, s, N¹-CH₃), 3.11 (1H, dd, *J*=10.3, 2.9 Hz, H-4a), 3.59 (1H, dd, *J*=10.3, 2.9 Hz, H-10a), 4.30 (1H, ddd, *J*=6.3, 2.9, 1.2 Hz, H-10), 4.49 (1H, ddd, *J*=6.3, 2.9, 1.2 Hz, H-5), 6.56 (1H, ddd, *J*=7.5, 6.3, 1.2 Hz, H-11), 6.68 (1H, ddd, *J*=7.5, 6.3, 1.2 Hz, H-12), 7.11 (3H, H-6, H-7, and H-8), 7.19 (1H, m, H-9). FABMS *m/z*: 269 (M+H)⁺.
3c: Colorless crystals; mp 99.5-102.0°C (hexane). ¹H-NMR (CDCl₃) : 2.63 (3H, s, N³-CH₃), 3.09 (3H, s, N¹-CH₃), 3.13 (1H, d, *J*=8.6 Hz, C4a-CH₂), 3.24 (3H, s, OCH₃), 3.44 (1H, d, *J*=2.3 Hz, H-10a), 4.10 (1H, d, *J*=8.6 Hz, C4a-CH₂), 4.16 (1H, dd, *J*=6.3, 1.7 Hz, H-5), 4.22 (1H, ddd, *J*=5.8, 2.3, 1.2 Hz, H-10), 6.52 (1H, ddd, *J*=7.5, 6.3, 1.2 Hz, H-12), 6.60 (1H, ddd, *J*=7.5, 5.8, 1.7 Hz, H-11), 7.0-7.2 (4H, aromatic-H). FABMS *m/z*: 313 (M+H)⁺.
3d: Colorless crystals; mp 94.0-96.0 °C (dichloromethane-hexane). ¹H-NMR (CDCl₃) : 2.64 (3H, s, N³-CH₃), 3.16 (3H, s, N¹-CH₃), 3.70 (1H, d, *J*=2.2 Hz, H-10a), 4.27 (1H, m, *J*=2.2, 6.4 Hz, H-10), 4.72 (1H, dd, *J*=1.7, 5.9 Hz, H-5), 6.06 (1H, dd, *J*=7.6, 5.9 Hz, H-12), 6.70 (1H, ddd, *J*=7.6, 6.4, 1.7 Hz, H-11), 7.11-7.22 (4H, aromatic H). FABMS *m/z*: 337(M+H)⁺.
3e: Colorless crystals; mp 147.0-149.0 °C (ethanol). ¹H-NMR (C₆D₆) δ: 2.65 (3H, s, N¹-CH₃), 2.79 (3H, s, OCH₃), 2.97 (1H, d, *J*=2.3 Hz, H-10a), 3.02(3H, s, N³-CH₃), 3.54 (1H, ddd, *J*=6.3, 2.3,1.2 Hz, H-10), 4.59 (1H, dd, *J*=6.3, 1.2 Hz, H-5), 6.19 (1H, ddd, *J*=7.5, 6.3, 1.2 Hz, H-11), 6.38 (1H, ddd, *J*=7.5, 6.3, 1.2 Hz, H-12), 6.8-7.0 (4H, aromatic-H). FABMS *m/z*: 299 (M+H)⁺.