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PHOTOCHEMICAL SYNTHESIS OF NAPHTHOCYCLOBUTA-PYRIMIDINES *VIA* 1,2-CYCLOADDITION OF 6-CHLORO-1,3-DIMETHYLURACIL WITH NAPHTHALENES

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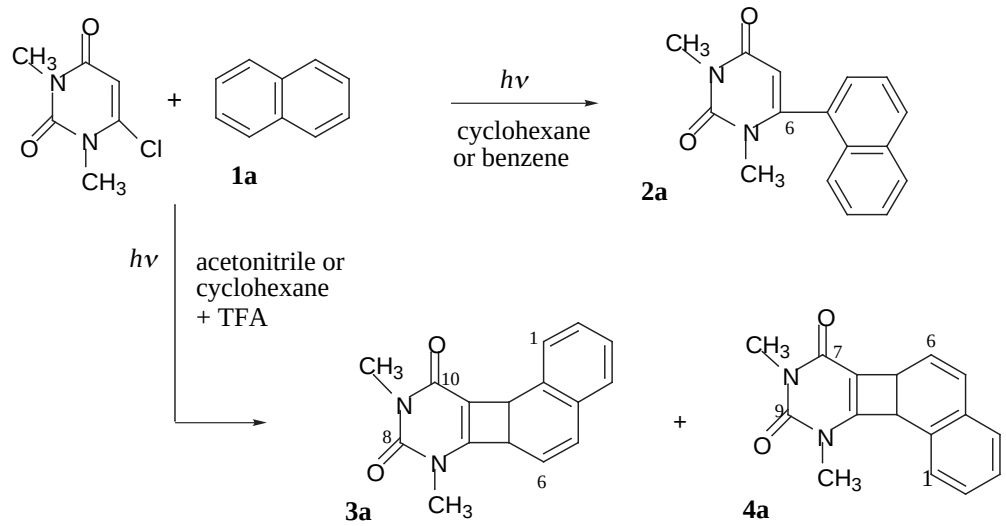
Abstract – UV-Irradiation of a solution of 6-chloro-1,3-dimethyluracil (6-ClDMU) and naphthalene in a non-polar solvent (cyclohexane) afforded 6-(1-naphthyluracil) as the sole product. In contrast, irradiation of a solution of 6-ClDMU and naphthalene in a polar medium in the absence of TFA effected 1,2-cycloaddition to give naphthocyclobutapyrimidines in moderate yields. This photocycloaddition reaction also proceeds in non-polar solvents in the presence of TFA.

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 the photoreaction of 6-chloro-1,3-dimethyluracil (6-ClDMU) with benzene derivatives proceeds by way of 1,2-cycloaddition to give cyclooctapyrimidines.[2] Certain cyclooctapyrimidines were further converted into various novel valence isomers,[3-5] by way of a variety of electrocyclic pathways depending on the reaction conditions and substituents on the cycloadducts. Similar photoreaction with 5-chloro-DMU (5-ClDMU) and these benzene derivatives proceeded through the conventional substitution reaction to give 5-aryl-DMUs (5-ArDMUs). The photosubstitution reaction was promoted significantly by the addition of TFA, while the analogous photosubstitution reaction with 5-fluoro-DMU (5-FDMU) in benzenes proceeded only in the presence of TFA.[6,7] However, no cycloaddition reaction products were observed under these conditions.[6] Meanwhile, naphthalene and its derivatives have been reported to add photochemically to alkenes in different manners[8-10] including 1,2-, 1,4-, and 1,8-cycloadditions to give various new ring systems. We have recently found that UV-irradiation of a solution of 5-FDMU and naphthalene in aprotic media effected a stereoselective 1,4-cycloaddition reaction to give a barrelene derivative in high yield.[11] This finding is of great interest since the reaction proceeds in different mode

form that of 6-ClDMU with benzene, and does not require the presence of acid. These results prompted us to extend our work to the photoreaction of 6-ClDMU with naphthalene (**1a**).

In the present paper, we describe our finding that the photoreaction of 6-ClDMU with naphthalene (**1a**) in a non-polar solvent resulted in a substitution reaction to yield 1,3-dimethyl-6-(1-naphthyl)uracil (**2**)[12] as the major product, while UV-irradiation of the reaction mixture in the polar solvent acetonitrile, induced 1,2-cycloaddition followed by subsequent dehydrochlorination to give novel naphthocyclobuta-pyrimidines (**3a**, **4a**) in moderate yields .

An equivalent molar solution of 6-ClDMU and naphthalene (**1a**) in various solvents was irradiated externally with a 500 W high-pressure mercury lamp for 1 h in a degassed Pyrex tube (λ>300 nm) at ambient temperature. Reaction in the non-polar aprotic solvents cyclohexane and benzene preferentially gave substituted product (**2**). In contrast, the reaction in acetonitrile predominantly gave two novel 1,2-cycloadducts, naphthocyclobutapyrimidine-8,10-dione (**3a**) and the 7,9-dione isomer (**4a**) in 58% and 12% yields (Scheme 1).



Scheme 1. Photoreaction of 6-ClDMU with naphthalene.

Interestingly, the reaction in cyclohexane or benzene in the presence of TFA gave 1,2-cycloadducts (**3a**, **4a**) preferentially, indicating that substitution reaction proceeded in non-polar solvents, while 1,2-cycloaddition was preferentially induced in polar media. The reaction in methanol however, gave no cycloadducts, and 6-methoxylated DMU (**5**)[13] was the only product obtained. These results are summarized in Table 1.

Table 1. Photoreaction of 6-ClDMU and naphthalene

Solvent	Yields† (%) of			Recovery (%) of
	6-ArDMU(**2**)	**3a**	**4a**	6-ClDMU
Cyclohexane	9 (39)	0	0	77
Cyclohexane + TFA	7 (11)	7 (11)	3 (5)	38
Benzene	10 (12)	0	0	81
Methanol¶	0	0	0	22
Acetonitrile	0	30 (58)	6 (12)	48

†: Yields based on 6-ClDMU consumed are given in the parentheses. ¶: 6-Methoxy-1,3-dimethyluracil (**5**) was obtained quantitatively.

Structural assignments for **3a**[14] and **4a**[15] were made on the basis of detailed MS and the NMR spectroscopic studies: The MS showed the expected molecular ion peak $[M]^+$ at m/z 266 as the base peak.

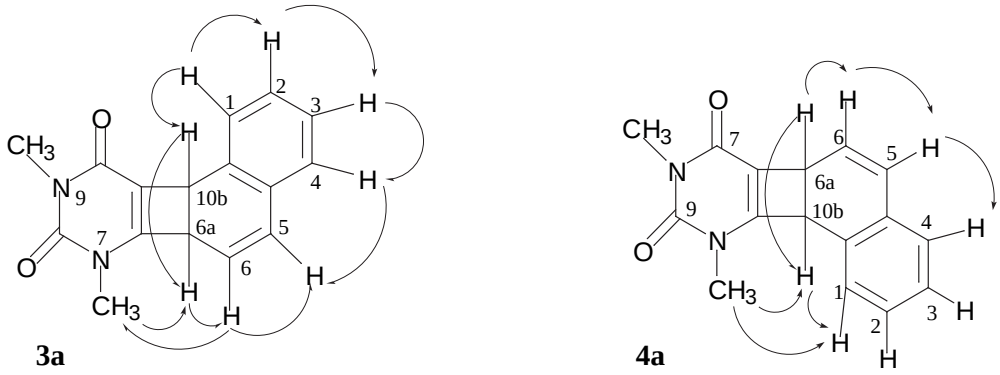


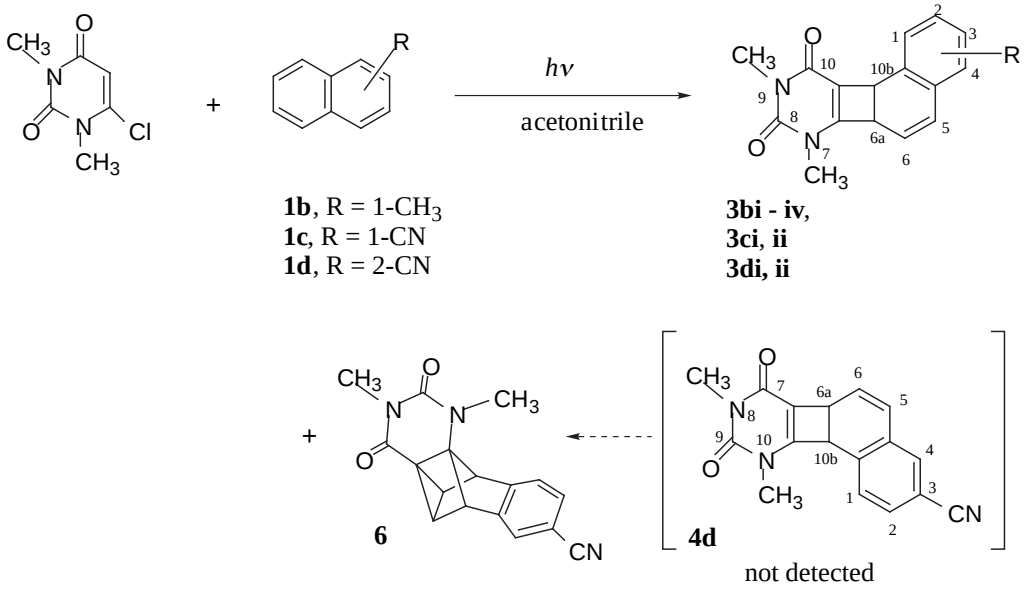
Figure 1. NOE correaltions for **3a** and **4a**.

The NOE experiments confirmed the structure assigned to **3a** and **4a**, respectively (Figure 1).

The present photoreaction (1 h) was subsequently applied to 1-methylnaphthalene (**1b**) to afford four regioisomeric 8,10-dione derivatives[16] as a result of the methyl substituent (**3bi**, R =1-CH_3; **3bii**, 10b-CH_3; **3biii**, R = 5-CH_3; **3biv**, R = 4-CH_3) in 27%, 25%, 21%, and 8% yields (Scheme 2).

The present reaction was then extended to 1-naphthonitrile (**1c**). Reaction with **1c** under the same conditions employed above gave 8,10-dione derivatives (**3ci**, R = 1-CN) and (**3cii,** R = 4-CN) in 11.5% and 10.5% yields (Scheme 2).[16]

Similar photoreaction (2 h) with 2-naphthonitrile (**1d**) preferentially afforded the regioisomeric 1,2-adduct (**3di**, 3-CN) (50%) and (**3dii**, 2-CN) (17%),[16] together with a highly strained cage compound (**6**, see Figure 2),[17] *albeit* in low yield (3%)(Scheme 2).



Scheme 2. Photoreaction of 6-ClDMU with substituted naphthalenes in acetonitrile.

The formation of **6** can be explained in terms of the subsequent secondary [2 + 2] cycloaddition of the intermediate (**4**) that we failed to isolate (Scheme 3). It is shown that 6-ClDMU preferably attacks the electron rich ring of naphthalene, *i.e*. the ring with no CN group, leading to the formation of naphtho[1',2':3,4]cyclobuta[1,2-*d*]pyrimidine-8,10-dione (**3**) more favorably than naphtho[1',2':4,3]cyclobuta[1,2-*d*]pyrimidine-7,9-dione (**4**).

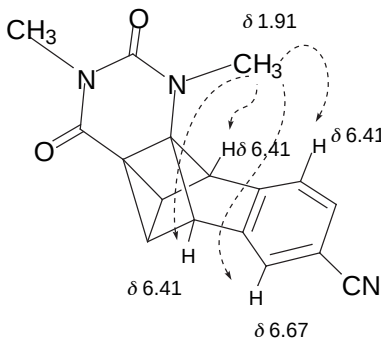
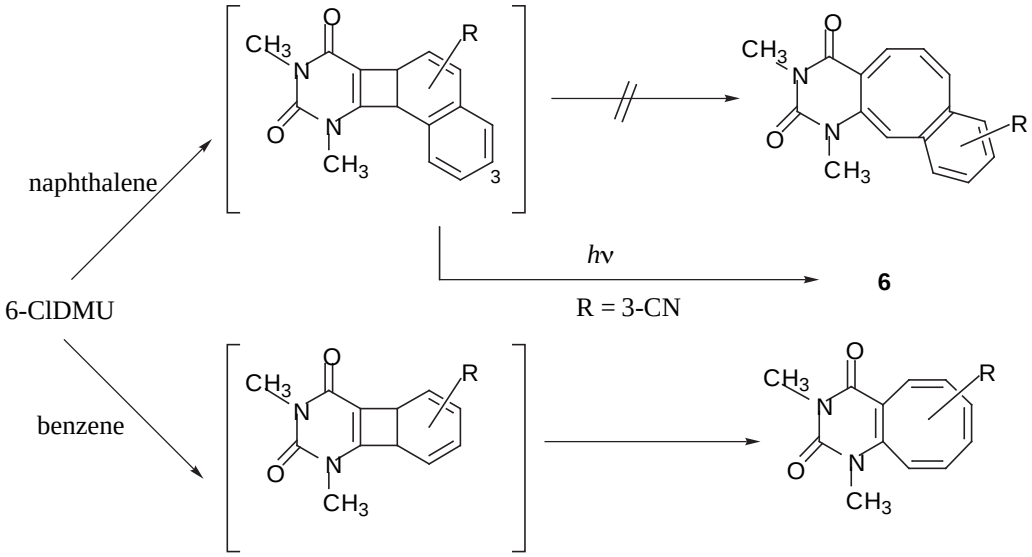


Figure 2. NOE correlation for **6**.

Thus, in competition with substitution, the photoreaction of 6-ClDMU with naphthalenes proceeds *via* 1,2-cycloaddition in a polar solvent to furnish novel 1,2-cycloadducts (**3**) in high regioselectivity with elimination of hydrogen chloride (HCl), so as to generate a conjugate enone moiety in the ring system, wherein the resulting cyclobutene ring remains intact, without undergoing an electrocyclic reaction to form a cyclooctatetraene moiety (see Scheme 3). The present photocycloaddition with naphthalenes is in contrast to the photoreaction with benzenes, whereby cyclooctapyrimidines are produced as the primary products by way of the initial 1,2-cycloaddition followed by dehydrochlorination and subsequent ring opening of the resulting cyclobutene moiety *via* an electrocyclic process.



Scheme 3. The formation of cycloadduct (**6**).

In conclusion, the present work represents a novel and simple method for the skeletal modification of the pyrimidine ring.

ACKNOWLEDGEMENTS

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References and notes

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12. Selected data for 1,3-dimethyl-6-(1-naphthyl)pyrimidine-2,4-dione (**2**): Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, s, N^3-CH_3), 3.48 (3H, s, N^1-CH_3), 5.83 (1H, s, H-5), 7.42 (1H, d, *J*=7.1 Hz, Ar-H), 7.53-7.67 (4H, m, Ar-H), 7.92-7.97 (1H, m, Ar-H), 8.00 (1H, d, *J*=8.4 Hz, Ar-H). HRMS: Calcd for $C_{16}H_{14}O_2N_2$: 266.1055. Found: 266.1066.

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14. Selected data for 6a,10b-dihydro-7,9-dimethylnaphtho[1',2':3,4]cyclobuta[1,2-*d*]pyrimidine-8,10-dione (**3a**): Colorless crystals. mp 202–203℃ (recrystallized from ether). ^{1}H-NMR ($CDCl_3$) δ: 3.26 (3H, s, N^9-CH_3), 3.33 (3H, s, N^7-CH_3), 4.32 (1H, dd, *J*=4.9, 4.7 Hz, H-6a), 4.57 (1H, d, *J*=4.9 Hz, H-10b), 5.85 (1H, dd, *J*=9.9, 4.7Hz, H-6), 6.47 (1H, d, *J*=9.9 Hz, H-5), 7.04 (1H, d, *J*=7.1 Hz, H-4), 7.16 (1H, t, *J*=7.3 Hz, H-3), 7.25 (1H, t, *J*=7,3 Hz, H-2), 7.45 (1H, d, *J*=7.3 Hz, H-1). HRMS: Calcd for $C_{16}H_{14}O_2N_2$: 266.1055. Found: 266.1055.

15. Selected data for 6a,10b-dihydro-8,10-dimethylnaphtho[1',2':4,3]cyclobuta[1,2-*d*]pyrimidine-7,9-dione (**4a**)**:** Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (3H, s, N^8-CH_3), 3.31 (3H, s, N^{10}-CH_3), 4.12 (1H, dd, *J*=4.0, 4.8 Hz, H-6a), 4.81 (1H, d, *J*=4.8 Hz, H-10b), 6.22 (1H, dd, *J*=10.1, 4.0 Hz, H-6), 6.31(1H, d, *J*=10.1 Hz, H-5), 7.11(1H, d-like, *J*=7.5 Hz, H-4), 7.21-7.26(3H, m, H-1, H-2, H-3). HRMS: Calcd for $C_{16}H_{14}O_2N_2$: 266.1055. Found: 266.1055.

16. Satisfactory spectral data (^{1}H-NMR, MS, HRMS) were obtained for the cycloadducts.

17. Selected data for adduct (**6**): Colorless crystals. mp 118–119℃ (recrystallized from ether). ^{1}H-NMR (C_6D_6) δ: 1.91 (3H, s, N-CH_3), 2.46 (2H, s) 2.97 (1H, s), 2.99 (1H, s), 3.35 (3H, s, N-CH_3), 6.41 (1H, d, *J*=7.7 Hz), 6.67 (1H, s), 6.86 (1H, d, *J*=7.7 Hz). HRMS: Calcd for $C_{17}H_{13}N_3O_2$: 291.1008. Found: 291.1015.