

Photocycloaddition of 6-Cyano-1,3-dimethyluracil to Alkenes; Synthesis of tetrahydrocyclobutapyrimidine-6a-carbonitriles

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Abstract-----UV-Irradiation of 6-cyano-1,3-dimethyluracil (6-CNDMU) and alkenes having electron-donating and electron-withdrawing groups afforded the corresponding cyclobutapyrimidine derivatives with head-to-tail regiochemistry in appreciable yields. Similarly 6-CNDMU coupled with 6-CNDMU or 1,3-dimethyluracil to give *trans-syn* type cyclobutene pyrimidine dimers, while the reaction with 1,3-dimethylthymine proceeded the coupling reaction non-regio- and stereoselectively.

The [2+2] photocycloaddition of alkenes to α,β -unsaturated carbonyl compounds are well recognized as one of the most widely used photochemical reaction in the synthetic organic chemistry. The synthetic applications¹ and the mechanistic aspects² of such photoannulation have been reviewed. The search for the regioselectivity of the cycloaddition remains still an intriguing subject.³

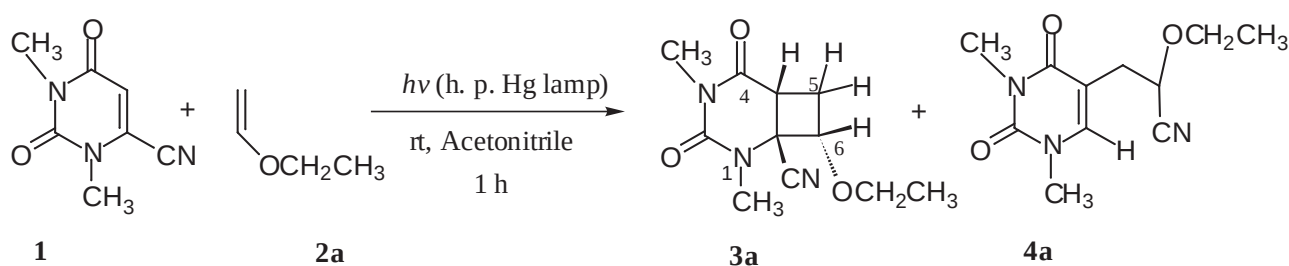
Photocycloaddition of pyrimidine bases with alkenes has also been investigated from synthetic and photochemical points of view.⁴ However attention has been paid largely on the photochemistry of 5-substituted uracils and little has been studied on that of 6-substituted derivatives.

In the course of our continuing studies on the photoreaction of 6-chloro-1,3-dimethyluracil (6-ClDMU) with unsaturated hydrocarbons,⁵ we have previously reported that the photoreaction of 6-ClDMU with alkenes furnished cyclobutapyrimidines in appreciable yields.⁶ Photoreaction of 6-cyano-1,3-dimethyluracil (6-CNDMU; **1**) with certain alkyl alkenes has been reported by Matsuura's group.⁷ Their attention, however, has been paid mainly on the reaction mechanism of the [3 + 2] cycloaddition, which

is involved competitively with the [2 + 2] process in the reaction and little has been studied on the [2 + 2] cycloaddition.

In an attempt to develop a general synthesis of cyclobutapyrimidines, we have investigated the photoreaction of **1** with alkenes. In the present paper, we describe our findings that the photoreaction produced [2 + 2] cycloadducts regioselectively in fair yields.

A solution of 6-cyano-1,3-dimethyluracil (**1**)(15 mM) and ethyl vinyl ether (**2a**)(1.5 M) in acetonitrile was irradiated at ambient temperature for 1 h to give [2 + 2] cycloadduct (**3a**) and pyrimidine-propanenitrile (**4a**) resulted from the initial [3 + 2] cycloaddition in fair yields (Scheme 1).



Scheme 1

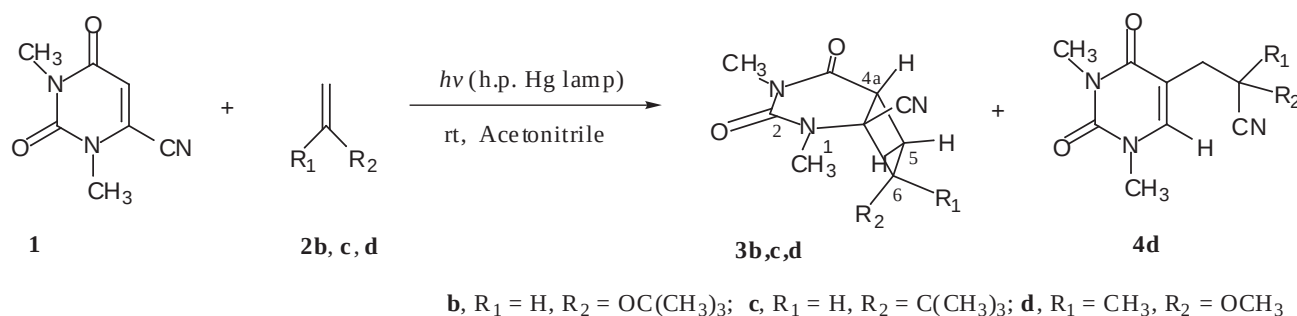
Similar photoreaction in acetone gave **3a** and **4a** in a similar yields but the ratio (**3a** vs. **4a**) was lower than that in acetonitrile. The photoreaction in dichloromethane afforded the same products, but the reaction proceeded sluggishly, suggesting that acetonitrile may be the most appropriate solvent for the synthesis of [2 + 2] adducts (Table 1). Hence, the following reactions were performed essentially in acetonitrile.

Table 1. Photoreaction of **1** with ethyl vinyl ether (**2a**).

Solvent	Yields ^{a)} (%) of		1 consumed (%)
	3a	4a	
Acetonitrile	33	6	21
Acetone	28	12	14
CH ₂ Cl ₂	24	3	3

a) Yields are given on the basis of **1** consumed.

UV-Irradiation of *t*-butyl vinyl ether (**2b**) in acetonitrile gave head-to-tail (h-t) [2 + 2] adduct (**3b**) predominantly (71%) (Scheme 2).



Scheme 2. Cycloaddition of **1** to electron-rich alkenes (**2b-d**)

We then carried out the photoreaction with *t*-butylethylene (3,3-dimethyl-1-butene) (**2c**) under the similar conditions to afford [2 + 2] adduct (**3c**) preferentially (50%). Similar photoreaction with 2-methoxypropene (**2d**; R₁ = CH₃, R₂ = OCH₃) gave [3 + 2] adduct (**4d**) as the major product (39%) and the [2 + 2] adduct (**3d**) only in modest yield (7%). These results are coincident with those expected from the mechanism proposed by Matsuura *et al.*⁷

Table 2. Photoreaction of **1** with alkenes.

2	Yields (%) ^a of		1 consumed (%)
	3	4	
b	71	-- ^b	99
c	50	-- ^b	44
d	7	39	45

^a) Yields are given on the basis of **1** consumed.

^b) Not detected.

Although the reaction with α,α -disubstituted alkene (**2d**) afforded the desired [2 + 2]

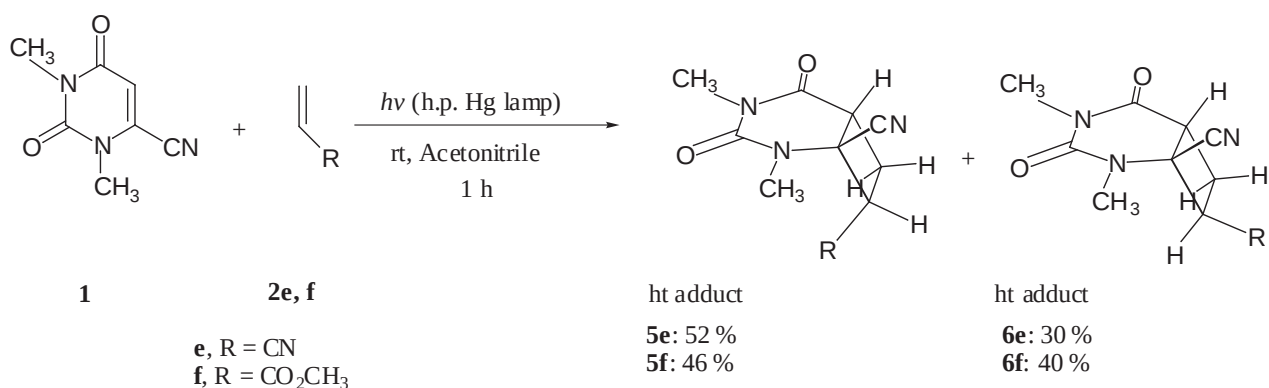
cycloadduct (**3d**) as the minor component, the other alkenes (**2a-c**) underwent photocycloaddition stereoselectively to form cyclobutapyrimidines (**3b-c**) with head-to-tail (h-t) regiochemistry (Table 2).

Then the present photoreaction was applied to the reaction with electron deficient alkenes, acrylonitrile (**2e**) and methyl acrylate (**2f**).

Photocycloaddition proceeded smoothly (1 h) with acrylonitrile (**2e**) to give the stereoisomeric [2 + 2] cycloadducts (**5e** and **6e**) with head-to-tail orientation in 52% and 30% yields, respectively (Scheme 3).

Similarly photoreaction with methyl acrylate (**2f**) furnished *trans*- and *cis*-cycloadducts with head-to-tail

orientation (**5f**, **6f**) in fair yields (46% and 40%) (Scheme 3).



Scheme 3. Cycloaddition of **1** to electron-deficient alkenes (**2e,f**)

Interestingly, these results are contrasting to our previous findings that the analogous photoreaction of 6-ClDMU with olefins having an electron-withdrawing group failed to effect cycloaddition. Thus, it is demonstrated that 6-CNDMU (**1**) undergoes photocycloaddition with either electron-rich or electron-deficient alkenes to give the corresponding [2 + 2] cycloadducts regioselectively.

Photodimerization of pyrimidine bases has been studied extensively from biological importance.⁸

Deering and Setlow studied on the photochemical behavior of thymine in aqueous solution and reported that thymine underwent dimerization upon irradiation with 280 nm light, and the resulting dimer was

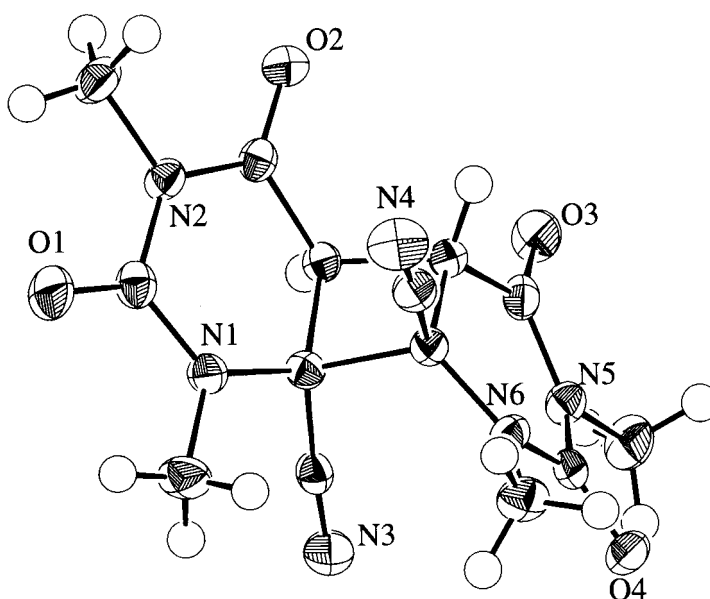
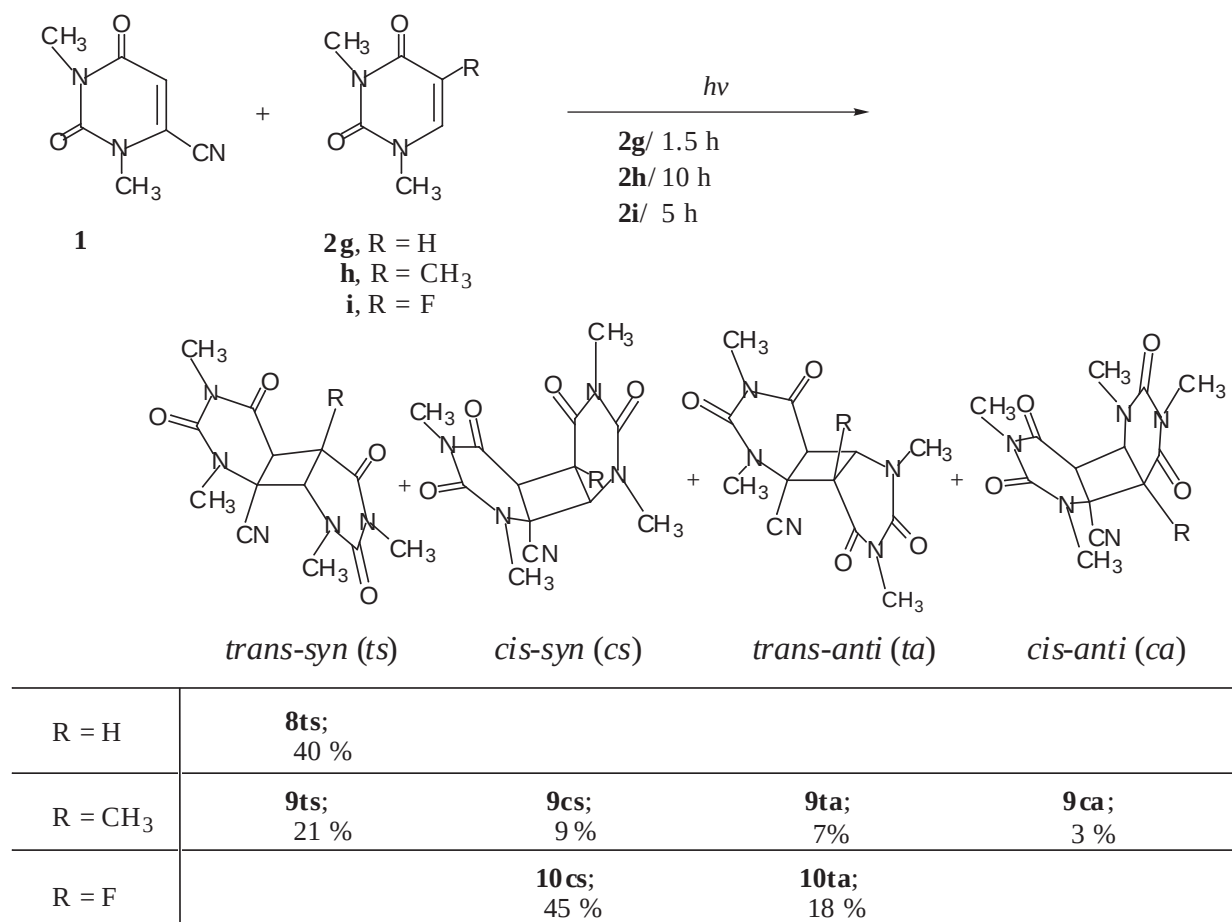


Figure 1. X-Ray crystallography of *trans-syn* **1** $\diamond$ **1** dimer (**7ts**)

reverted to the parent with 240 nm light, while it was insensitive to the light longer than 300 nm.⁹ As demonstrated above, irradiation of **1** at wavelength > 300 nm induced the cycloaddition to give cyclobutapyrimidines in high efficiency. Our attention was directed to the photoreaction with pyrimidine bases, which consist of an enamide component.

First, we examined the photodimerization of **1**. Upon irradiation of a solution of **1** in acetonitrile, the dimer of **1** (**1**⋈**1** dimer, **7ts**) was formed quantitatively. The ¹H-NMR spectrum of **7ts** showed two singlet peaks ascribable to N-methyl protons and a singlet peak due to methine protons. These data were insufficient to elucidate the structure including the stereochemistry. Therefore the X-Ray crystallographic analysis was performed to determine the structure as *trans-syn* **1**⋈**1** dimer (**7ts**) (Figure 1). Interestingly, such regio and stereoselectivity is analogous to that reported for orotic acid.¹⁰

UV-irradiation of **1** with 1,3-dimethyluracil (**2g**) effected regio- and stereo-selective coupling to give the *trans-syn* adduct (*trans-syn* **1**⋈**2g** adduct, **8ts**) in fair yield (40 %) (Scheme 4).



Scheme 4. Photoreaction of **1** with 1,3-dimethyluracil derivatives (**2g**, **h**, **i**)

Similar irradiation of **1** and 1,3-dimethylthymine (**2h**) resulted in the formation of the corresponding four regio- and stereoisomeric [2 + 2] cycloadducts, involving the *trans-syn* isomer (*trans-syn* **1**◊**2h** adduct, **9ts**) as the major product (21 %) and the other *cis-syn* (**9cs**) (9 %), *trans-anti* (**9ta**) (7 %), and *cis-anti* isomers (**9ca**) (3 %) as the minor components (Scheme 4).

In contrast to the above pyrimidines, photocoupling with 5-fluoro-1,3-dimethyluracil (**2i**) proceeded smoothly in the way as to give the *cis-syn* isomer (*cis-syn* **1**◊**2i** adduct, **10cs**, 45%) most preferentially together with *trans-anti* (**10ta**) (18%) isomers (Scheme 4).

In conclusion, UV-irradiation of **1** resulted in [2 + 2] photocycloaddition with various alkenes to give cyclobutanes regioselectively. Thus, the present reaction would provide a useful method for the skeletal modification of the pyrimidine ring.

EXPERIMENTAL

All melting points are uncorrected. NMR spectra were measured with a JEOL JNM-EX400 (400 MHz) spectrometer, and ¹H-NMR chemical shifts are given on the δ (ppm) scale based on those of the signals of solvents; CDCl₃ (δ 7.26), C₆D₆ (δ 7.15), CD₃CN (δ 1.93). MS spectra and high-resolution MS (HRMS) spectra were recorded with JEOL JMS-DX303 (EI) and LEOL JMS-HX110 (FAB). Short-column chromatography was performed on Kieselgel Si-60 (Merck). HPLC was conducted on a Shim-pac PREP-Sil (H) (25 cm x 20 mm *i. d.*) (silica gel), using a Shimadzu LC-6A apparatus with monitoring at 254 nm. UV-Irradiation was carried out externally with a 500 W high-pressure mercury (h. p. Hg) lamp (Eiko-sha) in a degassed Pyrex tube (> 300 nm) on a merry-go-round apparatus at room temperature.

6-CNDMU (**1**) was prepared according to the reported procedure.¹¹

General procedure of the photoreaction ----- A solution of **1** (12.4 mg, 0.075 mmol) and an alkene (100 equiv. molar; 7.5 mmol) (in the cases of uracil derivatives, 10 equiv. molar, 0.75 mmol) in acetonitrile (5 mL) in a degassed Pyrex test tube was irradiated externally for 1 h unless cited therein. The reaction mixture was concentrated *in vacuo*, and analyzed by means of ¹H-NMR spectroscopy with terephthalonitrile as an internal standard.

Typical procedure for the isolation of the cycloadduct ----- After the photoreaction according to the general procedure, the reaction mixtures in several Pyrex tubes were put together, and evaporated *in vacuo*. The residual oil was passed through a short column of silica gel with ethyl acetate. The eluate was submitted to HPLC with following solvent systems; ethyl acetate-hexane for **3b-i**, and ethyl acetate-dichloromethane for **3a**.

rel-(4aS, 6R, 6aR)-6-Ethoxy-1,3-dimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6a-carbonitrile (3a): Colorless oil. ¹H-NMR (CDCl₃) δ: 1.22 (3H, t, *J* = 7.0 Hz, OCH₂CH₃-6), 2.37 (1H, ddd, *J* = 8.3, 9.9, 11.7 Hz, βH-5), 2.86 (1H, ddd, *J* = 7.1, 9.0, 11.7 Hz, αH-5), 3.17 (3H, s, N¹-CH₃), 3.21 (3H, s, N³-CH₃), 3.29 (1H, dd, *J* = 9.0, 9.9 Hz, H-4a), 3.62 (2H, dq, *J* = 1.4, 7.0 Hz, OCH₂CH₃-6), 4.25 (1H, dd, *J* = 7.1, 8.3 Hz, H-6). EIMS *m/z* (%): 237 (M⁺, 1), 166 (5), 72 (100). HREIMS: Calcd for C₁₁H₁₅N₃O₃: 237.1113. Found: 237.1135.

2-Ethoxy-3-(1,3-dimethyl-2,4-dioxopyrimidin-5-yl)propanenitrile (4a): Colorless oil. ¹H-NMR (CDCl₃) δ: 1.23 (3H, t, *J* = 7.0 Hz, OCH₂CH₃-2), 2.73 (1H, dd, *J* = 7.2, 14.0 Hz, H-3), 2.93 (1H, dd, *J* = 7.2, 14.0 Hz, H-3), 3.35 (3H, s, N^{3'}-CH₃), 3.40 (3H, s, N^{1'}-CH₃), 3.54 (1H, dq, *J* = 7.0, 9.0 Hz, OCH₂CH₃-2), 3.78 (1H, dq, *J* = 7.0, 9.0 Hz, OCH₂CH₃-2), 4.46 (1H, t, *J* = 7.2 Hz, H-2), 7.20 (1H, s, H-6'). NOESY: H-4a and αH-5>H-6; H-6 and αH-5> OCH₂CH₃-6>H-4a, βH-5; αH-5 and βH-5> H-4a, H-6; N^{1'}-CH₃ and OCH₂CH₃-6. EIMS *m/z* (%): 237 (M⁺, 7), 153 (100), 96 (64). HREIMS: Calcd for C₁₁H₁₅N₃O₃: 237.1113. Found: 237.1098.

rel-(4aS, 6R, 6aR)-6-*t*-Butoxy-1,3-dimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6a-carbonitrile (3b): Colorless needles. mp 126-127 °C (recrystallized from hexane). ¹H-NMR (CDCl₃) δ: 1.24 (9H, s, OC(CH₃)₃-6), 2.41 (1H, ddd, *J* = 8.6, 10.4, 11.5 Hz, βH-5), 2.79 (1H, ddd, *J* = 7.1, 8.8, 11.5 Hz, αH-5), 3.18 (3H, s, N¹-CH₃), 3.21 (3H, s, N³-CH₃), 3.27 (1H, dd, *J* = 8.8, 10.4 Hz, H-4a), 4.41 (1H, dd, *J* = 7.1, 8.6 Hz, H-6). NOESY: H-4a and αH-5>H-6>>βH-5; H-6 and αH-5>H-4a>βH-5; αH-5 and βH-5> H-6> H-4a. EIMS *m/z* (%): 266 (1), 265(M⁺, 1), 166 (72), 57 (100). HREIMS: Calcd for C₁₃H₁₉N₃O₃: 265.1426. Found: 265.1403. *Anal.* Calcd for C₁₃H₁₉N₃O₃: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.78; H, 7.31; N, 15.82.

rel-(4aS, 6R, 6aR)-6-*t*-Butyl-1,3-dimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6a-

carbonitrile (3c) : Colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$ -6), 2.31 (1H, dd, $J = 6.0, 8.6$ Hz, H-6), 2.51-2.34 (2H, m, H-5), 3.06 (3H, s, N^1 - CH_3), 3.22 (3H, s, N^3 - CH_3), 3.62 (1H, dd, $J = 8.4, 9.9$ Hz, H-4a). NOESY: H-4a and H-5, H-6. EIMS m/z (%): 249 (M^+ , 1), 166 (66), 84 (43), 69 (100). HREIMS: Calcd for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_2$: 249.1477. Found: 249.1473.

rel-(4aS, 6R, 6aR)-6-Methoxy-1,3,6-trimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6a-carbonitrile (3d): Colorless oil. $^1\text{H-NMR}$ (C_6D_6) δ : 0.87 (3H, s, CH_3 -6), 1.55 (1H, dd, $J = 9.7, 12.6$ Hz, αH -5), 1.86 (1H, dd, $J = 5.7, 12.6$ Hz, βH -5), 2.42 (3H, s, OCH_3 -6), 2.75 (1H, dd, $J = 5.7, 9.7$ Hz, H-4a), 2.89 (3H, s, N^1 - CH_3), 3.11 (3H, s, N^3 - CH_3). NOESY: H-4a and αH -5 > CH_3 -6 > βH -5; CH_3 -6 and OCH_3 -6 > αH -5 > H-4a; αH -5 and βH -5 > CH_3 -6 > H-4a; βH -5 and αH -5 > OCH_3 -6 > H-4a; OCH_3 -6 and CH_3 -6 > βH -5. EIMS m/z (%): 238 (1), 237 (M^+ , 1), 166 (2), 72 (100). HREIMS: Calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_3$: 237.1113. Found: 237.1129.

3-(1,3-Dimethyl-2,4-dioxypyrimidin-5-yl)-2-methoxypropanenitrile (4d): Colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (3H, s, CH_3 -2), 2.81 (1H, d, $J = 14.0$ Hz, H-3), 2.85 (1H, d, $J = 14.0$ Hz, H-3'), 3.22 (3H, s, $\text{N}^{3'}$ - CH_3), 3.30 (3H, s, $\text{N}^{1'}$ - CH_3), 3.41 (3H, s, OCH_3 -2), 7.36 (1H, s, H-6'). EIMS m/z (%): 237 (M^+ , 6), 206 (6), 153 (100), 96 (75). HREIMS: Calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_3$: 237.1113. Found: 237.1101.

rel-(4aS,6R,6aR)-1,3-Dimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6,6a-dicarbonylnitrile (5e): Colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ : 2.73 (1H, dt, $J = 8.3, 12.6$ Hz, βH -5), 3.08 (1H, ddd, $J = 9.4, 10.1, 12.6$ Hz, αH -5), 3.26 (3H, s, N^1 - CH_3), 3.26 (3H, s, N^3 - CH_3), 3.76 (1H, dd, $J = 8.3, 9.4$ Hz, H-6), 3.84 (1H, dd, $J = 8.3, 10.1$ Hz, H-4a). NOESY: N^1 - CH_3 and H-6; H-4a and αH -5 > βH -5; βH -5 and αH -5; H-6 and αH -5 > βH -5. EIMS m/z (%): 218 (M^+ , 1), 165 (82), 108 (100). HREIMS: Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_2$: 218.0804. Found: 218.0794.

rel-(4aS,6S,6aR)-1,3-Dimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6,6a-dicarbonylnitrile (6e): Colorless crystals, mp 205-206 °C (recrystallized from isopropanol). $^1\text{H-NMR}$ (CD_3CN) δ : 2.70 (1H, ddd, $J = 6.2, 10.1, 12.6$ Hz, βH -5), 2.84 (1H, ddd, $J = 7.5, 10.6, 12.6$ Hz, αH -5), 3.03 (3H, s, N^1 - CH_3), 3.09 (3H, s, N^3 - CH_3), 3.78 (1H, ddd, $J = 1.1, 7.5, 10.1$ Hz, H-6), 3.98 (1H, ddd, $J = 1.1, 6.2, 10.6$ Hz, H-4a). NOESY: N^1 - CH_3 and H-6; H-4a and αH -5; βH -5 and αH -5, H-6; αH -5 and βH -5, H-4a; H-6 and βH -5, N^1 - CH_3 . EIMS m/z (%): 218 (M^+ , 1), 165 (84), 108 (100). HREIMS: Calcd for

C₁₀H₁₀N₄O₂: 218.0804. Found: 218.0788. *Anal.* Calcd for C₁₀H₁₀N₄O₂: C, 55.04; H, 4.62; N, 25.68. Found: C, 54.92; H, 4.73; N, 25.65.

rel-(4a*S*,6*R*,6a*R*)-Methyl 6a-cyano-1,3-dimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6-carboxylate (5f): Colorless oil. ¹H-NMR (CD₃OD) δ : 2.60 (1H, dt, *J* = 6.8, 12.6 Hz, β H-5), 2.79 (1H, ddd, *J* = 8.8, 10.0, 12.8 Hz, α H-5), 2.98 (3H, s, N¹-CH₃), 3.16 (3H, s, N³-CH₃), 3.83 (1H, dd, *J* = 8.8, 6.8 Hz, H-6), 3.84 (1H, dd, *J* = 6.8, 10.0 Hz, H-4a), 3.73 (3H, s, CO₂CH₃). NOE: irradiation at N¹-CH₃ with H-6 (19.0%); H-4a with α H-5 (7.1%) and β H-5 (5.1%); β H-5 with α H-5 (20.5%), H-4a (2.0%) and H-6 (2.0%); H-6 with α H-5 (3.9%) and β H-5 (3.0%); α H-5 with β H-5 (21.7%), H-4a (10.6%) and H-6 (7.9%). EIMS *m/z* (%): 251 (M⁺, 12), 191 (32), 165 (100), 108 (85). HREIMS: Calcd for C₁₁H₁₃N₃O₄: 251.0906. Found: 251.0905.

rel-(4a*S*,6*S*,6a*R*)-Methyl 6a-cyano-1,3-dimethyl-2,4-dioxo-4a,5,6,6a-tetrahydrocyclobutapyrimidine-6-carboxylate (6f): Colorless crystals, mp 72 °C (recrystallized from ether). ¹H-NMR (CDCl₃) δ : 2.55 (1H, ddd, *J* = 6.4, 9.2, 12.8 Hz, β H-5), 2.98 (1H, ddd, *J* = 7.2, 10.4, 12.8 Hz, α H-5), 3.17 (3H, s, N¹-CH₃), 3.24 (3H, s, N³-CH₃), 3.43 (1H, ddd, *J* = 1.1, 7.2, 9.2 Hz, H-6), 3.98 (1H, ddd, *J* = 1.1, 6.4, 10.4 Hz, H-4a), 3.87 (3H, s, CO₂CH₃). NOE: irradiation at N¹-CH₃ with H-6 (4.2%), and CO₂CH₃ (0.5%); β H-5 with α H-5 (27%) and H-6 (9.4%); α H-5 with β H-5 (28.2%) and H-4a (9.4%); H-6 with β H-5 (4.8%), N¹-CH₃ (3.6%), and CO₂CH₃ (0.7%). EIMS *m/z* (%): 251 (M⁺, 10), 191(35), 165 (100), 108 (85). HREIMS: Calcd for C₁₁H₁₃N₃O₄: 251.0906. Found: 251.0906.

trans-syn-6-Cyano-1,3-dimethyluracil dimer (1 $\diamond$ 1 dimer, 7ts): Colorless crystals. mp 162.5 °C (recrystallized from ether). ¹H-NMR (CDCl₃) δ : 3.30 (6H, s, N-CH₃ x 2), 3.34 (6H, s, N-CH₃ x2), 4.04 (2H, s, H-4a and H-4b). FABMS *m/z* (%): 331 (M+H)⁺, 166. HRFABMS: Calcd for C₁₄H₁₅N₆O₄: 331.1155. Found: 331.1178.

X-Ray crystallography of 1 $\diamond$ 1 dimer (7ts): Compound (7ts) crystallizes from ether and forms colorless prismatic crystals in the monoclinic space group P2₁/n with unit cell parameters *a* = 7.0938 (2) Å, *b* = 11.1178 (4) Å, *c* = 18.1877 (7) Å, *V* = 1432.80(9) Å³, *Z* = 4, *D_c* = 1.531 g/cm³. Data were collected on a Rigaku PAXIS-RAPID Imaging Plate with monochromated MoK α radiation at -150°C. The structure was solved by direct method (SIR92). *R* (*R_w*) = 0.067 (0.108) (for 3266 data with all reflections), *R₁* = 0.038 (for 2640 data with *I* > 2 σ (*I*)). The details of the structure will be deposited in the Cambridge Structural Database.

***trans-syn*-6-Cyano-1,3-dimethyluracil $\diamond$ 1,3-dimethyluracil adduct (*trans-syn*-1 $\diamond$ 2g adduct) (8ts):**

Colorless crystals. mp 175-177 °C (recrystallized from ethanol). ¹H-NMR (CDCl₃) δ : 3.18 (3H, s, N⁸-CH₃), 3.19 (3H, s, N¹-CH₃), 3.27 (3H, s, N-CH₃), 3.30 (3H, s, N-CH₃), 3.77 (1H, dd, *J* = 10.3, 4.6 Hz, H-4b), 3.97 (1H, dd, *J* = 4.6, 1.3 Hz, H-4a), 4.09 (1H, dd, *J* = 10.3, 1.3 Hz, H-8a). NOE: irradiation at H-4b with H-8a (8.0%) and H-4a (0.8%); H-8a with H-4b (10.5%), N⁸-CH₃ (5.7%), and N¹-CH₃ (2.1%). EIMS *m/z* (%): 305 (M⁺, 2), 278 (4), 140 (100). HREIMS: Calcd for C₁₃H₁₅N₅O₄: 305.1124. Found: 305.1125.

***trans-syn*-6-Cyano-1,3-dimethyluracil $\diamond$ 1,3-dimethylthymine adduct (*trans-syn*-1 $\diamond$ 2h adduct) (9ts):**

Colorless needles. mp 235~238°C (recrystallized from benzene). ¹H-NMR (CDCl₃) δ : 1.50 (3H, s, 4b-CH₃), 3.19 (3H, s, N⁸-CH₃), 3.19 (3H, s, N¹-CH₃), 3.29 (3H, s, N-CH₃), 3.30 (3H, s, N-CH₃), 3.70 (1H, s, H-8a), 4.00 (1H, s, H-4a). NOE: irradiation at H-4a with H-8a (0.1%); 4b-CH₃ with H-4a (1.4%) and H-8a (4.6%); H-8a with H-4a (1.1%), N⁸-CH₃ (5.8%), 4b-CH₃ (3.7%), and N¹-CH₃ (1.5%). FABMS *m/z* (%): 320 (M+H)⁺. HRFABMS: Calcd for C₁₄H₁₈N₅O₄: 320.1359. Found: 320.1388.

***cis-syn*-6-Cyano-1,3-dimethyluracil $\diamond$ 1,3-dimethylthymine adduct (*cis-syn*-1 $\diamond$ 2h adduct) (9cs):**

Colorless crystals recrystallized from benzene. mp 247-250 °C. ¹H-NMR (CDCl₃) δ : 1.73 (3H, s, 4b-CH₃), 2.97 (3H, s, N-CH₃), 3.14 (3H, s, N-CH₃), 3.20(3H, s, N-CH₃), 3.21(3H, s, N⁸-CH₃), 3.46 (1H, s, H-4a), 3.99 (1H, s, H-8a). NOE: irradiation at H-4a with H-8a (6.9%) and 4b-CH₃ (4.0%); 4b-CH₃ with H-4a (4.6%) and H-8a (3.2%); H-8a with H-4a (8.8%), N⁸-CH₃ (6.9%), and 4b-CH₃ (3.3%). FABMS *m/z* (%): 320 (M+H)⁺. HRFABMS: Calcd for C₁₄H₁₈N₅O₄: 320.1359. Found: 320.1380.

***trans-anti*-6-Cyano-1,3-dimethyluracil $\diamond$ 1,3-dimethylthymine adduct (*trans-anti*-1 $\diamond$ 2h adduct) (9ta):**

Colorless crystals. mp 164-166 °C(recrystallized from benzene). ¹H-NMR (acetone-*d*₆) δ : 1.53 (3H, s, 8a-CH₃), 3.02 (3H, s, N⁵-CH₃), 3.08 (3H, s, N¹-CH₃), 3.15 (3H, s, N-CH₃), 3.17 (3H, s, N-CH₃), 4.02 1H, d, *J* = 4.8 Hz, H-4b), 4.19 (1H, d, *J* = 4.8 Hz, H-4a). NOE: irradiation at H-4b with H-4a (0.7%), N⁵-CH₃ (4.8%), and 8a-CH₃ (3.1%); 8a-CH₃ with N¹-CH₃ (2.5%) and H-4b (4.1%); H-4a with H-4b (0.5%) and N⁵-CH₃ (2.0%). FABMS *m/z* (%): 320 (M+H)⁺. HRFABMS: Calcd for C₁₄H₁₈N₅O₄: 320.1359. Found: 320.1347.

***cis-anti*-6-Cyano-1,3-dimethyluracil $\diamond$ 1,3-dimethylthymine adduct (*cis-anti*-1 $\diamond$ 2h adduct) (9ca):**

Colorless crystals. mp 243-245°C(recrystallized from ethyl acetate). ¹H-NMR (acetone-*d*₆) δ : 1.74 (3H, s, 8a-CH₃), 2.98 (3H, s, N-CH₃), 3.03 (3H, s, N-CH₃), 3.08 (3H, s, N⁵-CH₃), 3.15(3H, s, N¹-CH₃), 4.33 (1H,

d, $J = 8.8$ Hz, H-4a), 4.46 (1H, d, $J = 8.8$ Hz, H-4b). NOE: irradiation at H-4b with H-4a (9.6%), N⁵-CH₃ (9.5%), and 8a-CH₃ (4.2%); 8a-CH₃ with N¹-CH₃ (3.5%) and H-4b (2.6%); H-4a with H-4b (4.5%). FABMS m/z (%): 320 (M+H)⁺. HRFABMS: Calcd for C₁₄H₁₈N₅O₄: 320.1359. Found: 320.1331.

***cis-syn* 6-Cyano-1,3-dimethyluracil $\diamond$ 5-fluoro-1,3-dimethyluracil adduct (*cis-syn*-1 $\diamond$ 2i adduct)**

(10cs): Colorless crystals. mp 194-196°C (recrystallized from ethyl acetate). ¹H-NMR (CDCl₃) δ : 3.00 (3H, s, N-CH₃), 3.19 (3H, s, N-CH₃), 3.21 (3H, s, N-CH₃), 3.27 (3H, s, N⁸-CH₃), 4.03 (1H, d, $J = 13.9$ Hz, H-4a), 4.51 (1H, d, $J = 17.9$ Hz, H-8a). NOE: irradiation at H-4a with H-8a (8.9%); H-8a with H-4a (6.5%) and N⁸-CH₃ (10.2%); N⁸-CH₃ with H-8a (3.4%) and N¹-CH₃ (2.0%). FABMS m/z (%): 324 (M+H)⁺. HRFABMS: Calcd for C₁₃H₁₅N₅O₄F: 324.1108. Found: 324.1120.

***trans-anti* 6-Cyano-1,3-dimethyluracil $\diamond$ 5-fluoro-1,3-dimethyluracil adduct (*trans-anti*-1 $\diamond$ 2i adduct)**

(10ta): Colorless crystals. mp 230.5°C (recrystallized from ethyl acetate). ¹H-NMR (CDCl₃) δ : 3.15 (3H, s, N⁵-CH₃), 3.24 (3H, s, N-CH₃), 3.30 (3H, s, N-CH₃), 3.36 (3H, s, N-CH₃), 3.48 (1H, d, $J = 10.0$ Hz, H-4a), 4.32 (1H, dd, $J = 26.1, 10.0$ Hz, H-4b). NOE: irradiation at H-4b with H-4a (7.3%) and N⁵-CH₃ (7.3%); H-4a with H-4b (4.5%) and N⁵-CH₃ (1.6%). FABMS m/z (%): 324 (M+H)⁺. HRFABMS: Calcd for C₁₃H₁₅N₅O₄F: 324.1108. Found: 324.1086.

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