Stereoselective Synthesis of Tetrahydronaphthocyclobuta[1,2-*d*]pyrimidinediones from 5-Fluoro-1,3-dimethyluracil and Naphthalenes

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Upon UV-irradiation in the presence of piperylene, 5-fluoro-1,3-dimethyluracil (5-FDMU) couples with naphthalenes having either an electron-withdrawing group or an electron-donating group by way of 1,2-cycloaddition *via* mode selectivity to give the corresponding naphthocyclobutapyrimidines regio- and stereo-selectively.

Key words stereoselective synsthesis; 1,2-photocycloaddition; 5-fluoro-1,3-dimethyluracil; naphthocyclobutapyrimidine; piperylene

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)] In this respect, we have extensively studied the photoreaction of halogenated pyrimidines with benzenes[2—9)] and olefins,[10)] and have demonstrated that photoreaction is a useful method for the modification of the pyrimidine ring. As an extension of this work, we have recently reported that UV-irradiation of a solution of 6-chloro-1,3-dimethyluracil and naphthalene in polar media effected a 1,2-cycloaddition reaction to give naphthocyclobutapyrimidine in moderate yield.[11)] We have also reported that UV-irradiation of 5-fluoro-1,3-dimethyluracil (5-FDMU) with naphthalene and its derivatives in an aprotic medium preferentially afforded ethenoquinazoline (barrelene) derivatives in fair yields by way of 1,4-cycloaddition.[12)] Quenching experiments with piperylene have suggested that excited singlet states may participate for the former reaction, while the excited triplet states may be involved in the latter reaction. In order to develop novel aspects of the photoreaction of 5-FDMU and naphthalenes that would lead to the construction of a cyclobutapyrimidine ring through 1,2-cycloaddition, we planned to investigate the photoreaction of 5-FDMU with naphthalenes in the presence of piperylene.

In the present paper, we describe our findings that UV-irradiation of a solution of 5-FDMU and naphthalenes (**1**) in the presence of piperylene preferentially undergoes 1,2-cycloaddition to give naphthalene ring fused cyclobutapyrimidines (**2**), and the reaction proceeds with high regio- and stereo-selectivity.

We first examined the photoreaction of 5-FDMU with a naphthalene bearing an electron-withdrawing group. A solution of equimolar amounts of 5-FDMU and methyl 2-naphthoate (**1a**) in acetonitrile (4.5 mM) was irradiated in the presence of piperylene (10 mM) in a degassed Pyrex tube with a 500 W high-pressure mercury lamp (λ>300 nm) for 25 min to furnish a novel cycloadduct (**2a**) in quantitative yield at the stage where 14% 5-FDMU had been consumed. Similar photoreaction in the absence of piperylene afforded 1,4-adduct (**3a**)[13)] exclusively (Chart 1).

The structure of **2a**[14)] was assigned to be the 1,2-adduct on the basis of ^{1}H-NMR and MS studies. FAB-MS analysis showed the expected molecular ion peak $[M+H]^+$ at *m/z* 345. The ^{1}H-NMR ($CDCl_3$) spectrum showed signals for N9-CH_3, N7-CH_3 and 6a-CO_2CH_3 at δ 2.90, 3.08 and 3.80 ppm, respectively. Two signals ascribable to the H-6b and H-10b methine protons appeared at δ 4.51 (1H, d, J=20.9 Hz) and 4.25 ppm (1H, d, J=19.2 Hz) respectively, indicating that the 6b and 10b carbons are both linked to the 10a carbon with the attached fluorine substituent. Two signals due to the H-5 and H-6 vinyl protons appeared at δ 6.49 (1H, d, J=9.7 Hz) and 5.53 ppm (1H, d, J=9.7 Hz) respectively. The aromatic protons were observed in the region between δ 6.90 and 7.20.

The stereochemistry of this product with the benzene ring and the pyrimidine ring fused to the cyclobutane moiety was determined to be *cis* by NOE experiments. Irradiation of the H-10b proton significantly affected the H-6b (5%) and H-1 protons (10%), and also had less but measurable impact on 6a-CO_2CH_3 (2.5%). Irradiation of the H-6b proton significantly affected the N7-CH_3 (7.5%) and H-10b (4.5%). Additional NOE studies confirmed the structure assigned to **2a**. These results indicate that photocoupling of 5-FDMU with **1a** proceeded stereoselectively to give a *cis*-type naphtho-[1′,2′:3,4]cyclobuta[1,2-*d*]pyrimidine-8,10-dione.

UV-irradiation of a solution of 5-FDMU and 2-cyanonaphthalene (**1b**) in acetonitrile in the presence of piperylene (10 mM) for 25 min gave the corresponding 1,2-adduct (**2b**)[15)] in 55% yield (Chart 2). Carbon–carbon bond formation

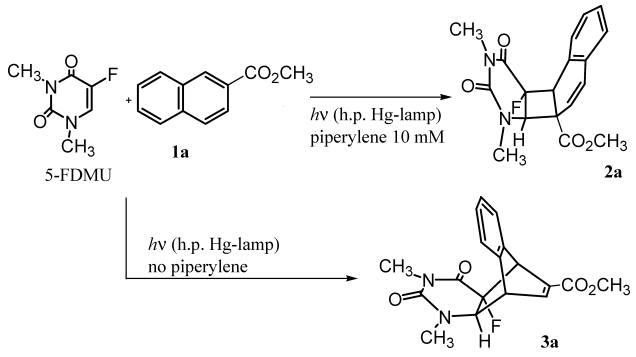
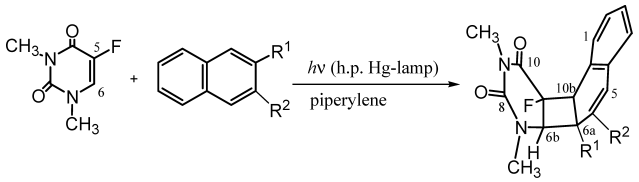


Chart 1



1b: R^1=CN, R^2= H
1c: R^1= CN, R^2= CN
2b: R^1=CN, R^2= H
2c: R^1= CN, R^2= CN

Chart 2

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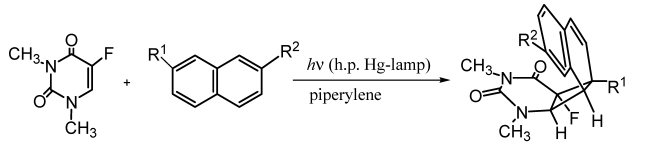
occurred between 5-FDMU at C-5 and naphthalene at the carbon adjacent to the substituent and also between C-6 of the pyrimidine ring and the carbon bearing the substituent. Bond formation took place in a face-to-face orientation to give the *cis* (*endo*)-isomer.

Similarly, we have carried out the photoreaction with 2,3-dicyanonaphthalene (**1c**) in the presence of piperylene in acetonitrile to give the substitution product as the sole product, and no cycloadducts were detected in the reaction mixture. When the reaction was performed in benzene, the desired 1,2-cycloadduct (**2c**)[16] was formed predominantly (50% yield) with analogous stereoselectivity and the regioselectivity to **2a** and **2b**, though the reaction proceeded slowly (4% 5-FDMU consumed).

We next examined the photoreaction with naphthalenes having an electron-donating group on the ring (**1d**, **e**). Photoreaction of 2-methoxynaphthalene (**1d**) in the presence of piperylene predominantly afforded the *endo*-type 1,2-adduct (**2d**)[17] in 50% yield at the stage where 32% 5-FDMU had been consumed (Chart 3). In accordance with the observations above, the stereochemistry of **2d** was *cis*, but the regioselectivity of **2d** was the reverse of that found for **2a**—**c**. In **2d**, the C-5 carbon is bonded to the carbon attached to the methoxy group, and the C-6 carbon is linked to the carbon adjacent to the substituent. Similarly, 2,7-dimethoxynaphthalene (**1e**) produced *endo*-type 1,2-adduct (**2e**)[18] regioselectively and in high yield (86%, based on the consumption of 32% 5-FDMU). The regioselectivity is in accordance with that found for **2d**.

Thus, the present work demonstrates that addition of piperylene perfectly changes the mode of the cycloaddition of 5-FDMU with naphthalenes from 1,4-addition to the 1,2-cycloaddition. The 1,2-cycloaddition proceeds with naphthalenes having both electron-donating and electron-withdrawing groups to give the corresponding 1,2-adducts in fair yields. The regioselectivity of the 1,2-cycloaddition has been shown herein, to depend on the electronic properties of the substituents on the naphthalene ring. The reaction mechanism remains unelucidated, however the fact that the present reaction proceeds in the presence of the triplet quencher piperylene, may suggest a mechanism involving an excited singlet state.



1d: R^1=OCH_3, R^2=H
1e: R^1=OCH_3, R^2=OCH_3

2d: R^1=OCH_3, R^2=H
2e: R^1=OCH_3, R^2=OCH_3

Chart 3

Further studies on the scope and the reaction mechanism of this reaction are now in progress.

References and Notes

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14) Adduct **2a**: Colorless crystals, mp 155.0—156.0 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.90 (3H, s), 3.08 (3H, s), 3.80 (3H, s), 4.25 (1H, d, J=19.2 Hz), 4.51 (1H, d, J=20.9 Hz), 5.53 (1H, d, J=9.7 Hz), 6.49 (1H, d, J=9.7 Hz), 6.97 (1H, d, J=7.1 Hz), 7.2 (3H, m). FAB-MS m/z: 345 $[M+H]^+$. HR-FAB-MS m/z: 345.1250 (Calcd for $C_{18}H_{18}FN_2O_4$: 345.1251).
15) Adduct **2b**: Colorless crystals, mp 176.5—179.0 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.94 (3H, s), 3.20 (3H, s), 4.30 (1H, d, J=19.1 Hz), 4.73 (1H, dd, J=20.7, 1.0 Hz), 5.44 (1H, dd, J=9.7, 1.0 Hz), 6.63 (1H, d, J=9.7 Hz), 7.07 (1H, dd, J=7.1, 1.5 Hz), 7.2—7.4 (3H, m). FAB-MS m/z: 312 $[M+H]^+$. HR-FAB-MS m/z: 312.1153 (Calcd for $C_{17}H_{15}FN_3O_2$: 312.1148).
16) Adduct **2c**: Colorless crystals, mp 193.0—196.0 °C (CH_2Cl_2–hexane). ^{1}H-NMR ($CDCl_3$) δ: 3.01 (3H, d, J=0.9 Hz), 3.35 (3H, s), 4.41 (1H, d, J=17.8 Hz), 4.86 (1H, d, J=19.5 Hz), 7.2—7.6 (5H, m). FAB-MS m/z: 337 $[M+H]^+$. HR-FAB-MS m/z: 337.1121 (Calcd for $C_{18}H_{14}FN_4O_2$: 337.1101).
17) Adduct **2d**: Colorless crystals, mp 125.5—126.5 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.49 (3H, s), 3.09 (3H, s), 3.35 (3H, s), 4.22 (1H, dd, J=9.2, 3.3 Hz), 4.37 (1H, dd, J=24.0, 9.2 Hz), 5.76 (1H, d, J=9.9 Hz), 6.75 (1H, d, J=9.9 Hz), 7.1—7.4 (4H, m). FAB-MS m/z: 317 $[M+H]^+$. HR-FAB-MS m/z: 317.1301 (Calcd for $C_{17}H_{18}FN_2O_3$: 317.1301).
18) Adduct **2e**: Colorless crystals, mp 42.0—44.0 °C (EtOH–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 3.09 (3H, s), 3.31 (3H, s), 3.80 (3H, s), 4.16 (1H, dd, J=9.2, 3.5 Hz), 4.32 (1H, dd, J=24.1, 9.2 Hz), 5.58 (1H, d, J=10.3 Hz), 6.7 (2H, m), 6.78 (1H, dd, J=8.6, 2.9 Hz), 7.08 (1H, d, J=8.6 Hz). FAB-MS m/z: 347 $[M+H]^+$. HR-FAB-MS m/z: 347.1413 (Calcd for $C_{18}H_{20}FN_2O_4$: 347.1407).