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DIASTEREODIFFERENTIATING [4+2]-PHOTOCYCLOADDITION OF TEGAFUR WITH NAPHTHALENE

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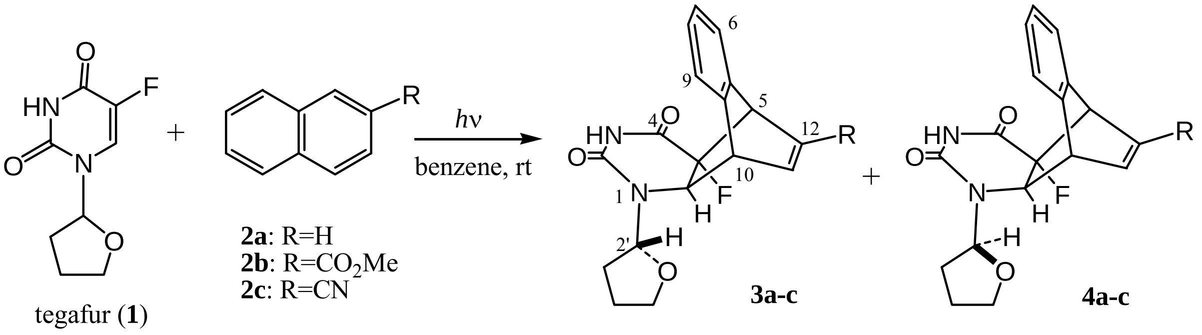
Abstract – Upon UV-irradiation, the prodrug of 5-fluorouracil, tegafur, that has an asymmetric carbon attached to N1 couples with naphthalenes by way of stereoselective [4+2]-cycloaddition, to give the corresponding ethenoquinazolines as diastereoisomers. The configuration of the resulting adducts is unambiguously derived from X-ray crystal structural analysis.

In our continuing research, we have extensively studied the photoreaction of halogenated-1,3-dimethyluracil with various aromatics, including cycloadditions and valence isomerizations of the resulting cycloadducts with or without the aid of acid.[1] Recently, we have revealed that UV-irradiation of 5-substituted-1,3-dimethyluracil (5-RDMU: R=F, H, CH_3) with naphthalene and its derivatives in an aprotic medium afforded ethenoquinazoline (barrelene) derivatives in high yield with good regio- and stereo-selectivity,[2] while addition of piperylene to the reaction mixture preferentially effected [2+2]-cycloaddition to give naphthalene ring-fused cyclobutapyrimidines.[3] We have further reported that UV-Irradiation of 1,3-diacetyl-5-fluorouracil and naphthalene initiated the photo-Diels-Alder reaction to give the corresponding [4+2]-cycloadduct.[4] Meanwhile, the development of conditions for the efficient control of molecular chirality is a challenging task in organic photochemistry. Enantioselective or diastereoselective photoreactions, such as [2+2]-cycloadditions and the Paterno-Büchi reaction are established tools in organic synthesis.[5] [4+2]-Photocycloaddition having enantio- or diastereoselectivity is also recognized to be a potential way for organic synthetic utility in current photo-induced reactions.[5,6] Hence, our attention was focused on the possible diastereodifferentiating photocoupling of a 5-FU derivative with naphthalene by introducing an asymmetric center at N1. In the present paper we report that UV-irradiation of tegafur (1-(2*RS*-tetrahydrofuryl)-5-fluorouracil) that has an asymmetric carbon attached to N1 in the presence of naphthalenes undergoes diastereodifferentiating [4+2]-addition to give ethenobenzoquinazolines in good yields. Irradiation of a benzene solution of tegafur (**1**) (4.5 mM) and naphthalene (**2a**) (4.5 mM) in a de-gassed Pyrex test tube with a 500 W high-pressure mercury lamp (λ>300 nm) afforded 4a-fluoro-5,10-ethenobenzo[*f*]quinazoline as a separable mixture of diastereomers (epimers at the 2'-position on the furan ring) in high yield. HPLC separation of the reaction mixture furnished the major diastereomer **3a** and minor diastereomer **4a** in 72.5 % and 17 % yield, respectively (at the stage of 72.5% **1** consumed).



Scheme 1

The structures of adducts **3a** and **4a** were assigned as 1,4-adducts on the basis of MS and ^{1}H-NMR spectroscopic studies.[7] The stereochemistry of **3a** and **4a** were determined to be *cis* by NOE experiments, wherein the benzene ring and the pyrimidine ring stand in face-to-face orientation through C5 and C10 bridgehead carbons. Finally, X-Ray structural analysis confirmed the structures of **3a** and **4a** as the diastereoisomers shown in Figures 1 and 2, respectively.[8,9]

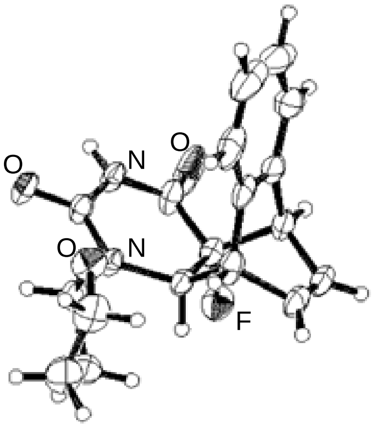


Figure 1. X-Ray crystal structure of **3a**.

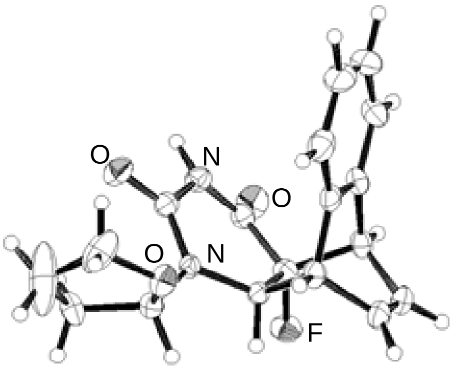


Figure 2. X-Ray crystal structure of **4a**.

Configuration analysis for **1,** using MM2 based calculation, showed that the pyrimidine ring and the furan ring stand perpendicularly at the lowest energy state (the dihedral angle of C2'—O5'—C2—C6 = -79°) (Figure 3). As shown in figure 3, the naphthalene ring approaches the pyrimidine ring from the up- or downside through π-π bonding overlap. The C2'-hydrogen atom stretching out toward the surface of the pyrimidine ring may hinder the approach more efficiently than the approach from the opposite side, resulting in the preferable formation of **3a** to **4a**.

In order to examine the substituent effect of the naphthalene ring on the diastereoselectivity in the present reaction, we carried out the photoreaction with substituted naphthalenes under similar conditions. UV-irradiation of methyl 2-naphthoate (**2b**) for 10 h afforded the corresponding ethenobenzoquinazolines bearing the carbomethoxy group on the olefinic carbon atom in *cis*-geometry, namely **3b** and **4b,** as diastereomers in 71 % and 29 % yield, respectively (at the stage of 85 % **1** consumed) (Scheme 1).

Similar irradiation with 2-naphthonitrile (**2c**) for 5 h furnished 12-cyanoethenobenzoquinazolines **3c** and **4c** as diastereomers in 81 % and 10 % yield respectively (at the stage of 62 % **1** consumed) with diastereomeric excess of up to 78 %. This regioselectivity is in accordance to that obtained in the case of **2b**.

Thus, the less bulky carbonitrile group worked more effectively on the diastereoselectivity, while the more bulky carbomethoxy group showed less stereoselectivity, suggesting that the diastereoselectivity can not be explained only in terms of steric hindrance.

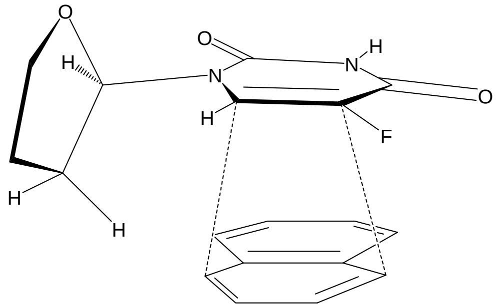


Figure 3

Although, factors causing the present diastereoselective cycloaddition remains unclear, it may be worthy to note that the present work demonstrates the first clear example of a diastereoselective photo-Diels-Alder reaction of naphthalene with tegafur, which is representative of an *N*3-H free 5-fluorouracil, resulting the synthesis of ethenobenzoquinazolines.

Among various chemotherapeutic agents, pyrimidine derivatives such as 5-fluorouracil have attracted much attention because of their biological and potential antitumor activity. Of particular note, photobiological studies have identified cases of allergic photosensitivity induced by 5-fluorouracil,[10] however little attention has been paid to this aspect of the photochemistry of tegafur. Further investigations on diastereodifferentiating photocycloadditions of pyrimidine derivatives are currently in progress.

REFERENCES AND NOTES

1. K. Ohkura and K. Seki, *Photochem. Photobiol.*, 2001, **74**, 385; K. Ohkura, S. Uchiyama, K. Aizawa,

K. Nishijima, and K. Seki, *Heterocycles*, 2002, **57**, 1403.

2. K. Ohkura, T. Sugaoi, K. Nishijima, Y. Kuge, and K. Seki, *Tetrahedron Lett*., 2002, **43**, 3113; K. Ohkura, T. Sugaoi, T. Ishihara, K. Aizawa, K. Nishijima, Y. Kuge, and K. Seki, *Heterocycles*, 2003, **61**, 377; K. Ohkura, T. Ishihara, Y. Nakata, and K. Seki, *Heterocycles*, 2004, **62**, 213.
3. K. Ohkura, T. Sugaoi, T. Ishihara, and K. Seki, *Heterocycles*, 2004, **64**, 57; K. Ohkura, T. Ishihara, H. Takahashi, H. Takechi, and K. Seki, *Heterocycles*, 2005, **66**, 143; K. Ohkura, T. Ishihara, K. Nishijima, J. Diakur, and K. Seki, *Chem. Pharm. Bull*., 2005, **53**, 258.
4. K. Ohkura, T. Ishihara, K. Nishijima, J. M. Diakur, and K. Seki, *Heterocycles*, 2006, **69**, 515.
5. B. Grosch and T. Bach, 'Enantioselective Photocycloaddition Reaction in Solution' in 'CRC Handbook of Organic Photochemistry and Photobiology', eds. by W. Horspool and F. Lenci, CRC press, Boca Laton, 2004, pp.61/1-61/14 and references cited therein.
6. K. Okada, F. Samizo, and M. Oda, *Tetrahedron Lett*., 1987, **28**, 3819; W. Adam and M. Prein, *Tetrahedron*, 1995, **51**, 12583; E. Salamci, H. Secen, Y. Sütbeyaz, and M. Balci, *J. Org. Chem*., 1997, **62**, 2453.
7. Selected data **3a**: mp 150-151 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.03-2.22 (3H, m), 2.29-2.42 (1H, m), 3.78 (1H, dd, J = 2.4, 31.0 Hz), 4.03 (1H, dd, J = 8.4, 15.2 Hz), 4.20 (1H, dd, J = 6.8, 15.2 Hz), 4.49 (1H, ddd, J = 1.3, 2.4, 6.4 Hz), 4.67 (1H, dd, J =1.7, 5.9 Hz), 5.90 (1H, dd, J = 4.2, 6.2 Hz), 6.74 (1H, dd, J = 1.3, 5.9 Hz), 6.89 (1H, dd, J = 1.7, 6.4 Hz), 7.25-7.27 (3H, m), 7.36-7.38 (1H, m). HRFAB-MS: Cacld for $C_{18}H_{18}O_3N_2F$: 329.1302. Found: 329.1286. **4a**: mp 157-158 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.90-2.04 (3H, m), 2.18-2.38 (1H, m,), 3.78 (1H, dd, J =2.5, 31.0 Hz), 3.94 (1H, dd, J =5.0, 14.9 Hz), 4.19 (1H, dd, J= 7.7, 14.9 Hz), 4.41 (1H, dd, J =2.5, 6.3 Hz), 4.58 (1H, dd, J =4.2, 5.9 Hz), 5.27 (1H, dd, J = 5.0, 7.7 Hz), 6.66 (1H, dd, J = 5.9, 7.7 Hz,), 6.78 (1H, dd, J= 6.3, 7.7 Hz), 6.92 (1H, brs), 7.16−7.34 (4H, m). HRFAB-MS: Cacld for $C_{18}H_{18}O_3N_2F$: 329.1302. Found: 329.1277.
8. X-Ray Crystallography of **3a**: The diffraction experiment was carried out using a colorless transparent prism with the dimensions 0.40 x 0.50 x 0.10 mm. A diffractometer RIGAKU AFC7S was used with monochromated CuKα radiation (λ = 1.5418 Å) at 25°C to obtain the following crystal data: $C_{18}H_{17}N_2O_3F$ Mr = 328.34., a = 15.695(4) Å, b = 8.497(3) Å, c = 11.674(2) Å, β = 91.89(2)°, V = 1556.0(6) Å^3, monoclinic, $P2_1/a$, Z = 4, Dx = 1.405 g/cm^3. The structure was solved by direct method and the model further refined full-matrix least-squares calculations on F_2. The final model with 3817 unique data used and 286 parameters varied, converged to values of $R1$=0.048 (for 2741 data with $I>2\sigma(I)$ and R (RW) = 0.092 (0.142) (all data).
9. X-Ray Crystallography of **4a**: The diffraction experiment was carried out using a colorless transparent prism with the dimensions 0.20 x 0.20 x 0.10 mm. A diffractometer RAXIS-IV

(RIGAKU) imaging plate area detector was used with graphite-monochromated MoKα radiation (λ = 0.71070 Å) to obtain the following crystal data: $C_{18}H_{17}N_2O_3F$ Mr = 328.34., a = 12.6892(7) Å, b=18.4209(8)Å, c = 6.8992(3) Å, α = 98.534(2)°, β = 90.2734(8)°, γ = 74.839(2)°, V = 1538.3(1) Å^3, triclinic, P1, Z = 4, Dx = 1.418 g/cm^3. The final model with 6755 unique data used and 570 parameters varied, converged to values of $R1$= 0.058 (for 4198 data with I>2 σ (I) and R (RW) = 0.088 (0.145) (all data).

10. A. Usuki, Y. Funasaka, M. Oka, and M. Ichihashi, *Int. J. Dermatol.*, 1997, **36**, 604.