HETEROCYCLES, Vol. 69, 2006, pp. 515 - 520. © The Japan Institute of Heterocyclic Chemistry
Received, 11th July, 2006, Accepted, 16th August, 2006, Published online, 18th August, 2006. COM-06-S(O)41

SYNTHESIS OF *N*1, *N*3-FREE PYRIMIDINE BRIDGED POLYCYCLIC COMPOUNDS *VIA* PHOTO-DIELS-ALDER REACTION OF *N*,*N*-DIACETYL- 5-FLUOROURACIL WITH NAPHTHALENES

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Abstract – UV-Irradiation of 1,3-diacetyl-5-fluorouracil and naphthalene initiated the photo-Diels-Alder reaction to give the corresponding 1,4-adduct. Removal of the acetyl groups at *N*1 and *N*3 through hydrolysis afforded *N*1 and *N*3 unprotected ethenobenzoquinazoline in fair yield.

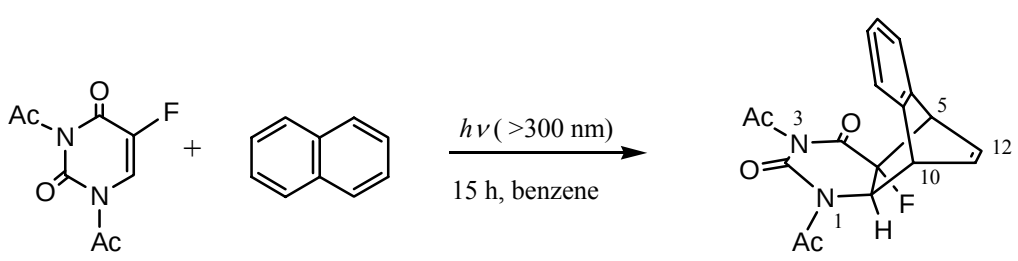
The importance of UV photolysis of DNA has been recognized for several decades in photobiological research. C-C Bond formation of pyrimidine bases with aromatics, alkenes or alcoholic compounds including halogenated nucleic bases or amino acids, have been studied intensively not only from biological but also from synthetic points of view.[1,2] Moreover, modified uracil derivatives have been recognized to be invaluable in the field of chemotherapy.[3]

From the viewpoint of developing new aspects of the chemical modification of pyrimidine rings, we have intensively studied for the past two decades, the photoreaction of halouracils with aromatic compounds such as benzene, naphthalene and their derivatives. We have hitherto reported versatile photoreactions including anomalous photosubstitution,[4] cycloaddition[5,6] and valence isomerizations of the cycloadducts with or without the aid of acids.[7,8] These reactions however, have been carried out with uracils capped with dimethyl groups at *N*1 and *N*3. Taking the biological importance of the *N*3-H of the pyrimidine ring into consideration, the presence of the *N*3-H function of the pyrimidine ring may

represent a significant pharmacophore for the development of useful chemotherapeutics. Direct photoreaction with an *N*1 and *N*3 free halouracil and aromatic substrates however, may be impractical since *N*1 and *N*3 free uracils are essentially insoluble in organic solvents that would dissolve aromatic substrates. Therefore, the starting halouracil must be elaborated with proper protective groups that can readily be released from the resulting products. Among the various possible protecting groups, the acetyl group was chosen for this purpose, although its introduction at *N*1 and *N*3 could change the photochemical behavior from that we have hitherto found for the reaction with 1,3-dimethyl derivatives by altering the electronic structure of the chromophore. Photochemistry of *N*-acyl uracil derivatives has not yet been reported, however, photochemical transformations of nitrogen-carbonyl system have been studied extensively in terms of cycloaddition, hydrogen abstraction, and rearrangement.[9,10]

As a preliminary study to establish the versatility of the acetyl protected pyrimidine as a reactive base for our continuing studies on the photochemical modification of pyrimidines with aromatic compounds, we intended to investigate the photoreaction of 5-fluoro-1,3-dimethyluracil (5-FDMU) with naphthalene by using 1,3-diacetyl-5-fluorouracil, in place of 5-FDMU whereby 1,4- or 1,2-cycloaddition proceeded mode-selectively in aprotic media.[11-14] In the present paper, we report that the photoreaction of 1,3-diacetyl-5-fluorouracil with naphthalene led to 1,4-cycloaddition analogous to that found with 5-FDMU, and that subsequent deacetylation of the cycloadducts afforded the desired *N*1 and *N*3 deprotected ethenobenzoquinazoline in fair yield.

UV-Irradiation of an equivalent molar solution of 1,3-diacetyl-5-fluorouracil (**1**) and naphthalene (**2a**) in benzene with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ>300 nm) for 15 h at ambient temperature resulted in 1,4-cycloaddition to give 4a-fluoro-5,10-ethenobenzo[*f*]quinazolines (**3a**) as the sole product in appreciable yield (60% at the stage where 64 % of **1** has been consumed) (Scheme 1).



1 **2a** **3a**

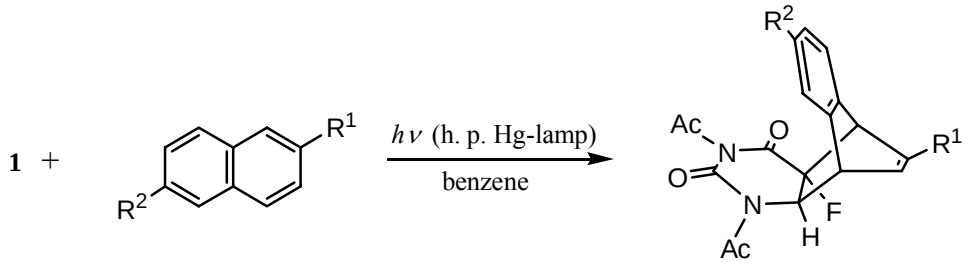
Scheme 1

The structural assignment of **3a** 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* 343, and the ^{1}H-NMR

($CDCl_3$) spectrum showed methyl singlets for N^1-$COCH_3$, and N^3-$COCH_3$ at δ 2.50, and 1.92 respectively. The stereochemistry of **3a** was determined to be *cis* (*endo*-orientation) with the aid of NOE experiments. Irradiation of the H-10a proton significantly affected the H-11 vinyl proton, as well as H-10.

The effect of the acyl groups of **1** on the chromophore in its photo-excited state compared to the behavior of the original uracil remained to be established. Thus upon photoreaction with naphthalene, the reaction proceeded by way of 1,4-addition analogous to that found with 5-FDMU. We then investigated the effect of a triplet quencher on the photoreaction of **1**. In contrast to the reaction with 5-FDMU wherein the 1,2-adduct was exclusively produced in the presence of piperylene, addition of piperylene to a solution of **1** with **2a** significantly suppressed 1,4-addition without the formation of 1,2-adduct.

Next we examined the application of this approach to the reaction of **1** with the substituted naphthalene methyl 2-naphthoate (**2b**). The corresponding ethenobenzoquinazoline (**3b**) with a carbomethoxy group on the olefinic carbon at C-12 was formed with high regioselectivity in fair yield (15 h, 60% at the stage where 66 % of **1** has been consumed).[13] Likewise, irradiation with 2,6-dimethylnaphthalene (**2c**) (6 h) readily afforded the 1,4-adduct, 8,12-dimethyl isomer (**3c**), in high yield (82% at the stage where 23% of **1** has been consumed) (Scheme 2). Their high regioselectivity for the addition reaction is in good agreement that was obtained by the photolysis of dimethyluracil derivative.

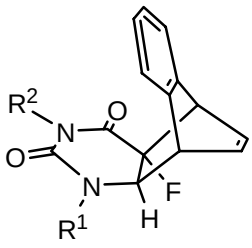


2b: R^1=CO_2CH_3, R^2=H
2c: R^1= R^2=CH_3

3b: R^1=CO_2CH_3, R^2=H
3c: R^1= R^2=CH_3

Scheme 2

Deprotection of **3a** in refluxing EtOH for 3 h gave the mono-deacetylated *N*3 free product (**4**) in 90% yield. When hydrolysis was performed with concentrated hydrochloric acid under reflux for 1 h, both acetyl groups were removed completely to furnish the adduct (**5**)[13] in 45 % yield (Figure 1). These results provide confirmation of formal [4 + 2]-adduct formation between *N*1 and *N*3 free (non-protected) fluorouracil and naphthalene.



4: R^1=$COCH_3$, R^2=H
5: R^1=R^2=H

Figure 1

It is noteworthy that the diacetyl derivatives, in place of dimethyluracil derivatives, would be useful synthons for the synthesis of various distinctive ring systems including an *N*3 non-protected pyrimidine ring. We have developed a facile methodology based on the readily removable *N* capped uracil to synthesize benzoquinazoline derivatives that can be regarded as building units with pharmacological and biological properties.

EXPERMENTAL

NMR spectra were measured with a JEOL JNM-EA500 (500 MHz) spectrometer, and ^{1}H-NMR chemical shifts are given on the δ (ppm) scale based on those of the signals of solvents. MS spectra and high-resolution MS (HRMS) spectra were recorded with JEOL JMS-HX110 (FAB). HPLC was conducted on a Shim-pac PREP-Sil (H) (25 cm x 20 mm *i*. *d*.) (silica gel), using a LC-6A apparatus (Shimadzu, Kyoto) with monitoring at 254 nm. UV-Irradiation was carried out externally with a 500 W high-pressure mercury (h. p. Hg) lamp (Eiko-sha, Osaka) in a degassed Pyrex tube (> 300 nm) on a merry-go-round apparatus. Yields are determined by means of ^{1}H-NMR spectroscopy with terephthalonitrile as an internal standard.

Photoreaction of 1 with 2----- An equivalent molar solution (1.5 mM) of **1** and **2** in benzene (160 mL) was put portionwise (5 mL each) into 32 degassed Pyrex tubes, and irradiated externally at rt for 15 h. The reaction mixture was concentrated *in vacuo*, and the residual oil was submitted to HPLC with 5-15% AcOEt-hexane.

***rel*-(4a*R*,5*R*,10*S*,10a*R*)-1,3-Diacetyl-4a-fluoro-4a,5,10,10a-tetrahydro-5,10-ethenobenzo[*f*]quinazoline-2,4(1H,3H)-dione (3a)**: Colorless crystals, mp 162-163.5 °C (from EtOH/Hexane). ^{1}H-NMR($CDCl_3$) δ; 1.92 (3H, s, N3-Ac), 2.50 (3H, s, N1-Ac), 4.24 (1H, ddd, *J*=6.3, 2.3, 1.2 Hz, H-10), 4.51 (1H, dd, *J*=29.8, 2.3 Hz, H-10a), 4.59 (1H, ddd, *J*=5.7, 5.2, 1.2 Hz, H-5), 6.67 (1H, ddd, *J*=7.5, 5.7, 1.2 Hz, H-12), 6.88 (1H, ddd, *J*=7.5, 6.3, 1.2 Hz, H-11), 7.2~7.3 (4H, H-6, 7, 8, 9). NOE; N1-Ac with H-10 (0.1%), H-10a (0.2%); H-10 with H-10a (5.8%), H-11 (7.5%), H-9 (5.9%); H-10a with H-10 (6.5%), H-11 (2.0%); H-5 with H-12 (7.2%), H-6 (6.0%); H-12 with H-5 (8.2%), H-11 (5.9%); H-11 with H-10 (7.0%), H-10a (1.8%), H-12 (7.7%). FAB-MS *m/z*; 343$[M+H]^+$. HRFAB-MS; Calcd for $C_{18}H_{16}FN_2O_4$: 343.1094. Found: 299.1417. *Anal*. Calcd for $C_{18}H_{15}FN_2O_4$: C, 63.15; H, 4.42; N, 8.18; F, 5.55. Found: C, 63.05; H, 4.61, N, 8.13, F, 5.48.

***rel*-(4a*R*,5*R*,10*S*,10a*R*)-1,3-Diacetyl-4a-fluoro-12-carbomethoxy-4a,5,10,10a-tetrahydro-5,10-ethen-**

obenzo[*f*]quinazoline-2,4(1H,3-H)-dione (3b): Colorless crystals, mp 178-179 °C. ^{1}H-NMR($CDCl_3$) δ: 1.94 (3H, s, N1-Ac), 2.49 (3H, s, N3-Ac), 3.80 (3H, s, CO_2CH_3), 4.37 (1H, dd, *J*=6.9, 2.9 Hz, H-10), 4.52 (1H, dd, *J*=30.4, 2.9 Hz, H-10a), 5.15 (1H, dd, *J*=5.8, 1.7 Hz, H-5), 7.2-7.4 (4H, aromatic), 7.75 (1H, dd, *J*=6.9, 1.7 Hz, H-11).NOE: H-5 with H-6 (7.1%); H-10a with H-10 (5.8%), H-11(2.9%). FABMS *m/z*: 401 $(M+H)^+$. HRFABMS: Calcd for $C_{20}H_{18}N_2O_6F$: 401.1149. Found: 401.1138.

***rel*-(4a*R*,5*R*,10*S*,10a*R*)-1,3-Diacetyl-4a-fluoro-8,12-dimethyl-4a,5,10,10a-tetrahydro-5,10-etheno-benzo[*f*]quinazoline-2,4(1H,3-H)-dione (3c)**: Colorless crystals, mp 98-100 °C. ^{1}H-NMR($CDCl_3$) δ: 1.91(3H, s, C8-CH_3), 2.01(3H, d, *J*=1.7 Hz), 2.29(3H, s, N1-Ac), 2.49 (3H, s, N3-Ac), 4.06 (1H, dd, *J*=6.9, 2.9 Hz, H-10), 4.27 (1H, dd, *J*=5.8, 1.7 Hz, H-5), 4.52 (1H, dd, *J*=30.4, 2.9 Hz, H-10a), 6.39 (1H, ddd, *J*=6.9, 1.7, 1.7 Hz, H-11), 6.9~7.2 (3H, H-6, 7, 9). NOE: H-10 with H-10a (5.5%), H-11(9.0%), H-9 (7.7%); H-5 with H-6 (6.9%), C12-CH_3 (3.5%); H-10a with N1-Ac, H-10(8.8%), H-11(1.8%); H-11 with H-10(7.5%), H-10a (1.9%), C12-CH_3(3.0%). FABMS *m/z*: 371 $(M+H)^+$. HRFABMS: Calcd for $C_{20}H_{20}N_2O_4F$: 371.1407. Found: 371.1416.

Deacetylation of 3a ----- Compound **3a** was dissolved in refluxing EtOH for 3 h to give **4** or in refluxing concentrated hydrochloric acid for 1 h to give **5**. The reaction mixture was concentrated *in vacuo*, and the residual oil was submitted to HPLC with 20% AcOEt in hexane for **4** or 90% AcOEt in hexane for **5**.

***rel*-(4a*R*,5*R*,10*S*,10a*R*)-1-Acetyl-4a-fluoro-4a,5,10,10a-tetrahydro-5,10-ethenobenzo[*f*]quinazoline-2,4(1H,3H)-dione (4)**: Colorless crystals, mp 162-164 °C. ^{1}H-NMR(DMSO-d_6) δ; 2.37(3H, s, N1-Ac), 4.17(1H, ddd, *J*=6.3, 2.3, 1.7 Hz, H-10), 4.31(1H, dd, *J*=30.4, 2.3 Hz, H-10a), 4.49(1H, ddd, *J*=5.7, 5.7, 1.7 Hz, H-5), 6.70(1H, ddd, *J*=7.5, 6.3, 1.7 Hz, H-11), 6.32(1H, ddd, *J*=7.5,5.7,1.7 Hz, H-12), 6.7~6.9(4H), 10.93(1H, s, N3-H). NOE: N1-Ac with H-10(0.2%), H-10a(0.2%); H-10a with H-10(6.1%), H-11(1.4%). FAB-MS *m/z*; 301$[M+H]^+$. HRFAB-MS; Calcd for $C_{16}H_{14}FN_2O_3$: 301.0988. Found: 301.0990. *Anal*. Calcd for $C_{16}H_{13}FN_2O_3$: C, 64.00; H, 4.36; N, 9.33; F, 6.33. Found: C, 63.88; H, 4.54; N, 9.29; F, 6.25.

***rel*-(4a*R*,5*R*,10*S*,10a*R*)-4a-Fluoro-4a,5,10,10a-tetrahydro-5,10-ethenobenzo[*f*]-quinazoline-2,4-(1H,3H)-dione (5)**: Colorless Crystals, mp 225 °C. ^{1}H-NMR (DMSO-d_6) δ; 3.60 (1H, dd, *J*=33.2, 2.3 Hz, H-10a), 4.09 (1H, ddd, *J*=6.3, 2.3, 1.7 Hz, H-10), 4.55 (1H, dd, *J*=5.2, 5.2 Hz, H-5), 6.63 (1H, dd, *J*=7.5, 6.3 Hz, H-12), 6.78 (1H, ddd, *J*=7.5, 6.3, 1.7 Hz, H-11), 7.1~7.3 (4H, H-6, 7, 8, 9), 7.94 (1H, s, N1-H), 10.18(1H, s, N3-H). NOE: H-10a with H-10 (184%), H-11 (27%), N1-H (27%); H-10 with H-10a (7.8%), H-11 (9.6%), H-9 (9.5%), N1-H (4.8%); H-12 with H-5 (11%), H-11 (6.8%); H-11 with H-10 (6.6%), H-12 (8.2%); N1-H with H-10a (9.5%), H-10 (7.2%). FAB-MS *m/z*; 259$[M+H]^+$.

HRFAB-MS; Calcd for $C_{14}H_{12}FN_2O_2$: 259.0883. Found: 259.0876.

ACKNOWLEDGMENTS

This work has been supported in part by "Academic Frontier" Project from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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