HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 459 - 464, Received, 6th August, 2002

ACID-CATALYZED PHOTOCYCLOADDITION OF 6-CHLORO-1,3-DIMETHYLURACIL TO POLYCYCLIC AROMATIC HYDROCARBONS

Kazue Ohkura,[a] Shun Uchiyama,[a] Masayuki Sato,[a] James M. Diakur,[b] and Koh-ichi Seki[a],*

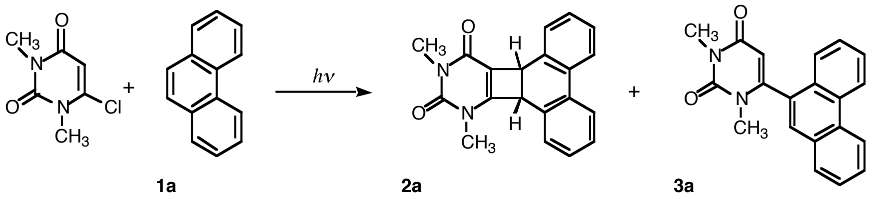
[a] *Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan*
[b] *Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Canada T6G 2N8*

Abstract – The acid-catalyzed photoreaction of 6-chloro-1,3-dimethyluracil (6-ClDMU) with various polycyclic arenes was investigated: UV-Irradiation of a solution of 6-ClDMU with phenanthrene (**1a**), 9-cyanophenanthrene (**1b**) and pyrene (**1f**) in cyclohexane effected 1,2-cycloaddition to furnish the corresponding cyclobutapyrimidines as the predominant adducts, while the substitution reaction with acenaphthene (**1e**) and chrysene (**1g**) proceeded to give the corresponding 6-aryl-1,3-dimethyluracils.

Although there are numerous publications describing the photocycloaddition of uracil and its derivatives to alkenes from the organic and biological points of view,[1,2] the photocycloaddition of uracils to aryl compounds has not yet been reported until our finding that the photoreaction of 6-chloro-1,3-dimethyluracil (6-ClDMU) with benzene derivatives in the presence of an acid proceeds by way of 1,2-cycloaddition to give cyclooctapyrimidines.[3] Certain cyclooctapyrimidines were further converted into various novel valence isomers[4-6] by way of a variety of electrocyclic pathways depending on the reaction conditions and substituents on the cycloadducts. We recently reported that photoreaction with 5-fluoro-DMU (5-FDMU) and naphthalenes in aprotic media effected a stereoselective 1,4-cycloaddition reaction to give barrelene derivatives in high yields.[7] More recently, we have found that UV-irradiation of a solution of 6-ClDMU and naphthalene in polar media effected a 1,2-cycloaddition reaction to give naphthocyclobutapyrimidine in moderate yield.[8] Naphthalene as well as phenanthrene and its derivatives have been reported to add photochemically to alkenes in different manners[9-11] including 1,2- and 1,4-addition, and these reactions have led to the formation of various new ring systems. In order to further explore the scope of this reaction, we aimed to extend our work to the photoreaction of 6-ClDMU with various polycyclic aromatic hydrocarbons. In the present paper we report our findings that the acid-catalyzed photoreaction of 6-ClDMU with phenanthrene and pyrene proceeds by way of 1,2-

cycloaddition to yield cyclobutapyrimidine derivatives, while the substitution reaction occurs exclusively with chrysene.

A molar equivalent solution of 6-ClDMU and the tricyclic aromatic hydrocarbon phenanthrene (**1a**) was irradiated externally with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ>300 nm) at ambient temperature in various solvents (Scheme 1).



Scheme 1. Photoreaction of 6-ClDMU with phenanthrene

Reaction in the non-polar solvents cyclohexane and benzene made slow progress. In contrast, 1,2-cycloaddition proceeded smoothly in the presence of TFA to give the novel cyclobutapyrimidine 1,2-cycloadduct (**2a**)[12] in 42% yield in cyclohexane at 59% conversion, and 55% yield in benzene at 40% conversion, respectively. The substitution reaction was significantly suppressed under these conditions (Table 1).

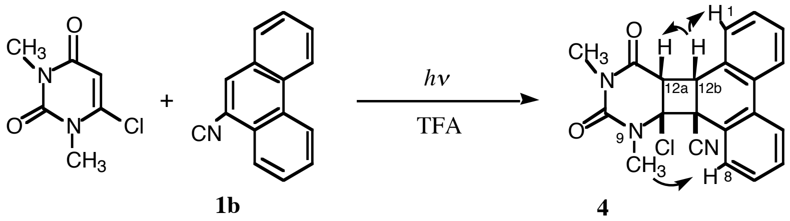
The addition of TFA to an acetonitrile solution of 6-ClDMU had no effect on the reaction modes. Among various conditions examined, the best result was obtained when the reaction was conducted in cyclohexane in the presence of TFA.

Table 1. Photoreaction of 6-ClDMU with **1a** under various conditions.

Solvent	Irradiation time (h)	Yields† (%) of		Conversion of 6-ClDMU (%)
		2a	**3a**[13]	
cyclohexane	2	0	0	10
cyclohexane + TFA	2	42	6	59
benzene	2	10	30	15
benzene+ TFA	2	55	5	40
acetonitrile	4	33	27	15
acetonitrile + TFA	4	39	30	15

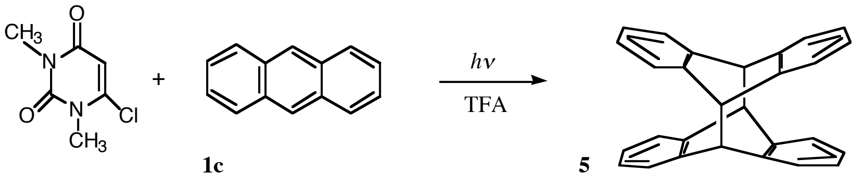
†: Yields are given on the basis of 6-ClDMU consumed.

Interestingly, photoreaction of 6-ClDMU with 9-cyanophenanthrene (**1b**) in cyclohexane containing TFA (4 h) gave the novel 1,2-cycloadduct (**4**)[14] as the major product (31% at 15% conversion of 6-ClDMU) wherein 12a-H and 8c-Cl remained intact in their original positions, though the reaction proceeded slowly (Scheme 2). The stereochemistry of **4** was determined as *cis* with the aid of NOE experiments. Irradiation of the proton at 12b (δ 5.02, d, J = 10.5 Hz), significantly affected the vicinal proton at 12a (δ 4.84, d, J = 10.5 Hz, H-12a), as well as the aromatic proton at 1 (δ 7.05, d, $J_{1,2}$ = 7.8 Hz).



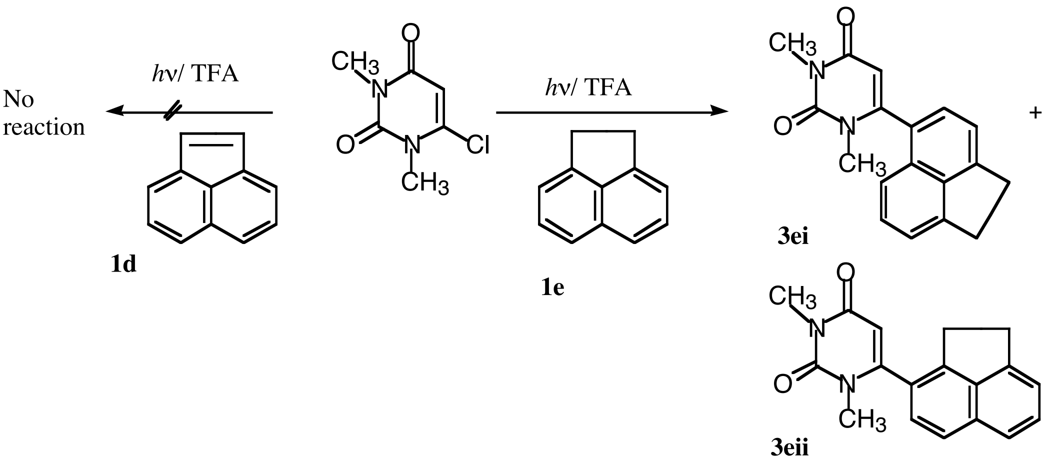
Scheme 2. Photoreaction of 6-ClDMU with 9-cyanophenanthrene (**1b**), and NOE correlation for **4**.

Photoreaction of 6-ClDMU with anthracene (**1c**) in cyclohexane, regardless of the addition of TFA, resulted only in the formation of [4+4] anthracene dimer (**5**),[15] and no formation of cyclobutapyrimidine was observed (Scheme 3).



Scheme 3. Photoreaction of 6-ClDMU with anthracene (**1c**).

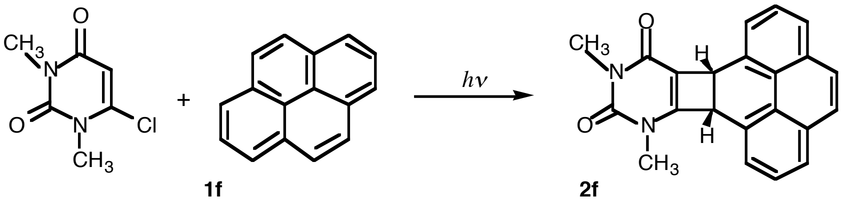
Similar photoreaction with acenaphthylene (**1d**) in the presence of TFA gave no product. In contrast, the dihydro derivative acenaphthene (**1e**), in the absence of TFA, afforded substitution product (**3ei**) in appreciable yield (38%). The photoreaction in the presence of TFA smoothly consumed the starting materials, but all reaction products except aryl uracil (**3ei**; 3%, **3eii**; 1%)[13] were so labile that their isolation or characterization failed (Scheme 4).



Scheme 4.

We have also studied this photoreaction with polycyclic aromatic hydrocarbons containing more than three ring systems. Thus, tetracyclic pyrene (**1f**) underwent 1,2-cycloaddition either in cyclohexane containing TFA or in acetonitrile to give the corresponding hexacyclic compound (**2f**)[16] in appreciable yield (Table 2).

Table 2. Photoreaction of 6-ClDMU with pyrene (**1f**).

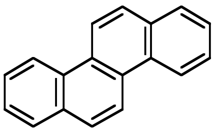


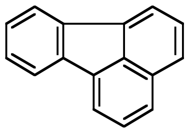
Solvent	Irradiation time (h)	Yields† (%) of **2f**	Conversion (%) of 6-ClDMU
cyclohexane + TFA	4	36	58
benzene + TFA	4	--	7
acetonitrile	4	7	14
acetonitrile	12	10	21

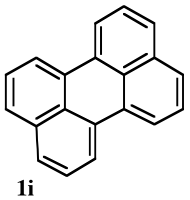
†: Yields are given on the basis of 6-ClDMU consumed.

Photoreaction of chrysene (**1g**) (4 h) with 6-ClDMU in cyclohexane gave no product in the absence of TFA. Addition of TFA however induced the substitution reaction to afford **2g** in fair yield (77%).[13]

Similar acid-catalyzed photoreaction with fluoranthene (**1h**) or pentacyclic perylene (**1i**) in cyclohexane, either in the presence or in the absence of TFA, gave no photoproduct.


1g


1h


1i

In order to obtain insight into the effect of TFA, the photoreaction with 6-ClDMU and phenanthrene (**1a**) was conducted in the presence of varying amounts of TFA (Table 3).

Interestingly, the addition of 2 to 10 molar equivalents of TFA effected cycloaddition as the predominant process, while further addition of TFA (more than 20 molar equivalents) shifted the reaction mode to the substitution process, furnishing 6-arylpyrimidines preferentially.

These findings may suggest that charge-transfer or exciplex formation participates in the present reaction.[17]

Table 3. Effect of TFA on the photoreaction of 6-ClDMU with phenanthrene (**1a**)

TFA (molar equiv.)	Yields† (%) of Cycloadduct **(2a)**	6-ArDMU (**3a**)	Conversion (%) of 6-ClDMU
0	0	0	9
2	42	6	59
5	40	7	59
10	35	8	61
20	30	14	57
40	15	23	60

†: Yields are given on the basis of 6-ClDMU consumed.

The UV spectrum of the starting mixture of 6-ClDMU and **1a** exhibited the sum of the individual absorption band of both compounds, and no charge-transfer absorption band in the ground state was observed. Addition of *trans*-piperylene showed no significant quenching effect on the 1,2-cycloaddition, while the substitution reaction was considerably suppressed. Moreover, a solution of **1a** and 6-ClDMU containing TFA in cyclohexane did not reveal any new fluorescence ascribable to exciplex formation. The fluorescence of **1a** was quenched in cyclohexane by 6-ClDMU (in the absence of TFA) with a Stern-Volmer rate constant of $k\mathrm{q} = 3.7 \text{ x } 10^{8}\ \mathrm{M^{-1}\cdot s^{-1}}$. The fluorescence was quenched more efficiently as the amount of TFA added to the solution (**1a** and 6-ClDMU) increased (with 2 molar equivalent TFA, $k\mathrm{q} = 8.5 \text{ x } 10^{8}\ \mathrm{M^{-1}\cdot s^{-1}}$; with 10 molar equivalent TFA, $k\mathrm{q} = 2.6 \text{ x } 10^{9}\ \mathrm{M^{-1}\cdot s^{-1}}$). These results suggest that the reaction of **1a** may proceed *via* the excited singlet state.

Neither the absorption spectrum nor ionization potential of the polycyclic aromatics could adequately account for the reaction features.[18]

In summary, we have surveyed the scope of the acid-catalyzed photoreaction of 6-ClDMU with various polycyclic arenes and have obtained the following results: 1) Reaction with phenanthrene (**1a**), 9-cyanophenanthrene (**1b**), and pyrene (**1f**) effected 1,2-cycloaddition as well as naphthalene and its derivatives. 2) In the case of both acenaphthene (**1e**) and chrysene (**1g**), substitution reaction proceeds favorably. 3) Anthracene (**1c**) affords its [4+4] dimer. 4) No reaction occurs with acenaphthylene (**1d**), fluoranthene (**1h**), and perylene (**1i**).

ACKNOWLEDGEMENT

This work was supported in part by a Grant-in-Aid for High Technology Research Programs from the Ministry of Education, Science, Sports, Culture, and Technology, Japan.

REFERENCES AND NOTES

1. D. Bryce-Smith, "Photochemistry", Vol. 6-17, The Royal Society of Chemistry, Cambridge, 1975-1986.
2. K. Ohkura, H. Nakamura, H. Takahashi, and K. Seki, *Heterocycles*, 2000, **52**, 867; K. Ohkura, H. Nakamura, T. Sugaoi, A. Sakushima, H. Takahashi, and K. Seki, *Heterocycles*, 2002, **57**, 665.
3. K. Seki, N. Kanazashi, and K. Ohkura, *Heterocycles*, 1991, **32**, 229; K. Ohkura, N. Kanazashi, and K. Seki, *Chem. Pharm. Bull.*, 1993, **41**, 239.
4. K. Ohkura, Y. Noguchi, and K. Seki, *Chem. Lett.*, **1997**, 99; K. Ohkura, Y. Noguchi, and K. Seki, *Heterocycles*, 1997, **46**, 141; K. Ohkura, Y. Noguchi, and K. Seki, *Heterocycles*, 1998, **47**, 429.
5. K. Ohkura, K. Nishijima, S. Uchiyama, A. Sakushima, and K. Seki, *Heterocycles*, 2001, **54**, 65.
6. K. Ohkura, K. Nishijima, A. Sakushima, and K. Seki, *Heterocycles*, 2000, **53**, 1247.
7. K. Ohkura, T. Sugaoi, K. Nishijima, Y. Kuge, and K. Seki, *Tetrahedron Lett.*, 2002, **43**, 3113.
8. K. Ohkura, S. Uchiyama, K. Aizawa, K. Nishijima, and K. Seki, *Heterocycles*, 2002, **57**, 1403.
9. J. J. Maccullough, *Chem. Rev.*, **1987**, 811.
10. S. J. Hanrock and R. S. Sheridan, *Tetrahedron Lett.*, 1998, **43**, 5509.
11. S. M. Sieburth, K. F. Jr. McGee, F. Zhang, and Y. Chen, *J. Org. Chem.*, 2000, **65**, 1972; K. Chiyonobu, G. Konishi, Y. Inoue, and K. Mizuno, *J. Chem. Res.*, **2001**, 135.
12. Selected data for **2a**: Colorless crystals. mp 224–225 . ^{1}H-NMR ($CDCl_3$): δ 3.23 (3H), 3.32 (3H), 4.73 (1H), 4.96 (1H), 7.27-7.40 (5H), 7.60 (1H), 7.92 (1H), 7.99 (1H). HREIMS: Calcd for $C_{22}H_{16}N_2O_2$: 316.1212. Found: 316.1200.
13. Satisfactory spectral data (^{1}H-NMR, MS, HRMS) were obtained for the substituted products.
14. Selected data for **4**: colorless crystals. mp 161.5-162.5 . ^{1}H-NMR-(acetone-d_6): δ 2.21 (3H, s, N^9-CH_3), 2.76 (3H, s, N^{11}-CH_3), 4.84 (1H, d, *J* = 10.5 Hz, H-12a), 5.02 (1H, d, *J* = 10.5 Hz, H-12b), 7.05 (1H, d, *J* = 7.8 Hz, H-1), 7.31 (1H, t, *J* = 7.8 Hz, H-2), 7.37 (1H, t, *J* = 7.8 Hz, H-3), 7.55 (1H, t, *J* = 7.8 Hz, H-7), 7.64 (1H, dd, *J* = 8.3, 7.8 Hz, H-6), 7.74 (1H, d, *J* = 7.8 Hz, H-8). 8.06 (1H, d, *J* = 7.8 Hz, H-4). 8.17 (1H, d, *J* = 8.3 Hz, H-5). HRFABMS: Calcd for $C_{21}H_{17}N_3O_2{}^{35}Cl$: 378.1010. Found: 378.1024.
15. H. -D. Becker, *Chem. Rev.*, 1993, **93**, 145; H. Bouas-Laurent, A. Castellan. J. -P. Desvergne, and R. Lapouyade, *Chem*. Soc. *Rev.*, 2000, **29**, 43.
16. Selected data for **2f**: mp 260–261 . ^{1}H-NMR (acetone-d_6): δ 3.09 (3H, s, N^{11}-CH_3), 3.37 (3H, s, N^9-CH_3), 5.03 (1H, d, *J*=4.7 Hz, H-12b), 5.52 (1H, d, *J*=4.7 Hz, H-8b), 7.64 (1H, dd, *J*=7.5, 7.7 Hz, H-2 or H-7), 7.68 (1H, dd, *J*=7.7, 7.5 Hz, H-7 or H-2), 7.76-7.85 (4H, m, Ar-H), 7.92 (2H, d, *J*=7.7 Hz, Ar-H). HRMS: Calcd for $C_{22}H_{16}N_2O_2$: 340.1212. Found: 340.1208.
17. K. Seki, K. Ohkura, Y. Fukai, and M. Terashima, *Heterocycles*, 1996, **42**, 341; K. Ohkura and K. Seki, *Photochem. Photobiol.*, 2002, **75**, 579.
18. J. Mattay, *Tetrahedron*, 1985, **41**, 2393; *ibid.,*1985, **41**, 2405.