ACID CATALYZED PHOTOREACTION OF 5-CHLORO-1,3-DIMETHYLURACIL WITH SUBSTITUTED BENZENES

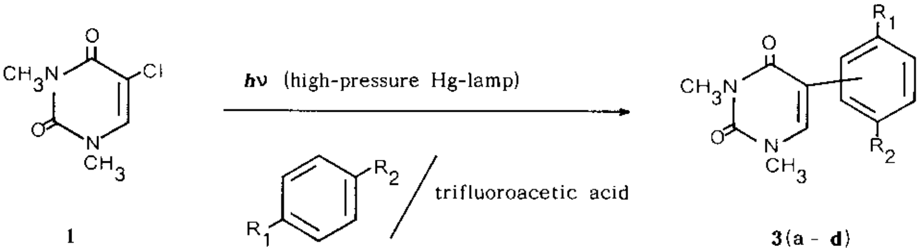
Kazue Ohkura, Kohki Matsuda, and Koh-ichi Seki*

Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University, Ishikari-Tobetsu, Hokkaido 061-02, Japan

Abstract——The photo-induced substitution of 5-chloro-1,3-dimethyluracil with substituted benzenes, affording the corresponding 5-aryl-1,3-dimethyluracils in appreciable yields, was significantly promoted by the addition of trifluoroacetic acid to the reaction mixture.

Several reports have appeared which dealt with photoreaction of electron acceptor-electron donor system wherein the photoreactivities and/or product distributions varied remarkably by addition of acids to the reaction mixtures.[1] Previously we have reported that photoreaction of 5-bromo-1,3-dimethyluracil (5-BrDMU) in substituted benzenes afforded 5-aryl-1,3-dimethyluracil (5-ArDMU) and the unexpected 6-isomers (6-ArDMU).[2] Protonation of 5-BrDMU was found to be essential for the formation of the latter isomers.[3] Furthermore, we have recently reported on the photolyses of 6-halo-1,3-dimethyluracil (6-XDMU; X = I, Br, Cl) in benzene:[4] The photolysis of 6-IDMU and 6-BrDMU gave 6-phenyl-1,3-dimethyluracil (6-PhDMU) as the major product and no significant effect of the added acid on the reaction was observed; contrastingly addition of trifluoroacetic acid (TFA) to a solution of 6-ClDMU in benzene resulted in the formation of a [2+2] photocycloaddition product, 1,3-dimethylcyclooctapyrimidine-2,4-dione, as the major product. To explore the general feature of the acid catalyzed photoreaction of halogenated uracils with substituted benzenes, we have extended our investigation to 5-chloro-1,3-dimethyluracil (5-ClDMU). In the present paper, we describe our findings that the photolyses of 5-ClDMU (**1**) in substituted benzenes (**2**) afforded 5-ArDMU (**3**) in efficiently improved yields by addition of TFA (Scheme 1).

The photoreaction of **1** in benzene (**2a**) in the absence of TFA was slow and gave 1,3-dimethyl-5-phenyluracil (5-PhDMU, **3a**) in 10.5 % yield. Contrastingly the photolysis under the similar conditions but in the presence of TFA (1.2 mmol = 48 equiv. molar) afforded **3a** in appreciably higher yield (30.4 %), together with the 62 % recovery of **1**. Similar results were observed in the reaction with toluene(**2b**). In this reaction 5-(methylphenyl)-1,3-dimethyluracil (**3b**) was



1 **2** (**a** - **d**) **3**(**a** - **d**)

a: R_1, R_2 = H b: R_1 = H, R_2 = CH_3

c: R_1 R_2 = CH_3 d: R_1 = CH_3, R_2 = Cl

Scheme 1

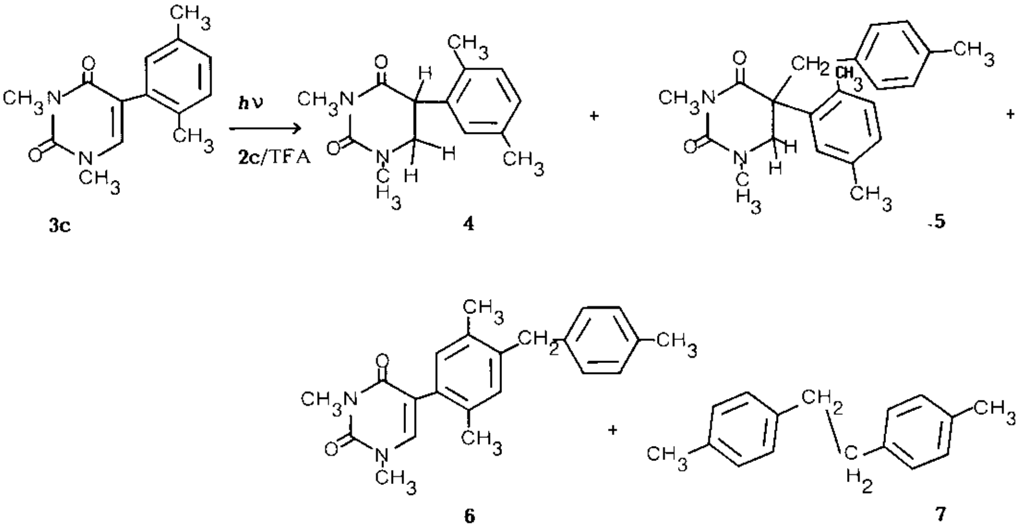
Table I. Photolysis of 5-ClDMU (**1**) in Substituted Benzenes (**2**)

2	TFA (mmol)	Reaction time(h)	Yields (%)[a] 5-ArDMU(**3**) [isomer ratio(%)]	DMU[b]	Consumed **1** (%)[a]
a	none	10	10.5 (75)[c]	--	14
	1.2	10	30.5 (80)[c]	--	38
b	none	10	8.5 (34)[c][i:ii:iii=47:30.5:22.5]	--	25
	0.05	10	35 (64)[c][i:ii:iii=47.5:17.5:35]	--	55
	1.2	10	56 (62)[c][i:ii:iii=37:37:24]	--	90
c	none	5	16 (48)[c]	--	33
	0.05	5	31 (50)[c]	0.4	61.5
	1.2	5	12.5 (13)[c]	0.9	96
d	none	5	16 (36)[c][i:ii:**3b**$_{iii}$ = 24:47:29]	--	45
	0.05	5	37 (61)[c][i:ii:**3b**$_{iii}$ = 27:42:31]	--	61

a) Determined by reversed-phase high performance liquid chromatography (hplc).
b) 1,3-dimethyluracil. c) Yields of **3** based on **1** consumed.

produced as a mixture of ortho (**3b**$_{i}$), meta (**3b**$_{ii}$), and para (**3b**$_{iii}$) isomers. The photoreaction with p-xylene (**2c**) under the similar conditions (TFA, 48 equiv. molar) furnished **3c** in low yield (12.5 %), though **1a** was consumed efficiently (96 %). However the yield of **3c** was improved appreciably by the reaction carried out with reduced amounts of TFA (0.05 mmol = 2 equiv. molar). This observation suggested that **3c** may be labile to uv light under the conditions containing a large amount of TFA. In fact, the photolysis of **3c** in **2c** under the similar conditions afforded the dihydro derivative (**4**), p-methylbenzyl adducts (**5** and **6**), together with 1,2-di(p-methylphenyl)ethane (**7**) (Scheme 2).[5]

Photoreaction of p-chlorotoluene (**2d**) under the conditions containing TFA (2 equiv. molar) afforded a mixture of 5-(2-chloro-5-methylphenyl)uracil (**3d**$_{i}$), 5-(3-chloro-6-methylphenyl)-1,3-dimethyluracil (**3d**$_{ii}$) and **3b**$_{iii}$ in appreciable yields. These results are summarized in Table I.



Scheme 2

The uv spectrum of **1** (λ_{max} 277 nm) shifted ca. 5 nm to the red in cyclohexane by the addition of TFA.[6] Furthermore, addition of a triplet quencher, piperylene, to the reaction with p-xylene (**2c**) was ineffective on the formation of **3**, suggesting that the present reaction may proceed via the singlet excited state of the protonated **1** or the charge transfer complex of **1** and TFA.

Thus, the added acid effected differently on the photoreaction of 5-ClDMU[7,8] from those reported for 5-BrDMU and 6-XDMU. The present reaction would provide a useful synthetic method for 5-substituted uracils as well as the photoreaction with iodo and bromo derivatives.[9]

EXPERIMENTAL

Melting points are uncorrected. Proton nuclear resonance (^{1}H-nmr) spectra were measured with a JNM-GX 270 (270 MHz) spectrometer in $CDCl_3$, and chemical shifts were given on the δ (ppm) scales with tetramethylsilane as an internal standard. Abbreviations are used as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Mass spectra (ms) were determined on a JEOL QH-100 mass spectrometer. Uv spectra were taken on a Shimadzu UV-240 at room temperature. High-performance liquid chromatograpy (hplc) was performed with a Shimadzu HPLC system (pump, LC-5A; detector, SPD-2A; controller, SIL-6A) equipped with a pre-packed column (Wakosil II-5C18, 4.6 mm i.d. x 250 mm, Wako), using caffeine as an internal standard. Uv-irradiation was carried out with a 500 W high-pressure mercury lamp (Eiko-sha) at room temperature (20-23°C).

General procedure for the photolysis of 5-chloro-1,3-dimethyluracil (1) in a Substituted Benzenes (2a-d) ——— Each Solution of 1 (4.36 mg, 0.025 mmol) in a substituted benzene (**2a-d**: **a**, benzene; **b**, toluene; **c**, p-xylene; **d**, 4-chlorotoluene) (5ml) containing trifluoroacetic acid (TFA) and no TFA was irradiated externally at the same time in degassed Pyrex tubes (13 mm i.d., 1 mm thickness) using a merry-go-round apparatus (Eiko-sha). The reaction mixture was evaporated under reduced pressure and the residual oil was submitted to hplc (methanol-H_2O, 25-100%; monitored at 254 nm). The products (**3a-c**) were identified by comparison of their spectroscopic (ms) and chromatographic behaviors with the authentic samples prepared photochemically from 5-BrDMU and **2a-c**.[2b]

Preparation of 5-(2-chloro-5-methylphenyl)-1,3-dimethyluracil (3d$_i$) and 5-(3-chloro-6-methylphenyl)-1,3-dimethyluracil (3d$_{ii}$)———A solution of a mixture of 1 (436 mg, 2.5 mmol) and TFA (0.370 ml, 5 mmol) in p-chlorotoluene (**2d**) (300 ml) was irradiated externally in a doughnut-type Pyrex vessel under argon atmosphere for 10 h. The reaction mixture was evaporated under reduced pressure and the residual oil was passed through a short column of silica gel (Kieselgel 60 F_{254}, Merck) (10 g) first with hexane (25 ml) and then with ether (150 ml). The ethereal eluate was submitted to silica gel column chromatography with ether-hexane (2 : 1) on the hplc apparatus equipped with a pre-packed column (Shim-Pac Prep-Sil, Shimadzu) to furnish a mixture of **3d**$_i$ and **3d**$_{ii}$ (90 mg, 13.5 %), **3b**$_{iii}$ (34 mg, 5.9 %), and **1** (284 mg, 65 %), subsequently. The mixture of **3d**$_i$ and **3d**$_{ii}$ was further chromatographed on a reverse phase C-18 column (Shim-Pac Prep ODS, Shimadzu) with 38 % methanol in H_2O to afford **3d**$_i$ (34 mg) and **3d**$_{ii}$ (55.0 mg), subsequently.

3d$_i$; mp 175.5-176.5° (from i-propanol). Anal. Calcd for $C_{13}H_{13}N_2O_2$: C, 58.98; H, 4.95; N, 10.58; Cl, 13.39. Found C, 58.89; H, 4.95; N, 10.50; Cl, 13.37. ^{1}H-Nmr ($CDCl_3$) : 7.15 (1H, s like, 2'-H), 7.33 (1H, ddm, 7.7 Hz, 2.2 Hz, 4'-H), 7.33 (1H, dm, 7.7 Hz, 5'-H). Ms m/z (%): 268(15), 267(12), 266(45), 265(16), 231(79), 230(90), 229 (100), 172(52), 145(34), 132(90), 115(40).

3d$_{ii}$; mp 181-181.5°(from i-propanol). Anal. Calcd for $C_{13}H_{13}N_2O_2$: C, 58.98; H, 4.95; N, 10.58;

Cl, 13.39. Found C, 58.96; H, 5.02; N, 10.59; Cl, 13.32. ^{1}H-Nmr ($CDCl_3$) δ : 7.10 (1H, d, J = 2.1 Hz, 6'-H), 7.16 (1H, d, J = 8.2 Hz, 3'-H), 7.23 (1H, dd, J = 2.1 and 8.2 Hz, 4'-H): Nuclear Overhauser effect (NOE); 4'-H and 6'-H by irradiation at C-CH_3. Ms m/z (%): 266(35), 265(30), 264(100), 263(31), 249 (36), 247(84), 229(21), 180(13), 178(31), 152(15), 150 (31).

Photolysis of 1,3-Dimethyl-5-phenyluracil (3c) in p-Xylene (2c) in the Presence of TFA——A solution of a mixture of **3c** (160 mg, 0.66 mmol) and TFA (2.8 ml, 37.7 mmol) in **2c** (160 ml) was irradiated externally in a doughnut-type Pyrex vessel under an argon atmosphere for 5 h. The reaction mixture was evaporated under reduced pressure and the residual oil was passed through a Sep-Pak C-18 cartridge column (Waters Associates) with methanol. The methanol eluate was submitted to column chromatography on a reverse-phase pre-packed column (Lobar column, LiChroprep RP-8, Merck) with methanol in H_2O (0—100 %) on the hplc apparatus to furnish 1,3-dimethyl-5,6-dihydro-5-(2,5-xylyl)uracil (**4**) (52 mg, 32.2 %), 1,3-dimethyl-5,6-dihydro-5-(p-methylbenzyl)-5-(2,5-xylyl)uracil (**5**) (90 mg, 39.2 %), and 1,3-dimethyl-5,6-dihydro-5-(p-methylbenzyl)-5-(2,5-xylyl)uracil (**6**) (17 mg, 7.5 %), together with 1,2-di(p-methylphenyl)ethane (**7**) (36 mg), subsequently.

4; mp 111.5-112.5° (fine needles from hexane). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found C, 68.15; H, 7.40; N, 11.34. ^{1}H-Nmr ($CDCl_3$) δ : 2.28 (3H, s , Ar-CH_3), 2.30 (3H, s, Ar-CH_3), 3.04 (3H, s, N-CH_3, 3.26 (3H, s, N-CH_3), 3.43 (1H, dd, J = 12.45 Hz and 6.59 Hz, 6-H), 3.50 (1H, dd, J = 12.5 and 10.1 Hz, 6-H), 4.08 (1H, dd, J = 10.1 and 6.6 Hz, 6-H), 6.84 (1H, bs, 6'-H), 7.01 (1H, dd, J = 7.7 and ca. 1.5 Hz, 4'-H), 7.09 (1H, d, J = 7.7 Hz). Ms m/z (%): 246(54), 245(40), 146(100).

5; mp 143.5-145°(prisms from hexane). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found C, 75.54; H, 7.48; N, 8.02. ^{1}H-Nmr ($CDCl_3$) δ : 2.27 (3H, s, Ar-CH_3), 2.30 (6H, s, Ar-CH_3 x 2), 2.81 (3H, s, N-CH_3), 3.15 (3H, s, N-CH_3), 3.32 (1H, d, J = 13.2 Hz, ArCH_2), 3.32 (1H, d, J = 13.2 Hz, 6-H), 3.48 (1H, d, J = 13.2 Hz, ArCH_2), 3.66 (1H, d, J = 13.2 Hz, 6-H), 7.01 (2H, d like, J = 8.0 Hz, ArH), 7.07 (2H, d like, J = 8.0 Hz), 6.90[10] (1H, J = $\sim$ 0, ArH), 6.91[10] (1H, J = 8.0 Hz, ArH), 6.91[10] (1H, J = 8.0 Hz). Ms m/z (%): 350(21), 258(18), 245(100), 160(64).

6; oil. High resolution ms m/z: Calcd for $C_{22}H_{26}N_2O_2$: 350.1995. Found 350.1984. Ms m/z (%): 350(100), 279(10), 250(78), 223(24), 209(31). ^{1}H-Nmr ($CDCl_3$) δ: 2.17, 2.27, 2.31 (9H, s, Ar-CH_3 x 3), 3.06 (3H, s, N-CH_3), 3.26 (3H, s, N-CH_3), 3.43 (1H, dd, J = 12.5 and 6.4 Hz, 6-H), 3.51 (1H, dd, J = 12.5 and 10.1 Hz, 6-H), 3.88 (2H, s, Ar-CH_2-Ar), 4.07 (1H, dd, J = 10.1 and 6.4 Hz), 6.81 (1H, s, Ar-H), 6.93 (1H, s, Ar-H), 7.00 (2H, d, J = 8.0 Hz, ArH), 7.08 (2H, d, J = 8.0 Hz, Ar-H).

7; mp 81.5-82.5 (needles from methanol). Anal. Calcd for $C_{16}H_{18}\cdot 1/2H_2O$: C, 89.83; H, 8.67. Found C, 90.05; H, 8.81. ^{1}H-Nmr ($CDCl_3$) (JEOL FX 90, 90 MHz) δ: 2.31 (6H, s, Ar-CH_3 x 2), 2.85 (4H, s, Ar-CH_2-CH_2-Ar), 7.07 (8H, s, Ar-H).

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5. The reaction mechanism for the formation of these products remains unclear, but in view of the findings that 1,2-di(p-methylphenyl)ethane was obtained in appreciable yields, it would be supposed that the products (**5**) and (**6**) were derived by the addition of the p-methylbenzyl radical to **3c**.
6. Similar shifts of uv spectra were observed for 5-IDMU and 5-BrDMU.
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8. Similar photoreactions with 5-IDMU in **2a** and **2c** afforded **3a** and **3c** in 86 % and 58 % yields, respectively, but no significant effect of the added acid on the reaction was observed.
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10. Analyzed by using a nmr analyzing program revised for PC-9801 (NEC) use by Dr. H. Ozawa (Computer Center, Tokyo University) on the basis of the "LAOCN 3" QCPE library program (# 111 by A. A. Bother-By and S. M. Castellano, 1966; Chemistry Department, Room 204, Indiana University, Bloomington, Indiana 47401).

Received, 15th May, 1991