EFFECT OF BROMIDES ON THE ANOMALOUS PHOTOARYLATION OF 5-HALO-1,3-DIMETHYLURACILS†

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Abstract ——— Photolysis of 5-chloro- and 5-fluoro-1,3-dimethyluracil in toluene in the presence of a bromide (*e.g.*, *p*-dibromobenzene, 1,2-dibromoethane, and benzyl bromide) and an acid (trifluoroacetic acid, HBr) afforded 1,3-dimethyl-5-tolyluracils and the 6-isomers as the isomeric mixture. 5-Arylation occurred most favorably at *ortho*, while *meta*-isomers were preferential products in 6-arylation. The 5-isomers are suggested to be derived from uracils excited in the singlet states, while the 6-isomers are presumed to result from the uracils excited in the triplet states.

Previously we reported that the photolysis of 5-bromo-1,3-dimethyluracil (5-BrDMU) in mono-substituted benzene afforded the corresponding 5-aryl-1,3-dimethyluracils (5-ArDMU's) and the unexpected 6-aryl isomers (6-ArDMU's).[2] The presence of an acid such as hydrogen bromide or trifluoroacetic acid (TFA) was essential for the formation of the 6-isomers. Interestingly substitution occurred mainly at the *ortho*-position of substituted benzenes for 5-ArDMU's, while *meta*-favored substitution occurred for 6-ArDMU's. The isomer distribution of 5-ArDMU's was analogous to those observed widely in aromatic photosubstitution reactions.[3] On the other hand, such a *meta*-oriented aromatic photosubstitution had been sparingly reported except the photo-induced proton exchanges of benzenes,[4] which is accepted as an electrophilic aromatic photosubstitution reaction.[5] With a view to exploring the scope of this uncommon reaction, we had extended the above photoreaction to 5-chloro- and 5-fluoro-1,3-dimethyluracils (**1a**, **1b**), and found that the presence of TFA gave rise to the formation of 5-ArDMU's in appreciably improved yields, however no 6-ArDMU's were produced in either case.[6, 7] These observations drew our attention to the effects of bromine atom on the C(6)-substitution. In the present paper, we describe our findings that photolyses of **1a** or **1b** in toluene (**2**) in the presence of a bromide (**3**: **a**, *p*-dibromobenzene; **b**, 1,2-dibromoethane; **c**, benzyl bromide; **d**, HBr) gave rise to the 6-arylation, in which substitution occurred most preferentially at the *meta*-position, together with the conventional 5-substitution.

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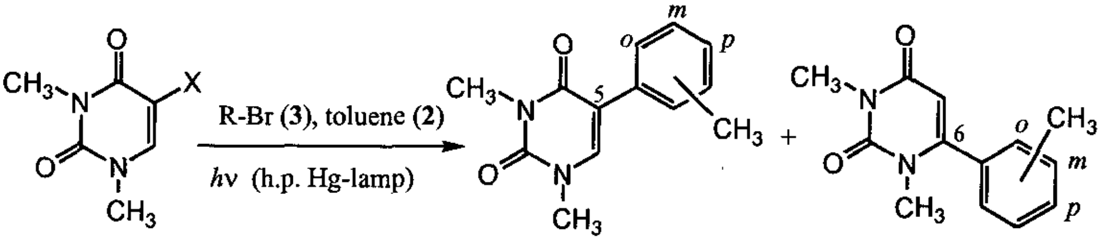
†Dedicated to the late Professor Yoshio Ban.

For the present study, toluene (**2**) was chosen as a mono-substituted benzene for the convenience of chromatographic (glc) analyses. Uv-irradiation of a solution of **1a** (0.025 mmol) in **2** (5 ml) in the presence of a bromide (R-Br) (**3**: **a-d**) afforded 1,3-dimethyl-5-tolyluracils (**4**) and the 6-isomers (**5**) as the mixtures of *ortho*, *meta*, and *para*-isomers as summarized in Table I. In any case, 6-substitution occurred most preferentially at *meta* (62—68%), while 5-substitution took place most favorably at *ortho* (*ca*. 60%) except the cases of **3b**, wherein *ortho* and *meta*-isomers are produced almost equally.



1a, X = Cl
1b, X = F

4

5

Scheme 1

Table I. Photoreaction of 5-chloro-1,3-dimethyluracil (**1a**) and toluene (**2**) in the presence of a bromide (**3**) (10 h)

Entry	Additive (R-Br) (3)	(mol. equiv.)	TFA (mol. equiv.)	4 Yield (%)a)	4 Isomer ratio (%)a) *o*	*m*	*p*	5 Yield (%)a)	5 Isomer ratio (%)a) *o*	*m*	*p*	1a re-covered (%)a)	HBr produced (mmol)b)
1	 (**3a**)	(20)	none	11	*63*	*13*	*24*	6.0	*22*	*67*	*11*	56	0.025
2	 (**3a**)	(20)	2	18	*63*	*15*	*22*	11	*24*	*63*	*13*	40	c)
3d)	 (**3a**) + Pyridine (100)	(20)	--	5.0	*44*	*18*	*38*	0.0	--	--	--	95	c)
4	$(BrCH_2)_2$ (**3b**)	(1400)	none	17	*40*	*35*	*25*	12	*22*	*63*	*15*	55	0.014
5	$(BrCH_2)_2$ (**3b**)	(1400)	2	16	*36*	*41*	*23*	10	*26*	*62*	*12*	45	c)
6e)	$PhCH_2Br$ (**3c**)	(12)	none	11	*56*	*28*	*16*	9.7	*23*	*67*	*10*	42	c)
7	HBr (**3d**)	(1.4)	none	16	*60*	*23*	*17*	9.1	*18*	*68*	*14*	42	c)

a) Determined by glc. *b*) Determined by titration with NaOH (0.01 M) and corrected by subtracting the amounts of HCl generated from **1a** consumed. *c*) Not determined. *d*) Reaction time, 2 h. *e*) No production of benzylated products was detected.

Similarly photolyses of **1b** in the presence of **3a** and TFA gave **4** and **5** in the yields of 18-23.5% and 9.3-5.3%, respectively. Although some changes were observed in the isomer ratios of the 5-isomers especially for *ortho* and *meta*, the pattern of the isomer distributions on the whole was analogous to that of the reactions with **1a** (Table II).

Table. II Photoreaction of 1,3-dimethyl-5-fluorouracil (**1b**) and toluene (**2**) in the presence of R-Br (**3**) (4 h)

Entry	R-Br (3) (mol. equiv.)	TFA (mol. equiv.)	4				5				1b recovered (%)$^{a)}$
			Yield (%)$^{a)}$	*Isomer ratio* (%)$^{a)}$ *o*	*m*	*p*	Yield (%)$^{a)}$	*Isomer ratio* (%)$^{a)}$ *o*	*m*	*p*	
1	**3a** (20)	2	23.5	*77*	*7*	*16*	5.3	*24*	*61*	*15*	17
2	**3b** (1400)	2	18	*40*	*39*	*21*	9.3	*27*	*62*	*11*	33
3	**3c** (12)	2	22	*52*	*28*	*20*	5.4	*23*	*62*	*14*	13

a) Determined by glc.

As shown in Table I, appreciable amounts of hydrogen bromide were found to be generated as the by-product in the reactions in the presence of **3**(**a**, **b**). Addition of pyridine to the solution (Entry 3) resulted in the formation of **4** and no 6-isomers (**5**) were produced, suggesting that protons are essential for the formation of **5**. Addition of piperylene (a triplet quencher) to a solution of **1a** or **1b** with **3a** in **2** was ineffective on the formation of **4** but blocked the formation of the 6-isomers completely. The fluorescence of **1**-H$^+$ (emission λ_{max} at 330 nm obtained by the excitation of a solution of **1a** (1.26×10^{-4} M) containing TFA (2 molar equivs.) in cyclohexane at 285 nm was quenched efficiently (*ca.* 55%) by **2** (0.63 molar equiv.). These findings suggest that the 5-isomers (**4**) are the products from the excited **1**-H$^+$ in the singlet states, while the 6-isomers (**5**) are derived from the triplet excited states. Similar results had been observed for the photoreaction of 5-BrDMU (**1c**) in benzenes.[2] Thus, bromides may serve as the sensitizer for the intersystem crossing from the excited singlet states into the triplet states.[8]

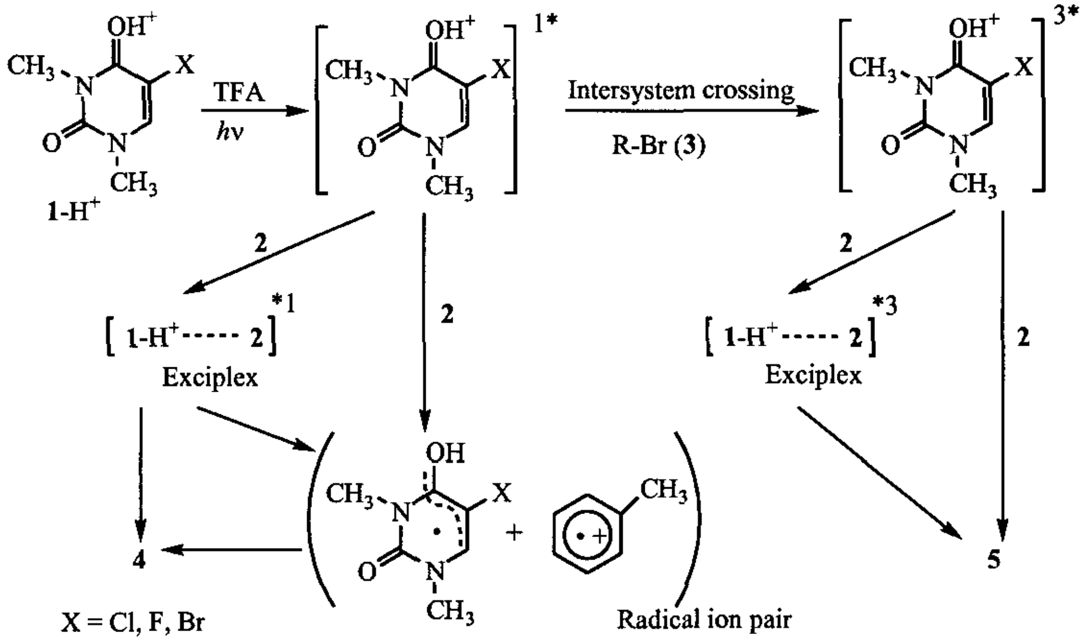
Table III. Effects of piperylene on the photoreaction of **1a** or **1b** and toluene (**2**) in the presence of *p*-dibromobenzene (**3a**) (20 molar equivs.) and TFA (20 molar equivs.) (2 h)

Entry	1	Piperylene (mol. equiv.)	4				5				1 recovered (%)$^{a)}$
			Yield (%)$^{a)}$	*Isomer ratio* (%)$^{a)}$ *o*	*m*	*p*	Yield (%)$^{a)}$	*Isomer ratio* (%)$^{a)}$ *o*	*m*	*p*	
1	**a**	none	10.1	*52.5*	*26.5*	*21.0*	7.7	*23*	*63*	*14*	52
2	**a**	1.3	12.3	*39*	*31.0*	*30*	0.0	--	--	--	73
3	**b**	none	19.2	*71.5*	*10.5*	*18*	2.3	*23*	*60*	*17*	34
4	**b**	1.3	18.1	*56*	*17*	*27*	0.0	--	--	--	60

a) Determined by glc.

The formation of the 5-isomers (**4**) might be interpreted by the similar mechanism to that proposed for the formation of **4** in the photoreaction with **1c**,[2] which involves an electron transfer from **2** to **1**-H$^+$ in the excited singlet state, followed by the coupling of the resulting radical ions. The concept may be supported by the MO calculations for **1**(**a**, **b**) showing a significant drop in the energies of the LUMO's (the electron affinities) by the protonation and the similarity in the isomer ratios of **4** (*e. g.*, Entries 1, 2, and 7 in Table I) to those of the aromatic photosubstitution reactions.[3] However, by contrast to the reaction with **1c**, free radicals such as the radical anion of **1**-H^+ or 1,3-dimethyluracil-5-yl radical may not participate importantly, since the hydrogen atom abstraction product, 1,3-dimethyluracil, was scarcely produced. Some changes were observed in the isomer ratios of the 5-isomers (**4**) (*e. g.*, Entries 4 and 5 in Table I and Entry 2 in Table II), implying that a different mechanism such as an exciplex formation may participate in their formation (Scheme 2). However, the fluorescence spectra or the uv spectra due to the formation of the exciplex or the charge-transfer complex was not observed.

In the presence of a bromide (**3**), excited **1**-H^+ in the singlet state would be converted effectively into the triplet state through the intersystem crossing. Taking the *meta*-favored isomer distribution into consideration, electron transfer may not be involved in the formation of **5**, which is presumed to result in the similar isomer distributions to those of the arylpyridines obtained from the photolysis of halopyridines.[3a] Presumably, the 6-isomers (**5**) are derived from the direct coupling between the excited **1**-H^+ in the triplet state and **2** in the ground state or through the triplet exciplex (Scheme 2). Excitation (at 300 nm) of protonated **1c** with TFA showed no phosphorescence spectrum, while *p*-xylene (2×10^{-4} M) showed the phosphorescence spectrum at the emission λ_{max} at 402 nm with excitation at 275 nm in methylcyclohexane. The phosphorescence was efficiently quenched (*ca.* 66%) by added **1c** (0.13 molar equiv.) and TFA (0.5 molar equiv.), but no phosphorescence spectrum due to the triplet exciplex formation was observed.



Scheme 2

In our previous study on the photoreaction with **1c**,[2] we attempted to explain the mechanism for the *meta*-favored 6-substitution, applying the rules proposed by Mutai *et al.*,[9] in terms of the one-step formation of the σ-complex through a direct interaction between the LUMO of the **1**-H^+ (the HSOMO in the excited state) and the LUMO of a benzene. This explanation may be justified only when these two frontier MO's are close in energy, whereas the LUMO's of **1**(**a**, **b**) were found to be separated further from that of **2** by the protonation at their O(4), suggesting that the regioselectivity of **5** could not be interpreted adequately by using the rules.[10]

Thus, the reaction mechanism remains unclear. However, it may be noteworthy that the present work provides a novel electrophilic aromatic photosubstitution reaction, wherein electrophiles are in the excited state and aromatic molecules are in the ground state.[5a]

EXPERIMENTAL

Uv spectra were taken on a Shimadzu UV-240 instrument at room temperature. Fluorescence and phosphorescence emission spectra were measured on a Shimadzu RF-540 or a Hitachi F-4500 spectrophotometer at room temperature. Phosphorescence spectra were measured on the same apparatus in a liquid nitrogen bath (-195.8°C). Gas-liquid chromatography (glc) was performed with a capillary column (CPB1-M50-025, Shimadzu) on a Shimadzu GC-7A gas chromatograph equipped with a hydrogen flame-ionization detector using helium as a carrier gas (initially at 150°C for 4 min, then elevated to 250°C at the rate of 4°C / min).

Photolysis of 1,3-dimethyl-5-substituted pyrimidine-2,4-diones (1a-e) in toluene (2)----- A solution of **1** (0.025 mmol) in **2** (5 ml) was irradiated externally with a 500 W high-pressure mercury lamp (>300 nm) (Eiko-sha) in a Pyrex tube under argon on a merry-go-round apparatus at room temperature, and the reaction mixture was subjected to glc analysis with 1,2-di(*p*-methylphenyl)ethane as an internal standard. The products were compared with the authentic samples prepared previously.[2]

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10. In our previous paper, MO calculations were performed for the chloro derivative (**1a**) instead of 5-BrDMU (**1c**) by using the MINDO/3 method. The later developed MOPAC method has allowed us to calculate the molecules including a bromine atom. MO calculations by this method showed that the MO's of **1c**-H^+ are close to those of **1a**-H^+ or **1b**-H^+ in their shapes and energies and apart further from the LUMO of **2**, suggesting that the *meta*-orientation could not be explained adequately in terms of the mechanism involving the direct formation of the σ-complex between excited **1**-H^+ and **2**.

Received, 29th March, 1995