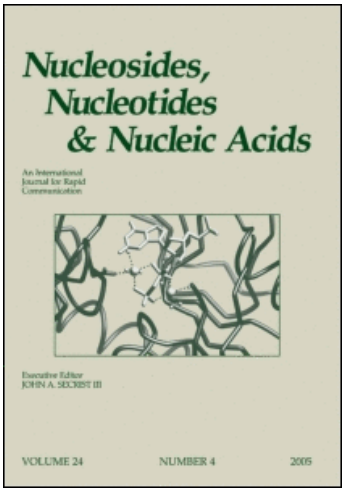



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# Photo-Induced *P*-Methylbenzylation of 1,3-Dimethylthymine and 1, 3-Dimethyluracil in the Presence of Trifluoroacetic Acid

Koh-ichi Seki[a]; Kazue Ohkura[a]
[a] Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University, Hokkaido

**To cite this Article** Seki, Koh-ichi and Ohkura, Kazue(1993) 'Photo-Induced *P*-Methylbenzylation of 1,3-Dimethylthymine and 1, 3-Dimethyluracil in the Presence of Trifluoroacetic Acid', Nucleosides, Nucleotides and Nucleic Acids, 12: 3, 323 — 329
**To link to this Article: DOI:** 10.1080/07328319308017829
**URL:** http://dx.doi.org/10.1080/07328319308017829

NUCLEOSIDES & NUCLEOTIDES, 12(3&4), 323-329 (1993)

# PHOTO-INDUCED *P*-METHYLBENZYLATION OF 1,3-DIMETHYLTHYMINE AND 1,3-DIMETHYLURACIL IN THE PRESENCE OF TRIFLUOROACETIC ACID

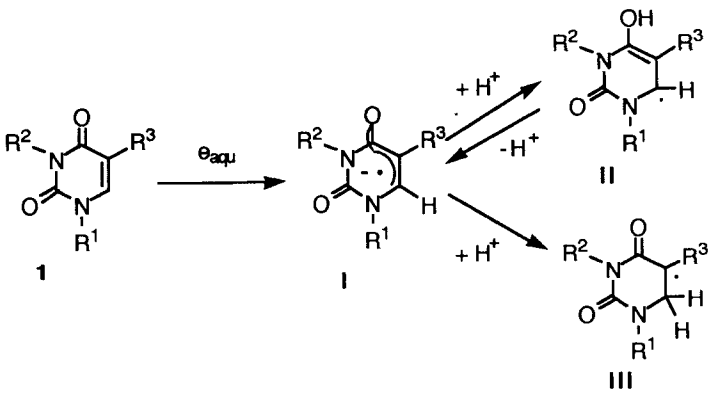
Koh-ichi Seki* and Kazue Ohkura

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

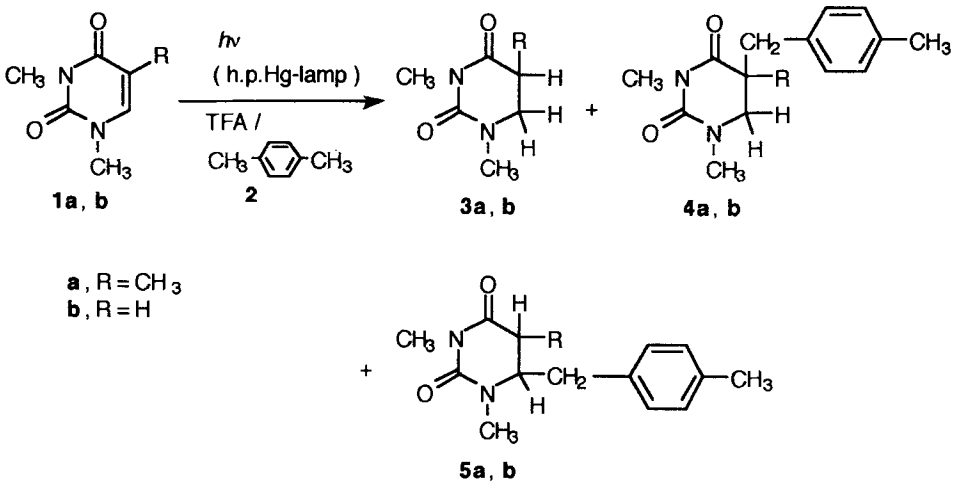
**ABSTRACT:** Photolysis of a solution of a pyrimidine (*i. e.*, 1,3-dimethylthymine and 1,3-dimethyluracil) in *p*-xylene in the presence of trifluoroacetic acid afforded mainly the 5, 6-dihydropyrimidine derivative together with the 5-*p*-methylbenzylated product and the 6-isomer as well. It is suggested that the first two products result from the $C^6$-protonated pyrimidine electron adduct (**III**), while the 6-isomer is derived from the $O^4$-protonated isomer (**II**).



Protonation of the electron adducts of pyrimidine derivatives such as uracil, thymine and the related compounds is of considerable interest from the synthetic and the biological points of view: Upon ionizing radiation in an aqueous solution, solvated electrons add to pyrimidines to form the electron adducts (=radical anions) (**I**), which undergo protonation at O-4 and C-6 to give the radicals, **II** and **III** (Scheme 1).[1] The latter **III** is noted as an




**Scheme 1**

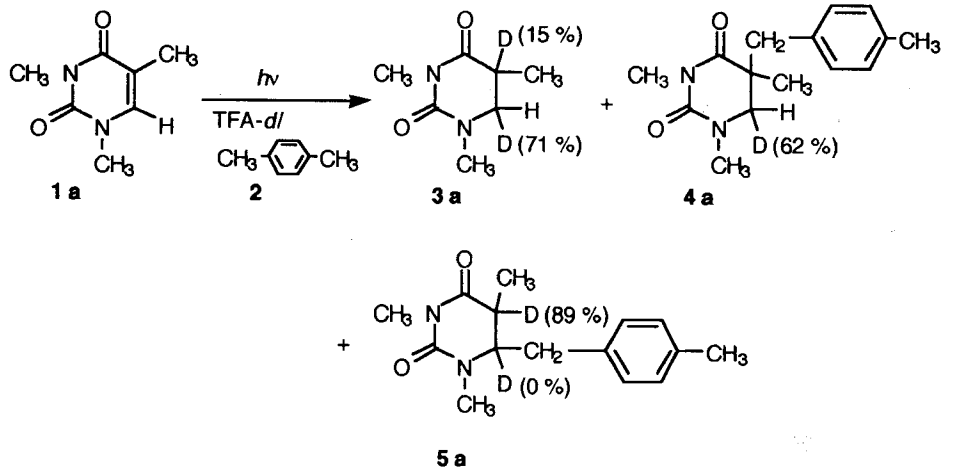



**Scheme 2**



important reactive intermediate in the process of DNA strand breakage since it can react with oxygen resulting in the destruction of the pyrimidine moiety.[1d] However the degradation products have neither been isolated nor identified. Ishida *et al.* have investigated the γ-ray irradiation of uracils in alcohols as a model of crosslinking between DNA-sugars and amino acids having an alcoholic side chain, and found that hydroxyalkylation occurred regioselectively at C-6.[2] They also reported the photochemical synthesis of 6-hydroxymethyluracils *via* $O^4$-protonated radical intermediates (**II**) by photoredox reactions in methanol in the presence of Eu(III)/Eu(II).[3] However the formation of the products from the $C^6$-protonated radicals (**III**) has not yet been reported.

In our continuing studies on the photoreaction of halouracils with substituted benzenes in the presence of trifluoroacetic acid (TFA), we recently reported that the photolysis of 5-fluoro-1,3-dimethyluracil (5FDMU) in a solution of *p*-xylene (**2**) was accompanied by the formation of bixylyl,[4] which was presumed to be derived by coupling of *p*-methylbenzyl radicals generated through detachment of protons from the initially produced radical cations of **2** *via* an electron transfer from **2** to 5FDMU. In this reaction, **2** served as an electron-donor and a radical source. Application of this photoredox system to non-halogenated pyrimidines such as 1,3-dimethylthymine (**1a**) and 1,3-dimethyluracil (**1b**) was expected to provide a useful reaction system for studying the alkylation of the protonated pyrimidine radicals. We now describe the photolysis of **1a** and **1b** in *p*-xylene (**2**) in the presence of TFA.




**1a** **2** **3a** **4a** **5a**

**Scheme 3**

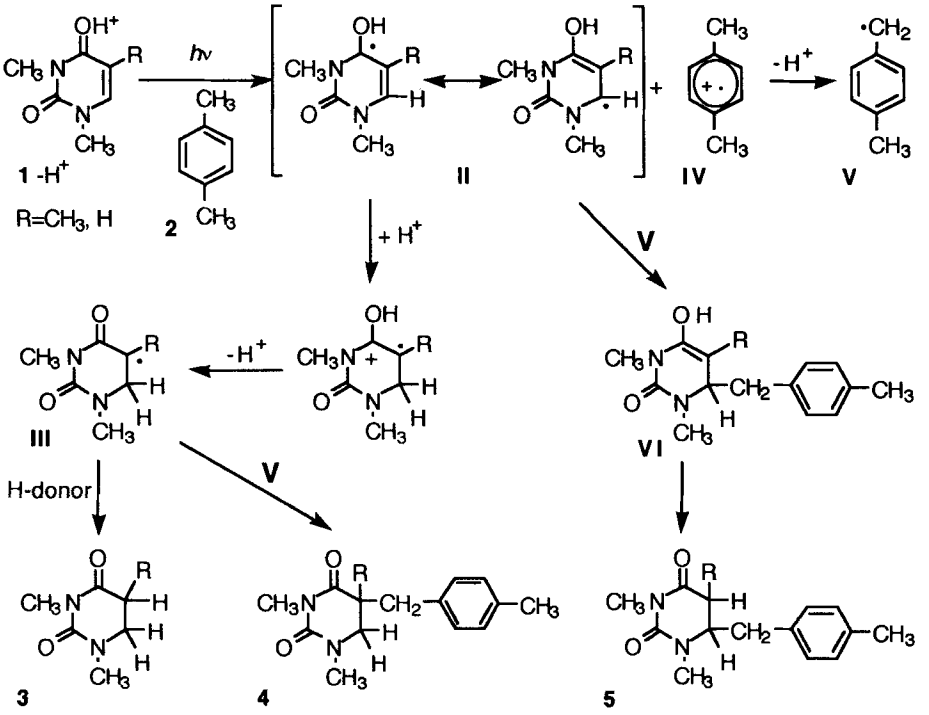


UV-irradiation of **1a** in **2** in the absence of TFA failed to give any detectable amounts of photoproducts, while photolysis of the solution in the presence of TFA (48 mmol) (4h) afforded 5,6-dihydro-1,3-dimethylthymine (**3a**)[5] (43.9%), 5,6-dihydro-1,3-dimethyl-5-(*p*-methylbenzyl)thymine (**4a**) (27.0%), and 5,6-dihydro-6-(*p*-methylbenzyl)thymine (**5a**) (10.7%) as the single stereo isomer,[6] together with recovered **1a** (1.3%) (Scheme 2).

Similarly, the photoreaction of 1,3-dimethyluracil (**1b**) in the presence of TFA (1h) afforded the dihydro derivative (**3b**)[5] (33.5%), the 5-benzylated uracil **4b** (4.7%) and the 6-isomer **5b** (3.3%) with 37.0% recovery of **1b** (Scheme 1).

In order to explore the origin of the newly introduced hydrogen atoms into the products, we have carried out the photoreaction with **1a** in the presence of TFA-*d*, and determined the deuterium incorporation in the products by $^1$H-NMR spectroscopy (Scheme 3). Deuterium incorporation in **3a** took place preferentially at C-6 (71% ) than at C-5 (15%). Deuterium incorporation into **5a** was 89% at C-5, while the uptake of deuterium by **4a** was significant at C-6 (62%). No deuterium was incorporated in **1a** upon irradiation of the solution of **1a** in TFA-*d* in the absence of an electron donor (e.g., **2**), suggesting that the direct addition of TFA to the $C_5$=$C_6$ bond of **1a** may not participate in the deuterium incorporation into the products **3** and **4** at C-6.

These observations suggest that **5** was derived from the $O^4$-protonated radical (**II**) by radical coupling with the *p*-methylbenzyl radical (**V**), while the product **4** resulted



**Scheme 4**

from the $C^6$ protonated radical (**III**) by coupling with **V**, in competition with the formation of **3**[7] by hydrogen abstraction from such hydrogen-donors as **2**.

The UV spectrum of **1a** ($\lambda_{max}$ 266 nm) (0.027 mM) at the region longer than 270 nm shifted *ca.* 2~5 nm to the red in cyclohexane by the addition of TFA (49 equiv. molar), suggesting that protonated **1** (**1**-$H^+$) or the charge transfer complex of **1** and TFA is formed in the ground states. Hence upon UV-irradiation the $O^4$-protonated radicals (**II**) should be produced initially, which is ultimately converted into **III**, though the precise mechanism for the formation of the **III** is unclear. In view of the basicity of the radical **I**,[8] it seems unlikely that **III** was derived from **II** *via* **I** (Scheme 1)[1b,c] under such strong acidic conditions. Alternatively, the radical **III** is assumed to result from the protonation of **II** at C-6 followed by the subsequent deprotonation from O-4 (Scheme 4). This assumption is supported by the the reaction with **1a** under similar conditions but with a reduced amount of TFA (2 mmol) (4h) which proceeded less efficiently (consumed **1a**, 24 %) to give **3a** (1.7%) and **5a** (2.8 %) in the lower yields, whereas no significant change was observed in the yield of **4a** (8.6 %).

Thus, the present study provides the first example of the $C^5$-alkylation and the hydrogenation of pyrimidines *via* the $C^6$-protonation of the radical anion of the pyrimidines. Further work on the mechanism of the present reaction is now in progress.

## EXPERIMENTAL

$^1$H-NMR spectra were measured with a JEOL JNM-EX400 (400 MHz) spectrometer, and chemical shifts are given on the $\delta$ (ppm) scale with tetramethylsilane as an internal standard. Mass spectra (MS) and high resolution MS (HR-MS) were determined on a Shimadzu GCMS 9100-MK spectrometer. UV spectra were taken on a Shimadzu UV-240 instrument at room temperature. Gas-liquid chromatography (GLC) was performed with a capillary column (CPB1-M50-025, Shimadzu) on a Shimadzu GC-7A gas chromatogaraph equipped with a hydrogen flame-ionization detector using helium as a carrier gas. Short-column chromatography was conducted on Kieselgel Si-60 (Merck). Reverse-phase liquid chromatography (RP-LC) was carried out on a Shim-pac PREP-ODS (25 cm x 20 mm *i.d.*)(Shimadzu) eluting with aqueous methanol (25 %), using a Shimadzu LC-6A apparatus with monitoring at 254 nm. Silica gel LC (Si-LC) was conducted on a Shim-pac PREP-Sil (25 cm x 20 mm *i.d.*), using the same apparatus.



**Photolysis of 1,3-Dimethylthymine (1a) and 1,3-Dimethyluracil (1b) in *p*-Xylene (2) in the Presence of Trifluoroacetic acid (TFA)**-----A solution of **1** (0.025 mmol) in **2** (5 ml) in the presence of TFA was irradiated externally with a 500 W high pressure mercury lamp (Eiko-sha) in a degassed Pyrex tube (>300 nm) on a merry-go-round apparatus (4 h for **1a** and 1h for **1b**), and the reaction mixture was subjected to GLC analysis, using 5-chloro-1,3-dimethyluracil as an internal standard.

**General Procedure for the Preparation of 3, 4, and 5 (Preparative scale Photoreaction of 1 in 2)**-----A solution of **1a,b** (1 mmol) in **2** (200 ml) in the presence of TFA (48 mmol) was irradiated in a doughnut-type Pyrex vessel with a 500 W high-pressure mercury lamp under an argon atmosphere for 20 h. After removal of the solvent, the reaction mixture was passed through a short column of silica gel with benzene, and then with ethyl acetate-ethanol (10 : 1). The ethyl acetate-ethanol eluate was submitted to RP-LC to give the 5-*p*-methylbenzyl derivative **4** (**a**, 10.2%; **b**, 2.0%), the 6-isomer **5** (**a**, 7.8%; **b**, 14.3%), and a mixture of **1** and the 5,6-dihydro derivative **3**, respectively. The Si-LC of the mixture afforded **3** (**a**, 28.7%; **b**, 40.4%) and unreacted **1** (**a**,.15%; **b**, 28.5%).

5,6-Dihydro-1,3-dimethyl-5-(*p*-methylbenzyl)thymine (**4a**): Colorless oil: MS *m/z* (%) 260 ($M^+$, 15), 155 (54), 105 (100); $^1$H-NMR ($CDCl_3$): $\delta$ 1.17 (3H, s, $C^5$-$CH_3$), 2.33 (3H, s, Ar-$CH_3$), 2.77 (1H, *d*, $J$ = 13.6 Hz, Ar-$CH_2$-), 2.94 (1H, d, $J$ =13.6 Hz, Ar-$CH_2$-), 2.94 (1H, d, $J$ = 12.8 Hz, H-6), 3.02 (3H, s, N-$CH_3$), 3.06 (1H, d, $J$ = 12.8

Hz, H-6), 3.19 (3H, s, N-$CH_3$), 6.98 (2H, d, $J$ = 7.7 Hz, Ar-H), 7.11 (2H, d, $J$ = 7.7 Hz, Ar-H). HR-MS: *Anal.* Found: 260.1502. Calcd for $C_{15}H_{20}N_2O_2$: 260.1525.

5,6-Dihydro-1,3-dimethyl-6-(*p*-methylbenzyl)thymine (**5a**): Colorless oil: MS *m/z* (%) 261 ($MH^+$, 0.7), 260 ($M^+$, 0.3), 155 (100); $^1$H-NMR ($CDCl_3$): $\delta$ 1.33 (3H, d, $J$ = 7.0 Hz, $C^5$-$CH_3$), 2.31 (3H, s, Ar-$CH_3$), 2.55 (1H, dd, $J$ = 14.2, 8.4 Hz, Ar-$CH_2$-), 2.68 (3H, s, N-$CH_3$), 2.87 (1H, dd, $J$ =14.2, 4.4 Hz, Ar-$CH_2$-), 2.93 (1H, qd, $J$ = 7.0, 5.9 Hz, H-5), 3.01 (3H, s, N-$CH_3$), 3.48 (1H, ddd, $J$ = 8.4, 5.9, 4.4 Hz, H-6), 6.97 (2H, d, $J$ = 7.7 Hz, Ar-H), 7.10 (2H, d, $J$ = 7.7 Hz, Ar-H). HR-MS: *Anal.* Found: 260.1524. Calcd for $C_{15}H_{20}N_2O_2$: 260.1525.

5,6-Dihydro-1,3-dimethyluracil (**3b**): mp 51-52 °C (recrystallized from ether) (lit. 54.5-56°C)[5]; MS *m/z* (%) 143 (44), 142 ($M^+$,100); HR-MS:*Anal.* Found: 142.0727. Calcd for $C_6H_{10}N_2O_2$: 142.0742.

5,6-Dihydro-1,3-dimethyl-5-(*p*-methylbenzyl)uracil (**4b**): Colorless oil: MS *m/z* (%) 247 (27), 246 ($M^+$, 44), 141 (100); $^1$H-NMR ($CDCl_3$): $\delta$ 2.34 (3H, s, Ar-$CH_3$), 2.63 (1H, dd, $J$ = 13.6, 10.6 Hz, Ar-$CH_2$-), 2.85 (1H, dddd, $J$ =10.6, 8.4, 5.5, 4.0 Hz, H-5), 2.98 (3H, s, N-$CH_3$), 3.03 (1H, dd, $J$ = 12.5, 8.4 Hz, H-6), 3.17 (1H, dd, $J$ = 12.5, 5.5 Hz, H-6), 3.20 (3H, s, N-$CH_3$), 3.31 (1H, dd, $J$ = 13.6, 4.0 Hz, Ar-$CH_2$-), 7.06 (2H, d, $J$ = 7.7 Hz, Ar-H), 7.14 (2H, d, $J$ = 7.7 Hz, Ar-H). HR-MS: *Anal.* Found: 246.1372. Calcd for $C_{14}H_{18}N_2O_2$: 246.1368.

5,6-Dihydro-1,3-dimethyl-6-(*p*-methylbenzyl)uracil (**5b**): Colorless oil: MS *m/z* (%) 247 ($MH^+$, 0.6), 246 ($M^+$, 0.1), 141 (100); $^1$H-NMR ($CDCl_3$): $\delta$ 2.34 (3H, s, Ar-$CH_3$), 2.61 (1H, dd, $J$ = 16.9, 1.8 Hz, H-5), 2.69 (1H, dd, $J$ =13.6, 8.1 Hz, Ar-$CH_2$-), 2.78 (1H, dd, $J$ = 16.9, 6.6 Hz, H-5), 2.87 (1H, dd, $J$ = 13.6, 5.1 Hz, Ar-$CH_2$-), 3.01 (3H, s, N-$CH_3$), 3.06 (3H, s, N-$CH_3$), 3.52 (1H, dddd, $J$ = 8.1, 6.6, 5.1, 1.8 Hz, H-6), 7.01 (2H, d, $J$ = 8.1 Hz, Ar-H), 7.12 (2H, d, $J$ = 8.1 Hz, Ar-H). HR-MS: *Anal.* Found: 247.1437. Calcd for $C_{14}H_{19}N_2O_2$ ($MH^+$): 247.1446.

**Deuterium Labeling Experiment** -----The photoreaction of 1,3-dimethylthymine (**1a**) in *p*-xylene (**2**) in the presence of trifluoroacetic acid-*d* (TFA-*d*) was performed preparatively in the same manner as described above.

## REFERENCES AND NOTES

1) a) E. O. Hole, E. Sagstuen, W. H. Nelson, and D. M. Close, *J. Phys. Chem.*, **95**, 1494 (1991) and references cited therein; b) C. von Sonntag, *Life Chemistry Reports*, **3**, 70 (1985); c) D. J. Deeble, S. Das, and C. von Sonntag, *J. Phys. Chem.*, **89**, 5784 (1985); d) D. J. Deeble and C. von Sonntag, *Int. Radiat. Biol*, **51**, 791 (1987).

2) A. Ishida, S. Toki, and S. Takamuku, *Radiat. Phys. Chem.*, **27**, 165 (1986).

3) A. Ishida, S. Toki, and S. Takamuku, *J. Chem. Soc. Chem. Commun.*, **1985**, 1482: J-L. Fourrey, G. Henry, and P. Jouin, *Tetrahedron Lett.*, **1979**, 951.

4) K. Seki and K. Ohkura, *Nucleosides & Nucleotides*, **11**, 521 (1992).

5) Y. Kondo and B. Witkop, *J. Am. Chem. Soc.*, **91**, 5264 (1969).

6) In view of the NMR spectrum ($J_{5\text{-}6}$ = 5.9 Hz) and the NOE observation (H-5 > H-6 ≈ ArC<u>H</u> upon irradiation at $C^5$-$CH_3$), the configuration about the $C^5$ and $C^6$ presume to be *cis* .

7) The uptake of deuterium into **3a** at C-5 (15%) may suggest that a part of **3** resulted from the hydrogen abstraction by the $O^4$-protonated radical (**II**).

8) The p$K_a$ value of **II** in an aqueous solution was given as 7.2; E. Hayon, *J. Chem. Phys.*, **51**, 4881 (1969).

Received 12/3/92
Accepted 1/14/93