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# Reaction of $N^3$-benzyluracil and *N*-hydroxymethylphthalimide with the Mitsunobu reagent: synthesis of hydrazylmethyluracils

Shigetada Kozai, Shigeru Takaoka and Tokumi Maruyama*

*Faculty of Pharmaceutical Sciences, Tokushima Bunri University, 180 Yamashiro-cho, Tokushima 770-8514, Japan*

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**Abstract**—$N^3$-Benzyluracil was treated with *N*-hydroxymethylphthalimide in the presence of the Mitsunobu reagent to give an unusual product bearing a hydrazylmethyl group (**2**) and/or the condensate (**3**). 

Since $N^3$-benzyluridine showed hypnotic activity on mice by intracerebroventicular (i.c.v.) administration,[1] the structure–activity relationship (SAR) has been further explored. It was demonstrated that the sugar-modified congeners such as $N^3$-substituted thymidine[2] and arabinofuranosyluracil[3] also show anti-depressant activity. This background prompted us to prepare some 1-substituted $N^3$-benzyluracil. Especially interesting are the imidomethyl analogues since these residues have another amide or imide structure like that of thalidomide.

Mannich reported that an aminomethyl group has been introduced onto active methylene by the reaction of formaldehyde and ammonia, primary amines or secondary amines.[4] Also, amidomethylation of aromatics using *N*-hydroxymethylphtalimide has attracted much attention, and this method was applied to uridine and its nucleotide to give the corresponding 5-aminomethyl derivatives.[5] However, little is known about the amidoalkylation at the nitrogen of a base moiety of nucleosides. In 1991, Khutova et al. reported that the reaction of uracil or *N*-acylcytosine with chloroalkylamides gave the corresponding *N*-amidoalkyl derivative.[6] However, the chloroalkylamide is difficult to handle because of its unstability.[7] In this report, we describe the reaction of a uracil derivative with *N*-hydroxymethylphthalimide in the presence of the Mitsunobu reagent to give two products, a 1-hydrazylmethyl compound (**2**) and/or the condensating product, *N*-(3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimid-1-yl)methylphthalimide (**3**) (Table 1).

**Table 1.** Reaction of uracil derivative with the Mitsunobu reagent[a]

| Run | Substrate | Solvent | Azo-reagent | Phosphine | **1** (% remained) | **2** (%) | **3** (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1** | THF | 2 equiv. TMAD | 2 equiv. TPP | 23.5 | 73.1 | 0.8 |
| 2 | **1** | DMF | 2 equiv. TMAD | 2 equiv. TPP | 0 | 96.1 | 0.3 |
| 3 | **1** | Benzene | 2 equiv. TMAD | 2 equiv. TPP | 20.8 | 71.4 | 2.1 |
| 4 | **1** | 1,4-Dioxane | 2 equiv. TMAD | 2 equiv. TPP | 53.6 | 40.2 | 0 |
| 5 | **1** | THF | 2 equiv. DIAD | 2 equiv. TPP | 2.7 | 18.3 | 49.4 |
| 6 | **1** | DMF | 2 equiv. DIAD | 2 equiv. TPP | 29.8 | 57* (Isolated) | 4.7 |
| 7 | **1** | Benzene | 2 equiv. DIAD | 2 equiv. TPP | 24.9 | 0 | 43.1 |
| 8 | **1** | 1,4-Dioxane | 2 equiv. DIAD | 2 equiv. TPP | 8.5 | 12.6 | 50.4 |
| 9 | **1** | Benzene | 3 equiv. DIAD | 3 equiv. TPP | 14.7 | 0 | 54.4 |
| 10 | **1** | Benzene | 4 equiv. DIAD | 4 equiv. TPP | 5.3 | 0 | 58.8 |
| 11 | Uracil | DMF | 2 equiv. TMAD | 2 equiv. TPP | ND | 85* (Isolated) | ND |
| 12 | Adenine | DMF | 2 equiv. TMAD | 2 equiv. TPP | ND | 74* (Isolated) | ND |

[a] The yield is calculated from the results of HPLC analysis.

*Keywords*: condensation; nucleic acid analogues; nucleosides; Mitsunobu reaction.

* Corresponding author. Tel.: +81-88-622-9611; fax: +81-88-655-3051; e-mail: maruyama@ph.bunri-u.ac.jp

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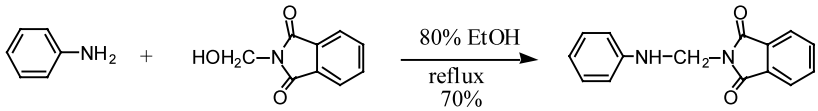



Introduction of methylphthalimide onto the nitrogen of aromatic amines was carried out by Winstead and Heine.[8] We examined this procedure for the preparation of compound **3**. Thus, $N^3$-benzyluracil (**1**) was subjected to the reaction with *N*-hydroxymethylphthalimide in refluxing 80% EtOH. However, no spot of **3** was recognized on thin-layer chromatography (TLC), indicating the basicity of **1** is insufficient for the nucleophilic attack of the reagent. Next, the Mitsunobu reagent[9] was employed to condense **1** with the *N*-hydroxymethyl compound. According to the procedure of the earlier report, **1** was subjected to the reaction of *N*-hydroxymethylphthalimide in the presence of *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide [TMAD,[10] 1,1′-azobis-(*N*,*N*-dimethylformamide)] and triphenylphosphine (TPP) in tetrahydrofuran (THF) (Scheme 1). The reaction was monitored by high-performance liquid chromatography (HPLC),[11] which revealed the formation of **2a** as a main product (run 1). After work-up of the solution, **2a** was obtained as colorless crystals[12] in 69% yield, and a small amount of the starting material was recovered. The proton NMR of **2a** revealed the presence of two dimethylamino groups at 2.76 and 2.72 ppm and a methylene group as two broad singlets separated to 5.32 and 5.08 ppm.[13] The molecular formula of **2a** was estimated as $C_{18}H_{24}N_6O_4$ from mass spectrometory and elementary analysis. Consequently, the new product was determined as the hydrazylmethyl derviative, and this structure was finally confirmed by X-ray crystallographic analysis as shown in Fig. 1. When 1,4-dioxane or benzene was employed as the solvent, the conversion yield by HPLC was similar to that of THF (run 3 and 4). The best result was obtained in *N*,*N*-dimethylformamide (DMF) solution (run 2, isolated in 92% yield). Next, diisopropyl azodicarboxylate (DIAD) was examined as the Mitsunobu reagent (run 5–10). Thus, **1** was treated with DIAD in THF in a similar way as described above. After work-up of the reaction mixture, the products were separated by silica gel chromatography. From the first fraction, the condensate (**3**),[14] which shows the signals of 1,2-disubstituted benzene on the proton NMR spectrum, was obtained. The polar substance from the second fraction was proven as the hydrazylmethyl compound (**2b**).[15] Although the reaction in 1,4-dioxane was similar to that in THF, **3** was the sole product on HPLC in benzene. On the contrary, **2b** was the main product when the reaction was carried out in DMF. When uracil was subjected to a similar reaction, the 1-substituted product (**2c**)[16] was obtained in good yield (run 11). A similar reaction of adenine also gave 9-substituted adenine (**2d**)[17] in 74% yield (run 12). Then, a trial to cleave the N–N bond of **2c** was examined by reduction using Zn powder in acetic acid,[18] however, the isocyanate (**4**)[19] was the sole product.

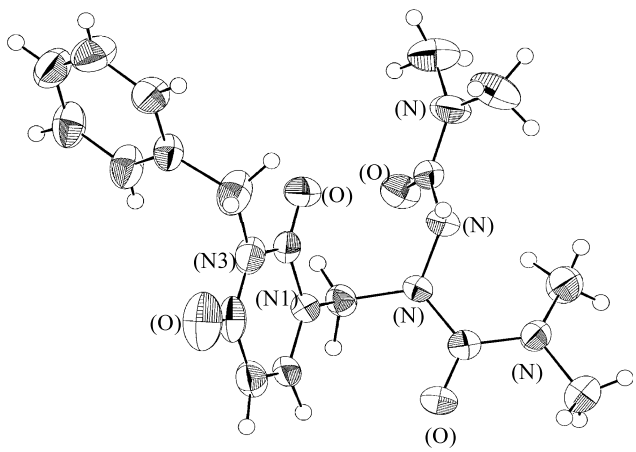
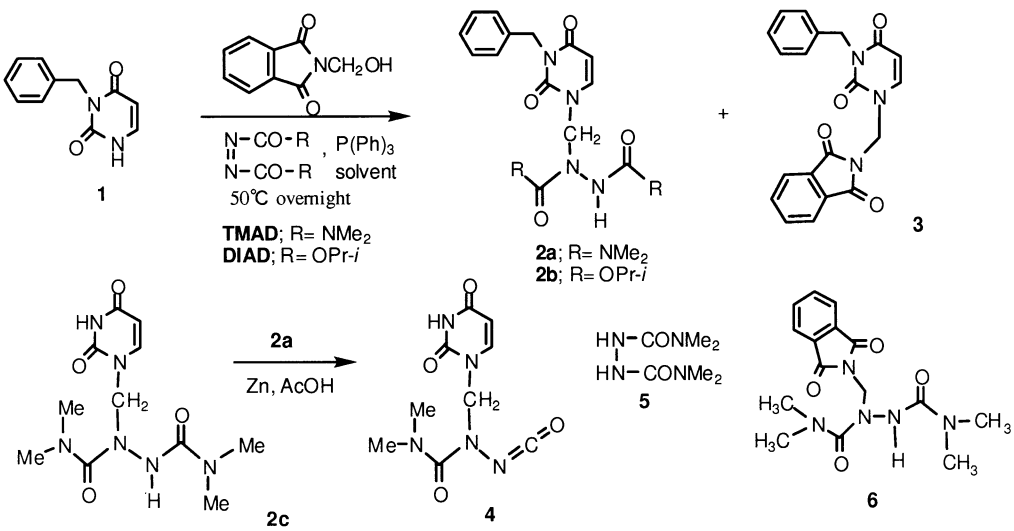
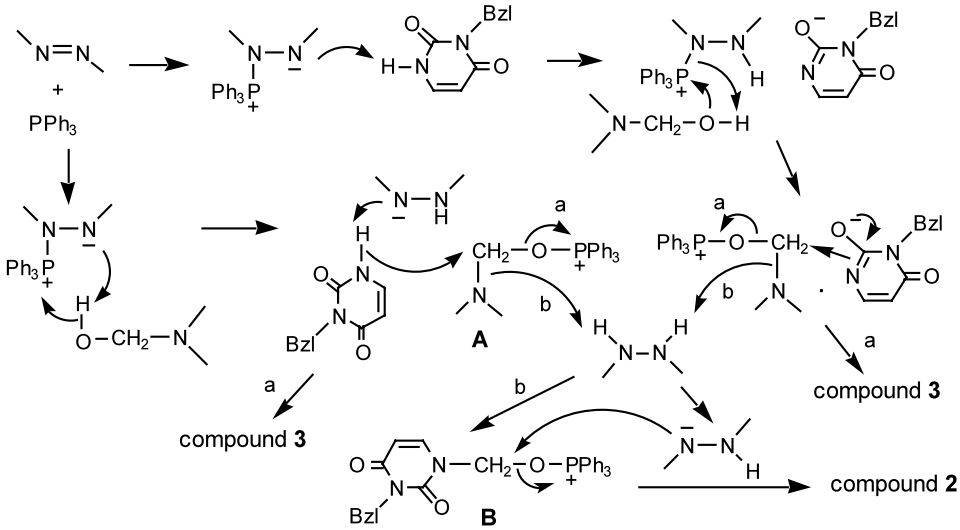



**Figure 1.** ORTEP drawing of compound **2a**.




**Scheme 1.**




The mechanism to form the unusual products (**2a**,**b**) was explored as follows: When **1** was treated with *N*-hydroxymethylphthalimide in the presence of the Mitsunobu reagent, we expected that the condensate (**3**) was formed in any case and the initially formed **3** received the nucleophilic displacement of 1,2-hydrazobis(*N*,*N*-dimethylformamide) (**5**) which was formed during the condensation. Under the assumption described above, **3** was exposed to **5** in the presence or absence of $K_2CO_3$ in DMF. However, no spot corresponding to **2a** was observed on TLC. A further trial to react **3** with TMAD or reduced reagent, **5**, in the presence of TPP in DMF also gave no peak of **2a** on HPLC. To explore another route, the *N*-(hydrazylmethyl)phthalimide (**6**),[20] which is supposed to be a candidate intermediate for **2a**, was treated with **1** in the presence of TPP in DMF. Again, **2a** was not detected in the resulting solution.

It was concluded that the hydrazylmethyl derivatives (**2a**,**b**) were prepared from an intermediate other than **3**. Therefore, the following mechanism could be postulated. It is widely believed that alkoxyphosphonium salt (**A**) is formed during the Mitsunobu reaction. Then **A** receives the nucleophilic displacement of the anion species of uracil to give **3** leaving triphenylphosphine oxide (pathway a). Since phthalimide is also active as a leaving group, however, the (3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimid-1-yl)-methylphosphonium salt (**B**) is formed (pathway b). Then, **B** reacts with the hydrazyl anion to give **2**. The non-proton polar solvent, DMF, should stabilize the intermediary cation, **B**, and promote the nucleophilic displacement of pathway b. An alternative explanation is the removal of the uracil proton by the initially formed betaine and subsequent reaction with *N*-hydroxymethylphthalimide to give an intermediary ion pair. Nucleophilic displacement inside this ion pair should proceed similarly as described in **A** to give compounds **2** or **3** according to the pathway.

We are looking forward to exploring further reactions of the synthesis of the hydrazylmethyl derivatives of amides.

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11. High-performance liquid chromatography: Apparatus of high-performance liquid chromatography (HPLC) were CCPD pump (Toso Co.) and SPD-M10A photo diode array UV–vis detector (Shimadzu Co.). The HPLC conditions were as follows: the columns, connection with Cosmosil Guard Column 5C18-MS (4.6×10 mm, Nacalai Tesque INC.) and Cosmosil Packed Column 5C18-MS (4.6×150 mm, Nacalai Tesque INC.); detector λ, 260 nm; eluent, 45% MeOH; flow rate, 1 ml/min; column temper-

ature, 50°C. The measurement was carried out by the absolute calibration method.

12. Colorless crystals (hexane–AcOEt) (69%): mp 185–185.5°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.70 (1H, s, N-N-H), 7.88 (1H, d, $J$=8.0 Hz, H6), 7.22–7.29 (5H, m, Ph), 5.74 (1H, d, $J$=8.0 Hz, H5), 5.32 (1H, br s, one of -N-C$H_2$-N-), 5.08 (1H, br s, one of -N-C$H_2$-N-), 4.94 (2H, s, N$^3$-C$H_2$), 2.76 (6H, s, $CH_3$×2), 2.72 (6H, s, $CH_3$×2); UV $\lambda_{max}$ (MeOH) nm: 264; MS $m/z$: 388 [M$^+$]. Anal. calcd for $C_{18}H_{24}N_6O_4$: C, 55.66; H, 6.22; N, 21.64. Found: C, 55.68; H, 6.42; N, 21.31.
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14. White crystals (hexane–AcOEt) (run 5, 43%): mp 196.5–197°C; $^1$H NMR ($CDCl_3$) $\delta$ 7.90 (2H, dd, $J$=3.3, 5.5 Hz, phthalimide), 7.77 (2H, dd, $J$=3.0, 5.5 Hz, phthalimide), 7.64 (1H, d, $J$=8.0 Hz, H6), 7.25–7.50 (5H, m, Ph), 5.78 (1H, d, $J$=8.0 Hz, H5), 5.61 (2H, s, $CH_2$), 5.08 (2H, s, $CH_2$); UV $\lambda_{max}$ (MeOH) nm: 293, 259 (log $\varepsilon$=4.04); MS $m/z$: 361 [M$^+$]. Anal. calcd for $C_{20}H_{15}N_3O_4$: C, 66.48; H, 4.18; N, 11.63. Found: C, 66.37; H, 4.26; N, 11.62.
15. Syrup (run 6, 57%): $^1$H NMR ($CDCl_3$) $\delta$ 7.22–7.54 (6H, m, Ph, H6), 6.83 (1H, br s, N-N-H), 5.76 (1H, d, $J$=8.0 Hz, H5), 5.32 (2H, br s, $CH_2$), 5.10 (2H, s, $CH_2$), 4.86–4.99 (2H, m, CH×2), 1.24–1.29 (12H, m, $CH_3$×4); UV $\lambda_{max}$ (MeOH) nm: 262 (log $\varepsilon$=3.91); MS $m/z$: 418 [M$^+$]; HR-MS $m/z$: 418.1869 (M$^+$, $C_{20}H_{26}N_4O_6$ requires 418.1886).
16. Colorless crystals (85%): mp 218–220°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.13 (1H, br s, N$^3$-H), 8.69 (1H, br s, N-N-H), 7.75 (1H, d, $J$=7.9 Hz, H6), 5.54 (1H, d, $J$=7.9 Hz, H5), 5.24 (1H, br s, one of $CH_2$), 5.02 (1H, br s, one of $CH_2$), 2.77 (12H, br s, $CH_3$×4); UV $\lambda_{max}$ (MeOH) nm: 261; MS $m/z$: 298 [M$^+$]. Anal. calcd for $C_{11}H_{18}N_6O_4$: C, 44.29; H, 6.07; N, 28.18. Found: C, 44.28; H, 6.13; N, 27.99.
17. Mp 205–206°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.69 (1H, s, N-N-H), 8.17 (1H, s, H8), 8.11 (1H, s, H2), 7.18 (2H, br s, $NH_2$), 5.76 (1H, br s, one of $CH_2$), 5.31 (1H, br s, one of $CH_2$), 2.76 (6H, s, $CH_3$×2), 2.71 (6H, s, $CH_3$×2); UV $\lambda_{max}$ (MeOH) nm: 261; MS $m/z$: 321 [M$^+$].
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19. Colorless crystals (46%): mp 246.5–247°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 11.38 (1H, br s, N$^3$-H), 7.63 (1H, d, $J$=8.1 Hz, H6), 5.63 (1H, d, $J$=7.7 Hz, H5), 5.43 (2H, s, $CH_2$), 2.83 (6H, s, $CH_3$×2); UV $\lambda_{max}$ (MeOH) nm: 257; MS $m/z$: 253 [M$^+$]. Anal. calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.37; N, 27.66. Found: C, 42.54; H, 4.43; N, 27.26.
20. Colorless crystals (81%): mp 201–201.5°C; $^1$H NMR ($CDCl_3$) $\delta$ 7.85–7.88 (2H, m, phthalimide), 7.73–7.77 (2H, m, phthalimide), 7.24 (1H, br s, N-N-H), 5.27 (2H, br s, $CH_2$), 2.97 (12H, s, $CH_3$×4); UV $\lambda_{max}$ (MeOH) nm: 293; MS $m/z$: 333 [M$^+$]. Anal. calcd for $C_{15}H_{19}N_5O_4$: C, 54.05; H, 5.74; N, 21.01. Found: C, 54.08; H, 5.91; N, 21.02.