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The Benzoylation of 6-Methyluracil and 5-Nitro-6-methyluracil

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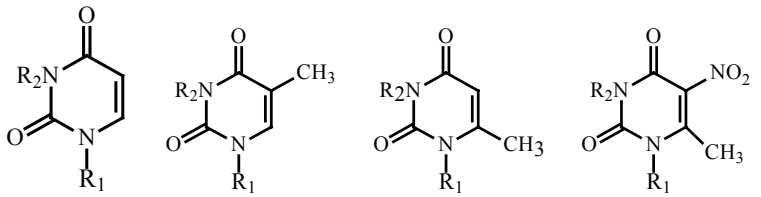
Abstract: 6-Methyluracil and 5-nitro-6-methyluracil react with variable molar quantities of benzoyl chloride in acetonitrile–pyridine at room temperature to give 1-N, 3-N-dibenzoyl-6-methyluracil **3b** and 1-N-benzoyl-5-nitro-6-methyluracil **4b**. The reactive rates of debenzoylation of **3b** and **4b** were investigated.

Keywords: 1-N, 3-N-Dibenzoyl-6-methyluracil, 1-N-benzoyl-5-nitro-6-methyluracil, 6-methyl-uracil, 5-nitro-6-methyluracil, benzoylation.

Site-specific protection reaction of the N_1 or N_3 position of the uracil ring is very important for preparation of the desired N-substituted derivatives. While it seems clear from the literature that both uracil **1a** and thymine **2a** react with benzoyl chloride to give their 1-N-benzoyl **1b**, **2b** and 1-N, 3-N-dibenzoyl derivatives[1,2] **1c**, **2c**, the benzoylation of 6-methyluracil and 5-nitro-6-methyluracil has not been investigated. It has been reported[1] when uracil or thymine heated with excess of benzoyl chloride in dioxane-pyridine, the corresponding 1-N, 3-N-dibenzoyl derivative is obtained, while 1-N, 3-N-dibenzoyluracil **1c** decomposes during chromotography on alumina to give 3-N-benzoyluracil in good yield. However Chambers[1] has shown that uracil reacted with benzoyl chloride in pyridine to give a mixture of 1-N and 3-N-benzoyluracil but the evident presented was not conclusive.



1 **2** **3** **4**

a	R_1=R_2 =H	**a**	R_1=R_2 =H	**a**	R_1=R_2 =H	**a**	R_1=R_2 =H
b	R_1=B_Z R_2 =H	**b**	R_1=B_Z R_2 =H			**b**	R_1=B_Z R_2 =H
c	R_1=R_2 = B_Z	**c**	R_1=R_2 = B_Z	**b**	R_1=R_2 = B_Z	**c**	R_1=R_2 = B_Z

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We now reported that when 6-methyluracil **3a** and 5-nitro-6-methyluracil **4a** reacted with benzoyl chloride in acetonitrile-pyridine, the results obtained are not similar to uracil and thymine system. When 6-methyluracil **3a** was reacted with a slight excess of benzoyl chloride (1.1 mol equiv) in acetonitrile-pyridine (5:2/v:v) at room temperature for 3 h, 1-N, 3-N-dibenzoyl-6-methyluracil **3b** was obtained as crystalline solid, m.p. 78~80℃, isolated yield in 7%[3], much more starting material **3a** was recovered in 90%. The TLC monitor shows that it did not prove possible to produce intermediate 1-N and 3-N-benzoyl derivatives. Attempts to increase the yield of **3b** by this method were failed (yield less 10%), even prolonged the reaction time to 20 h. The structure of **3b** is confirmed by the ^{1}H and ^{13}C NMR spectra[3]. Under the similar conditions, 5-nitro-6-methyluracil **4a** reacted with benzoyl chloride to give 1-N-benzoyl-5-nitro-6-methylluracil **4b** in 85% isolated yield. No 3-N-benzoyl and 1-N, 3-N-dibenzoyl derivatives were isolated. The compound **4b** was also characterized by ^{1}H and ^{13}C NMR[3].

When 6-methyluracil **3a** and 5-nitro-6-methyluracil **4a** were each reacted with an excess (2.5 mol equiv) of benzoyl chloride in acetonitrile-pyridine (5:2/v:v) at room temperature for 20 h, they were converted into 1-N, 3-N-dibenzoyl-6-methyluracil **3b** and 1-N-benzoyl-5-nitro-6-methyluracil **4b**, compound **3b, 4b** were isolated as pure crystalline solids in 90% and 85% yields, respectively. In heating conditions 5-nitro-6-methyluracil **4a** was treated with larger excess (3.3 mol equiv) of benzoyl chloride to give 1-N-benzoyl-5-nitro-6-methyluracil **4b** as a crystalline solid in 80% isolated yield. In attempt to use more benzoyl chloride (3.3 mol) to generate 1-N, 3-N-dibenzoyl-5-nitro-6-methyluracil **4c**, compound **4c** could not be isolated. In this condition compound **4b** was obtained in 90% yield.

The 1-N-benzoyl-5-nitro-6-methyluracil **4b** was characterized by converting it into the corresponding 3-N-methyl derivative. The chemical shift of 6-CH_3 can be used to distinguish the 1-N-benzoyl derivative of **4** from its 3-N-substituted derivative. The 6-CH_3 resonance signal of 1-N-benzoyl-5-nitro-6-methyluracil significantly shifted downfield (by>3 ppm) when 1-N-benzoyl was introduced.

In order to investigate suitability of benzoyl group for protection of 6-methyluracil and 5-nitro-6-methyluracil residuals, we attempted to measure the relative rates of debenzoylation of the monobenzoyl **4b** and dibenzoyl **3b** derivatives.

The debenzoylation agent was 1.5 mol/L ammonia in water-methanol. The results showed that the time for half and complete debenzoylation of **3b** is 2, 20 min, respctively. The debenzoylation of **4b** needed less than 1 min[4]. Indeed, debenzoylation of the 1-N-

Table 1 ^{1}H and ^{13}C NMR spectroscopic data

Entry No.	Compound	δ_H NH	δ_C 6-CH_3
1	6-methyluracil **3a**	10.80, 10.86	18.18
2	1-N,3-N-dibenzoyl-6-methyluracil **3b**	–	23.58
3	5-nitro-6-methyluracil **4a**	11.80, 11.84	16.63
4	1-N-benzoyl-5-nitro-6-methyluracil **4b**	–	19.46

benzoyl derivative was too fast to measure accurately. It may be concluded that benzoyl group is likely to be useful for the 1-N, 3N-diprotection of the 6-methyluracil and related pyrimidine, but they are limited to use for the 1-N-protection of these systems.

On the basis of the experimental results, we have observed that 1-N-benzoyl derivative of 5-nitro-6-methyluracil and 1-N, 3-N-dibenzoyl derivative of 6-methyluracil can be prepared in good yields, but the preparations of 3-N-benzoyl or 1-N, 3-N-dibenzoyl-5-nitro-6-methyluracil and 1-N, or 3-N-benzoyl derivative of 6-methyluracil in pyridine–acetonitrile were unsuccessful. Increase or decease of the quantities of benzoyl chloride did not result in formation of 1-N, 3-N-dibenzoyl-5-Nitro-6-methyluracil **4c** and 1-N-benzoyl-6-methyluracil.

Acknowledgment

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References and Notes

1. R.W. Chambers, *Biochemistry*, **1965**, *4*, 219.
2. A. Novacek, D. Hesoun, J. Gut, *Collection Czechoslov. Chem. Common.*, **1965**, *30*, 1890.
3. Spectra data for **3b**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.67 (S, 3H), 7.25 (S, 1H), 7.43-7.68 (m, 6H), 8.20-8.23 (m, 4H); ^{13}C NMR (300 MHz, DMSO-d_6, δ ppm): 23.6, 111.5, 127.4, 127.5, 128.5, 129.2, 129.3, 129.9, 130.1, 130.3, 132.8, 134.8, 134.9, 159.9, 162.9, 163.6, 166.7, 174.2; MS (FAB) *m/z* 334; (KBr, cm^{-1}) υ: 3101, 1750, 1599, 1450, 1356. Compound **4b**: ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.29 (s, 3H), 8.22-8.25(t, 2H, J=7.5 Hz), 8.78-8.82 (m, 1H), 9.85-9.87 (m, 2H); ^{13}C NMR (500 MHz, DMSO-d_6, δ ppm): 19.46, 127.51, 138.79, 140.55, 149.01, 153.30, 155.81, 162.94; MS (FAB) *m/z* 276 (M+1); (KBr, cm^{-1}) υ: 3133, 3035, 1613, 1511, 1991, 1277, 1146.
4. The experiments were carried out by adding methanol-water solution of 1.5 mol/L ammonia to the methanol solution of the substrate. The reaction mixture was stirred at 20℃, and the reaction process was monitored by TLC.

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