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Free Radical Reaction of 1,3-Dimethyluracils and Caffeine with Benzoyl Peroxide in γ-Butyrolactone

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Synopsis. Treatment of 1,3-dimethyluracil, 1,3-dimethylthymine, and caffeine with benzoyl peroxide in γ-butyrolactone at 80 °C resulted in a free radical alkylation.

Recently we reported that the treatment of 1,3-dimethyluracils (**1**) and caffeine (**2a**) with benzoyl peroxide in cyclohexane, acetonitrile, and alkyl acetates led to a free radical alkylation of **1** and **2a** with alkyl radicals formed by abstraction of hydrogen atom from the solvents.[1] The previous work has also shown that alkyl acetates were favorable solvents for the free radical alkylation of **1** and **2a**, compared with the corresponding ethers and ketones, although the abstraction of hydrogen atom from ethers by the radicals derived from benzoyl peroxide is well-known.[2] Furthermore, several types of natural products[3] containing γ-butyrolactone ring such as canescin[4] and conocarpin[5] are known. These observations led us to examine a reaction of 1,3-dimethyluracil (**1a**), 1,3-dimethylthymine (**1b**), and **2a** with benzoyl peroxide in γ-butyrolactone, compared with that in tetrahydrofuran and cyclopentanone.

A solution of **1a** in γ-butyrolactone in the presence of benzoyl peroxide was heated at 80 °C under argon atmosphere. The reaction mixture was submitted to chromatography on silica gel. By elution of a mixture of hexane and ethyl acetate, two main products **1c** and **1d** were isolated together with a small amount of **1e**. Under similar conditions, the reaction of **1b** gave **1f** and **1g** and that of **2a** gave **2c** and **2d**. The results are summarized in Table 1. In order to compare with the reaction in γ-butyrolactone, treatment of **1a** and **2a** with benzoyl peroxide in tetrahydrofuran and cyclopentanone was further investigated. The reaction of **1a** and **2a** in tetrahydrofuran gave **1h** and **2h**, respectively, but almost no alkylation occurred in the case of the treatment of **1a** and **2a** in cyclopentanone (Chart 1). The results suggest that not only alkyl acetates[1] but also γ-butyrolactone may be favorable solvents on free radical alkylation with benzoyl peroxide.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and uncorrected. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained with a JEOL GSX400 spectrometer using tetramethylsilane as an internal standard in $CDCl_3$. Mass spectra were obtained with a JEOL JMS-D300 spectrometer. The elemental analyses were performed by the Analytical Center of Kyoto University.

General Procedure for the Reaction of 1,3-Dimethyluracil (1a), 1,3-Dimethylthymine (1b), and Caffeine (2a) with Benzoyl Peroxide. A solution of **1a**, **1b**, and **2a** (1.5 mmol) and benzoyl peroxide (3 mmol) in γ-butyrolactone (50 ml) or tetrahydrofuran (200 ml) was heated at 80 °C or at reflux temperature (in tetrahydrofuran) under argon atmosphere. The reaction mixture was evaporated under reduced pressure to give a residue, which was then chromatographed on silica gel (Fuji gel packed column NQ-2, 24 mmϕ×360 mm), eluted with a mixture of hexane and ethyl acetate, with low-pressure pump (Chemco Low-prep pump 81-M-2R) and UV-monitor (Shimadzu UV-detector SPC-6A, detected at 250 nm), to give the products and recovered substrate. The results are shown in Table 1. The spectral data of the products are given below.

5-(2-Oxotetrahydro-3-furyl)-1,3-dimethyluracil (1c): Mp 157—159 °C; ^{1}H NMR δ=7.26 (s, 1H, 6-H), 4.51 (ddd, 1H, J=8.8, 8.8, 2.5 Hz, 5′-H), 4.32 (ddd, 1H, J=8.8, 8.8, 6.8 Hz, 5′-H), 3.59 (t, 1H, J=10.0, 3′-H), 3.41 (s, 3H, Me), 3.35 (s, 3H, Me), 2.64 (m, 1H, 4′-H), 2.34 (m, 1H, 4′-H); ^{13}C (^{13}C–^{1}H COSY) NMR δ=176.84, 162.55, 151.43, 141.93 (δ 7.26), 109.29, 66.95 (δ 4.59 and 4.32), 39.60 (δ 3.59), 37.08 (δ 3.41), 28.77 (δ 2.64 and 2.34), 27.94 (δ 3.35); MS m/z (rel intensity, %) 225 (M^{+}+1, 13), 224 (M^{+}, 75), 180 (85), 179 (21), 166 (29), 165 (61), 94 (100). Calcd for $C_{10}H_{12}N_2O_4$:

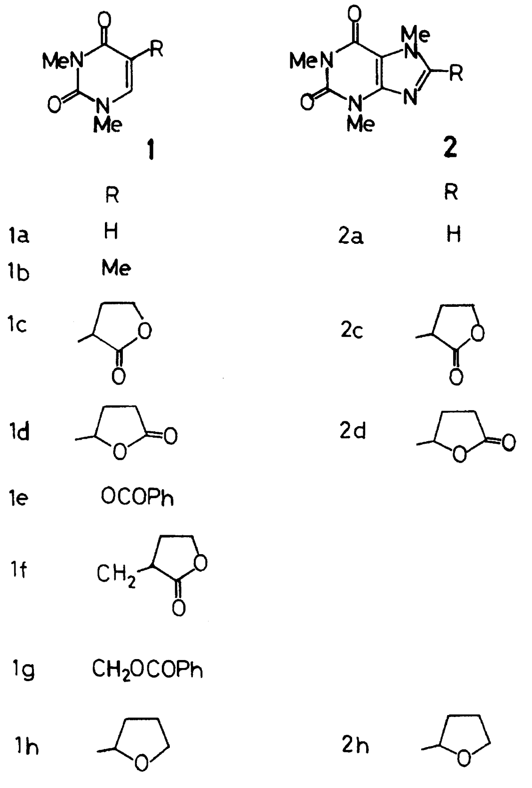

Chart 1.

Table 1. Free Radical Reaction of 1,3-Dimethyluracils and Caffeine with Benzoyl Peroxide[a)]

Substrate	Solvent (ml)	Conv. %	Product /Isolated yield %[b)]
1a	γ-Butyrolactone (50)	40	**1c**/56; **1d**/20; **1e**/2
1b	γ-Butyrolactone (50)	38	**1f**/12; **1g**/5
2a	γ-Butyrolactone (50)	52	**2c**/52; **2d**/24
1a	Tetrahydrofuran (200)	15	**1h**/88
2a	Tetrahydrofuran (200)	40	**2h**/85

a) Reaction conditions: substrate (1.5 mmol), benzoyl peroxide (3 mmol), 7h reaction at 80 °C in γ-butyrolactone and 15 h reaction at reflux temperature in tetrahydrofuran. b) Yield based on substrate consumed.

C, 53.57; H, 5.39; N, 12.50%. Found: C, 53.80; H, 5.37; N, 12.59%.

5-(5-Oxotetrahydro-2-furyl)-1,3-dimethyluracil (1d): Mp 110—111 °C; ^{1}H NMR δ=7.26 (s, 1H, 6-H), 5.38 (t, 1H, J=7.5 Hz, 2′-H), 3.42 (s, 3H, Me), 3.35 (s, 3H, Me), 2.75 (m, 1H, 3′-H), 2.55—2.68 (m, 2H, 4′-H), 2.11 (ddt, 1H, J=7.5, 12.4, 8.8 Hz, 3′-H); ^{13}C (^{13}C–^{1}H COSY) NMR δ=176.59, 161.75, 151.40, 139.27 (δ 7.26), 111.77, 75.96 (δ 5.38), 37.23 (δ 3.42), 28.48 (δ 2.75 and 2.11), 28.27 (δ 2.55—2.68), 27.82 (δ 3.35); MS m/z (rel intensity, %) 225 (M$^+$+1, 6), 224 (M$^+$, 39), 196 (97), 169 (97), 169 (100), 167 (56), 140 (72). Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50%. Found: C, 53.36; H, 5.28; N, 12.24%.

5-Benzoyloxy-1,3-dimethyluracil (1e): Mp 150.5—152 °C; ^{1}H NMR δ=8.15 (dd, 2H, J=8.2, 1.0 Hz, Ph), 7.45—7.80 (m, 3H, Ph), 7.34 (s, 1H, 6-H), 3.44 (s, 3H, Me), 3.40 (s, 3H, Me); ^{13}C NMR δ=164.53, 158.72, 150.84, 134.72, 134.07, 130.42, 128.64, 128.19, 126.57, 37.15, 28.41; MS m/z (rel intensity, %) 260 (M$^+$, 3), 105 (100), 77 (38). Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77%. Found: C, 59.94; H, 4.69; N, 11.06%.

5-[(2-Oxotetrahydro-3-furyl)methyl]-1,3-dimethyluracil (1f): Mp 77—78 °C; ^{1}H NMR δ=7.21 (s, 1H, 6-H), 4.32 (ddd, 1H, J=8.8, 8.8, 2.2 Hz, 5′-H), 4.17 (ddd, 1H, J=8.8, 8.8, 5.8 Hz, 5′-H), 3.40 (s, 3H, Me), 3.36 (s, 3H, Me), 2.92 (ddt, 1H, J=6.2, 5.9, 8.8 Hz, 3′-H), 2.80 (dd, 1H, J=14.0, 6.2 Hz, 5-CH$_2$), 2.61 (dd, 1H, J=14.0, 5.9 Hz, 5-CH$_2$), 2.38 (m, 1H, 4′-H), 2.02 (m, 1H, 4′-H); ^{13}C (^{13}C–^{1}H COSY) NMR δ=178.86, 163.84, 151.68, 141.89 (δ 7.21), 109.48, 66.53 (δ 4.32 and 4.17), 38.85 (δ 2.92), 36.99 (δ 3.40), 28.38 (δ 2.02 and 2.38), 28.04 (δ 3.36), 27.39 (δ 2.61 and 2.81); MS m/z (rel intensity, %) 239 (M$^+$+1, 5), 238 (M$^+$, 31), 192 (20), 165 (11), 154 (30), 153 (100), 140 (12). Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76%. Found: C, 55.26; H, 5.87; N, 11.68%.

8-(2-Oxotetrahydro-3-furyl)caffeine (2c): Mp 211—213 °C; ^{1}H NMR δ=4.69 (ddd, 1H, J=8.8, 8.8, 2.2 Hz, 5′-H), 4.47 (ddd, 1H, J=8.8, 8.8, 7.6 Hz, 5′-H), 4.09 (s, 3H, Me), 3.99 (t, 1H, J=8.8 Hz, 3′-H), 3.54 (s, 3H, Me), 3.40 (s, 3H, Me), 3.12 (m, 1H, 4′-H), 2.67 (m, 1H, 4′-H); ^{13}C (^{13}C–^{1}H COSY) NMR δ=173.26, 155.29, 151.62, 147.63, 147.58, 108.52, 67.85 (δ 4.69 and 4.47), 38.37 (δ 3.99), 32.18 (δ 4.09), 29.72 (δ 3.54), 27.94 (δ 3.40), 27.23 (δ 3.12 and 2.67); MS m/z (rel intensity, %) 279 (M$^+$+1, 18), 278 (M$^+$, 100), 219 (48), 149 (68). Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14%. Found: C, 51.55; H, 4.89; N, 20.06%.

8-(5-Oxotetrahydro-2-furyl)caffeine (2d): Mp 190—192 °C; ^{1}H NMR δ=5.61 (dd, 1H, J=6.0 and 7.0 Hz, 2′-H), 4.07 (s, 3H, Me), 3.55 (s, 3H, Me), 3.40 (s, 3H, Me), 3.10 (m, 1H, 3′-H), 2.85 (m, 1H, 4′-H), 2.58—2.70 (m, 2H, 3′-H and 4′-H); ^{13}C (^{13}C–^{1}H COSY) NMR δ=175.83, 155.48, 151.57, 148.24, 147.19, 108.98, 71.78 (δ 5.61), 32.26 (δ 4.07), 29.75 (δ 3.55), 28.00 (δ 3.40), 27.90 (δ 2.85 and 2.58—2.70), 25.13 (δ 3.10 and 2.58—2.70); MS m/z (rel intensity, %) 279 (M$^+$+1, 16), 278 (M$^+$, 100), 234 (16), 223 (22), 219 (27). Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14%. Found: C, 51.79; H, 5.06; N, 20.02%.

5-(Tetrahydro-2-furyl)-1,3-dimethyluracil (1h): Mp 92—93 °C (lit,[6)] 94—95 °C); ^{1}H NMR δ=7.24 (s, 1H), 4.79 (t, 1H, J=7 Hz), 3.97—4.03 (m, 1H), 3.86 (q, 1H, J=7 Hz), 3.41 (s, 3H), 3.34 (s, 3H), 2.37—2.46 (m, 1H), 1.90—2.00 (m, 1H), 1.63—1.72 (m, 1H); ^{13}C NMR δ=162.50, 151.78, 138.25, 115.29, 74.71, 68.44, 37.01, 32.36, 27.72, 25.69.

8-(Tetrahydro-2-furyl)caffeine (2h): Mp 127—128 °C (lit,[7)] 127—128 °C); ^{1}H NMR δ=5.03 (t, 1H, J=7 Hz), 4.04 (s, 3H), 3.91—3.97 (m, 2H), 3.56 (s, 3H), 3.39 (s, 3H), 2.53—2.63 (m, 1H), 2.23—2.33 (m, 1H), 2.12—2.22 (m, 1H), 2.00—2.10 (m, 1H); ^{13}C NMR δ=155.51, 152.40, 151.73, 147.37, 108.37, 72.66, 68.92, 32.26, 29.72, 29.60, 27.88, 25.97.

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