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Regioselective Free Radical Alkylation of Uracils with Diacyl Peroxides

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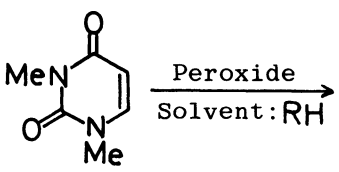
Heating of a solution of uracils containing diacyl peroxides such as benzoyl peroxide, lauroyl peroxide, and 2,4-dichlorobenzoyl peroxide in 1,4-dioxane at 80 °C under nitrogen atmosphere yielded 5-(2,5-dioxanyl)uracils. Similar treatments of uracils in cyclohexane, cyclooctane, ethyl acetate, 1,2-diacetoxyethane, tert-butyl acetate, and acetonitrile gave the corresponding 5-alkyluracils.

5-Substituted uracils and their deoxyribonucleosides are known to have important biological activity such as antiviral drugs.[1] Therefore, synthesis of 5-substituted uracil derivatives has been extensively investigated. The use of organometalic intermediates in the synthesis from 5-iodo- or 5-chloromercuriuracil derivatives is well known.[2] Furthermore, the synthesis by photochemistry of 5-iodouracils[3] and 5-fluorouracils[4] has been reported. However, little attention has been paid to the synthesis from 5-unsubstituted uracils except for the oxidative coupling between uracils and olefins by palladium acetate.[5] In this paper we describe free radical alkylation of uracils such as 1,3-dimethyluracil (1a) and uracil (2a) with diacyl peroxides. The reaction provides an easy and efficient method for 5-alkyluracils.

While photo-irradiation to pyrimidine bases such as 1a in 1,4-dioxane[6] are known to yield the corresponding pyrimidine dimers, heating of a solution of 1a containing diacyl peroxides such as benzoyl peroxide,[7] lauroyl peroxide, and 2,4-dichlorobenzoyl peroxide in 1,4-dioxane at 80 °C under nitrogen atmosphere gave 1,3-dimethyl-5-(2,5-dioxanyl)uracil (1d) as almost the only product. Similar treatments of 1a in cyclohexane and in cyclooctane gave 5-cyclohexyl- and 5-cyclooctyl-1,3-dimethyluracils (1b) and (1c), respectively. Furthermore, the reaction of 1a in ethyl acetate gave a mixture of (1e) and (1f) and in 1,2-diacetoxyethane gave (1g) and (1h) while the reaction in tert-butyl acetate and in acetonitrile gave (1i) and (1j), respectively. The separation of the reaction mixture from 1a was performed by liquid chromatography with a low pressure pump.[8] The results of the free radical alkylation of 1a are summarized in Table 1.[9]

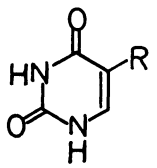
Table 1 shows that good yields of alkylated products are obtained when benzoyl peroxide is used on 1a, while almost no reaction occurred in 1a when treated with tert-butyl peroxide instead of diacyl peroxides. Furthermore, the products 1d and 1j were obtained from the reaction of 1a in a mixture of dioxane and water and in acetonitrile and water, respectively, although in lesser amounts.



1a 1b-1j

R

1b: cyclohexyl
1c: cyclooctyl
1d: dioxanyl
1e: $CH(CH_3)OCOCH_3$
1f: $CH_2COOCH_2CH_3$
1g: $CH(OCOCH_3)CH_2OCOCH_3$
1h: $CH_2COOCH_2CH_2OCOCH_3$
1i: $CH_2COOC(CH_3)_3$
1j: CH_2CN



R

2a: H
2d: dioxanyl
2j: CH_2CN

Table 1. Alkylation of 1,3-Dimethyluracil with Peroxides[a)]

Peroxide (mmol)	Solvent (ml)	Reaction time/ h	Conversion %	Products (Yield/ %[b)])
Benzoyl (1)	Cyclohexane (125)	14	52	1b(96)
Lauroyl (2)	Cyclohexane (125)	14	55	1b(99)
2,4-Dichlorobenzoyl (1)	Cyclohexane (125)	14	27	1b(93)
Benzoyl (1)	Cyclooctane (125)	14	24	1c(88)
Benzoyl (1)	Dioxane (50)	4	19	1d(99)
Benzoyl (1)	Dioxane (35), Water (15)	4	9	1d(99)
Benzoyl (2)	Dioxane (50)	7	24	1d(99)
Lauroyl (1)	Dioxane (50)	7	19	1d(90)
tert-Butyl (2)	Dioxane (50)	7	1	1d(99)
Benzoyl (2)	Ethyl acetate (50)	7	62	1e(55) 1f(36)
Lauroyl (1)	Ethyl acetate (50)	7	40	1e(58) 1f(38)
Benzoyl (1)	Diacetoxyethane (50)	7	58	1g(48) 1h(40)
Benzoyl (2)	Diacetoxyethane (50)	7	70	1g(49) 1h(37)
Benzoyl (1)	tert-Butyl acetate(50)	7	24	1i(75)
Benzoyl (1)	Acetonitrile (50)	4	14	1j(93)
Benzoyl (1)	Acetonitrile(40),Water(10)	4	7	1j(99)
Benzoyl (2)	Acetonitrile (50)	7	21	1j(91)
Lauroyl (2)	Acetonitrile (50)	7	4	1j(99)
2,4-Dichlorobenzoyl (1)	Acetonitrile (50)	7	13	1j(62)

a) Reaction conditions: 1a (1 mmol), at 80 °C or reflux temperature when the boiling point of solvent is below 80 °C, under nitrogen atmosphere. b) Yield based on 1a consumed.

The alkylation of 1a with benzoyl peroxide may be explained in terms of formation of alkyl radicals derived by abstraction of hydrogen atom from the solvents by benzoyloxy radical and/or phenyl radical which is formed by decarboxylation of benzoyloxy radical. Therefore, it is of interest not only synthetically but mechanistically that the present free radical alkylation of 1a occurred regioselectively and no 6-alkyl substituted uracils were obtained, because reaction of pyrimidine bases such as thymine and uracil with free radicals

is not, to our knowledge, sufficiently clear. While photo-reaction of uracils in iso-propyl alcohol[10] and in tetrahydrofuran[11] gives 6-substituted 5,6-dihydrouracils together with other products, it is known that hydroxy radical preferentially adds to the 5-position of pyrimidine bases.[12] Our results suggest that the alkyl radicals may attack the 5-position of 1a.

The reaction was further applicable to alkylation of 2a. Treatment of 2a (3 mmol) with benzoyl peroxide (6 mmol) in dioxane (200 ml) at 80 °C under nitrogen atmosphere for 7 h gave 5-(2,5-dioxanyl)uracil (2d) (0.42 mmol) and recovered 2a (2.04 mmol). Similarly, the reaction of 2a (3 mmol) with benzoyl peroxide (6 mmol) in a mixture of acetonitrile (150 ml) and water (50 ml) at reflux temperature under nitrogen for 7 h gave 5-cyanomethyluracil (2j)[13] (0.3 mmol) and recovered 2a (2.16 mmol). The isolation of 2d and 2j was performed by droplet countercurrent chromatography.[14]

References

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7) Benzoyl peroxide was obtained from Wako pure chemical and Nakalai tesque (with 25% water) and was used without further purification for the reaction.
8) Separation conditions. Fuji-gel packed column NQ-2 (silica gel 24 mmφx360 mm). Mobile phase: a mixture of ethyl acetate (50%) and hexane (50%) to ethyl acetate (100%). Detected at 250 nm.
9) Spectral data of the products are as follows. 1b: mp 104.5-105.5 °C; ^{1}H-NMR ($CDCl_3$) δ 6.87 (s, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.6 (m, 1H), 1.7-1.9 (m, 5H), 1.3-1.4 (m, 2H), 1.1-1.3 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 163.39, 151.62, 137.75, 119.19, 36.85, 35.60, 32.47, 27.92, 26.61, 26.20; mass: m/z (relative intensity) 223 (M^++1, 15), 222 (M^+, 100). 1c: oil; ^{1}H-NMR ($CDCl_3$) δ 6.92 (s, 1H), 3.40 (s, 3H), 3.35 (s, 3H), 2.85 (m, 1H), 1.5-1.8 (m, 14 H); ^{13}C-NMR ($CDCl_3$) δ 163.38, 151.62, 137.84, 120.78, 36.87, 35.39, 31.88, 27.94, 26.81, 26.23, 25.64; mass: m/z 251 (M^++1, 23), 250 (M^+, 78), 153 (100). 1d: mp 129-130 °C; ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 1H), 3.42 (s, 3H), 3.33 (s, 3H), 3.0-4.8 (m, 7H); ^{13}C-NMR ($CDCl_3$) δ 161.96, 151.48, 140.29, 110.81, 71.50, 71.24, 67.31, 66.38, 37.13, 27.83; mass: m/z 227 (M^++1, 7), 226 (M^+, 54), 140 (100). 1e: oil; ^{1}H-NMR ($CDCl_3$) δ 7.26 (s, 1H), 5.81 (q, 1H, J=7 Hz), 3.43 (s, 3H), 3.34 (s, 3H), 2.08 (s, 3H), 1.50 (d, 3H, J=7 Hz); ^{13}C-NMR ($CDCl_3$) δ 169.93, 161.95, 151.50, 140.22, 113.41, 66.60, 37.16, 27.86, 21.50, 19.79; mass: m/z 227 (M^++1, 1), 226 (M^+, 4), 183 (100). 1f: mp 79-80 °C (lit.[15] mp 78-80 °C); ^{1}H-NMR ($CDCl_3$) δ 7.29 (s, 1H), 4.17 (q, 2H, J=7 Hz), 3.42 (s, 3H), 3.34 (s, 5H), 1.27 (t, 3H, J=7 Hz); ^{13}C-NMR ($CDCl_3$) δ 170.90, 163.26, 151.69, 141.70, 106.87, 61.15, 36.96, 32.36, 28.00, 14.15; mass: m/z 227 (M^++1, 6),

226 (M^+, 38), 153 (100). 1g: oil; ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 1H), 5.90 (d, 1H, J=5 Hz), 4.42 (d, 2H, J=5 Hz), 3.43 (s, 3H), 3.34 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.59, 169.86, 161.77, 151.37, 142.06, 108.67, 68.38, 63.98, 37.30, 27.95, 21.04, 20.78; mass: m/z 285 (M^++1, 1), 284 (M^+, 1), 169 (100). 1h: mp 89-90 °C; ^{1}H-NMR ($CDCl_3$) δ 7.26 (s, 1H), 4.31 (m, 4H), 3.42 (s, 3H), 3.39 (s, 2H), 3.35 (s, 3H), 2.08 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.76, 170.66, 163.17, 151.65, 141.65, 106.56, 62.89, 61.96, 36.99, 32.16, 28.03, 20.81; mass: m/z 285 (M^++1, 1), 284 (M^+, 7), 153 (100). 1i: mp 90-91 °C; ^{1}H-NMR ($CDCl_3$) δ 7.20 (s, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.27 (s, 2H), 1.47 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 170.21, 163.26, 151.73, 141.36, 107.33, 81.47, 36.97, 33.25, 28.07, 24.11; mass: m/z 255 (M^++1, 3), 254 (M^+, 16), 154 (100). 1j: mp 120-121 °C (lit.[15] mp 116-118 °C); ^{1}H-NMR ($CDCl_3$) δ 7.39 (s, 1H), 3.49 (s, 5H), 3.37 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 162.10, 151.33, 140.84, 116.65, 103.43, 37.25, 28.19, 16.15; mass: m/z 180 (M^++1, 11), 179 (M^+, 100). 2d: mp 256-263 °C; ^{1}H-NMR (d_6-DMSO) δ 11.2 (broad, 1H), 11.0 (broad, 1H), 7.23 (s, 1H), 4.36 (d, d, 1H, J=10.2, J=2.4 Hz), 3.76-3.84 (m, 2H), 3.63-3.72 (m, 2H), 3.43-3.46 (m, 1H), 3.21 (d, d, 1H, J=10.2, J=11.4 Hz); ^{13}C-NMR (d_6-DMSO) δ 162.91, 150.78, 138.75, 109.44, 70.32, 70.18, 66.58, 65.54; mass: 199 (M^++1, 5), 198 (M^+, 33), 112 (100). 2j: mp 253-256 °C; ^{1}H-NMR (d_6-DMSO) δ 10.6-11.4 (broad, 2H), 7.53 (s, 1H), 3.46 (s, 2H); ^{13}C-NMR (d_6-DMSO) δ 163.21, 151.00, 140.42, 118.15, 102.65, 14.68; mass: m/z 152 (M^++1, 9), 151 (M^+, 94), 80 (100).

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13) The compound 2j was found to inhibit herpes simplex virus type 1. The authors thank Dr. Ichiro Takase (Ajinomoto Co.) for the biological assay.

14) Separation conditions. Tokyo Rikakikai Co., DCC-300-G2. $CHCl_3$-MeOH-H_2O (5:5:3) by the descending method. The compound 2d was further purified by liquid chromatography with a low pressure pump (Fuji-gel packed column RQ-2 ODS silica gel 24 mmøx360 mm, mobile phase: water, detected at 250 nm).

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