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The Oxidative Iodination of Pyrimidine Bases and their Nucleosides using Iodine/Dimethylformamide/ m-Chloroperbenzoic Acid

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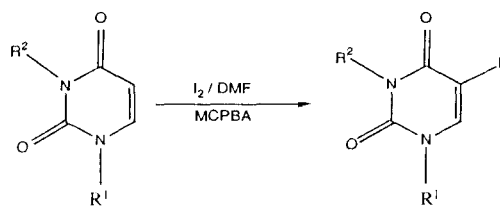
Abstract □ Pyrimidine bases and their nucleosides were oxidatively iodinated at C-5 position by the reaction of iodine in DMF (dimethylformamide) with MCPBA (m-chloroperbenzoic acid) under mild conditions. For uracil derivatives such as uracil **1a**, 1,3-dimethyluracil **1b**, uridine **1c**, and 2′-deoxyuridine **1d**, the corresponding 5-iodo derivatives were obtained in high yields (71-95%). The iodination of cytidine **3a** and 2′-deoxycytidine **3b** was achieved in moderate yields (41-56%).

Keywords □ Iodination, pyrimidine nucleosides, m-chloroperbenzoic acid.

Halogenation of pyrimidine nucleosides is important because of the potent activity of 5-halogenopyrimidine nucleosides as anticancer and antiviral chemotherapeutic agents[1] as well as the usefullness of these compounds as intermediates for further conversion of nucleosides[2].

Iodination of pyrimidine bases was achieved by using iodine/nitric acid[3], N-iodosuccinimide[4], iodine monochloride[5], and iodine/cerium ammonium nitrate system[6]. They have some limitations in most cases such as vigorous reaction conditions and the use of protected nucleoside derivatives, thus development of mild iodination method is still required.

In our studies on the oxidative halogenation of nucleosides[7] and aromatic compounds[8], we examined the oxidative iodination at the C-5 position of pyrimidine bases and their nucleosides. Thus, treatment of uracil derivatives **1a-d** in DMF with slight excess amount of elemental iodine followed by MCPBA at room temperature afforded the corresponding 5-iodo derivatives in good yields within 30 min (equation 1).



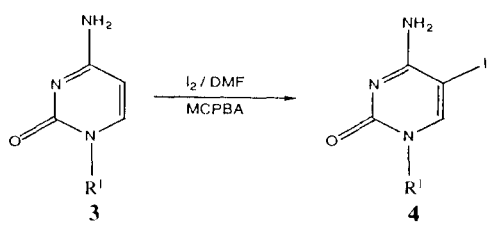
(1)

1

a. R^1 = H.
b. R^1 = Me.
c. R^1 = β-D-ribofuranosyl.
d. R^1 = 2′-deoxy-β-D-ribofuranosyl.

2

R^2 = H
R^2 = Me
R^2 = H
R^2 = H



(2)

3

a. R^1 = β-D-ribofuranosyl
b. R^1 = 2′-deoxy-β-D-ribofuranosyl

4

For cytosine nucleosides **3a-b** desired 5-iodo derivatives **4a-b** were obtained in moderate yields by the analogous procedure within 1 h (equation 2).

The 5-iodo derivatives were all characterized by their mp, ^{1}H NMR spectra, mass spectra, and elemental analysis (C, H, and N). It is noteworthy that

Table I. Iodination of Pyrimidine Bases and Their Nucleosides

Entry	Substrate	Oxidant	Time (h)	Product	Yield (%)
1	**1a**	MCPBA	0.5	**2a**	95
2	**1a**	Oxone	3	**2a**	73
3	**1b**	MCPBA	0.5	**2b**	93
4	**1b**	Oxone	3	**2b**	82
5	**1c**	MCPBA	0.5	**2c**	77
6	**1c**	Oxone	5	**2c**	55
7	**1d**	MCPBA	0.5	**2d**	71
8	**1d**	Oxone	5	**2d**	50
9	**3a**	MCPBA	1	**4a**	41
10	**3b**	MCPBA	1	**4b**	56

the use of Oxone (potassium peroxymonosulfate, Aldrich) instead of using MCPBA as oxidant showed somewhat lower yield. These results were summarized in Table I.

EXPERIMENTAL

Melting points were measured with a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded with a Varian Gemini-200 NMR spectrometer. TMS served as the internal standard. Electron impact mass spectra were measured on a Shimadzu QP 1000 mass spectrometer. Chemical ionization mass spectra were obtained with methane as the reagent gas with a JEOL JMS-DX-303 spectrometer. Elemental analysis (C, H, and N) were performed with Perkin-Elmer 240 C elemental analyzer.

General procedure for the synthesis of 2a-b

To a stirred solution of **1a** or **1b** (1 mmol) in DMF (4 m*l*) was added a slight excess of elemental iodine (153 mg, 0.6 mmol) followed by MCPBA (225 mg, 80-85% purity) at one portion at room temperature. The reaction mixture was stirred for 30 min. Most of the solvent was removed under reduced pressure (up to ca. 0.5 m*l*), and the residue was triturated with ether (10 m*l*). The resulting solid was washed with ether (5 m*l*), and recrystallized from ethanol to give the desired product as a white solid.

5-Iodouracil, 2a[6]

Yield: 95%; mp: 259℃, dec. (ref. 198℃ dec. 245℃ sublimation 264℃; ^{1}H NMR (DMSO-d_6) δ 7.88 (s, 1H, H6); MS (20 eV) m/z (rel. intensity) 168 (19), 194 (27), 195 (44), 238 (M^+, 100); Anal. calcd. for $C_4H_3IN_2O_2$: C, 20.19: H, 1.27: N, 11.77, Found: C, 19.73: H, 1.28: N, 11.53.

5-Iodo-1,3-dimethyluracil, 2b[6]

Yield: 93%; mp: 226-228℃ (ref. 210-230℃, sublimation); ^{1}H NMR (DMSO-d_6) δ 3.22 (s, 3H), 3.32 (s, 3H), 8.25 (s, 1H, H6); MS (20 eV) m/z (rel. intensity) 44 (65), 168 (35), 209 (27), 266 (M^+, 100); Anal. calcd. for $C_6H_7IN_2O_2$: C, 27.09: H, 2.65: N, 10.53, Found: C, 26.92: H, 2.56: N, 10.28.

General procedure for the synthesis of 2c-d and 4a-b

To a stirred solution of **1c-d** or **3a-b** (1 mmol) in DMF (3 m*l*) was added a slight excess of elemental iodine (153 mg, 0.6 mmol) followed by MCPBA (225 mg, 80-85% purity) at one portion at room temperature. The reaction mixture was stirred for 30 min (1 h for **3a-b**). Then, the reaction mixture was applied directly to a silica gel column (Merck silica gel 60, 70-230 mesh), and eluted with solvent (EtOAc/i-PrOH/H_2O, 4 : 1 : 2, upper phase). Appropriate portions, which were monitored by TLC, were collected. Evaporation of the solvent gave the desired product.

5-Iodouridine, 2c[6]

Yield: 77%; mp: 206-208℃ (ref. 208-209℃, dec.); ^{1}H NMR (DMSO-d_6) δ 3.50-3.80 (m, 2H, H5′, H5″), 3.82-3.92(m, 1H, H4′), 3.92-4.10(m, 2H, H3′, H2′), 5.07 (d, 1H, OH), 5.26(t, 1H, OH), 5.42(d, 1H, OH), 5.72 (d, J=4.6 Hz, 1H, H1′), 8.48 (s, 1H, H6), 11.65 (brs, 1H, NH); MS (20 eV) m/z (rel. intensity) 58 (100), 69 (21), 73 (55), 133 (41), 238 (5-iodouracil, 100); MS (CI, CH_4) m/z 371 (M^++1), 399 (M^++29); Anal. calcd. for $C_9H_{11}IN_2O_6$: C, 29.21: H, 3.00: N, 7.51, Found: C, 29.37: H, 2.94: N, 7.33.

5-Iodo-2′-deoxyuridine, 2d[6]

Yield: 71%; mp: 180-183℃ (ref. 164-184℃, dec.); ^{1}H NMR (DMSO-d_6) δ 2.05-2.20 (m, 2H, H2′, H2″), 3.50-3.70 (m, 2H, H5′, H5″), 3.70-3.85 (m, 1H, H4′), 4.20-4.30 (m, 1H, H3′), 5.14 (t, 1H, OH), 5.24 (d, 1H, OH), 6.09 (t, J=6.6 Hz, 1H, H1′), 8.39 (s, 1H, H6), 11.65 (brs, 1H, NH); MS (20 eV) m/z (rel. intensity) 73 (18), 117 (100), 238 (66), 354 (M^+, 6); Anal. calcd. for $C_9H_{11}IN_2O_5$: C, 30.53: H, 3.13: N, 7.91, Found: 30.62: H, 3.16: N, 7.79.

5-Iodocytidine, 4a[9]

Yield: 41%; mp: 149-151℃ (ref. 152-155℃); ^{1}H NMR (DMSO-d_6) δ 3.40-3.80 (m, 2H, H5′, H5″), 3.80-3.90 (m, 1H, H4′), 3.90-4.05 (m, 2H, H3′, H2′), 4.99 (d, 1H, OH), 5.21 (t, 1H, OH), 5.39 (d, 1H, H1′), 6.60 and 7.80 (brs, 2H, NH_2), 8.42 (s, 1H, H6); MS (20 eV) m/z (rel. intensity) 45 (35), 110 (100), 237 (5-iodocytosine, 100), 238 (32); Anal. calcd. for $C_9H_{12}IN_3O_5$: C, 29.29: H, 3.28: N, 11.38, Found: C, 29.41: H, 3.20: N, 11.13.

5-Iodo-2′-deoxycytidine, 4b[9]

Yield: 56%; mp: 175-177℃, dec. (ref. 176-182℃); ^{1}H NMR (DMSO-d_6) δ 1.90-2.20 (m, 2H, H2′, H2″), 3.50-3.65 (m, 2H, H5′, H5″), 3.70-3.85 (m, 1H, H4′), 4.15-4.28 (m, 1H, H3′), 5.10 (t, 1H, OH), 5.20 (d, 1H, OH), 6.09 (t, 1H, H1′), 6.60 and 7.80 (brs, 2H, NH_2), 8.30 (s, 1H, H6); MS (CI, CH_4) m/z 352 (M^+-1), 398 (M^++43); Anal. calcd. for $C_9H_{12}IN_3O_4$: C, 30.61: H, 3.43: N, 11.90, Found: C, 30.79: H, 3.44: N, 11.95.

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