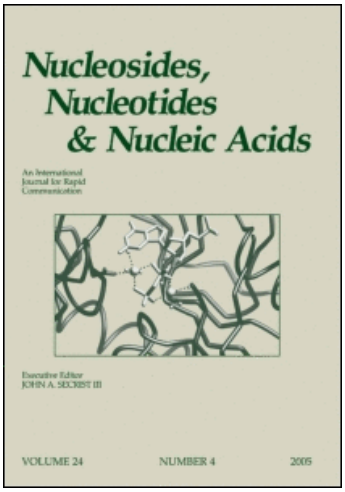

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Ryu, E. K. and Kim, J. N.(1989) 'The Oxidative Chlorination of Pyrimidine and Purine Bases, and Nucleosides Using Acyl Chloride-Dimethyl-Formamide-*m*-Chloroperbenzoic Acid System[1]', Nucleosides, Nucleotides and Nucleic Acids, 8: 1, 43 — 48
To link to this Article: DOI: 10.1080/07328318908054157
URL: http://dx.doi.org/10.1080/07328318908054157

NUCLEOSIDES & NUCLEOTIDES, 8(1), 43-48 (1989)

THE OXIDATIVE CHLORINATION OF PYRIMIDINE AND PURINE BASES, AND NUCLEOSIDES USING ACYL CHLORIDE-DIMETHYLFORMAMIDE- m-CHLOROPERBENZOIC ACID SYSTEM[1]

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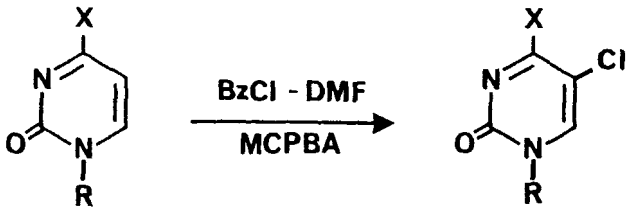
Abstract: Pyrimidine and purine bases, and nucleosides were chlorinated by the reaction of acyl chloride in DMF with MCPBA under mild conditions in moderate yields.

The chlorination of pyrimidine and purine derivatives has been less extensively studied than bromination. Previous methods for chlorination of pyrimidine derivatives at C-5 have included the use of Cl_2-H_2O in the presence of UV irradiation[2] and of N-chlorosuccinimide-acetic acid.[3] In contrast to the ease of bromination at C-8 of purine derivatives,[4,5] greater difficulty has been noted with regard to chlorination. Attempts at direct chlorination, analogous to bromination, have been unsuccessful. However, direct chlorination at C-8 of adenosine and its nucleotides has been performed by using tetrabutylammonium iodotetrachloride[6] or t-butyl hypochlorite,[7] although the yields are very low. Recently a facile method for the direct chlorination of pyrimidine and purine nucleosides has been developed by using MCPBA and HCl in an aprotic solvent such as DMF, DMA or HMPA.[8] Herein we describe the first example of the oxidative chlorination of the nucleosides and bases using an acyl chloride such as benzoyl chloride or acetyl chloride as a chloride ion source.[9] Thus, to solutions of various ribo- or 2'-deoxyribo-nucleosides or their corresponding bases in DMF[10] was added a slight excess of benzoyl chloride followed by a solution of MCPBA in DMF over a period of 10 min at room temperature. After about 20-30 min, TLC examination of the reaction mixture on silica gel 60 F-254 (Merck) using $CHCl_3$-MeOH (7:3) revealed that the

starting material had disappeared. After appropriate workup procedure, the pure chlorinated analog was separated by column chromatography on silica gel using 5% MeOH in $CHCl_3$. The 5-chloro substituted uracil nucleosides 2a-c and the 5-chloro substituted cytosine nucleosides 2d-f were prepared in moderate yields (eq. 1 and TABLE I).

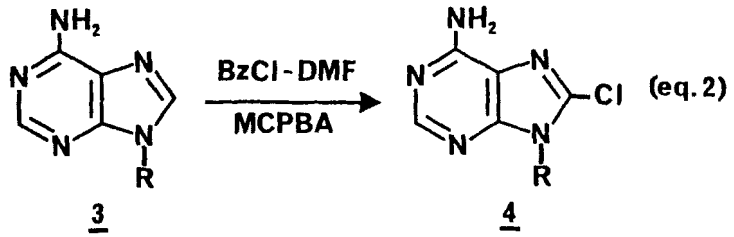


1 2 (eq.1)

a. X = OH, R = H
b. X = OH, R = β -D-ribofuranosyl
c. X = OH, R = 2'-deoxy- β -D-ribofuranosyl
d. X = NH_2, R = H
e. X = NH_2, R = β -D-ribofuranosyl
f. X = NH_2, R = 2'-deoxy- β -D-ribofuranosyl

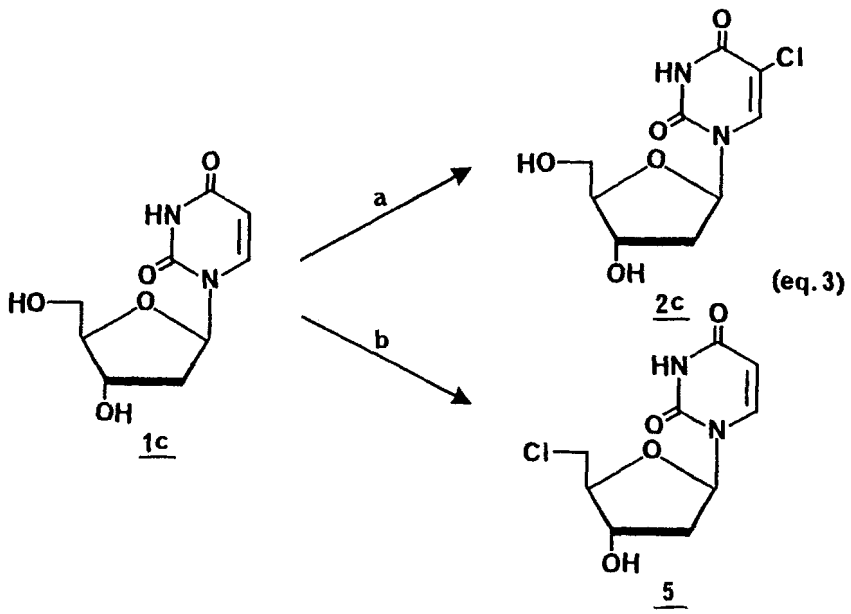
The 8-chloro substituted adenine and its nucleosides 4a-c were also synthesized in a one-pot reaction as described above, followed by column chromatographic separation (eq. 2). However, for the adenine derivatives the yields of the chlorinated products were usually lower than for the pyrimidine derivatives, as shown in TABLE I. TLC examination of the reaction mixture showed several by-products which were not investigated in detail. No N-oxides resulting from the reaction conditions could be detected. Attempts to prepare pure 8-chloro substituted guanine and the corresponding nucleoside have been unsuccessful due to its insolubility and the difficulties of product separation of the reaction mixtures.

It is of interest to note that the reaction of a nucleoside, e.g., 2'-deoxyuridine, with a complex of benzoyl chloride in DMF in the absence of MCPBA on gentle warming (40-50°C) for 2 days afforded 5'-chloro-2', 5'-dideoxyuridine (5). However, by addition of MCPBA to this reaction mixture at room temperature, 5-chloro-2'-deoxyuridine (2c) was obtained within 20 min (eq. 3). Previous reports have shown that the reaction of pyrimidine nucleosides with thionyl chloride, phosphorous oxychloride or arsenic trichloride gave the corresponding 5'-chloro-5'-deoxy pyrimidine nucleosides when carried out in DMF.[11,12,13]



3 4 (eq. 2)

a. R = H
b. R = β -D-ribofuranosyl
c. R = 2'-deoxy-β -D-ribofuranosyl



(eq. 3)

Reaction conditions: (a) BzCl-DMF-MCPBA, r.t., <20 min;
(b) BzCl-DMF, 40-50°C, 2 days

We have also further investigated the oxidative chlorination reaction by replacing benzoyl chloride with other reagents containing reactive chlorine. The reaction of uracil (1a) as a model compound with acetyl chloride, followed by treatment of MCPBA for 20 min at room temperature, formed 5-chlorouracil (2a) almost quantitatively, on the basis of examination on TLC (Merck silica gel 60, F-254, 30% MeOH in $CHCl_3$).

The mechanism of the oxidative chlorination reaction is believed to be as follows. Chloride ion generated from the acyl chloride-DMF complex[15] is oxidized, producing positive chlorine ion that could undergo

TABLE I[14]

The oxidative chlorination of bases and related nucleosides.

entry	X	R	(%) Yield[a]	ref
2a	OH	H	75	16
2b	OH	β -D-ribofuranosyl	54	2
2c	OH	2'-deoxy- β -D-ribofuranosyl	53	17
2d	NH_2	H	40	18
2e	NH_2	β -D-ribofuranosyl	44	2
2f	NH_2	2'-deoxy- β -D-ribofuranosyl	47	19
4a		H	18	20
4b		β -D-ribofuranosyl	20	6
4c		2'-deoxy- β -D-ribofuranosyl	25	21
5		5'-chloro-2',5'-dideoxyuridine	65	22

[a]Yields are of the isolated products and are not optimized.

concomitant electrophilic attack at C-5 of pyrimidine or C-8 of the purine moieties to give the corresponding chloro substituted derivatives.

In conclusion, the oxidative chlorination procedure described herein is a convenient and efficient method for the chlorination of pyrimidine and purine nucleosides, and further application of the chlorination reaction is under investigation.

EXPERIMENTAL

General procedure for the synthesis of chloro substituted derivatives on the heterocyclic moiety (2a-2f, 4a-4c). To a solution of nucleosides or heterocyclic bases (10 mmol) in DMF (20-30 ml) was added a slight excess of benzoyl chloride (1.25 ml, 10.8 mmol) followed by a solution of MCPBA (2.40 g, 80-85% purity) in DMF (10 ml) over a period of 10 min at room temperature. The mixture was stirred for 20 min and then poured into cold water (100 ml). The resulting precipitate was filtered and washed with water (5 ml). The combined filtrate was washed with ether (100 ml x 3) and concentrated under reduced pressure to a syrup. The syrup was applied to a silica gel column (Merck silica gel 60,70-230 mesh, prepacked by a slurry of silica gel in 5% MeOH-$CHCl_3$), and eluted with 5% MeOH in $CHCl_3$. Appropriate portions, which were monitored by TLC, were collected. Evaporation of the solvent gave the desired product.

Synthesis of 5'-chloro-2',5'-dideoxyuridine (5). To a solution of 2'-deoxyuridine (0.22 g, 0.96 mmol) in DMF (6 ml) was added benzoyl chloride (0.13 ml, 1.10 mmol). The reaction mixture was stirred for 2 days with gentle warming (40-50°C). Water (30 ml) was added to the

reaction mixture. The resulting solution was extracted with ether (30 ml x 2), and the aqueous layer evaporated under reduced pressure to a small volume (~2 ml). This was applied to a silica gel column, and eluted with 5% MeOH in $CHCl_3$. Appropriate portions were pooled and evaporated to dryness, affording the desired 5^{22} (0.17 g, 65%). ^1H NMR (DMSO-d_6, D_2O) δ 7.60(d, 1H, H5, J=8.2Hz), 6.15(t, 1H, H1', J=7.3Hz), 5.63(d, 1H, H6, J=8.2Hz), 4.20(m, 1H, H3'), 3.70-4.05(m, 3H, H4', H5', H5"), 2.05(m, 2H, H2', H2").

ACKNOWLEDGEMENT

The financial support of the Korea Science and Engineering Foundation is gratefully acknowledged.

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Received September 29, 1987.