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PRACTICAL HALOGENATIONS OF NUCLEOSIDES USING TETRABUTYLAMMONIUM PEROXYDISULFATE

Vasu Sampath, Vidyadhar Jadhav, Hee Yoon Lee,* and Yong Hae Kim*

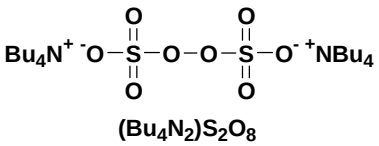
Center for Molecular Design and Synthesis, Department of Chemistry,
Korea Advanced Institute of Science and Technology,
Taejon 305-701, South Korea. kimyh@kaist.ac.kr

Abstract - Direct halogenation of a wide range of acetylated pyrimidine and purine nucleosides was achieved with high regioselectivity in good yields using tetrabutylammonium peroxydisulfate **1**. Treatment of protected nucleosides with HCl/DMF or inorganic salts such as LiCl or NaCl in MeCN/AcOH in the presence of **1** gave the corresponding chlorinated nucleosides and bromination was achieved with *N*-bromosuccinimide in MeCN in the presence of **1**.

Direct halogenations of various pyrimidine ribosides and deoxyribosides have long been known to give the corresponding 5-halogenated pyrimidine nucleosides.[1-6] Interest in recent years in the biochemistry of nucleic acids has stimulated improvement in halogenation procedures[7-11] and study of the 5-halogenated pyrimidine nucleosides as therapeutic agents.[12-14] The bromination of RNA and DNA has been studied by various investigators.[15-18] 5-Halo-substitited pyrimidine nucleosides and 8-halo-substituted purine nucleosides have been shown to exhibit interesting chemotherapeutic, biochemical and biophysical properties.[19] In addition, they have served as useful synthetic intermediates for the preparation of related nucleosides of biological interest.[20,21] A number of 5-substituted uracil derivatives, especially 2'-deoxyuridines have been investigated extensively for the experimental and clinical treatment of neoplastic and viral diseases.[22] The direct bromination of uracil derivatives at C5 has been achieved previously by using Br_2–acetic anhydride,[23] Br_2–DMF,[24] Br_2–H_2O[2,5] or *N*-bromosuccinimide.[25] The brominated purine nucleosides for incorporation into RNA and DNA seemed especially attractive for future biochemical studies.[26] Bromination of purine derivatives at C8 has been reported by using Br_2-H_2O or Br_2 in sodium acetate buffer.[27] The chlorination of purine and pyrimidine derivatives has been somewhat less extensively studied due to the difficulty of chlorination and previous methods for chlorination of pyrimidine nucleosides at C5 have included the use of Cl_2-H_2O under the UV irradiation[4] and *N*-chlorosuccinimide-acetic acid.[28] In contrast to the ease of bromination at C8 of purine derivatives[21,27] greater difficulties have been noted with regard to chlorination. Ryu and MacCoss reported that 3-

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

chloroperbenzoic acid serves as an oxidant to effect chlorination of nucleosides in aprotic solvents containing hydrogen chloride or bromide.[29] Moreover Asakura and Robins have recently reported CAN (ceric ammonium nitrate) mediated halogenation at C5 of uracil derivatives with elemental iodine or metal halogenides in MeCN/AcOH at 80 °C.[30] But those methods require long reaction time and somewhat tedious work up procedures. Due to the wide medicinal applications of halogenated purine and pyrimidine nucleosides, new methods for the convenient halogenations of pyrimidine and purine are of current interest in nucleoside chemistry. Herein we describe the practical and simple halogenations of nucleosides using tetrabutylammonium peroxydisulfate **1** under mild reaction conditions.



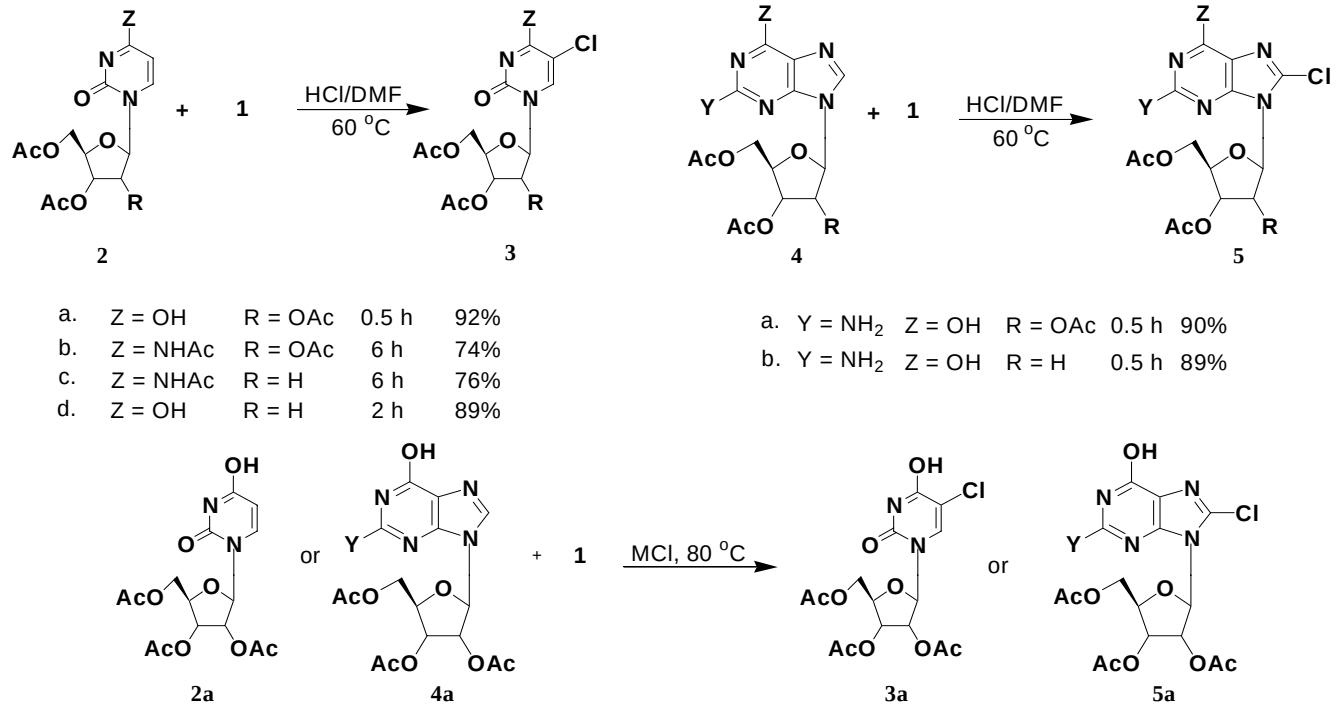
$(Bu_4N_2)S_2O_8$

1

Figure 1

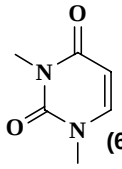
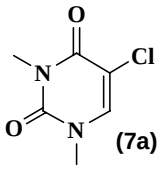
The peroxide **1** turned out to be a useful source of tetrabutylammonium sulfate radical, which shows oxidizing ability and can be readily converted to sulfate anion by one electron transfer from the substrate.[31] In contrast to the metal peroxydisulfates such as $K_2S_2O_8$, $Na_2S_2O_8$ or $(NH_4)_2S_2O_8$, **1** is readily soluble in various organic solvents such as acetonitrile, acetone, methanol and methylene chloride and therefore it can be easily used in general organic reactions. The compound **1** was successfully prepared by mixing two equivalents of tetrtabutylammonium hydrogen sulfate and potassium persulfate in water. After stirring for 30 min at 25 °C, the desired product was extracted with methylene chloride, washed with distilled water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the pure white solid of which elemental analysis met **1**.[31] The white solid **1** is stable for a couple of months at 25 °C and can be stored in the refrigerator indefinitely.

Various acetylated pyrimidine and purine nucleosides have been chlorinated with HCl/DMF in the presence of one equivalent of tetrabutylammonium peroxydisulfate **1** in DMF at 60 °C, to give 5-chloro-pyrimidine and 8-chloropurine nucleosides in good yields with high regioselectivity. We have systematically investigated the reaction between **1** and other pyrimidine and purine derivatives in DMF containing HCl (Scheme 1). In the pyrimidine series, both uridine (**2a**) and 2'-deoxyuridine (**2d**) gave the corresponding 5-chloro derivatives in DMF at 60 °C in good yields. The cytidine (**2b**) and 2'-deoxycytidine (**2c**) gave the corresponding products in good yield with 6.0 equivalents of HCl/DMF. Applying the same reaction conditions to the purine derivatives gave the 8-chloronucleosides in high yield thus giving an efficient method for the preparation of 8-chloroguanosine (**5a**) and 8-chloro-2'-deoxyguanosine (**5b**) utilizing lesser amount of HCl/DMF in short reaction time. We have also developed an alternative source for the chlorination of nucleosides using one equivalent of **1** with inorganic salts (MCl) such as LiCl or NaCl. Good yields were achieved under this reaction conditions (Table 1). It is noteworthy that the absence of AcOH in the reaction didn't affect the formation of 8-chloroguanosine (**5a**) in good yield (Entry 3).



Scheme 1. Chlorination of Acetylated Nucleosides with **1**

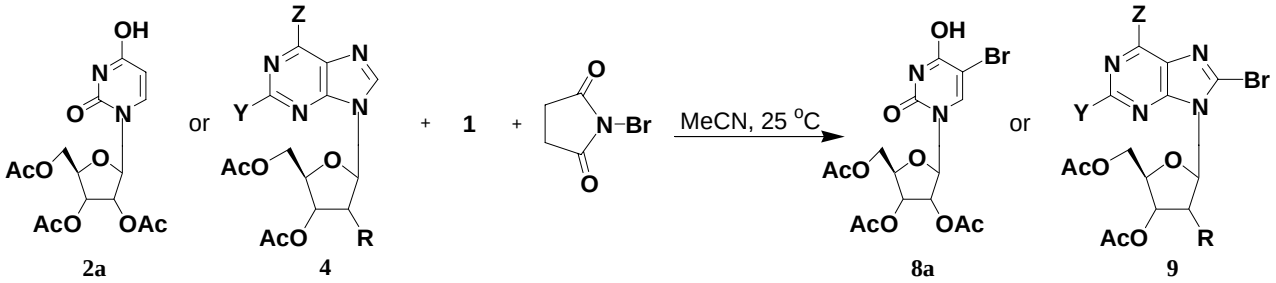
Table 1. $(Bu_4N)_2S_2O_8$ Mediated Chlorination Using MCl

Entry	Substrate	MCl (eq.)	Solvent	Time (h)	Product	Yield (%)[b]
1	**2a**	LiCl (6.0)	MeCN/AcOH[a]	10	**3a**	81
2	**2a**	NaCl (5.0)	MeCN/AcOH[a]	9	**3a**	84
3	**4a**	LiCl (5.0)	MeCN	4	**5a**	80
4	 (6a)	LiCl (3.6)	MeCN/AcOH[a]	6	 (7a)	87
5		NaCl (3.0)	MeCN/AcOH[a]	10		71[c]

a. Ratio of the solvent used is 1:1. b. Isolated yield. c. Starting material (20%) was recovered.

We have also examined the bromination of acetylated nucleosides with **1** (1.0 eq.) and *N*-bromosuccinimide (1.0 eq.) in MeCN at room temperature. The corresponding brominated nucleosides were obtained with good yields with high regioselectivity (Scheme 2). Acetylated uridine (**2a**) gave high yield of 91% by utilizing 1.0 equivalent of NBS. It is interesting to note that the acetylated guanosine (**4a**) and acetylated 2'-deoxyguanosine (**4b**) gave high yields of 93% and 81% respectively.

The reaction mechanism is ambiguous. But it appears to be initiated by the homolytic cleavage of **1** to form the sulfate radical. This sulfate radical may react with HCl or inorganic chloride to give cationic chloride species Cl^+ and sulfate anion. This chloride species reacts with the substrate to form chlorine-bridged intermediate. Finally the sulfate anion abstracts the α-proton from the intermediate to give the product.[32]



a. Y = NH_2 Z = OH R = OAc 0.5 h 93% 2 h 91%

b. Y = NH_2 Z = OH R = H 1.5 h 81%

Scheme 2. Bromination of Acetylated Nucleosides with **1**

In conclusion, the halogenation procedure described herein using tetrabutylammonium peroxydisulfate **1** has several advantages over those currently available methods. The compound **1** can be synthesized very easily and can be handled safely and it is stable. This is a practical method for the synthesis of acetylated 5-chlorouridine, 8-chloroguanosine, 8-chloro-2'-deoxyguanosine, 5-bromouridine, 8-bromoguanosine and 8-bromo-2'-deoxyguanosine in good yields under mild reaction conditions. Thus **1** mediated halogenations of nucleosides can be applied, for the synthesis of wide range of 5-halopyrimidine and 8-halopurine nucleosides.

Typical Procedure of Chlorination Using 1 with MCl: (Table 1, Entry 4)

To a solution of **1** (335 mg, 0.5 mmol) in MeCN/AcOH (1:1, 6 mL) was added 1, 3-dimethyluracil (70 mg, 0.5 mmol) and LiCl (37.8 mg, 0.9 mmol). It was heated at 80 °C under reflux conditions. Then the reaction mixture was allowed to stir until the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give the crude product, which was washed with brine (2 x 20 mL) and then extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography (Ethyl Acetate/Hexane 3:1).

Typical Procedure of Bromination Using 1 with NBS: (Scheme 2, 4a)

A well-dried round bottom flask was charged with **1** (134 mg, 0.2 mmol) in MeCN (4 mL) with a mechanical stirrer. Acetylated guanosine (82 mg, 0.2 mmol) and NBS (35 mg, 0.2 mmol) was added at rt. The reaction completed after 30 min. The solvent was evaporated under reduced pressure to give the crude compound. Saturated sodium sulfite solution to the residue was added and extracted with chloroform (3 x 25 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography ($CHCl_3$/MeOH 5:1)

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Spectral Data of Typical Products:

(3a) ^{1}H-NMR ($CDCl_3$, 400 MHz). δ 9.53 (s, 1H), 7.71 (s, 1H), 6.05 (d, *J* = 4.5 Hz, 1H), 5.32 (m, 2H), 4.37 (m, 3H), 2.16 (s, 3H) 2.08 (d, *J* = 8.0 Hz, 6H) ^{13}C NMR ($CDCl_3$, 100 MHz). δ 170.12, 169.92, 169.46, 158.66, 149.28, 135.95, 110.16, 87.59, 80.38, 73.10, 70.14, 62.88, 20.65, 20.34, 20.24.

(**3b**) ^{1}H-NMR (DMSO-d_6, 400 MHz). δ 9.10 (s, 1H), 8.13 (s, 1H), 5.87 (d, *J* = 4.9 Hz, 1H,), 5.46 (t, *J* = 5.0 Hz, 1H), 5.32 (dd, *J* = 5.7, 6.1 Hz, 1H), 4.34 (m, 3H), 2.06 (m, 12H).

(**3c**) ^{1}H-NMR ($CDCl_3$, 300 MHz). δ 8.78 (s, 1H), 7.77 (s, 1H), 6.29 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.21 (dd, *J* = 4.2, 2.31 Hz, 1H), 4.41 (m, 5H), 2.09 (s, 3H) 2.07 (d, *J* = 6.1 Hz, 6H).

(**3d**) ^{1}H-NMR ($CDCl_3$, 300 MHz). δ 9.39 (s, 1H), 7.77 (s, 1H), 6.30 (t, *J* = 5.9 Hz, 1H), 5.21 (m, 1H), 4.39 (m, 3H), 2.55 (m, 2H**),** 2.13 (d, *J* = 5.5 Hz, 6H).

(**5a**) ^{1}H-NMR (DMSO-d_6, 400 MHz). δ 10.93 (s, 1H), 6.62 (br, 2H), 5.95 (m, 2H), 5.62 (t, *J* = 6.1 Hz, 1H), 4.40 (m, 3H), 2.09, 2.05, 1.98 (3s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz). δ 170.08, 169.44, 169.27, 156.01, 154.52, 152.18, 131.42, 86.92, 79.81, 71.72, 70.37, 63.19, 20.86, 20.72, 20.59.

(**5b**) ^{1}H-NMR (DMSO-d_6, 300 MHz). δ 10.85 (s, 1H), 6.55 (br, 2H), 6.18 (t, *J* = 7.0 Hz, 1H), 5.37 (m, 1H), 4.34 (m, 1H), 4.15 (d, *J* = 2.3 Hz, 2H), 2.46 (m, 2H), 1.97, 1.95 (2s, 6H).

(**7a**) ^{1}H-NMR ($CDCl_3$, 300 MHz). δ 7.38 (s, 1H), 3.40 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz). δ 159.41, 150.87, 139.78, 107.99, 37.05, 28.84.

(8a) ^{1}H-NMR ($CDCl_3$, 400 MHz). δ 9.63 (s, 1H), 7.80 (s, 1H), 6.05 (d, *J* = 4.7 Hz, 1H), 5.32 (m, 2H), 4.36 (m, 3H), 2.17 (s, 3H), 2.09 (d, *J* = 8.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz). δ 170.07, 169.61, 169.57, 158.64, 149.64, 138.52, 97.88, 87.25, 80.15, 73.02, 69.96, 62.86, 20.83, 20.41, 20.31.

(**9a**) ^{1}H-NMR (DMSO-d_6, 300 MHz). δ 10.80 (br, 1H), 6.56 (br, 2H), 5.99 (t, *J* = 3.6 Hz, 1H), 5.85 (d, *J* = 6.0 Hz, 1H), 5.63 (t, *J* = 3.9 Hz, 1H), 4.40 (m, 3H), 2.06 (s, 3H), 2.0 (d, *J* = 1.6 Hz, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 179.43, 170.12, 169.50, 169.43, 155.45, 153.82, 120.14, 117.20, 87.66, 79.31, 71.30, 69.93, 62.76, 20.48, 20.30, 20.25.

(**9b**) ^{1}H-NMR (DMSO-d_6, 300 MHz). δ 11.00 (br, 1H), 6.52 (br, 2H), 6.15 (t, *J* = 6.7 Hz, 1H), 5.38 (m, 1H), 4.35 (m, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 2.89 (m, 2H), 2.03, 1.99 (2s, 6H).