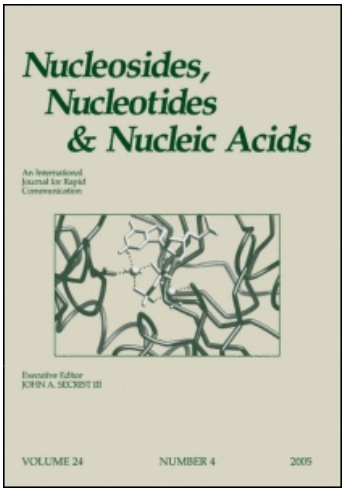

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Tadakazu Tsuji[a]; Keiko Takenaka[a]
[a] Department of Chemistry, Japan Women's University, Tokyo, Japan

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FACILE 5'-HALOGENATION OF UNPROTECTED NUCLEOSIDES

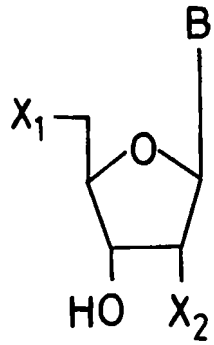
Tadakazu Tsuji* and Keiko Takenaka

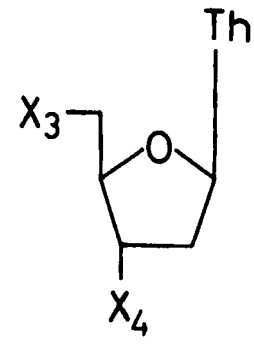
Department of Chemistry, Japan Women's University,
2-8-1 Mejirodai, Bunkyo-ku, Tokyo 112, Japan

Abstract: Facile and efficient 5'-bromination and 5'-iodination of unprotected nucleosides, such as uridine, thymidine, 5-ethyluridine, inosine, cytidine and adenosine, were achieved by the use of carbon tetrahalide and triphenylphosphine in N,N-dimethylacetamide or hexamethylphosphoramide.

5'-Deoxy-5'-halonucleosides, particularly the 5'-deoxy-5'-iodo derivatives, are important as precursors for the synthesis of nucleotides, deoxy-, and unsaturated sugar nucleosides, etc.,[1] and as biologically active substances.[2]

Several methods[3-6] for the bromination and chlorination of the hydroxyl group in unprotected nucleosides have been reported. However, we found by reexamination that none of them are efficient for a wide variety of nucleosides. Furthermore, only one method was available for iodination. Thus, Verheyden et al.[3] obtained 5'-iodinated products by the action of methyltriphenylphosphonium iodide (**1**) on uridine (**2a**) and thymidine (**3a**). On the other hand, amino group protection was required for the 5'-iodination of cytidine (**4a**) and adenosine (**5a**).[3] Meanwhile, the same research group reported the chlorination of **3a** and the





2a : B=Ur, X_1=X_2=OH
2b[3]: B=Ur, X_1=I, X_2=OH
2c[4]: B=Ur, X_1=Br, X_2=OH
2d[6]: B=Ur, X_1=X_2=Br
4a : B=Cy, X_1=X_2=OH
4b[8]: B=Cy, X_1=I, X_2=OH
4c[5]: B=Cy, X_1=Br, X_2=OH
5a : B=Ad, X_1=X_2=OH
5b[7]: B=Ad, X_1=I, X_2=OH
5c[5]: B=Ad, X_1=Br, X_2=OH
6a : B=Hy, X_1=X_2=OH
6b[7]: B=Hy, X_1=I, X_2=OH
6c : B=Hy, X_1=Br, X_2=OH
7a : B=5-EtUr, X_1=X_2=OH
7b : B=5-EtUr, X_1=I, X_2=OH

3a : X_3=X_4=OH
3b[3]: X_3=I, X_4=OH
3c[4]: X_3=Br, X_4=OH
3d[4]: X_3=X_4=Br

bromination of **2a** and **3a** through reaction with commercially available carbon tetrahalide (CX_4) and triphenylphosphine (Ph_3P) in N,N-dimethylformamide (DMF).[4] The method was found to be inefficient for iodination and bromination except for the bromination of **2a**. With the aim of extending the halogenation by the CX_4-Ph_3P method, an investigation was performed by changing the amount of the reagent, solvent, and temperature. This paper deals with the facile 5'-iodination and 5'-bromination of unprotected nucleosides including **4a** and **5a** by the use of CX_4 and Ph_3P in N,N-dimethylacetamide (DMA) or hexamethylphosphoramide (HMPA) under mild conditions. The results are given in Table 1.

The 5'-iodinated products of **2a**, **3a**, inosine (**6a**) and 5-ethyluridine (**7a**) were obtained in 54-79% yields by CI_4 and Ph_3P in DMA (runs 1-4). On the other hand, the 5'-iodination of **2a** in DMF gave the product only in 17% yield and that of **6a** did not occur. In the cases of the direct 5'-iodination (CI_4 and Ph_3P) of **4a** and **5a**, HMPA was used as a well suited solvent. No iodinated product was obtained by the use of DMF or DMA. The yields of the corresponding iodo

TABLE 1. Halogenated Nucleosides

Run	Nucleoside (Ns)	CX_4 X=	Molar ratio of Ns:Ph_3P:CX_4	Solv.	Conditions Temp. (°C)	Time	Yield (%)	
1	**2a**	I	1 : 2 : 2	DMA	23	24 h	**2b**	79
2	**3a**	I	1 : 5 : 5	DMA	30	1 h	**3b**	77
3	**6a**	I	1 : 5 : 2	DMA	40	30 min	**6b**	57
4	**7a**	I	1 : 5 : 5	DMA	30	30 min	**7b**	54
5	**4a**	I	1 : 5 : 5	HMPA	60	1 h	**4b**	58
6	**5a**	I	1 : 5 : 5	HMPA	60	1 h	**5b**	93
7	**2a**	Br	1 : 2 : 2	DMA	23	24 h	**2c**	82
8	**2a**	Br	1 : 5 : 5	DMA	40	24 h	**2d**	82
9	**3a**	Br	1 : 2 : 5	DMA	40	30 min	**3c**	75
10	**3a**	Br	1 : 5 : 5	DMA	60	1 h	**3d**	55
11	**6a**	Br	1 : 3 : 5	DMA	30	1 h	**6c**	65
12	**4a**	Br	1 : 2 : 2	HMPA	40	10 h	**4c**	58
13	**5a**	Br	1 : 2 : 2	HMPA	40	10 h	**5c**	82

derivatives, (**4b**) and (**5b**), are 58 and 93%, respectively (runs 5 and 6). Throughout these reactions, diiodination did not take place. In order to examine the efficiency of 5'-deoxy-5-ethyl-5'-iodouridine (**7b**) as a synthetic intermediate, **7b** was converted to 5'-deoxy-5-ethyluridine (**8**), an analogue of antiviral 2'-deoxy-5-ethyluridine,[9] by catalytic hydrogenolysis.

Subsequently, the 5'-bromination of unprotected nucleosides was carried out using CBr_4 and Ph_3P in DMA or HMPA. The results (runs 7-13) are shown in Table 1. The reaction proceeded under mild conditions to give the desired 5'-

brominated compounds in 55-82% yields. The reaction of **3a** and **6a** with CBr_4 and Ph_3P in DMF under similar conditions with those of runs 9 and 11 gave the products, (**3c**) and (**6c**), in yields of 30 and 20% after 1 and 6 days, respectively. The advantages, in terms of both rate and yield, of using DMA as a solvent are clear. 5'-Bromo-5'-deoxyinosine (**6c**) was previously obtained by the treatment of **6a** with N-bromosuccinimide in DMF as a syrup without characterization,[10] while **6c** was prepared as a crystalline form by the present method. In an attempt to prepare the dibrominated derivatives by the reaction of nucleosides with an excess amount of Ph_3P-CBr_4, only **2a** and **3a** gave the desired products, (**2d**) and (**3d**), in 82 and 55% yields, respectively (runs 8 and 10).

EXPERIMENTAL

All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken on a Hitachi R-22 spectrophotometer (90 MHz) using Me_4Si as an internal standard. Mass spectra (MS) were measured by a JEOL JMS-DX 300 mass spectrometer at 75 ev by the direct inlet system. Ultraviolet (UV) spectra were recorded on a Hitachi 340 recording spectrophotometer. Preparative TLC was carried out on Kiesel gel $60PF_{254}$ (Merck) using $CHCl_3$-MeOH (17:3).

General Procedure for the Halogenation of Sugar Moiety of Nucleosides. A solution of the nucleoside (1 mmol), Ph_3P and CX_4 in DMA (10 ml) or HMPA (5 ml) was stirred under conditions described in Table 1 and the reaction was monitored by TLC using $CHCl_3$-MeOH (17:3). The solution was diluted with MeOH and concentrated under diminished pressure. The residue was then subjected to preparative TLC and recrystallized from dil. EtOH or H_2O to give a pure sample. Compounds **4b** and **5b** were washed with AcOEt repeatedly prior to recrystallization. In the iodination of **2a**, **3a** and **7a**, the resulting solution was extracted with CH_2Cl_2. The extract was washed with 5% sodium thiosulfate and water, evaporated to dryness in vacuo and then subjected to preparative TLC. Known products were identified in comparison to the authentic sample by mp, IR, UV and TLC.

5'-Bromo-5'-deoxyinosine (6c): Colorless prisms, mp 186°C (from dil. MeOH). UV λ_{max}^{MeOH} nm: 245, 250, 272. NMR (DMSO-d_6) : 3.69 (1H, dd, 5''-H), 3.89 (1H, dd, 5'-H), 4.09 (1H, dd, 4'-H), 4.16 (1H, dd, 3'-H), 4.67 (1H, dd, 2'-H), 5.91 (1H, d, 1'-H), 8.06 (1H, s, 2-H), 8.32 (1H, s, 8-H). Anal. Calcd for $C_{10}H_{11}O_4N_4Br.0.5H_2O$: C, 35.31; H, 3.55; N, 16.47. Found: C, 35.28; H, 3.33; N, 16.49.

5'-Deoxy-5-ethyl-5'-iodouridine (7b): Colorless prisms, mp 138-139°C (from MeOH-AcOEt). UV λ_{max}^{MeOH} 274nm. MS m/z: 382. Anal. Calcd for $C_{11}H_{15}O_5N_2I$: C, 34.57; H, 3.96; N, 7.33. Found: C, 34.70; H, 4.01; N, 7.02.

5'-Deoxy-5-ethyluridine (8) A solution of **7b** (191 mg) and AcOH (0.08 ml) in MeOH (4 ml) was hydrogenated in the presence of Pd/C (prepared from $PdCl_2$ (10.8 mg) and active carbon (108 mg)) and Dowex-X8 (100-200 mesh, acetate form, 300 mg). After completion of the reaction, the catalyst was filtered off and washed with MeOH. The filtrates and the washings were evaporated to dryness and the residue was recrystallized from EtOH to give **8** as colorless plates, mp 180-181°C. Yield, 93%. UV λ_{max}^{EtOH} nm(ε): 267 (9330). NMR (DMSO-d_6): 1.05 (3H, t, 5-CH_3), 1.31 (3H, d, 5'-H), 2.30 (2H, q, 5-CH_2), 3.34 (2H, s, 2'- and 3'-OH), 3.96 (2H, q, 2'- and 3'-H), 5.74 (1H, d, 1'-H), 7.36 (1H, s, 6-H). MS m/z: 256 (M^+). Anal. Calcd for $C_{11}H_{16}O_5N_2$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.38; H, 6.27; N, 10.74.

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