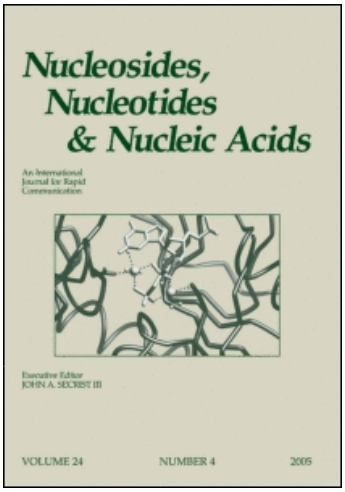

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PREPARATION OF 8-CHLOROPURINE NUCLEOSIDES THROUGH THE REACTION BETWEEN THEIR C-8 LITHIATED SPECIES AND p-TOLUENESULFONYL CHLORIDE

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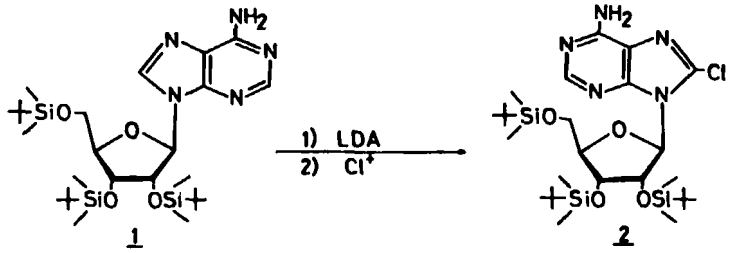
Abstract: Chlorination of purine nucleosides protected with tert-butyldimethylsilyl (TBDMS) group was examined by the reaction of the C-8 lithiated species, generated by LDA, with p-toluenesulfonyl chloride as an electrophile. This provides a new method for the preparation of 8-chloropurine nucleosides.

Although halogenation of nucleosides is one of the key-reactions for the transformation of the base moiety of nucleosides, most reports on the halogenation reaction have dealt with bromination.[1] Procedures for the chlorination of nucleosides in general and for that of purine nucleosides in particular are surprisingly few in number. Only three methods are so far available for the preparation of 8-chloroadenosine[2-4] and 8-chloroguanosine.[4] Moreover, the reported yields of the isolated products are not satisfactory.

Quite recently, we have reported on the LDA (lithium diisopropylamide) lithiation of 2',3',5'-tris-O-TBDMS naturally occurring purine nucleosides,[5] which furnished a simple entry to the 8-carbon-substituted derivatives. During the course of this study, we thought that a high-yield C-8 chlorination of purine nucleosides might be possible on the basis of the LDA lithiation by using an appropriate electrophile which could generate chlorine cation.

We first examined the use of N-chlorosuccinimide (NCS). The choice of this reagent was motivated by the fact that it was an inexpensive chemical and was easily handled.[6] When the 8-lithio derivative of 2',3',5'-tris-O-TBDMS adenosine (1) was treated with NCS in THF at below −70 °C for 1 h, TLC

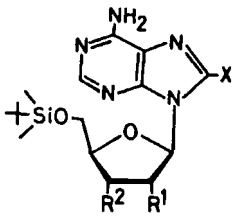


1 2

analysis of the reaction mixture showed the formation of the desired 8-chlorinated product (2). However, based upon the PMR spectrum of the isolated 2, it appeared that column chromatographic purification was unsatisfactory because of contamination by a considerable amount of succinimide.

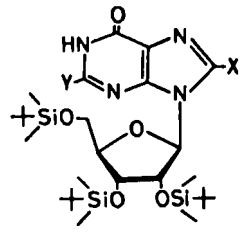
We found that p-toluenesulfonyl chloride (TsCl)[7] was a suitable reagent for our purpose. Thus, when 1 was lithiated with 5 equiv of LDA[5] in THF and then treated with 2 equiv of TsCl (1 h, below −70 °C), pure 2 (mp 184-186 °C) was isolated in 48% yield after column chromatography on silica gel. The use of 4 equiv of TsCl increased the isolated yield to 74%. It should be noted that only 7% yield of 2 was obtained by the use of 1 equiv of the chlorinating agent, due to its preferential reaction with an excess of LDA to form lithium p-toluenesulfinate,[8] which is highly polar and therefore easily removable by column chromatography.

The above reaction sequence is, of course, applicable to other adenine nucleosides as exemplified by the chlorination of 3',5'-bis-O-TBDMS 2'-deoxyadenosine (3)[9] and 2',5'-bis-O-TBDMS cordycepin (4). Yields of the products (5 and 6) are shown in parentheses.



3 R^1= H, R^2= OTBDMS, X= H
4 R^1= OTBDMS, R^2= H, X= H
5 R^1= H, R^2= OTBDMS, X= Cl (90%)
6 R^1= OTBDMS, R^2= H, X= Cl (78%)

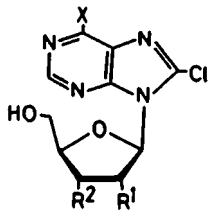
Similarly, the chlorination of 2',3',5'-tris-O-TBDMS inosine (7) was accomplished with 5 equiv of LDA and 4 equiv of TsCl to produce the corresponding 8-chloro derivative (8: mp 223-224 °C) in 87% yield.



7 X= H, Y= H
8 X= Cl, Y= H
9 X= H, Y= NH_2
10 X= Cl, Y= NH_2

In contrast to the above cases, the reaction of 2',3',5'-tris-O-TBDMS guanosine (9) under similar conditions gave a complex mixture of products, from which the 8-chlorinated product (10: mp >300 °C) was isolated only in 31% yield.

Finally, deprotection of these 8-chlorinated products



11 R^1= R^2= OH, X= NH_2
12 R^1= H, R^2= OH, X= NH_2
13 R^1= OH, R^2= H, X= NH_2
14 R^1= R^2= OH, X= OH

was carried out with tetrabutylammonium fluoride in THF to furnish 8-chloropurine nucleosides (11-14)[10]

Since no acidic treatment is involved in the present procedure, this would be a method of choice for chlorination of purine nucleosides which are known to be rather labile in acidic conditions.[11]

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. PMR spectra were measured with TMS (tetramethylsilane) as an internal standard, with a JEOL JNM-GX 400 NMR spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use by diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out either on silica gel (Wakogel® C-200) or on mag-

nesium silicate (Florisil®). TLC was performed on precoated silica gel plates F_{254}, Merck. Compounds 1, 3, 7, and 9 were prepared according to the published procedure.[5,9]

General procedure for the chlorination —— LDA (5 equiv) in THF was placed in a three-necked flask equipped with a gas inlet adaptor, thermometer, and rubber septum. To this, a solution of a TBDMS nucleoside in THF was added, under positive pressure of dry argon, at a rate such that the temperature did not exceed −70 °C. After the mixture was stirred for 1 h, a THF solution of TsCl (4 equiv) was added, while maintaining the temperature below −70 °C. The reaction mixture was stirred for 1 h, quenched with AcOH and evaporated to dryness. The whole residue was chromatographed on a silica gel column to give the corresponding 8-chlorinated product.

8-Chloro-2',3',5'-tris-O-TBDMS adenosine (2) —— This compound was crystallized from EtOH-H_2O (mp 184-186°C). Anal. Calcd. for $C_{28}H_{54}ClN_5O_4Si_3$: C, 52.21; H, 8.45; N, 10.87. Found: C, 52.24; H, 8.56; N, 10.65. UV absorption in MeOH: max 261.5 nm (ε 14600), min 230 nm (ε 1500). PMR ($CDCl_3$) δ: −0.33, −0.05, −0.01, 0.03, and 0.15 (18H, each as s, SiMe), 0.80, 0.84, and 0.96 (27H, each as s, SiBu-t), 3.70-3.74 (1H, m, H-4'), 4.05-4.08 (2H, m, CH_2-5'), 4.56-4.58 (1H, m, H-3'), 5.46-5.48 (3H, m, NH_2 and H-2'), 5.95 (1H, d, J= 5.9 Hz, H-1'), 8.28 (1H, s, H-2). MS m/z: 631 and 629 (M−Me), 589 and 587 (M−Bu-t).

2',5'-Bis-O-TBDMS cordycepin (4) —— To a mixture of TBDMSCl (1.8 g, 12 mmol) and imidazole (1.36 g, 20 mmol) in DMF (10 ml), was added cordycepin (1.0 g, 4 mmol) and the resulting solution was stirred at room temperature overnight. The mixture was poured into EtOAc-H_2O and the organic layer separated was dried (Na_2SO_4) and evaporated to dryness. Column chromatographic purification (1% MeOH in $CHCl_3$) of the residue gave 4 (1.86 g, 97%), which was crystallized from EtOH-H_2O to give an analytical sample (mp 129-130 °C). Anal. Calcd. for $C_{22}H_{41}N_5O_3Si_2$: C, 55.10; H, 8.61; N, 14.60. Found: C, 54.87; H, 8.61; N, 14.37. UV absorption in MeOH: max 259.5 nm (ε 14700), min 228.5 nm (ε 2300). PMR ($CDCl_3$) δ: 0.08,

0.12, 0.13, and 0.14 (12H, each as s, SiMe), 0.89 and 0.94 (18H, each as s, SiBu-t), 1.74-1.89 and 2.23-2.29 (2H, each as m, H-3'), 3.77 and 4.11 (2H, each as dd, CH_2-5'), 4.53-4.57 (1H, m, H-4'), 4.62-4.64 (1H, m, H-2'), 5.54 (2H, br, NH_2), 6.00 (1H, d, J= 1.5 Hz, H-1'), 8.31 (1H, s, H-8), 8.33 (1H, s, H-2). MS m/z: 464 (M–Me), 422 (M–Bu-t).

8-Chloro-3',5'-bis-O-TBDMS 2'-deoxyadenosine (5) —— This compound was crystallized from EtOH-H_2O (mp 158-159 °C). Anal. Calcd. for $C_{22}H_{40}ClN_5O_3Si_2$: C, 51.41; H, 7.84; N, 13.63. Found: C, 51.65; H, 7.96; N, 13.59. UV absorption in MeOH: max 262 nm (ε 14600), min 229 nm (ε 1000). PMR ($CDCl_3$) δ: –0.04, 0.00, and 0.14 (12H, each as s, SiMe), 0.83 and 0.94 (18H, each as s, SiBu-t), 2.20-2.26 (1H, m, H-2'), 3.58-3.70 (2H, m, H-2' and H-5'), 3.87-3.97 (2H, m, H-4' and H-5'), 4.84-4.87 (1H, m, H-3'), 5.41 (2H, br, NH_2), 6.36 (1H, t, H-1'), 8.28 (1H, s, H-2). MS m/z: 500 and 498 (M–Me), 458 and 456 (M–Bu-t).

8-Chloro-2',5'-bis-O-TBDMS cordycepin (6) —— This compound was crystallized from EtOH-H_2O (mp 129-130 °C). Anal. Calcd. for $C_{22}H_{40}ClN_5O_3Si_2$: C, 51.41; H, 7.84; N, 13.63. Found: C, 51.32; H, 7.98; N, 13.53. UV absorption in MeOH: max 262 nm (ε 15400), min 229 nm (ε 2600). PMR ($CDCl_3$) δ: –0.08, –0.02, and 0.00 (12H, each as s, SiMe), 0.84 and 0.85 (18H, each as s, SiBu-t), 2.00-2.04 and 2.68-2.75 (2H, each as m, H-3'), 3.76-3.84 (2H, m, CH_2-5'), 4.39-4.44 (1H, m, H-4'), 5.32-5.35 (1H, m, H-2'), 5.46 (2H, br, NH_2), 5.90 (1H, d, J= 2.6 Hz, H-1'), 8.30 (1H, s, H-2). MS m/z: 500 and 498 (M–Me), 458 and 456 (M–Bu-t).

8-Chloro-2',3',5'-tris-O-TBDMS inosine (8) —— This compound was crystallized from EtOH-H_2O (mp 223-224 °C). Anal. Calcd. for $C_{28}H_{53}ClN_4O_5Si_3$: C, 52.13; H, 8.28; N, 8.68. Found: C, 52.39; H, 8.52; N, 8.82. UV absorption in MeOH: max 249 nm (ε 9100), shoulder 252 nm (ε 8800) and 267 nm (ε 4200), min 223 nm (ε 1300). PMR ($CDCl_3$) δ: –0.31, –0.04, 0.02, 0.05, and 0.15 (18H, each as s, SiMe), 0.80, 0.87, and 0.96 (27H, each as s, SiBu-t), 3.74 and 3.97 (2H, each as dd, CH_2-5'), 4.06-4.10 (1H, m, H-4'), 4.47 (1H, dd, H-3'), 5.25 (1H, dd, H-2'), 6.00 (1H, d, J= 6.2 Hz, H-1'), 8.10 (1H, s, H-2), 12.95 (1H, br, NH). MS m/z: 590 and 588 (M–Bu-t).

8-Chloro-2',3',5'-tris-O-TBDMS guanosine (10) —— This compound was crystallized from EtOH-H_2O (mp >300 °C). Anal. Calcd. for $C_{28}H_{54}ClN_5O_5Si_3$: C, 50.94; H, 8.25; N, 10.61. Found: C, 50.74; H, 8.38; N, 10.83. UV absorption in MeOH: max 261 nm (ε 15300), shoulder 272 nm (ε 12500), min 222 nm (ε 1200). PMR ($CDCl_3$) δ: −0.22, −0.02, 0.04, 0.06, 0.15, and 0.16 (18H, each as s, SiMe), 0.82, 0.89, and 0.96 (27H, each as s, SiMe-t), 3.75 and 3.95 (2H, each as dd, CH_2-5'), 4.02-4.05 (1H, m, H-4'), 4.45 (1H, dd, H-3'), 5.27 (1H, dd, H-2'), 5.85 (1H, d, J= 5.9 Hz, H-1'), 6.18 (2H, br, NH_2), 11.86 (1H, br, NH). MS m/z: 646 and 644 (M−Me), 604 and 602 (M−Bu-t).

General procedure for deprotection of the TBDMS groups —— A protected 8-chloropurine nucleoside was treated with TBAF·$3H_2O$ (3.5 equiv) in THF at room temperature for 1 h. After evaporation of the solvent, the whole residue was chromatographed on a column of Florisil (5-10% MeOH in $CHCl_3$) to give the corresponding 8-chloropurine nucleoside.

8-Chloroadenosine (11) —— This compound was obtained in 86% yield as crystals from EtOH (mp 185-187 °C). Anal. Calcd. for $C_{10}H_{12}ClN_5O_4$: C, 39.81; H, 4.01; N, 23.21. Found: C, 39.82; H, 4.15; N, 22.98. UV absorption in MeOH: max 262.5 nm (ε 15300), min 230 nm (ε 1300). PMR (DMSO-d_6) δ: 3.50-3.56 and 3.65-3.70 (2H, each as m, CH_2-5'), 3.97-4.00 (1H, m, H-4'), 4.18-4.21 (1H, m, H-3'), 5.04 (1H, dd, H-2'), 5.22 (1H, d, OH), 5.46-5.49 (2H, m, OH), 5.84 (1H, d, J= 6.6 Hz, H-1'), 7.54 (2H, br, NH_2), 8.14 (1H, s, H-2). MS m/z: 171 and 169 (B+1).

8-Chloro-2'-deoxyadenosine (12) —— This compound was obtained in 81% yield as crystals from EtOH (mp 190-191 °C). Anal. Calcd. for $C_{10}H_{12}ClN_5O_3$: C, 42.04; H, 4.23; N, 24.50. Found: C, 42.08; H, 4.33; N, 24.47. UV absorption in MeOH: max 262 nm (ε 14500), min 230 nm (ε 2600). PMR (DMSO-d_6) δ: 2.18-2.23 and 2.49-2.51 (2H, each as m, H-2'), 3.44-3.50 and 3.61-3.66 (2H, each as m, CH_2-5'), 3.86-3.89 (1H, m, H-4'), 4.46-4.50 (1H, m, H-3'), 5.20 (1H, br, 5'-OH), 5.31 (1H, d, 3'-OH), 6.31 (1H, t, H-1'), 7.49 (2H, br, NH_2), 8.13 (1H, s, H-2). MS m/z: 171 and 169 (B+1).

8-Chlorocordycepin (13) —— This compound was obtained in 75% yield as crystals from EtOH (mp 189-190 °C). Anal. Calcd. for $C_{10}H_{12}ClN_5O_3$: C, 42.04; H, 4.23; N, 24.50. Found: C, 42.26; H, 4.25; N, 24.48. UV absorption in MeOH: max 262 nm (ε 15300), min 230 nm (ε 2500). PMR (DMSO-d_6) δ: 2.00-2.04 and 2.49-2.51 (2H, each as m, H-3'), 3.41-3.45 and 3.54-3.58 (2H, each as m, CH_2-5'), 4.29-4.31 (1H, m, H-4'), 5.04-5.07 (1H, m, H-2'), 5.15 (1H, br, 5'-OH), 5.57 (1H, d, 2'-OH), 5.76 (1H, d, J= 4.0 Hz, H-1'), 7.49 (2H, br, NH_2), 8.14 (1H, s, H-2). MS m/z: 171 and 169 (B+1).

8-Chloroinosine (14) —— This compound was obtained in 86% yield as crystals from MeOH-H_2O (mp >202 °C, dec.). Anal. Calcd. for $C_{10}H_{11}ClN_4O_5$: C, 39.68; H, 3.66; N, 18.51. Found: C, 39.93; H, 3.71; N, 18.28. UV absorption in MeOH: max 249 nm (ε 9700), shoulder 252 nm (ε 9600) and 267 nm (ε 4700), min 223 nm (ε 1400). PMR (DMSO-d_6) δ: 3.48-3.54 and 3.61-3.66 (2H, each as m, CH_2-5'), 3.91-3.94 (1H, m, H-4'), 4.16-4.18 (1H, m, H-3'), 4.91 (1H, t, 5'-OH), 4.96 (1H, t, H-2'), 5.23 and 5.49 (2H, each as d, OH), 5.83 (1H, d, J= 6.6 Hz, H-1'), 8.13 (1H, s, H-2), 12.65 (1H, br, NH). MS m/z: 172 and 170 (B+1).

REFERENCES AND NOTES

1) W. W. Zorbach and R. S. Tipson, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, John Wiley and Sons, Inc., New York, 1968.
2) H. J. Brentnall and D. W. Hutchinson, Tetrahedron Lett., 1972, 2595.
3) M. Ikehara, Y. Ogiso, and T. Maruyama, Chem. Pharm. Bull., 25, 575 (1977).
4) E. K. Ryu and M. MacCoss, J. Org. Chem., 46, 2819 (1981).
5) H. Hayakawa, K. Haraguchi, H. Tanaka, and T. Miyasaka, Chem. Pharm. Bull., 35, 72 (1987).
6) Other reagents, such as Cl_2 and trichloroisocyanuric acid, are known to react with organolithium compounds but these are either toxic or moisture sensitive.
7) For an example of the reaction of TsCl with organolithium compounds: D. W. Slocum and P. L. Gierer, J. Org. Chem., 41, 3668 (1976).

8) p-Toluenesulfinic acid (MS m/z: 156 M^+, 139 M–OH) was isolated from the reaction of LDA (2 equiv) and TsCl under similar conditions.

9) K. K. Ogilvie, Can. J. Chem., 51, 3799 (1973).

10) Deprotection of 10 was not examined due to a small quantity of the material.

11) R. Romero, R. Stein, H. G. Bull, and E. H. Cordes, J. Am. Chem. Soc., 100, 7620 (1978) and references cited therein.

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