ger, *J. Chem. Phys.*, **96**, 3636 (1992); J. Fournier, P. G. Fournier, M. L. Langford, M. Mosselmal, J. M. Robbe, and G. Gandara, *J. Chem. Phys.*, **96**, 3594 (1992).
2. P. J. Miller, S. A. Rogers, J. Senekowitsch, S. V. ONeil, S. R. Leone, H.-J. Werner, and P. J. Knowles, *Int. J. Mass Spectrom. Ion Processes*, **100**, 505 (1990) and references therein.
3. K. F. Freed, *Acc. Chem. Res.*, **16**, 137 (1983); *Lect. Notes in Chem.*, **52**, 1 (1989); T. Takada and K. F. Freed, *J. Chem. Phys.*, **80**, 3253, 3296 (1984); X. C. Wang and K. F. Freed, *J. Chem. Phys.*, **86**, 2899 (1987); **91**, 1142 (1989); **94**, 5253 (1991); A. W. Kanzler and K. F. Freed, *J. Chem. Phys.*, **94**, 3778 (1991); H. Sun and K. F. Freed, *J. Chem. Phys.*, **88**, 2659 (1988); **89**, 5355 (1988); J. K. Park and H. Sun, *Bull. Kor. Chem. Soc.*, **11**, 34 (1990); A. W. Kanzler, H. Sun, and K. F. Freed, *Int. J. Quantum. Chem.*, **39**, 269 (1991); A. W. Kanzler, K. F. Freed, and H. Sun, *J. Chem. Phys.*, **96**, 5245 (1992).
4. H. Sun (unpublished results).
5. W. Koch, G. Frenking, H. Schwarz, F. Maquin, and D. Stahl, *J. Chem. Soc. Perkin Trans.*, **2**, 757 (1986); A. Banichevich, S. D. Peyerimhoff, M. C. van Hemert, and P. G. Fournier, *Chem. Phys.*, **121**, 351 (1988).
6. S. A. Pope, I. H. Hillier, M. F. Guest, and J. Kendric, *Chem. Phys. Lett.*, **95**, 247 (1983); S. A. Pope, I. H. Hillier, and M. F. Guest, *Faraday Symp. Chem. Soc.*, **19**, 109 (1984).
7. A. Veillard, *Theoret. Chim. Acta*, **12**, 405 (1968); G. C. Lie and E. Clementi, *J. Chem. Phys.*, **60**, 1275 (1974); P. J. Bruna and G. Hirsch, *Mol. Phys.*, **61**, 1359 (1987).
8. J. K. Park and H. Sun, *Chem. Phys. Lett.*, **194**, 485 (1992).

Facile Synthesis of 4-N-Benzoyl-5-bromo-2′-deoxycytidine

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Several 5-halopyrimidines, their ribosides and deoxyribosides, have interesting inhibitory effects upon growth of bacteria, bacteriophage, molds and tumors. Some of these antimetabolites inhibit thymidine synthesis, others prevent thymidine utilization, and depending to some extent on the size of the halogen[1,2], the abnormal pyrimidine may be incorporated into RNA or DNA[3]. In addition to the possible usefulness of these derivatives in the studies of nucleic acid metabolism, genetics and as chemotherapeutic agents, these compounds are potential replacements for 5-methyl-2′-deoxycytidine found in some plants and animal DNA and 5-hydroxymethyl-2′-deoxycytidine in the coliphage DNA of the even varieties[4]. The unusual important activities of the above derivatives initiated many workers to participate in studies of these compounds.

For studies on the mechanism of restriction endonuclease catalyzed reactions and on drug-DNA interaction, we were forced to synthesize 4-N-protected-5-bromo-2′-deoxycytidine as a building block for synthesis of oligodeoxyribonuclotides which contain 5-bromo-2′-deoxycytidine. In this note we report the facile synthesis of 4-N-benzoyl-5-bromodeoxycytidine and its derivative.

Results and Discussion

It seemed likely that we would first prepare 5-bromo-2′-deoxycytidine by using the reported procedure[4,5] and then protect 4-N-exocyclic amino group to 5-bromo-2′-deoxycytidinewith appropriate protecting group[6]. We, therefore, treated 2′-deoxycytidine with bromine in dry pyridine using the reported procedure[4]. The reaction mixture showed several spots on TLC and the reported procedure appeared to be impractical. It seemed that it would be necessary to use fully protected 2′-deoxycytidine for the bromination. Our first choice of the fully protected deoxycytidine was 4-N-3′,5′-O-tribenzoyl-2′-deoxycytidine. 4-N-3′,5′-O-tribenzoyl-2′-deoxycytidine was converted to 5-bromo derivative with bromine in satisfactory yield (70%). After the product was purified by short column chromatography, the product was treated with NaOMe for removing of 3′,5′-O-dibenzoyl groups to give 4-N-benzoyl-5-bromo-2′-deoxycytidine 1. Surprisingly, it was depyrimidinated completely. It was probably due to bromo-substituent of 2′-deoxycytidine which has electron withdrawing property. Thus, our next starting material was 4-N-protected-2′-deoxycytidine, 4-N-benzoyl-2′-deoxycytidine 3, which was treated with bromine and yielded many products on TLC. But when we changed bromine for N-bromosuccinimide, it has been found that bromination of 4-N-benzoyl-2′-deoxycytidine was conveniently accomplished in practical yield (52%).

Derivatization of the 5′-hydroxy group of 4-N-benzoyl-5-bromo-2′-deoxycytidine 1 was achieved by treatment of 4-N-benzoyl-5-bromo-2′-deoxycytidine 1 with 9-chloro-9-phenylxanthene (pixyl chloride) in pyridine by following the reported procedure[7]. Alternatively, 5′-pixyl-4-N-benzoyl-2′-deoxycytidine 4 was allowed to react with N-bromosuccinimide in pyridine in a manner analogous to that described for bromination of N-benzoyl-2′-deoxycytidine 3 and converted to the 4-N-benzoyl-5-bromo-5′-O-pixyl-2′-deoxycytidine 2 as outlined in Figure 1. Both procedures gave the 4-N-benzoyl-5-bromo-5′-O-pixyl-2′-deoxycytidine 2 in good yield.

The stabilities of the titled compound and its pixyl derivative were tested under various conditions which are applied in oligodeoxyribonucleotide synthesis[8]. They are stable enough to be used as building blocks. Thus, the titled compound and its pixyl derivative are safely using as building blocks in the synthesis of oligodeoxyribonucleotides which contain 5-bromodeoxycytidine in this laboratory.

Experimental

^{1}H-NMR spectra were measured with a Bruker 300 MHz spectrometer. TLC was carried out on Merck silica gel $60F_{254}$ plates. Merck silica gel H was used for short column chromatography[9]. Pyridine was dried by refluxing with calcium hydride and was then distilled at atmospheric pressure.

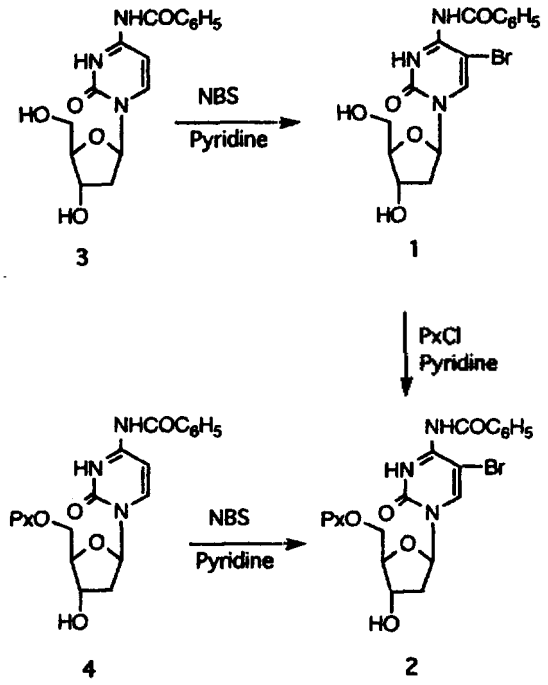

Figure 1. Synthesis of 4-N-Benzoyl-5-Bromo-5'-O-Pixyl-2'-deoxycytidine.

Synthesis of 4-N-benzoyl-5-bromo-2'-deoxycytidine. N-Bromosuccinimide (1.068 g, 6.000 mmol) was added to a solution of 4-N-benzoyl-2'-deoxycytidine (1.657 g, 5.000 mmol) in dry pyridine (40 m*l*) at room temperature. After overnight (16 h),the products were poured into saturated $NaHCO_3$ solution (70 m*l*) and extracted with $CHCl_3$ (2×70 m*l*). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude yellowish product. The product was crystallized from methanol. Yield 1.07 g (52%). R_f 0.24 (10% methanol in chloroform) mp. 154-156℃ (dec).

^{1}H-NMR(DMSO-d_6) δ 2.15-2.32(m, 2H, 2'-H), 3.56-3.72(m, 2H, 5'-H), 3.86-3.90(m, 1H, 4'-H), 4.25-4.32(m, 1H, 3'-H), 5.18-5.26(t, 1H, 5'-OH) 5.26-5.33(d, 1H, 3'-OH), 6.07-6.13(t, 1H, 1'-H), 7.48-7.65(m, 3H, aromatic), 8.10-8.17(m, 2H, aromatic), 8.65(s, 1H, 6-H), 12.80(bs, 1H, NH). Anal. Calcd. for $C_{16}H_{16}N_3O_5Br$: C, 46.85; H, 3.93; N, 10.24. Found: C, 46.71; H, 4.06; N, 10.30.

Synthesis of 4-N-Benzoyl-5-bromo-5'-O-(9-phenyl-9 H-xanthen-9-yl)-2'-deoxycytidine. To the dry pyridine solution (35 m*l*) of 4-N-benzoyl-5-bromo-2'-deoxycytidine (1.657 g, 5.000 mmol) was added pixyl chloride (1.757 g, 6.000 mmol) in dry pyridine (35 m*l*) dropwise over a period of 1 h. The reaction mixture was added to H_2O (4 m*l*). The reaction mixture was stirred for 10 min and $CHCl_3$ was added to it. After cooling with a few chips of ice, the reaction mixture was washed with $NaHCO_3$ solution. Aqueous layer was reextracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The product was purified by short column chromatography over silica gel eluting with 10% ethyl acetate in benzene (60.8% yield).

Alternatively, N-Bromosuccinimide (1.068 g, 6.000 mmol) was added to a solution of 4-N-benzoyl-5'-pixyl-2'-pdeoxycytidine (2.938 g, 5.000 mmol) in dry pyridine (40 m*l*) at room temperature. After overnight (16 h), the products were poured into saturated $NaHCO_3$ solution (70 m*l*) and extracted with $CHCl_3$ (2×70 m*l*). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude yellowish product. The product was purified by short column chromatography over silica gel eluting with 3% ethanol in $CHCl_3$ (68.6% yield): R_f 0.68 (10% methanol in chloroform) ^{1}H-NMR (DMSO-d_6) δ 2.26-2.42(m, 2H, 2'-H), 3.02-3.20 (m, 2H, 5'-H), 3.92-4.04(m, 1H, 4'-H), 4.20-4.30(m, 1H, 3'-H), 5.24(m, 1H, 3'-H), 5.24(bs, 1H, 3'-OH), 6.08-6.20(t, 1H, 1'-H), 7.10-8.20(m, 18H, aromatic), 8.30(s, 1H, 6H), 12.80(bs, 1H, NH). Anal. Calcd. for $C_{34}H_{28}N_3O_6Br$: C, 62.39; H, 4.31; N, 6.43. Found: C, 62.43; H, 4.39; N, 6.40.

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References

1. S. Zamenhof, B. Reiner, R. De Giovanni, and K. Rich, *J. Biol. Chem.*, **219**, 165 (1956).
2. D. B. Dann and J. B. Smith, *Nature*, **174**, 305 (1954).
3. Shive and Skinner in *Ann. Rev. Biochem.*, 27, 643 (1958).
4. D. M. Frisch and D. W. Visser, *J. Am. Chem. Soc.*, **81**, 1756 (1959).
5. T. K. Fukuhara and D. W. Visser, *J. Am. Chem. Soc.*, **77**, 2393 (1955).
6. S. A. Narang, *Tetrahedron*, **39**, 3 (1983).
7. J. B. Chattopadhyaya and C. B. Reese, *J. C. S. Chem. Comm.*, 639 (1978).
8. B. J. Moon and K. L. Huh, *Bull. Korean Chem. Soc.*, **12**, 196 (1991).
9. B. J. Hunt and W. Rigby, *Chem. Ind (London)*, 1868 (1967).

Reduction of Disulfides to Thiols with Lithium Tris(dialkylamino)aluminum Hydrides

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Lithium tris(dialkylamino)aluminum hydrides[1], such as lithium tris(diethylamino)aluminum hydride (LTDEA), lithium tris(di-*n*-butylamino)aluminum hydride (LTDBA) and lithium tris(di-*n*-hexylamino)aluminum hydride (LTDHA), appear to be attractive selective reducing agents, especially in the conversion of carboxylic acid derivatives into the corresponding aldehydes[2]. In addition to that these reagents readily reduce both aliphatic and aromatic disulfides to the corresponding thiols without any evolution of hydrogen. Consequently, it is now possible to reduce disulfides under the practical con-