

Facile Chlorination of Sugar Moiety of Nucleosides
by Use of Tris(2,4,6-tribromophenoxy)dichlorophosphorane

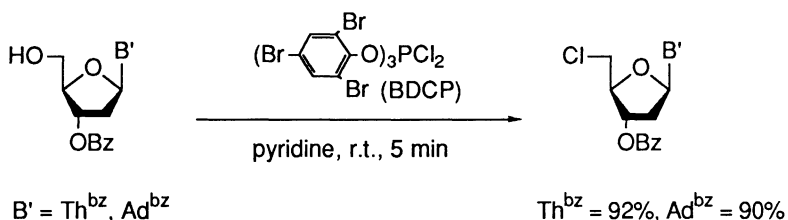
Shokichi OHUCHI, Ramendra K. SINGH, Takeshi WADA, and Tsujiaki HATA*

Department of Life Chemistry, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 227

A versatile chlorinating reagent, tris(2,4,6-tribromophenoxy)dichlorophosphorane was applied for 5'- and 3'-chlorination of nucleosides. It was found that the reaction proceeded via S_N2 mechanism.

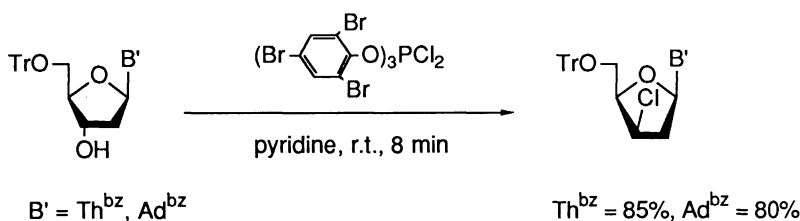
Recently, we have developed a new methodology for the synthesis of oligonucleotides by use of tris(2,4,6-tribromophenoxy)dichlorophosphorane (BDCP).^{1,2)} In the course of the experiment, BDCP converted successfully an appropriately protected 3'-phosphate into the corresponding nucleoside 3'-phosphorochloridate.¹⁾ But a small amount of an unidentified nucleoside derivative was detected. It seemed to be a halo-nucleoside. In order to clarify this side product, we have examined the reaction of BDCP with 5'-hydroxyl group of nucleosides.

In the first place, the reaction of 3-*N*, 3'-*O*-dibenzoylthymidine (300 mg, 0.67 mmol) with BDCP (554 mg, 1.21 mmol) in pyridine (10 ml) was carried out at room temperature for 5 min. After usual work-up, the product was purified by silica gel column chromatography. 5'-Chloro-5'-deoxy-3-*N*, 3'-*O*-dibenzoylthymidine was obtained in 92% yield (287 mg).³⁾ In a similar manner, 5'-chloro-5'-deoxy-6-*N*, 3'-*O*-dibenzoyldeoxyadenosine also was obtained from 6-*N*, 3'-*O*-dibenzoyldeoxyadenosine.⁴⁾ It was found that these reactions proceeded smoothly, compared with the oligonucleotide synthesis using BDCP via the phosphoryl chloride intermediate.¹⁾



Next, the reaction of 5'-*O*-trityl 3-*N*-benzoylthymidine and 5'-*O*-trityl 6-*N*-benzoyldeoxyadenosine with BDCP in pyridine were tested and gave the 3-*N*-benzoyl-1- β -(3'-chloro-2',3'-dideoxy-5'-*O*-tritylxylofuranosyl)-thymine and 6-*N*-benzoyl-9- β -(3'-chloro-2',3'-dideoxy-5'-*O*-tritylxylofuranosyl)adenine in good yield.^{5,7)} Their NOE spectra^{6,8)} showed that the chlorination proceeds via S_N2 reaction mechanism. Coe reported that the conversion of optically active alcohol to the halide by using a triphenoxydihalophosphorane also proceeded via S_N2 mechanism.⁹⁾ The reaction of 3'-hydroxyl group of nucleoside with BDCP might proceed via S_N2 type

conversion at the 3' position by an attack of chloride ion along with the formation of the tris(2,4,6-tribromophenyl) phosphate.



References

- 1) H. Hotoda, T. Wada, M. Sekine, and T. Hata, *Tetrahedron Lett.*, **28**, 1681 (1987); H. Hotoda, T. Wada, M. Sekine, and T. Hata, *Nucleic Acids Res.*, **17**, 5291 (1989).
- 2) T. Wada, H. Hotoda, M. Sekine, and T. Hata, *Tetrahedron Lett.*, **29**, 4143 (1988); T. Wada, H. Hotoda, M. Sekine, and T. Hata, *J. Org. Chem.*, **56**, 1243 (1991).
- 3) 5'-Chloro-5'-deoxy-3-*N*, 5'-*O*-dibenzoylthymidine; yield 92%; $R_f = 0.22$ (CH_2Cl_2 : hexane = 10 : 1); $^1\text{H-NMR}$ (270 MHz, CDCl_3): $\delta = 1.99$ (s, 3H, 5- CH_3), 2.35 - 2.46, 2.58 - 2.65 (m, 2H, 2'-H), 4.00 (dd, $J = 12.2$ and 21.1 Hz, 2H, 5'-H), 4.43 - 4.44 (m, 1H, 4'-H), 5.51 - 5.49 (m, 1H, 3'-H), 6.41 - 6.47 (m, 1H, 1'-H), 7.26 - 8.01 (m, 11H, Ar-H and 6-H of thymine).
- 4) 5'-Chloro-5'-deoxy-6-*N*, 3'-*O*-dibenzoyldeoxyadenosine; yield 90%; $R_f = 0.77$ (CH_2Cl_2 : CH_3OH = 20 : 1); $^1\text{H-NMR}$ (270 MHz, CDCl_3): $\delta = 1.84$ (br, 1H, 5'-OH), 2.63 - 2.70, 3.27 - 3.38 (m, 2H, 2'-H), 4.02 - 4.05 (m, 2H, 5'-H), 4.47 (s, 1H, 4'-H), 5.83 - 5.98 (m, 1H, 3'-H), 6.45 - 6.51 (m, 1H, 1'-H), 7.47 - 8.16 (m, 10H, Ar-H), 8.81 (s, 1H, 2-H of adenine), 9.12 (s, 1H, 8-H of adenine).
- 5) 3-*N*-Benzoyl-1- β -(3'-chloro-2',3'-dideoxy-5'-*O*-tritylxylofuranosyl)thymine; yield 85%; $R_f = 0.36$ (CH_2Cl_2 : hexane = 10 : 1); $^1\text{H-NMR}$ (270 MHz, CDCl_3): $\delta = 1.92$ (d, 3H, 5- CH_3), 2.39 - 2.45, 2.86 - 2.97 (m, 2H, 2'-H), 3.42 - 3.48, 3.68 - 3.75 (m, 2H, 5'-H), 4.29 - 4.34 (m, 1H, 4'-H), 4.46 - 4.49 (m, 1H, 3'-H), 5.96 - 6.42 (m, 1H, 1'-H), 7.26 - 8.00 (m, 21H, Ar-H and 6-H of thymine).
- 6) $^1\text{H-NMR}$ NOE showed that the compound was xylofuranosyl derivative of thymine; 1'-H to 2'-H (9%) and 4'-H, 2'-H to 1'-H (20%) and 3'-H (16%), 3'-H to 2'-H (7%) and 4'-H (9%), 4'-H to 1'-H (4%) and 3'-H (9%).
- 7) 6-*N*-Benzoyl-9- β -(3'-chloro-2',3'-dideoxy-5'-*O*-tritylxylofuranosyl)adenine; yield 80%; $R_f = 0.73$ (CH_2Cl_2 : CH_3OH = 20 : 1); $^1\text{H-NMR}$ (270 MHz, CDCl_3): $\delta = 2.73$ - 2.79, 2.93 - 3.18 (m, 2H, 2'-H), 3.37 - 3.47, 3.56 - 3.70 (m, 2H, 5'-H), 4.34 - 4.40 (m, 1H, 4'-H), 4.58 - 4.62 (m, 1H, 3'-H), 6.42 - 6.78 (m, 1H, 1'-H), 7.14 - 7.86 (m, 20H, Ar-H), 8.42 (s, 1H, 2-H of adenine), 8.63 (s, 1H, 8-H of adenine).
- 8) $^1\text{H-NMR}$ NOE showed that the compound was xylofuranosyl derivative of adenine; 1'-H to 2'-H (7%) and 4'-H (5%), 2'-H to 1'-H (34%) and 4'-H (13%), 3'-H to 2'-H (7%) and 4'-H (14%), 4'-H to 1'-H (11%) and 3'-H (11%).
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(Received May 20, 1992)