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Nucleoside Phosphite, *O*-Bis(1,1,1,3,3,3-hexafluoro-2-propyl) Deoxyribonucleosid-3'-yl Phosphites. A Versatile Synthetic Intermediate for Phosphonate Modified Nucleotide and Oligonucleotide Synthesis

Hideo HOSAKA, Hiroyuki NAKAMURA, Hidenori FUNAKOSHI, and Hiroshi TAKAKU*
Department of Industrial Chemistry, Chiba Institute of Technology, Tsudanuma, Narashino, Chiba 275

The *O*-bis(1,1,1,3,3,3-hexa-fluoro-2-propyl) deoxyribonucleosid-3'-yl phosphite units could be converted into the *O*-nucleosid-3'-yl phosphonate, *O*-2-cyanoethyl *O*-nucleosid-3'-yl phosphonate, and *O*-1,1,1,3,3,3-hexafluoro-2-propyl *O*-nucleosid-3'-yl phosphonothioate. The phosphite unit reacted with 3'-*O*-benzoylthymidine in the presence of MeIm to give the dithymidylate derivatives.

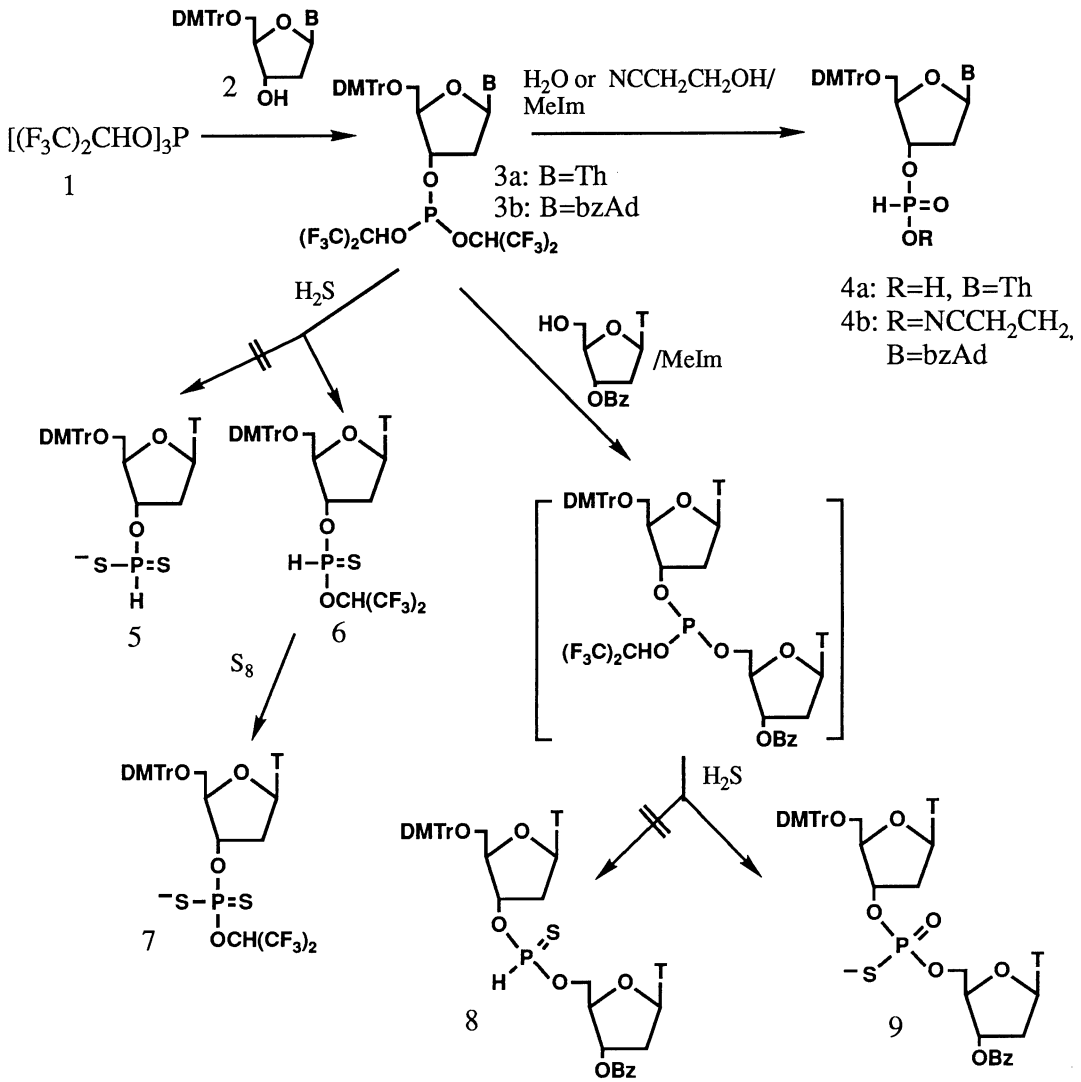
The *O*-nucleosidyl phosphonates have been frequently used for oligonucleotide synthesis.[1] They are useful intermediates for the preparation of several phosphate esters and their analogues. The internucleotidic phosphonate can be converted into the phosphate,[1] phosphoramidate,[2] alkylphosphonate,[3] phosphorothioate,[4] and phosphorodithioate.[5] These analogues have found to be applied to inhibitors of the translation of RNA into protein biosynthesis and potential anti-viral agents.[6-13]

Recently, we have described[14] bis(1,1,1,3,3,3-hexa-fluoro-2-propyl) phosphonate for the synthesis of deoxyribonucleosid-3'-yl phosphonates. Based upon the utility of 1,1,1,3,3,3-hexafluoro-2-propyl group, *O*-bis-(1,1,1,3,3,3-hexafluoro-2-propyl) deoxyribonucleosid-3'-yl phosphites (**3**)[15] were prepared and applied successfully to the synthesis of medium size oligodeoxyribonucleotides on a solid support.[16]

In this paper, we wish to report an efficient transformation of **3** to the phosphonate and several kinds of internucleotidic phosphate analogues.

First, we examined the preparation of 5'-*O*-dimethoxytritylthymidin-3'-yl phosphonate (**4a**) and *O*-2-cyanoethyl 5'-*O*-dimethoxytrityl-N^6-benzoyl-deoxyadenosin-3'-yl phosphonate (**4b**) from the corresponding *O*-bis-(1,1,1,3,3,3-hexafluoro-2-propyl) deoxyribonucleosid-3'-yl phosphites (**3**):

The phosphitylating reagent, tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite (**1**)[16] (1.1 mol equiv.) was treated with appropriately protected nucleosides (**2**) (1.0 mol equiv.) in CH_2Cl_2 at room temperature for 10 min, followed by treatment with H_2O or 2-cyanoethanol in the presence of N-methylimidazole (MeIm). After the usual work-up, silica gel chromatography was performed by use of CH_2Cl_2/MeOH (96:4). Compounds, **4a** (648 mg, 91%) and **4b**[17] (762 mg, 96%) were obtained, respectively. ^{31}P-NMR spectrum of **4b** showed that the 3'-3' linked side product and the decyanoethylated product from **4b** were not detected. These phosphonate units were known to be employed for the synthesis of oligodeoxyribonucleotides[1] and their analogues.[2-5]



When **3a** (521 mg, 1 mmol) was treated with a solution of dry H_2S saturated in THF for 30 min, the ^{31}P-NMR spectrum of the reaction mixture showed that the signal of **3a** completely disappeared and new signals were observed at 81.18 and 84.57 ppm. The chemical shift suggested that **3a** was not converted into the desired **5**[5a] (53.64 and 53.02 ppm) but into the corresponding phosphonothioate (**6**) and it was isolated in 89% (999 mg) yield after purification by silica gel chromatography. In order to prepare *O*-1,1,1,3,3,3-hexafluoro-2-propyl 5'-*O*-dimethoxytritylthymidine-3'-yl phosphorodithioate (**7**) we examined disulfurization reaction of **3**. The reaction mixture of **6** was treated in situ with 5% S_8 in CS_2/pyridine/triethylamine (45:45:10) for 2 h. After removal of solvent, a gummy substance was dissolved in ethyl acetate and washed with 1 M TEAB (pH 7.4). The desired compound **7** was isolated in 75% yield [946 mg; ^{31}P-NMR (85% H_3PO_4) 119.22 ppm] after purification by silica gel column chromatography. It was noteworthy that the phosphothionate (**6**) was not detected in the product by means of ^{31}P-NMR.

Further, we examined the synthesis of dinucleoside (3'-5') phosphonothioate (**8**)[5a,b] starting from **3a**. The phosphite (**3a**) (1.0 mole equiv.) was treated with 3'-*O*-benzoylthymidine (1.2 mole equiv.) in the presence of MeIm in dry CH_3CN at room temperature. After 10 min, the mixture was treated with a solution of dry H_2S saturated in THF for 30 min. After usual work-up involving extraction with CH_2Cl_2, coevaporation, and column chromatography, a colorless oily substance was obtained. To our surprise, ^{31}P-NMR analysis of the purified compound suggested the compound contained only one sulfur atom (56.89, 57.04 ppm). Based upon this data, we concluded that the structure of the compound should be assigned as the dinucleoside (3'-5') phosphorothioate (**9**)[5a,b] (85%). This reaction embraces the sulfurization and oxidation reactions occurring at the phosphorus atom.

In conclusion, the phosphite (**3**) described here is widely applicable to the synthesis of several kinds of phosphonate units and internucleotidic phosphate analogues.

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