

A FACILE CONVERSION OF DIALKYL PHOSPHONATES TO DIALKYL PHOSPHORODITHIOATES

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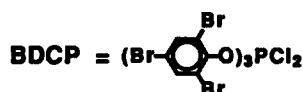
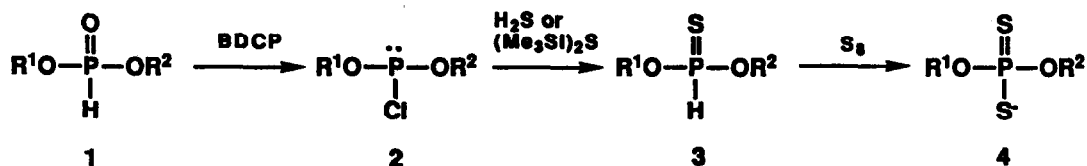
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SUMMARY: Dialkyl phosphonates were converted into the corresponding phosphorodithioates in three steps by one-pot procedure. The reaction was applied to the synthesis of nucleoside phosphorodithioate derivatives.

Oligonucleotides having phosphonate diester linkages are versatile intermediates for the synthesis of oligonucleotides and their analogues. The internucleotidic phosphonate linkages can be transformed into the phosphate¹, phosphorothioate², phosphoramidate^{2b}, acylphosphonate³, and alkylphosphonate⁴ linkages. However, transformation of the phosphonate diesters into the phosphorodithioates has not been reported. Recently, oligonucleotides having phosphorodithioate linkages were found to be stable against nucleases⁵ and applied to the inhibition of gene expression as antisense DNAs. Therefore, several methods for the synthesis of oligonucleotide phosphorodithioates have been proposed.⁶

Here, we report a facile conversion of dialkyl phosphonates **1** (phosphonate diesters) to dialkyl phosphorodithioates **4** as a model study for the synthesis of oligonucleotide phosphorodithioates.

Diethyl phosphonate **1a** (³¹P-NMR, 7.27 ppm, 13 μ l, 0.1 mmol) was converted into diethyl phosphorochloridite **2a** (166.24 ppm) in pyridine quantitatively using tris(2,4,6-tribromophenoxy)dichlorophosphorane (BDCP) as a chlorinating reagent.⁷ **2a** was treated with dry H₂S saturated THF for 5 min. ³¹P-NMR suggested the quantitative formation of diethyl phosphonothioate **3a**⁸ (69.65 ppm, *J*_{PH} = 648.4 Hz).



a; R¹ = R² = C₂H₅

b; R¹ = 5'-O-dimethoxytrityl-N³-benzoylthymidine-3'-yl,
R² = CH₃

Hexamethyldisilathiane was also an effective liquid reagent for the transformation of **2** to **3**. To a solution of **2a** in pyridine, hexamethyldisilathiane (210 μ l, 1.0 mmol) was added. After 5 min, quantitative formation of **3a** was observed by ^{31}P -NMR. In this reaction, diethyl *S*-trimethylsilyl phosphite was not detected. Resulting phosphonothioate **3a** was further treated with S_8 (5 equiv) in pyridine-water (98:2, v/v)⁹ for 1.5 h to give diethyl phosphorodithioate **4a** (114.22 ppm, pyridinium salt) in 98% yield.¹⁰

The reaction was applied to the synthesis of nucleotide derivatives. Methyl 5'-*O*-dimethoxytrityl-*N*³-benzoylthymidine-3'-yl phosphorochloridite **2b** (167.02 ppm, mmol), in situ prepared from the corresponding phosphonate **1b**^b (9.12 ppm, 73 mg, 0.1 mmol) and BDCP (164 mg, 0.15 mmol), was treated with hexamethyldisilathiane (105 μ l, 0.5 mmol) in pyridine for 5 min to afford the nucleoside 3'-phosphonothioate **3b** (72.46, 72.95 ppm, $J_{\text{PH}} = 664.2$ Hz). It was in situ treated with S_8 (5 equiv) in pyridine-water (98:2, v/v) for 2 h. The mixture was extracted with 0.5 M triethylammonium hydrogencarbonate and purified by preparative TLC, the nucleoside 3'-phosphorodithioate **4b** (117.71 ppm, 62 mg, triethylammonium salt) was obtained in 71% yield (based on **1b**).

REFERENCES AND NOTES

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- (9) The addition of water enhanced the sulfurization of **3a**. Hexamethyldisilathiane was hydrolyzed to generate H_2S and probably it was oxidized by air to form disulfide or polysulfide. It might act as a reagent for sulfurization. For instance, water was added to the mixture of **3a** and hexamethyldisilathiane in pyridine. After 2.5 h, 20% of **4a** was formed without addition of S_8 .
- (10) The yield was estimated by ^{31}P -NMR.