2-Cyanoethyl $N,N,N',N'$-Tetraisopropylphosphorodiamidite

Compiled by Jichao Zhang

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Introduction

2-Cyanoethyl $N,N,N',N'$-tetraisopropylphosphorodiamidite is a colorless viscous liquid, which is soluble in most organic solvents. It is a widely used phosphitylating reagent for the preparation of various phosphorylated biomolecules, such as nucleoside carbohydrate conjugates, phospholipids and glycopeptides. In particular, this reagent is highly effective for automated solid-phase DNA/RNA oligonucleotide synthesis.

2-Cyanoethyl $N,N,N',N'$-tetraisopropylphosphorodiamidite has shown great utility in the coupling of nucleobases or carbohydrates via their phosphotriesters in the presence of activators such as $1H$-tetrazole, in moderate yields under mild conditions. Additionally, 2-cyanoethyl $N,N,N',N'$-tetraisopropylphosphorodiamidite is cheaper and more stable than 2-cyanoethyl $N,N$-diisopropylchlorophosphorodiamidite, the other commonly used phosphinylating reagent.

2-Cyanoethyl $N,N,N',N'$-tetraisopropylphosphorodiamidite is commercially available but can also be prepared in an inexpensive manner using a two-step, one-pot procedure and purified by vacuum distillation (Scheme 1).

Abstracts

(A) 2-Cyanoethyl-$N,N,N',N'$-tetraisopropylphosphorodiamidite was used by Sheppard and co-workers to prepare carbohydrate phosphoramidites as nucleoglycoconjugate building blocks in good yield in the presence of diisopropylammonium tetrazolide under anhydrous conditions. Then, the monosaccharide phosphoramidite was coupled with DNA oligonucleotides by solid-phase chemistry.

(B) Recently, Yamada and co-workers used 2-cyanoethyl $N,N,N',N'$-tetraisopropylphosphorodiamidite to synthesize the uridine $3'$-phosphoramidite building block in good yield with diisopropylammonium tetrazolide as a catalyst under anhydrous conditions, for developing oligonucleotides containing new $2'$-O-modified ribonucleosides as nucleic acid based drugs.
(C) Lin and colleagues used 2-cyanoethyl N,N,N′,N′-tetraisopropylphosphorodiamidite as the phosphinylation reagent in the presence of disopropylammonium tetrazolide to couple with 2′,3′-di-O-acetyl adenosine to generate boron-containing ADP analogues. A 5-O-protected diol was firstly reacted with the phosphinylation reagent and 1H-tetrazole as an activator at room temperature, followed by oxidation, generating cyclic phosphate triester diastereoisomers in high yield.

(D) Smith and co-workers developed an efficient method to prepare aldose phosphate diesters using 2-cyanoethyl N,N,N′,N′-tetraisopropylphosphorodiamidite. A 5-O-protected diol was firstly reacted with the phosphinylation reagent and 1H-tetrazole as an activator at room temperature, followed by oxidation, generating cyclic phosphate triester diastereoisomers in high yield.

(E) 2-Cyanoethyl- N,N,N′,N′-tetraisopropylphosphorodiamidite was used to prepare glycoconjugate polymers which carry GGPL analogues, bioactive segments of main cell membrane glycolipids of Mycoplasma fermentas. Therein, Nishida and co-workers reacted 4-nitrophenyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside with 2-cyanoethyl N,N,N′,N′-tetraisopropylphosphorodiamidite in the presence of 1H-tetrazole, then reacted with choline tosylate, followed by oxidation and removal of the cyanoethyl group, generating 4-nitrophenyl 2,3,4-tri-O-benzyl-6-O phosphorycholine-α-D-glucopyranoside (in an overall 54% yield).

(F) Rodriguez and co-workers reported the synthesis of glucose nucleoside conjugates as anti-HIV prodrugs by using 2-cyanoethyl N,N,N′,N′-tetraisopropylphosphorodiamidite as the phosphinylation reagent. Glucosyl phosphoramidite was firstly prepared in the presence of pyridinium trifluoroacetate under anhydrous conditions, and then coupled with nucleosides generating the desired compounds.

References


(8) Smith, J. M.; Borsenberger, V.; Raftery, J.; Sutherland, J. D. Chem. Biodiv. 2004, 1, 1418.
