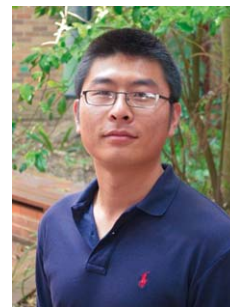


SYNLETT Spotlight 420

2-Cyanoethyl *N,N,N',N'*-Tetraisopropylphosphorodiamidite

Compiled by Jichao Zhang



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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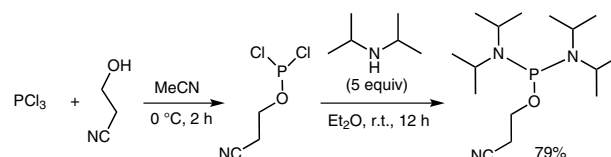
Introduction

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.¹ In particular, this reagent is highly effective for automated solid-phase DNA/RNA oligonucleotide synthesis.²

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 1*H*-tetrazole, in moderate yields under mild conditions.^{1,2} Additionally, 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite is cheaper and more stable than 2-cyanoethyl *N,N*-diisopropyl-

chlorophosphorodiamidite, the other commonly used phosphitylating reagent.³

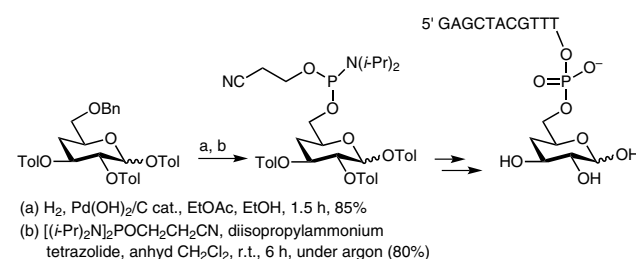
2-Cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite is commercially available but can also be prepared in an inexpensive manner using a two-step, one-pot procedure and purified by vacuum distillation (Scheme 1).⁴



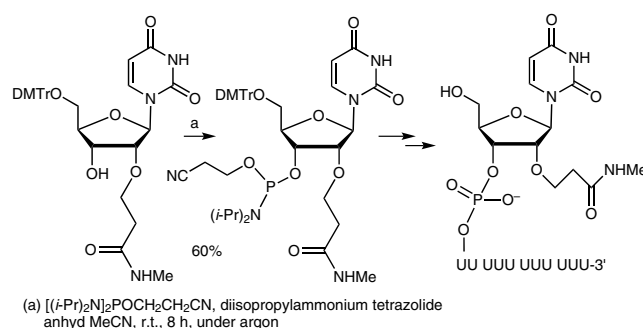
Scheme 1 Synthesis of 2-cyanoethyl 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite

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 tetrazolidine under anhydrous conditions. Then, the monosaccharide phosphoramidite was coupled with DNA oligonucleotides by solid-phase chemistry.⁵



(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 tetrazolidine as a catalyst under anhydrous conditions, for developing oligonucleotides containing new 2'-*O*-modified ribonucleosides as nucleic acid based drugs.⁶



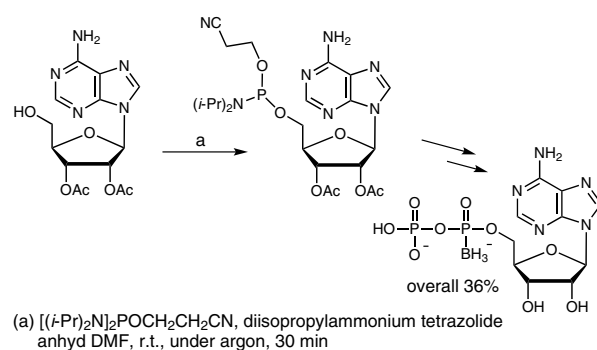
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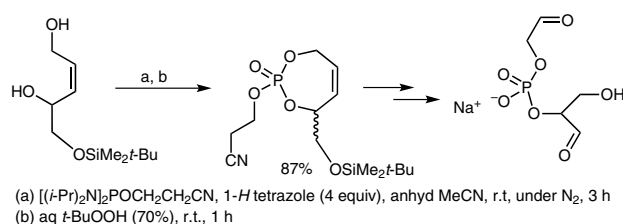
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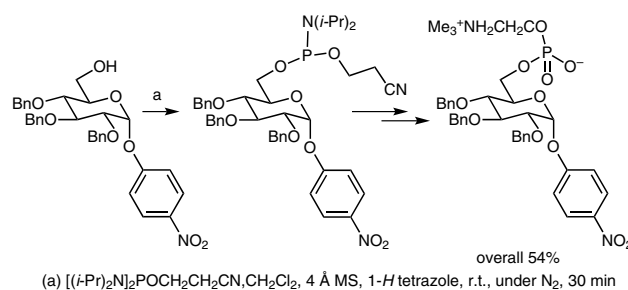
(C) Lin and colleagues used 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite as the phosphinylating reagent in the presence of diisopropylammonium tetrazolide to couple with 2',3'-di-*O*-acetyladenosine to generate boron-containing ADP analogues (in an overall yield of 36%).⁷



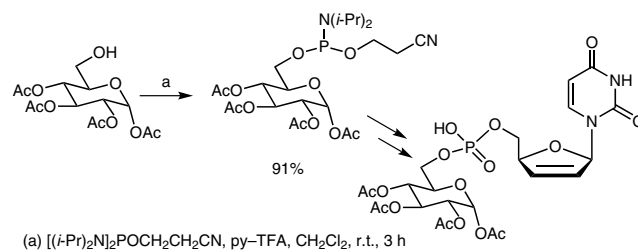
(D) Smith and co-workers developed an efficient method to prepare aldose phosphate diesters using 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite.⁸ A 5-*O*-protected diol was firstly reacted with the phosphinylating reagent and 1*H*-tetrazole as an activator at room temperature, followed by 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-workers⁹ reacted 4-nitrophenyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside with 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite in the presence of 1*H*-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*-phosphorylcholine- α -D-glucopyranoside (in an overall 54% yield).



(F) Rodríguez 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 phosphinylating reagent.¹⁰ Glucosyl phosphoramidite was firstly prepared in the presence of pyridinium trifluoroacetate under anhydrous conditions, and then coupled with nucleosides generating the desired compounds.



References

- (1) (a) Anraku, K.; Inoue, T.; Sugimoto, K.; Kudo, K.; Okamoto, Y.; Morii, T.; Mori, Y.; Otsuka, M. *Bioorg. Med. Chem.* **2011**, *19*, 6833. (b) Hada, N.; Shida, Y.; Shimamura, H.; Sonoda, Y.; Kasahara, T.; Sugita, M.; Takeda, T. *Carbohydr. Res.* **2008**, *343*, 2221. (c) Steven, V.; Graham, D. *Org. Biomol. Chem.* **2008**, *6*, 3781.
- (2) (a) Hentschel, S.; Alzeer, J.; Angelov, T.; Scharer, O. D.; Luedtke, N. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 3466. (b) Münzel, M.; Lischke, U.; Stathis, D.; Pfaffeneder, T.; Gnerlich, F. A.; Deiml, C. A.; Koch, S. C.; Karaghiosoff, K.; Carell, T. *Chem.-Eur. J.* **2011**, *17*, 13782. (c) Seio, K.; Kurohagi, S.; Kodama, E.; Masaki, Y.; Tsunoda, H.; Ohkubo, A.; Sekine, M. *Org. Biomol. Chem.* **2012**, *10*, 994.
- (3) (a) Pedersen, D. S.; Rosenbohm, C.; Koch, T. *Synthesis* **2002**, 802. (b) Sanghvi, Y. S.; Guo, Z. Q.; Pfundheller, H. M.; Converso, A. *Org. Process Res. Dev.* **2000**, *4*, 175.
- (4) Ching, S. M.; Tan, W. J.; Chua, K. L.; Lam, Y. *Bioorg. Med. Chem.* **2010**, *18*, 6657.
- (5) Sheppard, T. L.; Wong, C.-H.; Joyce, G. F. *Angew. Chem. Int. Ed.* **2000**, *39*, 3660.
- (6) Yamada, T.; Okaniwa, N.; Saneyoshi, H.; Ohkubo, A.; Seio, K.; Nagata, T.; Aoki, Y.; Takeda, S.-i.; Sekine, M. *J. Org. Chem.* **2011**, *76*, 3042.
- (7) Lin, J.; He, K.; Ramsay Shaw, B. *Helv. Chim. Acta* **2000**, *83*, 1392.
- (8) Smith, J. M.; Borsenberger, V.; Raftery, J.; Sutherland, J. D. *Chem. Biodiv.* **2004**, *1*, 1418.
- (9) Nishida, Y.; Takamori, Y.; Matsuda, K.; Ohru, H.; Yamada, T.; Kobayashi, K. *J. Carbohydr. Chem.* **1999**, *18*, 985.
- (10) Rodríguez-Pérez, T.; Fernández, S.; Sanghvi, Y. S.; Detorio, M.; Schinazi, R. F.; Gotor, V.; Ferrero, M. *Bioconjugate Chem.* **2010**, *21*, 2239.