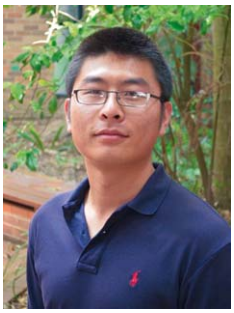
SYNLETT
Spotlight 420

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

2-Cyanoethyl *N,N,N′,N′*-Tetraisopropylphosphorodiamidite

Compiled by Jichao Zhang



Jichao Zhang was born in Dalian, Liaoning Province, P. R. of China. He graduated from Shenyang Pharmaceutical University and received a B.E. in pharmaceutical engineering. Currently, he is working under the supervision of Dr. Danielle Skropeta in Organic and Medicinal Chemistry at the University of Wollongong, Australia, towards his M.Sc. (research) degree and will start his PhD afterwards. His research interests focus on the development of glycosyltransferase inhibitors as anticancer agents.

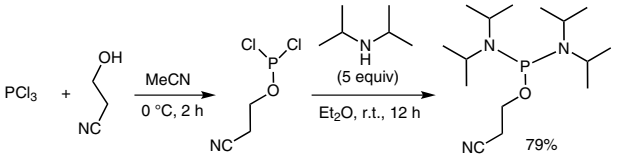
School of Chemistry and Centre for Medicinal Chemistry, University of Wollongong, Wollongong 2522, NSW, Australia
E-mail: jz417@uowmail.edu.au

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*-diisopropylchlorophosphorodiamidite, the other commonly used phosphinylating reagent.[3]

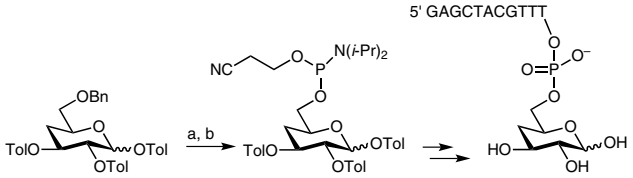
2-Cyanoethyl *N,N,N′,N′*-tetraisopropylphosphorodiamidite is commercially available but can also be prepared in an inexpensive manner using a two-step, one-pot procedure and purified by vacuum distillation (Scheme 1).[4]



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

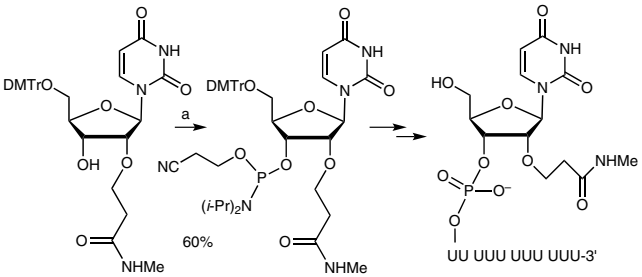
Abstracts

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



(a) H_2, $Pd(OH)_2$/C cat., EtOAc, EtOH, 1.5 h, 85%
(b) $[(i\text{-}Pr)_2N]_2POCH_2CH_2CN$, diisopropylammonium tetrazolide, anhyd CH_2Cl_2, r.t., 6 h, under argon (80%)

(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.[6]

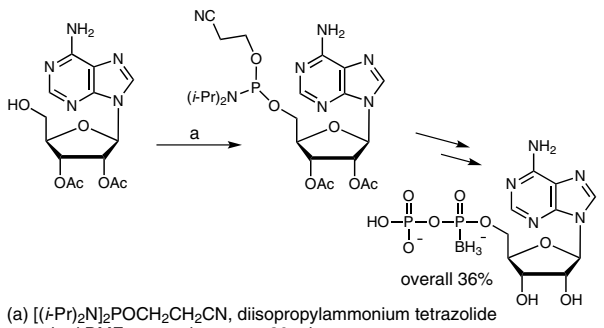


(a) $[(i\text{-}Pr)_2N]_2POCH_2CH_2CN$, diisopropylammonium tetrazolide anhyd MeCN, r.t., 8 h, under argon

SYNLETT 2013, 24, 0266–0267
Advanced online publication: 19.12.2012
DOI: 10.1055/s-0032-1317955; Art ID: ST-2012-V0430-V
© Georg Thieme Verlag Stuttgart · New York

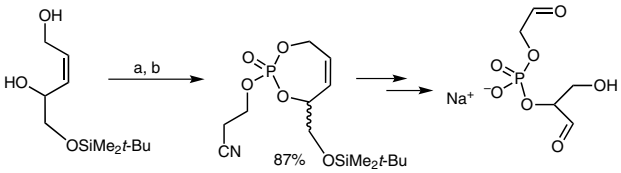
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(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]



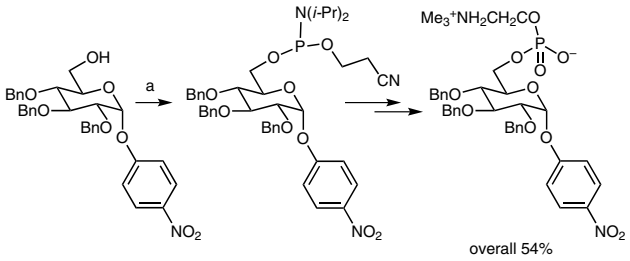
(a) $[(i\text{-Pr})_2N]_2POCH_2CH_2CN$, diisopropylammonium tetrazolide anhyd DMF, r.t., under argon, 30 min

(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.



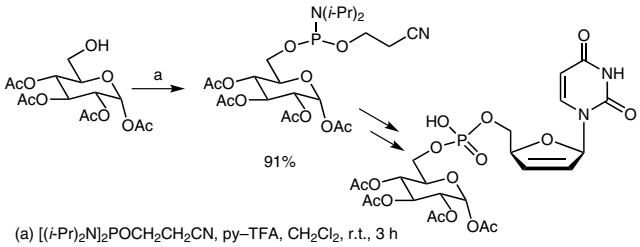
(a) $[(i\text{-Pr})_2N]_2POCH_2CH_2CN$, 1-*H* tetrazole (4 equiv), anhyd MeCN, r.t, under N_2, 3 h
(b) aq *t*-BuOOH (70%), r.t., 1 h

(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[9] 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).



(a) $[(i\text{-Pr})_2N]_2POCH_2CH_2CN,CH_2Cl_2$, 4 Å MS, 1-*H* tetrazole, r.t., under N_2, 30 min

(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 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.



(a) $[(i\text{-Pr})_2N]_2POCH_2CH_2CN$, py–TFA, CH_2Cl_2, r.t., 3 h

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.; Ohrui, 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.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.