

This article was downloaded by:

On: 26 January 2011

Access details: Access Details: Free Access

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

2-Cyanoethyl *H*-Phosphonate. A Reagent for the Mild Preparation of Nucleoside *H*-Phosphonate Monoesters

Tomas Szabó^a; Helena Almer^a; Roger Strömberg^a; Jacek Stawinski^a

^a Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden

To cite this Article Szabó, Tomas , Almer, Helena , Strömberg, Roger and Stawinski, Jacek(1995) '2-Cyanoethyl *H*-Phosphonate. A Reagent for the Mild Preparation of Nucleoside *H*-Phosphonate Monoesters', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 715 – 716

To link to this Article: DOI: 10.1080/15257779508012456

URL: <http://dx.doi.org/10.1080/15257779508012456>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

2-CYANOETHYL *H*-PHOSPHONATE. A REAGENT FOR THE MILD
PREPARATION OF NUCLEOSIDE *H*-PHOSPHONATE MONOESTERS

Tomas Szabó, Helena Almer, Roger Strömberg and Jacek Stawinski*

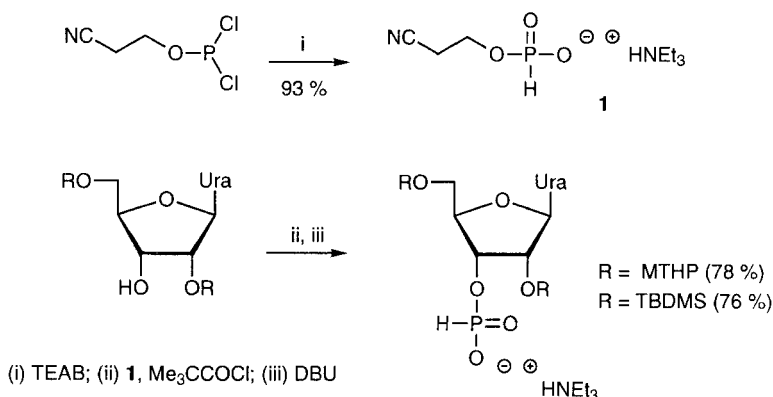
Department of Organic Chemistry, Arrhenius Laboratory,
Stockholm University, S-106 91 Stockholm, Sweden

Abstract. 2-Cyanoethyl *H*-phosphonate was condensed with protected nucleoside derivatives and the cyanoethyl group subsequently removed by anhydrous base to give the corresponding nucleoside *H*-phosphonate in good yield.

Chemical synthesis *via H*-phosphonate intermediates has proven to be a reliable route to oligonucleotides and some of their analogs.¹ The required monomeric building blocks are most commonly prepared from reactive trivalent phosphorus compounds, e.g., phosphorus triazolides or salicylchlorophosphite. Normally, the large excess of phosphorus triazolidine used to avoid diester formation in the phosphitylation reaction, is removed by aqueous extraction during work-up. When working with hydrophilic nucleoside *H*-phosphonates, this extraction step may cause problems since efficient silica gel chromatography of the product usually necessitates complete extractive removal of phosphonic acid and azoles, which in turn may lead to some loss of the product.

Here we describe the preparation of nucleoside *H*-phosphonate monoesters *via* neutral diester intermediates. A protected nucleoside derivative is condensed with 2-cyanoethyl *H*-phosphonate using normal *H*-phosphonate methodology, the diester isolated by extraction, and the 2-cyanoethyl group eliminated with DBU in MeCN. After ion-exchange and silica gel chromatography the desired nucleoside *H*-phosphonate monoesters are obtained in good yields. The synthetic steps are summarized in Scheme 1.

The title reagent has previously been used for the introduction of terminal 5'-phosphates in solid phase DNA synthesis² and as a capping reagent.³ Nucleoside *H*-



SCHEME 1

phosphonate monoesters have been prepared by elimination of the 2-cyanoethyl derivative which was prepared by hydrolysis of the corresponding amidite.⁴

2-Cyanoethyl *H*-phosphonate triethylammonium salt. 2-Cyanoethyl phosphorodichloridite⁵ (25 mL, 0.20 mol) was added dropwise over a period of 1 h to cold triethylammonium bicarbonate (2 M, 400 mL). The reaction mixture was evaporated *in vacuo* and triethylammonium chloride removed by triturating the residue with cold MeCN (3 × 400 mL), filtration and evaporation of the organic layer. 2-Cyanoethyl *H*-phosphonate triethylammonium salt was obtained as a viscous oil (44 g, 93 %) and stored as a 0.5 M solution in MeCN. δ_P (MeCN) 2.18 ppm, $^1J_{PH}$ 604 Hz, $^3J_{PH}$ 8.5 Hz

Nucleoside *H*-phosphonate monoesters. A protected nucleoside (1.0 mmol) and 2-cyanoethyl *H*-phosphonate (0.5 M, 1.3 mmol) were mixed and dried by evaporation of added pyridine, dissolved in pyridine (10 mL) and pivaloyl chloride (4.0 mmol) added. After stirring for 15 min the reaction mixture was partitioned between CHCl₃ (2 × 50 mL) and aqueous NaHCO₃ (50 mL), the organic layer dried (Na₂SO₄) and evaporated *in vacuo*. The oily residue was dissolved in MeCN (10 mL) and DBU (1.4 mmol) added. After stirring for 15 min, the reaction mixture was applied on an ion-exchange column (triethylammonium form) and eluted with MeCN. Evaporation followed by silica gel chromatography (CHCl₃-MeOH-Et₃N, 995:0:5 to 835:160:5) afforded the monoesters as white foams.

REFERENCES

- (1) Stawinski, J. In *Handbook of Organophosphorus Chemistry*; R. Engel, Ed.; Marcel Dekker, Inc.: New York, 1992; pp 377-434.
- (2) Venijaminova, A.G.; Levina, A.S.; Repkova, M.N.; Chentsova, N.A. *Bioorg. Khim.* **1989**, *15*, 844-846.
- (3) Gaffney, B.L.; Jones, R.A. *Tetrahedron Lett.* **1988**, *29*, 2619-2622.
- (4) Garegg, P.J.; Regberg, T.; Stawinski, J.; Strömberg, R. *Chem. Scripta* **1985**, *25*, 280-282.
- (5) Nagai, H.; Fujiwara, T.; Fujii, M.; Sekine, M.; Hata, T. *Nucleic Acids Res.* **1989**, *17*, 8581-8593.