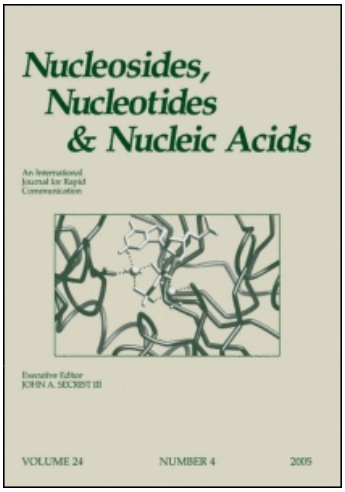

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2-Cyanoethyl *H*-Phosphonate. A Reagent for the Mild Preparation of Nucleoside *H*-Phosphonate Monoesters

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

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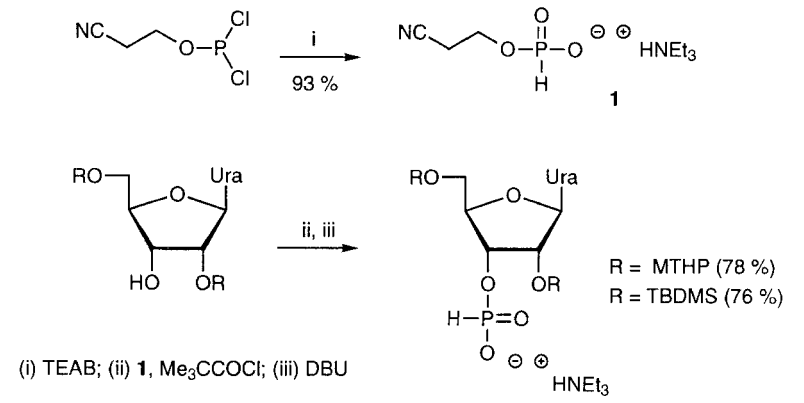
Abstract. 2-Cyanoethyl *H*-phosphonate was condensed with protected nucleoside derivatives and the cyanoethyl group subsequently removed by anhydrous base to give the corresponding nucleoside *H*-phosphonate in good yield.

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 trisazolide 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 synthesis[2] 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 phosphorodichloridite[5] (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 $CHCl_3$ (2 × 50 mL) and aqueous $NaHCO_3$ (50 mL), the organic layer dried (Na_2SO_4) 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 ($CHCl_3$-MeOH-Et_3N, 995:0:5 to 835:160:5) afforded the monoesters as white foams.

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