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Nucleoside H-phosphonates. Part 19: Novel nucleotide analogues—H-phosphonoselenoate mono- and diesters

Martin Bollmark,[a] Martin Kullberg[a] and Jacek Stawinski[a,b,*]

[a]*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden*
[b]*Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland*

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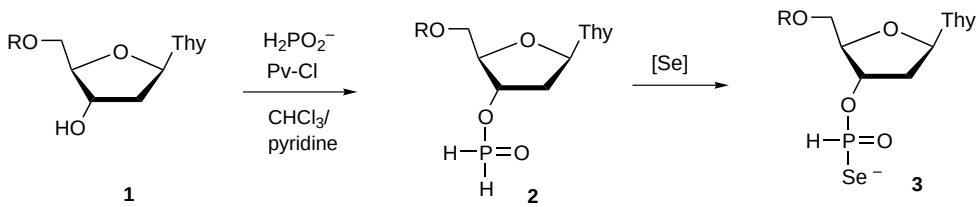
Abstract—Efficient protocols for the preparation of novel synthetic intermediates, H-phosphonoselenoate monoesters and the corresponding dinucleoside H-phosphonoselenoate diesters, have been developed.

Despite the well-documented role of phosphoroselenoates in the metabolism of selenium-containing compounds,[1] selenophosphorus derivatives have received relatively little attention and their structural variations are almost exclusively confined to P(V) compounds.[2]

Since most synthetically useful methods for the preparation of selenophosphates rely on an oxidative conversion of P(III) to P(V) compounds using electrophilic selenium,[3,4] we searched for an alternative methodology utilizing as a starting material selenophosphorus compounds at a lower oxidation state. This would provide an alternative way for preparing selenophosphate derivatives and permit the synthesis of novel selenophosphate analogues, not accessible via traditional methods.

For this purpose we embarked on the exploration of H-phosphonoselenoates as new types of synthetic intermediates bearing selenium bound to a phosphorus(III) atom. This distinctive feature of H-phosphonoselenoates should enable further oxidative transformations at the phosphorus center that could be exploited in the synthesis of new phosphate analogues.

H-Phosphonoselenoate monoesters are an entirely unknown class of compounds and for the preparation of the corresponding diesters only two methods are described in the literature. One of these consists of treatment of dialkyl chlorophosphites with hydrogen selenide[5] and the other one involves reduction of 2-chloro-4-methyl-1,3,2-dioxaphosphinane (a chlorophosphite) with tri-*n*-butyl tin hydride to produce the corresponding phosphonite, followed by its oxidation with selenium.[6] Unfortunately, these approaches do not appear to be general or applicable to natural product derivatives, and this may explain why H-phosphonoselenoates have for a long time remained as a largely unexplored class of phosphorus compounds.



R = 4,4'-dimethoxytrityl; Thy= thymin-1-yl

Scheme 1.

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* Corresponding author. E-mail: js@organ.su.se

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To elaborate a comprehensive methodology for utilizing H-phosphonoselenoates as synthetic intermediates we set out to develop general methods for the preparation of H-phosphonoselenoate monoesters and for their efficient conversion into H-phosphonoselenoate diesters.

As a viable synthetic route to H-phosphonoselenoate monoesters (e.g. nucleoside 3′-H-phosphonoselenoate **3**, Scheme 1) we considered selenization of phosphinate intermediates **2**, analogously to sulfurization during the preparation of H-phosphonothioate monoesters.[7] Since alcohols can be efficiently converted in situ into the corresponding phosphinate esters, this approach might provide a convenient access to H-phosphonoselenoates of type **3**.

The generation of nucleoside phosphinate **2** ($\delta_P = 14.22$ ppm, $^1J_{PH} = 572$ Hz, $^3J_{PH} = 9.8$ Hz, td) in pyridine from the corresponding nucleoside **1** (1.5 equiv.) and triethylammonium phosphinate in the presence of pivaloyl chloride (1.5 equiv.) was uneventful and proceeded in virtually quantitative yield as revealed by ^{31}P NMR spectroscopy. However, the next step, selenization of the produced phosphinate **2**, required considerable experimentation to develop the best conditions of solvents and reagents.[8] In pyridine, the formation of H-phosphonoselenoate **3** ($\delta_P = 48.2$ and 47.2 ppm, $^1J_{PH} = 564$ and 569 Hz, $^1J_{PSe} = 713$ and 713 Hz) was rather slow (3–4 h) and its amount in the reaction mixture did not exceed 30–40%. The ^{31}P NMR spectra usually revealed the generation of significant amounts of selenophosphonic acid, H-phosphonate mono- and H-phosphonate diesters (total 60–70%), probably due to the competing selenization of the phosphinate salt and high propensity of phosphinates **2** for disproportionation. Sonication of the reaction mixture shortened the reaction time to ca. 30 min but without noticeable changes in product distribution. However, decreasing the amount of pyridine in the reaction mixtures by adding various co-solvents (chloroform, acetonitrile, toluene) tended to suppress some side-product formation. Unfortunately, the reaction become rather slow (overnight) and more side-products were formed as the reaction approached completion. Eventually, the reaction in chloroform in the presence of pyridine (2 equiv.) and triethylamine (2 equiv.), led to a reasonably fast (4 h) and clean (ca. 80%, ^{31}P NMR) formation of H-phosphonoselenoate **3**. These conditions, when applied on a preparative scale, afforded product **3** in 45–60% isolated yield (vide infra).

We also assessed other selenizing reagents for the conversion of phosphinate intermediate **2** into H-phosphonoselenoate **3**. 3*H*-1,2-Benzothiaselenol-3-one[4,9] and potassium selenocyanate,[10] somewhat unexpectedly, did not produce any H-phosphonoselenoate **3** but mixtures of the corresponding symmetrical phosphoroselenoates and H-phosphonate monoesters (^{31}P NMR spectroscopy). However, using triphenylphosphine selenide[11] (TPPSe) in combination with trimethylsilyl chloride, furnished clean and fast selenization of phosphinate intermediate **2** (see Method B below). This protocol has the advantage that selenization occurs under homogenous conditions and the purification of nucleoside H-phosphonoselenoate **3** (ca. 80% yield) does not require additional reverse-phase chromatography.

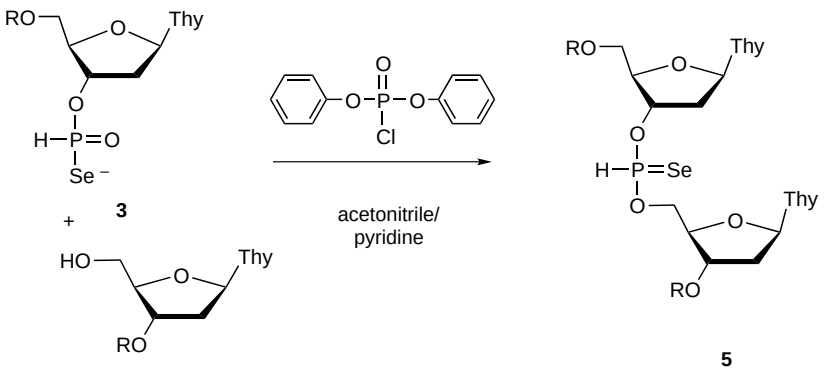
For the synthesis of H-phosphonoselenoate diester **5**, first we tried the reaction conditions developed previously for their thio congeners.[12] To this end, nucleoside H-phosphonoselenoate **3** and a suitably protected nucleoside **4** (1.2 equiv.) in acetonitrile–pyridine (4:1, v/v) were treated with diphenyl phosphorochloridate (DPCP, 2.5 equiv.). The reaction was rapid (<5 min, ^{31}P NMR), completely chemoselective, and produced the desired dinucleoside H-phosphonoselenoate diester **5** ($\delta_P = 76.0$ and 75.3 ppm, $^1J_{PH} = 653$ and 657 Hz) practically quantitatively.[13] However, isolation of **5** posed certain problems. Firstly, excess hydroxylic component **4** was difficult to remove by silica gel chromatography and, secondly, H-phosphonoselenoate **5** appeared to hydrolyze partly during work-up. To overcome these difficulties, we used a slight excess of the nucleotidic component **3** to ensure that all nucleoside **4** was consumed during the coupling, and to increase the hydrolytic stability of product **5** during work-up, we reduced the amount of pyridine used for the reaction.

The efficacy of these new reaction conditions was assessed by carrying out the condensation of nucleoside H-phosphonoselenoate **3** (1.2 equiv.) with nucleosidic component **4** (1.0 equiv.) in acetonitrile containing pyridine (5 equiv.) using DPCP (2.5 equiv.) (Scheme 2). The reaction turned out to be only slightly slower than that when more pyridine was used (completed within 10 min) and produced cleanly, dinucleoside H-phosphonoselenoate **5**. As expected, **5** obtained in this way was more stable during work-up and could be isolated by silica gel chromatography in ca. 80% yield (vide infra).

In conclusion, we have developed efficient and simple methods for the preparation of nucleoside H-phosphonoselenoate monoesters and their conversion into nucleoside H-phosphonoselenoate diesters. Since the presence of the H-P=Se functionality can be exploited in various oxidative transformations, the easy access to H-phosphonoselenoates will expand and complement the present H-phosphonate and H-phosphonothioate methodologies for the preparation of biologically important phosphate analogues.[14] Further studies are in progress in this laboratory.

Typical protocol for the preparation of nucleoside H-phosphonoselenoate 3

Method A: Anhydrous nucleoside **1** (1.5 equiv.) and triethylammonium phosphinate (1.0 mmol) were dissolved in chloroform (16 ml) containing pyridine (2 equiv.). Elemental selenium (3.0 equiv.) and pivaloyl chloride (1.5 equiv.) were then added and, after 10 min, triethylamine (2.0 equiv.). The mixture was stirred for ca. 4 h and, after excess selenium was filtered off, the product was purified by silica gel chromatography



R = 4,4-dimethoxytrityl; Thy= thymin-1-yl

Scheme 2.

using a stepwise gradient of methanol (0–4%) in dichloromethane containing 0.1% triethylamine. The product was often contaminated by symmetrical nucleoside phosphoroselenoate and phosphorodiselenoate diesters (ca. 5%), and to remove these impurities, reverse-phase silica gel chromatography using a stepwise gradient of acetone in water was necessary. After precipitation with pentane, H-phosphonoselenoate **3** (ca. 1:1 mixture of the two diastereomers, triethylammonium salt) was obtained as an off-white powder. Yield 45–60% (purity >98%, ^{1}H NMR spectroscopy). HRMS $[M]^+$ found: 717.0860. $C_{31}H_{32}N_2Na_2O_8PSe$ requires: 717.0857. ^{31}P NMR ($CDCl_3$, δ in ppm) 48.1 ($^1J_{PH}=564$ Hz, $^3J_{PH}=12.2$ Hz, dd; $^1J_{PSe}=713$ Hz) and 47.1 ($^1J_{PH}=569$ Hz, $^3J_{PH}=12.8$ Hz, dd; $^1J_{PSe}=713$ Hz). Selected spectroscopic data: ^{1}H NMR ($CDCl_3$, δ in ppm) 8.69 and 8.62 (2d, $^1J_{PH}=565$ and 569 Hz, 1H, P-H), 6.46 (m, 1H, H1′), 5.42 (m, 1H, H3′); ^{13}C NMR ($CDCl_3$, δ in ppm) 76.74 and 76.13 (2d, $J=5.0$ Hz, C3′)

Method B: Nucleoside phosphinate intermediate **2** was generated in situ by reacting anhydrous nucleoside **1** (1.5 equiv.) with triethylammonium phosphinate (1.0 mmol) in chloroform–pyridine (16 ml, 3:1 v/v) in the presence of pivaloyl chloride (1.5 equiv.). Selenization was carried out by adding (after 10 min) triphenylphosphine selenide (2 equiv.) and trimethylsilyl chloride (3 equiv.). After 15 min the mixture was partitioned between satd aq. $NaHCO_3$ (50 mL) and dichloromethane (150 mL). Product **3** (triethylammonium salt) was isolated as described in Method A. In this instance no reverse-phase silica gel chromatography was necessary. Yield, 80% (purity >98%, ^{1}H NMR spectroscopy). Compound **3** obtained in this way was identical to that synthesized by Method A.

Typical protocol for the preparation of dinucleoside H-phosphonoselenoate 5

H-Phosphonoselenoate **3** (triethylammonium salt, 0.1 mmol) and nucleoside **4** (0.09 mmol) were dissolved in acetonitrile (4 mL) containing pyridine (0.5 mmol), and diphenyl chlorophosphate (0.25 mmol) was added. After ca. 10 min (TLC analysis) the reaction was quenched with saturated sodium chloride (1 mL) and partitioned between toluene (2×50 mL) and brine (20 mL). The organic phase was dried, the solvent evaporated and the residue was purified on a silica gel column using ethyl acetate–toluene (1:1, v/v) containing 0.02% triethylamine.

Compound **5** (ca. 1:1 mixture of diastereomers) was isolated in 81% yield as a white foam (purity >98%, ^{1}H NMR spectroscopy). HRMS $[M]^+$ found: 1221.3145. $C_{62}H_{63}N_4NaO_{14}PSe$ requires: 1221.3141. ^{31}P NMR ($CDCl_3$, δ in ppm) 74.8 ($^1J_{PH}=648$ Hz, $^3J_{PH}=10.6$ Hz, dq; $^1J_{PSe}=877$ Hz) and 76.7 ($^1J_{PH}=644$ Hz, $^3J_{PH}=10.6$ Hz, dq; $^1J_{PSe}=879$ Hz). Selected spectral data: ^{1}H NMR ($CDCl_3$, δ in ppm) 6.40 and 6.35 (m, 1H, H_a1'), 6.32 and 6.23 (m, 1H, H_b1'), 5.52 (dd, 1H, H_a3'), 4.26 and 4.20 (d, 1H, H_b3'); ^{13}C NMR ($CDCl_3$, δ in ppm) 78.96 and 78.38 (2d, $J=5.0$ Hz, C3′-OP).

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