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New examples of mixed seleno-sulfides; reactions with triphenylphosphine

Arkadiusz Chworoś, Lucyna A. Woźniak and Wojciech J. Stec*

Centre of Molecular and Macromolecular Studies PAS, Department of Bioorganic Chemistry, Sienkiewicza 112, 90-363 Łódz, Poland. E-mail: wjstec@bio.cbmm.lodz.pl; Fax: 48 42 6815483; Tel: 48 42 6819744

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The formation of mixed seleno-sulfides by means of activation of methanephosphonoseleno(thio)ic acids with arylsulfenyl chloride is rationalized on the basis of NMR and identification of the products of their reactions with triphenylphosphine.

Nucleoside 3′-*O*-methanephosphonothioic acid upon appropriate activation can provide intermediates useful for the synthesis of oligo(nucleoside methanephosphonate)s[1] and so far undescribed oligo(nucleoside methanephosphonothioate)s. In our search for the effective route to an access of their *S*-aryl esters we studied reactions of parent acid with arylsulfenyl chlorides aiming the subsequent desulfuration of mixed disulfides with Ph_3P.[2] It appeared that instead of expected sulfur extrusion we observed deoxygenation, accompanied by clean formation of *S*-aryl esters of the corresponding methanephosphonodithioic acid. To gain better insight into the mechanism of this complex process we performed model studies on nucleoside 3'-*O*-methanephosphonoselenoic and methanephosphonoselenothioic acids derivatives.

Reaction of triethylammonium 5′-*O*-TBDMS-thymidin-3′-yl methanephosphonoselenoate (**1**)[3] or 5′-*O*-TBDMS-thymidin-3′-yl methanephosphonoselenothioate (**2**)[4] with a two-fold molar excess of *o*-nitrophenylsulfenyl chloride at −50 °C in $CHCl_3$ solution provides the (until now unreported in the literature) mixed seleno-sulfides **4** and **5**, respectively.[5]

Unambiguous assignment of the structures of **4** and **5** (Scheme 1) is based upon ^{31}P NMR spectral characteristics (Fig. 1). Most relevant are the values of direct spin–spin coupling constants between 31-phosphorus and 77-selenium nuclei, $^1J_{P–Se}$, indicative of a single P–Se bond.[6] Attempts at isolation of pure **4** and **5** by means of silica gel column chromatography were only partially successful. FAB MS analysis of the isolated **4** confirmed the existence of the molecular peak (MS FAB$^+$[M + H]: 650.4, calc. 651.0) with the pattern characteristic for selenium isotopes composition.

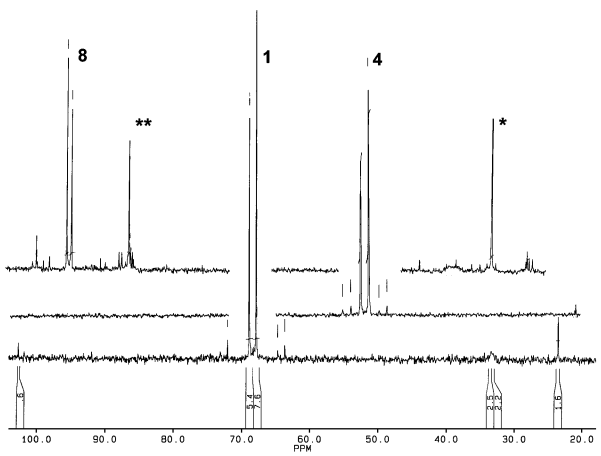
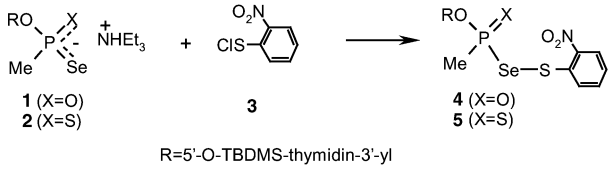
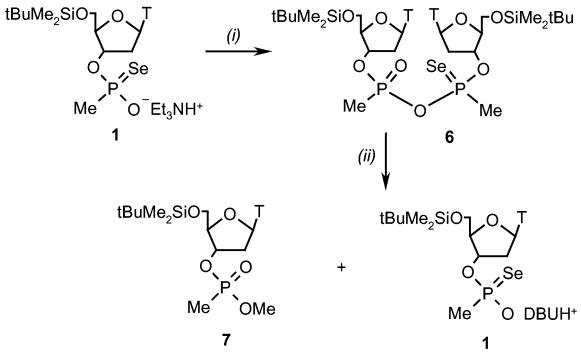


Fig. 1 ^{31}P NMR spectra of substrate **1** (bottom), crude reaction mixture of **4** (middle), and the products of its deoxygenation with triphenylphosphine (top), with additional signals of Ph_3PO (*) and $Ph_3P^+SAr\ Cl^-$ (**) (all recorded at rt).



Scheme 1 *Reagents: o*-nitrophenylsulfenyl chloride (1.2–2 equiv.), $CHCl_3$, temp. −50 °C, 10 min.

It was found that an excess of *o*-nitrophenylsulfenyl chloride **3** in reaction with **1** or **2** was essential for the product composition, since 0.5–0.8 molar equivalent of **3** with respect to **1** or **2** resulted in formation of methanepyrophosphonoselenoate **6** in 90% isolated yield (Scheme 2).[7]

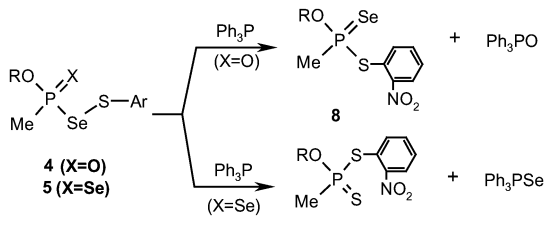


Scheme 2 *Reagents: (i) o*-nitrophenylsulfenyl chloride (0.5–0.8 equiv.), $CHCl_3$, temp. −50 °C, 10 min., *(ii)* MeOH (5equiv.), DBU (5 equiv.), rt.

The reaction of *in situ* generated **4** (100% of molar excess of **3**) with 1.2 molar equivalent of triphenylphosphine provided 5′-*O*-TBDMS-thymidin-3′-yl-*S*-*o*-nitrophenyl methanephosphonoselenothioate (**8**) and Ph_3PO in nearly quantitative yield.

Identification of **8** was based upon ^{31}P NMR characteristics: chemical shift values were typical for *O*-alkyl methanephosphonoselenothioates[8] and values of spin–spin coupling constants ($^1J_{P–Se}$ ~840 Hz) indicated the presence of a P–Se double bond.[6]

Compound **5**, generated under similar conditions as described for compound **4**, in the reaction with Ph_3P (Scheme 3) afforded triphenylphosphine selenide [^{31}P NMR δ ($CDCl_3$): 36.2 ppm, $^1J_{P–Se}$ = 740 Hz] and 5′-*O*-TBDMS-thymidin-3′-yl-*S*-*o*-nitrophenyl methanephosphonodithioate **9.**[9]



Scheme 3 *Reagents*: Ph_3P (2 equiv.), $CHCl_3$, rt, 15 min.

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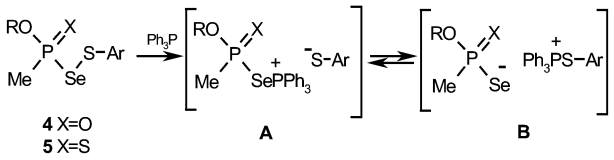
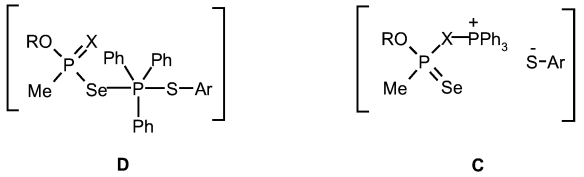
The suggested mechanism of the reaction between **4** or **5** with triphenylphosphine can be tentatively postulated as the process of nucleophilic attack of triphenylphosphine on sulfur or selenium of seleno-sulfide resulting in the equilibrium of possible ion pairs **A**, **B**, and **C** (Scheme 4).



Scheme 4



The common intermediate for both **A** and **B** can be the product of insertion of triphenylphosphine into the Se–S bond representing pentacovalent phosphorane-type structure **D**.[10] High affinity of triphenylphosphine towards oxygen must be responsible for the migration of the triphenylphosphine moiety in the ion pair **A** (X = O) from selenium to oxygen and participation of ion pair **C**.

Further attack of *o*-nitrophenylthioate anion (present due to the reaction of excessive **3** with triphenylphosphine) at the phosphorus atom of the ion pair **C** (X = O) results in the formation of the product **8**.

In contrast, in the absence of an excess of *o*-nitrophenylthioate anion, the anionic part of the ion pair **B** is able to attack methanephosphonate phosphorus of **A** either **C** providing the corresponding methanepyrophosphonates **6** (Scheme 2).[7]

In the case of compound **5** and its reaction with triphenylphosphine there is no driving force for migration of triphenylphosphine from selenium to sulfur within the ion pair **A** (X = S); therefore an attack of *o*-nitrophenylthioate at the methanephosphonate phosphorus results in formation of the product **9**.

Since for generation of compounds **4** and **5** diastereomeric mixtures of **1** and **2** were used (R = 5′-*O*-*t*butyldimethylsilylthymidine-3′-yl), the stereochemical course of the reactions under investigation was relevant for at least partial elucidation of the mechanism of reaction of mixed seleno-sulfides **4** and **5** with triphenylphosphine. Stereoinvertive outcome of these conversions (data not presented) strongly enforces the proposed mechanism.

Earlier studies on the iodine–potassium iodide oxidation of *O*,*O*-dialkyl phosphoroselenothioates postulated the formation of *Se*,*S*-diphosphylated seleno-sulfides with the structural proof based upon interpretation of ^{1}H NMR spectra of the products of that reaction.[11] Its reinvestigation by means of ^{31}P NMR contradicted those early conclusions providing the evidence that the only products of the aforementioned reaction were symmetrical bis(dialkoxyphosphinothioyl)diselenides.[12]

Studies reported herein demonstrate that under appropriate conditions the mixed seleno-sulfide can be generated, confirming that the activation of phosphoroselenoate ions by means [RS$^+$][13] provides stable intermediates **4** and **5** and those undergo deoxygenation/deselenation with triphenylphosphine if a phosphyl group is attached to the selenium atom of seleno-sulfide.

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Notes and references

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2 A. Chworos, L. A. Woźniak and W. J. Stec, *Tetrahedron Lett*., 2000, **41**, 1219–1222.

3 Compound **1** was obtained in 86% yield [^{31}P NMR δ ($CDCl_3$): 67.16 ppm, $^1J_{P–Se}$ = 691 Hz; 68.19 ppm, $^1J_{P–Se}$ = 691 Hz; MS FAB [M − H]: 497.5, calcd: 497] from 5′-*O*-TBDMS-thymidine 3′-*O*-methane phosphonoselenoanilidate [^{31}P NMR δ ($CDCl_3$): 76.16 ppm, $^1J_{P-Se}$ = 821 Hz, 76.84 ppm, $^1J_{P–Se}$ = 825 Hz, diast. ratio 1:1] according to the previously described procedure: L. A. Woźniak, J. Pyzowski, M. Wieczorek and W. J. Stec, *J. Org. Chem*., 1994, **59**, 5843–5846.

4 Compound **2** was obtained from the corresponding methanephosphonoselenoanilidate, after activation with NaH, followed by treatment with CS_2, according to the previously described procedure: W. J. Stec, L. A. Woźniak, J. Pyzowski and W. Niewiarowski, *Antisense Nucleic Acid Drug Dev*., 1997, **7**, 383–397. ; After the reaction was complete the product was extracted and isolated by means of silica gel column chromatography in 84% yield: ^{31}P NMR δ ($CDCl_3$): 95.45 ppm, $^1J_{P–Se}$ = 651 Hz; MS FAB [M − H]: 513.2, calcd: 512.6.

5 To a solution of **1** or **2** (diast. mixtures) in $CHCl_3$, cooled to −50 °C, a solution of **3** (2 equiv.) was added in one portion. After the reaction was complete, the reaction mixture was warmed up to ambient temperature, washed with water, dried with $MgSO_4$, and concentrated. Mixed selenosulfides were obtained in nearly quantitative yields. *Sp*-**4**; ^{31}P NMR: 52.5 ppm, $J_{P–Se}$ = 440 Hz. *Rp*-**4**; ^{31}P NMR: 51.1 ppm, $J_{P–Se}$ = 435 Hz. *Sp*-**5**; ^{31}P NMR: 92.3 ppm, $J_{P–Se}$ = 440 Hz. *Rp*-**5**; ^{31}P NMR: 93.3 ppm, $J_{P–Se}$ = 445 Hz.

6 W. J. Stec, A. Okruszek, B. Uznanski and J. Michalski, *Phosphorus*, 1972, **2**, 97.

7 Pyrophosphonate **6** was obtained, as diastereomeric mixture, in the reaction of **1** with **3** (0.8 equiv.) added dropwise at temp. −50 °C within 10 min. Product **6** was isolated in 90% yield by means of silica gel column chromatography: ^{31}P NMR δ ($CDCl_3$): 30.3 ppm (m) and 90 ppm (m) with 1:1 integration; MS FAB [M − H]: 914.6, calcd 914.2. Pyrophosphonate **6** was solvolyzed by means of MeOH–DBU, and its products, after silica gel column chromatography were identified as **1** (46%) and *O*-methyl methanephosphonate **7** (49%): ^{31}P NMR δ ($CDCl_3$): 33.8 ppm, 33.7 ppm; ^{1}H NMR δ ($CDCl_3$): 1.52 ppm (d, $^2J_{P–CH3}$ = 17.6 Hz), 1.54 ppm (d, $^2J_{P–CH3}$ = 17.6 Hz), 3.73 ppm (d, $^3J_{P–OCH3}$ = 11.9 Hz); MS FAB [M − H]: 447.2, calcd 448.2.

8 *General procedure for ester preparation*: To the crude reaction mixture containing **4** or **5** in chloroform, a solution of Ph_3P (2 equiv.) in $CHCl_3$ were added in one portion at rt. After 15 min. the reaction mixture was concentrated to 1/3 volume and directly applied to a silica gel column. Products were eluted under acidic conditions ($CHCl_3$–0.1% acetic acid). **8**: ^{31}P NMR δ ($CDCl_3$): 96.2 ppm, $^1J_{P–Se}$ = 846 Hz; 96.9 ppm, $^1J_{P–Se}$ = 838 Hz.

9 Compound **9** obtained as above: ^{31}P NMR δ ($CDCl_3$): 97.4 ppm, 97.2 ppm, ^{1}H NMR δ ($CDCl_3$): 2.36 ppm (3 H, d, $^2J_{P–CH3}$ = 15.4 Hz); MS FAB [M − H]: 587.5, calcd 587.1.

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