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A new selenium-transferring reagent—triphenylphosphine selenide

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Triphenylphosphine selenide and its polymer-supported counterpart are found to be efficient selenium-transferring reagents for the conversion of H-phosphonate diesters and phosphite triesters into the corresponding phosphoroselenoate derivatives.

In the last two decades organoselenium chemistry became a rapidly expanding field of organic chemistry as various selenium-based reagents have enabled chemists to perform important synthetic transformations simply and in high yields.[1]

In 1957 Schwarz and Foltz[2] found that selenium is an essential nutrient for mammals (previously known as Factor 3 present in yeast) and prevents dietary necrotic degeneration of liver, heart and other organs. This unexpected nutritional role of selenium[3] has been a powerful incentive to study the biochemistry of organoselenium compounds.[4] Kindled by hopes of finding novel, useful theraputic properties, selenium has been incorporated into various biologically important compounds,† *e.g.* carbohydrates,[5] lipids,[6,7] nucleosides[8] and oligonucleotides.[9–11]

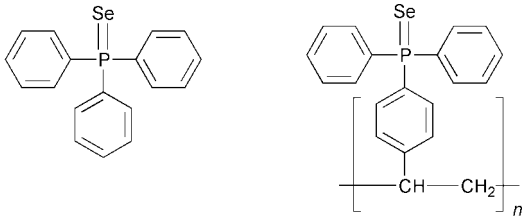
Organoselenophosphorus compounds are usually prepared[12] *via* P^{III} intermediates (*e.g.* phosphite triesters,[9,10,13] H-phosphonate-[6,11] or H-phosphonothioate[11] diesters), with a crucial step involving an oxidative transfer of selenium to phosphorus. As a source of electrophilic selenium in such transformations elemental selenium[6,14,15] and potassium selenocyanate,[10,13,16] are most commonly used. However, the low reactivity of these reagents and serious problems in their application in solid phase synthesis, led to the development of two selenizing agents soluble in organic solvents, 3*H*-1,2-benzothiaselenol-3-one (BTSe),[11] and bis(di-*O*,*O*-isopropyl phosphinothionyl)diselenide.[17]

To expand this short list of available selenizing reagents, we have embarked on investigations of a selenium exchange phenomenon between phosphine selenides and various P^{III} compounds as a viable route to selenophosphates. The rationale behind this was the observation that selenium-transfer from tertiary phosphine selenides to tertiary phosphines,[18] in contradistinction to phosphine sulfides, occurs readily at ambient temperature to produce an equilibrium mixture of the corresponding P^{III} and P^{V} species, as shown in Scheme 1.

Although established in a general sense, this reaction has not been recognised as a possible way of synthesising selenophosphorus compounds.

To find out if the selenium exchange process also occurs readily between phosphine selenides and other P^{III} compounds, we first investigated the reaction of triphenylphosphine selenide (TPPSe, **1**) with triethyl phosphite. Triphenylphosphine selenide **1**[14,16] seemed most attractive as a possible source of electrophilic selenium, since it is a stable, crystalline, inexpensive, commercial reagent, with good solubility in organic solvents.‡

Scheme 1

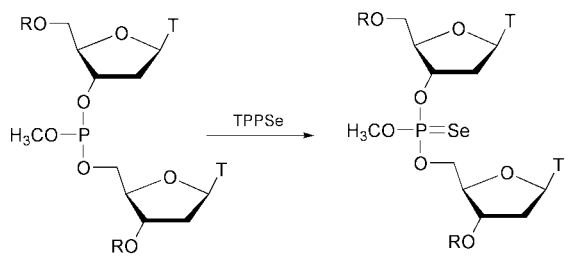


TPPSe **1** PS-TPPSe **2**

Thus, triethyl phosphite in chloroform was treated with selenide **1** (1.1 equiv.) and progress of the reaction was followed by ^{31}P NMR spectroscopy. It was rewarding to find that transfer of selenium from **1** (δ_P = 36.5, $^1J_{PSe}$ = 640 Hz) to triethyl phosphite (δ_P = 139.0) occurred rapidly (within 5 min) and quantitatively with the formation of triethyl phosphoroselenoate§ (δ_P = 72.0, $^1J_{PSe}$ = 938 Hz) and triphenylphosphine (δ_P = −4.2). Encouraged by this result we assessed TPPSe as a selenizing reagent for dinucleoside phosphite **3**¶ (Scheme 2). The reaction of **3** with 1.1 equiv. of selenide **1** was only slightly slower than that with triethyl phosphite (completion within 20 min) and produced the expected phosphoroselenoate triester **4** as a *ca.* 1 : 1 mixture of diastereomers (δ_P = 74.6 and 74.2, $^1J_{PSe}$ = 969 and 970 Hz). Compound **4** was isolated by silica gel chromatography (*ca.* 70% yield) and its structure was confirmed by NMR spectroscopy and MALDI data.

Somewhat surprisingly, attempted selenization of diethyl H-phosphonate with selenide **1** (2 equiv.) failed as no selenium-transfer occurred within 24 h (^{31}P NMR spectroscopy) in pyridine or in chloroform in the presence of triethylamine (5 equiv.). However, the conversion of diethyl H-phosphonate (δ_P = 7.6) into the corresponding silyl phosphite‖ (δ_P = 128.5) furnished rapid (< 10 min) and clean selenization upon addition of selenide **1** (1.1 equiv.) with the formation of diethyl phosphoroselenoate diester (δ_P = 56.2, $^1J_{PSe}$ = 934 Hz). We also found that selenization of diethyl H-phosphonate with **1** (2 equiv.) in pyridine could be effected without presilylation, when diazabicyclo[5.4.0]undec-7-ene (DBU, 5 equiv.) was used as base (completion within 25 min).

The efficacy of this approach for selenization of nucleoside H-phosphonate diesters was evaluated by reacting dinucleoside H-phosphonate **5a** with TPPSe (1.1 equiv.) in pyridine in the



3 **4**

R = 4,4′-dimethoxytrityl
T = thymin-1-yl

Scheme 2

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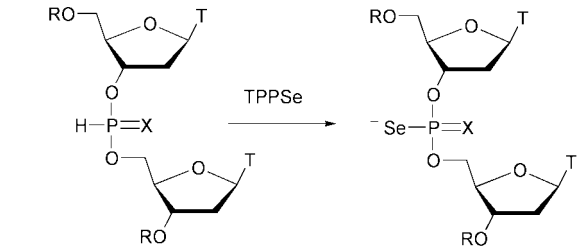
presence of trimethylsilyl chloride (TMS-Cl, 6 equiv.) as a silylating agent (Scheme 3). The reaction was clean and went to completion within 15 min producing the silylated phosphoroselenoate **6a** (δ_P = 56.9 and 56.6) as the sole nucleotidic product. Similarly to diethyl H-phosphonate, selenization of H-phosphonate **5a** with **1** (1.1 equiv.) also occurred rapidly (< 5 min) and cleanly in pyridine in the presence of DBU (5 equiv.) as a base. The produced dinucleoside phosphoroselenoate **6a** was isolated from the reaction mixture by silica gel chromatography in *ca*. 90% yield and it was identical to **6a** prepared in another way.[11]



Scheme 3

The above conditions were also found to be most efficient for the preparation of phosphorothioselenoate **6b**[11] (δ_P = 104.2 and 103.8, $^1J_{PSe}$ 759.0 and 756.0 Hz) from the corresponding H-phosphonothioate **5a** (80% isolated yield).** Preliminary data from selenization of **5a** and **5b** containing different ratios of both diastereomers showed that selenide **1** furnished transfer of selenium to H-phosphonate and H-phosphonothioate diesters in a stereospecific manner (most likely with retention of configuration).

As the final part of these studies we also investigated the possibility of using a polymer-supported phosphine selenide **2** (PS-TPPSe) as a selenium-transferring reagent. Thus, a commercially available polystyryl diphenylphosphine resin was converted into selenide **2**†† and reacted with selected P^{III} derivatives. Preliminary ^{31}P NMR experiments showed that **2** can indeed act as an efficient selenium-transferring reagent. When triethyl phosphite was treated in dichloromethane with polymer-supported selenide **2** (4 equiv.), complete conversion to the corresponding phosphoroselenoate occurred within a few minutes. Also selenization of dinucleoside H-phosphonate **5a** with selenide **2** (3 equiv.) in the presence of DBU (5 equiv.) proceeded rapidly (> 5 min) producing the expected dinucleoside phosphoroselenoate **6a**.‡‡

In conclusion, we have developed a new and efficient method for the selenization of P^{III} compounds based on selenium exchange. Triphenylphosphine selenide **1**, which is proposed as a new source of electrophilic selenium in this method, is a stable, easy to handle, inexpensive and commercially available reagent, with good solubility in organic solvents. Efficiency of **1** as a selenium-transferring reagent was demonstrated by using it for the conversion of phosphite triesters and H-phosphonate diesters into the corresponding phosphoroselenoates, as well as in the transformation of H-phosphonothioate diesters into the phosphorothioselenoate derivatives. The reactions were fast and occurred under mild, homogeneous conditions. A polymer-supported counterpart of reagent **1**, triphenylphosphine selenide **2**, also showed favourable selenium-transferring properties. This reagent can be considered as an alternative to **1**, especially if separation problems arise.

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Notes and references

† Selenium compounds are generally toxic to animals. However, toxicity *per se* does not rule out a compound for drug use although it frequently prevents the administration of an effective dose that is also safe.

‡ Triphenylphosphine selenide **1** can also be easily prepared *via* selenization of triphenylphosphine in 1,4-dioxane with elemental selenium or according to the Nicpon and Meek procedure,[16] using KSeCN. Approximate solubility of **1** in organic solvents (solvent, mg mL^{-1}): acetonitrile, 6; THF, 80; pyridine 100; dichloromethane 130; chloroform, 230.

§ Identity of this and other phosphoroselenoates obtained in these studies (*e.g.* **4**, **6a**, **6b**) was confirmed by independent synthesis of these compounds *via* selenization of the corresponding P^{III} precursors with elemental selenium.

¶ Dinucleoside phosphite **4** was generated *in situ* from 5′-*O*-dimethoxytritylthymidin-3′-yl methyl *N*,*N*-bis(diisopropyl)phosphoramidite and 3′-*O*-dimethoxytritylthymidine in chloroform in the presence of tetrazole. Besides **4**, the reaction mixture contained *ca*. 10% hydrolysis products and *ca*. 5% of the unreacted phosphoramidite.

‖ Reaction in chloroform, using bis(trimethylsilyl)acetamide (BSA) and triethylamine.

** In a typical experiment, H-phosphonate **5a** or H-phosphonothioate **5b** (0.1 mmol) was dissolved in pyridine (4 mL) containing triphenylphosphine selenide **1** (2.0 equiv.), and DBU (5 equiv.) was added. After 5 min the reaction mixture was diluted with dichloromethane (20 mL), extracted with 0.5 M TEAB buffer (pH = 6.5, 4 × 50 mL) and the organic phase was subjected to silica gel chromatography using a stepwise gradient of methanol (0–2%) in chloroform containing 0.2% triethylamine. Yields: **6a** 90%, **6b** 80%.

†† Polymer-supported phosphine selenide **2** was synthesized by shaking in THF polystyryl diphenylphosphine resin with KSeCN (3 equiv.) for 4 h. After that time the ^{31}P NMR spectrum of the suspended polymer beads showed a complete disappearance of the broad signal at −5.4 ppm due to the phosphine and a new broad signal at 35.5 ppm due to phosphine selenide.

‡‡ *Ca*. 10% of the corresponding nucleoside 3′- and 5′-*H*-phosphonate monoesters were present in the reaction mixture, probably as a result of hydrolysis of **6a**.

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