Atom-economic thiophosphoroselenenylations of C-H acid esters and amides

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ABSTRACT: Three improved thiophosphoroselenenylation procedures of CH-acids, including derivatives of malonic and acetyl-, phosphono-, 4-nitrophenyl- and 3-pyridylacetic acids, have been described and compared to previously reported thiophosphoroselenylation of diethyl malonate using *bis*(disopropoxyphosphinothioyl)diselenide alone or with the aid of methyl iodide. The use of iodine makes it possible to utilize both equivalents of the selenenylating agent. The procedures work well for the majority of nucleophiles in a pKa range between more acidic malononitrile or Meldrum acid and less acidic phenylacetates. The reaction carried out on diethyl malonate in boiling rectified ethanol yields selenoacetate, which cannot be obtained by direct phosphoroselenenylation. Crystal structure of one of the selenomalonamides confirms the stabilization effects of both carbonyl oxygens on selenium atom. The P-Se bond splitting, using TBAF in 3-molar excess in the presence of alkylating agent yields the respective *C*,*Se*-dialkyl derivatives.

Keywords: Selenenylation; C-H methylene compounds; thiophosphoryl protective group

α-Selenylcarbonyl compounds are versatile reagents used as intermediates in stereocontrolled synthesis of α,β-unsaturated compounds (*via* selenoxide elimination) or 1,2-diketones (seleno-Pummerer reaction). They are also well-known precursors of synthetically useful *Se*-stabilized carboanions and ylides. [1] Electrophilic selenenylation is generally performed by the use of cheap commercial diphenyl diselenide or more reactive phenylselenyl halides (generated *in situ* from diphenyl diselenide). The other advantage of the procedure is relatively low electrophilicity of introduced selenium compared to Se-alkyl derivatives. This approach, however, closes off the way to further elaboration leading to diorganyl selenides due to the non-cleavable Se-phenyl bond. Nevertheless, both synthetic and biological applications of 2-phenylselanyl esters are still studied. [2]
2-Phenylselenomalonate was obtained for the first time by Byers in 54% yield in an ionic phenylselenelynation reaction [3] and it was successfully involved for radical transformations, especially in selenium-transfer radical addition.[4] Its preparation was not efficient, however, due to disproportionation. Even using malonate anion in a 10-molar excess, the reaction between sodium diethyl malonate **1a**-Na and phenylselenyl chloride gave significant amounts of 2,2-*bis*(phenylselenyl)malonate. Additionally, it was shown that the product undergoes disproportionation already during excess diethyl malonate distillation and after isolation in the light. [5] The same procedure was applied by Byers for the synthesis of 2-phenylselanyl-3-ketoesters [6] and phenylselanyldiphosphonomethanes [7] as selenium transfer reagents (Scheme 1).

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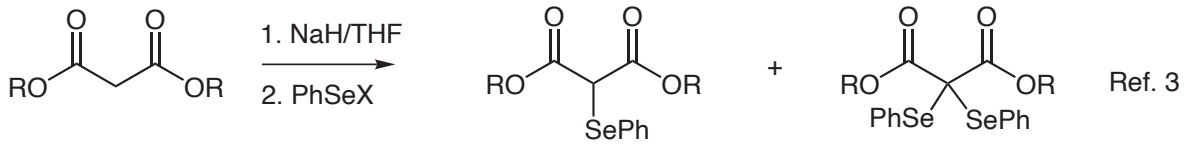
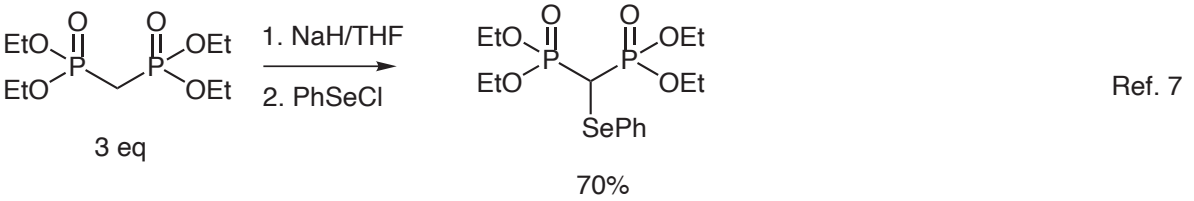


R = Et (4 eq); X = Cl	54%	5%
R = Me (8 eq); X = Br	75%	nd
R = Me (1 eq); X = Br	nd	70%



Scheme 1 Byer's results of the phenylselenenylation of malonates and a malonate phosphonic analog at different molar ratios (nd = no data).

Hondal found that selenenic acids RSeOH (or even seleninic acids $RSeO_2H$) as products of selenoproteins oxidation can add to dimedone to give the corresponding 2-selenyl derivatives (detected by LCMS). [8] The reaction is not unequivocal since it gives diselenides and dimeric dimedone as the end products. Thus, also in that case the 10-fold excess of dimedone should be used for the alkylation reaction to outcompete disproportionation. Liotta used weak electrophilic selenium metal for enolate-selenoate transformation of both carbonyl [9] and α,β-dicarbonyl compounds [10]. He stated that selenylation of the former enolates is a very slow process, therefore its success depends on providing strictly anhydrous and anaerobic conditions for up to 24 hours and the use of the defined amount of HMPA.

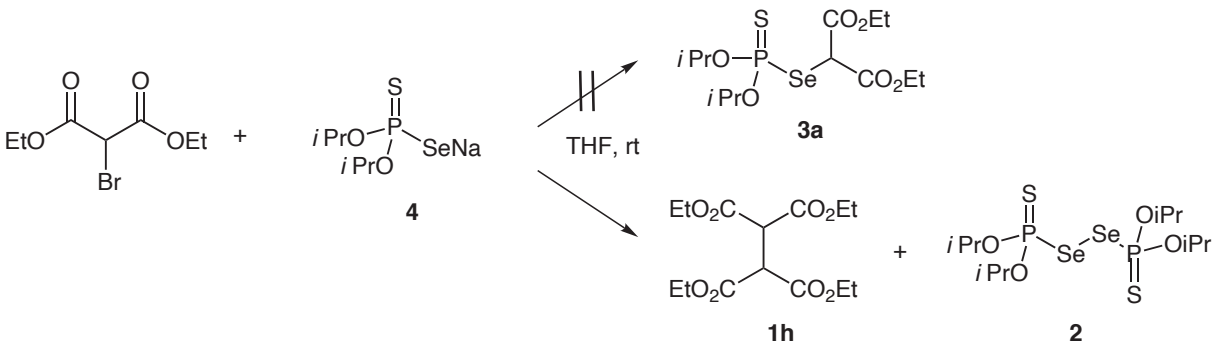
Skowrońska developed an efficient phosphoroselenenylation procedure of 2-formyl cycloalkanones using *in situ* generated phosphoroselanyl bromides and pyridine as a base at -80°C. Next, thus obtained intermediates underwent rearrangement to 2-methylene ketones upon reduction with $NaBH_4$ at -85°C. [11]

The use of *bis*(diisopropoxyphosphinothioyl)diselenide **2** as an electrophilic selenium source mimics a well-known natural biosynthetic mechanism of selenium incorporation where phosphoroselenoic acid H_3SePO_3 takes part. [12] We used **2** successfully and we proved the synthetic advantages of the products of its reaction with diethyl malonates (**3a-3b**) [13] and indoles [14] over the respective phenylseleno derivatives. Due to the presence of an easily removable thiophosphoryl group, they have the potential to become versatile precursors to a wide variety of selenides, as the TBAF/electrophile treatment gives good yields of stable diorganyl selenides which are not accompanied by diselenides.

Herein, we demonstrate the usefulness of modified procedures with participation of **2** for the preparation of a broad spectrum of 2-phosphoroselenenyl substituted CH acids including 2-substituted malonates, β-ketoesters, phenylacetates, 3-pyridylacetates and the respective secondary and tertiary amides or thioamides. These products can be used for diorganyl selenide synthesis and potentially as radical or ylide/carboanion precursors.

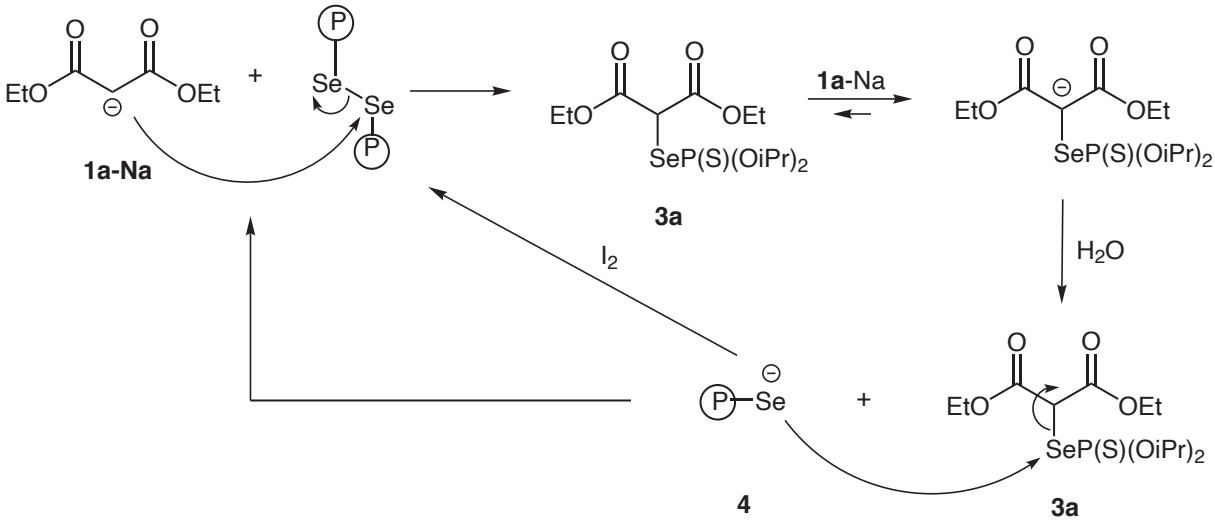
Results and Discussion

2-Thiophosphoroselenomalonates **3** can be theoretically formed in the alternative „Umpolung route" using nucleophilic selenium reagent **4** (Scheme 2). However, we have found that instead of the desired malonate **3a**, **1h** and **2** (X-philic substitution products) are formed.



Scheme 2. Unsuccessful alternative „Umpolung route" to **3a**.

In a previous paper [13], we characterized the title reaction with regard to its mechanism (Scheme 3). The reaction is very fast and is over in few seconds even at low temperature (-78°C). ^{31}P NMR analysis showed that the mixture of diselenide **2** and sodium diethyl malonate **2a** in THF consists of only two phosphorus products. Their chemical shifts correspond to $(iPrO)_2P(S)SeNa$ **4** (δ_P 96.7; $^1J_{P\text{-}Se}$=614 Hz) and **3a**-Na (97.3 ppm, $^1J_{P\text{-}Se}$ =726 Hz). However, the product **3a** was isolated in 22% yield. Therefore, not a low conversion but the isolation procedure is the main problem in thiophosphoroselenenylation process under the study. A standard aqueous workup leads to protonation of **3a-Na**, leaving a high concentration of free >P(S)SeNa **4**, which can act as a strong nucleophile in a reverse reaction, *i.e.* dethiophosphoroselenenylation. We noticed that the concentration of **3a** drops to 20% of its initial value 3h after addition of selenolate **4**, which confirms that the reaction is reversible. To overcome the limitation concerning an adverse equilibrium of malonate **1a** thiophosphoroselenenylation, methyl iodide as phosphothioselenoate **4** quencher was used that gives products **3** in much better yields (up to 90%). Next, we found that iodine (instead of methyl iodide) is more efficient as it allows both equivalents of >P(S)Se to react with diethyl malonate [15] and indoles [14] and resulting in 100% atom economy. Based on the results of additional experiments we proved that iodide itself does not cause malonate anion oxidation under the reaction conditions (and during workup of the reaction mixture) nor react with diselenide **2**.

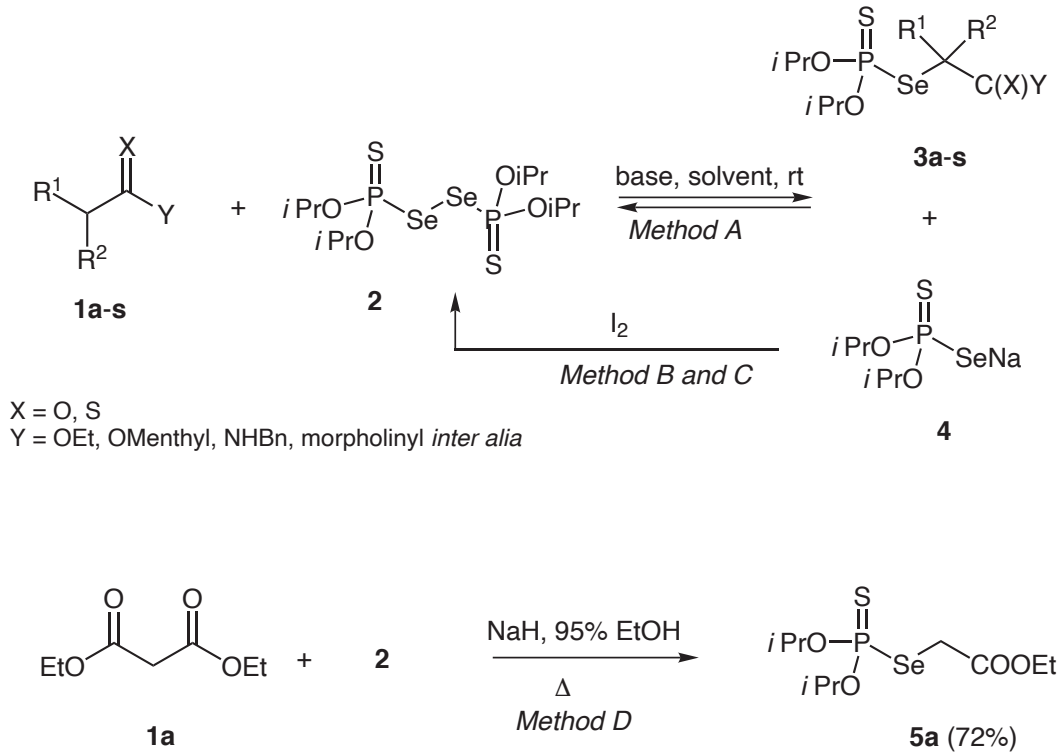


Scheme 3 Proposed mechanism of malonates phosphoselenenylation justifying the need for phosphothioselenoate **4** removal from the reaction medium.

Therefore, we did not detect either diethyl malonyl dimer **1h** or thiophosphoroselenenyl iodide in the reaction mixtures (proved by TLC, ^{1}H and ^{31}P NMR analysis). Thus, the iodine role is a simple recycling of diselenide **2** resulting from the subsequent oxidation of

thiophosphoroselenoate **4**. These experimental facts could be explained by a much higher oxidation potential of diethyl malonate anion (as compared to the oxidation potential of **4**) and with a significant difference in rates of thiophosphoroselenenylation and diselenide **2** oxidizing by iodide (Scheme 4). Therefore, the absence of **4** in the equilibrium reaction mixture is critical to the success of the phosphoroselenylation, but from the other side its presence as a soft base is very important due to its ability to be quenched with methyl iodide or easy oxidation leading to recovery of diselenide **2**.
As a result of simple iodine addition to the mixture of **1-Na** and **2** the yields of all products **3** were remarkably increased. The conversion even reaches 200% that means that both selenylating equivalents of **2** were totally consumed. Under these conditions (Method B) even product **3j** can be obtained, although moderate in yield (36%). We found that sodium hydride can reduce diselenide **2** in cases when deprotonation of the CH-acid is a slow process. After a series of preliminary experiments on malonate phosphoselenenylation, fortunately we noticed that the complete CH deprotonation of the CH acid was not necessary for the reaction to take place with a satisfactory yield. Therefore, Method C is a slight modification of Method B, *i.e*. DBU was used as a base instead of NaH.

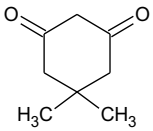
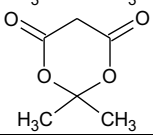
In order to study the scope and limitation of the thiophosphoroselenenylation, a series of esters and amides/thioamides of 2-substituted malonic, phosphonoacetatic, phenylacetic, β-pyridylacetic, β-keto acids (ethyl 2-methylacetylacetate) and 1,3-diketones (2-ethoxycarbonylcyclohexanone) were chosen (Table 1). Our intention was to assign the effect of the acidity and steric hindrance, both at the 2-carbon atom and at the O-alkyl/N-alkyl residue, in the starting material **1**.
We found that phosphonate group in the place of carboxylate has no influence on the progress of the reaction (entry 9), however for 2-isopropylphosphonoacetate the reaction is ambiguous (see below).
Meanwhile, surprisingly we found that bulky 2-substituted malonates proved to be no less nucleophilic than unsubstituted ones, and unexpectedly they led to products **3** with much better yields even without iodine as an additive (Method A, entries 4 and 6). It seems that products **3d-3f** are not prone for the reverse substitution with **4** due to an additional steric hindrance around the Se atom. We found that **4** reacts with **3d** very slightly, regenerating less than 20% of **2** after 3h.
Therefore, the results of our set of experiments indicate that the reaction is sensitive to steric hindrance around tertiary C-2 carbon atom. In case of thiophosphoroselenenylation of phosphonoacetate **1j** gives product **3j** in only 6% (Method A) and 36% (Method B) yield due to unknown side reactions (diethyl phosphate and elemental selenium as products were found).
Among C-H acidic compounds **1** some of them are inert toward phoshothioselenylation because their deprotonation using NaH failed (**1g**), they give anions of too low nucleophilicity (**1v-1x**), they undergo autocondensation (ketones), they react in a different manner (primary amides **1m** and **1t**) or they give unstable products **3** (**1u**). **1h** (entry 8) forms unexpectedly 1,1,2,2-tetraetoxycarbonylethylene as a result of the well-known **1h-Na** oxidation by iodine.[16] Apparently, **1h-Na** oxidation is faster than selenenylation, which is additionally suppressed due to steric reasons.



Scheme 4 Thiophosphoroselenenylations of CH-acids **1** leading to **3** and **5**. Method A: NaH/THF, Method B: NaH/THF/I_2, Method C: DBU/THF/I_2, Method D: NaH/95% EtOH/I_2.

During optimization of thiophorosphoselenylation procedure, we found that heating of the reaction mixture leading to **3a** in rectified ethanol gives the respective deethoxycarbonylated product. First, we postulated that the highly nucleophilic sodium thiophosphoroselenoate (Method A) or sodium iodide (Method B) participate in the alkyl-oxygen bond splitting similar to Krapcho dealkoxycarbonylation. [17] However, the absence of diisopropylthiophosphoroselenic acid *Se*-ethyl ester in the reaction mixture (NMR) confirms that **5a** is, in fact, the product of hydrolysis of **3a**.

Table 1. Thiophosphoroselenenylation of **1** leading to **3** $R^1R^2C[C(=X)Y]SeP(S)(OiPr)_2$ (yields per equivalent of diselenide **2**).

Entry	CH acid	R^1	R^2	X Y	**3**	Yield [%] (Method)
1	**1a**	CO_2Et	H	O OEt	**3a**	22(A) 91(B)
2	**1b**	CO_2All	H	O OEt	**3b**	24 (A) 87 (B)
3	**1c**	CO_2t-Bu	H	O OEt	**3c**	25 (A) 80 (B)
4	**1d**	CO_2Et	Me	O OEt	**3d**	48 (A) 87 (B)
5	**1e**	CO_2Et	Et	O OEt	**3e**	80 (B)
6	**1f**	CO_2Et	Bn	O OEt	**3f**	35 (A) 69 (B)
7	**1g**	CO_2Et	*t*-Bu	O OEt	**3g**	0 (B)
8	**1h**	CO_2Et	$CH(COOEt)_2$	O OEt	**3h**	0[a] (B)
9	**1i**	$P(O)(OEt)_2$	H	O OEt	**3i**	31 (A) 81 (B)
10	**1j**	$P(O)(OEt)_2$	*i*-Pr	O OEt	**3j**	6 (A) 36 (B)
11	**1k**	$CON(CH_2CH_2)_2O$	H	$O/N(CH_2CH_2)_2O$	**3k**	64 (C)
12	**1l**	$CONHCH_2Ph$	H	$O/NHCH_2Ph$	**3l**	66 (C)
13	**1m**	C_6H_5	H	O/NH_2	**3m**	0 (B)
14	**1n**	C_6H_5	H	O/O-Menthyl	**3n**	2 (B)[b]
15	**1o**	p-$NO_2C_6H_4$	H	O/O-Menthyl	**3o**	82 (C)
16	**1p**	3-pyridyl	H	$O/N(CH_2CH_2)_2O$	**3p**	31 (C)
17	**1q**	3-pyridyl	H	$S/N(CH_2CH_2)_2O$	**3q**	65 (C)
18	**1r**	$COCH_3$	Me	O/OEt	**3r**	72 (B)
19	**1s**	$-CO(CH_2)_4-$		O/OEt	**3s**	62 (B)
20	**1t**	$CONH_2$	H	O/NH_2	**3t**	0 (B)
21	**1u**	CN	H	O/OEt	**3u**	0 (A) 0 (B)
22	**1v**	CN	H	CN	**3v**	0 (A) 0 (B)
23	**1w**				**3w**	0 (A) 0 (B)
24	**1x**				**3x**	0 (A) 0 (B)

Among compounds **3** only **3l** crystallizes quickly and easily from hexane–ethyl acetate giving crystals suitable for X-Ray analysis (Figure 1, Table S1). [18] It exhibits an intermediate conformation between the the *U*- and *W*-shaped forms as it is typical for malonic acid derivatives including malonamides. [19,20] However, in simple malonamides both carbonyl groups are orthogonal to each other [20], while in **3l** they are almost coplanar (angle of 6.0°). The geometry around the selenium atom in **3l** is unique. The distances between the Se and carbonyl oxygens of 3.004 and 3.207 Å are 0.416 and 0.213 Å shorter, respectively, than the sum of the corresponding van der Waals radii, which clearly indicates the existence of stabilizing O…Se interactions in **3l**. Obviously, this causes a change in the geometry of the intermolecular interactions. As a consequence, molecules of **3l** form a different pattern of

intermolecular H-bonding, *i.e.* a linear tape structure of 2D H-bonding pattern (Figure S46), while known malonamides create 3D H-bonding networks.

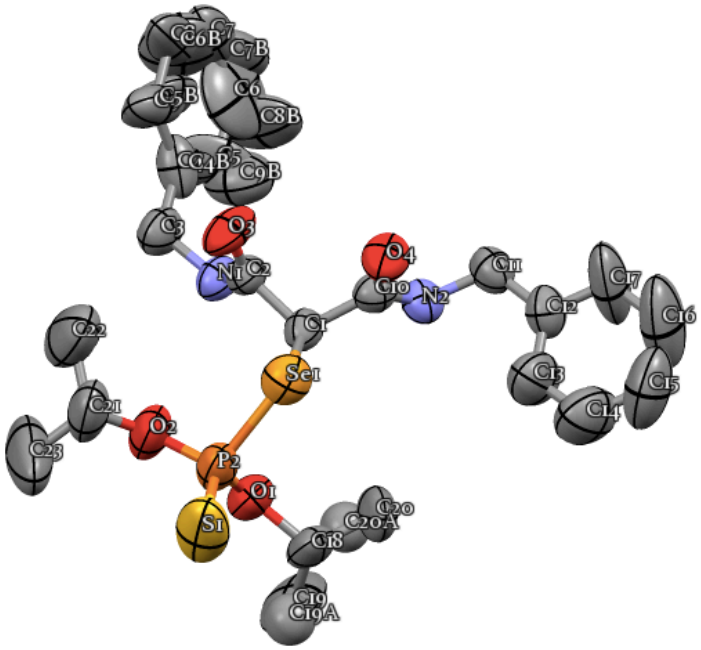
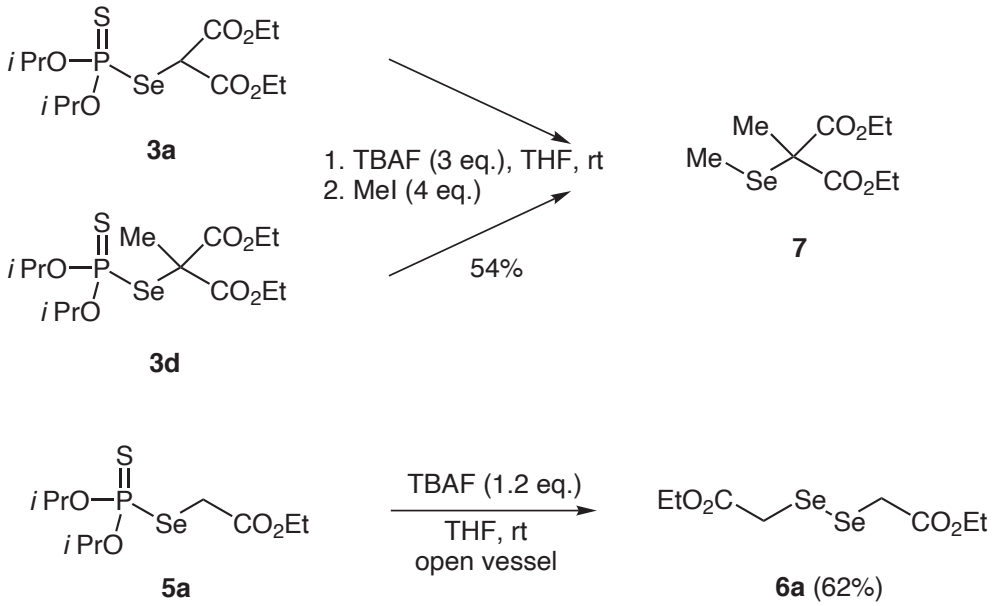


Figure 1. ORTEP diagram of **3l**. Thermal ellipsoids are drawn at the 50% probability level.

Preliminary experiments on the P-Se bond cleavage directed to release malonyl selenoate showed that Bu_4NF (TBAF) must be used in 3-molar excess together with immediate quenching of arising selenoate to shift the reaction toward expected product. For true, a parallel experiment performed on thiophosphoroselenoacetate **5a** confirmed that the cleavage reaction with the use of TBAF in the abscence of electrophile proceeds smoothly giving the respective diselenide in good yield (62%, Scheme 5). However, in the same reaction conditions **3a** behaves quite different and it is not split into desired malonyl selenoate. ^{31}P NMR analysis of the reaction mixture of **3a** and Bu_4NF in 1:1 molar ratio performed at its early stages showed the presence of two phosphorus products, *i.e* the expected phosphorus fluoride $(iPrO)_2P(S)F$, and thiophosphoroselenoate $(iPrO)_2P(S)Se^-$ **4**. (Fig. S44). Instead, we postulate the formation of unstable phosphopolyselenoates $(iPrO)_2P(S)Se_nSe^-$ that spontaneously decompose into $(iPrO)_2P(S)Se^-$ **4** and atomic selenium during the course of the reaction (Fig. S45). Therefore, we believe that the anions of thiophosphoropolyselenide are responsible for the rapid cleavage of the C-Se bond in **3a**, starting (*in statu nascendi*) to compete with fluoride anion (cleavage of the P-Se bond). Next, we performed a series of experiments with a 3-molar excess of TBAF in the presence of methyl iodide. Proceeding with the reaction on both **3a** and **3d** led to obtaining the same product **7** with comparative yields (Scheme 5), meaning that *C*-alkylation occurs parallel to *Se*-alkylation. This excludes the possibility of using **3** with a residual C-H acidic proton (*i.e.* **3a**-**3c**) when the target of the synthesis is not the corresponding *C*,*Se*-dialkyl derivatives. Further studies toward optimization of TBAF/electrophile procedure are in progress.



Scheme 5. Fluorolysis of **3a** and **3d** (in the presence of methyl iodide) and **5a** (on the air) with TBAF.

Conclusions

The present work describes the first example of involving diselenide as an efficient thiophosphoroselenenylating agent for active methylene compounds. The success of methodology depends on oxidation of thiophosphoroselenolate, that is formed during the course of the reaction.

As a large number of active methylene compounds are available, it is reasonable to assume that many of the new phosphoroselenenyl derivatives can be synthesized by these procedures, allowing a novel, easy and practical multigram-scale synthesis of this interesting class of compounds by the use of *bis*(phosphorothioyl)diselenides. The procedure for removing the phosphorothioyl protection, that have been refined, opens the way to obtaining a wide range of appropriate asymmetric diorganyl selenides.

Experimental

All NMR spectra were recorded on a Varian Unity 500 Plus spectrometer operating at 500 MHz (^{1}H), 126 MHz (^{13}C), 202 (^{31}P) and 95 MHz (^{77}Se) in deuterochloroform at ambient temperature. TMS was used as an internal standard. The standard abbreviations for multiplicities were used (s = singlet, d = doublet, t = triplet, q =quartet, qu = quintet, se = sextet, spt = septet, dspt = doublet of septets, m = multiplet). HRMS spectra were recorded on Mariner ESI-TOF (Applied Biosystems) mass spectrometer using ESI system with positive ion mode.

Column chromatography was performed using Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapor.

THF was distilled from sodium benzophenone ketyl prior to use. Triethylammonium *O*,*O*-diisopropylphosphoroselenothioate was obtained from *O*,*O*-diisopropyl hydrogen phosphorothioite and selenium and was recrystallized from AcOEt/Et_2O selenium. [21] Diselenide **2** was prepared by oxidation of triethylammonium *O*,*O*-diisopropyl phosphoroselenothioate with iodine [22] and was twice recrystallized from isopropanol (m.p. 90-92^{o}C, lit. [22] m.p. 86-88 ^{o}C). Malonates **1b** and **1c** were obtained from malonic acid monoethyl ester with the respective alcohols in presence of DCC. Malonates **1d, 1e** and phosphonoacetate **1j** were prepared by alkylation of the corresponding ethyl esters sodium salts using appropriate alkyl halide in THF. Diethyl *tert*butylmalonate **1g** was prepared from diethyl isopropylidenemalonate according to described procedure. [23] Diethyl malonate amono- and aminolysis with morpholine and benzylamine provided malonodiamides **1t** (80%, mp 170-172°C), **1k** (51%, mp 135-136°C), and **1l** (55%, mp 140-142°C), respectively. [24] Treating of phenylacetic acids with *L*-menthol and

3-pyridylacetic acid with morpholine in the presence of DCC/DMAP yielded the corresponding menthyl esters **1n**, **1o** (69%, mp 82-84°C) and morpholide **1p**.
All the other reagents (malonates **1a** and **1h**, phosphonoacetate **1i**, 3-pyridylacetic acid, phenylacetic acids, thiomorpholide **1q**, ethyl 2-methylacetoacetate **1r**, 2-ethoxycarbonylcyclohexanone **1s**, ethyl cyanoacetate **1u**, malononitrile **1v**, dimedone **1w**, Meldrum acid **1x**, sodium hydride, alkyl halides, DCC, DBU) were commercial compounds (Merck).

General procedures

Method A
Reaction of C-H acid sodium salts 1-Na with diselenide 2 in the absence of iodine in THF
Reaction were performed as previously described. [13]

Method B
Reaction between sodium salts of C-H acids 1 and diselenide 2 with a subsequent addition of iodine in THF
Diethyl 2-(diisopropoxyphosphinothioyl)seleno-2-ethylmalonate (3e)
To a suspension of 60% NaH (0.054 g, 1.35 mmol) in THF (5 ml) diethyl 2-ethyl malonate **1e** (0.24 g, 1.25 mmol) was added with stirring. After evolution of hydrogen completely ceased (ca. 0.5 h) *bis*(disopropoxyphosphinothioyl) diselenide **2** (0.26 g, 0.5 mmol) was added in one portion at room temperature. After diselenide **2** dissolution, a THF iodine solution (0.134 g, 0.52 mmol, 1.05 eq, 2 ml) was added dropwise for 15 min. Next the reaction mixture was poured onto water–ethyl acetate mixture (1:2 v/v) and both layers were separated. The organic phase was washed with 5% $Na_2S_2O_3$ solution, water and dried over $MgSO_4$. Evaporation of the solvent left an oily residue which was purified on silica gel column. n-Hexane–EtOAc (14:1) solvent system was used to afford 0.36 g (80%) chromatographically pure **3e** as a colourless oil.
^{1}H NMR: δ = 0.98 (t, 3H), 1.26 (t, 6H), 1.33 (2 x d, 12H), 2.39 (q, 2H), 4.23 (2 x q, 4H), 4.87 (dspt, J_1 = 6 Hz, J_2 = 12 Hz, 2H).
^{13}C NMR: δ = 10.2, 14.2, 23.6 (d, $^3J_{PC}$ = 5 Hz), 24.0 (d, $^3J_{P\text{-}C}$ = 4 Hz), 28.0, 62.5, 64.8 (d, $^2J_{PC}$ = 5 Hz), 74.32(d, $^2J_{PC}$ = 8 Hz), 168.3 (d, $^3J_{PC}$ = 5 Hz).
^{31}P NMR: δ = 75.5 ($^1J_{PSe}$ = 495 Hz).
HRMS (ESI): *m/z* calcd for $C_{15}H_{29}O_6NaPSSe$ $[M + Na]^+$: 471.0485; found: 471.0486.

Method C
Reaction between DBU salts of C-H acids 1 and diselenide 2 with a subsequent addition of iodine in THF
2-(Diisopropoxyphosphinothioyl)selenomalonic acid dimorpholide (3k)
DBU (0.120 g, 0.788 mmol) was added dropwise with stirring to a solution of malonic acid dimorpholide **1k** (0.120 g, 0.49 mmol) and diselenide **2** (0.102 g, 0.2 mmol) in THF (3 ml) at room temperature. Next a THF solution of iodine (0.054 g, 0.2 mmol,1.05 eq, 1 ml) was added until a persistent brown coloration was obtained. After 10 min the reaction mixture was poured on water (30 ml) and was extracted with DCM (3 x 15 ml), washed with water (3 x 15 ml), a 5% $Na_2S_2O_3$ solution (10 ml), brine and dried over $MgSO_4$. After solvent removal, the residue was chromatographed on silica gel column (n-hexane–EtOAc gradient 1:1 to 1:2) to yield 0.127 g (64%) of **3k** as a light yellow oil.
^{1}H NMR: δ = 1.30 and 1.32 (2 x d, 12H), 3.64 (m, 16H), 4.77 (dspt, J_1 = 6 Hz, J_2 = 12 Hz, 2H), 5.14 (d, $^3J_{P\text{-}H}$ = 15 Hz, 1H).
^{13}C NMR: δ = 23.6 and 23.9 (2 x d, $^3J_{PC}$ = 5 Hz), 43.6, 47.5, 52.3, 66.9 (d, $^2J_{PC}$ = 18 Hz), 74.6 (d, $^2J_{PC}$ = 7 Hz), 165.0 (d, $^3J_{PC}$ = 4 Hz).
^{31}P NMR: δ = 64.6 (d, $^1J_{PSe}$ = 442 Hz).
HRMS (ESI): *m/z* calcd for $C_{17}H_{31}N_2O_6NaPSSe$ $[M + Na]^+$: 525.0703; found: 525.0704.

Method D
Reaction between sodium salts of C-H acids 1 and diselenide 2 with a subsequent addition of iodine in boiling 95% ethanol
Ethyl (Diisopropoxyphosphinothioyl)selenoacetate (5a)
60% NaH (0.100 g, 2.5 mmol) and diethyl malonate **1a** (0.334 g, 2.08 mmol) were added to rectified ethanol (20 ml) with stirring. After evolution of hydrogen completely ceased (ca. 0.5 h) diselenide **2** (0.524 g, 1.04 mmol) was added in one portion. The mixture was heated to boiling and then the ethanolic iodine solution (0.264 g of iodine crystals dissolved in 3 ml of 95% ethanol) was added dropwise with stirring. After 1h the cooled mixture was poured onto water (30 ml) and extracted with DCM (3 x 15 ml). The combined organic extracts were washed with water (10 ml), 5% $Na_2S_2O_3$ (10 ml), brine (10 ml), dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column with n-hexane–ethyl acetate (14:1) to give ethyl (diisopropoxyphosphinothioyl)selenoacetate **5a** (521 mg, 72%) as a colorless oil.

^{1}H NMR: δ = 1.24 (t, 6H), 1.34 (2 x d, 12H), 3.57 (d, $^3J_{PH}$ = 14 Hz, 2H), 4.15 (q, 2H), 4.84 (dspt, J_1 = 6 Hz, J_2 = 12 Hz, 2H).
^{13}C NMR: δ = 14.3, 23.5 (d, $^3J_{PC}$ = 5 Hz), 23.9 (d, $^3J_{PC}$ = 4 Hz), 29.3 (d, $^2J_{PC}$ = 4 Hz), 61.9, 73.9 (d, $^2J_{PC}$ = 7 Hz), 169.7 (d, $^3J_{PC}$ = 5 Hz).
^{31}P NMR: δ = 80.2 ($^1J_{PSe}$ = 453 Hz).
HRMS (ESI): *m/z* calcd for $C_{10}H_{21}O_4NaPSSe$ $[M + Na]^+$: 370.9961; found: 370.9961.

The P-Se bond cleavage experiments

Diethyl 2-methyl-2-methylselenylmalonate 7

Methyl iodide (0.16 g, 1.09 mmol) was added to a stirred solution of **3d** (0.12 g, 0.27 mmol) in THF (2 ml) at 0^{o}C under argon atmosphere. Next, a 1M solution of TBAF in THF (0.82 ml, 0.82 mmol) was added dropwise. After 2 h the reaction mixture was poured onto 30 ml of water and was extracted with DCM (3 x 15 ml). Organic extracts were washed with water (3 x 5 ml), brine, and were dried over $MgSO_4$. Evaporation of the solvent leave oily residue which was chromatographed using hexane–ethyl acetate 14:1 solvent system to give 0.04 g (54%) of pure **7** as a colourless oil.
^{1}H NMR: δ = 1.27 (t, 6H), 1.78 (d, $^3J_{H-Se}$ = 8 Hz, 3H), 2.11 (d, $^2J_{H-Se}$ = 12 Hz, 3H), 4.23 (q, 4H).

***Bis*(ethoxycarbonylmethyl)diselenide 6a [25]**

To a stirred solution of **5a** (0.28 g, 0.80 mmol) in THF (5 ml) in open flask a 1M solution of TBAF in THF (0.95 ml, 0.95 mmol) was added dropwise. After 30 min the reaction mixture was poured onto 30 ml of water and was extracted with DCM (3 x 15 ml). Organic extracts were washed with water (3 x 15 ml), brine, and were dried over $MgSO_4$. Evaporation of the solvent leave oily residue which was chromatographed using hexane–ethyl acetate 14:1 solvent system to give 0.082 g (62%) of pure **6a** as a colourless oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, J = 7.1 Hz, 6H); 3.35 (s, 4H); 4.16 (t, 4H).
^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.6, 24.2 ($^1J_{C-Se}$ = 65 Hz), 61.9, 171.4.

Supporting Information:
Full experimental detail, ^{1}H, ^{13}C, ^{31}P, ^{77}Se NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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