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Direct α-chlorination of *O,O*-dialkyl chalcogenophosphonates with phosphorus oxychloride

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Abstract—α-Chlorination of phosphonates, and *O,O*-dialkyl thio- and selenophosphonates involving the direct reaction of their lithiated anion with phosphorus oxychloride is described. The reaction gives good results where previously known methods fail. The role of the chalcogen atom, and the influence of the nature of the alkyl chain with respect to the reactivity are discussed.

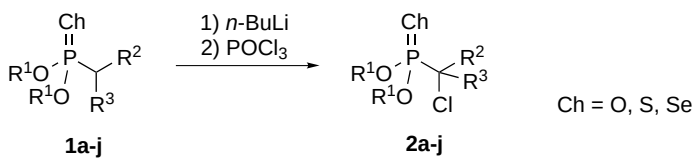
α-Halogenation of phosphonates, and their thio- and seleno-derivatives, is an important way to selectively activate the phosphonate alkyl chain in order to introduce a substituent α to the phosphonyl moiety. Only a few methods are described in the literature; they usually involve the substitution of an existing α-hydroxyl group,[1–6] the reaction of the carbanion of the phosphonate with a halogen donor,[7–18] or a radical[19–21] or electrochemical[22,23] halogenation. Most of the time, the α-position is activated by a substituent, which proved necessary in some cases for the reaction to take place, or to ensure better yields. Finally, no α-halogenation of *O,O*-dialkyl thio- or selenophosphonate is described in the literature.

In the course of our work on the synthesis of non-hydrolyzable analogs of polyphosphates, we investigated the reaction between lithiated anions of *O,O*-dialkyl selenophosphonates and phosphorus oxychloride. We discovered that α-chlorination of the starting material takes place instead of the expected phosphonylation reaction. The use of other potentially chlorinating reagents (*N*-chlorosuccinimide, tetraethylammonium trichloride,[24] sulfuryl chloride) left the selenophosphonates unreacted. Herein, we present the scope of this new halogenation reaction.

We investigated the title reaction with a series of phosphonates, seleno-, and thiophosphonates varying the nature of the phosphorus substituents (Scheme 1). Results are listed in Table 1.

Typical procedure

Dibenzyl methaneselenophosphonate **1a**[26] (335 mg, 0.988 mmol) in 5 ml anhydrous THF at −78°C was treated with 1.6 M *n*-butyllithium in hexane (650 μl, 1.05 equiv.) for 3 min.[27] Then freshly distilled phosphorus oxychloride (100 μl, 1.07 mmol) was rapidly added and the reaction mixture allowed to warm up to room temperature. The solution was hydrolyzed with saturated aqueous ammonium chloride and extracted with ether. The organic layer was dried over magnesium sulfate, and the solvent removed in vacuo. The crude



1a-j **2a-j**

Scheme 1.

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Table 1. α-Chlorination of *O*,*O*-dialkyl chalcogenophosphonates

Entry	Substrate[a]	Ch	R^1	R^2	R^3	Product	Yield (%)[b]		
							n-BuLi, $POCl_3$	*n*-BuLi, CCl_4	NCS, $(BzO)_2$
1	**1a**	Se	Bn	H	H	**2a**	50 [21]	0 [22]	0 [0]
2	**1b**	Se	Bu	H	H	**2b**	52 [19]	0 [9]	0 [0]
3	**1c**	Se	Et	H	H	**2c**	51 [12]	0 [17]	0 [0]
4	**1d**	Se	Et	Pr	H	**2d**	8 [46]	6 [61]	0 [0]
5	**1e**	Se	Et	Me	Me	**2e**	3 [21][c]	2 [83][c]	0 [0]
6	**1f**	Se	Et	Ph	H	**2f**	69 [0]	37 [18]	0 [0]
7	**1g**	Se	Bu	Bn	H	**2g**	25 [60]	Nd	0 [0]
8	**1h**	S	Bu	H	H	**2h**	21 [53]	0 [18]	Nd
9	**1i**	O	Bn	H	H	**2i**	13 [67]	0 [29]	Nd
10	**1j**	O	Bu	Ph	H	**2j**	23 [43]	62 [18]	Nd

[a] Methaneselenophosphonates **1a** and **1b** and methanethiophosphonate **1h** were prepared using a 'one-pot' procedure. Dichloromethylphosphine was reacted with 2 equiv. of an alcohol in the presence of triethylamine, immediately followed by the oxidation of the resulting phosphonite by selenium or sulphur powder. Selenophosphonate **1c–f** were prepared in 85–96% yield by reacting the adequate alkylmagnesium bromide with triethyl phosphite, followed by oxidation with selenium powder. α-Benzylation of **1b** afforded compound **1g** in excellent yield. Phosphonates **1i** and **1j** were prepared as described in the literature.[25]

[b] Recovered starting material is indicated in brackets.

[c] Yield determined by ^{31}P NMR. nd: not determined.

residue was purified by chromatography over silica gel (hexane/ether 98:2 to 95:5) to afford the dibenzyl chloromethaneselenophosphonate **2a**[28] (184 mg, 50%) along with some unreacted starting material **1a** (70 mg, 21%).

Chlorination of methaneselenophosphonates **1a**, **1b**, and **1c** with phosphorus oxychloride proceeded smoothly to afford the α-chlorinated products **2a**, **2b**, and **2c** in almost identical yields, which suggests that the nature of the *O*-alkyl groups is not crucial. By contrast, an increase in the steric hindrance of the *P*-alkyl subsituent of selenophosphonates led to low yields (entries 4 and 5), except when electronic effects may stabilize the intermediate anion (entries 6 and 7).

In the phosphonate and thiophosphonate series (entries 8–10), both yields and completions are lower and decrease in the order Se>S>O. It is likely that complexation of the lithium cation by the chalcogen plays an important role here.[29,30]

For comparison purposes, α-halogenations using *n*-butyllithium/carbon tetrachloride[12,13] and *N*-chlorosuccinimide[20,21] were investigated. As already described by Savignac et al.,[27a] α-chlorination of phosphonates with *n*-butyllithium/carbon tetrachloride does not take place with methanephosphonates such as **1i** (entry 9), but it does for **1j** (entry 10) because of the greater stability of the intermediate anion. For the same reasons, α-chlorination of the thio- and selenophosphonates described here could not be achieved satisfactorily when using this method (entries 1–5 and 8) unless the corresponding anion is stabilized (entries 6 and 7). Also, radical conditions do not seem to be compatible with *O*,*O*-dialkyl selenophosphonates which are fully decomposed within minutes with release of a red selenium precipitate.

In conclusion, we describe herein the first direct α-chlorination of *O*,*O*-dialkyl seleno- and thiophosphonates using a novel reaction involving phosphorus oxychloride as a halogen donor. The procedure we developed proved to be efficient to perform α-chlorination of methanechalcogenophosphonates whereas other existing methods require the activation of the α-position by substituents. Furthermore, selenophosphonates can be conveniently and quantitatively converted into the corresponding phosphonate with oxone[31] or *m*-chloroperbenzoic acid,[32] providing an indirect way to α-halogenated phosphonates. Also, it is noteworthy that direct reaction of the lithiated anions of phosphonates and, to our own experience, of selenophosphonates with iodine hardly affords the α-iodo derivatives, whereas substitution of an existing chlorine atom using sodium iodide gives excellent results.[33] α-Chloroselenophosphonates may then serve as precursors for their α-iodo analogs, as well as for selenophosphonic analogs of α-amino acids.[20] Optimization and further studies of this new halogenation reaction are in progress.

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26. Selected spectral data for compound **1a**: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.41–7.29 (m, 10H); 5.15 (ABX, 2H, $J=11.7$, 12.8 Hz); 4.90 (ABX, 2H, $J=11.7$, 10.2 Hz); 2.01 (d, 3H, $J=14.7$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) 136.14 (d, $J=7.2$ Hz); 128.57; 128.42; 128.19; 69.00 (d, $J=5.8$ Hz); 25.01 (d, $J=103$ Hz). ^{31}P NMR ($CDCl_3$, 121 MHz) 101.2. ^{77}Se NMR ($CDCl_3$, 57 MHz) −268.9 (d, $J=848$ Hz). MS (CI/NH_3) 339 $[M+H]^+$ (34%); 356 $[M+NH_4]^+$ (100%)
27. Deuteration of the anion by addition of D_2O in the reaction mixture indicated that deprotonation is complete after 2 min at −78°C. A deprotonation time of 15 min was used for phosphonates and thiophosphonates, as usually described in the literature. For example, see: (a) Petrova, J.; Coutrot, P.; Dreux, M.; Savignac, P. *Synthesis* **1975**, 658–660; (b) Iorga, B.; Eymery, F.; Savignac, P. *Synthesis* **2000**, 576–580.
28. Selected spectral data for compound **2a**: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.38–7.27 (m, 10H); 5.17 (ABX, 2H, $J=11.7$, 12.3 Hz); 5.02 (ABX, 2H, $J=11.7$, 10.6 Hz); 3.75 (d, 2H, $J=6.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) 135.6 (d, $J=7.2$ Hz); 128.65; 128.61; 128.30; 70.0 (d, $J=5.8$ Hz); 43.3 (d, $J=108$ Hz). ^{31}P NMR ($CDCl_3$, 121 MHz) 93.0. ^{77}Se NMR ($CDCl_3$, 57 MHz) −309.0 (d, $J=885$ Hz). MS (CI/NH_3) 374 $[M+H]^+$ (39%); 391 $[M+NH_4]^+$ (100%).
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