Synthesis and reactivity of *O*-acyl selenophosphates†

Janusz Rachon,* Grzegorz Cholewinski and Dariusz Witt

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The synthesis of several new *O*-acyl selenophosphates were investigated. The stability and reactivity of the products were studied and related to their structure.

O-acyl dithiophosphates are unstable and isomerise to *O*-thioacyl monothiophosphates and *S*-acyl monothiophosphates. Treatment of the above mixture with dithiophosphoric acid gives exclusively *S*-acyl dithiophosphates. These compounds have proved to be efficient, chemoselective thioacylating agents.[1] So far however, the mechanism of the isomerisation has remained undetermined.

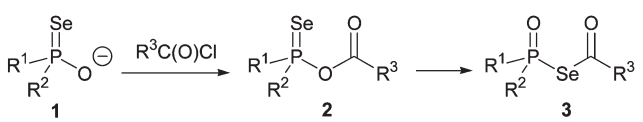
Organoselenium compounds play an important role in biological processes[2,3] and their synthesis has been intensively studied.[4]

The synthesis of the selenium analogues of mixed anhydrides, followed by an investigation of their thermodynamic stability and reactivity, may lead to new and interesting reagents.

To the best of our knowledge, *O*-acyl selenophosphates **2** have not been the subject of systematic studies. Nonetheless, the reaction of monoselenophosphoric acid salts **1** with acyl chlorides has been reported to yield *O*-acyl derivatives **2** exclusively,[5] even though monoselenophosphoric acid salts **1** are ambidentate nucleophiles.

We have synthesized a wide range of mixed anhydrides: *O*-acyl monoselenophosphates, monoselenophosphonates and monoselenophosphinites **2**, and also investigated their thermodynamic stability and reactivity (Scheme 1).

The results of our experiments are presented in Table 1. Syntheses of type **2** compounds were complete after 15 min at room temperature in THF solvent. Subsequently, we observed that some mixed anhydrides of type **2** isomerised to their *Se*-acyl derivatives **3**. The diagnostic ^{31}P NMR coupling constant $^{1}J_{P–Se}$ was useful for monitoring the isomerisation process.[6] The yield of isomerised product depended on the substituents at the P and C_{acyl} atoms (see Table 1). Cyclic derivatives **2a–b**, **2e–f** (entries 1, 2, 5 and 6) displayed higher degrees of isomerisation than acyclic derivatives **2k–n** (entries 11–14). Higher yields of *Se*-acyl derivatives **3** were observed for alkyl carboxylic acid mixed anhydrides **2b**, **2f** and **2l** (entries 2, 6, 12) than for aryl carboxylic acid mixed anhydrides **2a**, **2e** and **2k** (entries 1, 5, 11). The



Scheme 1 The synthesis of mixed anhydrides of types **2** and **3**.

† Electronic Supplementary Information (ESI) available: Experimental conditions and characterisation of all presented compounds. See http://www.rsc.org/suppdata/cc/b5/b502473k/

*rachon@chem.pg.gda.pl

anhydrides containing electron-withdrawing (**2d**) and electron-donating (**2c**) groups attached to their carboxyl functionalities could not be isomerised to a corresponding **3** derivative, whereas this was seen for compounds **2a** and **2e**. This observation excludes the possibility that the isomerisation takes place *via* an ionic mechanism.

When a mixture of anhydrides **2h** and **2o** were stirred together at room temperature overnight, acyl group exchange was observed that lead to the formation of all possible anhydrides (**2g**, **2h**, **2o** and **2p**). Moreover, there was no isomerisation of these anhydrides either in the mixture or separately (Table 1, entries 7, 8, 15, and 16). When a mixture of **2b** and **2k** was stirred overnight, acyl exchange again occurred and anhydrides **2a**, **2b**, **2k**, and **2l** were formed. In this case however, isomerisation was observed in the mixture and derivatives **3a**, **3b**, **3k** and **3l** were formed respectively—similar to the behaviour of the separate anhydrides (Table 1, entries 1, 2, 11, and 12). As can be seen, the rapid acyl group exchange of type **2** compounds is responsible for the formation of crossover products **3a** and **3l**. The most interesting behaviour of all was observed for two mixtures; one of **2b** and **2o**, and the other of **2k** and **2p**. Upon acyl group exchange, all possible anhydrides were observed. However in these mixtures, only **3b** plus **3a** and **3k** plus **3l** were formed respectively. We can therefore conclude (i) acyl group exchange is more rapid than isomerisation and (ii) isomerisation of one type **2** anhydride cannot initiate the isomerisation of another (*i.e.* there is no entrainment effect).

In the next stage of the study we took further steps to verify our proposed isomerisation mechanism. Our working hypothesis assumed O–C(O) bond homolysis and formation of monoselenophosphoric and carbonyl radicals. Further recombination *via* selenium could thus afford the isomeric derivatives **3**.

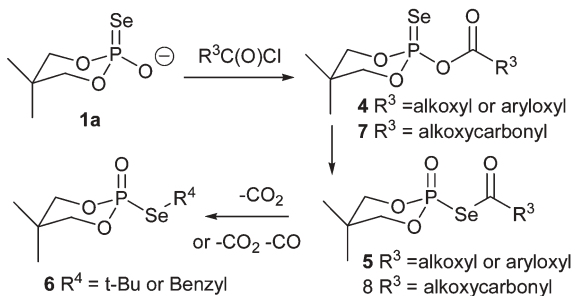
We therefore performed the reactions of monoselenophosphoric acid salt **1a** with various chloroformates (Scheme 2 and Table 2, R^3 = alkoxy or aryloxy). ^{31}P NMR analysis of the crude reaction mixtures indicated that *Se*-alkoxycarbonyl-monoselenophosphates **5** were the major products together with traces of *O*-alkoxycarbonyl-monoselenophosphates **4**. This means that isomerisation is very rapid and occurs upon formation of the type **4** compound.

Surprisingly, in the reaction of salt **1a** with benzyl chloroformate, the *Se*-benzyl ester **6a** was obtained, probably *via* decarboxylation of **4a** or **5a**. **5a** was also detected and isolated from the reaction mixture (Table 2). The formation of **6a** in the mixture supports the hypothesis of O–C(O) bond homolysis. The benzyloxycarbonyl and monoselenophosphoric radicals can react together to give compound **5a**, or undergo decarboxylation to give a benzyl radical. This radical may then react with **4** or a monoselenophosphoric radical to afford **6a**. Decarboxylation of the benzyloxycarbonyl radical is very rapid,[7] meaning the

Table 1 Preparation of mixed anhydrides **2a–x** and their isomerisation to the corresponding *Se*-acyl selenophosphates **3**

		R^1	R^2	R^3	Yield[a] of **2**(%)	^{31}P NMR (ppm)/J_{P-Se} (Hz) **2**	**3**	Yield[a] of **3** (%)
1	**2a**			*p*-ClPh	71	51.9/1056	3.22/416	29
2	**2b**			t-Bu	[c]	53.0/1059	3.42/419	97
3	**2c**			*p*-MeOPh	69	52.4/1057		[d]
4	**2d**			*p*-NO_2Ph	45	51.4/1064		[d]
5	**2e**			Ph	[c]	52.1/1055	3.39/446	33
6	**2f**			CH_3	[c]	51.2/1048	3.51/420	86
7	**2g**	i-PrO	i-PrO	*p*-ClPh	75	60.1/990		[d]
8	**2h**			t-Bu	71	60.4/983		[d]
9	**2i**			*p*-MeOPh	67	60.0/984		[d]
10	**2j**			*p*-NO_2Ph	68	60.1/996		[d]
11	**2k**	PhO	PhO	*p*-ClPh	66	53.2/1055	7.36/480	8
12	**2l**			t-Bu	[c]	53.7/1049	9.84/510	23
13	**2m**			*p*-MeOPh	[c]	53.4/1047	3.83/473	17
14	**2n**			*p*-NO_2Ph	53	53.0/1060	6.04/[b]	5
15	**2o**	EtO	Ph	*p*-ClPh	53	87.4/918		[d]
16	**2p**			t-Bu	45	86.5/911		[d]
17	**2r**			*p*-MeOPh	43	86.5/918		[d]
18	**2s**			*p*-NO_2Ph	45	88.2/924		[d]
19	**2t**	Ph	Ph	*p*-ClPh	46	81.2/859		[d]
20	**2u**			t-Bu	43	78.6/852		[d]
21	**2w**			i-Bu	48	78.4/852		[d]
22	**2x**			CH_3	53	78.9/852		[d]

[a] Isolated yield. [b] Signal too small to measure. [c] Too unstable to isolate, formation confirmed by ^{31}P NMR. [d] Isomerisation of the type **2** anhydride was not observed.



Scheme 2 The reactions of chloroformates or alkoxalyl chlorides with salt **1a**.

Table 2 The products of the reactions of salt **1a** with chloroformates or alkoxalyl chlorides

R^3	^{31}P NMR (ppm)/J_{P-Se} (Hz)		
$PhCH_2O$		**5a** 4.48/415 (31%)[a]	**6a** 14.4/486 (65%)[a]
CH_3CH_2O		**5b** 4.480/418	[b]
$(CH_3)_2CHCH_2O$		**5c** 4.77/421	[b]
CH_2=$C(CH_3)O$		**5d** 4.00/414	[b]
PhO		**5e** 3.69/411	[b]
$PhCH_2OC(O)$	**7a** 62.0/942	**8a** 4.03/428	**6a** 14.4/486
$CH_3CH_2OC(O)$	**7b** 49.8/[c]	**8b** 5.62/414	[b]
$(CH_3)_3COC(O)$	**7f** 61.0/936	**8f** 4.46/424	**6b** 16.4/571

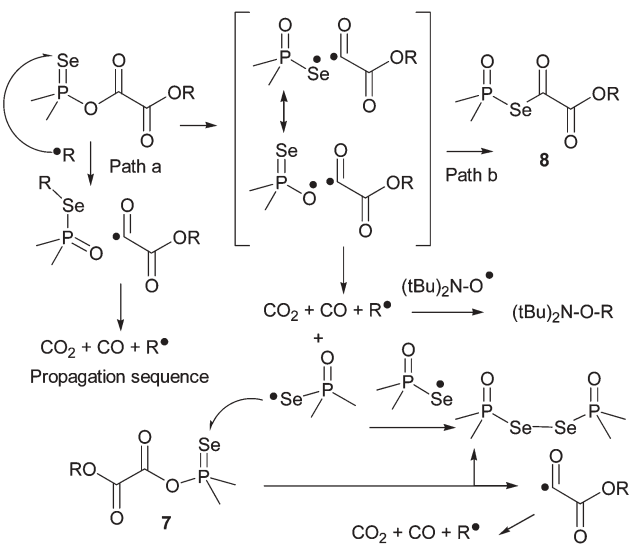
[a] Yield based on ^{31}P NMR data. [b] Formation of the corresponding type **6** compound was not observed. [c] Signal too small to measure.

formation of the stable benzyl radical is likely to be the mechanism's most crucial stage. This explains why products **6b–e** were not formed from compounds **5b–e**.

In the next stage of our study we carried out reactions of monoselenophosphoric acid salt **1a** with alkoxalyl chlorides (Scheme 2, R^3 = alkoxycarbonyl). Benzyloxalyl chloride and *tert*-butoxalyl chloride gave *O*-alkoxalyl-monoselenophosphates **7a** and **7f**. Subsequently **7a** and **7f** yielded *Se*-alkyl esters **6a** and **6b** respectively. Additionally, *Se*-alkoxalyl-monoselenophosphates **8a** and **8f** were detected in these reaction mixtures.

In contrast, the reaction of salt **1a** with ethoxalyl chloride gave *Se*-ethoxalyl-monoselenophosphate **8b** as the predominant product. The formation of the corresponding type **6** compound in the reaction mixture was not observed (Table 2).

The results of our experiments strongly suggest a radical mechanism for the reaction (Scheme 3). Stable alkyl radicals (R$^\bullet$) could be generated by O–C(O) bond homolysis, this would then be followed by decarbonylation and decarboxylation. R$^\bullet$ could



Scheme 3 The proposed mechanism of isomerisation.

attack the selenium atom of a type **7** structure to start the propagation sequence to produce the type **6** ester (Path a). Alternatively, the isomeric type **8** anhydride could be the main reaction product if the stability of $R^{\bullet}$ was relatively low (Path b).

Isomerisation of **7a** and **7f** in the presence of di-*tert*-butyl nitroxide gave bis-(2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinanyl) diselenide and *N*,*N*-di-*tert*-butyl-*O*-alkyl-hydroxylamine. Isolation of the latter demonstrated the presence of benzyl and *tert*-butyl radicals in the reaction mixture and strongly supports our proposed radical mechanism for the reactions of types **2**, **4** and **7** anhydrides (>P(Se)O–). According to our results, O–C(O) bond homolysis is the most likely first step in the isomerisation of these anhydrides to their type **3**, **5** and **8** Se-bonded derivatives (>P(O)Se–) respectively.

Janusz Rachon,* Grzegorz Cholewinski and Dariusz Witt
Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, Narutowicza 11/12, 80-952, Gdansk, Poland. E-mail: rachon@chem.pg.gda.pl; Fax: 48 58 347 2694; Tel: 48 58 347 1234

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