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Oxidation in Organophosphorus Chemistry: Potassium Peroxymonosulphate

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Abstract : *Potassium peroxymonosulphate (Oxone®) is used as an efficient, chemoselective and stereoselective oxidizing agent for a wide variety of phosphorous, phosphothio- and phosphoseleno-compounds.* © 1999 Elsevier Science Ltd. All rights reserved.

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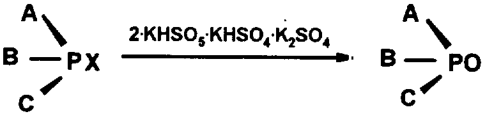
In our search for an effective oxidizing agent capable of converting nucleoside methanephosphononothio(seleno)ates to the corresponding methanephosphonates (PS→PO) *with retention of configuration, and without reaction at other reactive centres* in nucleotides [1] we have turned our attention to potassium peroxymonosulphate (Oxone®) [2,3]. Here we present the results of our studies on an application of Oxone for chemoselective and stereospecific oxidations of various P(III), phosphothio-, and phosphoseleno derivatives [4-7].



X = lone electron pair, S, Se
A, B, C = R, RO, RS, R_2N

Standard procedure: Into a vigorously stirred solution of substrate (0.1 mmol) in THF/MeOH (1:1 v/v, 2mL), a buffered solution of Oxone (2 mL, 0.1 M., pH 6.5-7) was added in one portion, at ambient temperature. After the reaction was completed (TLC or ^{31}P NMR assay), aqueous $Na_2S_2O_3$ (0.065 M, 2 mL) was added, with stirring continued for additional 2 min., followed by extraction of the reaction mixture (3-4 times) with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and solvents were removed under reduced pressure. Products were purified by means of a silica gel column chromatography, or distillation under reduced pressure.

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Under the above conditions P(III) compounds can be oxidized in minutes providing corresponding phosphoryl derivatives in satisfactory yields. Oxidation of $(Me_2N)_3P$ and $(MeO)_3P$ occurs relatively quickly (2-5 minutes) but the product of oxidation of $(MeO)_3P$ contains about 20% of $(MeO)_2P(O)H$, resulting from competitive hydrolysis of the substrate in the reaction medium. Similarly, *O,O,O*-triethyl phosphate obtained from oxidation of $(EtO)_3P$ with Oxone under the conditions specified above was contaminated with about 10% of $(EtO)_2P(O)H$.

Ph_3PS dissolved in THF and stirred with 2 molar equivalents of Oxone in a buffered solution of sodium acetate (pH 6-7) is quantitatively converted into Ph_3PO within 30 minutes, while treatment of Ph_3PSe with buffered Oxone solution under identical conditions causes immediate and quantitative formation of Ph_3PO.

O,O,O-trimethyl phosphorothioate is completely converted under the standard conditions into *O,O,O*-trimethyl phosphate within 30 minutes (Entry 11), while complete conversion of potassium *O,O*-dimethyl phosphorothioate into potassium *O,O*-dimethyl phosphate (pH 7, ambient temperature) requires 18 hours (Entry 12).

The results of our experiments are collected in Table 1.

TABLE 1

Entry	**Substrate**	**^{31}P NMR δ (ppm)**	**Product**	**^{31}P NMR δ (ppm)**	**Yield (%)[a]**
1	$(MeO)_3P$	142.07	$(MeO)_3PO$	2.84	75[b](72)
2	$(EtO)_3P$	140.1	$(EtO)_3PO$	-0.36	85[c](78)
3	$PhP(OMe)_2$	158.3	$PhP(O)(OMe)_2$	22.5	85 (80)
4	$(Me_2N)_3P$	122.4	$(Me_2N)_3PO$	26.29	93
5	Ph_3P	-4.84	Ph_3PO	30.05	100 (98)
6	Ph_3Pse	36.1; $J_{P\text{-}Se}$=738 Hz	Ph_3PO	30.05	100 (96)
7	$(iPrO)_2MePSe$	109.85; $J_{P\text{-}Se}$=1023 Hz	$(iPrO)_2MePO$	34.2	85(80)
8	$(EtO)_3Pse$	71.8; $J_{P\text{-}Se}$=935 Hz	$(EtO)_3PO$	-0.36	90 (85)
9	Ph_3PS	43.93	Ph_3PO	30.5	100 (98)
10	(R)MeP(S)NHPh[d] diast. SLOW- [Sp]	78.58	(R)MeP(O)NHPh diast. SLOW- [Rp]	30.93	95 (92)
11	$(MeO)_3PS$	73.95	$(MeO)_3PO$	0.95	83 (70)
12	$(EtO)_2PSOK$	55.39	$(EtO)_2POOK$	1.4	100 (90)
13	$(EtO)_2P(O)SEt$	27.12	No reaction		[e]

[a] Yields calculated from ^{31}P spectra; in brackets are given yields after purification.

[b] Product was contaminated with $(MeO)_2POH$ (δ 11.18 ppm)

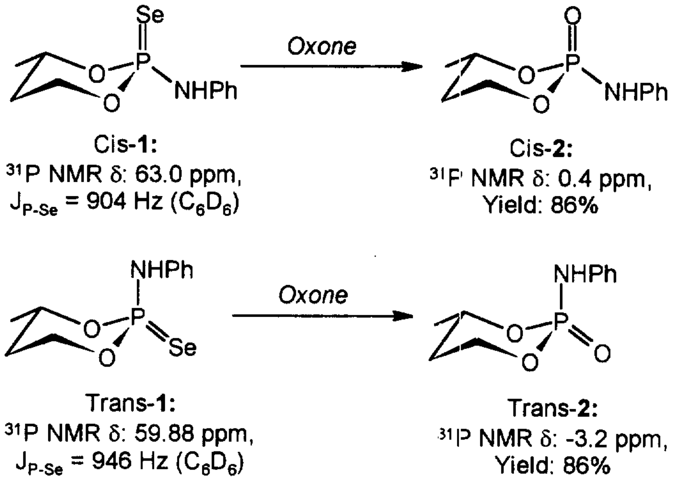
[c] Product was contaminated with $(EtO)_2POH$ (δ 7.97 ppm)

[d] R: protected nucleoside moiety, R = *2'*-Deoxy-5'-*O*-(4,4'-dimethoxytrityl)-7,8-dihydro-(N^{6}-benzoyl) adenin-8-yl (diastereomer SLOW corresponds to a slower migrating isomer during a silica gel column chromatography)

[e] After 24 hours no changes were observed

It is worth emphasising that under the mild conditions the thioalkyl substituent (Entry 13) in *O,O,S*-triethyl phosphorothiolate stays intact, in contrast to more drastic conditions of detoxification of some warfare agents containing substituted *S*-alkyl ligands by means of Oxone (0.1M Oxone pH 1.9)[6].

The stereochemistry of P(Se)→P(O) conversion was elucidated using the diastereomers of acyclic methanephosphonothioanilidates (entry 10 in Table above) and, independently, *cis*- and *trans*-2-anilino-2-seleno-4-methyl-1,3,2-dioxaphosphorinanes **1**, since their stereochemistry, and that of their 2-oxo analogues **2**, had been established earlier [9,10]. 2-Anilino-2-seleno-4-methyl-1,3,2-dioxaphosphorinanes (**1**), separated into *cis-1* and *trans-1* isomers, were individually treated with Oxone (Scheme 1) under standard conditions.



Cis-**1**: ^{31}P NMR δ: 63.0 ppm, $J_{P\text{-}Se}$ = 904 Hz (C_6D_6)

Cis-**2**: ^{31}P NMR δ: 0.4 ppm, Yield: 86%

Trans-**1**: ^{31}P NMR δ: 59.88 ppm, $J_{P\text{-}Se}$ = 946 Hz (C_6D_6)

Trans-**2**: ^{31}P NMR δ: -3.2 ppm, Yield: 86%

Scheme 1

The complete conversion of **1** into **2** occurred in ca. 5 minutes. As depicted within Scheme 1, this conversion **occurs with predominant retention of configuration at the phosphorus atom.** However, during oxidation of *cis*-**1** about 5% of the isomer *trans*-**2** was formed, as calculated from ^{31}P NMR spectrum, while product *trans*-**2**, resulting from oxidation of *trans*-**1** was contaminated with 8% of *cis*-**2** isomer. The reasons of partial P-epimerisation are obscure. However, the results of oxidation of other diastereomerically well defined acyclic phosphoramidothioates (Entry 10, and others not presented here, [11]) confirm the conclusion concerning the highly stereoretentive mode of the reaction under discussion here [1,7].

In conclusion, Oxone can be used for mild oxidation of wide variety of P(III), P(S) and P(Se) compounds, without affecting other functional groups like thioalkyl or amino groups attached to the phosphorus atom [12].

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