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STEREOSELECTIVE AND CHEMOSELECTIVE OXIDATION OF PHOSPHOROTHIONATES USING MMPP

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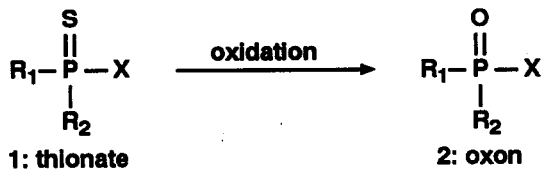
Abstract: *MMPP (monoperoxyphthalic acid, magnesium salt) converts phosphorothionates to the corresponding oxons in good yield with excellent chemoselectivity and stereoselectivity.*

The oxidative conversion of a phosphorothionate (1; P=S) linkage to a phosphate or oxon (2; P=O) is an important biochemical process (Eq. 1).[1] This transformation is responsible for the *in vivo* metabolic activation of phosphorothionate insecticides, a precursory step in route to the intoxication of the target organism. The oxon form is more hydrolytically labile than the thionate[2] and the rate, extent, and specificity of this oxidation also bears impact on the detoxication of the insecticide. Conversely, a thionate linkage adds stability to phosphoester bonds, making the P=S moiety a protecting group or prodrug when selective carboxyester hydrolysis is desired.[3] As such, reagents that can precisely simulate the biological oxidation process are valued tools in organophosphorus chemistry.



1: thionate 2: oxon

Eq. 1.

Our interest in this process evolved from an investigation concerning the oxidation of the phosphorodithioate insecticide, malathion (1: $R_1 = R_2 = OMe$, $X = SCH(CO_2Et)CH_2CO_2Et$) to malaoxon (2: $R_1 = R_2 = OMe$, $X = SCH(CO_2Et)CH_2CO_2Et$). In this instance, both thionate and thiolate (P-S-R) functional groups are present and subject to oxidation. Therefore, we sought a chemoselective reagent for this transformation. Prior work showed that several oxidants had been used for the thionate-oxon conversion including organic peracids,[4] enzymatic systems,[5] hydrogen peroxide,[6] dimethyl selenoxide,[7] trifluoroacetic anhydride,[8] dimethyldioxirane[9] and potassium permanganate.[10] A brief study of the malathion to malaoxon conversion with these oxidants showed that meta-chloroperoxybenzoic acid (m-CPBA) was superior, although the yield was modest (20-25%). We turned our attention to MMPP (monoperoxyphthalic acid, magnesium salt) as a substitute.[11] We were pleased to find that MMPP cleanly oxidized malathion to malaoxon in improved yield (50-55%). This may be due, in part, to the lower reactivity of MMPP (refluxing CH_2Cl_2) as compared to m-CPBA (0 °C in CH_2Cl_2).

Based on this success, we examined the oxidation of a series of simple phosphorothionate compounds (Eq. 1; $R_1 = R_2 = OMe$) with MMPP. In a representative experiment, 1.1 equivalents of MMPP was added to a 1.0 M CH_2Cl_2 solution of phosphorothionate. The reaction was refluxed for a minimum of 12 h, extracted twice with saturated carbonate and once with brine, dried over sodium sulfate, and concentrated to an oil. Phosphorus-31 analysis (P-31) of the reaction generally showed one peak corresponding to the oxon. The results of this study are shown in Table 1. In all cases, good

yields of the corresponding oxons were obtained with water soluble products giving lower recovery. No racemization at the chiral thiosuccinate carbon in **1a/1b** was observed. The oxidation of chlorpyriphos methyl (**1d**) gave no N-oxide formation.

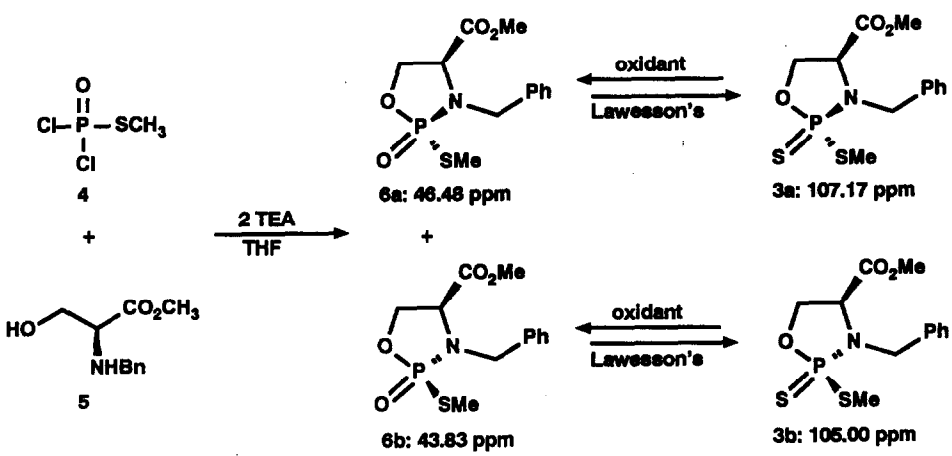
Table 1. Conversion of Thionates to Oxons (Eq. 1)

Entry	X	substrate δ P-31[a]	yield (%)[b]	product δ P-31[a]
1a (R_C-malathion)	-SCH(CO_2Et)CH_2CO_2Et	96.01	52	28.29
1b (S_C-malathion)	-SCH(CO_2Et)CH_2CO_2Et	96.01	53	28.29
1c (parathion methyl)	-O-Ph-p-NO_2	66.07	72	-4.31
1d (chlorpyriphos methyl)	-O-3,5,6-Cl_3-2-pyridinyl)	65.45	44	-4.75
1e (fenchlorphos)	-O-2,3,5-Cl_3-Ph	66.73	56	-4.18
1f	-NHBn	75.75	62	11.81
1g	-SMe	100.08	51[c]	32.54

a. H_3PO_4 external standard, b. Following column chromatography, c. non-aqueous work-up

Several investigators used chemical oxidants, particularly m-CPBA, to imitate the stereoselectivity of the mixed function oxidases. Since MMPP required more rigorous conditions than m-CPBA for complete conversion to oxon, we postulated that the mild nature of MMPP may be useful in the corresponding stereoselective process. Thus, we prepared the serine-based, diastereomeric 1,3,2-oxazaphospholidines **3a** and **3b** as model substrates for the study of the relative efficacy of oxidizing agents (Scheme 1). Compounds **3a** and **3b** were prepared according to our prior report using thiomethylphosphoric dichloride (**4**) and N-benzyl methyl serinoate (**5**).[12] The P=O diastereomers

Scheme 1



(**6a/6b**)[13] were separated and treated in parallel reactions with Lawesson's reagent[14] to afford the 2-thiooxo-1,3,2-oxazaphospholidines (**3a/3b**)[15] in 90% yield. With diastereomeric pairs of thiones and

oxons available, the oxidation could be monitored for % conversion and stereoselectivity by P-31 NMR.

Compound **3a** was treated with several different oxidizing agents, the product evaluated by P-31 for diastereomeric excess and the yield recorded (Table 2). Our studies show that MMPP was superior with respect to the combined features of degree of stereoselectivity introduced (100% retention of configuration) and the yield obtained. Compound **3b** gave similar results. Potassium permanganate ($KMnO_4$), trifluoroacetic anhydride (TFAA) and dimethyldioxirane (DMD) gave excellent stereoselectivity but low yields. TFAA oxidation also led to a complex mixture of phosphorus-containing products. Oxone ($2KHSO_5/KHSO_4/K_2SO_4$) did not react with **3a** or **3b**. Particularly noteworthy was the somewhat poorer stereoselectivity obtained with m-CPBA, which gave superior results in other systems. Again, this disparity may be due to the high reactivity of m-CPBA.

An interesting addition to this study was the finding that Lawesson's reagent thionates the P=O moiety with 100% retention of stereochemistry. Thus, the P=O to P=S interchange can be conducted with retention of configuration using the combination of Lawesson's reagent and MMPP.

Table 2. Conversion of 3a to 6a or 3b to 6b

Oxidant (eq.)	Conditions	Yield (%)	d.e.	Comment/Result (P-31)
3a				
MMPP (1.1)	CH_2Cl_2/reflux	100 (62[a])	100	only product observed
30% H_2O_2	Dioxane/reflux	0	0	3a and decomposition
$KMnO_4$	18-Cr-6/CH_2Cl_2/reflux	10	100	3a and decomposition
5.5 M tBuOOH	Dioxane/reflux	0	0	99% 3a recovered
m-CPBA	CH_2Cl_2/0 °C	100	79	3.85:1 ratio, only products
TFAA	neat/reflux	44	100	56% other P=O products
DMD (1.5)	CH_2Cl_2/rt	26	100	74% 3a observed
oxone (1.1)	CH_2Cl_2/rt	0	0	no reaction
3b				
MMPP (1.1)	CH_2Cl_2/reflux	100 (48[a])	100	only product observed

a. isolated yield

In conclusion, MMPP is a mild, stereoselective and chemoselective reagent for the oxidation of phosphorothionates and phosphorothiolothionates to the corresponding oxons.

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13. **Methyl (2*S*, 4*S*)- and (2*R*, 4*S*)-2-thiomethyl-2-oxo-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylate (6a and 6b).** Purification by flash chromatography (100% diethyl ether) produced non-polar (R_f = 0.24) and polar fractions (R_f = 0.14) in a net yield of 4.18 g (63%). Anal. Calcd for; C, 47.84, H, 5.35, N, 4.65: Found; C, 48.10, H, 5.34, N, 4.71. **6a (non-polar):** $[\alpha]_D^{26}$ +1.36 (c, 0.88, $CHCl_3$). ^1H NMR: δ 7.43-7.26 (m, 5), 4.55 (dd, 1, *J* = 14.5, 8.45 Hz), 4.53-4.47 (m, 1), 4.30 (ddd, 1, *J* = 15.65, 9.3, 3.9 Hz), 4.18 (dd, 1, *J* = 14.7, 10.0 Hz), 3.89 (ddd, 1, *J* = 9.5, 7.9, 3.9 Hz), 3.72 (s, 3), 2.35 (d, *J* = 16.4 Hz). ^{13}C NMR: δ 170.60 (d, *J* = 5.3 Hz), 135.35 (d, *J* = 2.8 Hz), 128.76 (2), 128.68 (2), 128.04, 66.71 (d, *J* = 2.5 Hz), 56.60 (d, *J* = 15.7 Hz), 52.52, 46.98 (d, *J* = 6.6 Hz), 13.28 (d, *J* = 5.0 Hz). **6b (polar):** $[\alpha]_D^{26}$ -6.03 (c, 1.21, $CHCl_3$). ^1H NMR: δ 7.39-7.30 (m, 5), 4.57-4.44 (m, 2), 4.35-4.23 (m, 2), 3.75 (s, 3), 3.74 (ddd, 1, *J* = 16.3, 7.2, 1.9 Hz), 2.36 (d, 3, *J* = 15.5 Hz). ^{13}C NMR: δ 170.51 (d, *J* = 4.9 Hz), 135.32 (d, *J* = 2.7 Hz), 128.74 (2), 128.66 (2), 128.01, 66.76 (d, *J* = 2.6 Hz), 56.69 (d, *J* = 15.7 Hz), 52.61, 47.90 (d, *J* = 6.4 Hz), 13.47 (d, *J* = 5.1 Hz).
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15. **Methyl (2*S*, 4*S*)- and (2*R*, 4*S*)-2-thiomethyl-2-thioxo-3-benzyl-1,3,2-oxazaphospholidine-4-carboxylate (3a and 3b).** Refluxing a 0.25 M solution of **6a** or **6b** in toluene with 0.55 eq of Lawesson's reagent for 3 h followed by concentration *in vacuo* gave a yellow oil that was purified by flash chromatography (50:50, petroleum ether : ether). Anal. Calcd for; C, 45.42, H, 5.08, N, 4.41: Found; C, 45.33, H, 5.05, N, 4.27. **3a (non-polar):** 92% yield. $[\alpha]_D^{26}$ +6.40 (c, 1.00, $CHCl_3$). ^1H NMR: δ 7.49-7.43 (m, 2), 7.38-7.30 (m, 3), 4.62 (dd, 1, *J* = 14.6, 11.0 Hz), 4.50 (ddd, 1, *J* = 9.3, 9.3, 7.7 Hz), 4.38 (ddd, 1, *J* = 14.0, 9.4, 4.5 Hz), 4.25 (dd, 1, *J* = 14.6, 9.4 Hz), 3.87 (ddd, 1, *J* = 10.4, 7.7, 4.4 Hz), 3.70 (s, 3), 2.39 (d, 3, *J* = 17.9 Hz). ^{13}C NMR: δ 170.59, 135.55 (d, *J* = 3.9 Hz), 128.93 (2), 128.68 (2), 128.01, 67.27 (d, *J* = 5.0 Hz), 57.21 (d, *J* = 13.4 Hz), 52.57, 47.59 (d, *J* = 7.5 Hz), 16.96 (d, *J* = 4.7 Hz). **3b (polar):** 93% yield. $[\alpha]_D^{26}$ -7.20 (c, 0.45, $CHCl_3$). ^1H NMR: δ 7.39-7.29 (m, 5), 4.56 (dd, 1, *J* = 14.9, 9.5 Hz), 4.52 (ddd, 1, *J* = 22.4, 9.5, 1.5 Hz), 4.40 (ddd, 1, *J* = 9.55, 6.7, 2.1 Hz), 4.28 (dd, 1, *J* = 14.9, 5.4 Hz), 3.82 (ddd, 1, *J* = 17.7, 6.8, 1.4 Hz), 3.79 (s, 3), 2.42 (d, 3, *J* = 17.85 Hz). ^{13}C NMR: δ 170.43, 135.94 (d, *J* = 6.4 Hz), 128.80 (2), 128.60 (2), 128.05, 68.17 (d, *J* = 5.5 Hz), 57.72 (d, *J* = 11.3 Hz), 52.70, 47.14 (d, *J* = 7.9 Hz), 17.34 (d, *J* = 3.9 Hz).

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