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Selective Sulfur Oxygenation in Phosphoroamidate, Thionophosphate, and Thiophosphate Agrochemicals by Perfluoro-*cis*-2,3-dialkyloxaziridine

Marco Terreni[a], Massimo Pregnolato*[a], Giuseppe Resnati[b] and Emilio Benfenati[c]

[a] Dip. di Chimica Farmaceutica, Università degli Studi, V. Taramelli 12, I-27100 Pavia, Italy.

[b] CNR- Centro Studio Sostanze Organiche Naturali, Politecnico, V. Mancinelli 7, I-20131 Milano, Italy.

[c] Lab. di Farmacologia e Tossicologia Ambientale, Ist. di Ricerche Farmacologiche "Mario Negri", V. Eritrea 62, I-20157 Milano, Italy.

Abstract: Several organophosphorus agrochemicals **2a-g** with thioether, phosphoramidic, phosphorothioic, and phosphorothionic functions were reacted with perfluoro *cis*-2-*n*-butyl-3-*n*-propyloxaziridine **1**. The selective oxygenation of sulfide function to give sulfoxide derivatives **3a-g** occurred in high yields without overoxidation to sulfone products. Sulfoxides **3a-e** were further oxidized under mild conditions to the corresponding sulfones **4a-e**. All the products are themselves of interest as analytical environmental standards and their preparation is described in detail.

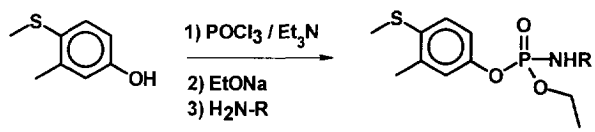
Oxidation of sulfides to sulfoxides and sulfones is a very important pathway in the metabolism of biologically active compounds such as sulfur containing aminoacids, proteins, vitamins, drugs, and other xenobiotics.[1,2] Many examples of sulfur oxygenation in pesticide metabolism are reported.[3] As part of a project aimed at monitoring organophosphorus agrochemicals **2** in the environment,[4] we needed easy, efficient access to their oxidative metabolites. Preparation of these products through direct oxidation of commercially available pesticides and related compounds **2** appeared particularly convenient. However, the literature showed that the reaction was not straightforward. For instance, hydrogen peroxide oxidation of demeton-S-methyl **2d** afforded the corresponding sulfoxide only in a 66% yield.[5-7]

A wide range of electrophilic, nucleophilic, or one electron transfer type oxidants have been employed for sulfide oxygenation, but few of them are highly selective and able to stop at the sulfoxide level without significant overoxidation to sulfones.[8] Recently, perfluoro-*cis*-2,3-dialkyloxaziridines have been shown to work as new, effective, neutral, and aprotic oxidizing agents. They oxidize secondary alcohols[9] and ethers[10] to the corresponding ketones at room temperature, hydroxylate unactivated tertiary aliphatic C-H bonds[11,12] and transform alkenes into epoxides.[13] More interestingly, aliphatic and aromatic sulfides have been oxidized chemoselectively to the corresponding sulfoxides and sulfones.[14] The reaction conditions were notably mild and we thus decided to study the oxygenation of organophosphorus agrochemicals **2** by 3-fluoro-3-(heptafluoropropyl)-2-(nonafluorobutyl)-*cis*-oxaziridine **1**. In this paper we describe how the corresponding sulfoxides **3** and sulfones **4** and **6** can be obtained in almost quantitative yields when respectively one and two equivalents of the oxidizing agent are used.

RESULTS AND DISCUSSION

Synthesis of thioethers. (1-Methylethyl)phosphoramidic acid ethyl 3-methyl-4(methylthio)phenyl ester **2b** (Fenamiphos)[15] is a phosphoramido ester pesticide used for the control of soil and leaf nematodes.[16] Its metabolism includes hydrolysis[17] and dealkylation[18,19] of the phosphoramido group to form 3-methyl-4-methylthiophenol **2a** and phosphoramidic acid ethyl 3-methyl-4(methylthio)phenyl ester **2c** (des-isopropyl fenamiphos), respectively. Other important metabolic pathways involve oxidative elaboration of the thioether function directly on **2b** or on metabolic products **2a,c** to give the corresponding sulfoxides **3a-c** and sulfones **4a-c**[17].

Phosphoramidates **2b,c** were obtained by reaction of 3-methyl-4-methylsulfenylphenol **2a** with phosphorodichlorhydric acid *O*-alkyl ester and the desired amine (eq. 1).



(eq. 1)

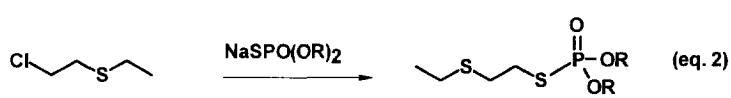
2a

2b R = C_3H_7-*iso*

2c R = H

O,O-Dimethyl *S*-[2-(ethylthio)ethyl]phosphorothioate **2d** (demeton-S-methyl) and its ethyl ester analogue demeton-S[20] **2e** are used as acaricides[16] and as systemic and contact insecticides. Metabolism involves oxidation of the thioether moiety[3,21] to give the corresponding sulfoxides **3d,e** and sulfones **4d,e** also for these compounds. In vitro rearrangement of demeton-S-methyl **2d** and demeton-S **2e** to the corresponding thiono analogues can occur[22] to produce phosphorothioic acid *O,O*-dimethyl *O*-[2-(ethylthio)ethyl] ester **2f** (demeton-O-methyl) and phosphorothioic acid *O,O*-diethyl *O*-[2-(ethylthio)ethyl] ester **2g** (demeton-O) respectively. Once again, a metabolic pathway of these latter pesticides involves oxidation at the thioether moiety[23,24] to give phosphorothioic acid *O,O*-dimethyl *O*-[2-(ethylsulfinyl)ethyl] ester **3f** and its *O,O*-diethyl analogue **3g** as well as to the corresponding sulfones, phosphorothioic acid *O,O*-dimethyl *O*-[2-(ethylsulfonyl)ethyl] ester and phosphorothioic acid *O,O*-diethyl *O*-[2-(ethylsulfonyl)ethyl] ester.

Phosphorothioates **2d** and **2e** were prepared by reaction between sodium *O,O*-dialkylphosphorothioates and 2-chloroethylethylsulfide[25] (eq. 2).

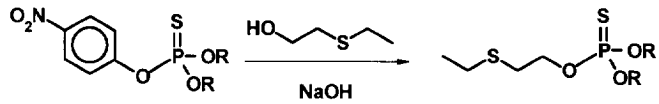


(eq. 2)

2d R = CH_3

2e R = C_2H_5

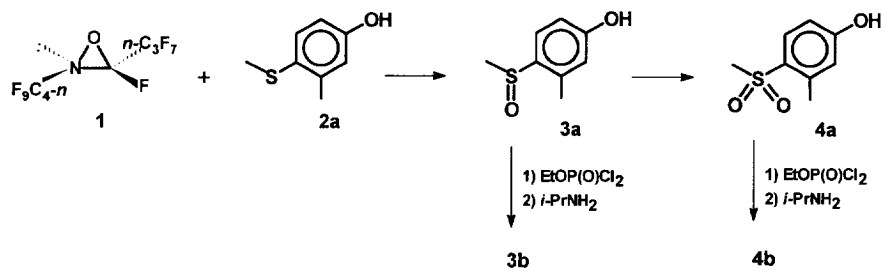
The best approach to phosphorothionates **2f** and **2g** involved the reaction of sodium *para*-nitrophenate and phosphorothionylchloride *O,O*-dialkyl ester[26] to give mixed esters **7a,b** that were then converted to target compounds **2f,g** through transesterification with 2-ethylthioethanol in a basic, two-phase system[27] (eq. 3).



(eq. 3)

7a R = CH_3 **2f** R = CH_3
7b R = C_2H_5 **2g** R = C_2H_5

Sulfur oxygenation with perfluoro cis-2-n-butyl-3-n-propyloxaziridine. The thioether **2a** was oxidized to the sulfoxide **3a** by an equimolecular amount of the oxaziridine **1** in good isolated yield when the reaction mixture was stirred at 0°C (Scheme 1, Table 1).

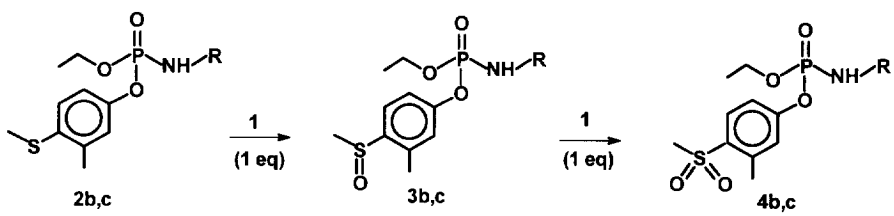


1 **2a** **3a** **4a** **3b** **4b**

Scheme 1

Further oxidation of sulfoxide **3a** to the sulfone **4a** was achieved simply by using another equivalent of oxidizing agent at the same temperature (Table 2).

Oxygenation of methylthio substituted phosphoroamidates **2b,c** with one and two equivalents of oxaziridine **1** afforded the corresponding sulfoxides **3b,c** and sulfones **4b,c** in near quantitative yields (Scheme 2).



2b,c **3b,c** **4b,c**

2-4b R = C_3H_7-*iso*
2-4c R = H

Scheme 2

Selective attack at sulfur was observed in both cases without any oxidation at nitrogen (to give hydroxylamino derivatives) as shown by proton NMR and by an independent synthesis of **3b** and **4b** starting from sulfinyl and sulfonyl substituted phenols **3a** and **4a** (Scheme 1).

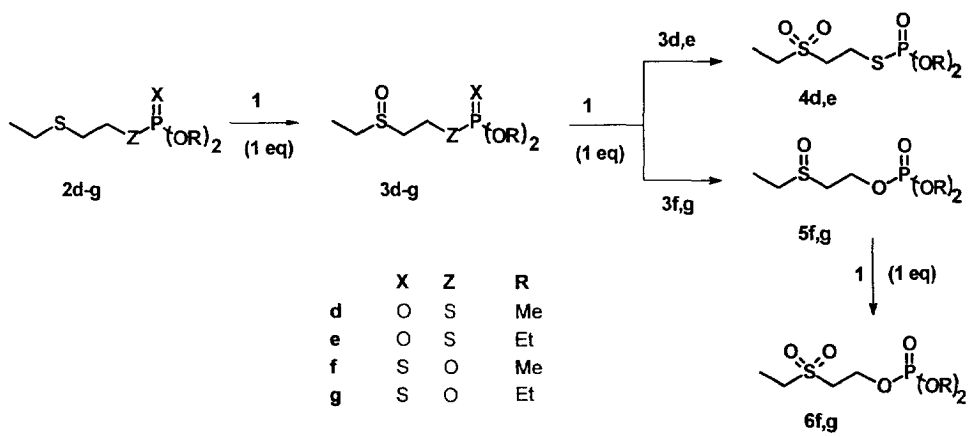
Table 1. Perfluoro *cis*-2-*n*-butyl-3-*n*-propyloxaziridine **1** oxidation of sulfide substrates to the corresponding sulfoxides.

Sulfure	Solvent[a]	Temp. (°C)	Sulfoxide	Yield (%)	Reaction time (min)
2a	A	0	**3a**	88	10
2b	B	0	**3b**	> 98	10
2c	C	0	**3c**	94	10
2d	A	0	**3d**	> 98	10
2e	B	0	**3e**	> 98	10
2f	C	-30	**3f**	> 98	60
2f	C	0	**3f**	93	60
2g	C	-30	**3g**	> 98	60
2g	C	0	**3g**	95	60

[a] A=CF_3CH_2OH; B=$CFCl_3$; C=$CFCl_3/CHCl_3$ 1/1.

The thioether moiety of thiophosphates **2d,e** was oxidized selectively and the corresponding sulfoxides **3d,e** (Scheme 3, Table 1) and sulfones **4d,e** (Scheme 3, Table 2) were isolated in quantitative and high yields, respectively. The presence of the thioester function did not interfere.

No interference was shown by the thionic function of phosphorothionic derivatives **2f,g** in the first oxidation step. In fact, when one equivalent of oxidizing agent was used, the sulfinyl substituted products **3f,g** were formed exclusively.



Scheme 3

Table 2. Perfluoro *cis*-2-*n*-butyl-3-*n*-propyloxaziridine **1** oxidation of sulfoxide substrates to the corresponding sulfones.

Sulfoxide	Solvent[a]	Temp. (°C)	Sulfone	Yield (%)	Reaction time (min)
3a	A	0	**4a**	80	30
3b	A	25	**4b**	90	480[b]
3c	A	25	**4c**	95	480[b]
3d	A	0	**4d**	87	30
3e	B	0	**4e**	82	30
5f	B	-30	**6f**	>98	480[b]
5f	B	25	**6f**	93	480[b]
5g	B	-30	**6g**	90	480[b]
5g	B	25	**6g**	84	480[b]

[a] A= CF_3CH_2OH; B=$CFCl_3/CHCl_3$ 1/1.
[b] Reaction was not monitored for more than 4 h

Yields were quantitative in reactions run at -30°C and slightly lower at higher temperatures (0°C, Table 1). However, when sulfinyl phosphorothionates **3f,g** were further treated with the oxaziridine, sulfinyl phosphates **5f,g** were initially formed through a clean oxidative desulfurization and sulfonyl phosphates **6f,g** were finally obtained in high yields by using an excess of the oxidizing agent.

The selectivity of oxidation did not change on performing the reaction in the cold (-30°C) or at room temperature.

Evidences of the conversion of the thiophosphoryl into phosphoryl group came from spectral data. In ^1H NMR spectra of **5f,g** the methylene groups adjacent to sulfur retained the diastereotopic pattern typical of protons α to a sulfinyl group and in ^{31}P NMR a shift was observed from values typical for the phosphorothionic group (δ ≅70 ppm) to values typical for the phosphoric group (δ ≅0 ppm).

Further structural confirmation came from mass spectral analysis of compounds **5f,g** which showed molecular and the topic ions at 16 m/z unit values lower than those for the starting compounds **3f,g** and the fragmentation pattern typical of the other sulfinyl derivatives being maintained.

Some general comments can be made on the reactions described. Yields of isolated sulfoxides **3** and sulfones **4** and **6** were invariably high, often quantitative. The yields were lower for the oxidation of compound **2a** (88% to sulfinyl derivative **3a** and 80% to sulfonyl product **4a**). However, with this substrate other oxidizing agents proved even less effective. *m*-Chloroperbenzoic acid (*m*-CPBA)[28] afforded sulfoxide **3a** in 77% yield (CH_2Cl_2; 0°C; 30 min), and sulfone **4a** was formed in a definitely lower yield.

Osmium tetraoxide and *N*-methylmorpholine-*N*-oxide (NMO)[29] (acetone/water 2/1; r.t.; 12 h) performed better in this latter oxidation step, but yields higher than 73% could not be obtained.

With our method the oxidation products were often isolated in nearly pure form by simply removing, under reduced pressure, the solvent, any excess reagent, and the perfluoro *cis*-5-aza-4-nonene (obtained as "coproduct" from the oxidation reaction).

Results prove further[14] that oxaziridine **1** can oxidize sulfides to sulfoxides without detectable overoxidation to sulfones. This is a particularly interesting property for a reagent which at the same time is sufficiently reactive to oxidize sulfoxides to sulfones in quantitative yield when used in stechiometric amounts. Some new compatibility of functional groups has also been established.

Under these reaction conditions, the presence of particularly electron rich phenolic rings, of phosphoric, phosphoramidic, and phosphorothioic moieties never interfered in either sulfoxide or sulfone preparation.

The phosphorothionic function remained unaffected in the oxidation of thioethers, but underwent oxidative desulfurization before the oxidation of sulfoxides to sulfones.

In conclusion, the procedure employed seems to be particularly attractive for the preparation of metabolites and analytical standards of biochemical, toxicological and environmental compounds in view of the high chemical yields, the simplicity of the workup, and the possibility of handling the oxaziridine **1** without particular precautions. Furthermore, the behaviour with the phosphorothionic function suggests the possibility of using oxaziridine **1** in oxygenative desulfurizations[30-33] of biologically interesting compounds and as a mimic for P-450 cytochrome catalyzed biotransformations or other biooxidative metabolic processes.

EXPERIMENTAL SECTION

Perfluoro-*cis*-2,3-dialkyloxaziridine **1** was easily prepared from perfluoro tri-*n*-butylamine as previously reported.[34,35] Oxaziridine **1** has a pungent odour, it has been handled in a hood and no problems have ever been encountered. Melting points were determined on a Kofler hot-stage apparatus and were not corrected. Identities and quantities of products synthesized were established by MS, ^{1}H NMR and ^{31}P NMR, against authentic samples when they were available. ^{1}H and ^{31}P NMR spectra were recorded with a Bruker AC 250 spectrometer. TMS (internal) and phosphoric acid (external) were used as standard and $CDCl_3$ as solvent. Chemical shifts are reported in ppm. DIS-MS spectras were obtained on a VG TS 250 instrument by EI at 70 eV. Flash chromatography was done with silica gel 60 (63-200 μm) and TLC were run on silica gel 60 F_{254} plates (Merck). Commercially available reagent grade solvents were employed without purification.

(1-Methylethyl)phosphoramidic acid ethyl 3-methyl-4(methylthio)phenyl ester (2b). To a cooled (0°C) solution of $POCl_3$ (5 mmol, 750 mg) in dry ether (20 mL), a solution of **2a** (5 mmol, 770 mg) and triethylamine (5 mmol, 500 mg) in the same solvent (20 mL), was added dropwise under vigorous stirring. The reaction mixture was stirred for 4h at 0°C then treated with an ethanolic solution of sodium ethylate (5 mmol, 2 mL). After a further 2 h the resulting suspension was filtered and treated at 0°C with isopropylamine (10 mmol) in ether (20 mL). The mixture was stirred for 2 h then the suspension was washed twice with water, and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (SiO_2, $CHCl_3/CH_3OH$ 95/5) afforded 480 mg (46% yield) of **2b**: mp 43-5°C; ^{1}H NMR ($CDCl_3$) δ: 1.13, 1.17 (dd each, $J_{H,H}$= 5.0 Hz, $J_{H,P}$ = 0.8 Hz, $(CH_3)_2CH$, 6H), 1.37 (dt, $J_{H,H}$= 7.0 Hz, $J_{H,P}$= 1.3 Hz, CH_3CH_2OP, 3H), 2.32 (s, CH_3Ar, 3H), 2.42 (s, CH_3S, 3H), 2.55 (brt, P-NH-*i*Pr), 3.45 (m, $(CH_3)_2CHNH$, 1H), 4.14, 4.17 (q each, $J_{H,H}$= 7.0 Hz, CH_3CH_2OP, 2H), 7.05-7.15 (m, Ar, 3H); ^{31}P NMR ($CDCl_3$) δ: 4.10 (brs); MS m/z (ra %): 303 (M^+, 100), 288 (83), 260 (62), 243 (12), 217 (46), 195 (34), 154 (97), 122 (36), 80 (37).

Phosphoramidic acid ethyl 3-methyl-4(methylthio)phenyl ester (2c). The above procedure was followed as described except that dry NH_3 was employed instead of isopropylamine in the final stage. Flash chromatography purification (SiO_2, $CHCl_3/CH_3OH$ 95/5) afforded 220 mg (34% yield) of pure **2c**: mp 87-9°C; ^1H NMR ($CDCl_3$) δ: 1.38 (dt, $J_{H,H}$= 7.0 Hz, $J_{H,P}$= 1.3 Hz, CH_3CH_2OP, 3H), 2.32 (s, CH_3Ar, 3H), 2.44 (s, CH_3S, 3H), 3.00 (brs, P-NH_2, 2H), 4.18, 4.23 (q each, $J_{H,H}$= 7.0 Hz, CH_3CH_2OP, 2H), 7.05-7.15 (m, Ar, 3H); ^{31}P NMR ($CDCl_3$) δ: 5.5 (brs); MS m/z (ra %): 261 (M^+, 86), 233 (10), 216 (14), 154 (100), 139 (21), 80 (33).

***O,O*-Dimethyl *S*-[2-(ethylthio)ethyl]phosphorothioate (2d)**. To a stirred suspension of sodium (5 mmol) in anhydrous toluene (20 mL), a solution of dimethylphosphite (5 mmol) in the same solvent (20 mL), was added dropwise. The reaction mixture was stirred at 25°C for 3 h, treated with sulfur (160 mg) at 90°C and stirred for another 2 h. The cooled mixture was treated dropwise with 2-chloroethylethylsulfide (5 mmol, 310 mg) in toluene (15 mL) then stirred at 60°C for 144 h. The reaction mixture was diluted with toluene (50 mL), washed with acidic water, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (SiO_2, hexane/EtOAc 6/4) afforded 160 mg (13% yield) of pure **2d** as an oil: ^1H NMR ($CDCl_3$) δ: 1.37 (t, $J_{H,H}$= 7.5 Hz, CH_3CH_2S, 3H), 2.60 (q, $J_{H,H}$= 7.5 Hz, CH_3CH_2S, 2H), 2.75-2.90 (m, S-CH_2CH_2SP, 2H), 2.92-3.12 (m, CH_2CH_2SP, 2H), 3.81 (d, J_{HP}= 12,5 Hz, CH_3OP, 6H); ^{31}P NMR ($CDCl_3$) δ: 31.5 (m); MS m/z (ra %): 230 (M^+, 6), 142 (7), 125 (10), 109 (25), 89 (30), 88 (100), 60 (48).

***O,O*-Diethyl *S*-[2-(ethylthio)ethyl]phosphorothioate (2e)**. The above procedure was followed as described except that diethylphosphite was employed. Flash chromatography purification (SiO_2, hexane/ethylacetate 9/1) afforded 300 mg (23% yield) of pure **2e** as an oil: ^1H NMR ($CDCl_3$) δ: 1.28 (t, $J_{H,H}$= 8.0 Hz, CH_3CH_2S, 3H), 1.38 (dt, $J_{H,H}$= 7.0 Hz, CH_3CH_2OP, 6H), 2.60 (q, $J_{H,H}$= 8.0 Hz, CH_3CH_2S, 2H), 2.82-2.88 (m, S-CH_2CH_2SP, 2H), 2.95-3.12 (m, CH_2CH_2SP, 2H), 4.18 (m, CH_3CH_2OP, 4H); ^{31}P NMR ($CDCl_3$) δ: 28.3 (m); MS m/z (ra %): 258 (M^+, 2), 170 (17), 143 (14), 126 (18), 114 (22) 89 (15), 88 (100), 60 (34).

Phosphorothioic acid *O,O*-dimethyl *O*-(4-nitrophenyl) ester (7a). To a stirred solution of thiophosphoryl chloride (23.4 mmol, 3.96 g) in dry benzene (45 mL) at 0°C a methanol solution (45 mL) of sodium methoxide (from 46.8 mmol of sodium) was added dropwise over 3 h. The resulting mixture was stirred for 3 h at room temperature then concentrated *in vacuo* to a thick slurry. The residue was partitioned between 50 mL of toluene and 30 mL of water. The organic phase was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude *O,O*-dimethylchlorophosphorothionate was dissolved in 50 mL of dry ethanol, and added dropwise to an ethanolic solution (100 mL) of sodium *para*nitrophenate (23.4 mmol, 3.77 g). The reaction mixture was refluxed for 1 h, cooled to room temperature and the resulting suspension was filtered and the solvent concentrated *in vacuo*. The crude residue was dissolved in toluene (80 mL) and the organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, hexane/EtOAc 9/1) afforded 3.21 g (53% yield) of pure **7a** as an oil: ^1H NMR ($CDCl_3$) δ: 3.99 (d, J_{HP}= 12,5 Hz, CH_3OP, 6H), 7.32, 8.25 (AA'XX', Ar, 4H); ^{31}P NMR (CDCl3) δ: 66.0 (m); MS m/z (ra %): 263 (M^+, 72), 125 (65), 109 (100), 79 (44), 63 (63).

Phosphorothioic acid *O,O*-diethyl *O*-(4-nitrophenyl) ester (7b). The above procedure was followed as described except that *O,O*-diethylchlorophosphorothionate was employed. Flash chromatography (SiO_2, hexane/EtOAc 9/1) afforded 2.82 g (42% yield) of pure **7b** as an oil: ^1H NMR ($CDCl_3$) δ: 1.40 (dt, $J_{H,H}$= 6.0 Hz, $J_{H,P}$= 1.8 Hz, CH_3CH_2OP, 6H), 4.25 (m, $J_{H,H}$= 6.0 Hz, J_{HP}= 12.5 Hz, CH_3CH_2OP, 4H), 7.44, 8.25

(AA'XX', Ar, 4H); ^{31}P NMR ($CDCl_3$) δ: 68.1 (m); MS m/z (ra %): 291 (M^+, 92), 186 (27), 155 (38), 139 (52), 125 (38), 109 (100), 97 (95).

Phosphorothioic acid *O,O*-dimethyl *O*-[2-(ethylthio)ethyl] ester (2f). To a solution of **7a** (3.8 mmol, 1g) in cyclohexane (30 mL) 2-hydroxyethyl ethylsulfide (0.8 g, 7.6 mmol) in the same solvent (10 mL) was added followed by aqueous NaOH (7.5 mL of a 50 % solution) dropwise over 10 min. The reaction mixture was stirred at 50°C for 144 h. After cooling to room temperature the organic layer was washed twice with acidic water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography (SiO_2, hexane/EtOAc 9/1) afforded 310 mg (35% yield) of pure **2f** as an oil: ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, $J_{H,H}$= 7.0 Hz, C*H*$_3$CH$_2$S, 3H), 2.60 (q, $J_{H,H}$= 7.0 Hz, CH$_3$C*H*$_2$S, 2H), 2.80 (t, $J_{H,H}$= 6.5 Hz, S-C*H*$_2$CH$_2$OP, 2H), 3.78 (d, $J_{H,P}$= 12.5 Hz, CH$_3$OP, 6H), 4.18 (dt, $J_{H,H}$= 6.5 Hz, $J_{H,P}$= 11 Hz, CH$_2$C*H*$_2$OP, 2H); ^{31}P NMR ($CDCl_3$) δ: 71.8 (m); MS m/z (ra %): 230 (M^+, 5), 169 (7), 143 (5), 109 (18), 89 (90), 88(100), 60 (21).

Phosphorothioic acid *O,O*-diethyl *O*-[2-(ethylthio)ethyl] ester (2g): The above procedure was followed as described except that compound **7b** (7 mmol, 200 mg) was employed. Flash chromatography (SiO_2, hexane/EtOAc 9/1) afforded 100 mg (55% yield) of pure **2g** as an oil: ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, $J_{H,H}$= 7.0 Hz, C*H*$_3$CH$_2$S, 3H), 1.33 (dt, $J_{H,H}$= 7.0 Hz, $J_{H,P}$= 2.0 Hz, C*H*$_3$CH$_2$OP, 6H), 2.59 (q, $J_{H,H}$= 7.0 Hz, CH$_3$C*H*$_2$S, 2H), 2.80 (t, $J_{H,H}$= 6.0 Hz, S-C*H*$_2$CH$_2$OP, 2H), 4.15 (dt, $J_{H,H}$= 6.5 Hz, $J_{H,P}$= 11 Hz, CH$_2$C*H*$_2$OP, 2H); ^{31}P NMR ($CDCl_3$) δ: 68.2 (t); MS m/z (ra %): 258 (M^+, 5), 171 (10), 143 (20), 115 (12), 89 (75), 88 (100), 60 (41).

General Procedure for the Preparation of Sulfoxides (3a-g). Reaction conditions (solvent and temperature) and yields for the sulfide (**2a-g**) oxidation to the corresponding sulfoxide (**3a,g**) by an equimolecular amount of **1**, are reported in Table 1.

4-Methylsulfinyl-3-methylphenol (3a). A cooled solution (0°C) of sulfide **2a** (1 mmol, 154 mg) in CF_3CH_2OH (15 mL) was treated with oxaziridine **1** (1.16 mmol, 524 mg) under N_2, and the reaction mixture was stirred for 10 min. The volatile materials were removed *in vacuo* to give an oily solid. Flash chromatography (SiO_2, $CHCl_3$/CH_3OH 9/1) afforded 150 mg (88% yield) of pure **3a**: mp 115-17°C; ^{1}H NMR ($CDCl_3$) δ: 1.7 (brs, OH, 1H), 2.34 (s, CH_3Ar, 3H), 2.70 (CH_3S, 3H), 6.70 (s, H-2, 1H), 6.89 (dd, H-6, 1H), 7.73 (d, H-5, 1H); MS m/z (ra %): 170 (M^+, 92), 155 (100), 139 (8), 123 (17), 109 (22), 94 (50), 77 (19).

(1-Methylethyl)phosphoramidic acid ethyl 3-methyl-4(methylsulfinyl)phenyl ester (3b): mp 65-7°C; ^{1}H NMR ($CDCl_3$) δ: 1.14, 1.19 (dd each, $J_{H,H}$= 6.0 Hz, $J_{H,P}$= 0.5 Hz, (C*H*$_3$)$_2$CH, 6H), 1.34 (dt, $J_{H,H}$= 8.0 Hz, C*H*$_3$CH$_2$OP, 3H), 2.37 (s, CH_3Ar, 3H), 2.68 (s, CH_3SO, 3H), 3.14 (m, NH, 1H), 3.35-3.50 (m, C*H*(CH$_3$)$_2$, 1H), 4.16 (dq, $J_{H,H}$= $J_{H,P}$= 8.0 Hz, CH$_3$C*H*$_2$OP, 2H), 7.12 (m, H-6, 1H), 7.28 (m, H-2, 1H), 7.90 (d, ^{3}J= 8.5 Hz, H-5, 1H); ^{31}P NMR ($CDCl_3$) δ: 5.5 (brs); MS m/z (ra %): 319 (M^+, 42), 304 (100), 276 (7), 234 (6), 196 (27), 150 (19), 122 (68), 80 (25).

Synthesis of 3b by reaction with 4-methylsulfinyl-3-methylphenol (3a) (Scheme 1). To a solution of $POCl_3$ (5 mmol, 750 mg) and triethylamine (5 mmol, 500 mg) in dry CH_2Cl_2 (20 mL) at 0°C a solution of **3a** (5 mmol, 830 mg) in the same solvent (30 mL) was added dropwise over 15 min, under vigorous stirring. The reaction mixture was stirred at 0°C (4 h) then treated with an ethanolic solution of sodium ethylate (5 mmol, 2

mL). After a further 2 h the resulting suspension was filtered and treated at 0°C with isopropylamine (10 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 2 h then the suspension was washed twice with water, and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (SiO_2, $CHCl_3/CH_3OH$ 9/1) afforded 670 mg (42% yield) of **3b**.

Phosphoramidic acid ethyl 3-methyl-4(methylsulfinyl)phenyl ester (3c): mp 120-3°C; ^{1}H NMR ($CDCl_3$) δ: 1.38 (dt, $J_{H,H}$= 8.0 Hz, $J_{H,P}$= 0.5 Hz, C*H*$_3$CH$_2$OP, 3H), 2.35 (s, CH_3Ar, 3H), 2.66 (s, CH_3SO, 3H), 3.21 (brs, N*H*$_2$, 1H), 4.24 (dq, $J_{H,H}$= $J_{H,P}$= 8.0 Hz, CH_3C*H*$_2$OP, 2H), 7.14 (m, H-6, 1H), 7.30 (m, H-2, 1H), 7.92 (d, ^{3}J= 8.5 Hz, H-5, 1H); ^{31}P NMR ($CDCl_3$) δ: 5.3 (brs); MS m/z (ra %): 277 (M^+, 37), 262 (100), 234 (50), 189 (13), 154 (31), 127 (11), 112 (18), 94 (15), 80 (29).

***O,O*-Dimethyl *S*-[2-(ethysulfinyl)ethyl]phosphorothioate (3d)**: oil; ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, $J_{H,H}$= 7.0 Hz, C*H*$_3$CH$_2$SO, 3H), 2.79 (q, $J_{H,H}$= 7.0 Hz, CH_3C*H*$_2$SO, 2H), 2.93-3.45 (m, C*H*$_2$C*H*$_2$SP, 4H), 3.82 (d, $J_{H,P}$= 12.5 Hz, CH_3OP, 6H); ^{31}P NMR ($CDCl_3$) δ: 30.2 (m); MS m/z (ra %): 246 (M^+, 3), 169 (37), 125 (20), 109 (85), 88 (100), 60 (53).

***O,O*-Diethyl *S*-[2-(ethysulfinyl)ethyl]phosphorothioate (3e)**: oil; ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, $J_{H,H}$= 7.0 Hz, C*H*$_3$CH$_2$SO, 3H), 1.38 (brt, $J_{H,H}$= 7.0 Hz, C*H*$_3$CH$_2$OP, 6H), 2.79 (q, $J_{H,H}$= 7.5 Hz, CH_3C*H*$_2$SO, 2H), 2.95-3.43 (m, C*H*$_2$C*H*$_2$SP, 4H), 4.18 (m, CH_3C*H*$_2$OP, 4H); ^{31}P NMR ($CDCl_3$) δ: 26.8 (m); MS m/z (ra %): 274 (M^+, 6), 197 (42), 169 (14), 138 (21), 109 (69), 81 (82), 59 (100).

Phosphorothioic acid *O,O*-dimethyl *O*-[2-(ethylsufinyl)ethyl] ester (3f): oil; ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, $J_{H,H}$= 7.0 Hz, C*H*$_3$CH$_2$SO, 3H), 2.80, 2.81 (q each, $J_{H,H}$= 8.0 Hz, CH_3C*H*$_2$SO, 2H), 2.86-2.98 (m, CH_2C*H*SO, 1H), 3.01-3.13 (m, CH_2C*H*SO, 1H), 3.78 (d, $J_{H,P}$= 13.0 Hz, CH_3OP, 6H), 4.49 (m, $^2J_{H,H}$= 8.0 Hz, $J_{H,P}$= 11.0 Hz, CH_2C*H*OP, 1H), 4.51 (m, $^2J_{H,H}$= 8.0 Hz, $J_{H,P}$= 13.0 Hz, CH_2C*H*OP, 1H); ^{31}P NMR ($CDCl_3$) δ: 71.6 (m); MS m/z (ra %): 246 (M^+, 7), 217 (52), 169 (94), 143 (23), 125 (100), 109 (57), 91 (32).

Phosphorothioic acid *O,O*-diethyl *O*-[2-(ethylsulfinyl)ethyl] ester (3g): oil; ^{1}H NMR ($CDCl_3$) δ: 1.34 (t, $J_{H,H}$= 7.5 Hz, C*H*$_3$CH$_2$OP, 6H), 1.39 (t, $J_{H,H}$= 7.0 Hz, C*H*$_3$CH$_2$SO, 3H), 2.80, 2.81 (q each, $J_{H,H}$= 8.0 Hz, CH_3C*H*$_2$SO, 2H), 2.86-2.97 (m, CH_2C*H*SO, 1H), 3.01-3.13 (m, CH_2C*H*SO, 1H), 4.15 (dq, $J_{H,H}$= 7.5 Hz, $J_{H,P}$= 9.5 Hz, CH_3C*H*$_2$OP, 4H), 4.49 (m, $^2J_{H,H}$= 8.0 Hz, $J_{H,P}$= 11.0 Hz, CH_2C*H*OP, 1H), 4.51 (m, $^2J_{H,H}$= 8.0 Hz, $J_{H,P}$= 13.0 Hz, CH_2C*H*OP, 1H); ^{31}P NMR ($CDCl_3$) δ: 68.1 (m); MS m/z (ra %): 274 (M^+, 20), 255 (27), 244 (48), 197 (63), 182 (50), 155 (90), 141 (100), 125 (52), 99 (46).

General Procedure for the Preparation of Sulfones (4a-e) and (5f,g). Reaction conditions and yields for the sulfoxide **3a-e** and **4f,g** oxidation to the corresponding sulfones, by an equimolecular amount of **1**, are reported in Table 2.

4-Methylsulfonyl-3-methylphenol (4a). A cooled solution (0°C) of sulfoxide **3a** (1 mmol, 170 mg) in CF_3CH_2OH (15 mL) was treated with oxaziridine **1** (1.16 mmol, 524 mg) under N_2, and the reaction mixture was stirred for 30 min. The volatile materials were removed *in vacuo* to give an oily solid. Flash chromatography (SiO_2, $CHCl_3/CH_3OH$ 9/1) afforded 149 mg (80% yield) of pure **4a**: mp 100-102°C; ^{1}H NMR ($CDCl_3$) δ: 1.75 (brs, OH, 1H), 2.63 (s, CH_3Ar, 3H), 3.07 (s, CH_3SO_2, 3H), 6.17 (s, H-2, 1H), 6.77 (m, H-6, 1H), 7.89 (d, H-5, 1H); MS m/z (ra %): 186 (M^+, 100), 171, (80), 123 (40), 107 (89), 77 (23).

(1-Methylethyl)phosphoramidic acid ethyl 3-methyl-4(methylsulfonyl)phenyl ester (4b): mp 83-85°C; ^{1}H NMR ($CDCl_3$) δ: 1.16, 1.19 (dd each, $J_{H,H}$= 6.0 Hz, $J_{H,P}$= 0.5 Hz, $(CH_3)_2CH$, 6H), 1.38 (dt, $J_{H,H}$= 8.0 Hz, $J_{H,P}$= 0.5 Hz, CH_3CH_2OP, 3H), 2.68 (s, CH_3Ar, 3H), 3.00 (m, NH, 1H), 3.08 (s, CH_3SO_2, 3H), 3.47 (m, $CH(CH_3)_2$, 1H), 4.20 (dq, $J_{H,H}$= $J_{H,P}$= 8.0 Hz, CH_3CH_2OP, 2H), 7.22 (m, H-6 and H-2, 2H), 8.00 (d, ^{3}J= 8.5 Hz, H-5, 1H); ^{31}P NMR ($CDCl_3$) δ: 3.8 (brs); MS m/z (ra %): 335 (M^+, 13), 320 (100), 292 (59), 249 (8), 122 (14), 80 (23).

Phosphoramidic acid ethyl 3-methyl-4(methylsulfonyl)phenyl ester (4c): mp 70-3°C; ^{1}H NMR ($CDCl_3$) δ: 1.45 (brt, $J_{H,H}$= 8.0 Hz, CH_3CH_2OP, 3H), 2.66 (s, CH_3Ar, 3H), 3.02 (s, CH_3SO_2, 3H), 3.60 (brs, NH_2, 1H), 4.22 (dq, $J_{H,H}$= $J_{H,P}$= 8.0 Hz, CH_3CH_2OP, 2H), 7.21 (m, H-6 and H-2, 2H), 8.98 (d, ^{3}J= 10 Hz, H-5, 1H); ^{31}P NMR ($CDCl_3$) δ: 5.1 (brs); MS m/z (ra %): 293 (M^+, 100), 278 (15), 265 (87), 250 (32), 214 (30), 186 (61), 171 (20), 123 (29), 107 (52), 80 (66).

***O,O*-Dimethyl *S*-[2-(ethylsulfonyl)ethyl]phosphorothioate (4d)**: mp 49-51°C; ^{1}H NMR ($CDCl_3$) δ: 1.43 (t, $J_{H,H}$= 8.0 Hz, $CH_3CH_2SO_2$, 3H), 3.05 (q, $J_{H,H}$= 8.0 Hz, $CH_3CH_2SO_2$, 2H), 3.10-3.30 (m, CH_2CH_2SP, 2H), 3.40-3.50 (m, CH_2CH_2SP, 2H), 3.83 (d, $J_{H,P}$= 12.5 Hz, CH_3OP, 6H); ^{31}P NMR ($CDCl_3$) δ: 29.7 (m); MS m/z (ra %): 262 (M^+, 5), 169 (100), 142 (12), 125 (35), 109 (82), 79 (24).

***O,O*-Diethyl *S*-[2-(ethylsulfonyl)ethyl]phosphorothioate (4e)**: mp 117-119°C; ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, $J_{H,H}$= 7.0 Hz, $CH_3CH_2SO_2$, 3H), 1.43 (dt, $J_{H,H}$= 8.0 Hz, $J_{H,P}$= 0.5 Hz, CH_3CH_2OP, 6H), 3.07 (q, $J_{H,H}$= 7.0 Hz, $CH_3CH_2SO_2$, 2H), 3.11-3.28 (m, CH_2CH_2SP, 2H), 3.41 (m, CH_2CH_2SP, 2H), 4.19 (m, CH_3CH_2OP, 4H); ^{31}P NMR ($CDCl_3$) δ: 26.2 (m); MS m/z (ra %): 290 (M^+, 6), 197 (100), 169 (29), 141 (61), 109 (64), 81 (32).

Phosphoric acid *O,O*-dimethyl *O*-[2-(ethylsulfonyl)ethyl] ester (6f): oil; ^{1}H NMR ($CDCl_3$) δ: 1.43 (t, $J_{H,H}$= 7.0 Hz, $CH_3CH_2SO_2$, 3H), 3.20 (q, $J_{H,H}$= 7.0 Hz, $CH_3CH_2SO_2$, 2H), 3.33 (brt, $J_{H,H}$= 6.0 Hz, $CH_2CH_2SO_2$, 2H), 3.82 (d, $J_{H,P}$= 12.0 Hz, CH_3OP, 6H), 4.48 (m, $J_{H,H}$= 6.0 Hz, $J_{H,P}$= 6.3 Hz, CH_2CH_2OP, 2H); ^{31}P NMR ($CDCl_3$) δ: 1.4 (m); MS m/z (ra %): 246 (M^+, 5), 217 (23), 153 (88), 127 (100), 109 (45), 96 (12).

Phosphoric acid *O,O*-diethyl *O*-[2-(ethylsulfonyl)ethyl] ester (6g): oil; ^{1}H NMR ($CDCl_3$) δ: 1.36 (dt, $J_{H,H}$= 7.0 Hz, $J_{H,P}$= 0.5 Hz, CH_3CH_2OP, 6H), 1.41 (t, $J_{H,H}$= 7.5 Hz, $CH_3CH_2SO_2$, 3H), 3.09 (q, $J_{H,H}$= 7.5 Hz, $CH_3CH_2SO_2$, 2H), 3.32 (brt, $J_{H,H}$= 6.0 Hz, $CH_2CH_2SO_2$, 2H), 4.15 (dq, $J_{H,H}$= 7.0 Hz, $J_{H,P}$= 9.5 Hz, CH_3CH_2OP, 4H), 4.46 (m, $J_{H,H}$= 6.0 Hz, $J_{H,P}$= 7.5 Hz, CH_2CH_2OP, 2H); ^{31}P NMR ($CDCl_3$) δ: -0.7 (m); MS m/z (ra %): 274 (M^+, 5), 246 (13), 180 (48), 154 (33), 152 (29), 124 (100), 99 (88), 81 (46).

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