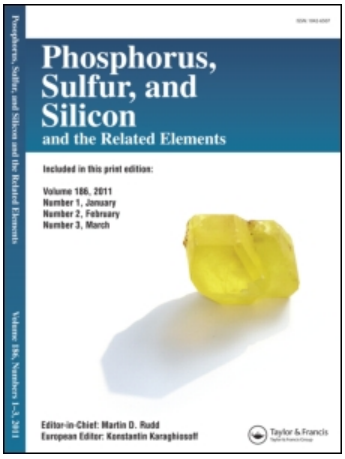

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$Hg_{(II)}$-ACTIVATION IN THE CHEMOSELECTIVE SUBSTITUTION OF CHLORINE BY THE AZIDE ION IN CHLOROPHOSPHOROTHIONATE ESTERS

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$Hg_{(II)}$-ACTIVATION IN THE CHEMOSELECTIVE SUBSTITUTION OF CHLORINE BY THE AZIDE ION IN CHLOROPHOSPHOROTHIONATE ESTERS

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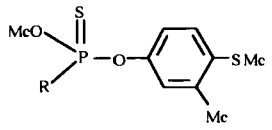
In chlorophosphorothionate or dichlorophosphorothionate esters, $Hg_{(II)}$-coordination to the S-atom facilitates nucleophilic attack at P of the azide ion, to afford the corresponding azido derivatives in good yields. The chemoselectivity of this reaction *vs* C-substitution is also greatly improved.

Key words: Azidothiophosphates; fenthion; $Hg_{(II)}$-catalysis; $Hg_{(II)}$-sulphur affinity; nucleophilic P-attack, photoaffinity labelling.

INTRODUCTION

Phosphorothionate esters have wide-ranging importance as insecticides,[1] transition-state analogues,[2] and oligonucleotide phosphotriester analogues for the investigation of biochemical systems.[3] In our continuing study of the biological activity of Fenthion (**1**), a commercial insecticide, we required a radiolabelled azido-derivative **2** for use as a potential photoaffinity labelling reagent[4] to identify a hypothetical target protein in tomato plants. We wish to report here a simple and efficient method for the preparation of the azidophosphorothionates, which may have potential as a route to radiolabelled biochemical probes of this type.



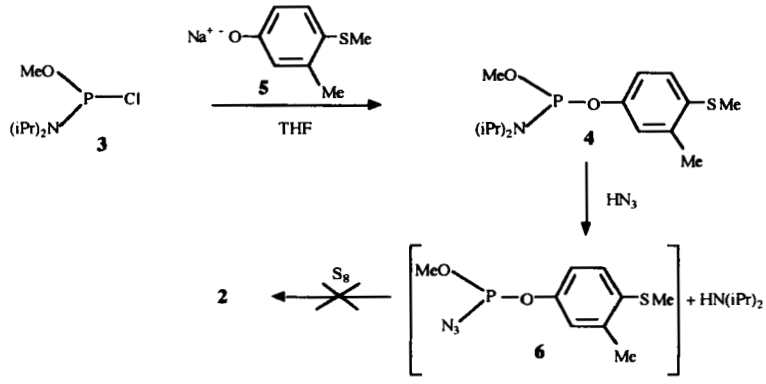
1 R = MeO (Fenthion)

2 R = N_3

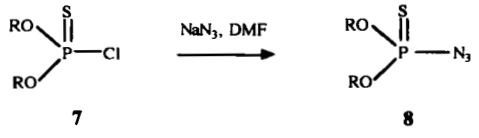
RESULTS AND DISCUSSION

We initially explored standard procedures for the preparation of the azidophosphorothionate compounds. Thus, *via* the phosphoramidite approach from chloro-(N,N-diisopropylamino)-methoxyphosphine (**3**), a synthesis was envisaged which would incorporate the sulphur atom at the last step (Scheme 1), and thereby be adaptable to the preparation of the [^{35}S]-labelled derivative **[^{35}S]-2**.

The phosphoramidite **4** was easily obtained by reaction at −30°C of **3** with the sodio derivative of 4-methylthiometacresol (**5**). Reaction of 2 equivalents of hydrazoic acid[5] with the phosphoramidite **4**, monitored by ^{1}H NMR, allowed the obtention of a new compound, presumably the azidophosphosphine **6** which was not isolated. However, this compound did not react with molecular sulphur at room



SCHEME 1 Attempted synthesis of methyl (4-methylthio-3-tolyl) azidophosphorothionate (**2**) *via* the phosphoramidite approach.

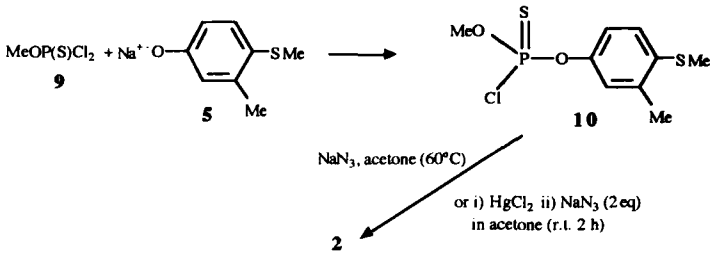


SCHEME 2 Synthesis of azidophosphorothionates esters from chloro precursors.[8]

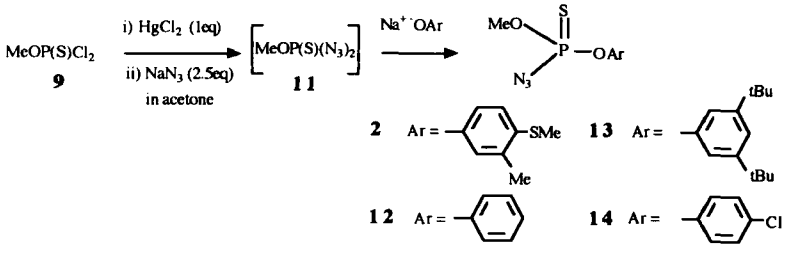
temperature, and gave a complex mixture of products on heating.[6] A very likely cause of failure here is the inherent reactivity of trivalent azidophosphorus compounds. In particular, Staudinger-type reactions between azides and trivalent phosphorus compounds might be expected.[7] Such reactions have previously been observed between azidophosphorothionates and phosphites.[8] Consequently, attention was directed towards a synthetic route *via* the less reactive pentavalent phosphorus system.

A survey of the literature on azidophosphorothionates revealed a synthesis of the symmetrical dialkylazido-compounds **8** from the corresponding chloro-precursors **7** *via* NaN_3 in DMF in moderate yields[8a] (Scheme 2). Diphenylphosphoryl azide, an oxygen analogue of the azidophosphorothionates, has similarly been prepared by the reaction of the corresponding chloride with sodium azide in acetone at room temperature.[9] The reaction of the thiophosphoryl chloride **10** [prepared from methyl dichlorothiophosphate (**9**) and the phenate **5**], with sodium azide in acetone needed heating to 60°C, and afforded a mixture containing the expected product **2** in variable amount (Scheme 3). HPLC of the reaction mixtures revealed the presence of polar products possibly arising from the substitution at the C-atom of the methoxy group. Indeed, this side reaction was confirmed by ^1H NMR by the loss of the MeO doublet and presence of a singlet at δ 2.35 probably due to methyl azide.

Bearing in mind the affinity of sulphur for group A and B transition metals *via* soft-soft interactions, a means of increasing the electrophilicity of the P-atom by coordination to sulphur of the P=S bond was investigated.[10] Thus, when the chlorophosphorothionate **10** was treated with NaN_3 in acetone-D_6 in the presence of a stoichiometric amount of $HgCl_2$ at room temperature for 2 h with monitoring



SCHEME 3 Uncatalyzed or $Hg_{(II)}$-catalyzed two-steps synthesis of **2** from methyl dichlorophosphorothionate (**9**).



SCHEME 4 One-pot $Hg_{(II)}$-catalyzed synthesis of methyl aryl azidophosphorothionates from methyl dichlorophosphorothionate (**9**).

by ^{1}H NMR, the desired azidophosphorothionate **2** was obtained almost quantitatively. The absence of other Me doublets during the reaction coupled with satisfactory mass spectral data, suggest that the product was not the thiolo-isomerised derivative.[11] The presence of a small singlet at δ 2.35 possibly indicates a minor amount of demethylated product. Use of catalytic quantities of $HgCl_2$ (0.05–0.5 eq) resulted in greatly-reduced reaction rates, with concomitant increase in attack at the methyl group, although satisfactory results could be obtained with 0.5 eq $HgCl_2$ over 16 h. Thus it is clear that $Hg_{(II)}$ exerts a catalytic effect on the reaction of substitution at phosphorus, resulting in improved chemoselectivity *vs* C-substitution. Such a catalytic effect of $Hg_{(II)}$ had been previously observed in the transesterification of triethyl phosphorothionates.[12] Other soft cations like Ag^+ or Cu^+ may also exert an activation in similar reactions.[10]

For the purposes of obtaining radiolabelled azido-analogues of azidophosphorothionates similar to **2** *via* this methodology, the most convenient approach would appear to be by use of a tritiated thiophenol, and incorporation of this group into the molecule at the final step. Thus a synthesis was envisaged *via* the putative bisazide **11**, derived from methyl dichlorothiophosphate (**9**) (Scheme 4).

Methyl dichlorothiophosphate (**9**), in the presence of 1 equivalent of mercuric chloride reacted at room temperature in acetone with an excess of sodium azide to give the expected diazide **11** over 3 h. Monitoring the reaction by ^{1}H NMR showed the disappearance of the methyl doublet of **9**, which was successively replaced by two new doublets, as expected for the formation of an intermediate chloro-azido derivative. Addition of the phenolate was effected at low temperature (−78°C), the reaction occurring when the mixture was gradually warmed to room

temperature. In this manner, the reaction produced the azidophosphorothionates **2** and **12–14** in good yields, with limited amounts of diaryl-substituted products.

The $Hg_{(II)}$-approach would therefore appear to offer great potential for the synthesis of a wide range of thiophosphoryl derivatives. The compounds are obtained in good yields by a simple procedure, with little or no interference from the typical side-reactions. The preparation through this route of a ^3H-labelled azido-analogue of fenthion [^3H]-**2**, for protein photoaffinity labelling studies is under way.

EXPERIMENTAL

N,N-Diisopropyl methyl phosphonamidic chloride (**3**) was obtained from Aldrich Chemical Co., thiophosphoryl chloride, mercuric chloride and sodium azide were obtained from Janssen Chimica, and all were used without further purification. Anhydrous acetone and THF were obtained from Janssen Chimica, and stored over activated 4 Å molecular sieves or freshly distilled from Na-benzophenone, respectively. NMR spectra were recorded on a Jeol GSX 270-WB spectrometer using $CDCl_3$ as solvent with tetramethylsilane as internal reference. IR and UV spectra were recorded on Perkin-Elmer 841 and Perkin-Elmer lambda 2 spectrophotometers respectively, and mass spectral analyses were performed on a Varian MAT 311 spectrometer at the University of Rennes. Molecular formulas were established by HRMS, correct microanalysis data not being obtainable from chromatographically pure samples.

Methyl Dichlorophosphorothionate (**9**). To a round-bottomed flask containing thiophosphoryl chloride (30 ml, 0.30 mol) cooled to 0°C under N_2 was added dry methanol (22 ml, 0.54 mol) dropwise over 1 h, maintaining the temperature below 10°C throughout. After complete addition, distillation of the mixture under reduced pressure gave the pure desired monomethyl ester **9** (20 g, 41%) as the fraction obtained between 66–69°C/59 torrs. (Litt.[13] b.p. 70°C/40 torrs); ^1H NMR: 4.0 (d, J_{P-H} = 19, CH_3O).

N,N-Diisopropylamino-(4-methylthio-3-tolyloxy)-methoxyphosphine (**4**). To a solution of N,N-diisopropyl methyl phosphonamidic chloride (**3**) (355 mg, 1.8 mmol) in dry THF (9 ml) cooled to −78°C under N_2, was added dropwise a solution of sodium 3-methyl-4-methylthiophenoxide (320 mg, 1.8 mmol) in dry THF (2 ml). After gradual warming to room temperature over 1 h, the solution was stirred overnight. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel in hexane-EtOAc (6:1) to give the desired product **4** (380 mg, 67%) as a colourless oil. ^1H NMR δ 7.5–7.2 (3H, m, Ar—*H*), 4.07 (2H, m, 2 × *CH*—N), 3.86 (3H, d, J_{P-H} = 13.3 Hz, CH_3O), 2.76 (3H, s, CH_3S), 2.69 (3H, s, CH_3—Ar), 1.59–1.52 (12H, 4 × s, 4 × CH_3—CHN); m/z 315 (3%, M^+), 215 (3), 162 (100), 120 (17), 88 (23), 78 (18); (Found: M^+ 315.1423. $C_{15}H_{26}NO_2PS$ requires 315.1422).

Methyl (4-Methylthio-3-tolyl) Chlorophosphorothionate (**10**). In a similar manner to the above preparation of **4**, methyl dichlorothiophosphonate (2.14 g, 13 mmol) and sodium 3-methyl-4-methylthiophenoxide (2.29 g, 13 mmol) in dry THF gave upon chromatography on silica gel eluting with hexane-CH_2Cl_2 (1:1) the desired monoaryl ester **10** (2.25 g, 61%) as a pale yellow oil. ^1H NMR δ 7.3–7.1 (3H, m, Ar—*H*), 4.0 (3H, d, J_{P-H} = 14 Hz, CH_3O), 2.4 (3H, s, CH_3S), 2.3 (3H, s, CH_3—Ar); m/z 282–284 (63 and 27%, M^+), 169 (100), 153 (27); (Found: M^+, 281.9715. $C_9H_{12}{}^{35}ClO_2PS_2$ requires 281.9705).

One-Pot Preparation of Aryl Azidophosphorothionates. To a solution of methyl dichlorothiophosphate (**9**) (1.0 eq) in dry acetone (5 ml/mmol) under N_2 was added mercuric chloride (1.0 eq) with stirring for 5 min, followed by sodium azide (2.5 eq), and the mixture stirred a further 3 h at room temperature. The resultant suspension was cooled to −78°C and a solution of the phenoxide sodium salt (0.9 eq) in dry THF was added dropwise, followed by gradual warming to room temperature over 1 h and stirring for a further 2 h. The solvent was removed *in vacuo* and the residue suspended in Et_2O with stirring for 15 min, then filtered, evaporated, and purified by flash chromatography on silica gel to obtain the pure aryl Azidophosphorothionate ester as a colourless oil.

Methyl (4-Methylthio-3-tolyl) Azidophosphorothionate (**2**). Methyl dichlorothiophosphate (**9**) (1.14 g, 6.9 mmol), mercuric chloride (1.88 g, 6.9 mmol), sodium azide (1.12 g, 17.2 mmol) and sodium 3-methyl-4-methylthiophenoxide (1.10 g, 6.2 mmol) gave upon chromatography in hexane-EtOAc (5:1) the desired compound **2** (1.68 g, 94%). ν_{max} (cm^{-1}): 2083 (N_3); UV (MeOH): 253.3 nm (max), 233.5 nm (min); ^1H NMR δ 7.1 (3H, m, Ar—*H*), 3.86 (3H, d, J_{P-H} = 15 Hz, CH_3O), 2.43 (3H, s, CH_3S), 2.33 (3H, s, CH_3—Ar); m/z 289 (58%, M^+), 215 (100), 200(32), 153 (29); (Found: M^+, 289.0115. $C_9H_{12}N_3O_2PS_2$ requires 289.0109).

Methyl Phenyl Azidophosphorothionate (**12**). Methyl dichlorothiophosphate (**9**) (1.59 g, 9.6 mmol), mercuric chloride (2.62 g, 9.6 mmol), sodium azide (1.56 g, 24.0 mmol) and sodium phenoxide (0.92 g, 7.9 mmol) gave upon chromatography in hexane-EtOAc (5:1) the desired phenyl azidoester **11** (1.53 g, 85%). ^{1}H NMR δ 7.48–7.26 (5H, m, Ar—*H*), 3.97 (3H, d, J_{P-H} = 14.8 Hz, CH_3O); m/z 229 (100%, M^+), 187 (23), 178 (8), 169 (11), 155 (38), 109 (25), 91 (14), 77 (80); (Found: M^+, 229.0073. $C_7H_8N_3O_2PS$ requires 229.0075).

Methyl (3,5-Di-t-butyphenyl) Azidophosphorothionate (**13**). Methyl dichlorothiophosphate (**9**) (921 mg, 5.6 mmol), mercuric chloride (1.52 g, 5.6 mmol), sodium azide (910 mg, 14 mmol) and sodium 3,5-di-t-butylphenoxide (1.14 g, 5.0 mmol) gave upon chromatography in hexane-EtOAc (8:1) the desired ester **12** (750 mg, 44%). ^{1}H NMR δ 7.28 (1H, d, J = 1.65 Hz, OAr—*pH*), 7.03 (2H, d, J = 1.65 Hz, 2 × OAr—*oH*), 3.90 (3H, d, J_{P-H} = 14.8 Hz, CH_3O); m/z 341 (94%, M^+), 326 (100), 266 (17), 242 (33), 210 (33), 57 (97); (Found: M^+, 341.1324. $C_{15}H_{24}N_3O_2PS$ requires 341.1327).

Methyl (4-Chlorophenyl) Azidophosphorothionate (**14**). Methyl dichlorothiophosphate (**9**) (619 mg, 3.75 mmol), mercuric chloride (1.02 g, 3.75 mmol), sodium azide (610 mg, 9.4 mmol) and sodium 4-chlorophenoxide (510 mg, 3.37 mmol) gave upon chromatography in hexane-EtOAc (3:1) the desired ester (**13**) (715 mg, 80%). ^{1}H NMR δ 7.43 (2H, d, J = 8.5 Hz, 2 × Ar—*H*), 7.25 (2H, d, J = 8.7 Hz, 2 × Ar—*H*), 3.99 (3H, d, J_{P-H} = 14.8 Hz, CH_3O); m/z 263–265 (100 and 36%, M^+), 221–223 (22 and 8), 203–205 (11 and 6), 189–191 (78 and 25), 111–113 (45 and 15); (Found: M^+, 262.9682. $C_7H_7{}^{35}ClN_3O_2PS$ requires 262.9685).

Reaction of Methyl 4-Methylthio-3-tolyl Chlorophosphorothionate (**10**) *with Sodium azide*. To a solution of the chloride **10** (430 mg, 1.52 mmol) in dry acetone (20 ml) was added mercuric chloride (415 mg, 1.52 mmol) with stirring for 5 min, followed by sodium azide (200 mg, 3.05 mmol), and the mixture stirred a further 2 h at room temperature. The solvent was evaporated *in vacuo* and the residue suspended in Et_2O (20 ml) with stirring for 15 min. The mixture was filtered, evaporated, and purified by flash chromatography on silica gel eluting with hexane-EtOAc (5:1) to give the desired azido-derivative **2** (210 mg, 48%) identical in all respects to the product obtained above *via* the one-pot procedure, along with 11 mg of a demethylated product which was not further characterised.

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