Mechanism of the sulfurisation of phosphines and phosphites using 3-amino-1,2,4-dithiazole-5-thione (xanthane hydride)†‡

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Contrary to a previous report, the sulfurisation of phosphorus(III) derivatives by 3-amino-1,2,4-dithiazole-5-thione (xanthane hydride) does not yield carbon disulfide and cyanamide as the additional reaction products. The reaction of xanthane hydride with triphenyl phosphine or trimethyl phosphite yields triphenyl phosphine sulfide or trimethyl thiophosphate, respectively, and thiocarbamoyl isothiocyanate which has been trapped with nucleophiles. The reaction pathway involves initial nucleophilic attack of the phosphorus at sulfur next to the thiocarbonyl group of xanthane hydride followed by decomposition of the phosphonium intermediate formed to products. The Hammett ρ-values for the sulfurisation of substituted triphenyl phosphines and triphenyl phosphites in acetonitrile are ~ -1.0. The entropies of activation are very negative (-114 ± 15 J mol^{-1} K^{-1}) with little dependence on solvent which is consistent with a bimolecular association step leading to the transition state. The negative values of $\Delta S^{\neq}$ and ρ values indicate that the rate limiting step of the sulfurisation reaction is formation of the phosphonium ion intermediate which has an early transition state with little covalent bond formation. The site of nucleophilic attack has been also confirmed using computational calculations.

Introduction

There is increasing use of phosphorothioate analogues of oligonucleotides in nucleic acid research.[1] The stability of the phosphorothioate linkage and its resistance to hydrolysis by nucleases together with the improved pharmacokinetic profiles of these analogues have led to their incorporation into therapeutic oligonucleotides.[2] Phosphorothioates have been used as inhibitors of gene expression[3] and have also been introduced into oligonucleotides for mechanistic studies on DNA–protein and RNA–protein interactions.[4] Therefore, the synthesis of oligonucleotide phosphorothioate analogues is of considerable interest. Synthesis is normally achieved by the sulfurisation of the corresponding nucleotide-phosphite through reaction of the P(III) analogue, supported on a solid support, with an organic sulfurising agent which is present in an organic solvent. As with all the steps involved in the synthesis of oligonucleotide based phosphorothioates, the sulfurisation step of the synthesis must be rapid and have a near quantitative yield. The sulfurisation of phosphorus(III) compounds has been achieved with a number of reagents such as: phenylacetyl disulfide (PADS),[5] 3*H*-1,2-benzodithiol-3-one-1,1-dioxide (Beaucage reagent),[6] tetraethylthiuram disulfide (TETD),[7] dibenzoyl tetrasulfide,[8] bis(*O*,*O*-diisopropoxyphosphinothioyl) disulfide (S-Tetra),[9] benzyltriethylammonium tetrathiomolybdate (BTTM),[10] bis(*p*-toluenesulfonyl) disulfide,[11] 3-ethoxy-1,2,4-dithiazoline-5-one (EDITH),[12] 1,2,4-dithiazolidine-3,5-dione (DTSNH),[12] bis(ethoxythiocarbonyl)tetrasulfide,[13] 3-methyl-1,2,4-dithiazolin-5-one (MEDITH)[14] and 3-amino-1,2,4-dithiazole-5-thione (**1a**) (ADTT, xanthane hydride).[15] The last reagent, in particular, appears to have an optimal combination of properties that suggest it will be an advantageous alternative to existing sulfurising reagents.[15]

To date there have been very few mechanistic studies of the sulfurisation reactions of phosphorus(III) analogues using heterocyclic sulfurisation reagents. We report here the results of our product and kinetic studies which provide a detailed mechanism for the sulfurisation of substituted triphenyl phosphines (**2a–g**), triphenyl phosphites (**3a–e**) and trialkyl phosphites (**4a–f**) with 3-amino-1,2,4-dithiazole-5-thione (**1a**) and 3-dimethylamino-1,2,4-dithiazole-5-thione (**1b**) (Scheme 1).

Results and discussion

Products of the sulfurisation reaction

Sulfurisation reactions of triphenyl phosphines (**2a–g**), triphenyl phosphites (**3a–e**) and trialkyl phosphites (**4a–f**) with 3-amino-1,2,4-dithiazole-5-thione (**1a**) and 3-dimethylamino-1,2,4-dithiazole-5-thione (**1b**) were studied in acetonitrile, ethanol and dichloromethane at 25 °C. Under these conditions sulfurisation proceeds smoothly and the yield of the corresponding phosphine

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† Dedicated to Professor Vojeslav Štěrba on the occasion of his 85th birthday

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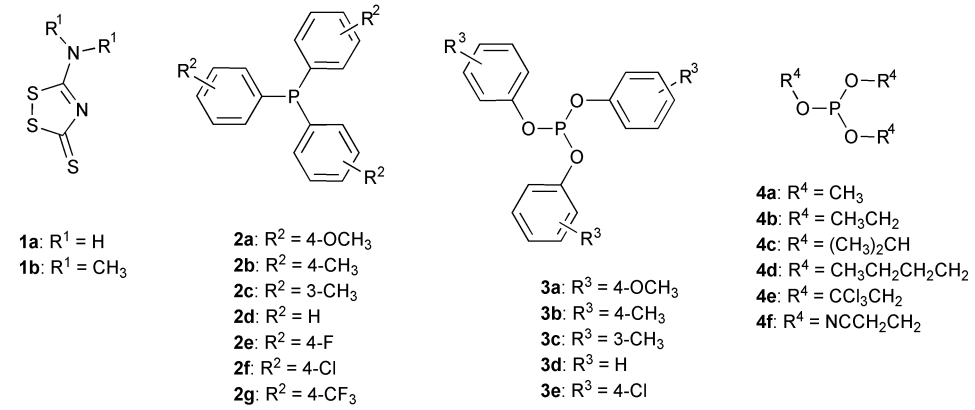
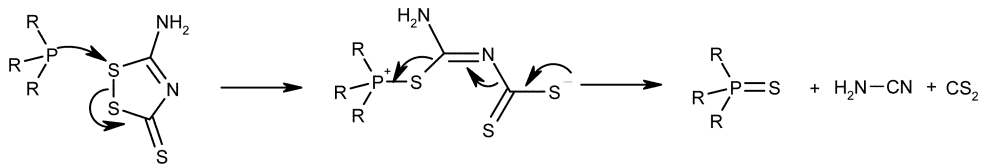


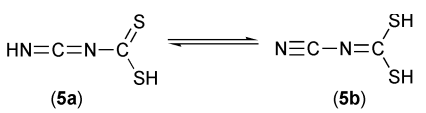
Scheme 1



Scheme 2

sulfide or phosphorothioate is almost quantitative. In reporting the use of 3-amino-1,2,4-dithiazole-5-thione (**1a**) as a sulfurisation agent Tang *et al.* proposed[15] that carbon disulfide and cyanamide or carbodiimide were additional reaction products and that the reaction likely proceeded *via* nucleophilic attack at the sulfur adjacent to the amino group, to generate an intermediate phosphonium ion (Scheme 2). Although this suggestion has been widely accepted, no evidence was provided for the proposed reaction products or the mechanism.

In the current study, the reactions of triphenyl phosphine (**2d**) with **1a** and triphenyl phosphite (**3d**) with **1a** in acetonitrile were analysed by ^{1}H, ^{13}C and ^{31}P NMR and by GC-MS. All attempts to detect carbon disulfide and cyanamide or carbodiimide failed. A possible explanation of this result could lie in the possible formation of *N*-cyanocarbonimidodithioic acid (**5b**) instead of carbodiimide and carbon disulfide. *N*-Cyanocarbonimidodithioic acid (**5b**) is a tautomer of the proposed intermediate carbodiimide (**5a**) (Scheme 3).

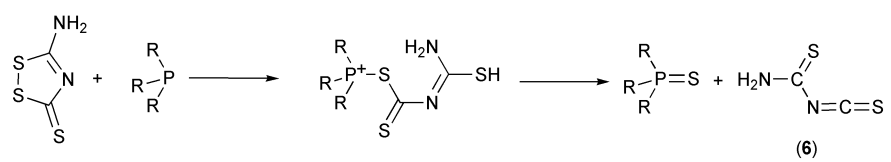


Scheme 3

N-Cyanocarbonimidodithioic acid (**5b**) is an unstable compound[16] and its characterisation in a pure state was unsuccessful. On the other hand, the dipotassium salt of (**5b**) is stable and is easily available from the reaction of cyanamide and carbon disulfide in aqueous or ethanolic potassium hydroxide[16,17] solutions or by hydrolysis of 3-amino-1,2,4-dithiazole-5-thione (**1a**) in aqueous potassium hydroxide.[16] Although *N*-cyanocarbonimidodithioic acid (**5b**) itself is an unstable compound, it is an important intermediate[18] during synthesis of **1a**. The analysis of the reaction products from the sulfurisation of triphenyl phosphine (**2d**) with **1a** in acetonitrile, after work up with potassium hydroxide, showed only trace levels of the dipotassium salt of **5b**.

The ^{1}H and ^{13}C NMR spectra of the crude by-products show major signals that are more typical of a H_2N–(C=S)–N grouping, *i.e.* two broad singlets at 7.85 and 8.43 ppm in ^{1}H NMR, and a signal at 186.7 ppm in ^{13}C NMR. This is not consistent with the previously proposed products and mechanism[15] and an alternative reaction pathway must occur. A possible reaction pathway involves nucleophilic attack of the phosphorus at sulfur next to the thiocarbonyl group of **1a** and subsequent decomposition of the phosphonium intermediate formed into triphenyl phosphine sulfide and thiocarbamoyl isothiocyanate (**6**) (Scheme 4).

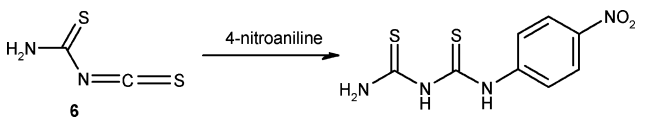
Thiocarbamoyl isothiocyanate (**6**) itself has not been described in the literature, presumably because of its high reactivity and instability. *N*,*N*-Dimethylthiocarbamoyl isothiocyanate has been characterised and is stable for a couple of days[19] at −15 °C; at ambient temperature *N*,*N*-dimethylthiocarbamoyl isothiocyanate readily undergoes[19,20] dimerisation ([4 + 2] cycloaddition)



Scheme 4

to give 2-dimethylamino-5-dimethylthiocarbamoyl-1,3,5-thiadiazine-4,6-dithione.

To prove the presence of the reactive thiocarbamoyl isothiocyanate (**6**) during the course of the sulfurisation reaction we added an external nucleophile, 4-nitroaniline, to the reaction mixture to act as a trap. After reaction work up, 1-(4-nitrophenyl)dithiobiuret was obtained which is the expected product of nucleophilic addition of 4-nitroaniline to thiocarbamoyl isothiocyanate (Scheme 5). The analogous product (*i.e.* 1-(4-nitrophenyl)-5,5-dimethyldithiobiuret) was obtained when 3-dimethylamino-1,2,4-dithiazole-5-thione (**1b**) was reacted with triphenyl phosphine (**2d**) in the presence of 4-nitroaniline. Further evidence supporting the involvement of thiocarbamoyl isothiocyanate as a reaction product was sought from performing the reaction in ethanol as solvent. Although ethanol is a weak nucleophile a reaction with the reactive thiocarbamoyl isothiocyanate was possible. However, the desired ethyl thiourea *N*-thiocarboxylate was not isolated after 24 hours at ambient temperature, but instead, *O*-ethyl-*S*-potassium *N*-cyanocarbonimidothioate (**8**) was obtained as the main by-product (Scheme 6).



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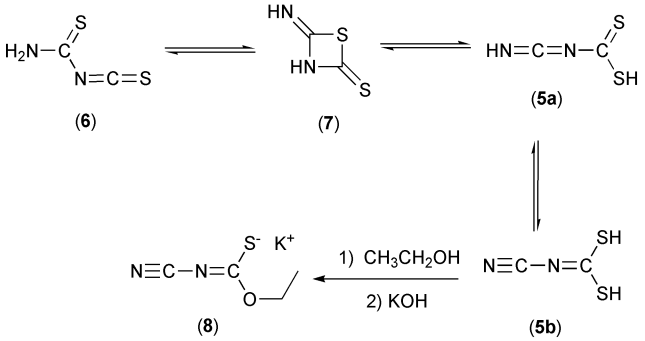
Scheme 5

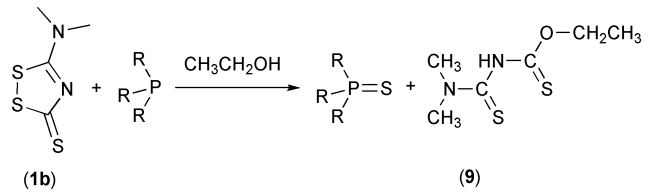


(6) **(7)** **(5a)** **(8)** **(5b)**

Scheme 6

There are two possible explanations of this unexpected behaviour. One explanation is that changing the solvent alters the site of attack; attack at the sulfur adjacent to the amino group would generate *N*-cyanocarbonimidodithioic acid (**5b**) which could undergo esterification with ethanol to give a half ester which, after work up with potassium hydroxide, gives (**8**). Our preferred explanation involves initial formation of the unstable thiocarbamoyl isothiocyanate (**6**) which then undergoes a slow intramolecular cyclisation giving intermediate 4-imino-1,3-thiazolidine-2-thione (**7**) which ring opens[18] to generate *N*-cyanocarbonimidodithioic acid (**5b**) (Scheme 6).

N-Substituted xanthane hydrides, such as 3-dimethylamino-1,2,4-dithiazole-5-thione (**1b**), cannot form the corresponding *N*-cyanocarbonimidodithioic acid (**5**) because the tautomerisation of the thiocarbamoyl isothiocyanate (**6**) (Scheme 3) *via* the intermediate (**7**) is not possible. Confirmation of our proposed pathway comes from the observation that the sulfurisation of (**1b**) in ethanol gives the expected *O*-ethyl *N*,*N*-dimethylthiourea-*N*′-thiocarboxylate (**9**) (Scheme 7) and a small amount of the dimer (2-dimethylamino-5-dimethylthiocarbamoyl-1,3,5-thiadiazine-4,6-dithione).

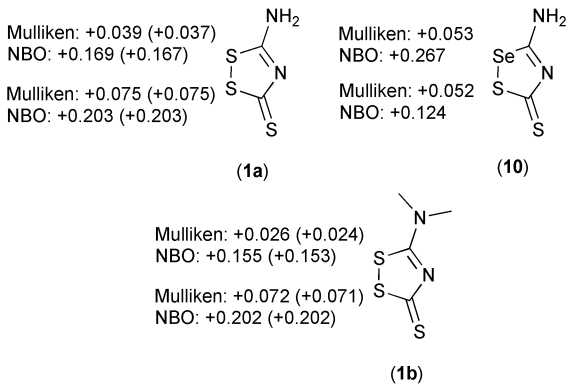


(1b) **(9)**

Scheme 7

In order to gain more information about the site of attack the selenium analogue of **1a**, *i.e.* 3-amino-1,2,4-thiaselenazole-5-thione (**10**), was prepared. Reaction of this compound with triphenyl phosphine in acetonitrile-d_3 was monitored using ^{31}P NMR spectroscopy. It was found that the major product was triphenyl phosphine sulfide (96%) and less than 5% triphenyl phosphine selenide was generated. In methanol-d_3 the ratio of products was similar (93% of triphenyl phosphine sulfide and 7% of triphenyl phosphine selenide). The formation of the sulfide in preference to the selenide supports nucleophilic attack on sulfur adjacent to the thione.

The site of nucleophilic attack has been also confirmed using computational calculations—GAUSSIAN 03 as described in the Experimental section. The structures of **1a**, **1b** and **10** as depicted in Scheme 8 were found to be the most stable tautomers (99.998%). In the case of **1a** and **1b**, both in acetonitrile as well as in ethanol, there is lower electron density at sulfur close to the thiocarbonyl group (S-1) than at the sulfur (S-2) close to the amino group (Scheme 8) based on both Mulliken charges and charges calculated using natural bond analysis (NBO). Presumably this is due to the electrons at S-1 being more involved in conjugation with the –C=S– grouping compared with the level of conjugation between S-2 and C=N. This is consistent with differences in bond lengths between (C-5)–(S-1) and (C-3)–(S-2) determined in the crystal[21] structure. Population analysis also shows higher electron density between S-1 and C-5 than between S-2 and C-3. Such differences in conjugation will lead to a polarisation of the S–S bond which is comparable with the polarisation of a C–S bond. From the data presented in Scheme 7 it is also clear that the solvent has little influence on the electron densities at either of the two sulfur atoms.



(1a) **(10)** **(1b)**

Scheme 8 Mulliken charges and natural bond analysis (NBO) charges in acetonitrile and ethanol (values given in parentheses) for **1a**, **1b** and **10**.

Mulliken charges were calculated and NBO analysis was also performed for 3-amino-1,2,4-thiaselenazole-5-thione (**10**) in acetonitrile (Scheme 8). In this case the electron densities at sulfur and selenium are almost the same in terms of Mulliken charges and, using NBO analysis, the positive charge at selenium is predicted to be larger and this is probably caused by the lower electronegativity of selenium. This result could suggest nucleophilic attack might be expected to occur at both selenium and sulfur. In order to get a further insight into the factors that control the reactivity of **10**, we made use of the NBO analysis. Valence electrons at selenium are further away from the core and are therefore less involved in conjugation with –C=N– as compared with conjugation of (S-1) with C=S. The calculated shapes and energy levels of the LUMO orbitals at sulfur and selenium indicate that the electron density at selenium, in the direction of potential nucleophilic attack, is approximately three times higher than at the adjacent sulfur.

Kinetic studies of the sulfurisation reaction

The kinetics of the sulfurisation reaction were determined by monitoring the decrease in concentration of **1a**, **1b** and **10** spectrophotometrically at 360 nm in various solvents in the presence of excess phosphine or phosphite. The absorbance decreased exponentially with time from which was obtained a pseudo-first-order rate constant which varied linearly with the concentration of the phosphorus(III) derivative to give the corresponding second-order rate constant. Rate constants were determined for the sulfurisation reactions of substituted triphenyl phosphines (**2a–g**), triphenyl phosphites (**3a–e**) and trialkyl phosphites (**4a–f**) using **1a**, **1b** and **10** as sulfurisation agents (Tables 1 and 2).

The single exponential decay of absorbance both for phosphites and phosphines indicates that the reaction proceeds in one observable step, which is also supported by the observation that no consecutive reactions are seen at any wavelength in the UV-Vis spectrum. It is concluded that if the reaction proceeds through a reactive intermediate then its concentration is negligible compared to that of the reactants throughout the entire reaction time.

Table 1 Second order rate constants k (l mol^{-1} s^{-1}) for reaction of **1a**, **1b** and **10** with substituted triphenyl phosphines (**2a–g**) in acetonitrile at 25 °C

Phosphine	k(**1a**) × 10^{-4}	k(**1b**) × 10^{-4}	k(**8**) × 10^{-4}
2a	5.947	4.465	—
2b	3.404	2.791	—
2c	1.782	1.335	—
2d	1.323	1.220	0.041
2e	0.787	0.519	—
2f	0.410	0.251	—
2g	0.026	0.015	—

Table 2 Second order rate constants k (l mol^{-1} s^{-1}) for reaction of **1a** with substituted triphenyl phosphites (**3a–e**, **4a–f**) in acetonitrile at 30 °C

Phosphite	k(**1a**)	Phosphite	k(**1a**)
3a	26.24	**4a**	3030
3b	6.746	**4b**	3122
3c	3.991	**4c**	3655
3d	3.263	**4d**	3870
3e	0.509	**4e**	5.641
		4f	702.3

A Hammett plot for the data, the logarithm of the second-order rate constants against σ, is presented in Fig. 1 for seven substituted triphenyl phosphines (**2a–g**). The plot is linear, for both of the sulfurisation agents, (**1a**) and its dimethyl derivative (**1b**), the slope of which generates reaction constants ρ(**1a**) = −0.86 and ρ(**1b**) = −0.92 (Fig. 1). A similar value is also seen for the sulfurisation of substituted triphenyl phosphites (**3a–e**) in acetonitrile, ρ(**1a**) = −1.10. The correlation shown is against σ^- which is better than that against σ, presumably because there is some conjugation between the P lone pair and the aromatic ring.

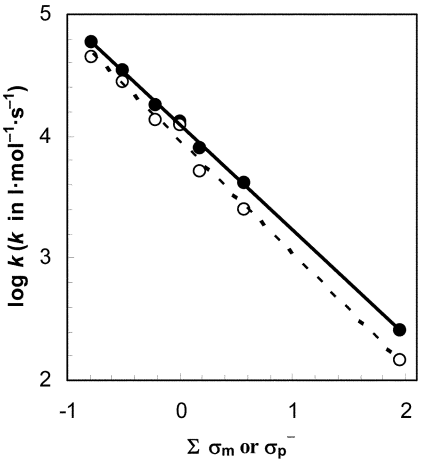


Fig. 1 Hammett correlation for sulfurisation of triphenyl phosphine (**2d**) with **1a** (solid points and solid line) and with **1b** (open points and dashed line).

The interpretation of the Hammett ρ-value in terms of charge distribution in the transition state requires a reference reaction, ideally a corresponding ρ-value for an equilibrium reaction. There are a limited number of Hammett correlations in the literature which relate to reactions of phosphorus(III) species, but they include kinetic values measured for the reaction of: aryldiethyl phosphines with ethyl iodide,[22] $\rho = -1.0$; triaryl phosphines with elemental sulfur,[23] $\rho = -2.5$; and triaryl phosphines and triaryl phosphites with[24] diphenyl trisulfide, $\rho = -1.1$. In determining possible transition state structures these values can be compared with equilibrium data measured for the protonation of phosphines, measured in nitromethane using Taft substituent constants[25] $\rho^* = -2.6$ which is very similar to the reaction constant determined for protonation of amines,[26] $\rho = -2.77$.

It is likely that the sulfurisation reaction proceeds by initial nucleophilic attack of phosphorus(III) on the disulfide linkage to generate a phosphonium ion intermediate as shown in Scheme 4.

Either formation or breakdown of the intermediate could be the rate limiting step and both steps would have transition states with positively charged phosphorus compared with the reactant state. The relatively small reaction constant measured here of about −1.0 indicates the development of a partial positive charge on phosphorus in the transition state. If the first step is rate limiting then the observed ρ-value suggests an early transition state with little build up of charge on phosphorus. If the second step is rate limiting then the reaction constant is the sum of two values for the two steps (Scheme 4), probably with opposite signs. The reaction constant for the formation of intermediate ρ is expected to be about −2.8. It is therefore unlikely that the second step is rate

limiting and the observed ρ-value is indicative of rate limiting formation of the phosphonium ion with less than half of the unit positive charge developed on phosphorus in the transition state as a result of bond formation.

In order to support this conclusion activation parameters for the sulfurisation reaction were also determined. Activation parameters were measured in both acetonitrile and ethanol for the sulfurisation of triphenyl phosphine (**2d**) and triphenyl phosphite (**3d**) with **1a** and **1b**. The measurements were carried out at four temperatures (Table 3) and from the dependence of $\ln(k/T)$ *vs.* $1/T$ activation enthalpies and entropies at 30 °C were calculated (Table 4). The entropies of activation are very negative (-114 ± 15 J mol^{-1} K^{-1}) and are consistent with a bimolecular association step leading to the transition state. This is consistent with the first step being rate limiting but may also contain a contribution from the entropy change associated with increased solvation of charge in the transition state. From Tables 3 and 4 it is clear that both the rate constants and activation parameters are only slightly dependent on solvent. To confirm this observation the kinetics of sulfurisation of triphenyl phosphine (**2d**) with **1b** in dichloromethane were also determined. The second order rate constant $k = 1.16 \times 10^4$ l mol^{-1} s^{-1} is similar to that in acetonitrile (Table 1). From this it can be concluded that the transition state of the rate limiting step is not very polar. For the reaction of triphenyl phosphines and phosphites with benzhydrylium cations in dichloromethane, where charge is neither created nor destroyed values of activation entropy $\Delta S^{\neq}$ around -90 J mol^{-1} K^{-1} have been reported.[27] The rate constants for this reaction in dichloromethane and acetonitrile are also similar.

The second order rate constants obtained for triphenyl phosphines (**2a–g**) are more than three orders of magnitude higher than those for the corresponding triphenyl phosphites (**3a–e**) and more than one order of magnitude higher than those for trialkyl phosphites (**4a–f**) (Tables 1 and 2) which is consistent with the higher nucleophilicity of phosphines. Even greater rate differences have been observed in the case of reactions of triphenyl phosphines and triphenyl phosphites with various carbocations.[27] Despite the rate differences we observe here, the ρ-values for both reaction series are very similar. This is also the case for the reaction of triarylphosphines, triaryl phosphinites and triaryl phosphonites with diphenyl trisulfide.[24]

Table 3 Bimolecular rate constants k (l mol^{-1} s^{-1}) for reaction of **1a** and **1b** with triphenyl phosphine (**2d**) in acetonitrile and ethanol and for reaction of **1a** and triphenyl phosphite (**3d**) at 25, 30, 35 and 40 °C

T/°C	k(**1a**) × 10^{-4} (acetonitrile)	k(**1b**) × 10^{-4} (acetonitrile)	k(**1a**) × 10^{-4} (ethanol)	k(**1a** + **3d**) (acetonitrile)
25	1.323	1.220	0.394	2.648
30	1.439	1.339	0.465	3.263
35	1.603	1.466	0.551	4.231
40	1.781	1.605	0.644	5.410

Conclusions

In summary, it can be concluded that the sulfurisation reaction involves nucleophilic attack of the phosphorus at sulfur next to the thiocarbonyl group of **1a** and **1b** to form a phosphonium intermediate. The intermediate then breakdowns in a unimolecular step by carbon–sulfur bond fission to generate the thiophosphoryl product and thiocarbamoyl isothiocyanate (Scheme 4). The negative values of $\Delta S^{\neq}$ and ρ values indicate that the rate limiting step of the sulfurisation reaction is formation of the phosphonium ion intermediate which has an early transition state with little covalent bond formation.

Experimental

^{1}H, ^{13}C, ^{31}P and ^{77}Se NMR spectra were recorded on a Bruker 400 MHz or Bruker AVANCE 500 MHz instrument. Chemical shifts δ are referenced to solvent residual peaks δ(DMSO-d_6) = 2.50 (^{1}H) and 39.6 ppm (^{13}C), and δ($CDCl_3$) = 7.27 (^{1}H) and 77.0 (^{13}C). ^{31}P NMR shifts are referenced to 85% phosphoric acid (external standard) and ^{77}Se NMR shifts are referenced to H_2Se. Coupling constants J are quoted in Hz.

The kinetic measurements were carried out on a Diode Array Stopped-Flow SX.18 MV-R (Applied Photophysics) spectrophotometer at 25 °C. The observed pseudo-first-order rate constants k_{obs} were calculated from the measured time dependence of absorbance at 360 nm with the help of an optimisation program.

Quantum chemical computations were carried out with the GAUSSIAN 03 program[28] employing the hybrid density functional B3LYP.[29] Full geometry optimisations were performed by using the TZVP basis set.[30] The nature of the stationary points was verified by analytical computations of harmonic vibrational frequencies. Solvation effects were included using the polarizable continuum model (PCM).[31] A natural bond orbital (NBO) analysis[32] was invoked using the population keyword in GAUSSIAN 03.

Triphenylphosphines (**2a–g**), triphenyl phosphite (**3d**) and trialkyl phosphites (**4a–d**) were purchased from Sigma-Aldrich and used without further purification. Triphenyl phosphites (**3a–c**, **3e**) and trialkyl phosphites (**4e–f**) were prepared and purified according to ref. 33. Due to potential oxidation of all phosphorus(III) compounds all the solutions were freshly prepared just before kinetic measurements. Solvents used were of HPLC quality. 3-Amino-1,2,4-dithiazole-5-thione (**1a**) was obtained from Avecia Biotechnology, Grangemouth, UK and recrystallised from a mixture of water and dimethyl sulfoxide. Dipotassium *N*-cyanocarbonimidodithioate was prepared according to ref. 17.

Table 4 Activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for reaction of **1a** and **1b** with triphenyl phosphine (**2d**) and triphenyl phosphite (**3d**) in acetonitrile (ACN) and ethanol (EtOH) at 30 °C

	1a + **2d** (ACN)	**1b** + **2d** (ACN)	**1a** + **2d** (EtOH)	**1a** + **3d** (ACN)
$\Delta H^{\neq}$/kJ mol^{-1}	13.3	11.7	23	36.5
$\Delta S^{\neq}$/J mol^{-1} K^{-1}	−121	−128	−99	−115

3-Dimethylamino-1,2,4-dithiazole-5-thione (1b)

This compound was prepared according to ref. 34 and purified by crystallisation from acetonitrile. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.26 and 3.36 (2 × s, 6H, 2 × NCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 42.2, 42.7, 181.7, 206.6.

3-Amino-1,2,4-thiaselenazole-5-thione (10)

This compound was prepared according to ref. 18 and used immediately for reaction with triphenyl phosphine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.37 and 10.00 (2 × bs, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.9, 209.6. ^{77}Se NMR (DMSO-d_6, 95 MHz) δ 738.2 (d, J 11.4).

Sulfurisations in acetonitrile

Reaction of 1a with triphenyl phosphine (2d). 3-Amino-1,2,4-dithiazole-5-thione (**1a**) (1 g, 6.7 mmol) was dissolved in 400 ml of acetonitrile under a nitrogen atmosphere at 30 °C and a solution containing 1.75 g (6.7 mmol) of triphenyl phosphine (**2d**) in 100 ml of acetonitrile was added in one portion. The reaction mixture was stirred for 40 min. and then acetonitrile was removed. The solid residue was mixed with 30 ml of aqueous potassium hydroxide solution. After filtration the insoluble material was practically pure triphenyl phosphine sulfide (1.8 g), the filtrate was evaporated to give a crude mixture of by-products. ^{1}H NMR (D_2O, 400 MHz) δ 7.85 and 8.43 (2 × bs, 2H, NH_2). ^{13}C NMR (D_2O, 100 MHz) δ 133.5, 186.7 (major signals), 121.6, 228.4 (minor signals corresponding[17] to dipotassium *N*-cyanocarbonimidodithioate) and 160.6, 171.1 (minor signals of unknown compound, possibly (**7**)).

Reaction of 1a with triphenyl phosphine (2d) and 4-nitroaniline. 3-Amino-1,2,4-dithiazole-5-thione (**1a**) (1 g, 6.7 mmol) was dissolved in 400 ml of acetonitrile under a nitrogen atmosphere at 30 °C and a solution containing 1.75 g (6.7 mmol) of triphenyl phosphine (**2d**) in 100 ml of acetonitrile was added in one portion. The reaction mixture was stirred for 5 min. and then 0.92 g (6.7 mmol) of 4-nitroaniline in 20 ml acetonitrile was added. After 15 hours the acetonitrile was removed and the solid residue was quickly extracted with 3 × 40 ml of 3% aqueous potassium hydroxide solution. After filtration the insoluble material, pure triphenyl phosphine sulfide (1.85 g, 94%), was recovered. The filtrate was immediately acidified by addition of concentrated HCl (pH = 3). Precipitated 1-(4-nitrophenyl)dithiobiuret was filtered off and dried. Yield 1.65 g (97%). Mp 168–170 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.97 (AA′XX′, J 9.05, 2H, Ar-2H), 8.25 (AA′XX′, J 9.1, 2H, Ar-2H), 9.1 and 9.42 (2 × bs, 2H, NH_2), 11.01 (bs, 1H, NH), 13.22 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 123.3, 124.6, 143.7, 144.3, 177.3, 179.2. m/z (ESI) 255.0016 (M^-.$C_8H_7N_4O_2S_2$ requires 255.0005).

Reaction of 1a with trimethyl phosphite (4a) and 4-nitroaniline. The reaction was carried out in the same way as for triphenyl phosphine. Yield of isolated 1-(4-nitrophenyl)dithiobiuret was 1.35 g (80%).

Reaction of 1b with triphenyl phosphine (2d) and 4-nitroaniline. 3-Dimethylamino-1,2,4-dithiazole-5-thione (**1b**) (1.78 g, 0.01 mol) was dissolved in 200 ml of acetonitrile under a nitrogen atmosphere at 30 °C and a solution containing 2.62 g (0.01 mol) of triphenyl phosphine (**2d**) in 100 ml of acetonitrile was added in one portion. The reaction mixture was stirred for 5 min and then 1.38 g (0.01 mol) of 4-nitroaniline in 30 ml of acetonitrile was added. After 20 hours precipitated 1-(4-nitrophenyl)-5,5-dimethyldithiobiuret (1.25 g) was filtered off and the acetonitrile was removed. The solid residue was quickly extracted with 2 × 50 ml portions of 3% aqueous potassium hydroxide solution. After filtration, the insoluble material pure triphenyl phosphine sulfide (2.9 g, 98%) was recovered and the filtrate was immediately acidified by the addition of concentrated HCl (pH = 3). Precipitated 1-(4-nitrophenyl)-5,5-dimethyldithiobiuret (1.2 g) was filtered off and dried. Overall yield 2.45 g (87%). Mp 155–156 °C (ref. 19 gives mp 188 °C). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.31 (s, 6H, 2 × NCH_3), 7.97 (AA′XX′, J 9.1, 2H, Ar-2H), 8.24 (AA′XX′, J 9.1, 2H, Ar-2H), 10.33 (bs, 1H, NH), 11.76 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 41.5, 42.4, 122.1, 124.3, 143.2, 144.9, 178.6, 178.9. m/z (ESI) 283.0313 (M^+. $C_{10}H_{11}N_4O_2S_2$ requires 283.0318).

Reaction of 10 with triphenyl phosphine (2d) (^{31}P NMR study). 3-Amino-1,2,4-thiaselenazole-5-thione (**10**) (21 mg, 106 μmol) was dissolved in 3 ml of acetonitrile-d_3 and 0.5 ml of DMSO-d_6. Triphenyl phosphine (**2d**) (28 mg, 107 μmol) in 0.5 ml of acetonitrile-d_3 was added and a ^{31}P NMR spectrum was recorded after 15 min, 45 min and 24 hours. All spectra contained two singlets belonging to triphenyl phosphine sulfide (43.2 ppm; in accordance with ref. 30) and triphenyl phosphine selenide (35.5 ppm; in accordance with refs. 30,31) in the ratio 23 : 1.

Sulfurisations in ethanol

Reaction of 1a with triphenyl phosphine (2d). 3-Amino-1,2,4-dithiazole-5-thione (**1a**) (1 g, 6.7 mmol) was dissolved in 200 ml of ethanol under a nitrogen atmosphere at 30 °C and a solution containing 1.75 g (6.7 mmol) of triphenyl phosphine (**2d**) in 100 ml of ethanol was added in one portion. The reaction mixture was stirred for 17 hours and then precipitated triphenyl phosphine sulfide was filtered off (0.7 g). Ethanol was removed and the solid residue was mixed with 30 ml of 3% aqueous potassium hydroxide solution. After filtration the insoluble triphenyl phosphine sulfide (1.1 g, overall yield 92%) was recovered and the filtrate was evaporated to dryness. The resulting solid was washed with ethanol to give 0.7 g (67%) of *O*-ethyl-*S*-potassium *N*-cyanocarbonimidothioate (**8**). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.13 (t, J 7.1, 3H, CH_3), 4.08 (q, J 7.1, 2H, OCH_2). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.6, 64.4, 120.2, 197.1. m/z (ESI) 129.0156 (M − K^+. $C_4H_5N_2OS$ requires 129.0117). m/z (ESI) 206.9398 (M + K^+. $C_4H_5K_2N_2OS$ requires 206.9391).

Reaction of 1b with triphenyl phosphine (2d). 3-Dimethylamino-1,2,4-dithiazole-5-thione (**1b**) (1.78 g, 0.01 mol) was suspended in 500 ml of ethanol under a nitrogen atmosphere at 30 °C and a solution containing 2.62 g (0.01 mol) of triphenyl phosphine (**2d**) in 100 ml of ethanol was added in one portion. The reaction mixture was stirred for 23 hours and then precipitated triphenyl phosphine sulfide was filtered off. The volume of the reaction mixture was reduced to 50 ml and the rest of the solid triphenyl phosphine sulfide (2.8 g, overall yield 95%), was filtered off. The filtrate was evaporated to give a yellow oil. ^{1}H NMR

($CDCl_3$, 500 MHz) δ 1.33 (t, J 7.2, 3H, CH_3), 3.23 and 3.41 (2 × s, 6H, 2 × NCH_3), 4.48 (q, J 7.2, 2H, OCH_2), 8.57 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 42.3, 43.6, 68.0, 179.3, 186.5. m/z (ESI) 191.0299 ($M - H^+$. $C_6H_{11}N_2OS_2$ requires 191.0307).

Reaction of 10 with triphenyl phosphine (2d) (^{31}P NMR study). 3-Amino-1,2,4-thiaselenazole-5-thione (**10**) (21 mg, 106 μmol) was dissolved in 2 ml of methanol-d_4 and 1 ml of DMSO-d_6. Triphenyl phosphine (**2d**) (28 mg, 107 μmol) in 1 ml of methanol-d_4 was added and a ^{31}P NMR spectrum was recorded after 2 hours. The spectrum contained two singlets belonging to triphenyl phosphine sulfide (43.2 ppm; in accordance with ref. 35) and triphenyl phosphine selenide (35.5 ppm; in accordance with refs. 35,36) in the ratio 1 : 0.07.

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