Mechanism of the Reaction of Lawesson's Reagent with *N*-Alkylhydroxamic Acids

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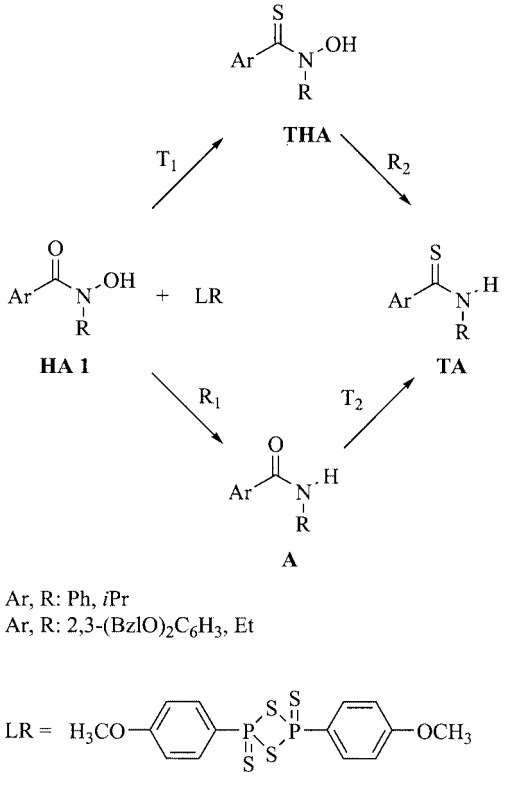
The mechanism of the reaction under discussion has been established by investigating the products of the reaction between 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent, LR) and *N*-alkylhydroxamic acids HAs **1**. The primary intermediate is an adduct, *O*-dithiophosphonylated hydroxamic acid **19**, which decomposes to yield metathiophosphonate (AnsPOS), a sulfur atom, and an amide. At the same time, owing to the co-existence of **19** and metadithiophosphonate (AnsPSS) in equilibrium, the carbonyl group is thionated. It has also been established that monomeric AnsPOS formed in both reduction and thionation processes does not undergo oligomerisation to cyclic trimer **5** and linear oligomers, which is typical for amides reacting with LR. Since there is unreacted HA **1** in the reaction mixture, AnsPOS takes part in a controlled transformation to form a dimer, the corresponding pyrothiophosphonate **3**, together with the intermediate *O*-thiophosphonylated hydroxamic acid **2**. A hydrolysed product of AnsPOS, namely (4-methoxyphenyl)thiophosphonic acid **4**, participates in the last reaction.

Introduction

It has often been reported that 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (Lawesson's reagent, LR) is a very effective thionating reagent of carbonyl compounds.[1] The key issue here is the chemoselectivity of the LR reaction when there is a nucleophilic centre other than a carbonyl group in the molecule. Direct thionation of hydroxamic acids (HAs) could potentially be very useful in the synthesis of the thioanalogues of natural hydroxamates and *N*-hydroxythiopeptides.[2] It is evident that this reaction could be of synthetic importance as it gives reasonable yields of thiohydroxamic acids (THAs).[3] As we have demonstrated before,[4] the action of LR in THF causes *N*-alkylbenzohydroxamic acids **1** to transform into three products: THAs, amides (A) and thioamides (TA). The reaction can be thought of as involving four stages of which two are competitive and two are subsequent. Thus, initially thionation (T_1) gives THA and reduction (R_1) affords A. Subsequent reduction (R_2) and thionation (T_2) ultimately yield TA (Scheme 1).

We have proved that both the stoichiometry and the solvent used, as well as the temperature, have an effect on the distribution of the reaction products and the yield of THA. In our experiments the maximum yield of THA was 55–60%.



Scheme 1.

The reactions of LR with selected representatives of compounds with a N–O bond, excluding HAs, have been investigated previously. Based on the presence of sulfur in the post-reaction mixture, Lawesson and co-workers as-

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sumed that nitrones and the *N*-oxides of pyridines react with LR to give labile *N*-sulfides as intermediates. These *N*-sulfides yield the corresponding deoxygenated products upon loss of the sulfur atom.[5] Meanwhile, the reaction of LR with oximes, namely with benzaldoxime and diphenyl ketoxime, yielded thiobenzaldehyde and a mixture of thiobenzanilide and benzanilide, respectively.[6] In their work, Lawesson and co-workers did not present any convincing evidence for the structures of the intermediates formed in these reactions, nor did he make any attempt to identify the products of the transformations. It appeared that the reaction of LR with nitrones does not always give deoxygenation or Beckmann rearrangement products. Bertrand and co-workers established that in the case of a sterically crowded *N*-(*tert*-butyl)-*C*-phenyl nitrone LR acts as a dipolarophile to give the appropriate cycloadduct.[7]

A full investigation of the reactions of LR with hydroxamic acids will significantly broaden the knowledge of the reaction mechanism and will also contribute to a rational selection of reaction conditions for HA thionation. Our former analysis of HA conversion products was not sufficient for us to suggest a mechanism for this reaction. Thus I have assumed that a thorough analysis of the transformation and fate of LR, and particularly of the metathiophosphonate species in the reaction with HAs **1** (mainly based on ^{31}P NMR spectroscopy), and identification of the stable reaction products, supplemented with the results obtained in the previous report, will enable the mechanism of this interesting reaction to be understood and explained.

Results and Discussion

Identification of the Phosphorus Products of LR Transformation

At a glance, the reaction does not resemble the generally accepted Wittig-like mechanism which assumes attack of metadithiophosphonate (AnsPSS) upon the carbonyl oxygen atom via 1,3,2-oxathiaphosphetane 2-sulfide. This would be the case when LR reacts with amides and other carbonyl compounds. The reaction of LR with HA **1** occurs immediately at room temperature and its rate is limited by the rate of dissolution of LR. The ^{31}P NMR spectra of the reaction mixtures containing HA **1** and LR in THF differ substantially from those of reaction mixtures containing amide A and LR (Figure 1).

A characteristic feature of these spectra is the presence of only three singlet signals from the three products of the LR transformation. This distinguishes this reaction from a typical reaction of A with LR, which produces a series of oligomeric phosphorus products and exhibits a more complex ^{31}P NMR spectrum with peak clusters centred at δ_P = 3 and 72 ppm. As is generally known, the oligomers of type [AnsP(S)(μ-O)$_n$] and [AnsP(O)(μ-O)$_n$] are formed by metathiophosphonate (AnsPOS) polymerisation.[8]

It should be stated here that the spectra obtained from the reaction mixture containing HA **1** and LR in THF differ considerably from the spectra obtained in benzene and nitrobenzene (reflux, 5 min). The latter exhibited character-

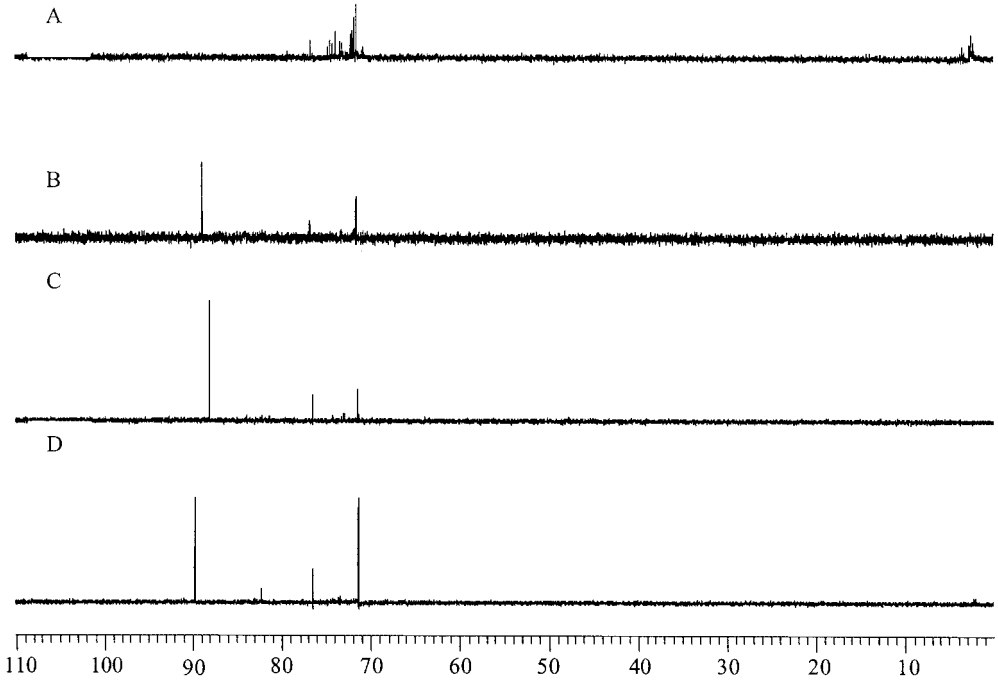
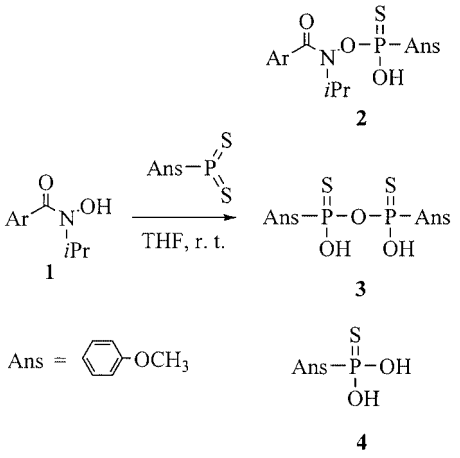


Figure 1. ^{31}P NMR spectra of the reaction mixtures (THF, room temp., 1 h) formed from LR and A) *N*-isopropylbenzamide, B) **1a** (Ar = Ph), C) **1b** (Ar = 4-MeOC$_6$H$_4$), and D) **1c** (Ar = 4-NO$_2$C$_6$H$_4$).

istic doublets of the dimeric products of the LR transformation which contain a bridging sulfur or oxygen atom with a typical coupling constant ($^3J_{PP}$ = 49 Hz).

The three phosphorus-containing products formed in the reaction of LR with HA **1** in THF have been identified, respectively, as *O*-thiophosphonylated HA **2**, pyrothiophosphonate **3**, and (4-methoxyphenyl)phosphonothioic acid (**4**) (Scheme 2). As it is impossible to isolate these compounds from the reaction mixture owing to their high polarity, it was decided to isolate their stable derivatives, authentic samples of which were also synthesised by an independent route.



Scheme 2.

Note also that the reaction of HA **1** with LR does not yield the LR transformation product most often isolated in the thionation reactions of other carbonyl compounds, namely the trimer of (4-methoxyphenyl)thiophosphane oxide **5**. From the data of McKenna[9] and Zubrikov[10] and their co-workers one could presume that the signal observed at δ = 71.4 ppm corresponds to trimer **5**. However, the ^{31}P NMR spectrum of trimer **5** synthesised by an alternative method exhibits the A_2B spin system [δ_P = 72.3 (d, 2 P, J = 49 Hz), 74.4 (t, 1 P, J = 49 Hz) ppm], in accordance with other literature data.[11] Moreover, the presence of trimer **5** in the reaction mixture has finally been excluded after investigating the results of reactions with derivatising reagents. Thus, it has been established that trimer **5** does not react with trimethyl orthoformate (TMOF) at room temperature, while the addition of trimethyl orthoformate to the reaction mixture leads to the disappearance of the signal at δ = 71.4 ppm and quantitative formation of *O*-methyl phosphonothioate **6** (vide supra).

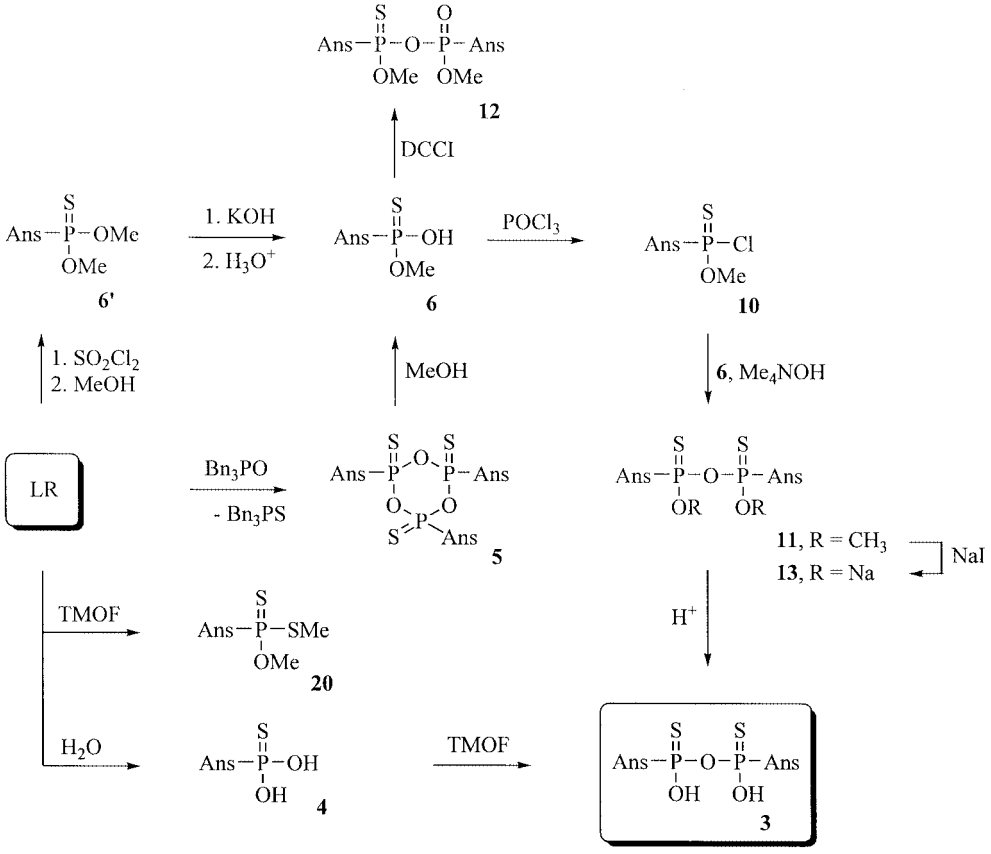
The suggested structure of the adduct of HA **1a** and AnsPOS − **2a** (δ_P = 88.8 ppm) − was confirmed by treating the post-reaction mixture with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of triethylamine. The derivative of adduct **2a** was isolated in a yield of 4% and identified as the *O*-TBDMS ester **7a** (δ_P = 83.9 ppm). Further evidence of the presence of adduct **2a** is provided by the ^{31}P NMR spectra of reaction mixtures treated with diazomethane and methyl iodide in the presence of triethylamine. In this way adduct **2a** was transformed in situ to a mixture of *O*- and *S*-methyl esters **8a** and **9a**, respectively (δ_P = 98.1 and 54.1 ppm). Authentic samples of adducts **8a** and **9a** were obtained by an independent method from *S*-methyl (4-methoxyphenyl)phosphonochloridothioate and *O*-methyl (4-methoxyphenyl)phosphonochloridothioate (**10**), respectively. The ^{31}P NMR chemical shifts of adducts **2** differ according to the structure of the initial hydroxamic acid. They are 88.8 ppm for **2a** (Y = H), 88.0 ppm for **2b** (Y = OCH_3), 89.7 ppm for **2c** (Y = NO_2), and 87.7 ppm for **2d** (Y = NMe_2), while the chemical shifts of the other two signals present in the spectra of the reaction mixtures are the same, regardless of the initial HA **1** used. This is additional proof of the structure of adducts **2**.

An authentic sample of pyrothiophosphonate **3** was obtained by two methods (Scheme 3). The first method did not lead to **3** in its pure form. Starting with *O*-methyl thiophosphonic acid **6** (δ_P = 84.1 ppm), the corresponding chloride **10** was prepared following the method of He et al.[12] The reaction of chloride **10** with the tetramethylammonium salt of acid **6** gave a symmetric anhydride **11** (δ_P = 80.05 and 80.18 ppm). Note that treatment of *O*-methyl thiophosphonic acid **6** with condensing agents (DCC or Cl_3CCN) gave only the mixed anhydride **12** (δ_P = 13.0 and 80.9 ppm, diastereomers). This is consistent with Mikołajczyk and Kiełbasiński's observation. They proved that dialkyl thiophosphoric acids attack the electrophilic DCC through the sulfur atom to produce mixed pyrophosphates and thiourea.[13] Next, anhydride **11** was demethylated with NaI in methyl ethyl ketone (MEK) to give the disodium salt of pyrothiophosphonate **13** which has poor solubility in methanol. Salt **13** was treated with hydrogen chloride in methanol to give a mixture of pyrothiophosphonate **3**, thiophosphonic acid **4** and its *O*-methyl ester **6** (δ_P = 70.4, 73.2 and 84.3 ppm) in a ratio of 4:1:1 (as determined from their ^{31}P NMR spectra). An attempt to obtain **3** directly from acid **4** in the presence of DCC led to a mixture of three isomeric pyrothiophosphonates which did not include the desired product **3** [^{31}P NMR: δ = 2.7 (s, 100%), 3.6, 64.2 (2×d, J = 34 Hz, 40%), 14.5 (s, 46%) ppm]. Quite unexpectedly, the reaction of acid **4** with a stoichiometric amount of TMOF (RT, 4 days) proved a more effective method for obtaining pyrothiophosphonate **3**. Analysis of the ^{31}P NMR spectrum of the crude product indicated that it was slightly (ca. 10%) contaminated with by-products **6** and methyl phosphonate (Scheme 4).

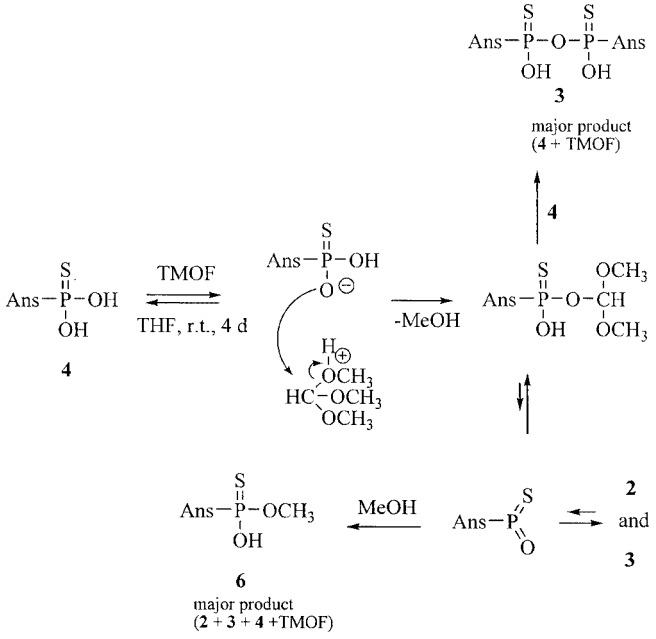
The addition of pyrothiophosphonate **3** obtained in such a way has confirmed its presence in reaction mixtures of HA **1** and LR.

Note that during the derivatisation of the reaction mixtures by the derivatising agents mentioned above I observed signals from the corresponding derivatives of pyrothiophosphonate **3**, that is, *O*,*O*-bis-TBDMS ester **14** (δ_P = 64.3 and 65.0 ppm) and *S*,*S*-dimethyl ester **15** (δ_P = 53.2 and 53.9 ppm) (Scheme 5).

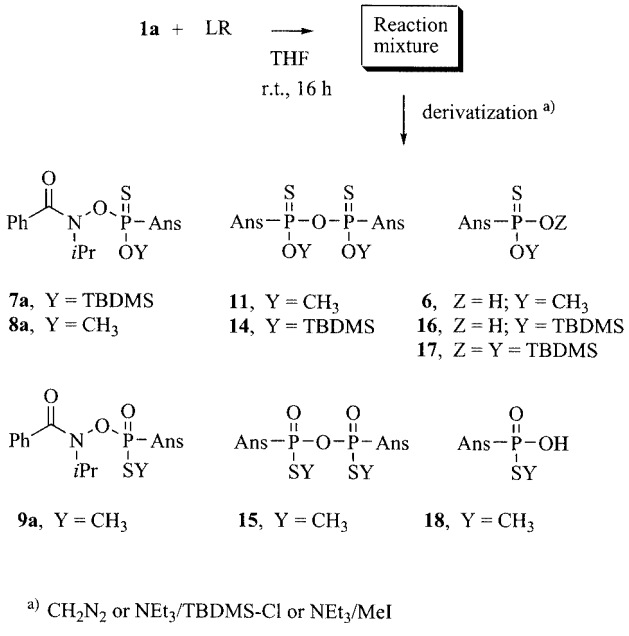
The ^{31}P chemical shift of pyrothiophosphonate **3** can be calculated by subtracting the effect of the methyl group determined for the *O*-methyl esters of (4-methoxyphenyl)thio-



Scheme 3.



Scheme 4.



Scheme 5.

phosphonic acid (**6** and **6′**) ($\Delta\delta$ = +8.1 ppm) from the chemical shift of the methyl diester of pyrothiophosphonate **11** (δ = 80 ppm). By estimation, $\delta_{Pcalcd.}$ = 71.9 ppm, which is similar to the value of the observed shift (δ_P = 71.4 ppm). A better agreement ($\delta_{Pcalcd.}$ = 71.1 ppm) can be obtained by subtracting from the chemical shift of derivative **14** the increment due to the TBDMS group determined from the chemical shifts of the corresponding *O*-TBDMS esters of (4-methoxyphenyl)thiophosphonic acid (**16** and **17**) ($\Delta\delta$ = –6.4 ppm).

The addition of an authentic sample of (4-methoxyphenyl)thiophosphonic acid (**4**) unequivocally confirmed its presence in the reaction mixture. Additionally, after silylation, its *O*-TBDMS derivatives were detected in the reaction mixture: monoester **16** (δ_P = 70.1 ppm) and diester **17** (δ_P = 63.7 ppm). Methylation with methyl iodide in the presence of NEt_3 led to the formation of the *S*-methyl ester **18** (δ_P = 39.3 ppm).

The results of the silylation experiments conducted on the reaction mixtures provide evidence beyond doubt that **2**, **3** and **4** are produced from the LR transformation. Silylation is an unambiguous reaction and leads solely to the stable *O*-TBDMS derivatives of the three phosphorus products detected. Methylation (CH_3I/NEt_3, diazomethane), on the other hand, gives a very complex mixture of *O*- and *S*-methyl products. Furthermore, under the reaction conditions the products are susceptible to thiono–thiolo isomerisation.[14] A different and greatly simplified result is obtained by treating the reaction mixture with an excess of TMOF. It is surprising that the sole reaction product obtained from mixtures of **2**, **3** and **4** is the monoester **6**. Although *O*-alkyl thiophosphonic acids react with TMOF to produce only their corresponding *S*-methyl esters,[15] the presence of the *S*-methyl ester in the reaction mixture has not been confirmed. As mentioned above, the control experiment involving the reaction of acid **4** and a stoichiometric amount of TMOF demonstrated that this reaction produces only pyrothiophosphonate **3**. The different reactivity of TMOF towards thiophosphonic acid **4** can only be explained through the formation of *O*-dimethoxymethyl thiophosphonate as an intermediate in the reaction. Like other active derivatives of thiophosphonic acid, *O*-dimethoxymethyl thiophosphonate is capable of generating electrophilic AnsPOS. Consequently, AnsPOS reacts with free acid **4**, which is in excess relative to the methanol, to give pyrothiophosphonate **3**. As mentioned before, **2** and **3** are also sources of AnsPOS; they react in turn with TMOF or with methanol present in the reaction mixture to give product **6** (Scheme 4).

O-Dithiophosphonylated Hydroxamic Acid as an Intermediate and Its Transformations

The results of these experiments indicate unequivocally that the initial reaction step involves the electrophilic attack of metadithiophosphonate (AnsPSS) on the oxygen atom of the hydroxy group in HA **1**. This leads to the formation of *O*-dithiophosphonylated adducts **19**. Metathiophosphonate adducts with neutral donors (tertiary amines, HMPA) are known, thermodynamically stable compounds.[16] For this reason one can expect that AnsPSS will preferentially attack the oxygen atom of the *N*-hydroxy group in **1** as it is more nucleophilic (α effect). During the first few minutes of reaction, adduct **19a** (δ_P = 109.7 ppm; δ_P = 112.5 ppm for **19c**) is present in the reaction mixture together with the unreacted LR (δ_P = 16.0 ppm) (Figure 2).

As the reaction progresses, the signals of **19a** and LR disappear, and the peaks of the above mentioned AnsPOS transformation products **2a**, **3** and **4** begin to appear. In all probability, the first step in the reaction is a reversible process. The results of experiments involving the addition of TMOF provide supporting evidence for this statement. TMOF totally inhibits the reaction of HA **1** with LR and produces a quantitative amount of the *O*,*S*-dimethyl ester of (4-methoxyphenyl)dithiophosphonic acid (**20**) (see Scheme 3). Attempts to capture adduct **19a** by diazomethane, vinyl acetate or methyl acrylate failed probably due to the low reactivity of these reagents rather than the rate of decomposition of adduct **19a**. The ^{31}P chemical shift of adduct **19a** is in accord with the proposed structure. The structure has also been confirmed by a comparative analysis of the differences between the chemical shifts observed for the *O*-alkyl (4-methoxyphenyl)dithiophosphonic acids, their salts and *S*-methyl esters,[17] and by referencing them to the triethylammonium salt **21a** (δ_P = 121.4 ppm) and *S*-methyl ester **22a** (δ_P = 113.4 ppm) (vide supra).

It seems rather unlikely under the reaction conditions that adduct **19a** could take part in the intramolecular thionation of HA **1** to THA. Although the thionating nature of

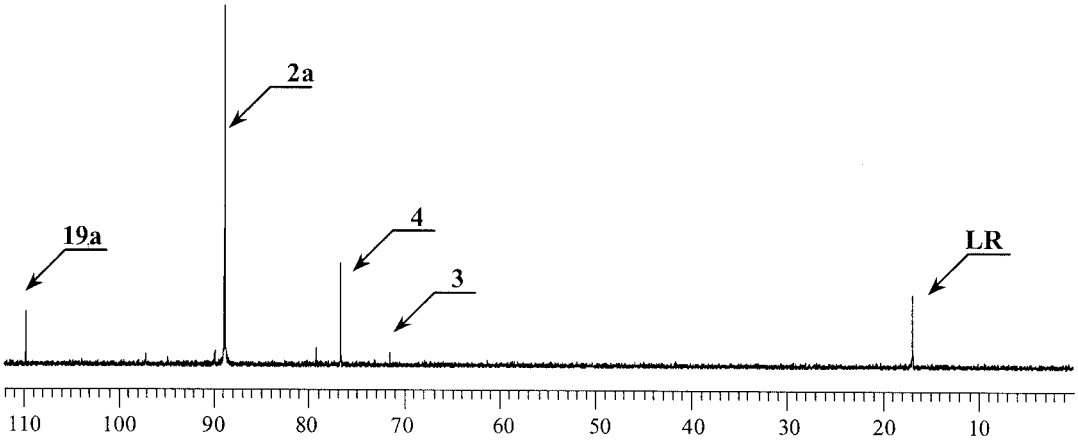
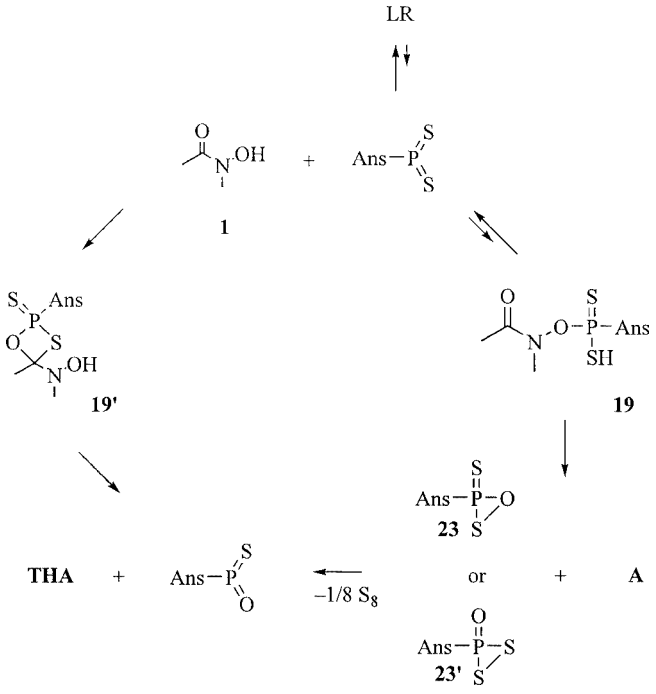


Figure 2. ^{31}P NMR spectrum of the crude reaction mixture obtained 2 min after LR was added to **1a** at room temperature.

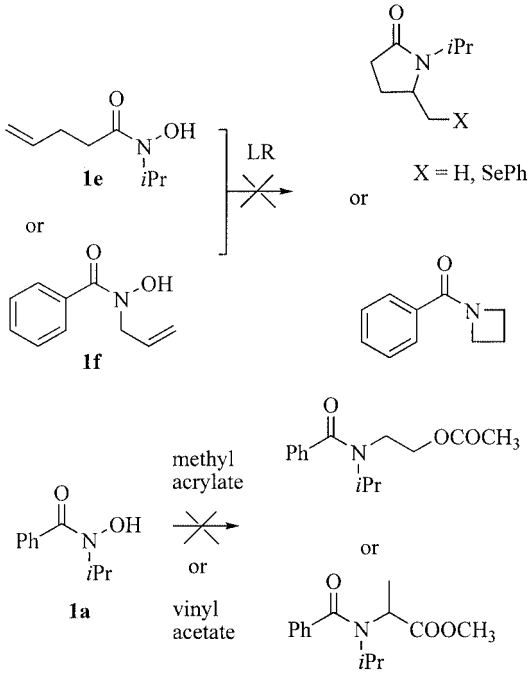
dithiophosphoric acids towards amides has been reported in the literature,[18] this reaction requires drastic conditions (125 °C). It is more likely that, due to the reversibility of adduct **19a** formation, AnsPSS reacts simultaneously with HA **1** by a mechanism typical of the thionation of carbonyl compounds (Scheme 6). Adduct **19a** should be recognised as a precursor of the amide which is a product of HA **1** reduction. The mechanism for the further transformation of adduct **19a** into amide and AnsPOS derivatives remains partially unsolved. The presence of sulfur in the reaction mixture indicates the existence of 3-(4-methoxyphenyl)oxathiaphosphirane 3-sulfide **23** or 3-(4-methoxyphenyl)dithiaphosphirane 3-oxide **23′** as further intermediates, which are direct precursors of AnsPOS. Although undetected as yet, it has been suggested that compounds of this type are LR transformation products formed in the deoxygenation of *S*-oxides.[19] The ^{31}P NMR spectra obtained for unsubstituted hydroxamic acid **1a**, which by reacting with LR produces a mixture of thionation and deoxygenation products, and for the hydroxamic acid undergoing reduction only (**1d**, Y = 4-NMe_2) are identical. This may prove that both processes, that is, thionation and deoxygenation, occur by the same mechanism and produce the same intermediates. However, one can see that AnsPOS can be produced via both 1,3,2-oxathiaphosphetane 2-sulfide **19′** (thionation) and *O*-dithiophosphonylated HA **19** (reduction). As the reaction rates of both processes are comparable, at this stage it is impossible to state whether there are one or two common intermediates. Confirmation of the reversibility of the process proves that the reactive electrophilic AnsPSS attacks both the oxygen atoms of HA **1** (Scheme 6). The N–O bond in HAs **1** with electron-donating substituents (**1b**, **1d**) is relatively weak, which leads to faster decomposition of **19**-type adducts to amides A. Also the results of earlier experiments,[4] in which the amount of amide formed increased with temperature, indicate the nature of **19** and its role in the deoxygenation of HA **1**.

Note that successive reduction of THA (R_2) takes place to a small extent. In a control experiment with *N*-isopropylthiobenzohydroxamic acid under the same conditions (THF, room temperature), TA was formed in only 11% yield (as based on the ^{1}H NMR spectrum). Thus, it can be stated that TA is formed as a result of amide A thionation (T_2).

The results of additional experiments have not provided convincing evidence as to whether the reduction reaction (R_1) is radical or nitrenic in character. The ^{31}P NMR spectra (relative intensities of product signals) of HA **1a** and LR mixtures for reactions performed in the dark and under UV light are identical. A series of experiments on hydroxamic acids with tethered internal functional groups, which would allow such intermediates as amidyl radicals or acyl nitrenes (4-pentenohydroxamic acid **1e**, *N*-allylbenzohydroxamic acid **1f**) to be trapped, and also in the presence of Ph_2Se_2,[20] have ruled out the formation of the corresponding cyclic products (Scheme 7). Similarly, the products of radical or nitrene addition to double bonds have not been observed in reaction mixtures to which external vinyl reagents, nucleophilic or electrophilic in character (vinyl acetate, methyl acrylate), were added.



Scheme 6.



Scheme 7.

It turned out that the reaction of HA **1a** with LR in the presence of triethylamine yields the triethylammonium salt of adduct **21a** (δ_P = 121.4 ppm), which is a relatively stable compound. Apart from the signal from this salt, the ^{31}P NMR spectrum of the reaction mixture included only a low intensity signal from the LR–triethylamine adduct (δ_P = 96.0 ppm). However, the ^{15}N NMR spectrum shows a trace

peak due to salt **1a** (δ_N = –177.5 ppm) in addition to the peak of the adduct **21a** salt (δ_N = –186.5 ppm).[21] Analysis of the ^{31}P and ^{15}N NMR spectra of the reaction mixture rules out the N–O–P (**21a**) → N–S–P (**21a′**) isomerisation reaction, which could result in a system with a weak N–S bond. Besides, attempts to capture the product of possible **21a′** isomerisation by TBDMSCl led to only *O*-silylated HA **1a** (vide supra) (Scheme 8).

The addition of water to salt **21a** causes the signal of adduct **19a** (δ_P = 109.7 ppm) to appear, while the addition of a stoichiometric amount of methanesulfonic acid or trifluoroacetic acid leads, again via adduct **19a**, to THA, A and TA in the same amounts as was observed in the case of a mixture of **1a** with LR. This is distinct evidence for the formation of adduct **19a** as an intermediate in this reaction. Acidifying the salt of adduct **21a** causes partial regeneration of LR (δ_P = 16 ppm), which confirms that the first stage of the reaction between HA **1** and LR, namely the formation of adduct **19**, is reversible. The experiment results in the salt of adduct **21a** and derivatizing agents prove that salt formation is reversible as well. The addition of TBDMSCl gives (after isolation) *O*-silylated HA **1a** in 40% yield, while the reaction with methyl iodide yields the *S*-methyl ester of adduct **22a** (δ_P = 113.4 ppm) almost quantitatively with 10% unreacted HA **1a** (Scheme 8).

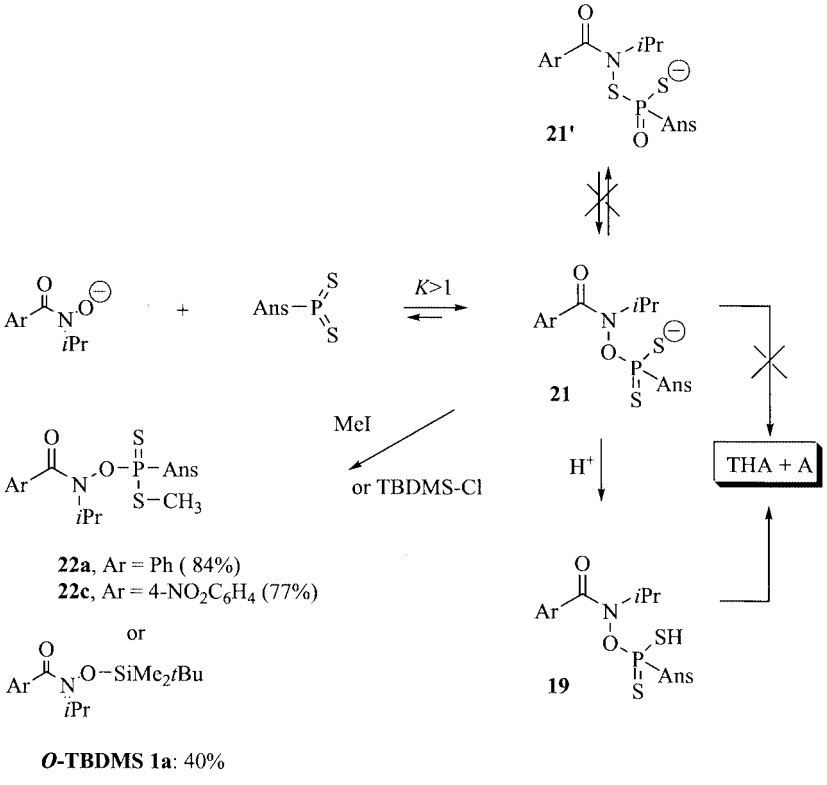
Note that in the case of adduct **19** formation, the equilibrium is shifted to the left, while the equilibrium for the formation of the salt of adduct **21** lies to the right. The stable salt **21** does not transform further. This confirms that the S–H proton is indispensable for HA **1** reduction and that concentration of negative charge on the oxygen atom of the HA **1** salt prevents thionation despite the reversibility of the reaction.

The reactions of the triethylammonium salts **21b** (δ_P = 120.8 ppm) and **21c** (δ_P = 123.8 ppm) follow a similar course. Under the same reaction conditions the corresponding *S*-methyl esters **22b** (δ_P = 110.1 ppm) and **22c** (δ_P = 115.8 ppm) were formed. While derivative **22c**, similarly to **22a**, is stable and has been isolated in 77% yield, derivative **22b** decomposed during isolation on a silica gel column. This result is in line with the domination of amide A over THA, as was observed in the reaction of **1b** with LR (Table 1), as it is evident that an electron-donating substituent in the acyl group of HA **1** weakens the N–O bond significantly.

Table 1. Effect of aryl substituents (Y) on product distribution for reaction of Y–C_6H_4CON(*i*Pr)OH **1** with LR.

1	Y	Yield [%][a]				
		1	**2**	THA	A	TA
a	H	18	14	38	3	17
b	4-MeO	13	11	14	41	11
c	4-NO_2	13	16	50	4	17
d	4-NMe_2	8	14	0	48	30

[a] The yields were determined on the basis of the signal intensities of the methyl and methine protons in the ^1H NMR spectra of the reaction mixtures.

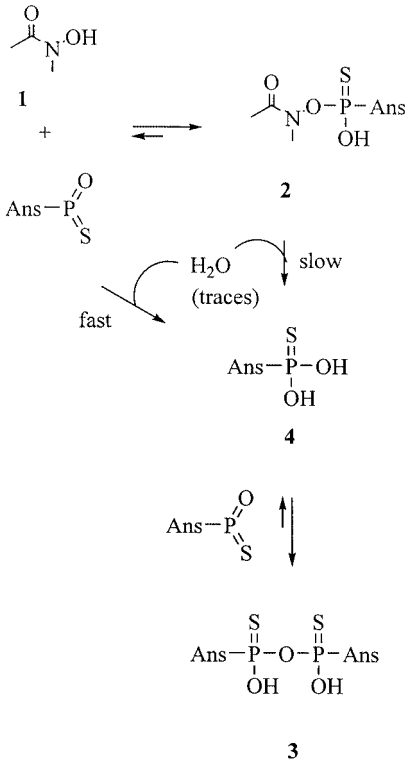


Scheme 8.

The Further Fate of Reactive Metathiophosphonate AnsPOS

Later in the reaction, the electrophilic AnsPOS, generated by thionation and reduction, reacts with the unreacted HA **1a** and with traces of moisture to give, respectively, adduct **2a** and acid **4**. The control experiment involving the addition of a stoichiometric amount of THA ruled out the possibility of the corresponding AnsPOS–THA adduct being formed. It is probably due to the fact that THA is significantly less nucleophilic than HA **1** that adducts of the type mentioned above are not formed in the reaction of HAs **1** with LR.[22] The successive reaction of HA **1** with AnsPOS resulting in adduct **2** is also a reversible process. The high reactivity and chemoselectivity (preferential *O*-methylation) of TMOF towards the reaction mixture containing adduct **2** can only be explained by the presence of AnsPOS. Control experiments with the *O*-methyl esters of (4-methoxyphenyl) thiophosphonic (**6**) and (4-methoxyphenyl)dithiophosphonic acids indicate that at room temperature TMOF preferentially alkylates the sulfur atom with yields of 9 and 100%, respectively, while the reaction with the reaction mixture gives only the *O*-methyl ester **6**.

The reactive AnsPOS also reacts with acid **4** present in the reaction mixture to give pyrothiophosphonate **3**. It can be concluded that the pyrothiophosphonate **3** is not formed in the reaction of adduct **2** with acid **4** as it has been established that a derivative more reactive than the adduct, acid chloride **10**, does not react with acid **4** under these conditions. In all probability, the pyrothiophosphonate **3** is also in equilibrium with AnsPOS (Scheme 9). This is confirmed by both the generation of **3** from the salt **13** in methanol, in which significant amounts of ester **6** are formed, and the fact that after treating the reaction mixture with TMOF, only ester **6** is formed (no traces of the corresponding methyl derivatives of the pyrothiophosphonate, **11** and **15**, were observed). Owing to the differences in the acidity of HA **1** and **4**, the equilibrium constant for the decomposition of **3** to AnsPOS should be significantly higher than that for the corresponding reaction of adduct **2**.



Scheme 9.

The reaction of LR with HA **1a** was followed for two weeks. The relative intensities of the ^{31}P NMR signals of the phosphorus compounds **2a**, **3** and **4** formed in this reaction are shown in Figure 3. As can be seen, after one hour the concentration of the adduct **2a** reaches a maximum (61%) and then, over 14 days, it decreases exponentially to zero. The concentration of the pyrothiophosphonate **3** reaches a maximum of 37% after 48 hours and then decreases slowly to about 30%. The intensity of the signals of the thiophosphonic acid **4** increases logarithmically, reaching 65% after 14 days. After a week, signals arising from (4-methoxy)phenylphosphonic acid and its anhydride (δ = 19.5 and 9.8 ppm) also appear. Despite the obvious differences in the stabilities of adduct **2a** and pyrothiophosphonate **3**, the higher rate of decrease in the concentration of **2a** over time is due to the increase in the concentration of the acid **4**. Acid **4** is a product of AnsPOS hydrolysis. AnsPOS generated from **2a** and **3** reacts preferentially with acid **4**, whose concentration increases gradually.

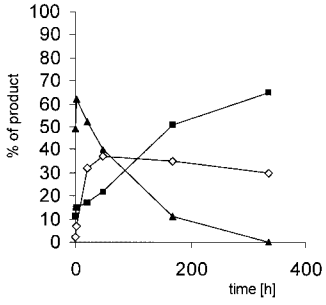


Figure 3. The time course for the formation of the phosphorus products in the reaction of **1a** with LR (transformations of the AnsPSO species): ▲, adduct **2a**; ◊, pyrothiophosphonate **3**; ■, thiophosphonic acid **4**.

The stabilities of adducts **2** vary depending on the structure of the parent HA **1**. Hence, adduct **2b** with a methoxy substituent in the ring is the most stable (the most intense peak in the ^{31}P NMR spectrum), while adduct **2c** (NO_2 substituent) generates significant amounts of pyrothiophosphonate **3** in the initial phase of reaction (see Figure 1). This can be explained by the fact that HA **1b** is a more powerful nucleophile and thus its formation equilibrium constant is higher. The observed decrease in the intensities of the signals of adducts **2** allowed their ^{1}H NMR spectra to be unequivocally assigned, and, consequently, their yields to be determined. Regardless of the nature of the aromatic ring substituent, the reaction with LR gives about 15% of adducts **2**. This may seem peculiar if one considers the observed differences in the nucleophilic properties of these ac-

ids. However, it does indicate that both the dominating original processes, that is the reduction (R_1) of **1b** and the thionation (T_1) of **1c**, are irreversible and likely to be faster than the subsequent reaction of AnsPOS with HA **1**. Moreover, the ^{1}H NMR spectra of the reaction mixtures recorded at various times show that no N–O bonds are broken in adducts **2** (unlike adducts **19**) in order to form amides (the yield of the amide does not increase), independently of the hydroxamic acid group, which is even more important.

The formation of adducts **2** has a significant benefit. Since the post-reaction mixture does not contain the basic product of LR transformation − the nonpolar trimer **5** − the process of transforming AnsPOS to pyrothiophosphonate **3** and ultimately to acid **4** makes the reaction of HA **1** with LR synthetically useful as there is no need for tedious chromatographic purification of thiocarbonyl products.

Conclusions

Analysis of the ^{31}P NMR spectra (relevant spectroscopic data are given in Table 2) and identification of the LR transformation products has allowed the mechanism for the reaction of *N*-alkylhydroxamic acids HAs **1** with LR to be established. The reaction proceeds via the formation of the intermediate *O*-dithiophosphonylated hydroxamic acid **19**. The hydroxamic acid acts as a carrier for the reactive metadithiophosphonate ($AnsPS_2$) in the thionation of the carbonyl group. It also plays a role in the controlled transformation of metathiophosphonate (AnsPOS) to pyrothiophosphonate **3** via the intermediate *O*-thiophosphonylated adduct **2**. This process distinguishes the reaction of LR with HAs **1** from the reactions of other carbonyl compounds with LR, in which a mixture of oligomers and trimer **5** are formed from AnsPOS. The adducts formed from the reaction of HAs **1** with AnsPSS **19** are unstable and transform into reduction products, that is, into the corresponding amides, by breaking the N–O bond. The experiments in which the reactive intermediates were captured have not confirmed the participation of radicals or nitrenes in the reaction. On the other hand, the salts of hydroxamic acids form stable salts of adducts **21** with LR, which do not isomerise to compounds with a N–S bond but upon acidification transform to THA and A via adduct **19**.

Experimental Section

General Remarks: All NMR spectra were recorded with a Varian Unity 500 Plus spectrometer operating at 500 MHz (^{1}H), 202.4 MHz (^{31}P), 125.7 MHz (^{13}C) and 50.7 MHz (^{15}N) and were measured in $CDCl_3$ solutions unless stated otherwise in standard NMR tubes (5 mm o.d.). ^{31}P NMR spectra were obtained by using broad-band ^{1}H decoupling and chemical shifts are reported relative to 85% H_3PO_4 as external standard. ^{15}N long-range gHMQC spectra were acquired as described previously.[21] ^{15}N chemical shifts are referenced to external CH_3NO_2. IR spectra were obtained with a Bruker IFS66 spectrometer in KBr pellets. MS spectra were measured with an AMD 604 mass spectrometer (AMD Intectra GmbH, Germany). Radial chromatography (RC) was performed with a Chromatotron Model 4924T (Harrison Research) on 2 mm glass plates. THF was distilled from potassium/benzophenone ketyl. Commercial Lawesson's reagent (Lancaster) was recrystallised from chlorobenzene prior to use. Acyl chlorides, tribenzylphosphane oxide, TMOF and methyl iodide were commercial compounds (Aldrich). *N*-Isopropyl hydroxylamine hydrogen oxalate was obtained from 2-methylnitroethane by reduction using zinc powder. *N*-Allyl hydroxylamine was prepared by a known method.[23] *N*-Isopropyl-*N*-hydroxythiobenzamide[4] was isolated from the reaction mixture of **1a** with LR. All reactions with LR were performed under argon in flame-dried flasks equipped with a stirring bar and a rubber septum.

Table 2. ^{31}P NMR chemical shifts of the (4-methoxyphenyl)phosphonic acid derivatives under investigation.

X	Y	δ_P [ppm]			
		AnsP(S)SXOY	AnsP(O)SXOY	AnsP(S)OXOY	AnsP(O)OXOY
H	H	79.2	–	**4**: 76.5	19.5
H	Me	92.1	39.3	**6**: 84.1	23.6
Me	$HN(c\text{-}hex)_2$	–	–	70.8	–
Me	Me	99.8	49.1	**6′**: 92.7	28.5
H	TBDMS	–	–	**16**: 70.1	–
TBDMS	TBDMS	–	–	**17**: 63.7	–
TBDMS	Me	–	–	78.4	–
H	HA **1a**	**19a**: 109.7		**2a**: 88.8	–
H	HA **1b**	–	–	**2b**: 88.0	–
H	HA **1c**	**19c**: 112.5		**2c**: 89.7	–
Me	HA **1a**	**22a**: 113.4	**9a**: 54.1	**8a**: 98.1	–
Me	HA **1c**	**22c**: 115.8	–	–	–
TBDMS	HA	–	–	**7a**: 83.9	–
H	AnsP(S)OH	–	–	**3**: 71.4	–
H	AnsP(O)OH	–	–	–	9.8
Me	AnsP(S)OMe	–	–	**15**: 80.05, 80.18	**12**: 13.0 (2d), 80.9 (2d)
Me	AnsP(O)SMe	–	**15**: 53.2, 53.9	–	–
Me	AnsP(O)OMe	–	–	–	13.3, 13.4
TBDMS	AnsP(S)OTBDMS	–	–	**14**: 64.3, 65.0	–
-OAnsP(S)OP(S)AnsO-		–	–	**5**: 72.3 (d), 74.4(t)	–

Typical Procedure for the Preparation of Hydroxamic Acids 1a–d: A stirred suspension of *N*-isopropylhydroxylamine hydrogen oxalate (1.98 g, 12 mmol) in CH_2Cl_2 (50 mL) containing triethylamine (3.04 mL, 20 mmol) was cooled in an ice bath and the appropriate acyl chloride (10 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 1 h. After an additional 2 h at room temperature the mixture was washed with water (2 × 15 mL), 1 M HCl (10 mL), water and brine, and dried with $MgSO_4$. The solvent was evaporated and the crude hydroxamic acid was crystallised or purified by radial chromatography (RC).

***N*-Hydroxy-*N*-isopropylbenzamide (1a):** Yield 76%; m.p. 101 °C.[4]

***N*-Hydroxy-*N*-isopropyl-4-methoxybenzamide (1b):** Yield 70%; m.p. 121–122 °C (ethyl acetate).[21]

***N*-Hydroxy-*N*-isopropyl-4-nitrobenzamide (1c):** Yield 60%; m.p. 107–110 °C (benzene/c-hexane).[21]

***N*-Hydroxy-*N*-isopropyl-4-dimethylaminobenzamide (1d):** Yield 32%; m.p. 134–135 °C (benzene). IR (KBr): $\tilde{\nu}$ = 3223 (OH), 1616, 1584 (C=O) cm^{-1}. ^1H NMR: δ = 1.29 (d, J = 6.5 Hz, 6 H, $CHCH_3$), 3.02 (s, 6 H, NCH_3), 4.33 (sept, J = 6.5 Hz, 1 H, $CHCH_3$), 6.69 (d, J = 9 Hz, 2 H, H-3/5), 7.46 (d, J = 9 Hz, 2 H, H-2/6) ppm. ^{13}C NMR: δ = 19.6 (CH_3CH), 39.5 (NCH_3), 53.5 (CH_3CH), 111.1 (C-3/5), 118.8 (C-1), 129.5 (C-2/6), 152.1 (C-4), 169.0 (C=O) ppm. $C_{12}H_{18}N_2O_2$ (222.28): calcd. C 64.84, H 8.16, N 12.60; found C 64.62, H 8.44, N 12.47.

***N*-Hydroxy-*N*-isopropyl-4-pentenamide (1e):** Yield 47%; oil (RC, chloroform). ^1H NMR (*Z*/*E* isomer = 3:5): δ = 1.17, 1.31 (2 × d, J = 6.5 Hz, 6 H, $CHCH_3$), 2.41, 2.55 (2 × br. m, 4 H, CH_2CH_2), 4.19, 4.68 (2 × m, 1 H, $CHCH_3$), 5.04 (d, J = 10.2 Hz, 1 H, CH_2=), 5.10 (d, J = 17.6 Hz, 1 H, CH_2=), 5.82 (m, 1 H, CH=), 8.90 (br. s, OH, 1 H) ppm; δ_H (55 °C): 1.31 (d, J = 6.5 Hz, 6 H, $CHCH_3$), 2.45 (m, 4 H, CH_2CH_2), 4.24 (m, 1 H, $CHCH_3$), 5.04 (d, J = 10.2 Hz, 1 H, CH_2=), 5.10 (d, J = 17.6 Hz, 1 H, CH_2=), 5.86 (m, 1 H, CH=), 8.22 (br. s, 1 H, OH) ppm. ^{13}C NMR: δ = 19.34, 20.36 (CH_3), 29.22, 29.57, 31.14, 32.59 (CH_2, C-2 and C-3), 47.69, 51.08 (CH–CH_3), 115.47, 116.48 (C-5), 136.89, 137.97 (C-4), 166.20, 174.03 (C=O) ppm. HRMS (EI): calcd. for $C_8H_{15}NO_2$: 157.11028; found 157.11096.

***N*-Allyl-*N*-hydroxybenzamide (1f):**[24] Compound **1f** was obtained following the standard procedure from *N*-allylhydroxylamine. Yield 77%, a colourless oil (RC, chloroform). ^1H NMR: δ = 4.27 (dt, J = 5.5, J = 2 Hz, 2 H, NCH_2), 5.31 (dt, J = 10, J = 2 Hz, 1 H, CH_2=), 5.34 (dt, J = 17, J = 2 Hz, 1 H, CH_2=), 5.95 (ddt, J = 10, J = 5.5, J = 2 Hz, 1 H, CH=), 7.4–7.6 (m, 5 H), 8.70 (br. s, 1 H, OH) ppm.

Reaction of Hydroxamic Acids 1a–1f with LR: LR (0.04 g, 0.1 mmol) was added to a stirred solution of the hydroxamic acid **1a**–**1f** (0.2 mmol) in THF (2 mL) at room temperature. Aliquots of the crude reaction mixture were analysed periodically by means of ^{31}P NMR spectroscopy in THF or after derivatisation and concentration in $CDCl_3$ solutions.

In the case of **1e** and **1f** the suspected products of intramolecular radical cyclisation reactions, that is, 5-substituted 1-isopropylpyrrolidin-2-one (diagnostic $\delta_{H\text{-}5}$ = 3.5–3.9 ppm[20]) and *N*-benzoylazetidine (diagnostic $\delta_{H\text{-}3}$ = 2.35 ppm[25]), were not detected even in the presence of diphenyl diselenide (0.125 g, 0.4 mmol, –50 °C to room temp.).

(4-Methoxyphenyl)phosphonothioic *O*,*O*′-Acid (4): (4-Methoxyphenyl)phosphonothioic acid (**4**) was identified as its *O*,*S*-dimethyl ester. LR (440 mg, 1 mmol) was treated with water (72 mg, 4 mmol) in THF (6 mL) and refluxed for 2 h. The resulting solution was concentrated in vacuo to give a clear colourless oil. Crystallisations from various solvent systems were unsuccessful. ^1H NMR: δ = 3.83 (s, 3 H, OCH_3), 6.90 (dd, $^4J_{HP}$ = 3.4, $^3J_{HH}$ = 8.8 Hz, 2 H), 7.83 (dd, $^3J_{HP}$ = 13.7, $^3J_{HH}$ = 8.8 Hz, 2 H), 8.55 (s, 2 H, OH) ppm. ^{31}P NMR ($CDCl_3$): δ = 73.2; (THF): 76.5 ppm.

The crude acid **4** was redissolved in THF (5 mL), TMOF (0.48 mL, 4.4 mmol) was added and the mixture was stirred for 16 h. ^{31}P NMR analysis showed that it contained two products: namely *O*,*S*-dimethyl (4-methoxyphenyl)phosphonothioate (δ_P = 49.3 ppm) and *O*,*O*-dimethyl (4-methoxyphenyl)phosphonothioate (**6**′) (δ_P = 92.7 ppm) in a 9:1 ratio. After chromatography through silica gel (chloroform), pure *O*,*S*-dimethyl (4-methoxyphenyl)phosphonothioate (0.3 g, 65%) was obtained as a colourless oil. ^1H NMR: δ = 2.12 (d, $^3J_{HP}$ 13.7, 3 H, SCH_3), 3.83 (s, 3 H, $ArOCH_3$), 3.84 (d, $^3J_{HP}$ = 12.2 Hz, 3 H, OCH_3), 6.96 (dd, $^4J_{HP}$ = 3.4, $^3J_{HH}$ = 8.8 Hz, 2 H), 7.78 (dd, $^3J_{HP}$ = 13.2, $^3J_{HH}$ = 8.8 Hz, 2 H) ppm. ^{31}P NMR: δ = 49.3 ppm. MS (EI): *m*/*z* (%) = 232 (21) $[M]^+$, 185 (100) $[M - SCH_3]^+$, 170 (8) $[AnsPO_2]^+$. HRMS (EI): calcd. for $C_9H_{13}O_3SP$: 232.03230; found 232.03244.

2,4,6-Tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-Trisulfide (5): A mixture of tribenzylphosphane oxide (3.2 g, 10 mmol) and LR (2.02 g, 5 mmol) in toluene (30 mL) was refluxed for 4 h. The resulting clear solution was cooled and solid tribenzylphosphane sulfide was filtered off. The filtrate was concentrated in vacuo and the residue was crystallised from benzene to yield pure trimer **5** (3.16 g, 94%). M.p. 153–155 °C (lit.[9] m.p. 158–159 °C). ^1H NMR: δ = 3.87 (s, 6 H, OCH_3), 3.89 (s, 3 H, OCH_3), 7.02 (dd, J = 8.8, J = 3 Hz, 4 H), 7.06 (dd, J = 8.8, J = 4 Hz, 2 H), 8.11 (dd, J = 8.8, J = 15.8 Hz, 4 H), 8.27 (dd, J = 8.8, J = 16.6 Hz, 2 H) ppm. ^{31}P NMR ($CDCl_3$): δ = 72.33 (d, J = 49 Hz, 2 P), 74.43 (t, J = 49 Hz, 1 P) ppm.

***O*-Methyl Hydrogen (4-Methoxyphenyl)phosphonothioate (6)**

From *O*,*O*-Dimethyl (4-Methoxyphenyl)phosphonothioate 6′: (4-Methoxyphenyl)phosphothioic dichloride (3.57 g, 14.8 mmol) (δ_P = 76.8 ppm) prepared from LR and SO_2Cl_2 according to the procedure of Lecher et al.[26] was added to a stirred solution of methanol in excess (12 mL) and triethylamine (5.2 mL, 37.2 mmol) at 5 °C. After 16 h the mixture was concentrated in vacuo and diethyl ether was added. The resulting suspension was washed three times with water, and then with saturated $NaHCO_3$ solution, water and brine. After drying with $MgSO_4$ and concentration the crude diester was purified by chromatography through silica gel (CH_2Cl_2/hexane, 1:1) to yield *O*,*O*-dimethyl (4-methoxyphenyl)phosphonothioate **6**′ (1.07 g, 31%). ^1H NMR: δ = 3.70 (d, J = 13.7 Hz, 6 H, $POCH_3$), 3.83 (s, 3 H, $ArOCH_3$), 6.94 (dd, J = 3.4, J = 8.8 Hz, 2 H), 7.82 (dd, J = 8.8, J = 13.7 Hz, 2 H) ppm. ^{31}P NMR ($CDCl_3$): δ = 92.7 ppm.

The diester (0.93 g, 4 mmol) was refluxed with KOH (0.18 g, 3.2 mmol) in dry methanol (2 mL) for 2 h. Methanol was then removed and the resulting oil was dissolved in water (10 mL). The aqueous solution was washed with diethyl ether and acidified with conc. HCl and then extracted with diethyl ether. Drying with $MgSO_4$ and concentration gave **6** (0.08 g, 8%) (δ_P = 84.3 ppm).

From LR: LR (0.4 g, 1 mmol) was treated with methanol (0.08 mL, 2 mmol) in dry THF (6 mL) and the resulting clear solution of *O*-methyl (4-methoxyphenyl)phosphonothioate was refluxed with 1 equiv. of water (0.036 mL, 2 mmol). Evaporation in vacuo left almost pure **6** (δ_P = 84.3 ppm).

From Trimer 5: Trimer **5** (0.056 g, 0.1 mmol) was refluxed in dry methanol (3 mL) for 2 h until the starting material had disappeared (TLC). The clear solution was concentrated in vacuo to yield pure

6 (0.06 g, 92%). ^{1}H NMR: δ = 3.71 (d, J = 14 Hz, 3 H, $POCH_3$), 3.84 (s, 3 H, $ArOCH_3$), 6.78 (br. s, 1 H, OH), 6.94 (dd, J = 3.4, J = 8.8 Hz, 2 H), 7.84 (dd, J = 8.8, J = 14.6, 2 H) ppm. ^{13}C NMR: δ = 50.65 ($ArOCH_3$), 52.83 (d, J = 6 Hz, $POCH_3$), 114.00 (d, J = 12.2 Hz, C-3), 124.92 (d, J = 159 Hz, C-1), 133.01 (d, J = 13.8 Hz, C-2), 162.93 (d, J = 3.3 Hz, C-4) ppm. ^{31}P NMR ($CDCl_3$): δ = 84.2 ppm. Dicyclohexylammonium salt: Yield 82%; m.p. 172–174 °C. ^{31}P NMR ($CDCl_3$): δ = 70.8 ppm. MS (EI): m/z (%) = 218 (24) $[M]^+$, 201 (2) $[M - OH]^+$, 169 (13) $[AnsPS + 1]^+$, 138 (100) $[AnsP]^+$. HRMS (EI): calcd. for $C_{20}H_{34}NO_3SP$ (399.51): C 60.12, H 8.58, N 3.51, S 8.03; found C 60.14, H 8.62, N 3.50, S 8.10.

***N*-Isopropyl-*N*-[(4-methoxyphenyl)(*tert*-butyldimethylsilyloxy)thiophosphonyloxy]benzamide (7a):** LR (0.3 g, 0.74 mmol) was added to a stirred solution of benzohydroxamic acid **1a** (0.265 g, 1.48 mmol) in THF (4 mL). After 16 h triethylamine (0.22 mL, 1.58 mmol) and TBDMSCl (0.223 g, 1.48 mmol) were added at 0 °C. After an additional 4 h the solvent was evaporated under reduced pressure. ^{31}P NMR analysis showed that the residue consisted of **17**, **14** and **7a** in nearly equal amounts. The mixture was purified by chromatography through silica gel with CH_2Cl_2/hexane (1:2) as eluent to give the following five fractions: THA, TA, **17** (δ_P = 63.7 ppm), a mixture of **17** (δ_P = 63.7 ppm) and **14** (δ_P = 64.3 and 65.0 ppm) and the desired product **7a** contaminated with **17**. Repeated chromatography of the last fraction yielded **7a** (0.03 g, 4%). ^{1}H NMR ([D$_6$]benzene): δ = 0.34 and 0.42 (2×s, 6 H, Me_2Si), 0.90 (s, 9 H, Me_3C), 1.22 (2×d, J = 6.5 Hz, 6 H, CH_3CH), 3.06 (s, 3 H, OCH_3), 3.93 (sept, J = 6.5 Hz, 1 H, CHCH$_3$), 6.94 (dd, J = 8.8, J = 3.4 Hz, 2 H, H-3′/5′), 6.95 (m, 3 H, H-3/4/5), 7.71 (dd, J = 7.5, J = 1.5 Hz, 2 H, H-2/6), 8.33 (dd, J = 14, J = 8.8 Hz, 2 H, H-2′/6′) ppm. ^{31}P NMR: δ = 83.9 ppm. MS (EI): m/z (%) = 421 (22) $[M - t\text{Bu}]^+$, 306 (65) $[M - OTBDMS - i\text{Pr}]^+$, 301 (38) $[AnsPSOTBDMS]^+$. $C_{23}H_{34}NO_4SPSi$ (479.65): calcd. C 57.59, H 7.14, N 2.92, S 6.69; found C 57.57, H 7.15, N 2.95, S 6.68.

***N*-Isopropyl-*N*-[(methoxy)(4-methoxyphenyl)thiophosphonyloxy]benzamide (8a):** *O*-Methyl (4-methoxyphenyl)phosphonochloridothioate (**10**) (vide supra) (0.24 g, 1 mmol) was added to a solution of **1a** (0.18 g, 1 mmol) and DBU (0.15 mL, 1 mmol) in dichloromethane (5 mL) at 0 °C. After being stirred for 16 h the solvent was evaporated in vacuo and the residue was purified by RC (CH_2Cl_2 → acetone/CH_2Cl_2, 1:20) to yield pure **8a** (0.28 g, 73%) as a colourless oil. ^{1}H NMR: δ = 1.04 and 1.12 (2×d, J = 6.5 Hz, 6 H, CH_3CH), 3.86 (s, 3 H, OCH_3), 3.94 (d, J = 14 Hz, 3 H, $POCH_3$), 4.09 (sept, J = 6.5 Hz, 1 H, CH_3CH), 6.97 (dd, J = 3, J = 8.5 Hz, 2 H, H-3′/5′), 7.42 (t, J = 7.5 Hz, 2 H, H-3/5), 7.44 (t, J = 7.5 Hz, 1 H, H-4), 7.62 (d, J = 7.5 Hz, 2 H, H-2/6), 7.95 (dd, J = 8.8, J = 13.5 Hz, 2 H, H-2′/6′) ppm. ^{13}C NMR: δ = 19.7 and 20.0, 54.4 and 54.5 (CH), 55.65 ($ArOCH_3$), 56.2 (d, J = 8 Hz, $POCH_3$), 113.8 (d, J = 16 Hz, C-3′/5′), 123.3 (d, J = 161 Hz, C-1′), 128.4 and 128.9 (C-2/6 and C-3/5), 131.7 (C-4), 133.9 (d, J = 13 Hz, C-2′/6′), 134.6 (C-1), 163.3 (C-4′), 173.3 (C=O) ppm. ^{31}P NMR: δ = 98.1 ppm. HRMS (EI): calcd. for $C_{18}H_{22}NO_4PS$: 379.10069; found 379.1008.

***N*-Isopropyl-*N*-[(4-methoxyphenyl)(methylthio)phosphonyloxy]benzamide (9a):** Prepared from AnsP(O)(SCH_3)Cl generated in situ from *O*,*O*-dimethyl (4-methoxyphenyl)phosphonothioate and phosphorus oxychloride by analogy to the procedure of Tang et al.[27] Yield 32%; m.p. 111–112 °C [RC, chloroform/hexane, 1:1]. ^{1}H NMR: δ = 1.18 and 1.37 (2×d, J = 6.5 Hz, 3 H, CH_3CH), 2.10 (d, J = 14.2 Hz, 3 H, SCH_3), 3.83 (s, 3 H, OCH_3), 4.18 (sept, J = 6.5 Hz, 1 H, CH_3CH), 6.96 (dd, J = 3.4, J = 8.8 Hz, 2 H, H-3′/5′), 7.40–7.56 (m, 3 H, H-3/4/5), 7.61 (dd, J = 7.5, J = 1.5 Hz, 2 H, H-2/6), 7.97 (dd, J = 8.8, J = 12.7 Hz, 2 H, H-2′/6′) ppm. ^{1}H NMR ([D$_6$]benzene): δ = 1.05 and 1.41 (d, 6 H), 2.05 (d, J = 14 Hz, 3 H), 3.08 (s, 3 H), 4.01 (sept, 1 H), 6.62 (dd, J = 8.8, J = 3.3 Hz, 2 H, H-3′/5′), 6.94–7.08 (m, 3 H, H-3/4/5), 7.68 (dd, J = 7.5, J = 1.5 Hz, 2 H, H-2/6), 8.28 (dd, J = 12.7, J = 8.8 Hz, 2 H, H-2′/6′) ppm. ^{13}C NMR: δ = 12.7 (d, J = 3 Hz), 19.5 and 20.5, 55.8 and 57.2 (CH and OCH_3), 114.5 (d, J = 16 Hz, C-3′/5′), 121.5 (d, J = 152 Hz, C-1′), 129.1 and 129.2 (C-2/6 and C-3/5), 131.2 (C-4), 134.8 (d, J = 12.5 Hz, C-2′/6′), 134.6 (C-1), 164.0 (C-4′), 174.8 (C=O) ppm. ^{31}P NMR: δ = 54.1 ppm. MS (EI): m/z (%) = 332 (6) $[M - SCH_3]^+$, 290 (2) $[M - SCH_3 - i\text{Pr}]^+$, 105 (100) $[PhCO]^+$. HRMS (LSIMS): calcd. for $C_{18}H_{22}NO_4PSNa$: 402.08976; found 402.0899.

***O*-Methyl (4-Methoxyphenyl)phosphonochloridothioate (10):** Prepared from **6** (4.36 g, 20 mmol) and phosphoric trichloride by analogy to the reported procedure.[12] Yield 1.56 g (33%) as a colourless oil (RC, CH_2Cl_2/hexane, 2:1). ^{1}H NMR: δ = 3.87 (s, 3 H, $ArOCH_3$), 3.96 (d, J = 16 Hz, 3 H, $POCH_3$), 6.99 (dd, J = 4.4, J = 8.8 Hz, 2 H, H-3/5), 7.96 (dd, J = 8.8, J = 15.6 Hz, 2 H, H-2/6) ppm. ^{31}P NMR: δ = 92.5 ppm. MS (EI): m/z (%) = 236 (100) $[M]^+$, 201 (47) $[M - Cl]^+$, 169 (13) $[AnsPS + 1]^+$, 139 (45) $[AnsP + 1]^+$. HRMS (EI): calcd. for $C_8H_{10}ClO_2PS$: 235.98277; found 235.98392.

***O*-*M*ethyl (4-Methoxyphenyl)phosphonothioic *O*,*O*-Anhydride (11):** A solution of tetramethylammonium *O*-methyl (4-methoxyphenyl) phosphonothioate prepared in situ from the corresponding acid **6** (0.26 g, 1.18 mmol) in dichloromethane (2 mL) was added dropwise to a solution of *O*-methyl (4-methoxyphenyl)phosphonochloridothioate (**10**) in CH_2Cl_2 (3 mL). After 16 h a white solid of tetramethylammonium chloride was filtered off and the filtrate was concentrated in vacuo to yield the crude product (0.43 g, 87%). Radial chromatography (CH_2Cl_2/hexane, 1:2 → 4:1) afforded pure pyrodithiophosphonate **11** (0.13 g, 30%) as a colourless oil. ^{1}H NMR: δ = 3.77 and 3.84 (2×d, J = 14.7 Hz, 6 H, $POCH_3$), 3.81 and 3.82 (2×s, 6 H, $ArOCH_3$), 6.88 and 6.92 (2×dd, J = 3.4, J = 8.8 Hz, 4 H, H-3/5), 7.77 and 7.83 (2×dd, J = 8.8, J = 13.7 Hz, 4 H, H-2/6) ppm. ^{31}P NMR: δ = 80.05 and 80.18 (2×s) ppm. MS (EI): m/z (%) = 418 (100) $[M]^+$, 201 (63) $[AnsPSOCH_3]^+$, 185 (45) $[AnsPSOH]^+$, 169 (21) $[AnsPS + 1]^+$, 139 (15) $[AnsP + 1]^+$. HRMS (EI): calcd. for $C_{16}H_{20}O_5P_2S_2$: 418.02273; found 418.02205.

***O*-[(Methoxy)(4-methoxyphenyl)phosphinyl] *O*′-Methyl (4-Methoxyphenyl)phosphonothioate (12):** DCC (0.206 g, 1 mmol) was added to a solution of **6** (0.41 g, 2 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 2 h DCTU was filtered off and the solution was concentrated in vacuo. Radial chromatography of the residue in CH_2Cl_2/acetone (1:1) gave 0.25 g of an inseparable mixture (low R_f values) of **12** along with unreacted **6** (signal intensity ratio, 9:1). ^{31}P NMR: δ = 13.0 (2×d, J = 33 Hz), 80.9 (2×d, J = 33 Hz) ppm.

(4-Methoxyphenyl)phosphonothioic *O*,*O*-Anhydride (3). Method a: NaI (73 mg, 0.48 mmol) was added to a solution of *O*-methyl (4-methoxyphenyl)phosphonothioic *O*,*O*-anhydride (**11**) (100 mg, 0.24 mmol) in methyl ethyl ketone (MEK) (2 mL). The resulting mixture was refluxed for 1 h. After cooling to room temperature the resulting precipitate was filtered, washed with MEK and dried to yield the disodium salt **13** (0.07 g, 67%). This was then suspended in methanol (3 mL) and a stoichiometric amount of $SOCl_2$ (0.012 mL, 0.16 mmol) was added whilst stirring. Methanol was removed to afford a mixture consisting of **3**, **4** and **6** according to ^{31}P NMR spectroscopy (δ_P = 70.4, 73.2 and 84.3 ppm; 4:1:1 intensity ratio). **Method b:** TMOF (0.04 mL, 0.37 mmol) was added through a syringe to a stirred solution of acid **4** (0.07 g, 0.33 mmol) in THF (3 mL). After 4 days at room temperature the clear solution was concentrated in vacuo to leave a light oil which according to ^{31}P NMR analysis contained almost pure **3**. ^{1}H NMR: δ = 3.80 (s, 6 H, OCH_3), 6.89 (dd, $^4J_{HP}$ = 3.4, $^3J_{HH}$ = 8.8 Hz, 4 H), 7.84 (dd, $^3J_{HP}$ = 13.7, $^3J_{HH}$ = 8.8 Hz, 4 H), 9.90 (s, 2 H, OH) ppm. ^{31}P

NMR: δ = 70.3 (100%), 24.4 (5%), 84.2 (6%) ppm. ^{31}P NMR (THF): δ = 71.4 (100%), 20.5 (10%), 84.6 (10%) ppm. HRMS (LSIMS): calcd. for $C_{14}H_{16}O_5P_2S_2Na$: 412.98120; found 412.9808.

***S*-Methyl (4-Methoxyphenyl)phosphonothioic *O*,*O*-Anhydride (15):** Methyl iodide (0.124 mL, 2 mmol) was added to a cooled solution of crude **4** (0.46 g, 2 mmol) and triethylamine (0.278 mL, 2 mmol) in THF (4 mL). After being stirred for 2 h the mixture was filtered and concentrated in vacuo to leave a light oil. ^{31}P NMR analysis showed that it contained a 4:1 mixture of the *S*-methyl ester of **4** (δ_P = 39.3 ppm) and *O*-methyl (4-methoxyphenyl)phosphonate (δ_P = 18.3 ppm). This mixture was dissolved in CH_2Cl_2 (2 mL) and treated with DCCI (0.206 g, 1 mmol). After 2 h DCU was filtered off and the solution was concentrated in vacuo. The residue was analysed by ^{31}P NMR spectroscopy which confirmed that it contained an inseparable 3:1 mixture (low R_f values) of pyrophosphate **15** (δ_P = 53.2 and 53.9 ppm) and dimethyl bis(4-methoxyphenyl)-diphosphonate (δ_P = 13.34 and 13.38 ppm).

***O*-*tert*-Butyldimethylsilyl Hydrogen (4-Methoxyphenyl)phosphonothioate (16):** A solution of crude **4** (0.38 g, 1.86 mmol) and TBDMS-OH (0.31 mL, 1.96 mmol) in benzene (20 mL) was refluxed for 3 h using a Soxhlet apparatus containing 4-Å molecular sieves. Concentration in vacuo gave a mixture of monoester **16** and diester **17** (δ_P = 70.1 and 63.7 ppm; intensity ratio: 6:1)

***O*,*O*-Bis(*tert*-butyldimethylsilyl) (4-Methoxyphenyl)phosphonothioate (17):**[28] DBU (0.3 mL, 2 mmol) and then TBDMSCl (0.3 g, 2 mmol) were added with cooling to a stirred solution of crude **4** (0.2 g, 1 mmol) in THF (10 mL). After 2 h at room temperature the mixture was concentrated in vacuo and dissolved in ethyl acetate. Washing with a saturated $NaHCO_3$ solution, water, brine, drying with $MgSO_4$ and concentration yielded the crude diester (0.31 g, 72%) as a colourless oil. Radial chromatography with CH_2Cl_2/hexane as eluent afforded **17** (0.15 g, 35%). ^{1}H NMR: δ = 0.17, 0.31 (2×s, 12 H, Me_2Si), 0.90 (s, 18 H, Me_3C), 3.84 (s, 3 H, OCH_3), 6.91 (dd, J = 3.3, J = 8.8 Hz, 2 H, H-3/5), 7.85 (dd, J = 14.5, J = 8.8 Hz, 2 H, H-2/6) ppm. ^{31}P NMR: δ = 63.7 ppm.

***O*,*S*-Dimethyl (4-Methoxyphenyl)phosphonodithioate (20):** LR (0.040 g, 0.1 mmol) was suspended in TMOF (1 mL). After 4 h at room temp. the resulting clear solution was concentrated in vacuo to yield pure **20** (0.045 g, 90%) of as a colourless oil. ^{1}H NMR: δ = 2.15 (d, J = 14.9 Hz, 3 H, $PSCH_3$), 3.81 (d, J = 15.4 Hz, 3 H, $POCH_3$), 3.85 (s, 3 H, OCH_3), 6.97 (dd, J = 3.3, J = 8.8 Hz, 2 H, H-3/5), 7.87 (dd, J = 13.7, J = 8.8 Hz, 2 H, H-2/6) ppm. ^{31}P NMR: δ = 98.9 ppm. MS (EI): m/z (%) = 248 (5) $[M]^+$, 233 (8) $[M - CH_3]^+$, 217 (100) $[M - OCH_3]^+$, 201 (15) $[M - SCH_3]^+$, 139 (36) $[AnsPS - OCH_3]^+$. HRMS (EI): calcd. for $C_9H_{13}O_2PS_2$: 248.00944; found 248.0092.

***N*-Isopropyl-*N*-[(4-methoxyphenyl)(methylthio)thiophosphonyloxy]-benzamide (22a) and *N*-*tert*-Butyldimethylsilyloxy-*N*-isopropylbenzamide:** LR (0.646 g, 1.6 mmol) was added in two equal portions to a stirred solution of benzohydroxamic acid **1a** (0.573 g, 3.8 mmol) and triethylamine (0.90 mL, 6.4 mmol) in THF (40 mL). The resulting colourless solution of triethylammonium salt **21a** [δ_P = 121.4 ppm; δ_N = –186.5 ppm. FAB MS: m/z (%) = 384 (100), 303 (28, AnPSS-NEt_3), 281 (92, **1a**-NEt_3] was divided into two equal parts. One of them was treated with methyl iodide (0.12 mL, 1.9 mmol) at 0 °C. After 4 h the solvent was evaporated under reduced pressure and the residue purified by chromatography through silica gel (chloroform) to yield **22a** (0.62 g, 84%). M.p. 93–94 °C. ^{1}H NMR: δ = 1.15, 1.18 (2×d, J = 6.5 Hz, 6 H, CH_3CH), 2.43 (d, J = 17 Hz, 3 H, $PSCH_3$), 3.86 (s, 3 H, OCH_3), 4.13 (sept, J = 6.5 Hz, 1 H, CH_3CH), 7.00 (dd, J = 8.8, J = 3.4 Hz, 2 H, H-3′/5′), 7.43 (t, J = 7.5 Hz, 2 H, H-3/5), 7.50 (t, J = 7.5 Hz, 1 H, H-4), 7.65 (dd, J = 7.5, J = 1.5 Hz, 2 H, H-2/6), 8.09 (dd, J = 8.8, J = 13.7 Hz, 2 H, H-2′/6′) ppm. ^{13}C NMR: δ = 15.7 (d, J = 4 Hz, $PSCH_3$), 19.8 and 20.6 (CCH_3), 55.7 (OCH_3), 56.4 (CH), 114.1 (d, J = 16 Hz, C-3′/5′), 125.6 (d, J = 120 Hz, C-1′), 128.6 and 128.9 (C-2/6 and C-3/5), 131.9 (C-4), 133.6 (d, J = 13 Hz, C-2′/6′), 134.6 (C-1), 163.4 (C-4′), 173.8 (C=O) ppm. ^{31}P NMR: δ = 113.4 ppm. IR: $\tilde{\nu}$ = 3047, 2966, 2931, 1691 (s, C=O), 1386 and 1367 (*i*Pr), 1259 (s, $ArOCH_3$), 895 (s), 718 (s) cm^{-1}. MS (EI): m/z (%) = 348 (41) $[M - SCH_3]^+$, 306 (5) $[M - SCH_3 - C_3H_6]^+$, 217 (76) $[AnsPSSCH_3]^+$, 187 (33) $[AnsPSSCH_3 - OCH_3 + 1]^+$, 169 (17) $[AnsP{=}S - 1]^+$, 139 (45) $[AnsP{=}S - OCH_3]^+$, 105 (85) $[PhC{\equiv}O]^+$, 77 (100) $[Ph]^+$. $C_{18}H_{22}NO_3S_2P$ (395.48): calcd. C 54.67, H 5.61, N 3.54, S 16.21; found C 54.83, H 5.64, N 3.50, S 15.89.

The second portion of triethylammonium salt **21a** was treated with TBDMSCl (0.29 g, 1.9 mmol). After 4 h the solvent was evaporated in vacuo and the residue was purified by chromatography on silica in benzene to afford the pure *O*-TBDMS ester of **1a** (0.2 g, 40%). ^{1}H NMR ([D_6]benzene): δ = 0.31 (s, 6 H, Me_2Si), 0.98 (d, J = 6.5 Hz, 6 H, CH_3CH), 1.06 (s, 9 H, Me_3C), 3.83 (sept, J = 6.5 Hz, 1 H, CH_3CH), 7.00 (m, 3 H, H-3/4/6), 7.42 (d, J = 7.5 Hz, 3 H, H-2/6) ppm. $C_{16}H_{27}NO_2Si$ (293.48): calcd. C 65.48, H 9.27, N 4.77; found C 65.35, H 9.40, N 4.52.

***N*-Isopropyl-*N*-[(4-methoxyphenyl)(methylthio)thiophosphonyloxy]-4-nitrobenzamide (22c):** LR (0.022 g, 0.05 mmol) was added to a stirred solution of *N*-hydroxy-*N*-isopropyl-4-nitrobenzamide **1c** (0.022 g, 0.1 mmol) and triethylamine (0.28 mL, 0.2 mmol) in THF (2 mL). The resulting colourless solution of the triethylammonium salt of **21c** (δ_P = 123.8 ppm) was cooled in an ice bath and treated with methyl iodide (0.01 mL, 0.15 mmol). After 4 h the solvent was evaporated under reduced pressure and the residue purified by chromatography through silica gel (chloroform/hexane, 1:1) to yield **22c** (0.034 g, 77%). M.p. 102 °C. ^{1}H NMR: δ = 1.20, 1.27 (2×d, J = 6.5 Hz, 6 H, CH_3CH), 2.37 (d, J = 17 Hz, 3 H, $PSCH_3$), 3.87 (s, 3 H, OCH_3), 4.17 (sept, J = 6.5 Hz, 1 H, CH_3CH), 6.96 (dd, J = 8.8, J = 3.4 Hz, 2 H, H-3′/5′), 7.74 (d, J = 8 Hz, 2 H, H-2/6), 7.94 (dd, J = 8.8, J = 13.7 Hz, 2 H, H-2′/6′), 8.21 (d, J = 8 Hz, 2 H, H-3/5′) ppm. ^{31}P NMR: δ = 115.8 ppm. MS (EI): m/z (%) = 393 (18) $[M - SCH_3]^+$, 351 (5) $[M - SCH_3 - C_3H_6]^+$, 217 (100) $[AnsPSSCH_3]^+$, 187 (14) $[AnsPSSCH_3 - OCH_3 + 1]^+$, 169 (14) $[AnsP{=}S - 1]^+$, 150 (47) $[4\text{-}NO_2C_6H_4C{\equiv}O]^+$ (47), 139 (29) $[AnsP{=}S - OCH_3]^+$ (29). $C_{18}H_{21}N_2O_5S_2P$ (440.48): calcd. C 49.08, H 4.81, N 6.36, S 14.56; found C 49.26, H 4.86, N 6.38, S 14.18.

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