Articles

Generation of Ethyl Metathiophosphate by Thermal Fragmentation of *O*-Ethyl *N*-Substituted Phosphoramidothioates†

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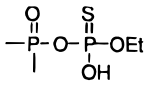
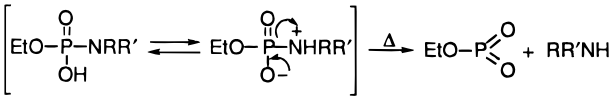
O-Ethyl *N*-1-adamantylphosphoramidothioate was synthesized and found to fragment on heating in inert solvents to form the pyrophosphate AdNHP(S)(OEt)OP(S)(OEt)OH. The proposed mechanism involves an elimination of the amine portion with release of ethyl metathiophosphate (EtOP(S)O), as was confirmed in previous work for the comparable structure with oxygen. This transient compound then phosphorylates the starting phosphoramidothioate. *O*-Ethyl *N*,*N*-diethylphosphoramidothioate was also synthesized, and while it gave a similar pyro compound on heating, the reaction mixture was more complex. Both phosphoramidothioates, however, served effectively as thiophosphorylating agents toward alcohols, a silanol, and the silanol groups on the surface of silica gel. Exploratory experiments showed that these phosphoramidothioates also could thiophosphorylate the OH group of a monoester of phosphoric acid, as well as that of phosphinic acids, forming anhydrides with the partial structure



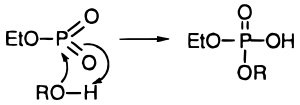
We recently presented a method for the generation of ethyl metaphosphate (**3**) by the thermal fragmentation of ethyl esters of *N*-substituted phosphoramidic acids **1**,[1] probably through the dipolar form **2**:[2]



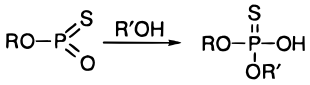
1 **2** **3**

The best results were obtained when one *N*-substituent was a very large group, such as adamantyl or mesityl; rate measurements showed that the fragmentation was faster with such substituents than with less sterically demanding groups and followed the first-order kinetics required by the elimination mechanism shown above. Since the starting phosphoramidates are rather easily prepared from phosphorus oxychloride, the method stands among the more attractive of the several known ones that can be considered for the generation of metaphosphates as practical phosphorylating agents for alcohols.[3] Several examples of phosphorylations with the transient metaphosphate that occur in excellent yield have been described.[3]

Thiono derivatives of metaphosphates **4** have been shown also to be phosphorylating agents for alcohols,



giving *O*,*O*-dialkyl phosphorothioates:[4]



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However, there is only one method that has been used for the generation of metathiophosphates, the thermal fragmentation of derivatives of the 2,3-oxaphosphabicyclo-[2.2.2]octene ring system **5**.[4−6] While the fragmentation is quite smooth and the phosphorylations proceed in good yield, the method suffers as a practical one from the complexity of the precursor, which requires several steps in its synthesis.[4−6]

It was the purpose of this study to explore the possible adaptation of the phosphoramidate fragmentation method to the generation of alkyl metathiophosphates, with the goal of making these substances more readily available as practical thiophosphorylating agents for OH groups

† Dedicated to Prof. Dr. Marianne Baudler on the occasion of her 75th birthday.

‡ On leave from Charles University, Prague, Czech Republic.

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(1) Quin, L. D.; Jankowski, S. *J. Org. Chem.* **1994**, *59*, 4402.

(2) Jankowski, S.; Quin, L. D.; Paneth, P.; O'Leary, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 11675.

(3) This aspect of metaphosphate chemistry has recently been reviewed, see: Quin, L. D. *Coord. Chem. Rev.* **1994**, *137*, 525.

(4) Quin, L. D.; Sadanani, N. D.; Wu, X.-P. *J. Am. Chem. Soc.* **1989**, *111*, 6852.

(5) Quin, L. D.; Wu, X.-P.; Sadanani, N. D.; Lukes, I.; Ionkin, A. S.; Day, R. O. *J. Org. Chem.* **1994**, *59*, 120.

(6) Bodalski, R.; Jankowski, S.; Glówka, M. L.; Filipiak, T.; Quin, L. D. *J. Org. Chem.* **1994**, *59*, 5173.

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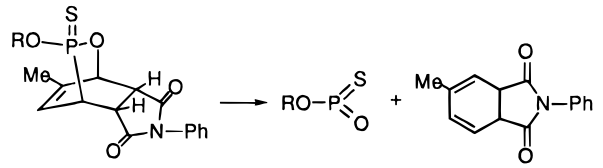

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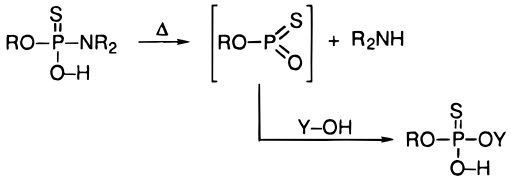
of various types, including alcohols, surface OH of solids, and phosphorus acids.

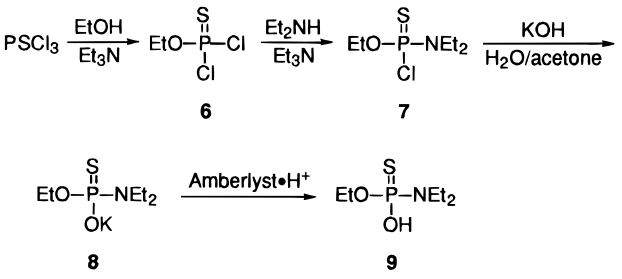


Results and Discussion

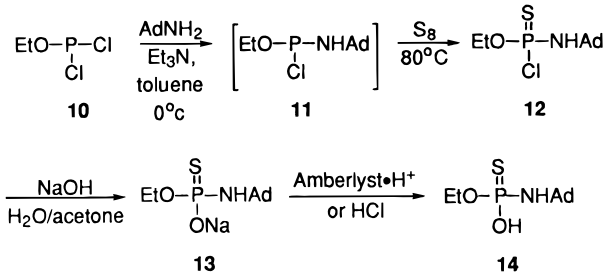
For the synthesis of *O*-ethyl *N*,*N*-diethylphosphoramidothioate (**9**), we were able to employ the same procedure that was effective for the phosphoryl compound,[1] starting with thiophosphoryl chloride rather than the oxychloride. As outlined in Scheme 1, the synthesis depends upon the successive displacements of the three chlorines, under conditions in the first two steps that allowed only a single chloride to be displaced. In fact, this specificity was rather easily achieved, and ^{31}P NMR analysis confirmed that side products constituted only a few percent of the reaction mixtures. The intermediates **6**, **7**, and **8** were obtained in pure form, and the yield in each step was about 60−75%, comparable to the yields reported for the phosphoryl counterparts.[1] However, the reactivity of the thio compounds was less than that of the phosphoryl compounds and required more forcing conditions. The final phosphoramidothioate **9**, when dry, was a stable crystalline solid that could be stored for several months for later use in studies of metathiophosphate generation. It was also possible to synthesize **7** by reacting $PSCl_3$ with diethylamine, followed by sodium ethoxide in ethanol.

Neither synthetic scheme was applicable to the *N*-adamantyl derivatives. The reaction of *O*-ethyl phosphorodichloridothioate ($EtOP(S)Cl_2$) with adamantylamine gave a complex mixture, and an attempt to reverse the sequence and react adamantylamine with thiophosphoryl chloride was also unsuccessful. Apparently the great steric bulk of the adamantyl substituent, coupled with the reduced reactivity in the thio series, makes the desired displacement impractical. Displacements on 3-coordinate phosphorus halides are generally more easily accomplished, and this led to the development of the synthetic method outlined in Scheme 2, which resembles a reported[7] procedure. The yield in the two-step conversion of phosphorodichloridite **10** to the crystalline phosphoramidochloridothioate **12** was rather poor (17.6%); the main impurity appeared to be $(AdNH)_2P(S)OEt$, which interfered with the crystallization. Some **12** remained in the mother liquor and could be hydrolyzed to provide an additional crop of acid **14** in 36.1% yield. The hydrolysis of crystalline **12** to the sodium salt **13** and its conversion to the free crystalline acid **14** were more successful, with yields of 87.1 and 85.4%, respectively. Acid **14** was stable at room temperature and was easily stored.

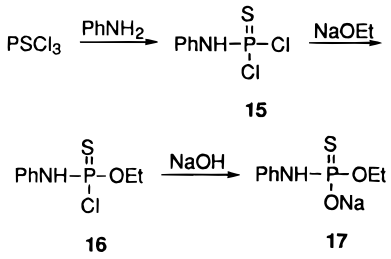
Scheme 1



Scheme 2



Scheme 3



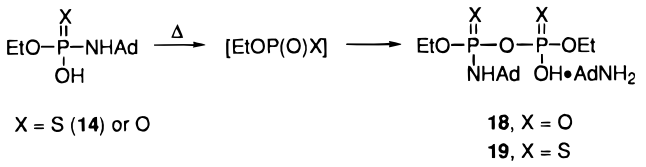
Attempts to synthesize *O*-ethyl *N*-phenylphosphoramidothioate were not successful. This compound was approached by synthesis of the known[8] *N*-phenylphosphoramidothioic dichloride (**15**), displacement of one chlorine with sodium ethoxide, and then hydrolysis to the sodium salt **17** (Scheme 3). The reaction with sodium ethoxide also produced some of the diethyl ester (about 15% of the product), but this compound was not hydrolyzed in the sodium hydroxide reaction and could be extracted unchanged from the hydrolysis mixture with chloroform. After crystallizations, sodium salt **17** was obtained in analytically pure form. Acidification with HCl or Amberlyst·H^+ produced initially the free acid according to the ^{31}P NMR spectrum, but the acid rapidly decomposed and was not a useful precursor of the metathiophosphate.

Thermal Fragmentation of the Phosphoramidothioates. (A) The *N*-Adamantyl Derivative. The behavior of *O*-ethyl *N*-adamantylphosphoramidothioate (**14**) upon thermolysis exactly paralleled that of the phosphoryl analog, which gave the pyrophosphate derivative **18**. In toluene solution at 80 °C, the phosphoramidate **14** was completely consumed after about 3 h and gave primarily the thiopyrophosphate derivative **19** as a mixture of diastereoisomers. This compound was easily recognized from its ^{31}P NMR spectrum, which consisted of two poorly-resolved sets of doublets of doublets (δ 41.81 and 53.47, $^2J_{PP}$ = 38.0 Hz; δ 41.83 and 53.51, $^2J_{PP}$ = 36.7

(7) Freeman, S.; Harger, J. P. *J. Chem. Soc., Perkin Trans 2* **1988**, 81.

(8) Piotto, M. E.; Granger, J. N.; Cho, Y.; Farschtschi, N.; Gorenstein, D. G. *Tetrahedron* **1991**, *47*, 2449.

Scheme 4

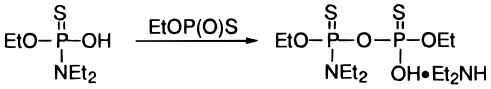


Hz) with the downfield signal arising from the *N*-substituted phosphorus, an effect observed previously.[1]

That the P═S group had been maintained at both phosphorus atoms was clearly established by the position of the ^{31}P NMR signals in the downfield region of δ 40−50. Had dicovalent S been created at either P, signals would have been much farther upfield (δ 15−25[9]). Small signals at δ 43.7, 41.9, and 56.1 were also present, but together only accounted for about 20−25% of the total signal area. These peaks have not been assigned, although the first two fall in the thionopyrophosphate region and the latter in the thiono phosphate region. Overall, the fragmentation was remarkably clean, and only a trace of insolubles formed in the process.

The formation of the thiopyrophosphate **19** is consistent with the two-step process shown in Scheme 4. Thus, the remarkable tendency for pyrophosphate formation from phosphoramidates[1] is reproduced here in a thiono derivative. A bimolecular reaction of the phosphoramidothioate could also provide the thiopyrophosphate, but would seem unlikely with these molecules of great steric crowding. As will be seen in a later section, determination of the kinetics of the process indeed rules out the bimolecular mechanism.

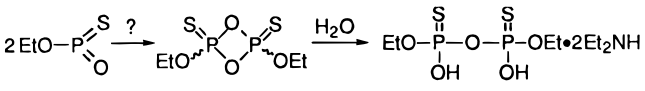
(B) The *N*,*N*-Diethyl Derivative. The thermolysis of compound **9** gave a much more complex product mixture. The main product was the mixed pyrophosphate **20**; in toluene, the two diastereomeric forms gave two close-lying doublets of doublets (δ 45.07 and 59.77, $^2J_{PP}$ = 34.3 Hz; δ 45.85 and 59.52, $^2J_{PP}$ = 38.5 Hz).



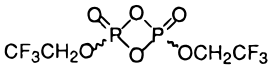
9 **20**

As before, this product can be accounted for by the initial formation of ethyl metathiophosphate which then reacts with the starting phosphoramidothioate, although a bimolecular reaction is also possible. The compound was isolated by silica gel chromatography and converted to the free acid on Amberlyst 15 (^{31}P NMR in $CDCl_3$ δ 50.6 and 62.0, $^2J_{PP}$ = 28.9 Hz; δ 51.0 and 61.9, $^2J_{PP}$ = 25.5 Hz). An attempt to stabilize it by conversion to the methyl ester with diazomethane resulted in a mixture of only 18% of the desired *O*-methyl ester (δ 54.9 and 62.7, $^2J_{PP}$ = 28.2 Hz) and 82% of the *S*-methyl isomer from methylation on sulfur[10] rather than on oxygen (δ 16.9 and 62.9, $^2J_{PP}$ = 34.4 Hz).

A second major product from the thermolysis appeared to have two close-lying singlets at δ 43.1 and 43.6, again suggestive of thiono phosphorus with the pyrophosphate structure. These signals persisted in the crude reaction mixture when it was protected from moisture. However, upon opening the tube they diminished in size and a white solid precipitated. This product appears to form via a hydrolysis, since addition of water to the tube accelerated the precipitation. The solid was isolated and recrystallized; it analyzed correctly for the symmetrical pyrophosphate **22**, and the ^{31}P NMR shift of δ 42.0 is consistent with this structure. The precursor for this hydrolysis product is presently unknown. One possibility would be the dimeric form (**21**) of the metathiophosphate, for which the two ^{31}P NMR signals observed in the original reaction mixture at δ 43.1 and 43.6 would be indicative of a *cis*−*trans* mixture. However, there is no other proof at this time for the dimeric structure. The ring system is, in fact, quite a rare one; no example with thiono phosphorus could be found in the literature, and only one compound with oxo phosphorus (**23**)[11] and one with trivalent phosphorus (**24**)[12] seem to be known.



21 **22**



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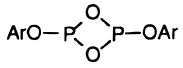

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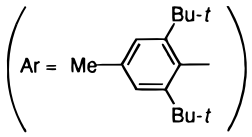
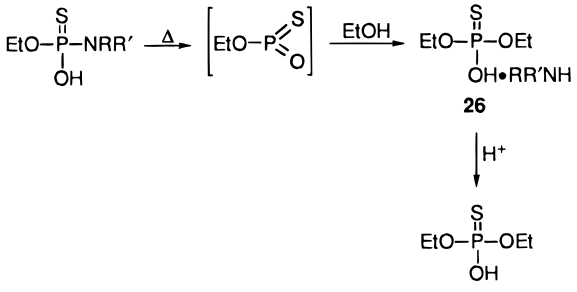


Other minor products were also present. One with δ 57.1 was identified as the diethylamine salt of *O*,*O*-diethyl phosphorothioate (**26**) by mixing experiments with a known specimen of this compound, isolated from the thermal fragmentation of the phosphoramidothioate in the presence of ethanol (*vide infra*).

Thermal Fragmentation of the Phosphoramidothioates in the Presence of Alcohols. When the phosphoramidothioates **9** and **14** were heated in pure ethanol, the only observable product was the amine salt of *O*,*O*-diethyl phosphorothioate (*e.g.*, **26**). The adamantylamino compound and the diethylamino derivative were fragmented under similar conditions (2.5 h at 80 °C). In the case of the *N*-adamantyl derivative, it may be assumed that the reaction proceeds through the intermediacy of the metathiophosphate, as indicated by the kinetics measurements (*vide infra*) in the inert solvent toluene. In the case of the diethylamino compound, this pathway is also allowed by the kinetics measurements,



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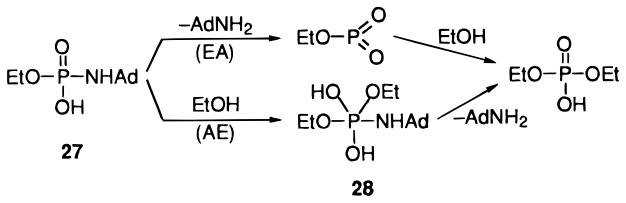
(9) Tebby, J. C. *Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*; CRC Press: Boca Raton, FL, 1991; pp 257−259.
(10) Mastryukova, T. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1976**, *1*, 211.
(11) Mahmood, T.; Shreeve, J. M. *Inorg. Chem.* **1986**, *25*, 3830.
(12) Chasar, D. W.; Fackler, J. F., Jr.; Komoroski, R. A.; Kroenke, W. J.; Mazany, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 5956.

Scheme 5



but is accompanied by a bimolecular process. In both cases, first-order kinetics were followed in pure ethanol, but this can be explained either by the rate-controlling amine elimination to form the metathiophosphate or by a bimolecular addition−elimination mechanism that displays pseudo-first-order kinetics due to the huge excess of ethanol. The mechanism is discussed further in the next section. Regardless of mechanism, it is clearly seen that both compounds are effective agents for thiophosphorylation purposes. An excess of alcohol is desirable, however, since there can be competition with the starting phosphoramidothioate for the intermediate metathiophosphate, thus leading to the same side products seen when the fragmentations were conducted in inert solvents. This problem is minimal when the *N*-adamantyl derivative **14** is used. The amine salt can be converted to the free acid by passage through Amberlyst 15.

Kinetics of the Thermal Fragmentations. In our earlier study on the thermal decomposition of phosphoramidate,[1] chemical kinetics were employed to search for a mechanism that involved slow release of a metaphosphate, which then reacted rapidly with a nucleophilic species in the medium (*e.g.*, an added alcohol or in its absence unreacted phosphoramidate). We found, for example, that with the *N*-adamantyl derivative **27** alone first-order kinetics were observed in a variety of solvents.[13] It was also observed that first-order kinetics were followed in the presence of a few equivalents of ethanol as a trapping agent. Both results pointed to the elimination−addition (EA) mechanism outlined in Scheme 5 and eliminated a process (AE) where alcohol directly attacks the phosphoramidate to form a 5-coordinate intermediate (**28**) or transition state that then collapses.[1] Such a process would follow second-order kinetics.

The kinetics measurements were conveniently made by following area changes of the ^{31}P NMR signals for starting material relative to an external standard of triphenylphosphine oxide. We have proceeded to apply these techniques to study the mechanism of decomposition of the corresponding phosphoramidothioate **14** in toluene and have observed first-order kinetics with added ethanol. This result compels the conclusion that ethyl metathiophosphate is an intermediate in the process. The plot of concentration of **14** against time at 80 °C is shown as Figure 1; a smooth first-order process prevailed over 2 half-lives. The adamantylamine salt of *O*,*O*-diethyl phosphorothioate was observed as the only product when at least 5 equiv of ethanol was present. With a smaller excess of alcohol, the thiopyrophosphate **19** was observed (30−35% by ^{31}P NMR). Because the pyrophosphate formation requires the decomposition of the substrate to the thiometaphosphate and then a secondary reaction with it, the observed first-order constant is increased slightly (Table 1). As for the phosphoryl counterpart,[2] it is likely that the phosphoramidothioates exist in equilibrium with the zwitterionic form and that it is this form

(13) Jankowski, S.; Chen, S.; Quin, L. D. Unpublished results.

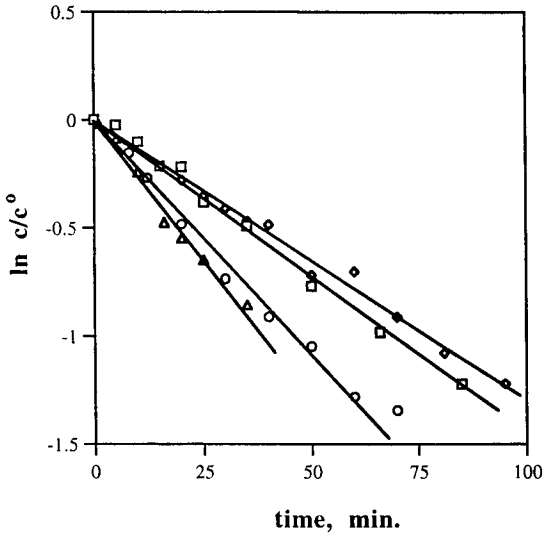
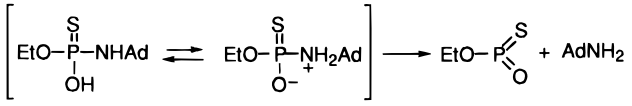


Figure 1. Kinetics of the thermolysis of **14** at 80 °C as a function of the number of equivalents of ethanol (relative to 1 equiv of **14**): (□) 10.3, (◇) 5.7, (○) 2.5, (△) 1.4.

Table 1. Kinetics of the Thermolysis of 9 and 14

			concn, mol/L		rate constant, $k \times 10^3$	
compd	solvent	T, °C	acid	ethanol	first order, s^{-1}	second order, L mol s^{-1}
9	ethanol	80	0.104		0.612 ± 0.012	
	toluene	100	0.108	0.498		79.0 ± 0.12
		100	0.207			2.53 ± 0.12
		100	0.126			38.2 ± 1.8
		100	0.050	-		89.2 ± 2.8
14	ethanol	80	0.047		0.688 ± 0.040	
		80	0.100		0.635 ± 0.013	
	toluene	80	0.103	0.147	0.428 ± 0.025	
		80	0.053	0.131	0.360 ± 0.012	
		80	0.025	0.143	0.217 ± 0.008	
		80	0.049	0.504	0.247 ± 0.005	

that undergoes the fragmentation; this point is presently being explored by the kinetic isotope effect of nitrogen and the deuterium solvent effect.[14]



The kinetics study[1] on *O*-ethyl *N*,*N*-diethylphosphoramidate had shown that both a first-order and a second-order process were involved, indicating that both the EA and the AE mechanisms were being followed. Again this result was duplicated for the thio counterpart **9**, with the analogous relation between rate constants and substrate concentrations (Table 1 and Figure 2). The importance of the steric bulk of the *N*-substituent in determining the mechanistic pathway therefore applies in both compound classes.

Thiophosphorylation of the Silanol Groups of Silica Gel. The OH groups on the surface of silica gel have been shown to be reactive to metaphosphates when generated in a suspension of the solid.[15] Since the presence of the phosphate group on the solid can easily be demonstrated by the use of CP/MAS ^{31}P NMR spectroscopy, the use of silica gel as a trapping agent for

(14) Jankowski, S.; Paneth, P.; O'Leary, M. H.; Quin, L. D. Unpublished results.

(15) Quin, L. D. In *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; Quin, L. D., Verkade, J. G., Eds.; VCH Publishers: New York, 1994; Chapter 32.

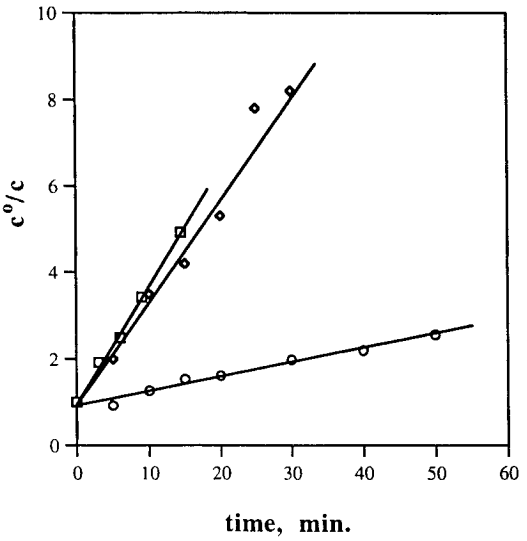
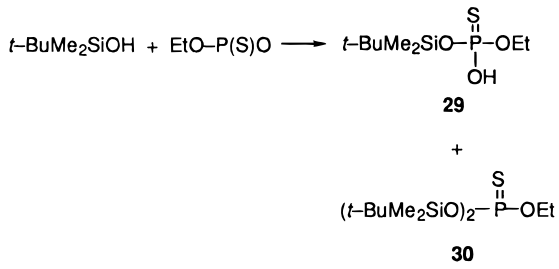


Figure 2. Kinetics of the thermolysis of **9** at 100 °C: (□) 0.050, (◇) 0.126, (○) 0.207 mol/L.

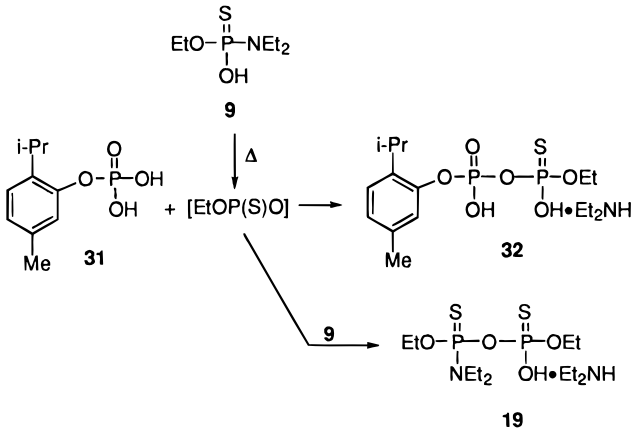
metaphosphates has been advocated.[15] This method was successfully used to trap ethyl metathiophosphate when it was generated by fragmentation of a derivative (**5**) of the 2,3-oxaphosphabicyclo[2.2.2]octene ring system.[4] We have therefore proceeded to use this trapping technique for ethyl metathiophosphate when generated by the new phosphoramidothioate fragmentation method. The reaction is easily conducted by heating a stirred suspension of silica gel in a toluene solution of the phosphoramidothioate **14**. The treated silica gel, which had about 1% P by analysis, was found to have a CP/MAS ^{31}P NMR signal centered at about δ 46. As is typical of phosphorylated silica gel, the signal was symmetrical but quite broad, extending over a range of 20 ppm. A similar broad signal was also obtained for the silica when thiophosphorylated in our earlier study with **5** as the precursor.[16] The observed shifts are about 20 ppm upfield of values for *O,O*-dialkyl phosphorothioates in solution (*e.g.*, $(EtO)_2P(S)OH$, δ 63.5 (neat)[9]), an effect consistent with observations on phosphates and attributed to the shielding action of the siloxy group. ^{29}Si NMR (CP/MAS) was also used to confirm the covalent attachment of the phosphorus group.[1,2] The signal for SiOH on silica gel (δ −103) was greatly reduced after the thiophosphorylation reaction. As with phosphates, we have confirmed this effect by using a simple silanol (*tert*-butyldimethylsilanol) as a trapping agent for ethyl metathiophosphate. The product had a major ^{31}P NMR signal at δ 44.3 assigned to compound **29**, in agreement with the thiophosphorylated silica. A second signal appeared at δ 32.3 and can be attributed to compound **30**. This compound would arise from the reaction of the initial phosphorothioate **29** with excess silanol, a reaction type observed also for phosphates.[17]

Thiophosphorylation of Phosphorus Acids. The powerful phosphorylating ability of metaphosphates suggested their use in the formation of the P−O−P bond by reaction with the free OH group of phosphorus acids. Our successful experiments on this reaction, to be described



elsewhere,[18] prompted exploratory consideration of the use of ethyl metathiophosphate in this process.

Thymyl phosphate (**31**), a crystalline, easily-dried solid, was found to be a useful representative of the family of monosubstituted phosphoric acids in this reaction. A 1/1 mixture of thymyl phosphate and *O*-ethyl *N,N*-diethylphosphoramidothioate was heated at 80−100 °C in chlorobenzene for 30 min. The ^{31}P NMR spectrum of the mixture showed that the reaction was nearly complete and that the only significant product was the desired mixed anhydride **32**. This compound was easily recognized from its ^{31}P NMR spectrum, which consisted of a doublet of doublets with the downfield signal in the P=S



region (δ 48.1) and the upfield signal in the P=O region (δ −18.4, $^2J_{PP}$ = 26.1 Hz). Both signals showed the upfield displacement from the monophosphate region that is very characteristic of compounds with the P−O−P link. The common side reaction between the metathiophosphate and the starting phosphoramidothioate formed only small amounts (5−10%) of the anhydride of type **19**, attesting to the remarkable efficiency of the thymyl phosphate as a trapping agent. Pyrophosphate **32** was stable in the reaction medium after formation and did not undergo disproportionation to a mixture of all possible pyrophosphates, as was observed in the reaction with alkyl metaphosphates.[18] The mono triethylamine salt of thymyl phosphate was also used in the reaction with ethyl metathiophosphates; the reaction was somewhat slower than that with the free acid, but after 1 h at 100 °C gave a salt with the same pyrophosphate moiety as in **26** having a very similar ^{31}P NMR spectrum (δ 45.4 and −18.2, $^2J_{PP}$ = 29.5 Hz).

The thiophosphorylation also occurred reasonably smoothly with two phosphinic acids. Diphenylphosphinic acid gave strong ^{31}P NMR signals for the expected pyro structure **33** at δ 49.8 (P=S) and at δ 23.4 (P=O; $^2J_{PP}$ = 35.4 Hz). A contaminant was the usual pyrophosphate from thiophosphorylation of the starting material. Di-

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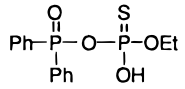
(17) Lukes, I.; Borbaruah, M.; Quin, L. D. *J. Am. Chem. Soc.* **1994**, *116*, 1737.

(18) Quin, L. D.; Hermann, P. Unpublished results.

methylphosphinic acid also gave strong signals attributable to pyro structure **34** (P═S, δ 47.7; P═O, δ 44.6; $^2J_{PP}$ = 28.8 Hz); unidentified contaminants (5−10% of total signal intensity) had signals at δ 43.4 and 54.7. If isolation procedures could be developed, the thiophosphorylation method could have practical value for the synthesis of mixed thiophosphate−phosphinate pyro structures.



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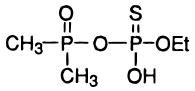

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The thiophosphorylation of two phosphonic acids (methyl and phenyl) was less satisfactory. Numerous signals were observed on the ^{31}P NMR spectra, along with those expected for the pyro products. The mixtures do not appear attractive for isolation studies.

This brief survey of thiophosphorylation of acidic phosphorus compounds therefore showed that the method could have practical value in the case of phosphoric and phosphinic acid derivatives and deserves further development. The synthesis of thiophosphoryl derivatives of nucleotides is a possibility that also deserves attention. An advantage of our new method is that a dialkyl ester can be synthesized; monothiopyrophosphates are rather well-known as the tetraalkyl esters,[20] but partially esterified derivatives are rare.

Experimental Section[21]

Synthesis of *O*-Ethyl *N,N*-diethylphosphoramidochloridothioate (7). *O*-Ethyl phosphorothioic dichloride (35.8 g, 0.20 mol) was stirred vigorously at −15 °C while it was treated simultaneously with 14.5 g (0.20 mol) of diethylamine and a solution of 7.9 g (0.20 mol) of NaOH in 30 mL of water in separate dropping funnels. The mixture was stirred an additional 2 h at about 0 °C and then washed successively with 100 mL of water, 100 mL of saturated $NaHCO_3$, and 100 mL of water. The organic phase was dried over anhydrous $MgSO_4$ and vacuum distilled. The product **7** (11.2 g, 64%) was collected at 95−100 °C at 3 mmHg (lit.[18] bp 105−106 °C at 10 mmHg): ^{31}P NMR (benzene) δ 75.0; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, $^3J_{HH}$ = 7.1 Hz, 6 H, NCH_2CH_3), 1.37 (d of t, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.9 Hz, OCH_2CH_3), 3.34 (m, 4 H, NCH_2CH_3), 4.21 (m, 2 H, OCH_2CH_3).

Synthesis of Potassium *O*-Ethyl *N,N*-diethylphosphoramidothioate (8). To a solution of 5.2 g (0.92 mol of KOH in 300 mL of acetone−water (2:1)) was added 10.0 g (0.046 mol) of **7**. The solution was kept at 30−35 °C while it was stirred for 3 days. The solvent was then removed with a rotary evaporator, and the residue was extracted with 200 mL of acetone. The extract was again evaporated to leave an oil, which was redissolved in 10 mL of acetone and diluted with 300 mL of ether. Crystals formed after overnight chilling; a second crop was obtained by duplicating the procedure with smaller solvent volumes. The procedure was performed a total of six times, yielding 8.2 g (75%) of white crystals, mp 179−180 °C (lit.[19] mp 163−165 °C). The structure was confirmed by ^{31}P NMR (d_6-acetone) δ 60.8 and ^{1}H NMR (d_6-acetone) δ 1.03 (t, $^3J_{HH}$ = 7.0 Hz, 6 H), 1.17 (t, $^3J_{HH}$ = 7.1 Hz, 3 H), 3.20 (m, 4 H), 3.74 (m, 2 H).

Synthesis of *O*-Ethyl *N,N*-diethylphosphoramidothioate (9). A column was prepared with 15 g of Amberlyst 15 (H^+) in acetone and washed with acetone until the eluate was colorless. A solution of 2.00 g (8.5 mmol) of sodium salt **8** in 10 mL of acetone was placed on the column and washed through with 150 mL of acetone. Solvent was stripped from the eluate, the residue was taken up in 10 mL of toluene, and the solvent was again stripped until the appearance of either crystals or oil. Several drops of toluene were then added, and the solution was kept at −15 °C overnight. The crystalline product was washed with a little cold toluene and then hexane. Reprocessing of the filtrates gave a second crop of crystals. The total yield of **9** was 1.22 g (73%): mp 74−75 °C; ^{31}P NMR ($CDCl_3$) δ 65.7; ^{1}H NMR similar to that of **8** with δ 1.32, 1.33, 3.31, 4.16. Anal. Calcd for $C_6H_{16}NO_2PS$: C, 36.53; H, 8.18; N, 7.10. Found: C, 36.77; H, 8.29; N, 7.14.

Synthesis of *O*-Ethyl *N*-Adamantylphosphoramidochloridothioate (12). A solution of 8.73 g (0.058 mol) of adamantylamine and 17.6 g (0.173 mol) of triethylamine in 60 mL of toluene was dropped during a 70 min period into a chilled (ice water) solution of 12.7 g (0.087 g) of ethyl phosphorodichloridite in 130 mL of toluene. Stirring and a nitrogen blanket were provided. After an additional hour at 0 °C and then 1 h at room temperature, the mixture containing **11** was treated with sulfur (5.2 g, 0.163 mol) and heated at 80 °C for 4 h. The mixture was filtered, and the residue was washed twice with 50 mL of toluene. The solvent was removed from the filtrates, and the residue was taken up in 200 mL of acetone. Some unreacted sulfur separated and was removed. The solvent was stripped, and the residue was extracted with 50 mL of ethyl acetate−hexane (1:4). The extract was passed through a silica gel column (2.5 × 30 cm) with the same solvent mixture. The recovered solid was dissolved in the minimum amount of chloroform (15 mL), a few milliliters were removed by evaporation, and the solution was then treated with 300 mL of hexane. White crystals formed overnight in the freezer. They were collected and washed with hexane. The mother liquor was preserved for later hydrolysis to **13** (*vide infra*). The recrystallized (chloroform−hexane) solid **12** (2.99 g, 17.6%) had the following: mp 120−122 °C; ^{31}P NMR ($CDCl_3$) δ 67.2; ^{1}H NMR ($CDCl_3$) δ 1.40 (d of t, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.7 Hz, 3 H), 1.66 (m, 6 H), 2.00 (m, 6 H), 2.1 (m, 3 H), 3.45 (br d, $^2J_{PH}$ = 14.3 Hz, 1 H), 4.25 (m, 2 H). Anal. Calcd for $C_{12}H_{21}ClNOPS$: C, 49.06; H, 7.21; N, 4.74. Found: C, 49.27; H, 7.11; N, 4.84.

Synthesis of Sodium *O*-Ethyl *N*-Adamantylphosphoramidothioate (13). A solution of 2.95 g (0.010 mol) of **12** in 120 mL of acetone was stirred with a solution of 0.80 g (0.02 mol) of NaOH in 30 mL of water for 1 h at room temperature. The acetone was stripped, and the remaining water solution was washed twice with 50 mL of chloroform. The water layer was evaporated to dryness, and the residue was taken up in acetone. Insoluble NaCl was filtered off, and the filtrate was evaporated to dryness. The residual oil was dissolved in 300 mL of ether; the salt **13** crystallized overnight. A second crop was obtained by evaporating the mother liquor and taking up the residue in 150 mL each of ether and hexane. The combined solids of **13** were recrystallized from methanol−ether (2.85 g, 85.4%): ^{31}P NMR ($CDCl_3$) δ 53.2; ^{1}H NMR (CD_3OD) δ 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3 H), 1.65 (m, 6 H), 1.91 (m, 6 H), 1.99 (m, 3 H), 3.92 (m, 2 H). Anal. Calcd for $C_{12}H_{21}NNaO_2PS\cdot 2H_2O$: C, 43.24; H, 7.56; N, 4.20. Found: C, 43.96; H, 7.47; N, 4.32.

Synthesis of *O*-Ethyl *N*-Adamantylphosphoramidothioate (14). The sodium salt **13** (1.70 g, 5.1 mmol) in 15 mL of methanol was passed through a column of 16 g of prewashed Amberlyst 15. The acid **14** was eluted with 200 mL of methanol, and the solvent was stripped to leave a thick residual oil. This was dissolved in about 8 mL of ether and treated with 200 mL of hexane. Acid **14** crystallized overnight in the freezer. It was collected, washed with hexane, and dried over P_2O_5 in a vacuum desiccator (1.22 g, 87.1%): mp 124−124.5 °C; ^{31}P NMR ($CDCl_3$) δ 61.3; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, $^3J_{HH}$ = 7.1 Hz, 3 H), 1.64 (m, 6 H), 1.98 (m, 6 H), 2.07 (m, 3 H), 3.5 (br s), 4.13 (m, 2 H). Anal. Calcd for $C_{12}H_{22}NPO_2S$: C, 52.34; H, 8.06; N, 5.09. Found: C, 52.60; H, 8.19; N, 4.96.

Additional **14** could also be obtained from the mother liquor using the crystallization procedure of **12** described earlier. This was accomplished by evaporation of the mother liquor to a

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(20) Michalski, J.; Reimschüssel, W.; Kaminski, R. *Russ. Chem. Rev.* **1978**, *47*, 814.

(21) Instruments and general techniques are described in refs 1 and 22.

thick oil, which was redissolved in 350 mL of acetone and treated with a solution of 1.84 g of NaOH in 170 mL of water. Some solids were removed by filtration, and the filtrate was stripped of acetone. After an extraction with four 100 mL portions of chloroform, the water phase was treated with 5% HCl to pH 1−2 and acid **14** was extracted with ether (four 100 mL portions). The extract was dried ($MgSO_4$), decolorized with charcoal, and then stripped to leave an oil that was crystallized as before from ether−hexane. The yield was 5.74 g (36.1% from adamantylamine); the product had the same properties as did the sample prepared on Amberlyst.

Synthesis of *N*-Phenylphosphoramidothioic Dichloride (15). To a mixture of 53.4 g (0.315 mol) of $PSCl_3$ and 10 mL of benzene at −15 °C were added simultaneously a solution of 15.0 g (0.375 mol) of NaOH in 60 mL of water and a solution of 35 g (0.375 mol) of aniline in 10 mL of benzene. The addition required 30 min; the mixture was then stirred at 0 °C for 3 h and diluted with 100 mL of water and 200 mL of benzene. The benzene layer was recovered, dried over Na_2SO_4, and evaporated to dryness. The residue was distilled at 125−128 °C (0.8 mmHg); the yield was 20.0 g (28.1%). For **15**: ^{31}P NMR ($CDCl_3$) δ 47.5 (lit.[7] δ 47.42).

Synthesis of Sodium *O*-Ethyl *N*-Phenylphosphoramidothioate (17). Sodium ethoxide (0.090 mol) in 250 mL of dioxane was dropped into a solution of 20.3 g (0.09 mol) of phosphoramidothioic dichloride **15** in 50 mL of benzene at room temperature over a period of 5 h. The reaction was incomplete, and an additional 0.022 mol of sodium ethoxide was added. The ^{31}P NMR spectrum then showed two products: the desired monoethyl chloro derivative **16** (δ 65.0, 85%) and the diethyl derivative (δ 63.4, 15%). The solvent was removed by rotary evaporation, and the residue was dissolved in 300 mL of acetone and treated with a solution of 4.1 g of NaOH in 100 mL of water. Some unchanged **16** remained (NMR), and the hydrolysis was repeated with 1.6 g of NaOH in 20 mL of water. Acetone was evaporated, and the residual basic solution was washed with three 100 mL portions of chloroform to remove the diester. The aqueous phase was evaporated to dryness, and the desired sodium salt **17** was extracted with anhydrous ethanol. The residue from stripping of ethanol was recrystallized twice from methanol−acetone to give 9.1 g (42.3%) of **17**: mp 211−213 °C; ^{31}P NMR (CD_3OD) δ 50.3; ^{1}H NMR (CD_3OD) δ 1.17 (t, $^3J_{HH}$ = 7.1 Hz, 3 H), 3.9 (m, 2 H), 6.6−7.1 (m, 5 H). Anal. Calcd for $C_8H_{11}NNaO_2PS$: C, 40.17; H, 4.64; N, 5.86. Found: C, 39.97; H, 4.59; N, 5.74. Attempts to convert the salt to the free acid in the usual way were not successful.

Thermal Fragmentation of the *O*-Ethyl Phosphoramidothioates (General Procedure). The reactions were performed in sealed NMR tubes (10 mm) that contained an inner 5 mm tube of D_2O as lock. Reaction solvents included toluene, dioxane, chlorobenzene, ethanol, and *tert*-butyl alcohol; generally the tubes contained 0.02−0.03 g of phosphoramidate in 1.4 mL of solvent, and the reactions were conducted by placing the sealed tubes in an oil bath at a temperature in the range 70−120 °C. The progress of the reactions was monitored by ^{31}P NMR. Fragmentations were also performed in toluene, dioxane, or chlorobenzene that contained ethanol, water, or *tert*-butyldimethylsilanol to trap the released metathiophosphate. ^{31}P NMR data for the products are presented in the Results and Discussion section. Silica gel, prepared as described previously,[17] was used as a trap in dioxane at 100 °C. The product was characterized by CP/MAS ^{31}P NMR as described[17] and had δ 46.3 (br).

Synthesis of Amine Salts of *O,O*-Diethyl Phosphorothioates. The adamantylamine salt was prepared by heating a solution of 0.25 g of thiophosphoramidate **14** in 10 mL of ethanol at 80 °C for several hours. The solvent was evaporated, and the residue was dissolved in 10 mL of acetone and mixed with 10 mL of ether. The salt crystallized on standing overnight in the refrigerator (0.18 g, 61.7%): mp over 300 °C; ^{31}P NMR (CD_3OD) 55.9; ^{1}H NMR (CD_3OD) δ 1.24 (t, $^3J_{HH}$ = 7.0 Hz, 6 H), 1.76 (m, 6 H), 1.90 (m, 6 H), 2.16 (m, 3 H), 3.9 (m, 4 H). Anal. Calcd for $C_{14}H_{28}NO_3PS$: C, 52.32; H, 8.78; N, 4.36. Found: C, 52.52; H, 8.90; N, 4.41.

The diethylamine salt was prepared similarly from 0.20 g (1.0 mmol) of thiophosphoramidate **9** in a mixture of 25 mL of dioxane and 0.88 mL (15 mmol) of ethanol. For the diethylamine salt: mp 42−43 °C; ^{31}P NMR ($CDCl_3$) δ 56.2; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 6 H), 1.40 (t, $^3J_{HH}$ = 7.3 Hz, 6 H), 3.00 (m, 4 H), 4.00 (m, 4 H). Anal. Calcd for $C_8H_{22}NO_3PS$: C, 39.49; H, 9.11; N, 5.76. Found: C, 39.59; H, 9.25; N, 5.62.

Isolation of a Pyrophosphate Derivative from the Fragmentation of *O*-Ethyl *N,N*-diethylphosphoramidothioate (9). A 0.40 g sample of acid **9** in 50 mL of dioxane was heated at 100 °C for 30 h. The flask was then left open to the atmosphere for 3 days. A white solid separated slowly and was filtered off and washed with acetone. A second crop was obtained by evaporating the combined filtrates to dryness and adding acetone; additional white solid precipitated and was recovered. The solid **22** was recrystallized from methanol by addition of acetone to yield 0.09 g (21%): mp 174−175 °C; ^{31}P NMR (CH_3OH) δ 42.0; ^{1}H NMR (CD_3OD) δ 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 6 H), 1.32 (t, $^3J_{HH}$ = 7.3 Hz, 12 H), 3.07 (q, $^3J_{HH}$ = 7.3 Hz, 8 H), 4.10 (m, 4 H). Anal. Calcd for $C_{12}H_{34}N_2O_5P_2S_2$: C, 34.94; H, 8.31; N, 6.79. Found: C, 35.01; H, 7.88; N, 6.64.

From the remaining solutions from the precipitation of **22** was recovered the pyrophosphate derivative **20**. This was accomplished by removing the solvent and chromatographing the residue on silica gel with chloroform−methanol (5:1). The elution was monitored by ^{31}P NMR of fractions. The product fraction was passed through Amberlyst 15 with acetone: ^{31}P NMR ($CDCl_3$) δ 50.6 and 62.0 (d of d, $^2J_{PP}$ = 28.9), 51.0 and 61.9 ($^2J_{PP}$ = 25.5 Hz). The acid was treated with ethereal diazomethane prepared from Diazald. The product was recovered by Kugelrohr distillation (0.08 g, 23%) and consisted of a mixture of 82% of the *S*-methylated product (^{31}P NMR ($CDCl_3$) δ 16.9 and 62.9, d of d, $^2J_{PP}$ = 34.4 Hz) and 18% of the *O*-methylated product (^{31}P NMR δ 54.9 and 62.7, d of d, $^2J_{PP}$ = 28.2 Hz). The mixture was not separated. Partial ^{1}H NMR: δ 2.33 (d, $^3J_{PH}$ = 16.6 Hz) and 3.76 (d, $^3J_{PH}$ = 14.3 Hz).

Kinetic Measurements. The samples were placed in NMR tubes in thermostats, and the reaction progress was monitored by ^{31}P NMR as described elsewhere.[1,22]

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