Tetrahedron Letters, Vol.31, No.28, pp 4081-4084, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

EFFICIENT OXYGENATION OF THIOPHOSPHORYL AND SELENOPHOSPHORYL GROUPS USING TRIFLUOROACETIC ANHYDRIDE

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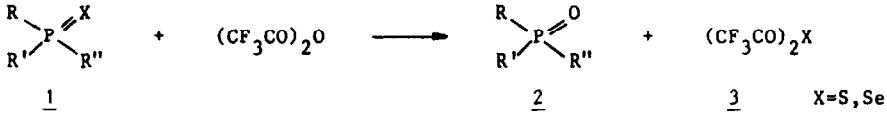
Abstract: Trifluoroacetic anhydride reacts with organophosphorus compounds containing thiophosphoryl and selenophosphoryl groups converting them in high yield to the corresponding oxygenated systems.

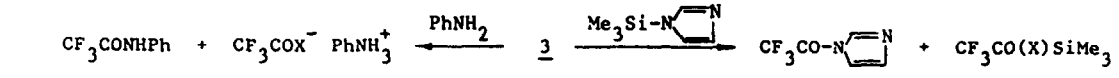
Thio- and selenoanalogues of organic phosphates are of considerable interest in nucleotide and carbohydrate chemistry.[1] A wide range of reagents have been proposed for the oxygenation of thiophosphoryl and selenophosphoryl groups.[2] However, in many cases their use is limited due to their low selectivity or the harshness of the reaction conditions. The development of new oxygenation procedures is therefore warranted.

In the course of our studies on thiophosphorus acid anhydrides we noticed that trifluoroacetic acid anhydride (TFAA) is capable of oxidizing both thiophosphoryl 1 (X=S) and selenophosphoryl 1 (X=Se) systems. We found that this reaction allows easy conversion of thiophosphoryl and selenophosphoryl groups to phosphoryl moieties in excellent yields.



1 2 3 X=S,Se

The course of oxygenation was followed by ^{31}P NMR spectroscopy and the structures of phosphorus compounds confirmed by comparison with authentic specimens. The structure of the second reaction product 3 was established by chemical transformations and ^{13}C NMR spectroscopy which showed only one quartet for the CO group at δ 150.8 ppm J^2_{CF}= 47.0 Hz for X=S and δ 199.99 ppm J^2_{CF}= 48.5 Hz for X=Se. Thus, the symmetric structure is indicated for the anhydride 3 with two equivalent carbonyl groups whilst the isomeric structure $CF_3C(X)-O-C(O)CF_3$ is excluded. Additional evidence came from reactions of 3 with two equivalents of aniline or N-trimethylsilylimidazole.



X=S,Se

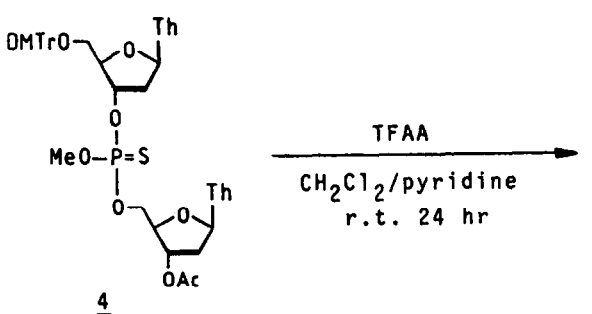
The thioanhydride 3 (X=S) can be evaporated in vacuo while the selenoanhydride decomposes on attempted distillation. We have not investigated any other properties of the anhydrides 3 which, to our knowledge, have not been described previously. When phosphorus systems are the desired reaction products, the anhydrides 3 can be readily removed from the reaction mixture by evaporation with the solvent. The representative examples of the transformation P=Se → P=O are given in Table 1. All reactions indicated in the Table were performed in methylene chloride solutions with a minute excess of the trifluoroacetic anhydride.

$$\underset{\underline{1}}{RR'R''P{=}X} \longrightarrow \underset{\underline{2}}{RR'R''P{=}O}$$

R	R'	R''	X	δ 1	δ 2	Yield %	Time
n-Bu	n-Bu	n-Bu	S	+48.24	+30.62	100	3 hr
Ph	Ph	Ph	S	+42.40	+26.89	100	3 hr
PhO	PhO	PhO	S	+37.16	-18.00	< 10	48 hr
Me_3CHO	Me_3CHO	MeO	S	+68.79	-1.51	100	24 hr
Me_3CHO	Me_3CHO	Me_3CHO	S	+67.08	-2.62	100	24 hr
EtO	EtO	EtO	S	+67.18	-2.42	100	24 hr
Bu^t	Ph	MeO	S	+106.56	+54.70	100	24 hr
Ph	Ph	Ph	Se	+35.12	+26.84	100	2 hr
n-Bu	n-Bu	n-Bu	Se	+36.52	+30.72	100	2 hr
EtO	EtO	EtO	Se	+71.31	-2.42	100	24 hr

Table 1

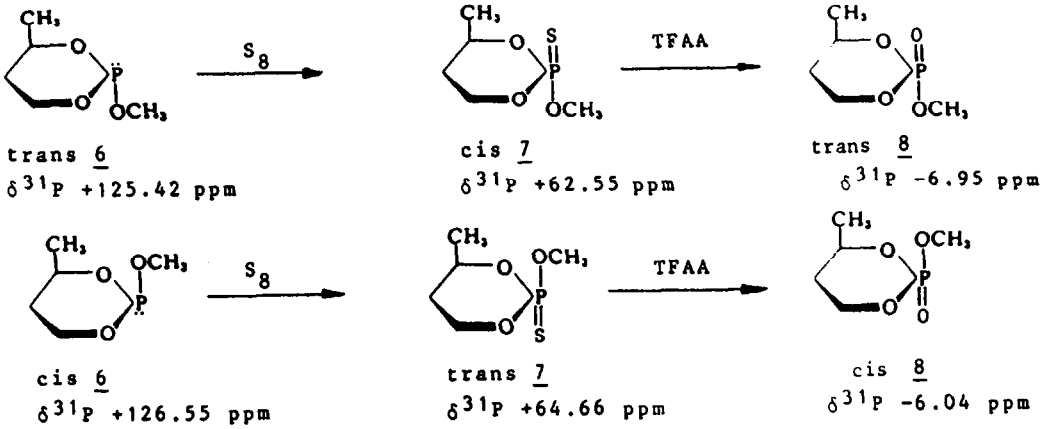
In pyridine solution, the oxidative transformation proceeds distinctly faster and in many cases is complete within 2 hr. We have exploited this new oxygenation procedure in developing a facile transformation of the dinucleotide phosphorothioate 4 into its oxygenated analogue 5. The starting thioester 4 was prepared by known procedures[3] and consisted of a 1:1 mixture of two diastereoisomers. The reaction of 4 with TFAA yielded two diastereoisomers of 5 in quantitative yield. They were identified by the appearance of two signals at -1.2 and 1.3 ppm in the ^{31}P NMR spectrum.



4 $\delta^{31}P$ 68.4 68.2 ppm

5 $\delta^{31}P$ -1.2 -1.3 ppm

The stereochemical course of the reaction was investigated with the aid of cyclic diastereoisomeric phosphorothionates 7. These model diastereoisomeric compounds were obtained by addition of elemental sulphur to the corresponding phosphites 6. The preparation and configurational assignments of phosphites 6 and phosphorothionates 7 as well as phosphates 8 are well known from earlier studies by Mikołajczyk, Stec at al.[4] The spectroscopic data were in full agreement with those of previous investigators.



trans 6 $\delta^{31}P$ +125.42 ppm

cis 7 $\delta^{31}P$ +62.55 ppm

trans 8 $\delta^{31}P$ -6.95 ppm

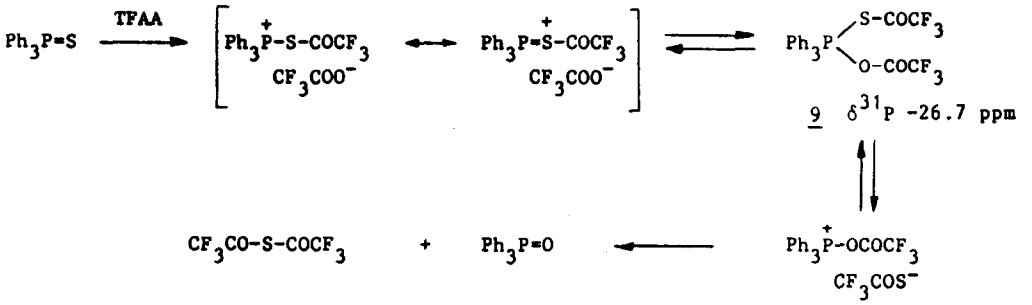
cis 6 $\delta^{31}P$ +126.55 ppm

trans 7 $\delta^{31}P$ +64.66 ppm

cis 8 $\delta^{31}P$ -6.04 ppm

The oxygenation proceeded in a stereospecific manner with retention of configuration at the phosphorus centre.

The mechanistic course of the oxygenation reaction is not fully clear. Employing triphenylphosphine sulphide as a model compound, we were able to observe by ^{31}P NMR spectroscopy the formation of one pentacoordinate (9), and two tetracoordinate transient species. Although the chemical shifts are indicative of tetracoordinate phosphonium intermediate formation, the definite assignments of ^{31}P NMR shifts prior to and after ligand exchange is at present not possible. We tentatively suggest the following mechanistic scheme of the reaction:



The experiment performed with optically active methyl phenyl isopropyl phosphine sulphide led to the racemic oxide which is consistent with the mechanism shown above. Moreover, when optically active phosphine oxides were subjected to the same reaction conditions as the sulphides, they also underwent racemisation. The reasons for a different stereochemical behaviour of cyclic phosphates 7 is yet unclear. Further mechanistic study on that subject is in progress.

The examples reported here show the wide applicability of TFAA oxygenation in synthetic phosphorus chemistry, which can probably be extended to other phosphorus acids, thio- and selenoesters of biological importance. In fact, in addition to the type of models mentioned above we have also oxidized dithiophosphates $(RO)_2P(S)SR'$ producing the corresponding monothiophosphates $(RO)_2P(O)SR'$.

It is clear that trifluoroacetic anhydride cannot be used as a capping reagent in any procedure leading to oligonucleotide thiono analogues.

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(Received in UK 30 May 1990)