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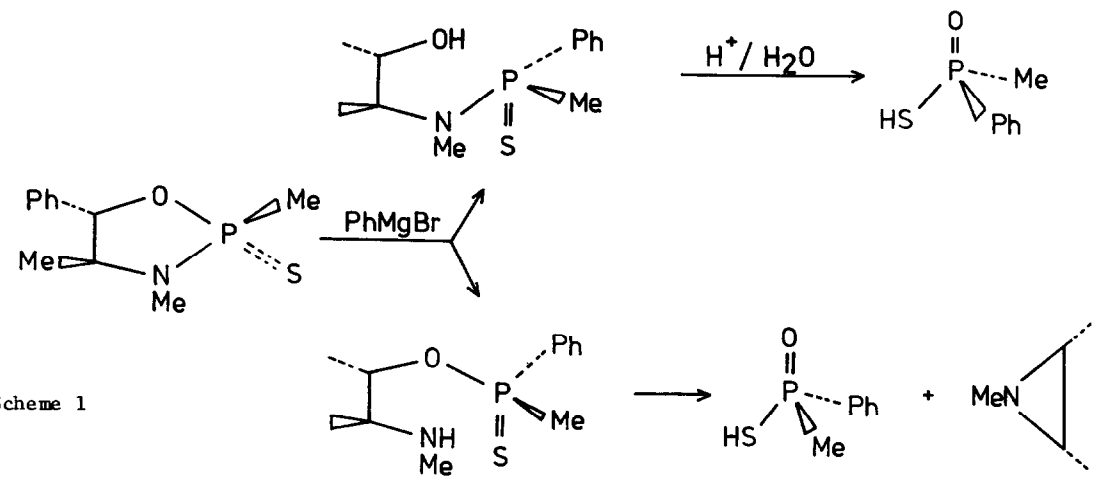
THE PREPARATION AND SOME REACTIONS OF 1,3,2-THIAZAPHOSPHOLIDINE-2-ONES

C. Richard Hall* and Nancy E. Williams

Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, SP4 OJQ

Summary: 1,3,2-Thiazaphospholidine-2-ones have been prepared by rearrangement of the corresponding 1,3,2-oxazaphospholidine-2-thiones. The stereochemical course of ring opening reactions has been investigated.

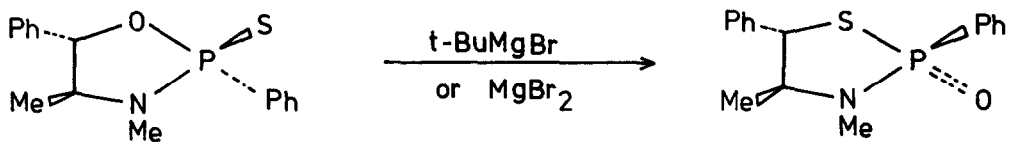
Treatment of the various isomers of 2-methyl-1,3,2-oxazaphospholidine-2-thione with phenyl magnesium bromide results in competitive P-N and P-O bond cleavage[1]. P-N cleavage occurs with inversion and P-O cleavage with retention of configuration at phosphorus. Thus, both enantiomers of methylphenylphosphinothioic acid can be prepared from a single precursor (Scheme 1).



Scheme 1

Attempts to prepare benzylphenyl or t-butylphenylphosphinothioic acid by treatment of the 2-phenyl-1,3,2-oxazaphospholidine-2-thione (1)[2] with the appropriate alkyl magnesium bromide were unsuccessful. Instead, for example Scheme 2, heating (1) and t-butyl magnesium bromide in boiling benzene for several hours resulted in the 1,3,2-thiazaphospholidine-2-one (5), (85%) as a white crystalline solid, m.p. 165-6°C (from diisopropyl ether-benzene), $[\alpha]_D$ -26° (c 1.0 in chloroform).

This rearrangement appears to be a general one for both the phosphono and phosphoro series, although in most cases the 1,3,2-thiazaphospholidine products are hydrolytically very unstable[3] and conventional processing results in only small yields of pure product.



(1) (5)

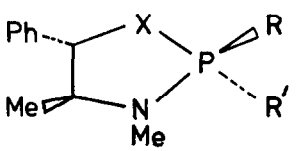
Scheme 2

The most likely course of the rearrangement is initial C-O bond cleavage by attack of bromide at the benzylic carbon, followed by recyclisation after selective alkylation on sulphur. The steric bulk of the benzyl or t-butyl group presumably prevents nucleophilic attack at phosphorus. This proposal is supported by the fact that the same rearrangement occurs on treatment of (1) with magnesium bromide etherate. Complexing of the magnesium ion must play an important role because neither potassium or ammonium bromide promote reaction.

The configuration of the 1,3,2-thiazaphospholidine-2-ones is assigned on the basis of their ^{1}H n.m.r. spectra (Table 1) and is supported by the proposed mechanism of the rearrangement.

Table 1

^{1}H and ^{31}P N.M.R. Parameters for the 1,3,2-Oxaza and Thiazaphospholidines.[a]



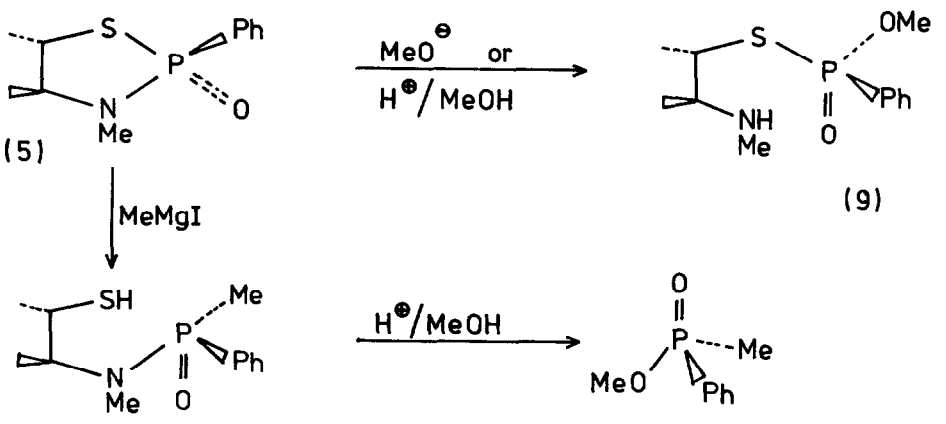
	R	R^1	X	δ NMe	δ H-4	δ H-5	^{31}P [b]
(1)	S	Ph	O	2.48	3.53	5.04	92.6
(2)	Ph	S	O	2.53	3.29	4.89	99.4
(3)	O	Ph	O	2.52	3.55	5.16	31.0
(4)	Ph	O	O	2.67	3.50	4.90	35.8
(5)	Ph	O	S	2.63	3.81	4.43	51.2
(6)	O	Ph	S	2.50	3.64	4.64	
(7) [c]	O	OEt	S	2.67	3.45	4.46	45.7
(8) [c]	OEt	O	S	2.72		5.03	44.3

(a) $CDCl_3$ solutions (b) ppm downfield from phosphoric acid

(c) (-)-ephedrine and not pseudoephedrine derivatives

The phosphono adduct (5) reacts rapidly with a dilute solution of anhydrous hydrogen chloride in alcohol or with the corresponding alkoxide in alcohol (eg. Scheme 3) to give an essentially quantitative yield of the P-N bond cleaved product (9), $[\alpha]_D$ + 81° (c 0.9 in methanol, as the hydrochloride). The reaction is stereospecific and, on the basis of the results of acid catalysed alcoholyses on similar systems[4], it can reasonably be assumed to occur with inversion of configuration. Treatment of (9) with an excess of methoxide results in dimethyl phenylphosphonate, presumably formed by nucleophilic displacement at phosphorus.

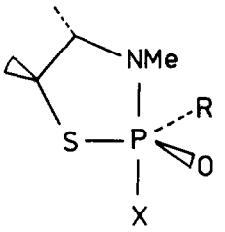
(5) also reacts rapidly and quantitatively with methyl magnesium iodide at room temperature to give the product of P-S bond cleavage (10), m.p. 136-7°C, $[\alpha]_D$ + 113° (c 0.5 in chloroform) (Scheme 3). Acid (hydrogen chloride or trifluoromethylsulphonic) catalysed methanolysis of (10) gives enantiomerically pure (+)-(R)-methyl methylphenylphosphinate (11)[5]. Since under the conditions used acid catalysed P-N bond cleavage in phosphinamidates occurs with inversion of configuration,[5] then P-S bond cleavage in (5) must occur with retention of configuration.



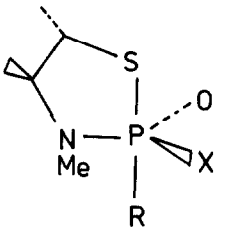
Scheme 3

The phosphoro adduct (7), $[\alpha]_D$ + 35° (c 2 in chloroform), reacts with both hydrogen chloride in methanol and with sodium methoxide to yield the same single product, ie. that resulting from P-N bond cleavage again presumably occurring with inversion of configuration.

An explanation of the stereochemical results of the ring opening reactions of (5) and (7) follows the supposition that, unlike their acyclic analogues, in the 1,3,2-thiazaphospholidine ring system, nitrogen has a greater apical potentiality[6] than sulphur. The mechanism of ring opening can be envisaged as involving attack of the nucleophile (x) opposite the endocyclic nitrogen to form a trigonal bipyramidal intermediate (tbp) such as (12). When the nucleophile is alkoxide, P-N cleavage occurs, resulting in product formed with inversion. When the nucleophile is alkyl, pseudorotation of (12) to the new tbp (13) is presumably fast compared to the rate of P-N bond cleavage. P-S bond cleavage in (13) results in product formed with retention. The pseudorotation of (12) to (13) is expected to be a favourable process because it involves the transfer of the poorly apicophilic alkyl group from an apical to an equatorial position.



(12)



(13)

These results constitute a further example[4,7] of how the confining of ligands within a five-membered ring can alter their relative apical potentiality and thus the stereochemistry and course of reactions compared to the acyclic analogues. Whether the reason for this is stereoelectronic, or straight forward steric hinderance by the nitrogen substituent to nucleophilic attack at phosphorus[4,7], is currently under further investigation

We wish to thank Dr T D Inch for his interest and advice.

REFERENCES

1. C.R. Hall and T.D. Inch, Polish J. Chem., 1980, 489.

2. The isomers (1) and (2) were prepared by condensing $PhP(S)Cl_2$ with (+)-pseudoephodrine in the presence of triethylamine. The configurations were tentatively assigned on the basis of the H-5 resonnance in the ^1H n.m.r. spectra of their oxygen analogues (3) and (4)[1], prepared (presumably with retention of configuration) by treatment respectively of (1) and (2) with m-chloroperbenzoic acid. Doping studies with $Eu(fod)_3$ show that for (4) the rate of change of shift ($\delta \Delta H_z$) of H-4 > H-5. For (3) the rates are more nearly equal.

3. P. Savignac, N.T. Thuong and P. Chabrier, C.R. Acad. Sci. Ser C, 1968, 1971; ibid. 1968, 1166.

4. C.R. Hall and T.D. Inch, Tetrahedron, 1980, 36, 2059.

5. M.J.P. Harger, J.C.S. Perkin I, 1979, 1294.

6. Apical potentiality is a concept intended to relate the likelihood, during nucleophilic attack at tetracoordinate phosphorus, of a ligand being in-line with the nucleophile and therefore of occupying an apical position in the initially formed tbp. It should be distinguished from apicophilicity, a term which refers to the propensity of a ligand to occupy an apical position in a tbp in thermodynamically controlled situations.

7. C.R. Hall and T.D. Inch, J.C.S. Perkin I, in preparation.

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