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RING OPENING OF 1,3,2-OXAZAPHOSPHOLIDINE-2-THIONES WITH ALKYL LITHIUMS; SYNTHESIS OF CHIRAL PHOSPHINOTHIOIC ACIDS

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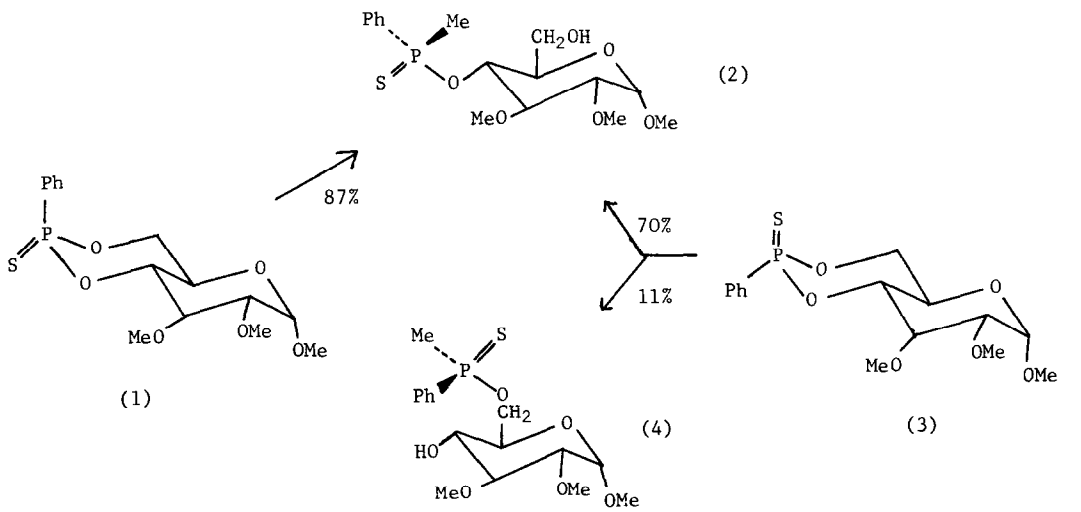
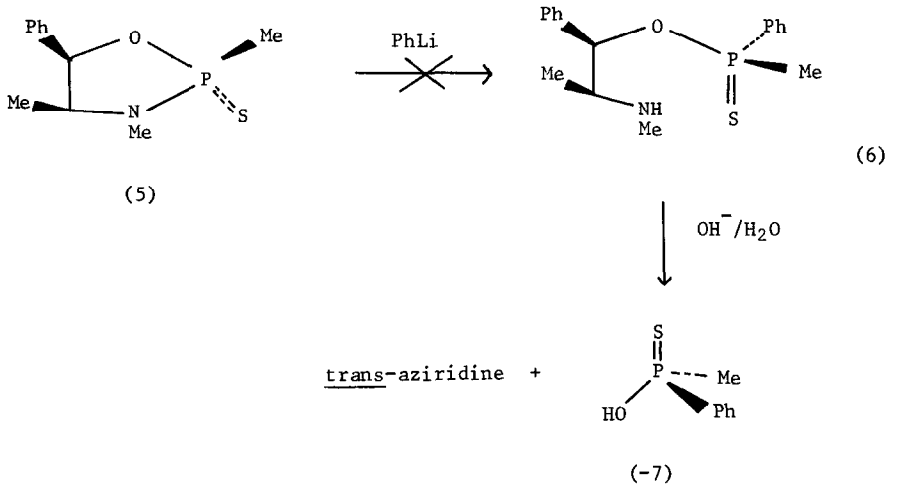
Summary: Chiral phosphinothioic acids are prepared by a novel synthesis involving an unexpected P - O bond cleavage with retention of configuration at phosphorus.

As experimental data on the stereochemistry of ring opening reactions of cyclic phosphorus esters accumulates[1-3] it is increasingly obvious that the interdependence of the many factors which determine the direction of ring cleavage, and whether or not configurational changes occur, are not sufficiently well understood to permit rationalisation of the products obtained. For example,[1] there is no completely satisfactory explanation, in stereochemical terms or otherwise, for the observation (Scheme 1) that on treatment with methylmagnesium iodide the 6-membered cyclic phosphonothioate (1) afforded (2) in 87% yield with inversion of configuration while (3) under similar reaction conditions also afforded (2) in 70% yield but with retention of configuration together with some (4) (11%). In this paper, results are reported which show that ring opening reactions of 1,3,2-oxazaphospholidine-2-thiones with alkyl and aryl lithiums are equally complex.



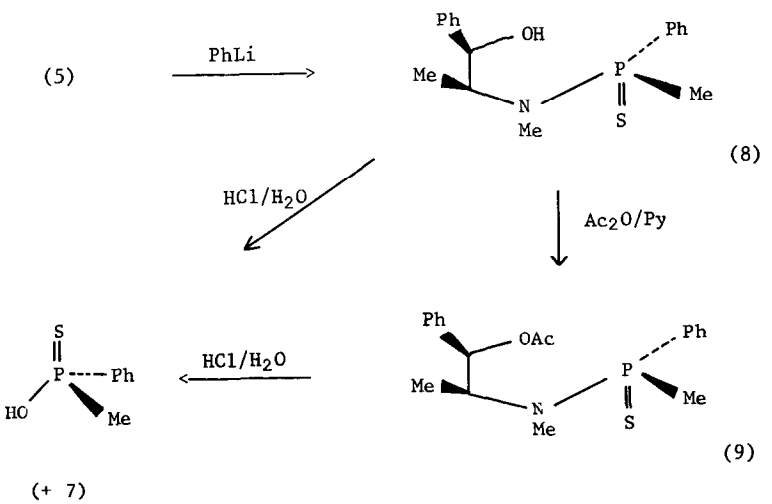
Scheme 1

The main purpose of such studies was to extend the utility of the 1,3,2-oxazaphospholidines derived from (-)ephedrine as intermediates for the stereospecific synthesis of chiral organophosphorus compounds[3,5] to the synthesis of phosphinothioic acids. By analogy[3,5] with



Scheme 2

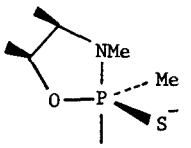
reactions of (5)[6] with sodium alkoxides one possibility was that with phenyllithium, (5) would undergo P - N bond cleavage with inversion of configuration to give (6) which under aqueous basic conditions would form an aziridine and (S)-methylphenylphosphinothioic acid (-7) (Scheme 2). In practice (Scheme 3) the preponderant ring opening reaction was P - O and not P - N bond cleavage to afford (8) which on direct treatment with HCl/H_2O or, after acetylation by acetic anhydride in pyridine to give (9) followed by HCl/H_2O, was converted into (+)-methylphenylphosphinothioic acid (+7). The n.m.r. spectrum of the acetate (9) showed that P - O bond fission was essentially stereospecific with only a trace of (10) being present. (N.m.r. data for ring opened products are given in Table 1. The isomeric ratios determined from the n.m.r. data are in Table 2).



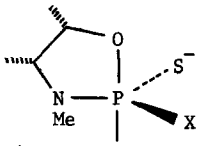
Scheme 3

Since (+)methylphenylphosphinothioic acid has the R configuration,[7] if the ring opening reaction occurred with inversion of configuration then the acidic hydrolysis must have occurred with retention of configuration at phosphorus or vice versa. All previously reported highly stereoselective acidic hydrolyses of phosphinic amidates occur with inversion of configuration[8] therefore the high probability is that the P - O bond cleavage occurred with retention of configuration. P - N bond cleavage was essentially (> 95%) stereospecific at acid concentrations up to at least 4.5N.

This result for the ring opening reaction is consistent with the implication from the reaction of 1,3,2-oxazaphospholidin-2-thiones with alkoxides that in such systems nitrogen is more apicophilic than oxygen. Thus nucleophilic attack may occur opposite nitrogen to generate the trigonal bipyramidal intermediate (15). Where X = OEt, direct apical P - N cleavage occurs. Where X = Ph, (15) pseudorotates to (16) and apical P - O cleavage results. That (15, X = Ph) apparently pseudorotates fast relative to P - N cleavage whereas (15, X = OEt) does not, presumably reflects a barrier to pseudorotation in the latter, caused by the much greater apicophilicity of OEt than Me. In (15, X = Ph) Ph and Me have similar apicophilicities.

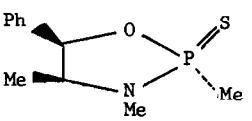


(15)



(16)

With n.butyllithium and ethyllithium, (5) reacted with similar stereoselectivity to its reaction with phenyllithium. N.m.r. parameters for the products (11), (12) and (13), (14) respectively are given in Table 1 and product ratios in Table 2 on the assumption that ring opening occurs with preponderant retention of configuration. In contrast the isomer of (5), i.e. (17) underwent much less stereoselective reactions with alkyl (aryl) lithium. Thus with phenyllithium (17) afforded only 70% of the retention product (10). Further if the

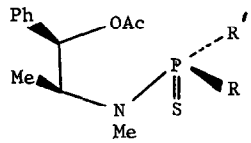


(17)

assumption is correct that (5) on treatment with n.butyllithium and ethyllithium ring opened with retention of configuration then the (17) — alkyllithium reactions proceed with preponderant inversion of configuration giving (11) and (13) as the major isomers.

Provided P - O bond cleavage is highly stereoselective the route in Scheme 3 is a useful synthetic sequence for chiral phosphinothioic acids. For example (R)-n.butylmethylphosphinothioic acid (-18) as well as (R)-methylphenylphosphinothioic acid (+7) has been prepared (Table 3). Further scope is offered because on treatment with alkyllithiums (as strong base) followed by alkylhalides, chain extension of the P - CH_3 group in e.g. (9) occurs. Thus with alkyllithium and methyl iodide, (9) was converted under carefully controlled conditions into the corresponding P - Et derivative which was degraded to (R)-ethylmethylphosphinothioic acid (+19) (Table 3). With excess methyliodide and alkyllithium P-CH_3 or P - CH_2CH_3 could be converted into P - iPr or P - t.Bu.

TABLE 1. P.m.r. Parameters

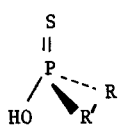


	R	R'	δ CMe	PMe	NMe	MeCH	PhCH
(9)	Me	Ph	1.21	1.91	2.54	4.12	5.73
(10)	Ph	Me	1.35	1.50	2.21	4.22	5.75
(11)	Me	n.Bu	1.22	1.53	2.53	4.62	5.74
(12)	n.Bu	Me	1.24	1.03	2.48	-	5.72
(13)	Me	Et	1.22	1.53	2.53	-	5.80
(14)	Et	Me	-	-	2.48	-	5.78

TABLE 2. Ratio of P - O Bond Cleaved Products

	Reactants: PhLi		n.BuLi		EtLi	
Starting Material	Products	[Ratio]	Products	[Ratio]	Products	[Ratio]
(5)	(9):(10)	[98:2]	(11):(12)	[95:5]	(13):(14)	[95:5]
(17)	(9):(10)	[30:70]	(11):(12)	[70:30]	(13):(14)	[75:25]

TABLE 3. Phosphinothioic Acids



	R	R'	$[\alpha]_D$ ($CHCl_3$)		Major Enantiomer
(+7)	Ph	Me	+19.5°	(c. 0.5)	95%[9]
(-18)	n.Bu	Me	- 3.6°	(c. 1.2)	90%
(+19)	Ph	Et	+24.4°	(c. 0.6)	98%

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5. C.R. Hall and T.D. Inch, J.Chem.Soc. Perkin I, papers in press.
6. In a previous paper (ref. 3) the n.m.r. parameters for (5) and its isomer (17) were reported incorrectly. The correct data are (5) δ 0.70 (3H,d), 2.02 (3H,d), 2.73 (3H, d, J = 12 Hz), 3.62 (1H, m, J_{P-H} = 11.8 Hz) and 5.62 (1H, dd, J = 6.0 and 2.2 Hz); (17) δ 0.78, 1.91, 2.65 (J = 13.5 Hz), 3.62 (J_{P-H} = 16.4 Hz) and 5.46 (J = 5.9 and 4.0 Hz).
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8. For example; T. Koizumi, Y. Kobayashi and E. Yoshii, Chem.Pharm.Bull. (Japan), 1976, 24, 834; M.J.P. Harger, J.Chem.Soc. Perkin I, 1977, 2057; D.A. Tyssee, L.P. Baucher and P. Haake, J.Amer.Chem.Soc., 1973, 95, 8066.
9. M.J.P. Harger, J.Chem.Soc. Perkin II, 1978, 326. The percentage major isomer was estimated by a ^1H nmr method.

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