Stereoretentive Conversion of Cyclic Phosphorothioates into [^{18}O]Phosphates using [^{18}O]Chloral

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P-Chiral cyclic dialkyl phosphorothioates are converted into the corresponding P-chiral [^{18}O]phosphates by [^{18}O]chloral with retention of configuration at phosphorus.

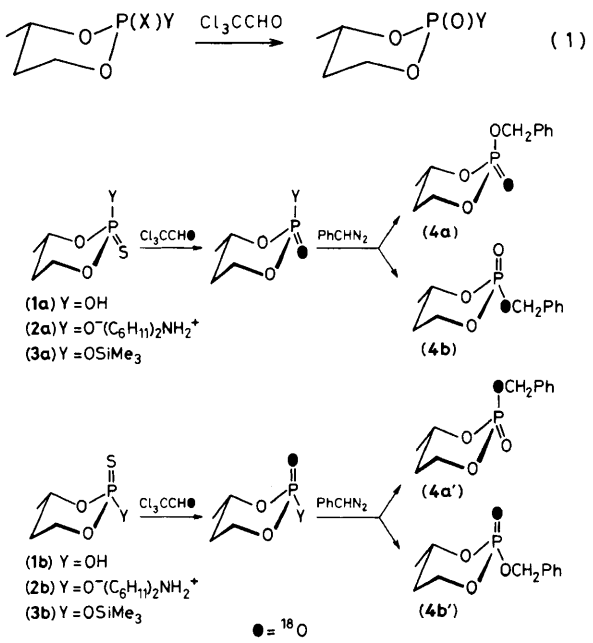
Recent developments in the synthesis and configurational analysis of P-chiral dialkyl [^{18}O]phosphates[1] and the relatively simple accessibility of diastereoisomeric dialkyl phosphorothioates[2,3] prompts us to publish our results on a new approach to the stereospecific replacement of sulphur (or selenium) attached to a phosphorus moiety by oxygen.

Following the original work of Sohr and Lohs[4] on the reaction of phosphorothioates ($X_1X_2X_3P{=}S$; X_1,X_2,X_3 = F, Cl,ArO,AlkO) with chloral (trichloroacetaldehyde) we have found that this reagent readily transforms P-chiral thio(or seleno)phosphoryl compounds into the corresponding oxo-derivatives *with retention of configuration at phosphorus*. As model compounds we used diastereoisomeric (but racemic) 2-X-2-thio(or seleno)-4-methyl-1,3,2-dioxaphosphorinanes. The *cis–trans* geometry of the starting compounds and that of the corresponding 2-oxo-derivatives was described in earlier

Table 1. Reactions of 2-X-2-Y-4-methyl-1,3,2-dioxaphosphorinanes with chloral [equation (1)].

Exp. no.	Substrate X	Substrate Y	Substrate Geometry[a]	Substrate δ(31P)[b]/ p.p.m.	Reaction time/ min	Product X	Product Y	Product Geometry	Product δ(31P)[c]/ p.p.m.	Yield[d] (%)
1	S	OMe	94% *trans* 6% *cis*	66.3 63.6	40	O	OMe	92% *cis* 8% *trans*	−5.5 −7.1	95
2	S	OMe	6% *trans* 94% *cis*	66.1 63.5	40	O	OMe	6% *cis* 94% *trans*	−5.3 −6.8	94
3	S	NHPh	100% *cis*	60.1	10	O	NHPh	100% *cis*	−4.5	98 (83)[e]
4	S	NHPh	100% *trans*	62.4	10	O	NHPh	100% *trans*	−0.7	100 (85)[e]
5	S	NMe_2	80% *trans* 20% *cis*	76.2 76.5	20	O	NMe_2	81% *trans* 19% *cis*	6.5 4.6	92
6	S	SeMe	100% *trans*	76.4	30	O	SeMe	100% *trans*	12.3	93
7	S	SMe	40% *cis* 60% *trans*	96.7 86.8	30	O	SMe	40% *cis* 60% *trans*	24.7 20.4	90
8	Se	NMe_2	90% *trans* 10% *cis*	75.9 76.3	30	O	NMe_2	92% *trans* 8% *cis*	6.4 4.6	86

[a] The *trans* geometry refers to the relative equatorial–axial arrangement of 4-Me and that of the X–Y substituents having the priority according to the Cahn–Ingold–Prelog rule. [b] Positive values for compounds absorbing at lower fields than 85% H_3PO_4, $CHCl_3$ solution. [c] Measured in chloral solution. [d] Calculated from the ^{31}P n.m.r. spectra of the reaction mixture. [e] Yield of purified product after evaporation of chloral, short-column chromatography, and recrystallization from ethyl acetate. *cis*-Anilidate m.p. 154—156 °C. *trans*-Anilidate m.p. 174—176 °C.



Scheme 1

work.[5] The reactions were performed by dissolving the thio(or seleno)phosphoryl reagent in chloral (10-fold molar excess) and heating under reflux until full conversion had occurred (^{31}P n.m.r spectroscopy and/or t.l.c. assay). The yields of oxo-products are nearly quantitative as estimated from the ^{31}P n.m.r. spectra of crude reaction mixtures. The results are summarized in Table 1.

Inspection of Table 1 reveals that in addition to total stereoselectivity the reaction with chloral is chemoselective and involves the 'thiono' sulphur atom and does not affect either the 'thiolo' and 'selenolo' functions (exp. 6,7) or the phenylamino-groups attached to phosphorus (exp. 3,4).

Following the stereochemical experiments described in Table 1, we investigated the stereochemistry of the reaction of chloral with dialkyl phosphorothioates using a reagent labelled with an oxygen isotope [^{18}O]Chloral was obtained in good yield by acid-catalysed hydrolysis of Cl_3C–CH=NPh† with a stoicheiometric amount of [^{18}O]H_2O. As model compounds we chose diastereoisomeric *cis*- and *trans*-2-hydroxy-2-thioxo-4-methyl-1,3,2-dioxaphosphorinanes whose stereochemistry has previously been described.[5] The reactions were performed with both free thioacids (**1a,b**), their dicyclohexylammonium salts (**2a,b**), and the *O*-trimethylsilyl derivatives (**3a,b**). The products were analysed in the form of the benzyl esters (**4a,b**) and (**4a′,b′**) which were obtained by treatment of the resulting [^{18}O]oxo- acids with phenyldiazomethane (Scheme 1). Separation of the diastereoisomers of (**4**) and assignment of the position of oxygen-18 with respect to the ring methyl group was performed according to the established procedure.[6,7] The results are collected in Table 2.

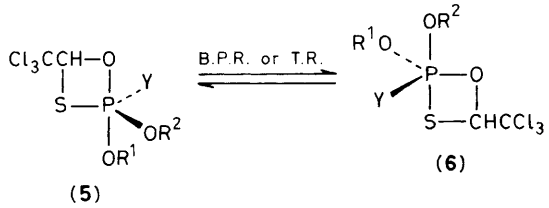
Table 2. Reactions of (**1**), (**2**), and (**3**) with [^{18}O]chloral.[a]

Exp. no.	Substrate	Stereoselectivity % Retention	Stereoselectivity % Inversion
1	(**1a**)	93.0	7.0
2	(**1b**)	91.8	8.2
3[b]	(**2a**)	92.7	7.3
4[b]	(**2b**)	92.9	7.1
5[c]	(**3a**)	91.5	8.5
6[c]	(**3b**)	93.2	6.8

[a] Reactions were run for 10 min at 96 °C with a 10-fold molar excess of [^{18}O]chloral (enrichment 53%). [b] The resulting ammonium salt was passed through an ion-exchange Dowex 50W × 8 column (H^+ form) before benzylation. [c] The product of the reaction of (**3**) with chloral was dissolved in wet methanol prior to treatment with phenyldiazomethane in order to remove the trimethylsilyl group.

Inspection of Table 2 clearly shows that chloral-induced conversion of dialkyl phosphorothioates into dialkyl [^{18}O]phosphates is highly stereoselective and proceeds with at least 92% retention of configuration at phosphorus. Preliminary results on the reaction of both R_P and S_P diastereoisomers of thymidine cyclic 3′,5′-phosphorothioates[8] with [^{18}O]-chloral have confirmed the high stereoselectivity of the

† Cl_3C–CH=NPh was prepared from chloral in benzene solution by a one-pot procedure, involving reaction with aniline, chlorination of the resulting adduct with $SOCl_2$–pyridine, and finally, treatment with triethylamine (b.p. 90 °C/1.2 mmHg, yield 77%).



(5) (6)

reaction under investigation and its applicability to the synthesis of nucleoside cyclic 3′,5′-[^{18}O]phosphates.

The stereochemical result of reactions of thiophosphoryl compounds with chloral can be rationalized in terms of nucleophilic attack by sulphur on the carbonyl group of chloral and participation of the pentacovalent intermediates (**5**) and (**6**) containing a four-membered ring in an axial–equatorial arrangement. One permutational isomerization [Berry pseudorotation (B.P.R.) or turnstile rotation (T.R.)][9] (**5**) → (**6**) would make sulphur axial thus allowing the decomposition of (**6**) into products with overall retention of configuration at phosphorus. However, no P^V intermediate of type (**5**) or (**6**) could be detected in the reaction mixture by ^{31}P n.m.r. spectroscopy.

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