Tetrahedron Letters,Vol.26,No.27,pp 3279-3280,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

STEREORETENTIVE CONVERSION OF DIALKYL $[^{18}O]$-PHOSPHORANILIDATES INTO DIALKYL HYDROGEN $[^{18}O]$-PHOSPHATES

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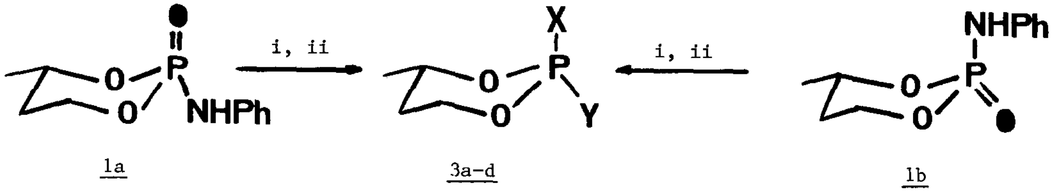
Abstract: Conversion of P-chiral dialkyl phosphoranilidates into corresponding dialkyl hydrogen phosphates by means of isoamyl nitrite proceeds with retention of configuration at phosphorus.

Reaction of dialkyl phosphoranilidates with nitrosyl chloride leading to dialkyl hydrogen phosphates, which was originally described by Bunyan and Cadogan [1], was modified and successfully adopted by Ikehara, et al. for oligonucleotide synthesis [2]. Similarly, treatment of nucleotides having phosphoranilidate function with either isoamyl nitrite [3] in pyridine -acetic acid [4] or nitrosyl chloride-sodium azide-acetic acid [5] leads in the satisfactory yield to the expected hydrogen phosphates. In view of our continuing interest on the use of phosphoranilidates as stereogenic intermediates in the stereospecific synthesis of phosphorothioates, phosphoroselenoates, and $[^{18}O]$-phosphates [6], we have studied the stereochemistry of PN → PO conversion by means of isoamyl nitrite in acetic acid-methanol medium.

As model compounds we chose the *trans* (1a, $\delta_{^{31}P}$ -1.0 ppm) and *cis* (1b, $\delta_{^{31}P}$ -4.5 ppm, $CHCl_3$) isomers of 2-phenylamino-2-$[^{18}O]$-oxo-4-methyl-1,3,2-dioxaphosphorinane, which were synthesized starting from the mixture of *cis*- and *trans*-2-hydrogen-2-$[^{18}O]$-oxo-4-methyl-1,3,2-dioxaphosphorinane, under Atherton-Todd reaction conditions [7]. The mixture of isomeric phosphoranilidates 1a and 1b was separated by column chromatography. The methanolic solution of 1a containing 15% (by weight) of acetic acid was treated with isoamyl nitrite (30-fold molar excess) for 5 hours at room temperature. The sample was subsequently concentrated, dissolved in water, and then washed twice with ethyl ether. The aqueous layer was evaporated to dryness under reduced pressure. The resulting 2-hydroxy-2-$[^{18}O]$-oxo-4-methyl-1,3,2-dioxaphosphorinane (2a) was quantitatively esterified with an ethereal solution of phenyldiazomethane. The diastereomeric benzyl esters 3a and 3b were then separated by means of preparative TLC [8]. Exactly the same procedure was repeated using the *cis*-isomer (1b), which gave the another pair of benzyl esters 3c and 3d. The position of the oxygen label in the isolated triesters 3a-d was determined by mass spectrometry (see Table) as described in our earlier report [9].

Scheme



● = ^{18}O

i - isoamyl nitrite in $MeOH/CH_3COOH$, ii - $PhCHN_2$ in Et_2O/THF

Table

Substrate	Tri-ester	^{18}O-Enrichment of 3 [a] (%)	Relative intensities		Stereoretention (%)	Substituents	
			$M-PhCH^{16}O$ m/z 138	$M-PhCH^{18}O$ m/z 136		X	Y
1a	3a	57.5	4.2	95.8	92.1	●CH_2Ph	O
	3b	57.5	57.2	42.8	99.5	●	OCH_2Ph
1b	3c	52.6	50.2	49.8	95.3	OCH_2Ph	●
	3d	52.6	0.8	99.2	98.5	O	●CH_2Ph

[a] *The ^{18}O-enrichment (measured on molecular ions m/z 244 and m/z 242) was exactly the same as in related starting phosphoranilidates 1*

An inspection of the Table reveals that *degradation of dialkyl phosphoranilidates with isoamyl nitrite proceeds with retention of configuration at phosphorus* and the stereoselectivity is not lower than 95±3%. The high stereoselectivity, mild reaction conditions and satisfactory yield of final dialkyl $[^{18}O]$-phosphate offer an attractive alternative to our former approach [6] to nucleoside 3'- or 5'-O-aryl $[^{18}O]$- or $[^{17}O]$-phosphates, since O-aryl N-phenyl $[^{18}O]$- or $[^{17}O]$-phosphoramidochloridates are easily available [10].

References and Notes

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(Received in UK 15 May 1985)