Tetrahedron Letters, Vol.31, No.31, pp 4443-4444, 1990
Printed in Great Britain

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

EVIDENCE OF THE LOSS OF CHIRALITY AT THE PHOSPHONIUM STEP IN THE ARBUZOV REARRANGEMENT .

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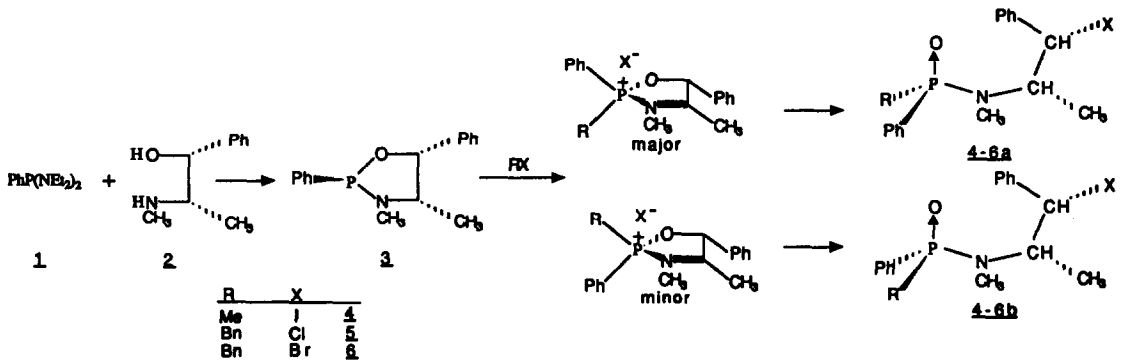
Abstract : Reaction of the diastereomerically pure oxazaphospholidine 3 with alkyl halides was monitored by ^{1}H, ^{13}C,^{31}P NMR and clearly showed the formation of two phosphonium intermediates with the same diastereomeric ratio as that of the final products. Benzyl halides reacted with 3 yielding a mixture of the two epimers a and b which syncrystallized into a rare addition compound.

A stereoselective transformation of chiral oxazaphospholidine into phosphinates and tertiary phosphine oxides has been previously described[1].The approach relies on the stereochemistry of the Michaelis Arbuzov (M.A.) rearrangement of an oxazaphospholidine 3 derived from (-)- ephedrine. It is known that the first step of the M.A. rearrangement, which involves phosphonium and/or phosphorane intermediates, usually proceeds with a predominant retention of configuration at the P centre[2]. To explain the loss of chirality in the M.A. rearrangement of a chiral dioxaphosphacycloheptane, Suga and coll.[2h] recently suggested a mechanism involving an equilibrium at the phosphonium stage.

A few years ago, we described[3] epimeric phosphoranes obtained from an *o*-hydroxybenzyl bromide in the M.A. conditions. We wish to report here the experimental proof of the loss of chirality of the phosphonium salt intermediate, formed in the reaction of the oxazaphospholidine 3 with other alkyl halides.



Scheme 1

The reaction of the optically pure oxazaphospholidine 3[1] with methyl iodide in C_6D_6 at 25°C, rapidly gave a turbid solution which was cleared by adding $CDCl_3$. After 20 mn, the ^{31}P NMR analysis[4] showed two signals at + 84.2 and +86.9 ppm corresponding to the formation of phosphonium species in a 80:20 ratio[5]. No NMR signals appeared in the P_V phosphorane region below +20 ppm. The multiplicity of the two signals, the coupling constant ($^{2}J_{PH}$=13 Hz) and the ^{13}C NMR signals in the 13-16 ppm region, are in agreement with the formation of a CH_3P^+ group . After 48 hrs, the ^{31}P NMR analysis revealed the formation of the phosphinamides 4a,b displaying two signals at +37.1 and +37.0 ppm, in a 85:15 ratio . Thus , the epimeric ratio of the end product 4 is the same as that of the phosphonium intermediate . Therefore, the loss of chirality had not occured during the second step of the rearrangement. Under similar conditions, benzyl chloride reacted with 3 to yield after 12 hrs, the phosphonium chloride intermediates ($\delta^{31}P$= +81.3, +82.0 ppm) in a 80:20 ratio . After several days , the corresponding phosphinamides 5a,b were obtained in the same epimeric ratio. At -40°C, benzyl bromide gave the analogous phosphonium bromide intermediates ($\delta^{31}P$= +81.1

and +81.9 ppm), and then the phosphinamides 6a,b in a 60:40 epimeric ratio. Interestingly, the phosphinamides 5 and 6 syncrystallized each into a 1:1 mixture of the two epimers a and b, which constitutes new examples of rare addition compounds[6]. Nevertheless, the major isomer 5a could be isolated from the mother liquor after several crystallizations of the diastereomeric mixture. The physical characteristics of the addition compounds 5a,b and 6a,b are reported in Table 1[4].

compounds	mp°C	^{31}P NMR	^{1}H NMR					J(Hz)		
		ppm	CH_3	NCH_3	PCH_2	H	H_β	PH	H H_β	$PNCH_3$
4a	154	+36.3	1.01	2.47	3.58	4.13	4.91	2	10	10
5a + 5b	175	+36.4-36.2	0.58	2.62	3.58	4.13	4.74	2	10	9
6a + 6b	180	+34.1-33.8	1.05	2.48	3.62	4.35	4.99	2	11	11
			0.62	2.60	3.62	4.13	4.83	2	10	9

Table 1

The loss of chirality observed is mainly due to the steric factor of the ring substituents, unfavorable to the electrophilic attack on the hindered side of the P^{III} compound. In the transition state or at the phosphonium stage, a permutation of the R and the phenyl groups can occur, facilitated by the geometry of the oxazaphospholidine ring with OPN and CPN angles of nearly 90° and 120° respectively[7], similar to the angular distribution of a P^{V} compound. Moreover, the flexibility of the ring[8] plays an evident role in the stereochemistry, as in the case of the rigid bicyclic oxazaphospholidine derived from prolinol[9], complete retention at the phosphorus atom was noted with benzyl halides[10]. At last, the influence of the nature of the halide observed on the diastereoisomeric ratio of the phosphonium, disproves the importance of the lifetime of this intermediate in the loss of chirality of the M.A. rearrangement previously suggested[2h].

In conclusion, we have provided here the experimental proof of the loss of chirality at the phosphonium step of the M.A. rearrangement. Although an extension of this mechanism to acyclic oxyphosphorus compounds is premature, these results clarify the factors that govern the stereochemistry of this important P C bond formation reaction.These factors are summarized by:

-the nature of the electrophilic reagent and its leaving group
-the nature of the organophosphorus compound (acyclic,cyclic, dioxa, oxazaphosphorane ...)
-the nature of the substituents on the phosphorus atom and of the carbon chain in the case of cyclic compounds
-the flexibility of the ring in the case of cyclic phosphorus compounds
-the conditions of the reaction (solvent, temperature...)

Acknowledgments : We wish to thank Dr.F.Acher for helpful discussions and the ELF Aquitaine company for financial support.

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(Received in France 24 February 1990)