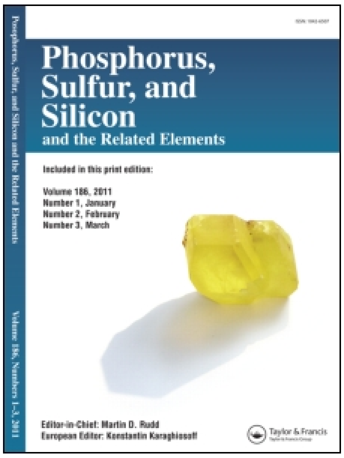


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

HYDROBORATION OF UNSATURATED AMINES X. HYDROBORATION-HALOGENATION OF ALLYL PHOSPHORAMIDATES ROUTE TO γ-HALOGENOPROPYL PHOSPHORAMIDATES AND γ-HALOGENATED AMINES

Z. Benmaarouf-khallaayoun[ab]; M. Baboulene[a]; V. Speziale[a]; Lattes[a]
[a] Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique, UA (CNRS) 470, Université Paul Sabatier, Toulouse Cedex, France [b] Laboratoire de Chimie Organique. Faculté des Sciences d'Agadir, Maroc

To cite this Article Benmaarouf-khallaayoun, Z. , Baboulene, M. , Speziale, V. and Lattes(1988) 'HYDROBORATION OF UNSATURATED AMINES X. HYDROBORATION-HALOGENATION OF ALLYL PHOSPHORAMIDATES ROUTE TO γ-HALOGENOPROPYL PHOSPHORAMIDATES AND γ-HALOGENATED AMINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 36: 3, 181 — 187

To link to this Article: DOI: 10.1080/03086648808079015

URL: http://dx.doi.org/10.1080/03086648808079015

Phosphorus and Sulfur, 1988, Vol. 36, pp. 181–187
Reprints available directly from the publisher
Photocopying permitted by license only

HYDROBORATION OF UNSATURATED AMINES X. HYDROBORATION–HALOGENATION OF ALLYL PHOSPHORAMIDATES ROUTE TO γ-HALOGENOPROPYL PHOSPHORAMIDATES AND γ-HALOGENATED AMINES

Z. BENMAAROUF-KHALLAAYOUN,†, M. BABOULENE,‡
V. SPEZIALE and LATTES

Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique, UA (CNRS) 470, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex France

(Received September 22, 1987; in final form October 30, 1987)

This paper describes the synthesis of γ-halogenopropyl phosphoramidates I by hydroboration–halogenation reaction of N-phosphorylated allylamines II (phosphoramidates and phosphoramides). Only the use of allyl phosphoramidates leads to a good regioselectivity of the addition of boron atom on the terminal carbon atom of the allyl structure (compounds III).

The absence of N→B complex formation permits a good reactivity of the trialkylboranes III and IV. The breaking of the P—N bond, in acidic medium of the compounds I gives corresponding γ-halogenated amines V.

INTRODUCTION

Phosphorylation of the amino nitrogen atom is of interest since:

– it can protect the amino function from reactions directed at other parts of the molecule,

– it can be used to substitute the nitrogen atom conveniently and selectively,

– it provides a route to secondary amines after removal of the phosphorylated protective group.

Both individually and in combination these advantages have been exploited in various synthetic methods. In the course of a general investigation of the hydroboration of unsaturated amines we used such a method in a new synthetic route to γ-halogenopropyl phosphoramidates I of general formula:

$(R^1)_2P(O)N(R^2)(CH_2)_3X$

I

R^1 – alkoxy
R^2 – alkyl, aryl
X – Br, I

The presence of a highly mobile halogen has considerable synthetic value. In addition the structural similarity with various compounds of pharmacological

---

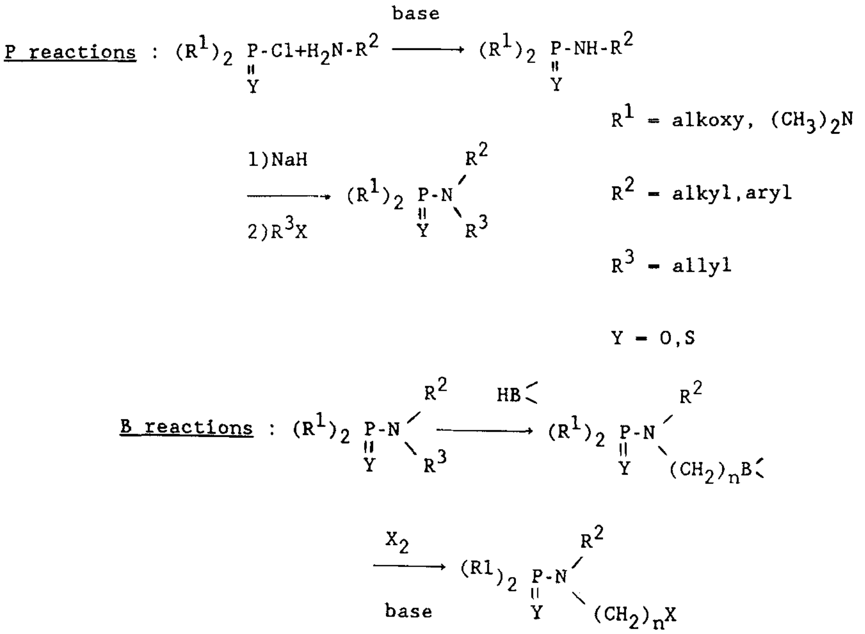
† Present address: Laboratoire de Chimie Organique. Faculté des Sciences d'Agadir (Maroc).

‡ Reprint requests.

importance[1] has led to widespread interest in these compounds.[2] Previous studies have been based on a synthetic route to the γ-halogenopropyl phosphoramidates I by condensation of a γ-halogenated amine with a dialkylchlorophosphate.

$$(R^1)_2P(O)Cl + HN(R^2)(CH_2)_3X \xrightarrow[\text{solvent}]{\text{base}} (R^1)_2P(O)N(R^2)(CH_2)_3X$$

Although dialkylchorophosphates are readily obtainable, the γ-halogenated amines are more difficult to produce. They are generally formed either by direct halogenation of the corresponding amino alcohols,[3] whose synthesis is sometimes difficult, or by a classical or modified Gabriel method from dihalogenoalkanes.[4] Various difficulties are encountered with these methods, and we therefore wanted to develop a general route to γ-halogenopropyl phosphoramidates by using a combination of reactive phosphorus and boron groups according to the following scheme:



The phosphorylated compounds provide a route to all required N-phosphorylated allyl amines, while the hydroboration reaction forms the carbon halogen bond.

DISCUSSION OF THE RESULTS

Organophosphorus reactions

Apart from its protective action on the amino group the phosphorylated derivatives, starting from a primary amine, can produce a whole series of N-phosphorylated allyl amines. Depending on the nature of the substituents R^1

and R^2, one can use an allyl amine followed by an alkyl–halide. This method, which has been described in other publications[5,6,7] has considerable synthetic scope. We are able to synthesize a whole series of N-phosphorylated allyl amines II in high yields.[8]

Unsuccessful results were obtained, however, when this process was investigated with secondary alkyl bromides or chlorides.[9] The compounds of type $(R^1)_2P(Y)N(R^2)CH_2—C(R^3) = CH—R^4(R^4 \neq H)$ are not used because the addition of the boron atom, in according literature, is not regioselective (steric hindrance effect)

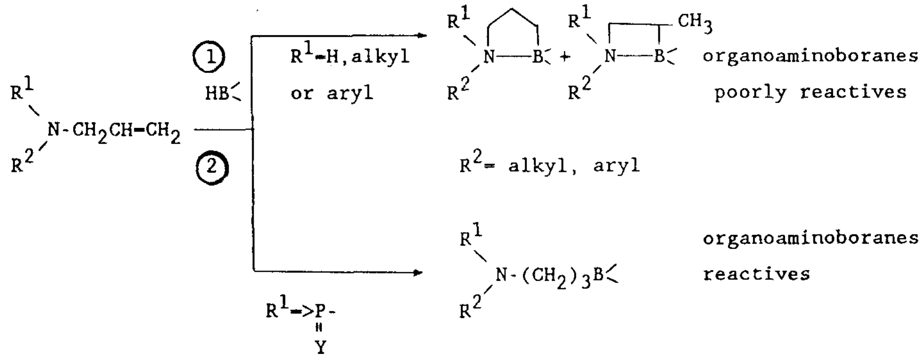
$$(R^1)_2P(Y)N(R^2)CH_2C(R^3)=CH_2$$

II

$R^1=C_2H_5O,\ (CH_3)_2N$
$R^2=CH_3, C_6H_5CH_2, C_6H_5, C_6H_{11}$
$R^3=H, CH_3$
$Y=O, S$

Organoboron reactions

We recently developed a method for the hydroboration of unsatured amines.[10] By protecting the amino group from attack of the boron derivatives, we were able to produce organoaminoboranes with equivalent reactivity to non-aminated organoboranes (way 2).[11]



Amongst the many methods used for the introduction of functional groups, the technique developed by Brown using organoboranes has widespread application. This is particularly the case for halogenation of a hydrocarbon chain. The reactivity of organoboranes to halogens can be used to produce alkylhalides with ease.[12]

The N-phosphorylated allyl amines II when reacted with borane dimethyl sulfide complex (BMS) at ambient temperature for 3 h lead to the corresponding trialkylboranes III which can be isolated as oils which decompose on distillation.

$$\underset{\text{II}}{(R^1)_2P(Y)N(R^2)CH_2CH=CH_2} \xrightarrow[\text{THF, 3 h, 25°}]{\text{BMS}} [(R^1)_2P(Y)N(R^2)(CH_2)_3]_3B \text{ and/or } \underset{\text{IV}}{[(R^1)_2P(Y)N(R^2)CH_2CHCH_3]_3B}$$

R^1=alkoxy, $(CH_3)_2N$
R^2=alkyl, aryl
Y=O, S

The structures of these compounds are given by ^1H, ^{11}B, ^{31}P NMR spectroscopy (see Experimental). The absence of the multiplet of the HC=CH (5.30 ppm) and the presence of the multiplet of the CH_2B group (0.80 ppm) confirmed the hydroborated compounds. The chemical shifts of the B and of the P atoms are according with these structures.

Sometimes two trialkylboranes are obtained due to the addition on either side of the double bond. The ^1H NMR spectra showed then the presence of a doublet at 0.85 ppm characteristic of the methyl group in a position of the boron atom ($-CH(CH_3)-B$) in according β addition in the hydroboration reaction. We therefore investigated various phosphorylated derivatives to obtain a good regioselectivity. Only the phosphoramidates $(C_2H_5O)_2P(Y)-N$ were found to add selectively to the terminal carbon atom (γ addition). Given the strongly nucleophilic nature of sulfur in the thiophosphorylated group (P=S)[13] and the nature of its reactivity[14] we decided not to employ—least not in the present set of experiments—the alkyl thiophosphoramidates $(C_2H_5O)_2P(S)-N\!<$. We therefore used the trialkylboranes derivatives of the allyl phosphoramidates $(C_2H_5O)_2P(O)-N\!<$ for the halogenation reaction. From the study of previous work[15] we tried various reaction conditions using different bases in both aqueous and organic media in order to optimize the reaction (Table I).

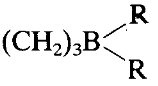
TABLE I
Halogenation of trialkylboranes III

Trialkylboranes III	Base / Solvent		Reaction time(h)	t°	X	yield % γ -halogenopropyl-phosphoramidate I *	
$[(C_2H_5O)_2P(O)\underset{CH_3}{N}-(CH_2)_3]_3B$ 1	NaOH	MeOH	0.5	25	I_2	1a	85
		H20	4	25	I_2		0
		H_2O	4	25	Br_2		47
	AcONa	MeOH	0.5	0	Br_2		73
	MeONa	MeOH	0.5	0	Br_2	1b	85
$[(C_2H_5O)_2P(O)\underset{C_6H_{11}}{N}-(CH_2)_3]_3B$ 2	NaOH	MeOH	0.5	25	I_2	2a	55
	MeONa	MeOH	0.5	0	Br_2	2b	70
$[(C_2H_5O)_2P(O)\underset{CH_2C_6H_5}{N}-(CH_2)_3]_3B$ 3	NaOH	MeOH	0.5	25	I_2	3a	75
	MeONa	MeOH	0.5	0	Br_2	3b	80
$[(C_2H_5O)_2P(O)\underset{C_6H_5}{N}-(CH_2)_3]_3B$ 4	NaOH	MeOH	1	25	I_2	4a	55
	MeONa	MeOH	1	0	Br_2	4b	60
$[(C_2H_5O)_2P(O)\underset{C_6H_{11}}{N}-CH_2CH(CH_3)CH_2]_3B$ 5	NaOH	MeOH	1	25	I_2	5a	45
	MeONa	MeOH	1	0	Br_2	5b	50
$[(C_2H_5O)_2P(O)\underset{CH_2C_6H_5}{N}-CH_2CH(CH_3)CH_2]_3B$ 6	NaOH	MeOH	0.5	25	I_2	6a	70
	MeONa	MeOH	0.5	0	Br_2	6b	60

* The compounds were purified by distillation or recristallization and the structures confirmed by ^1H, ^{31}P NMR, IR and mass spectrometry (see Experimental).

By judicious choice of base and solvent we could obtain the γ-halogenopropylphosphoramidates I in excellent yields. The value of a base to eliminate the boron group was quite clear. The yields were found to increase with increasing base strength, as has been found by other workers.[16] The results also confirmed previous work from this laboratory[11] which showed that the reactivity of organoaminoboranes is dependent on the strength of the N—B linkage.

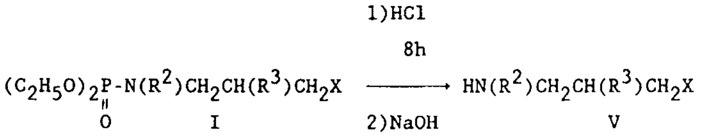
Use of the mixed trialkyboranes of the type $(C_2H_5O)_2P(O)N(CH_3)\cdot$



$(CH_2)_3B\begin{smallmatrix}R\\R\end{smallmatrix}$ (R = cyclohexyl, BBN thexyl) leads to mixtures with the R groups tending to be halogenated in preference to the single phosphoramidate group.

Formation of the γ-halogenated amines V

The conditions for breaking the P—N bond in acidic medium have been described in several studies,[17,18] and we based our hydrolysis of the γ-halogenopropyl phosphoramidates on these results. Distillation of the extracted oil produced the expected γ-halogenated secondary amines V:



$$\underset{\text{I}}{(C_2H_5O)_2\overset{}{\underset{\underset{O}{\|}}{P}}\text{-}N(R^2)CH_2CH(R^3)CH_2X} \xrightarrow[\text{2)NaOH}]{\text{1)HCl, 8h}} \underset{\text{V}}{HN(R^2)CH_2CH(R^3)CH_2X}$$

R^2=CH_3, $C_6H_5CH_2$, C_6H_{11}, C_6H_5
R^3=H, CH_3
X =I, Br

The structures were confirmed by NMR, IR and mass spectrometry (see examples in Experimental).

CONCLUSION

A new general route to γ-halogenopropyl phosphoramidates and γ-halogenopropyl amines from simple starting materials has been developed using a combination of reactions involving organophosphorus and organoboron derivatives. Hydroboration of unsaturated amines is of synthetic interest, as well as potential application for the synthesis of compounds (analogs of cyclophosphamide drugs) of pharmacological importance (chemotherapeutic agents).[1]

EXPERIMENTAL

IR spectra were recorded on films using a Perkin–Elmer 683 spectrograph. The ^{11}B and ^{31}P NMR spectra were recorded using a Brucker WH 90 apparatus, and the ^1H NMR spectra were recorded with a Varian 160. The purity of the compounds I and V was checked by vapor phase chromatography on an Intersmat IGC 120FL apparatus fitted with a 1% OV1 analytical column (2 m long). Mass spectra were obtained on a Varian Mat 311A.

Synthesis of N-phosphorylated allyl amines II. This has been described in a previous publication (7).

Synthesis of phosphorylated trialkylboranes III. 11 mM of the "borane dimethyl sulfide complex" is added to 30 mM N-phosphorylated allyl amine dissolved in 20 ml THF, under a stream of nitrogen. The reaction mixture is shaken at ambient temperature for 3 h. After evaporation of solvents the organoaminoborane is recovered quantitatively as a non-distillable viscous oil. The purity was adequate for the next steps. IR spectra of all these compounds are characterized by the absence of the C═C band, (see Table II).

TABLE II

Characteristic N.M.R. spectroscopy data

Products III	^1H N.M.R. $CDCl_3$; TMS ; δ ppm	^{31}P N.M.R. $CDCl_3$; 85 % H_3PO_4 δ ppm	^{11}B N.M.R. $CDCl_3$; $BF_3O(CH_3)_2$; δ ppm
$[(C_2H_5O)_2P(O)\underset{CH_3}{N}(CH_2)_3]_3B$ 1	0.85(m,2H,CH_2B);1.43(t,6H,CH_3) 1.56(m,2H,CH_2);2.65(d,3H,NCH_3) 3.00(m,2H,CH_2N);4.00(qt,4H,CH_2O)	10.3	3.1
$[(C_2H_5O)_2P(O)\underset{C_6H_{11}}{N}-(CH_2)_3]_3B$ 2	0.85(m,2H,CH_2B);1.36(t,6H,CH_3) 1.58(m,12H,CH_2);3.12(m,3H,CH_2N et CH-N); 4.00 (qt,4H,CH_2O)	9.9	2.8
$[(C_2H_5O)_2P(O)\underset{CH_2C_6H_5}{N}(CH_2)_3]_3B$ 3	0.85(m,2H,CH_2B); 1.32(t,6H,CH_3) 1.60(m,2H,CH_2);2.85(m,2H,CH_2N) 4.08(qt,4H,CH_2O);4.20(d,2H,CH_2Ar) 7.35(m,5H,Ar)	10.2	2.8
$[(C_2H_5O)_2P(O)\underset{C_6H_5}{N}-(CH_2)_3]_3B$ 4	0.83(m,2H,CH_2B);1.38(t,6H,CH_3); 1.55(m,2H,CH_2);2.85(m,2H,CH_2N) 3.98(qt,4H,CH_2O);7.32(m,5H,Ar)	10.5	2.9
$[(C_2H_5O)_2P(O)\underset{C_6H_{11}}{N}-(CH_2CH(CH_3)CH_2]_3B$ 5	0,80(m,2H,CH_2B);1,45(m,9H,CH_3) 1,61(m,11H,CH_2 et CH);2,86(m,3H) CH_2N et CH-N);4,00 (qt,4H,CH_2O)	10	3.1
$[(C_2H_5O)_2P(O)\underset{CH_2C_6H_5}{N}-CH_2CH(CH_3)CH_2]_3B$ 6	0.89(m,2H,CH_2B);1.38(m,9H,CH_3); 1.65(m,1H,CH);2.92(m,2H,CH_2N) 4.05(qt,4H,CH_2O);4.18(d,2H,CH_2) 7.25(m,5H,Ar)	10.2	2.8
$[(C_2H_5O)_2P(S)\underset{CH_3}{N}-(CH_2)_3]_3B$ 7	0.89(m,2H,CH_2B);1.30(t,6H,CH_3) 1.68(m,2H,CH_2);2.72(d,3H,N-CH_3) 3.10(m,2H,CH_2N);4.00(qt,4H,CH_2O)	76.3	2.2
$[(C_2H_5O)_2P(S)\underset{CH_2C_6H_5}{N}-(CH_2)_3]_3B$ 8	0.80(m,2H,CH_2B);1.35(t,6H,CH_3) 1.72(m,2H,CH_2);3.00(m,2H,CH_2N) 4.08(qt,4H,CH_2O);4.40(d,2H,CH_2Ar) 7.38(m,5H,Ar)	76.2	1.9

Synthesis of γ-halogenopropyl phosphoramidates I

(a) Iodinated derivatives

20 mM sodium hydroxide in 10 ml methanol are added to 10 mM of the trialkyl–borane in 10 ml of anhydrous THF. 20 mM of iodine in 10 ml methanol is then added dropwise. The reaction mixture is shaken at ambient temperature for 30 min. After extraction the organic phases are dried over anhydrous sodium sulfate. Evaporation under vacuum leaves a distillable oil or recristallisable solid. (see Table III).

(b) Brominated derivatives

The best yields were obtained using sodium methoxide and only this procedure is described below.

20 mM of bromine in 5 ml anhydrous THF are added dropwise to 15 mM trialkylborane in 10 ml anhydrous THF at around −10°. The mixture is left shaking for about 15 min. 6 ml of a methanolic solution of sodium methoxide (4.16 M) is added, keeping the temperature below 5°C. After a slow rise to ambient temperature, the reaction mixture is left for a further 30 min. The mixture is then poured into water and extracted with dichloromethane. The extract is dried over anhydrous sodium sulfate and the solvents are evaporated under vacuum. The oil that remains is purified by distillation or recristallization. (see Table III).

Synthesis of γ-halogenopropylamines V. 200 ml of 2N HCl is added to 18 mM of γ-halogenopropyl phosphoramidate under nitrogen. The reaction mixture is refluxed for 8 h and left to cool to ambient temperature. The pH is adjusted to around 12 with sodium hydroxide solution, and then extracted with chloroform. The organic phases are dried over anhydrous sodium sulfate and evaporated under vacuum. The residual oil is distilled.

N-benzyl N-(iodo-3 propyl)amine: $NH(CH_2C_6H_5)CH_2CH_2CH_2I$ (Va) Yield: 4.43 g (90%); bp/0.02 64°C. IR: $\nu(cm^{-1})$: 3260 (N—H): absence of P=O and P—O—C ^1H NMR ($CDCl_3$) δ ppm (TMS); 1.55 (s, 1H NH); 1.80 (m, 2H, C—CH_2—C); 2. 70 (t, 2H, N—CH_2); 3.42 (t, 2H, CH_2I); 3.75 (s, 2H, CH_2Ar); 7.28 (m, 5H, Ar). $C_{10}H_{14}IN$: 275.02 (M/S $M^+ = 275$).

N-methyl N-(bromo-3 propyl)amine: $NH(CH_3)CH_2CH_2CH_2Br$ (Vb) Yield: 2.45 g (90%); bp/0.02 59°C IR: $\nu(cm^{-1})$: 3300 (N—H): absence of P=O and P—O—C ^1H NMR ($CDCl_3$) δ ppm (TMS); 1.92 (m, 2H, CH_2); 2.23 (s, 1H, NH); 2.43 (s, 3H, CH_3); 2.75 (t, 2H—CH_2); 3.60 (t, 2H, CH_2Br). $C_4H_{10}BrN$: 151.99 (M/S $M^+ + 1 = 151$).

TABLE III

Characteristic N.M.R. spectroscopy data and physical constants

Product I	Molecular Formula [a] and M/S (M+) [b] (calcd)	^1H NMR ($CDCl_3$/TMS ; δ ppm)	b.p.(°C/torr) or m.p(°C)
1a	$C_8H_{19}INO_3P$ 335.12(335)	1.35(t,6H);2.15(m,2H);2.68(d,3H) 3.12(m,2H);3.20(t,2H);4.02(qt,4H)	100/0.05
1b	$C_8H_{19}BrNO_3P$ 288,13(288)	1,35(t,6H);2.12(m,2H);2.70(d,3H) 3.20(td,2H);3.45(m,2H);4.10(qt,4H)	87/0.05
2a	$C_{13}H_{27}INO_3P$ 403,24(403)	1,32(t,6H);1.58(m,12H);3.18(m,3H) 3,35(t,2H);4.05(qt,4H)	95
2b	$C_{13}H_{27}BrNO_3P$ 356,25(356)	1,35(t,6H);1.60(m,12H);3.20(m,3H) 3.42(t,2H);4.05(qt,4H)	105
3a	$C_{14}H_{23}INO_3P$ 411,22(411)	1,35(t,6H);1.95(m,2H);3.0(m,2H) 3.08(t,2H);4.20(m,6H);7.40(m,5H)	94/0.02
3b	$C_{14}H_{23}BrNO_3P$ 364,22(364)	1.30(t,6H),1.55(m,2H);3.16(m,2H) 3,58(t,2H);4.10(m,6H);7.28(m,5H)	127/0.03
4a	$C_{13}H_{21}INO_3P$ 397,19(397)	1,32(t,6H);2.07(m,2H);3.15(td,2H) 3.45(t,2H);4.06(qt,4H);7.08(m,5H)	105/0.1 decomposes
4b	$C_{13}H_{21}BrNO_3P$ 350,20(350)	1,35(t,6H);2.07(m,2H);3.20(td,2H) 3.42(t,2H);4.05(qt,4H);7.05(m,5H)	100/0.05 decomposes
5a	$C_{14}H_{29}INO_3P$ 417,27(417)	1,05(d,3H);1.38(t,6H);1.58(m,10H) 3,15(m,4H);3.52(m,2H);4.10(qt,4H)	115
5b	$C_{14}H_{29}BrNO_3P$ 370,27(370)	1.05(d,3H);1.35(t,6H);1.48(m,10H) 3,18(m,3H);3.58(m,2H);4.05(qt,4H)	132
6a	$C_{15}H_{25}INO_3P$ 425,25(425)	1.05(d,3H);1.35(t,6H);3.10(m,3H) 3.55(m,2H);4.10(m,6H),7.32(m,5H)	113/0.02
6b	$C_{15}H_{25}BrNO_3P$ 378,25(378)	1.08(d,3H);1.35(t,6H);3.10(m,3H) 3.48(m,2H);4.08(m,6H);7.35(m,5H)	158

a) All products gave correct elemental analyses : C∓0.35 ; H∓0.18 ; N∓0.29 ; P∓0.31 ; X∓0.21
b) The value given for the bromo compounds is $M^+ + 1$

REFERENCES

1. J. A. Montgomery, T. P. Johnston and J. F. Shealy, in Burger's Medicinal Chemistry. Ed. Wolff M. E., 1979, part II, p. 595.
2. P. Savignac and J. Chenault, *Tetrahedron Letters,* 1557 (1971) and cited references.
3. F. Cortese, in organic Synthesis John Wiley and Sons, Inc. New York, 1946, collect II, p. 91.
4. S. Patai, The Chemistry of Amino Groups. Ed. Interscience publ., 1968.
5. P. Coutrot, M. Dreux, P. J. Savignac, Chem. Research 308 (1977) and cited references.
6. J. P. Paugam, Thèse 3ème cycle, Brest 1976.
7. Z. Benmaarouf-Khallaayoun, M. Baboulène, V. Spéziale and A. Lattes, *Synth. Comm.* **15**(3), 233 (1985).
8. Physicochemical characteristics of these compounds are given in ref. 7.
9. A. Zwierzak, *Synthesis,* 920 (1982).
10. J. L. Torregrosa, M. Baboulène, V. Spéziale and A. Lattes, *J. Organomet. Chem.,* **277,** 159 (1984) and cited references.
11. Z. Benmaarouf-Khallaayoun, M. Baboulène, V. Spéziale and A. Lattes, *J. Organomet. Chem.,* **289,** 309 (1985).
12. H. C. Brown, Organic Synthesis via Boranes. John Wiley and Sons, 1975.
13. A. J. Burn and J. I. G. Gadogan, *J. Chem. Soc.,* 5532 (1961).
14. P. Savignac, J. Chenault and P. Chabrier, *C.R. Acad. Sci. Paris,* **270**(25), 2086 (1970).
15. G. W. Kabalka, K. A. R. Sastry, H. C. Hsu and M. D. Hylarides, *J. Org. Chem.,* **46,** 3113 (1981) and cited references.
16. C. F. Lanes, *Intra. Sci. Chem. Rep.,* **7,** 133 (1973).
17. P. Savignac, M. Dreux and G. Ple, *J. Organomet. Chem.,* **60,** 103 (1973) and cited references.
18. M. Dreux, Thèse d'Etat Orléans, 1974, n° AO CNRS 9886.