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SYNTHESIS OF α-AMINOPHOSPHONIC ACIDS BY Pd(0) ALKYLATION OF DIETHYL AMINOMETHYLPHOSPHONATE SCHIFF BASES.

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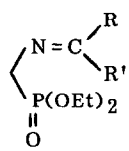
Abstract : γ, δ-Unsaturated α-amino phosphonic acids are obtained by alkylation of Schiff bases **2**, **3** in the presence of a palladium catalyst under neutral or basic conditions in THF or DME, using allylic carbonates, esters or halides (50-80 % yields).

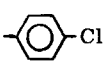
Aminoalkyl organophosphorus compounds have many interesting biological properties ; they are used as herbicides, insecticides, antibiotics and enzyme inhibitors.[1,2] Several approaches to the preparation of α-aminophosphonic acids have been reported.[1a,1b,2] One efficient method using the Schiff base of diethyl aminomethylphosphonate **1** has been developped, allowing alkylation at the α-carbon atom after deprotonation using strong bases such as lithium diisopropylamide (LDA).[3]

In our continuing program dealing with the synthesis of unusual α-aminoacids which relies on C-C bond formation by transition metal catalyzed reactions[4], we report here a method based on the palladium-promoted alkylation of diethyl aminomethylphosphonate Schiff bases **2** and **3** with η^3-allyl species **5** generated *in situ* from the allylic derivatives **4** (Scheme 1).

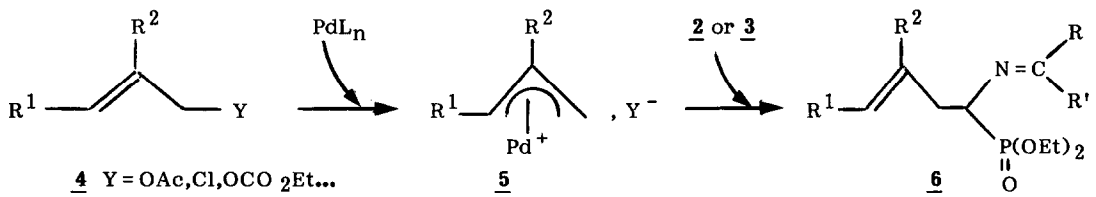
Scheme 1



1 R = H, R' = Ph

2 R = H, R' = 

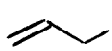
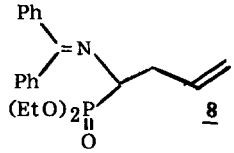
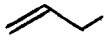
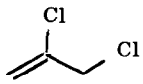
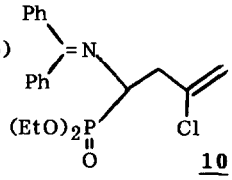
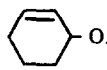
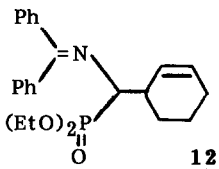
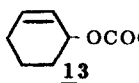
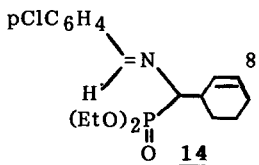
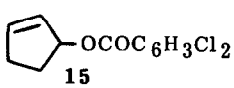
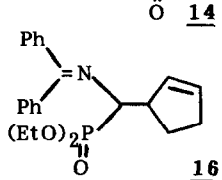
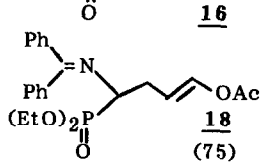
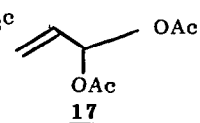
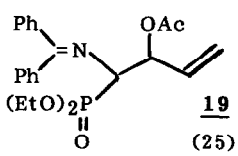
3 R = R' = Ph



4 Y = OAc, Cl, OCO$_2$Et... **5** **6**

The required Schiff bases **2**[5] and **3**[6] were prepared by treatment of diethyl aminomethylphosphonate hydrochloride[7] with p-chlorobenzaldehyde in the presence of triethylamine and with benzophenone imine,[8] respectively. These carbonucleophiles, as their lithium or sodium enolates, reacted with allylic esters in the presence of catalytic amounts of PdL_n ; in the palladium catalyzed alkylation of **2** and **3** the most efficient catalyst is the preformed $Pd(dppe)_2$ or this generated *in situ* from either $Pd(dba)_2$ or $Pd(OAc)_2$ by adding 2 equiv. of 1,2 bis(diphenylphosphino)ethane. The reaction works better in DME than in THF (entries 1,2). It is noteworthy that the ortho-paradichlorobenzoates under the same conditions are the most efficient electrophiles (compare entries 5 and 6). Thus, reaction of **2** and **3** with cycloalkenyl benzoates **13** and **15** gave the corresponding cyclohexenyl (**12** and **14**)[12] or cyclopentenyl (**16**) alkylated products in 78-80 % yields (entries 6,7,8). Schiff base **3** can be alkylated by allylic halides[9] (e.g. 2,3-dichloro-1-propene) at a low temperature (-60°C) in the presence of the palladium catalyst giving the derivative **10**[12] in 60 % yield ; under the same conditions but without catalysis, no reaction occured (compare entries 3,4). The geminal acetate **17** from acrolein, in the presence of Pd(0) catalyst, and BSA as base[10] gave a 75 : 25 mixture of the linear **18** and branched products **19** in refluxing THF (entry 9).

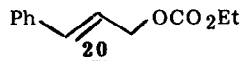
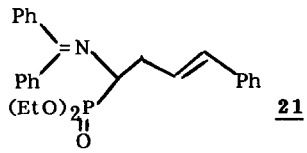
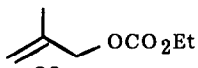
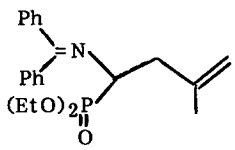
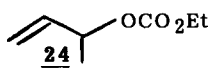
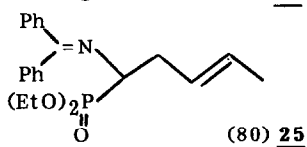
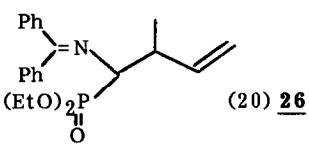
Table 1 : Palladium - catalyzed alkylation of Schiff bases 2, 3 under basic conditions.

Entry	Schiff* base	Allylic substrate	Conditions t(h)	T(°C)	Solvent	Catalyst % Ligand %	Product	Yield %
1	3[a]	 **7**	20	20	THF	$Pd(dba)_2$ (5) dppe (10)	 **8**	32
2	3[a]		10	-10	DME	"	"	70
3	3[b]	 **9**	5	-60	THF	$Pd(PPh_3)_4$ (5)	 **10**	60
4	3[b]	"	5	-60	THF	none		0
5	3[b]	 **11**	40	20	THF	$Pd(dba)_2$ (5) dppe (10)	 **12**	5
6	3[b]	 **13**	5	20	DME	$Pd(dppe)_2$ (5)	"	80
7	2[b]	"	5	20	DME	"	 **14**	80
8	3[b]	 **15**	5	20	DME	"	 **16**	78
							 **18** (75)	
9	3[c]	 **17**	10	60	THF	$Pd(dba)_2$ (5) dppe (10)	+  **19** (25)	50

* In the form of the corresponding enolate obtained by treatment of **2** or **3** with : (a) LDA ; (b) NaH ; (c) N,O - bis(trimethylsilyl)acetamide (BSA).

Interestingly, the ketimine Schiff base **3** reacted under neutral conditions with the allylic carbonates in the presence of catalytic amounts of Pd(0). This carbonucleophile appeared less reactive than its carboxylic analogue.[11] The reaction requires higher temperatures for a good conversion (70° - 80°C in DME) giving the corresponding alkylated Schiff bases **21**, **23**, **25**, **26** in 70 % yield as shown in table 2.

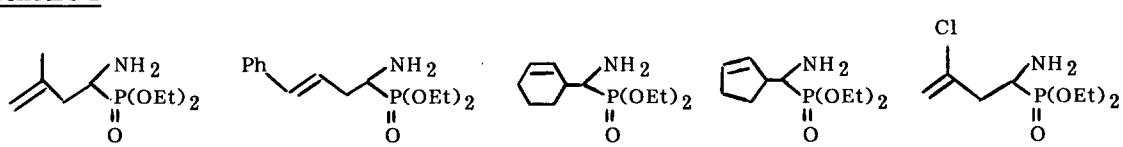
Table 2 : Palladium - catalyzed alkylation of Schiff base 3 under neutral conditions with allylic carbonates in DME (70° - 80°C).

Entry	Allylic carbonate	Catalyst % Ligand %	Product	Yield %
1	 **20**	$Pd(OAc)_2$ (5) dppe (10)	 **21**	70
2	 **22**	"	 **23**	70
3	 **24**	"	 (80) **25** +  (20) **26**	70

The alkylation of **3** with unsymmetrically substituted carbonates such as **20** and **24** showed a high tendency for alkylation at the less hindered allylic terminus. A mixture of the linear and branched products, **25** and **26** respectively, was obtained with the allylic carbonate **24** (entry 3). However the linear product **21** was obtained as the single product (entry 1) with cinnamyl carbonate **20**.

The α-alkylated products can be readily hydrolyzed (HCl, 4 equiv., 24 h, r.t.) into the corresponding α-alkylated α-aminophosphonic esters **27** - **31**[13] in 62 - 84 % yields and some illustrative examples are shown in scheme 2. For instance, we have prepared the phosphonic analogue **31** of the 2-chloroallyl glycine enzyme inhibitor of γ-cystathionase[14a] and the phosphonic analogue **28** of trans-2 amino-5 phenyl-4 pentenoic acid, which is an inhibitor of S-adenosyl transferase.[15]

Scheme 2[a]



27 (67 %) **28** (81 %) **29** (80 %) **30** (62 %) **31** (84 %)

[a] Yields are indicated in brackets. All the new compounds exhibited satisfactory spectroscopic and analytical data.[13]

In summary, this transition-metal catalyzed alkylation of diethyl aminomethylphosphonate Schiff bases provides an especially attractive approach for the synthesis of γ,δ-ethylenic α-aminophosphonic acids of biological interest.

References and notes

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2 - For some recent syntheses and leading references see : a) C. Yuan and Y. Qi, Synthesis, **1986**, 821 ; b) R. Huber and A. Vasella, Helv. Chim. Acta, **1987**, 70, 144 ; c) E. Elia Aboujaoude, N. Collignon, P. Savignac and J. Bensoam, Phosphorus and Sulfur, **1987**, 34, 93 ; d) U. Schöllkopf and R. Schütze, Ann. Chem., **1987**, 45.

3 - A. Dehnel and G. Lavielle, Bull. Soc. Chim. France, **1978**, II, 95.

4 - a) J.P. Genêt and D. Ferroud, Tetrahedron Lett., **1984**, 25, 3579 ; b) J.P. Genêt, D. Ferroud and R. Kiolle, Tetrahedron Lett., **1986**, 27, 23 ; c) J.P. Genêt, D. Ferroud, S. Jugé and J. Ruiz Montes, Tetrahedron Lett., **1986**, 27, 4573 ; d) J.P. Genêt, S. Jugé, S. Achi, S. Mallart, J. Ruiz Montes and G. Levif, Tetrahedron in press.

5 - **2** : IR : 2990, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 80 MHz) : 8.3 (d,J = 6 Hz, 1H) ; 7.9 - 7.3 (m, 4H) ; 4.2 (m, 4H) ; 4.1 (d,J = 18 Hz, 2H) ; 1.35 (t, J = 7 Hz, 6H).

6 - **3** : m.p. 60°C ; IR : 2990, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 80 MHz) : 7.8 - 7.2 (m, 10 H) ; 4.25 (m, 4H) ; 4 (d, J = 18 Hz, 2H) ; 1.35 (t, J = 7 Hz, 6H).

7 - Prepared according to : R.W. Ratcliffe and B.G. Christensen, Tetrahedron Lett., **1973**, 4645.

8 - These conditions have already been used for the synthesis of Schiff bases derived from aminoacids ; see : M.J. O'Donnell and R.L. Polt, J. Org. Chem., **1982**, 47, 2663.

9 - J.E. Bäckvall, Pure Appl. Chem., **1983**, 55, 1669 ; F.K. Sheffy and J.K. Stille, J. Am. Chem. Soc., **1983**, 105, 7173.

10 - For a use of this allylic geminal diacetate in the η^3 - allyl palladium alkylation see : B.M. Trost and J. Vercauteren, Tetrahedron Lett., **1985**, 26, 131 ; X. Lu and Y. Huang, ibid., **1986**, 27, 1615.

11 - For example the benzophenone imine of glycine methyl ester reacted at 0 - 25°C with allylic carbonates ; see : references 4c, 4d.

12 - **10** : I.R. : 3030, 2980, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 250 MHz) : 7.7 - 7.2 (m,10H) ; 5.15 (d,J = 6 Hz,2H) ; 4.3 - 4 (m,5H) ; 3.2 - 2.7 (m,2H) ; 1.35 (t, J = 7 Hz, 6H). **12** : ^1H - NMR ($CDCl_3$, 250 MHz) : 7.9 - 7.2 (m,10H) ; 5.9 - 5.6 (m,2H) ; 4.3 - 4 (m,4H) ; 3.8 (m,1H) ; 2.95 (m,1H) ; 2 - 1.4 (m,6H) ; 1.35 (t, J = 7 Hz, 6H). **14** : I.R. : 3030, 2980, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 80 MHz) : 8.3 (dxd, J = 5 Hz, J = 2 Hz,1H) ; 7.9 - 7.3 (m,4H) ; 5.8 (s,2H) ; 4.3 - 4 (m,4H) ; 3.6 (m,1H) ; 3 (m,1H) ; 2.2 - 1.5 (m,6H) ; 1.35 (t, J = 7 Hz, 6H). **16** : ^1H - NMR ($CDCl_3$, 80 MHz) : 7.7 - 7.2 (m,10H ; 5.9 - 5.5 (m,2H) ; 4.4 - 3.7 (m,5H) ; 3.5 (m,1H) ; 2.4 - 1.9 (m,4H) ; 1.35 (t, J = 7 Hz,6H).

13 - **27** : I.R. : 3450, 3080, 2990, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 80 MHz) : 4.9 (d, J = 6 Hz, 2H) ; 4.5 - 4 (m,4H) ; 3.4 - 3 (m,1H) ; 2.8 - 2 (m,2H) ; 1.8 (s,3H) ; 1.5 (s,2H,H_2N) ; 1.35 (t, J = 7 Hz,6H) ; **28** : I.R. : 3350, 3010, 1600, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 80 MHz) : 7.35 (s,5H) ; 6.7 - 6.2 (m,2H) ; 4.5 - 4 (m,4H) ; 3.4 - 2.2 (m,3H) ; 1.4 (s,2H, H_2N) ; 1.35 (t, J = 7 Hz, 6H). **29** : I.R. : 3400, 3000, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 250 MHz) : 5.85 (m,2H) ; 4.15 (m,4H) ; 3.2 - 2.8 (m,1H) ; 2.7 (m,1H) ; 2 (s,2H,H_2N) ; 1.9 - 1.5 (m,6H) ; 1.35 (t, J = 7 Hz, 6H). **30** : I.R. : 3400, 3060, 2990, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 80 MHz) : 6 - 5.6 (m,2H) ; 4.5 - 4 (m,4H) ; 3.4 - 2.9 (m,2H) ; 2.5 - 2 (m,4H) ; 1.5 (s,2H,H_2N) ; 1.35 (t, J = 7 Hz, 6H). **31** : I.R. : 3450, 3000, 1640, 1240, 1040 cm^{-1} ; ^1H - NMR ($CDCl_3$, 80 MHz) : 5.4 (s,2H) ; 4.5 - 4 (m,4H) ; 3.45 (m,1H) ; 2.85 - 2.3 (m,2H) ; 1.5 (s,2H,H_2N) ; 1.35 (t, J = 7 Hz, 6H).

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