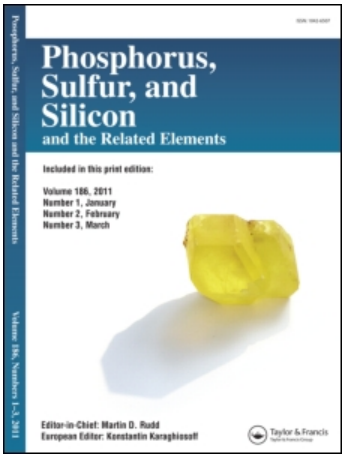


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A SIMPLE AND CONVENIENT SYNTHESIS OF 2-PHOSPHONOMETHYL PYRIDINES

Patrick Page[a]; Marie-Rose Mazières[a]; Jacques Bellan[ab]; Michel Sanchez[a]; Bruno Chaudret[c]
[a] Laboratoire Synthèse, Structure et Réactivité de Molécules Phosphorées (URA CNRS 454), Toulouse Cedex, France [b] Laboratoire de Chimie Pharmaceutique, Université Paul Sabatier, Toulouse Cedex, France [c] Laboratoire de Chimie de Coordination du CNRS Unité 824 liée par convention à l'Université Paul Sabatier et à l'Institut National Polytechnique de Toulouse, Toulouse Cedex, France

To cite this Article Page, Patrick , Mazières, Marie-Rose , Bellan, Jacques , Sanchez, Michel and Chaudret, Bruno(1992) 'A SIMPLE AND CONVENIENT SYNTHESIS OF 2-PHOSPHONOMETHYL PYRIDINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 70: 1, 205 — 210
To link to this Article: DOI: 10.1080/10426509208049168
URL: http://dx.doi.org/10.1080/10426509208049168

Phosphorus, Sulfur, and Silicon, 1992, Vol. 70, pp. 205–210
Reprints available directly from the publisher
Photocopying permitted by license only

A SIMPLE AND CONVENIENT SYNTHESIS OF 2-PHOSPHONOMETHYL PYRIDINES

PATRICK PAGE,[a] MARIE-ROSE MAZIÈRES,[a]† JACQUES BELLAN[a,b] and MICHEL SANCHEZ[a]

[a]*Laboratoire Synthèse, Structure et Réactivité de Molécules Phosphorées (URA CNRS 454);* [b]*Laboratoire de Chimie Pharmaceutique, Université Paul Sabatier, 118 Route de Narbonne 31062 Toulouse Cedex, France*

and

BRUNO CHAUDRET

Laboratoire de Chimie de Coordination du CNRS Unité 824 liée par convention à l'Université Paul Sabatier et à L'Institut National Polytechnique de Toulouse, 205 Route de Narbonne 31077 Toulouse Cedex, France

(Received April 15, 1992; in final form May 12, 1992)

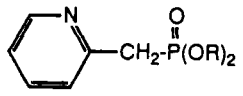
The Michaelis-Becker-Nylen reaction is well suited for the synthesis of 2-phosphonomethyl pyridines. We have improved this four steps method in a one pot reaction using commercial reagents. By this general procedure we have prepared seven new 2-phosphonomethyl pyridines (**Ia–g**) under mild conditions with higher yields.

Key words: 2-phosphono pyridines; 2-phosphonomethyl pyridines; Michaelis-Becker-Nylen reaction; new phosphonates; potential ligands.

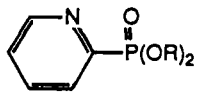
INTRODUCTION

The successful application of phosphonate containing compounds in biological field leaves no doubt about the scientific and industrial importance of these species. Thus they have medicinal value as antivirals,[1] antibiotics[2] and exhibit also herbicidal and insecticidal activities.[3]

In connection with our interest in synthesizing biologically active compounds containing phosphonate groups, we are investigating phosphonates bearing a pyridinic group such as compounds (**I**) and (**II**) with formula:



(**I**)



(**II**)

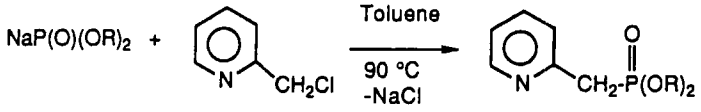
These derivatives can be considered as potential new ligands containing two different metal binding sites: pyridine nitrogen and phosphoryl (P=O) group. In this way we have used the $C_5H_4NP(O)(OEt)_2$ as ligands in the complexation with K_2RuCl_5.[4]

†To whom correspondence should be addressed.

This 2-phosphono pyridine (**II**) is obtained by an aromatic nucleophilic substitution (SRN[1] reaction) between the sodium anion of diethylphosphite and iodopyridine.[5] But this reaction is ineffective for the preparation of 2-phosphonomethyl pyridines and this paper describes synthetic routes for seven new 2-phosphonomethyl pyridines (**Ia–g**) from commercial reagents.

RESULTS AND DISCUSSION

The most appropriate procedure for the preparation of 2-phosphonomethyl pyridines (**I**) is the Michaelis-Becker-Nylen method[6] using as reagents the phosphonate anion **1** and the 2 chloromethyl pyridine **2** (Scheme [1]):

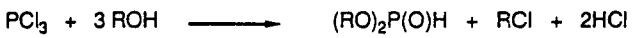
[1] 

1 **2** **(I)**

We have investigated two methods for the preparation of phosphonates (**I**): the first is a multisteps procedure and the second is a one pot synthesis.

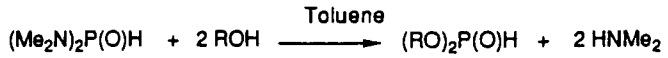
1. Multisteps synthesis

This method necessitates the preliminary synthesis of the starting materials **1** and **2**. The phosphonate anions **1** are obtained in situ by reaction of sodium hydride with phosphonates **3** $(RO)_2P(O)H$. The main types of synthesis of **3** are published in the literature[7]; it's generally an esterification of phosphorus trichloride [2]:

[2] 

3

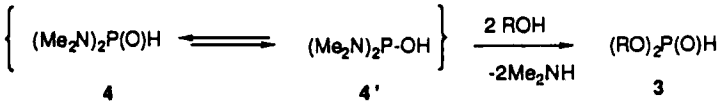
We now describe an easy and efficient synthesis of the compounds **3**: it involves the alcoholysis of the bis(dimethylamino) phosphonate **4**:

[3] 

4 **3a-3g**

This method [3] is applicable to different hydroxy compounds: alcohols, phenols, diols and aminoalcohols. The course of the reaction is monitored by titration of the dimethylamine which is eliminated from the mixture by an argon stream. This procedure is an interesting way to obtain this class of compounds with good yields (85%). We have summarized the properties of six phosphonates **3a–g** in Table I.

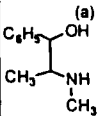
This reaction can be explained by an equilibrium between the phosphonate **4** and its tautomeric form the phosphite **4'** which is more reactive than **4**.

[4] 

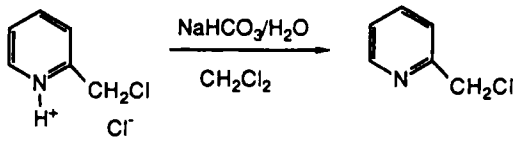
4 **4'** **3**

TABLE I

Conditions of reactions [3] and [1] concerning the synthesis of phosphonates **3a–g** and 2-phosphonomethyl pyridines **Ia–g**. a. Two diastereoisomers have been obtained.

Nu	Time(h) reaction [3]	Yield %	$(RO)_2P(O)H$	$\delta^{31}P$ (^1JPH)	Time(h) reaction [1]	Yield %	$(RO)_2P(O)$-CH_2- 	$\delta^{31}P$	($^2J_{PH}$) Hz
C_2H_5OH			**3a**	6.0 (683)	8	82	**Ia**	25.0	(22)
$C_8H_{17}OH$	2	96	**3b**	6.3 (681)	16	78	**Ib**	24.1	(21.9)
$C_{15}H_{33}OH$	2	98	**3c**	6.5 (686)	24	85	**Ic**	24.0	(22)
$pMeC_6H_4OH$	4	95	**3d**	0.1 (727)	18	80	**Id**	18.3	(22.3)
	8	86	**3e**	11.8 (730)	18	61	**Ie**	33.6	(21.5)
	1.5	96	**3f**	13.8 (700)	16	63	**If**	35.1	(21.4)
 + Ephedrine	6	88	**3g**	14.7 (650) 55% 8.0 (640) 45%	16	72	**Ig**	34.7 55% 36.8 45%	(21.6) (20.9)

Furthermore the 2 chloromethyl pyridine **2** is unstable and prior to it's use, one has to liberate the free base **2** from its commercial salt **2'** according to [5].

[5] 

2' **2**

The 2-phosphonomethyl pyridines (**Ia–g**) (Table II) are synthesized according to Scheme [1]. The 2 chloromethyl pyridine is immediately added to the phosphonate anion in a toluene solution at 90°C. After hydrolysis of the medium, extraction by ether and drying with $MgSO_4$, the solution is filtered and the solvent removed in vacuo. The ^{31}P NMR spectrum of the solution shows a unique signal at about $18 < \delta < 37$ ppm. No other signal except those of 2-phosphonomethyl pyridines is present in the ^{31}P NMR spectra during the process. The structures of the compounds are determined from their ^1H, ^{13}C and NMR data (Table II) and elemental analysis.

2. *One pot synthesis*

The multistep process in Scheme [1] involves four steps and our aim was to find a "one step" high yield method to avoid the preparation of the transient products. The Scheme [6] illustrates our process in the particular case of **Id**.

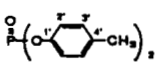
Id is obtained from four commercial products: tris-dimethylaminophosphine, p-cresol, sodium hydride and 2-chloromethyl pyridine hydrochloride. In the mixture we have observed only the entities **4** and **Id** by ^{31}P NMR.

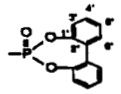
TABLE II

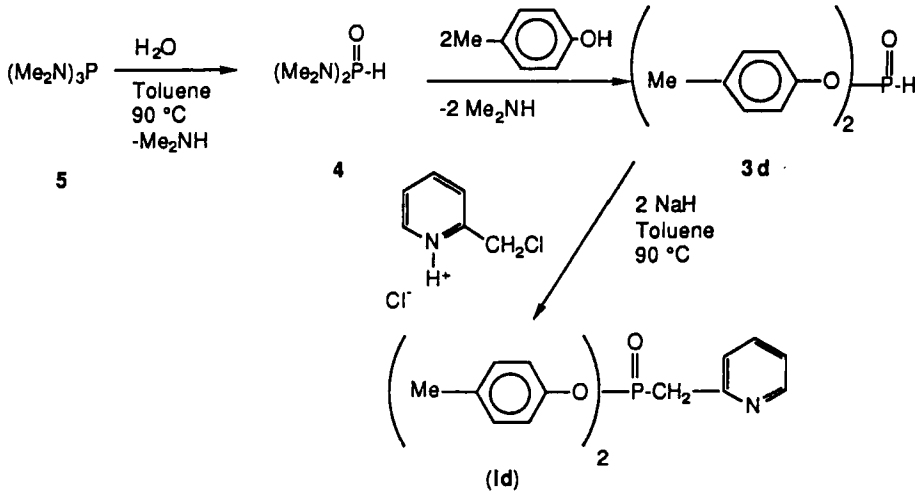
^1H and ^{13}C NMR data of the compounds **Ia–g**.

Products	Molecular Formula	I.R. ν(P=O) cm^{-1}	^1H NMR δ, J(Hz)	^{13}C NMR a) δ, J(Hz)
Ia	$C_{10}H_{16}NO_3P$ (229)	1252	1.3 (t, 6H, $^3J_{HH}$ = 1.3, $CH_2\underline{CH_3}$) 4.15 (dq, 4H, $^3J_{HP}$ = 8.15, O-$\underline{CH_2}$) 3.5 (d, 2H, $^2J_{HP}$ = 21.95, P-$\underline{CH_2}$ 8.55 (H_6), 7.2 < δ H_3, H_4, H_5 < 7.9	16.2 (d, $^3J_{CP}$ = 6, CH_2-$\underline{C}H_3$ 37.5 (d, $^1J_{CP}$ = 135.2, P-$\underline{C}H_2$ 62 (d, $^2J_{CP}$ = 6.7, O-$\underline{C}H_2$ * (voir légende table)
Ib	$C_{22}H_{40}NO_3P$ (397)	1245	0.84 (t, 6H, $^3J_{HH}$ = 6, $\underline{CH_3}$) 1.15 (m, 24H, $\underline{CH_2}$) 3.39 (d, 2H, $^2J_{HP}$ = 21.9, P-$\underline{CH_2}$) 3.95 (dq, 4H, $^3J_{HH}$ = 6.2, $^3J_{HP}$=7.5,O-$\underline{CH_2}$ 8.4 (H_6), 6.7 < δ H_3, H_4,H_5 < 7.3	14.1 (s, $\underline{C}H_3$) 29.6 (s, $\underline{C}H_2$) 36.8 (d, $^1J_{CP}$ = 135.6, P-$\underline{C}H_2$) 65.8 (d, $^2J_{CP}$ = 6.7, O-$\underline{C}H_2$)
Ic	$C_{38}H_{72}NO_3P$ (621)	1243	0.85 (t, 6H, $^3J_{HH}$ = 6, $\underline{CH_3}$) 1.23 (m, 56 H, $\underline{CH_2}$) 3.38 (d, 2H, $^2J_{HP}$ = 21.96, P-$\underline{CH_2}$) 3.95 (dq, 4H, $^3J_{HH}$ =6.3, $^3J_{HP}$ =7.4,O-$\underline{CH_2}$) 8.5 (H_6), 7.3 < δ H_3, H_4, H_5 < 7.7	14.0 (s, $\underline{C}H_3$) 29.3 (s, $\underline{C}H_2$) 36.5 (d, $^1J_{CP}$ = 135.8, P-$\underline{C}H_2$) 66.2 (d, $^2J_{CP}$ = 6.7, O-$\underline{C}H_2$)
Id	$C_{20}H_{20}NO_3P$ (353)	1250	2.3 (s, 3H, $\underline{CH_3}$) b) 3.65 (d, 2H, $^2J_{HP}$ = 22.3, P-$\underline{CH_2}$) 6.9 (d, 2H, $^3J_{HH}$ = 8.8, $H_{3'}$) 7.1 (d, 2H, $^3J_{HH}$ = 8.8, $H_{2'}$) 8.6 (H_6), 7.1 < δH_3, H_4, H_5 < 7.8	20.6 (s, $\underline{C}H_3$) b) 34.2 (d, $^1J_{CP}$ = 132, P-$\underline{C}H_2$) 120.9 (d, $^3J_{CP}$ = 5.2, $C_{2'}$) 130.7 (d, $^4J_{CP}$ = 1.3, $C_{3'}$) 135.1 (d, $^5J_{CP}$ = 1.7, $C_{4'}$) 148.6 (d, $^2J_{CP}$ = 8.7, $C_{1'}$)
Ie	$C_{18}H_{14}NO_3P$ (323)	1259	c) 3.62 (d, 2H, $^2J_{HP}$ = 21.5, P-$\underline{CH_2}$) 8.5 (H_6) 7.0 < δ H_3, H_4, H_5, $H_{1'}$,$H_{2'}$ < 7.8	c) 34.7 (d, $^1J_{CP}$ = 131.4, P-$\underline{C}H_2$) 122.2 (d, $^3J_{CP}$ = 3.8, $C_{2'}$) 126.7 (d, $^3J_{CP}$ = 1.6, $C_{3'}$) 129.2 (d, $^5J_{CP}$ = 1.6, $C_{5'}$) 130.4 (d, $^4J_{CP}$ = 0, $C_{4'}$) 148.2 (d, $^2J_{Cp}$ = 10.3, $C_{1'}$)
If	$C_{12}H_{18}NO_3P$ (255)	1267	0.87 (s, 6H, $\underline{CH_3}$) 1.12 (s, 6H, $\underline{CH_3}$) 3.46 (d, 2H, $^2J_{HP}$ = 21.4, P-$\underline{CH_2}$) 8.35 (H_6), 6.5 < δH_3,H_4,H_5 < 7.5	23.6 (d, $^3J_{CP}$ = 5.44, $\underline{C}H_3$) 24.7 (d, $^3J_{CP}$ = 2.82, $\underline{C}H_3$) 38.1 (d, $^1J_{CP}$ = 128.3, P-$\underline{C}H$) 66.4 (d, $^2J_{CP}$ = 0, O-$\underline{C}$)
Ig	$C_{16}H_{19}N_2O_2P$ (302)	1252	0.04 (d, 3H, $^3J_{HH}$ = 6,7, C-$\underline{CH_3}$) 0.44 (d, 3H, $^3J_{HH}$ = 6.55, C-$\underline{CH_3}$) 2.52 (d, 3H, $^3J_{HP}$ = 8.85, N-$\underline{CH_3}$) 2.41 (d, 3H, $^3J_{HP}$ = 9.1, N-$\underline{CH_3}$) 2.9 (d, 1H, $^3J_{HH}$ =5.9, N-$\underline{CH}$) 2.7 (d, 1H, $^3J_{HH}$ = 6.7, N-$\underline{CH}$) 3.59 (d, 2H, $^2J_{HP}$ = 21, P-$\underline{CH_2}$) 3.57 (d, 2H, $^2J_{HP}$ = 9.1, P-$\underline{CH_2}$) 5.5 (d, 1H, $^3J_{HH}$ =5.9, O-C-$\underline{H}$) 4.8 (dd, 1H, $^3J_{HH}$ = 6.7, $^3J_{HP}$=6.8, O-C-$\underline{H}$) 8.4 (H_6), 6.6 < Ar < 7;3	14.5(s, C-$\underline{C}H_3$) 13.2 (S, C-$\underline{C}H_3$) 29.7 (d, $^2J_{Cp}$ = 4.7, N-$\underline{C}H_3$) 28.4 (d, $^2J_{CP}$ = 4.3, N-$\underline{C}H_3$) 38.6 (d, $^1J_{CP}$ = 120, P-$\underline{C}H_2$) 37.6 (d, $^2J_{CP}$ = 116, P-$\underline{C}H_2$) 60.8 (d, $^2J_{Cp}$ = 8.7, N-$\underline{C}H$) 58.1 (d, $^2J_{CP}$ = 9.4, N-$\underline{C}H$) 82.2 (s, O-$\underline{C}H$) 80.0 (s, O-$\underline{C}H$)

a) ^{13}C NMR for  121.7 (d, $^5J_{CP}$= 3.2, C_5) ; 124.2 (d, $^3J_{CP}$= 4.8, C_3) ; 136.3 (d, $^4J_{CP}$= 2.8, C_4) 149.3 (d, $^4J_{CP}$= 2.4, C_6) ; 152.7 (d, $^2J_{CP}$= 8.3, C_2)

b) 

c) 



SCHEME [6]

In this procedure, the major difficulty is the use of the hydrochloride form of the 2 chloromethyl pyridine. This problem is resolved by the addition of two equivalents of sodium hydride in the last step; thus we liberate the free base simultaneously with the formation of the phosphonylanion. This reaction is very exothermic and the reactants must be added to 0°C. After hydrolysis of the mixture and extraction with diethyl ether, the solution is filtered and the solvent evaporated. We obtained the 2-phosphonomethyl pyridines **Id** with a 60% yield.

After distillation, the phosphonate **Id** exhibits the same spectroscopic parameters as a sample obtained by the multisteps method. We have also used this one pot synthesis for the preparation of four other phosphonates (**Ic, Ie, If, Ig**).

In conclusion, we have been able to accomplish the synthesis of new 2-phosphonomethyl pyridines. Our one pot method has two advantages: the reaction proceeds under mild conditions and we obtain good yields. The reactivity of these new compounds deserves further investigations.

EXPERIMENTAL

All manipulations were carried out under dry argon using standard Schlenk tube techniques. The solvents were degassed and distilled before used. Nuclear magnetic resonance spectra were obtained on multinuclear Bruker AC 80 and AC 200 spectrometers operating in the Fourier transform mode at 80 (^{1}H), 32.44 (^{31}P) and 20.15 (^{13}C) MHz for AC 80 and at 81.015 (^{31}P), 50.323 (^{13}C) MHz for AC 200. Chemical shifts are expressed in ppm downfield from internal TMS for ^{1}H and ^{13}C or external 85% H_3PO_4 for ^{31}P. Coupling constants are in Hertz. IR spectra were recorded on a Perkin-Elmer 783 spectrophotometer. Microanalysis were satisfying and performed in the "Service de Microanalyses" ENSCT, Toulouse.

2-Chloromethyl pyridine **2**. 2-Chloromethyl pyridine hydrochloride (12 g) was dissolved in 100 ml of dichloromethane and placed in a flask. $NaHCO_3$ (8 g) in 30 ml of water was added dropwise with vigorous stirring. After decantation, the water solution was extracted with methylene chloride (2 × 50 ml). The organic layer was dried on $MgSO_4$ and then filtered. The solvent was evaporated under vacuum. We obtained 7.9 g of 2-chloromethyl pyridine **2** (yield: 85%).

Synthesis of phosphonates **I**. *General procedure.* The preparation was identical for the seven phosphonates **Ia–g**. We describe the synthesis of **Ib**. 0.96 g (0.04 mol) of sodium hydride dispersed in 30 ml of toluene, were added dropwise to 12.25 g (0.04 mol) of phosphite, the reaction mixture was stirred

during 30 min and then 5.1 g (0.04 mol) of 2-chloromethyl pyridine were introduced. The mixture was refluxed for 16 h.

After evaporation of the solvent, 50 ml of ether were introduced and the solution was hydrolysed by 20 ml of water, the water layer was extracted with ether (3 × 30 ml) and the organic layer was dried on $MgSO_4$. After filtration, the solvent was evaporated under vacuum (15 mm Hg). We obtained 2.4 g of **Ib** (yield 78%).

Typical one pot synthesis of phosphonate **I–(Id)**. We added 0.27 g (0.015 mol) of water to a 30 ml toluene solution of 2.6 g (0.046 mol) of tris dimethylamino phosphine and this mixture was refluxed during 90 min; we followed the evolution of dimethylamine under an argon stream. The phosphonate **4** was not isolated and two equivalents of para cresol, 3.24 g (0.03 mol) was introduced to obtain with good yield the phosphonate **3d**.

Then the sodium hydride 0.73 g (0.03 mol) was added very slowly to the solution and afterwards 2-chloromethyl pyridine hydrochloride, 2.46 g (0.015 mol) was introduced during 10 min. This step was very exothermic. The suspension was stirred for 30 min at room temperature and heated at 100°C for 18 hours. After evaporation of the solvent, diethyl ether (50 ml) was added and the reaction mixture was poured into water (20 ml); the water layer was extracted three times with ether (50 ml). The combined organic layers were dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was distilled under vacuum: bp = 142°C (5.10^{-2} mm Hg). The yield of this reaction is 60% (the starting material being the tris dimethylaminophosphine).

REFERENCES

1. D. W. Hutchinson, P. A. Cload and M. C. Haugh, *Phosphorus Sulfur,* **14,** 285 (1983).
2. D. Hendlin, E. O. Stapley, M. Jackson, H. Wallick, A. K. Miller, F. J. Wolf, T. W. Miller, L. Chaiet, F. M. Kahan, E. L. Foltz, H. B. Woodruff, J. M. Mata, S. Hernandez and S. Mochales, *Science,* **166,** 122 (1969).
3. R. Engel, *Chem. Rev.,* **77,** 349 (1977); R. L. Hilderbrand, "The Role of Phosphonates in Living Systems," CRC Press: Boca Raton, FL (1983).
4. Y. S. Huang, B. Chaudret, J. Bellan and M. R. Mazières, *Polyhedron,* **10,** 2229 (1991).
5. J. J. Bulot, E. E. Aboujaoude, N. Collignon and P. Savignac, *Phosphorus Sulfur,* **21,** 197 (1984); R. A. Rossi and J. F. Bunnet, *J. Org. Chem.,* **28,** 1407 (1973).
6. Y. S. Michaelis, *Liebigs Ann. Chem.,* **38,** 293, 193 (1896).
7. L. Beslier, M. Sanchez, D. Houalla and R. Wolf, *Bull. Soc. Chim. Fr.,* 2563 (1971).