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A PRACTICAL SYNTHESIS OF α-AMINOPHOSPHONIC ACIDS.

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Key Words : Schiff bases of diterbutylaminomethylphosphonate ; Phase Transfert Catalysis ; Palladium-catalyzed allylic substitution ; Michael additions.

Abstract : The preparation of diterbutyl-N (diphenylmethylene) aminomethylphosphonate 3 in four steps (42% overall yield) from N-hydroxymethyl phtalimide 1 is described.Various α substituted α-aminophosphonic acids 5 containing functionalized unsaturated chains have been synthesized by alkylation of 3 under phase transfer catalysis with halides, Michael acceptors and palladium promoted reactions, followed by mild hydrolysis.

α-Aminophosphonic acids, the phosphonic analogues of α-aminoacids, are unnatural compounds presenting several interesting biological properties.[1] It is now well established that 1-aminoalkyl phosphonic acids act as substrates or inhibitors of several enzymes involved in the metabolism of aminoacids.[2] These important compounds have been synthesized by various routes.[3] Among them, the method based on the alkylation of nucleophilic precursors such as Schiff bases is one very attractive.[4] We have recently described the use of anion derived from diethyl-N-(diphenylmethylene) aminomethylphosphonate. However, wider applications of these methods are inhibited by their drastic conditions for the preparation of free α aminophosphonic acids. The hydrolysis conditions of diethyl phosphonate group requiring treatment with pure hydrochloric or hydrobromic acid for several hours is incompatible with functionalized chains. In addition,the reported alternative method of deprotection in the presence of trialkylsilyl halides [5] has been also unsuccessful when an allylic side chain is present in the molecule.[6]

We describe now an improved method for the preparation of α–aminophosphonic acids.[6] The synthesis involved preparation and alkylation of diterbutyl N-(diphenylmethylene) aminomethylphosphonate 3.

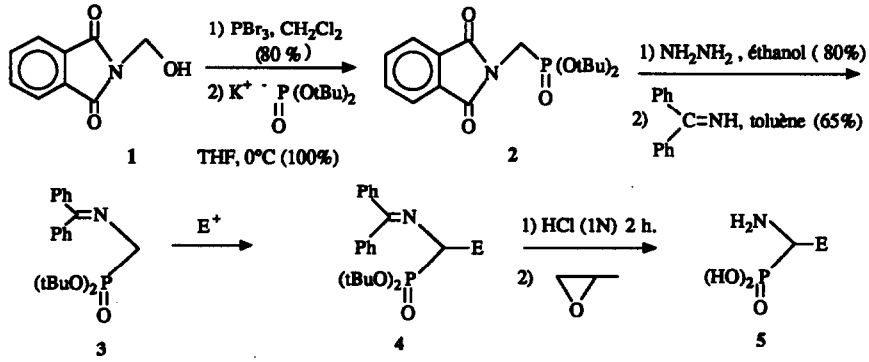
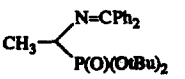
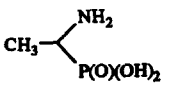
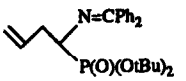
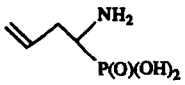
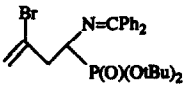
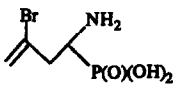
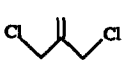
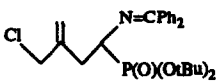
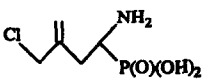
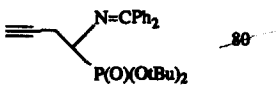
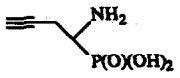
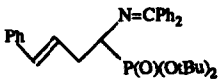
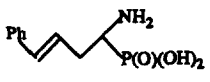
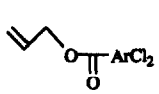
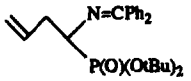
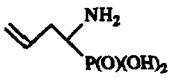
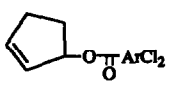
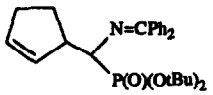
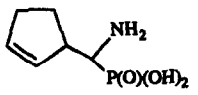
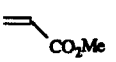
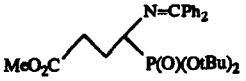
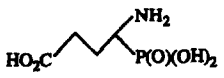
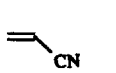
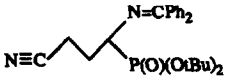
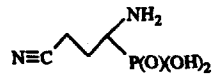


Table : Isolated yield of C-alkylated 4 and aminophosphonic acids 5

Entry	Electrophile	Product	Yield[a] (%)	aminophosphonic acid	Yield[a] (%)
1	CH_3I		72		85
2			98		80
3			74		60
4			55		76
5			80		63
6			80		60
7[b]			80		85
8[b]			72		70
9			60		70
10			94		96

a) Isolated yield : b) η^3 palladium electrophiles generated in situ by addition of Pd (OAc)2 and diphenylphosphinoethane or triphenylphosphine.

This Schiff base is synthesized (scheme) in large scale from easily available N-hydroxymethyl phtalimide **1**, which was converted into the N-bromomethylphtalimide with modification of the procedure of Martin [7] using PBr_3 in CH_2Cl_2 (80% yield).[8a] When the N-bromomethylphtalimide was reacted with sodium salt of diterbutylphosphite [8b] in toluene reflux for 8 h, diterbutyl N-phtalimidoaminomethyl phosphonate **2** was

obtained (55% yield). However the reaction of potassium salt generated from the terbutylphosphite with KHMDS at 0°C afforded 2 in a quantitative yield, classical deprotection of the phtalimido group with hydrazine afforded diterbutylaminomethyl phosphonate which was treated without purification with benzophenone imine in toluene reflux and diterbutyl-N (diphenylmethylene) aminomethyl phosphonate 3 was isolated as cristalline material (42% overall yield from 1).[9]

The Schiff base was subjected to alkylation reaction with different electrophiles (e.g. halides, Michael acceptors η3 palladium allyl species).[10] Firstly ketimine 3 has been alkylated with potassium hydroxide as base under solid-liquid phase transfer catalysis[11] without solvent in the presence of Aliquat 336 (trioctyl methylammonium chloride) and afforded the corresponding monoalkylated products in high yields up to 98% (entries1-6).[12] A synthetically useful reaction occurs between the benzophenone Schiff base and α,β-unsaturated derivatives (e.g. acrylonitrile, methyl acrylate) (entries 9 and 10) leading under phase transfer catalytic conditions to the Michael adducts. The reaction is performed by simply stirring the Schiff base 3 and the electrophilic olefin in dichloromethane in the presence of Aliquat 336 and potassium hydroxide at room temperature. The alkylation has also been successfully realized with allyl palladium electrophiles[13] obtained in situ from Pd (OAc)2, and phosphines as ligand (dppe or TPP) and the corresponding allylic 2,4-dichlorobenzoate in presence of lithium anion of 3 generated from lithium hexamethyldisilazane (entries 7 and 8). The diterbutyl protective group and ketimine in compounds 4 can be eliminated under mild condition (HCl 1,N 2h RT) providing an access to free α aminoacids with unsaturated chains. Thus we have prepared 2-bromoallyl, 2 propargyl, 2-cinnamyl, 2-cyclopentenyl phosphonoglycine, and the phosphonic analogs of glutamic acid (entries 3,5,6,8,9 and 10 respectively).

The present method affords good yields in the condensation reaction and high purity of the resultant products in both steps of the sequence and it is simple to perform.

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6 - Taken in part from J. Uziel. Thèse de l'Université Pierre et Marie Curie. May 1990.

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8 - Commercially available : a) from Aldrich ; b) from Lancaster Synthesis.

9 - All new products gave satisfactory analytical and spectral data in accord with the assigned structures.

10 - 3 mp = 102-103°C ; IR (neat) KBr : 3058, 2931, 1247, 977 cm^{-1} ; 1H-NMR (200 MHz, $CDCl_3$) : 1.5 (s, 18H) ; 3.85 (d, 2H, J = 18 Hz), 7.2-7.6 (m, 10H).

11 - PTC conditions have been used for the synthesis of carboxylic aminoacids see : M.J. O'Donnell, W.D. Bennett and S. WU ; J.Am.Chem.Soc., 111, 2353 (1989) and references cited therein.

12 - A mixture of 3 (1 mmole), aliquat 336 (20 mg, 0,05 mmol), the appropriate halide (1.5 mmol) and finely ground KOH (300 mg, 5 mmole) is stirred at r.t. The reaction is monitored by TLC (cyclohexane/ethyl acetate 1 : 1) till completion (3-48 h). After addition of dichloromethane and silicagel or fluorisil (50 mg) followed by filtration to removed the catalyzed the solvent is evaporated. The crude product is purified by flash chromatography (silica gel). Hydrolysis of the C-alkylated product : (1 mmole) in Et_2O (4 ml) with 10% aq. HCl (4 ml) is stirred (2 h) at r.t. The aqueous phase is extracted with Et_2O (5 X 1 ml) and evaporated in vacuo till dryness. Then, 2 ml of propylene oxide are added in refluxing ethanol (15 mn) giving the free aminophosphonic acids.

2-Bromoallyl Phosphonoglycine : mp 268-270°C ; IR (film) (3430,2970,1630,1180 cm^{-1}) ; ^1H NMR (80 MHz D_2O) : 2.7-3 (m, 2H) ; 3.4-3.8 (m, 1H) ; 5.7 (d, 2H, J = 8 Hz) ; ^{31}P NMR (250 MHz, D_2O) 12 ppm.

2-Cinnamyl Phosphonoglycine : mp = 268-270 °C; IR (KBr) : 3415, 3030, 2920, 1640, 1530 cm^{-1} ; ^1H NMR (80 MHz, D_2O/NaOD) : 2.5 (m, 2H) ; 6.3 (m, 2H); 7.2 (m, 5H) ; ^{31}P NMR (250 MHz, D_2O-NaOD) : 21. 3 ppm.

2-Cyclopentenyl Phosphonoglycine : ^1H NMR (250 MHz, D_2O) : 1.6-2.3 (m, 4 H) ; 2.86-3.2 (m 2 H- ; 5.64-6.86 (m, 2 H).

4-Amino-4-Phosphono-Butyric Acid : IR (film) 3428, 2983, 2933, 1726, 1276, 1195. ^1H NMR (D_2O, 200 MHz) 1.7-2.25 (m, 2 H), 2.35-2.6 (m, 2 H) ; 3-3.45 (m, 1 H).

13 - The palladium alkylation of carboxylic Schiff bases have been successfully developped in our laboratory see: a) D. Ferroud, J.P. Genêt and R. Kiolle , Tetrahedron Lett., 27, 23 (1986) ; b) ibid 27, 4573 (1986) ; c) J.P. Genêt, J. Ruiz-Montes, J.M. Gaudin and S. Juge, J.Chem.Soc.ChemComm., 718 (1988) ; d) J.P. GENET, S. Juge, S. Achi, S. Mallart, J. Ruiz-Montes and G. Levif, Tetrahedron 44, 5263 (1988).

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