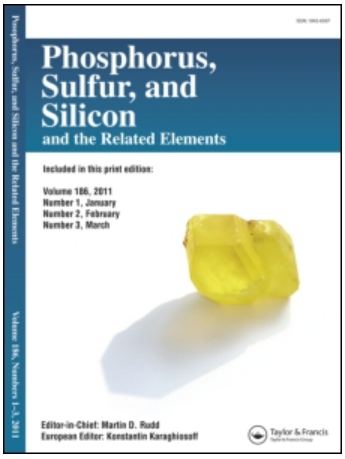

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DESULFURISATION OF PHOSPHONYLATED THIOAMIDES: A NEW WAY TO FUNCTIONALISED AMINOPHOSPHONATES

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DESULFURISATION OF PHOSPHONYLATED THIOAMIDES: A NEW WAY TO FUNCTIONALISED AMINOPHOSPHONATES*

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A new way to functionalised (aminomethyl)- or (aminoethyl)-phosphonates via the desulfurisation by nickel boride of phospho substituted thioamides [(thiocarbamoyl)- and (thiocarbamoylmethyl)-phosphonates], readily available from phosphono-dithioesters and functionalised amines, is described.

Keywords: (Thiocarbamoyl)phosphonates; aminophosphonates; (N-phosphonomethyl)aminoacids; N-(2-phosphonoethyl)aminoacids; desulfurisation; nickel boride

INTRODUCTION

The aminophosphonic acids were mentioned in 1943 for the first time with the synthesis of the aminomethylphosphonic acid **I**.[1] In the sixties, the aminoethylphosphonic acid and its derivatives were discovered in living organisms and after the discovery of biological activities of natural and synthesised aminophosphonates, a lot of work related to these compounds was published. Owing to their structural analogy with aminoacids, they often are their antagonists and can also act as enzyme inhibitors. Their physiological activities (antibacterial agents, neuroactive compounds, anticancer drugs, pesticides or herbicides) have been recently reviewed.[2]

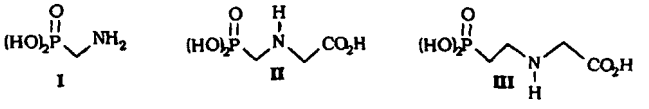


FIGURE 1

* Dedicated to Professor Robert Wolf.
† To whom correspondence should be addressed.

Among the biologically active aminoalkylphosphonic acids some have an amino group derived from aminoacids. The best example is the N-(phosphonomethyl)glycine **II** or glyphosate, a well-known herbicide[3,4] which was recently shown to also be a good ligand for divalent (Ni^{2+}, Fe^{2+}, Cu^{2+} ...) and trivalent (Fe^{3+}, Al^{3+}, La^{3+}) cations. The main syntheses in moderate to good yields for this type of aminomethylphosphonic acids with secondary amino groups, such as glyphosate, are: N-alkylation by chloromethylphosphonic acid[5] and a Mannich type reaction involving phosphonic acid, methanal and aminoacid.[6-12] The homologue N-(phosphonoethyl)glycine **III** has been synthesised by addition of glycine to a vinyl phosphonate.[13]

We have recently shown that (thiocarbamoyl)phosphonates **V** and (thiocarbamoylmethyl)phosphonates **VIII** are readily obtained by addition of amines or aminoacids to phosphonodithioformate **IV** and phosphonodithioacetate **VII,** respectively.[14,15] Therefore, we decided to investigate the reductive desulfurisation of (thiocarbamoyl)phosphonates of type **V** and **VIII,** as a general preparative method for the corresponding (aminomethyl)- and (aminoethyl)-phosphonates **VI** and **IX.**

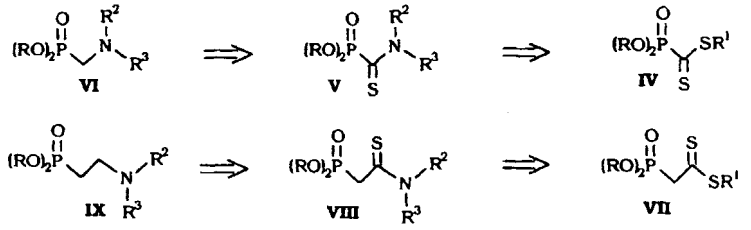
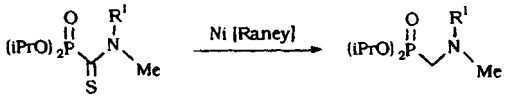


FIGURE 2

RESULTS

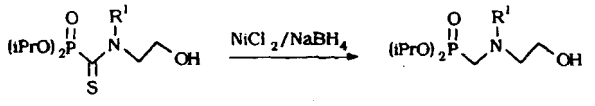
We first envisaged the alkylation of these thioamides (by methyl iodide or triethyloxonium tetrafluoroborate) followed by treatment with sodium borohydride, a method which was commonly used for the desulfurisation of thioamides[16,17]. However, (thiocarbamoyl)phosphonates **V** appeared unreactive towards alkylating agents. Then, we examined the use of Raney Nickel which is also known to be effective for the desulfurisation of thioamides, although this reagent is not always selective when other functions are present.[18] Starting from N-methyl and (N-dimethyl thiocarbamoyl)-phosphonate **1a** and **2a,** this reagent, in refluxing ethanol, was efficient at leading to the corresponding (aminomethyl)- and (aminoethyl)-phosphonates **1b** and **2b.** However, low yields and non reproducible results were observed with functionalised thioamides.



1a	R^1 = H	**1b**	75%
2a	R^1 = Me	**2b**	62%

FIGURE 3

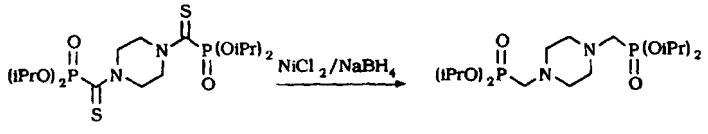
We therefore envisaged the use of nickel boride,[19] a reagent generated in situ from nickel choride hexahydrate and sodium borohydride, in alcohol or water.[20] This reagent was previously used for a desulfurisation of a thiopeptide derivative.[21] At first, starting from the hydroxylated thioamides **3a** and **4a,** the corresponding aminophosphonates **3b** and **4b,** were isolated in low yields from the black solid material formed in the reaction, although the desulfurisation seems to be clean and complete. These low yields can be explained by the complexing properties of aminophosphonates towards nickel cation. Indeed, the addition of a ligand such as EDTA in the mixture at the end of the reaction allowed us to increase the yields of pure products from 30 to 60%.



			without EDTA	with EDTA
3a	R1 = H	**3b**	33%	65%
4a	R1 = Me	**4b**	29%	61%

FIGURE 4

Starting from a piperazine derivative **5a,** the bis-aminophosphonate **5b** was obtained in a yield of 36% after purification.



5a **5b**

FIGURE 5

Using the same reagent, the desulfurisation of aminoacid derivatives: thiocarbamoylphosphonates **6a–9a** and (thiocarbamoylmethyl)phosphonates **10a–12a** led us to the corresponding N-(phosphonomethyl)- and N-(phosphonoethyl)-aminoacids **6b–9b** and **10b–12b** (compounds soluble in water) in yields of 30 to 70 % after purification. For these reactions, dimethylglyoxime was prefered to EDTA as nickel ligand because of its high complexing activity and the unsolubility of its nickel complex in a basic aqueous medium. Nevertheless, the use of a Dowex W80 resin was necessary for a complete salt elimination and purification.

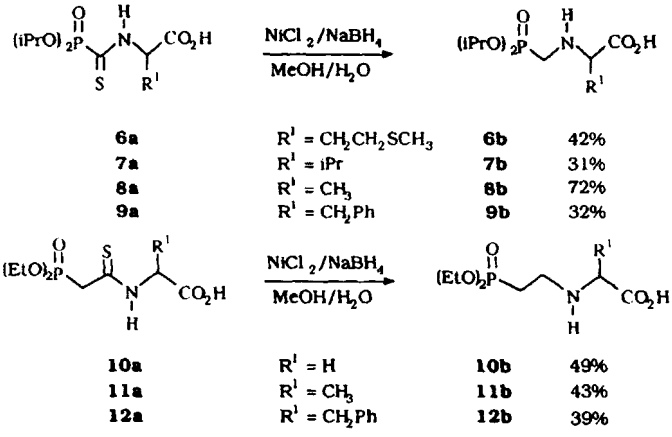


FIGURE 6

CONCLUSION

The desulfurisation of (thiocarbamoyl)- and (thiocarbamoylmethyl)-phosphonates by nickel boride is a new way for the synthesis of (aminomethyl)- and (aminoethyl)-phosphonates in reasonable yields (which very probably could be again optimised). Despite the relatively long purification process due to nickel complexation, this method, which is an alternative for the preparation of glyphosate analogues or homologues, could also be applied, more generally, to the synthesis of new aminosubstituted phosphonates starting from a large variety of functionalised amines.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 instrument operating at 250.13 MHz for ^{1}H and 62.89 for ^{13}C. The ^{31}P NMR spectra were recorded on a Bruker WP 80SY at 32.44 MHz. IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrometer. Mass spectra were recorded with a Nermag Riber R10 spectrometer (70 eV). Microanalyses were obtained from the "Laboratoire Central de microanalyse du CNRS" (Lyon). Analyses of sulfur were performed at Caen following Debal and Levy's method [*Bull. Chem. Soc. Fr.*, 426 (1968)]. Amino acid derivatives were found to be hygroscopic and consequently good elemental analysis were difficult to obtained. As it was previously observed for such derivatives,[22,23] in some cases microanalyses were found consistent with a compound containing molecules of water.

The characteristic signals (IR, ^1H NMR, ^{13}C NMR) of the diisopropyl and diethylphosphono groups, nearly the same for all compounds, are the following: Diisopropyl phosphono group: ^1H NMR: ~1.3 [d, $J_{HH} = 6$, $(C\underline{H}_3)_2CHO$]; ~4.7 [dsept, $J_{HH} = 6$, $J_{HP} = 2$, $(CH_3)_2C\underline{H}O$]; ^{13}C NMR: ~24 [d or dd, $J_{CP} = 4$, $(\underline{C}H_3)_2CHO$]; ~71 [d,$J_{CP} = 7$, $(CH_3)_2\underline{C}HO$].

Diethyl phosphono group: ^1H NMR ; ~1.3 [t, J_{HH}=7, $C\underline{H}_3CH_2O$]; 4.1 [dq~quint, J_{HH}~J_{HP}~7, $CH_3C\underline{H}_2O$]. ^{13}C NMR: 16.4 [d, J_{CP}~5,7, $\underline{C}H_3CH_2O$] ; 62.7 [d, J_{CP}~6.3, $CH_3\underline{C}H_2O$].

IR: $\nu_{P=O}$~1220; ν_{P-O}~1000.

These data are not repeated for each compound described below.

(Thiocarbamoyl)phosphonates **1a–9a** and (thiocarbamoylmethyl)phosphonates **10a–12a** were respectively prepared according to the described procedure[14,15] from methyl (diisopropylphosphono)dithioformate and methyl (diethylphosphono)dithioacetate with the corresponding amine, aminoalcohol or aminoacid.

Desulfurisation of 1a and 2a with Raney nickel

1a or **2a** (1 mmol) were refluxed in ethanol with an excess of Raney-Nickel for 3 h. The mixture was filtered through celite or silica gel. Ethanol was evaporated and then the residue was taken up with ether and washed with an aqueous solution of NH_4CL. The organic phase was then dried on Na_2SO_4 and after evaporation of the solvant crude (aminomethyl)phosphonates **1b** and **2b** were purified by flash chromatography on silica gel.

Diisopropyl (N-methyl-aminomethyl) phosphonate **1b:** R.N. = [72039–86–2]

Diisopropyl (N-dimethyl-aminomethyl) phosphonate **2b:** R.N. = [31710–53–9]

General procedure for the desulfurisation with nickel boride

To a solution of thiocarbamoyl- or thiocarbamoylmethyl-phosphonate (1eq.) and nickel chloride (6 eq.) in a mixture methanol/water (1/1), sodium borohydride (18 eq.) was slowly added (15mn). Then the suspension was stirred for 15 mn.

a) Treatment with EDTA (work-up for the purification of **3b** to **5b***).* EDTA (12 eq.) was added to the mixture which was then stirred for lh and filtered through celite. The solid phase was washed with ether. All the liquid phases were put together and evaporated. The residual oil was purified by passing through a silica gel column (eluent: petroleum ether/ethanol, 90/10). The following compounds were thus obtained:

Diisopropyl [N-(2-hydroxyethyl)-aminomethyl]phosphonate **3b**: oily product. ^1H NMR: 2.70 [t, J = 5, $NC\underline{H}_2CH_2$]; 2.87 [d, J_{HP} = 14, $PC\underline{H}_2N$]; 3.27 [broad s,

OH,NH]; 3.57[t, J = 5, CH_2O]. ^{13}C NMR: 45.2 [d, $^1J_{CP}$ = 156, PCH_2N); 52.7 [d, $^3J_{CP}$ = 12, $NHCH_2$]; 60.0 [CH_2OH]. ^{31}P NMR: +21.30. MS m/z(%): 240 ($M.^+$/93), 221 (21), 208 (15), 166 (13), 124 (25), 74 (100).

Diisopropyl [N-(2-hydroxyethyl)-N-methyl-aminomethyl]phosphonate **4b:** oily product. ^1H NMR: 2.41 [s, NCH_3]; 2.58 [t, J = 5, NCH_2]; 2.73 [d, J_{HP} = 11, PCH_2N]; 3.52 [t, J = 5, CH_2OH] ; 4,15 [s, OH]. ^{13}C NMR: 44.8 [d, $^3J_{CP}$ = 3.7, NCH_3]; 53.8 [d, $^1J_{CP}$ = 117, PCH_2N]; 59.4 [CH_2OH]; 61.1 [d, $^3J_{CP}$ = 10.4, $NHCH_2$]. ^{31}P NMR: +23,40. MS m/z(%): 254 ($M.^+$/36), 222 (27), 138 (26), 88 (100).

Tetraisopropyl piperazino-N,N'-bis-(methylphosphonate) **5b:** oily product. ^1H NMR: 2.68 [s, NCH_2CH_2N]; 2.70 [d, J_{HP} = 15, PCH_2N]. ^{13}C NMR: 54.7 [d, $^1J_{CP}$ = 165, PCH_2N]; 55.0 [d, NCH_2CH_2N]. ^{31}P NMR: +22,15. MS m/z(%): 442 ($M.^+$/1); 277 (2); 235 (12); 221 ($M.^+$/2 /3); 193 (28); 43 (100). Analysis: $C_{18}H_{40}N_2O_6P_2$ Calcd C: 48.86; H: 9.11; N 6.33. Found C: 48.92; H: 9.12; N: 6.11.

b) Treatment with N, N-dimethylglyoxime (work-up for the purification of aminoacid derivatives **6b–12b***):* Dimethylglyoxime (12 eq.) was added and the suspension which became red was stirred for lh and then filtered through celite. The solid was washed with water and all the filtrates were put together and concentrated under vacuo. The residue was taken up with the minimum of water and filtered again. The filtrate is then acidified by an aqueous HCl 5% solution and the aminoacid was purified with a Dowex W 80 resin (removal of the residual salts) followed by elution with aqueous ammonia (20%) and evaporation of water in vacuo. The following compounds were thus obtained:

N-[(Diisopropylphosphono)methyl]methionine **6b:** oily product: ^1H NMR: 1.59 to 1.93 [m, $CHCH_2CH_2$]; 2.07 [s, SCH_3]; 2.59 [m, CH_2S]; 2.87 and 3.04 [2dd~2t, J_{HH}~J_{PH}~14, $PhCH_2N$]; 3.13 [m, NHCH]; 4.50 [broad s, NH, CO_2H]. ^{13}C NMR: 15.4 [SCH_3]; 31.0 and 32.5 [$CHCH_2CH_2S$]; 40.9 [d, J_{CP} = 163, PCH_2N]; 57.8 [$CHCO_2H$]; 178.4 [CO_2H]. ^{31}P NMR: +24.61. Analysis $C_{12}H_{26}NO_5SP$ Calcd S: 9.79. Found S: 9.59.

N-[(Diisopropylphosphono)methyl]valine **7b:** White cristals, m.p. = 79°C. ^1H NMR: 0.96 and 1.02 [2d, J = 6, $(CH_3)_2CHCH$]; 2.06 [m, $(CH_3)_2CH$]; 2.94 and 2.99 [2dd~2t, J_{HH}~J_{HP}~14, PCH_2N]; 2.98 [~d, J = 6, $CHCO_2H$] ; 6.80 [NH, COOH]. ^{13}C NMR: 18.3 and 19.4 [$(CH_3)_2CHCH$]; 45.1 [d, PCH_2NH, J_{CP} = 159]; 68.5 [d, J_{CP} = 15, NCH]; 175.8 [COOH]. ^{31}P NMR: +23.46. Analysis $C_{12}H_{26}NO_5P$ Calcd C:48.80; H: 8.87; N: 4.74. Found C: 48.80; H: 8.71; N: 5.14.

N-[(Diisopropylphosphono)methyl]alanine **8b**: oily product. ^1H NMR: 1.65 [d, J = 6, CH_3CHN]; 3.48[2d, J_{HP} = 15, PCH_2N]; 4.08[m~q, J = 6, NCH]; 8.16 [broad s, NH, COOH]. ^{13}C NMR: 14.9 [CH_3CHN]; 40.8 [d, J_{CP} = 154, PCH_2N]; 57.2 [NCH]; 179.4 [COOH]. ^{31}P NMR: +21.59. MS m/z (%): 267 (2); 222 (5); 180 (7); 138 (11); 102 (20); 86 (39); 84 (41); 56 (68); 43 (100).

N-[(Diisopropylphosphono)methyl]phenylalanine **9b:** white cristals, m.p. = 81°C ^{1}H NMR: 2.61 and 2.88 [2dd~2t, J_{HH}~J_{PH}~14, PhC$\underline{H}_2$N]; 2.70 and 3.10 [~2d, J_{HH} = 7, C$\underline{H}_2$Ph]; 3.37 [m, NHC$\underline{H}$]; 4.75 [s, N$\underline{H}$, $CO_2\underline{H}$]; 7.10 to 7.26 [m, Ph]. ^{13}C NMR: 38.7 [$\underline{C}H_2$Ph]; 44.4 [d, J_{CP} = 158, P$\underline{C}H_2$N]; 63.4 [d, $\underline{C}HCO_2H$, $3J_{CP}$ = 14]; 126.9, 128.7, 129.4, 137.1 [Ph]; 175.0 [CO_2H]. ^{31}P NMR: +25.44. MS m/z (%): 343 (9); 208 (46); 132 (46); 124 (89); 91 (100); 77 (21). Analysis: $C_{16}H_{26}NO_5P$,1.5H_2O Calcd C: 51,84; H: 7,02. Found C: 51,83; H: 6,63.

N-[2-(Diethylphosphono)ethyl]glycine **10b:** oily product. ^{1}H NMR; 2.47 [m, PC$\underline{H}_2$CH_2]; 3.28 [m, PCH_2C$\underline{H}_2$]; 3.71 [s, NHC$\underline{H}_2CO_2H$]; 5.42 [s, N$\underline{H}$, CO_2H]. ^{13}C NMR: 22.5 [d, J_{CP} = 140, P$\underline{C}H_2$]; 41.8 [PC$H_2\underline{C}H_2$]; 49.8 [NH$\underline{C}HCO_2H$]; 173,0 [CO_2H]. ^{31}P NMR: +26.58. R.N.: [71460–01–0].

N-[2-(Diethylphosphono)ethyl]alanine **11b:** oily product. ^{1}H NMR: 1.54 [~d, C$\underline{H}_3$CH]; 2.47 [m, PC$\underline{H}_2$CH_2]; 3.22 [m, PCH_2C$\underline{H}_2$]; 3.68 [m~q, NHC$\underline{H}$CH_3]; 6.32 [s, N$\underline{H}$,$CO_2\underline{H}$]. ^{13}C NMR: 14.8 [CH$\underline{C}H_3$]; 22.8 [d, J_{CP} = 140, PC$\underline{H}_2$]; 40.1 [PC$H_2\underline{C}H_2$]; 57.2 [$\underline{C}HCO_2H$]; 173.4 [$\underline{C}O_2$H]. ^{31}P NMR: +26.55. Analysis: $C_9H_{20}NO_5P$, 2 H_2O Calcd C: 37.37; H: 6.97. Found C: 37.82; H: 7.14.

N-[2-(Diethylphosphono)ethyl]-phenylalanine **12b:** oily product. ^{1}H NMR: 2.30 to 2.51 [m, PC$\underline{H}_2$CH_2]; 3.07 and 3.38 [2m, PCH_2C$\underline{H}_2$ and C$\underline{H}_2$Ph]; 3.89 to 4.14 [m, NHC$\underline{H}$]; 7.19 to 7.41 [m, Ph]; 8.37 [broad s, N$\underline{H}$, $CO_2\underline{H}$]. ^{13}C NMR: 22.8 [d, P$\underline{C}H_2$, J_{CP} = 140]; 35.8 [$\underline{C}H_2$Ph]; 41.5 [$\underline{C}H_2$N]; 62.6 [NH$\underline{C}$H]; 127.4, 128.9, 129.4, 135.9 [Ph]; 171.5 [$\underline{C}O_2$H]. ^{31}P NMR: 26.49. Analysis: $C_{15}H_{24}NO_5P$, 2.5 H_2O Calcd C: 48.13; H: 7.22. Found C: 48.22; H: 7.22.

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