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First Synthesis of a (Mercaptomethylene) Diphosphonate *via* a Phosphorothiolate → Mercaptophosphonate Rearrangement.

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Abstract : Diisopropyl S-[(diisopropylphosphono)methyl] phosphorothiolate was deprotonated with butyllithium. The lithiated carbanion underwent a [1,2]- sigmatropic shift, and rearranged into the (mercaptomethylene) diphosphonate anion which, by protonation, led to a (mercaptomethylene) diphosphonate. Some derivatives were prepared.

Key-words : Phosphorothiolate-mercaptophosphonate rearrangement; [1,2]- sigmatropic rearrangement; (mercaptomethylene)diphosphonate.

INTRODUCTION

The synthesis of *gem*-diphosphonic acids has recently received much attention, partly due to the biological properties of some of them.[1] Their medical interest results from their structural analogy to pyrophosphoric acid $[(HO)_2(O)P]_2O$, an inhibitor of the precipitation of calcium phosphate, and from their P-C-P linkage which shows a larger hydrolytic stability than the anhydride function of pyrophosphoric acid.[1,2] Moreover, the technetium 99 complexes of the α-hetero (N,O,S)- substituted *gem*-diphosphonic acids have shown interest in detection and treatment of bone diseases.[1,2] Those acids are easily obtained by simple hydrolysis of the corresponding diphosphonates.[2,3] Some [α-alkylthio- (or α-alkoxy- analogues) methylene] diphosphonates have been prepared by phosphonylation of the carbanion of the [alkylthio- (or alkyloxy-) methyl] phosphonate.[2] Moreover, some (methylthiomethylene) diphosphonates have been obtained from a stable phosphonium ylide $[(RO)_2P(=O)C^-(SMe)P^+(OR)_3]$,[3] prepared by addition of two equivalents of trialkylphosphite to the phosphonodithioformate $[(RO)_2P(=O)C(=S)SMe]$. This ylide reacts quantitatively with hydrogen chloride to give (methylthiomethylene) diphosphonates *via* a protonation and an Arbuzov-type dealkylation.[3,4] However, (mercaptomethylene) diphosphonates or diphosphonic acids (free thiol) are not known. In the oxygenated series, the earliest report pointed out the difficulty to isolate (α–hydroxymethylene) diphosphonates, due to their very easy rearrangement into the corresponding phosphates.[5] Special experimental conditions to minimize this isomerisation have been mentioned.[6] However, in the **mono**phosphonate series,

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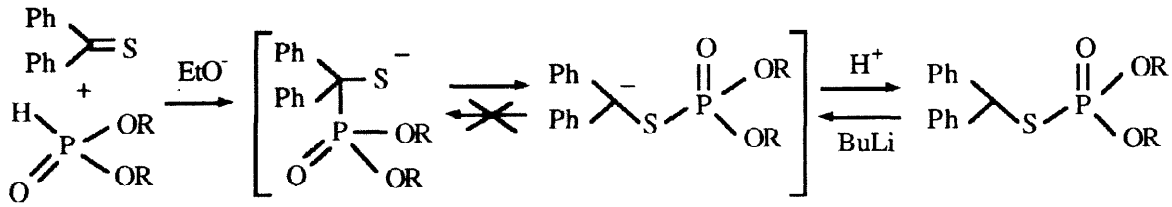
both side rearrangements are known, for phosphates and (hydroxymethyl) phosphonates, the most currently observed one being the easy conversion of (α-hydroxymethyl) phosphonates anions into the phosphates carbanions.[7] It is only for O-benzylic or O-allylic phosphates that the reverse transformation has been observed with good yield.[8-11] This isomerisation, whatever its direction, is not known for sulfur containing diphosphonates, and is scarcely described in the monophosphonates series. Some (phosphonomethyl) thiolates, prepared by C-addition of a dialkylphosphite anion onto thiocarbonyl compounds, were unstable and suffered rapid conversion into the phosphorothiolates, and it was suggested that the reverse transformation, from a S-(diphenylmethyl) phosphorothiolate and one equivalent of butyllithium between -60°C and +100°C, could not be achieved[12,13] (Scheme 1). Moreover, the stability of phosphorothiolate carbanions α-substituted by an ester function [EtOC(O)-CH⁻SP(O)(OR)$_2$] has also been evidenced, by trapping them with a ketone.[14]



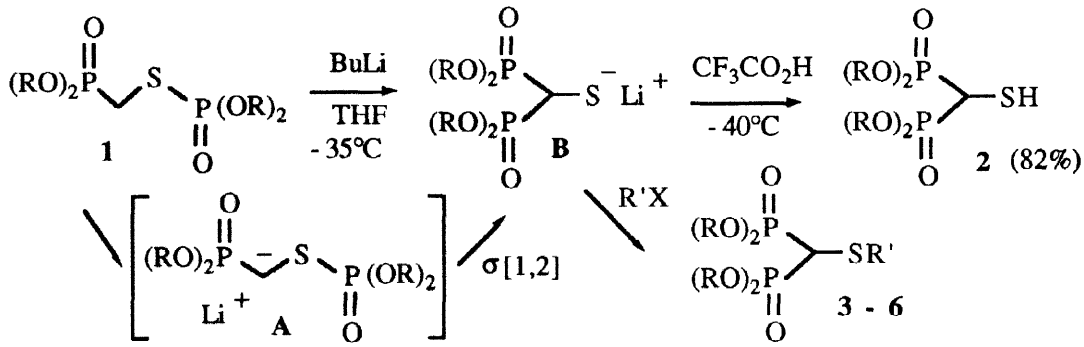
Scheme 1

In the course of our studies, related to the synthesis of mercapto-substituted phosphonates (much less known than their hydroxy or amino analogues), we describe herein the first example of the phosphorothiolate → mercaptophosphonate rearrangement leading to a (mercaptomethylene) diphosphonate (not previously described), and we report the syntheses of some derivatives of this phosphorylated thiol.

RESULTS AND DISCUSSION

The diisopropyl S-(diisopropylphosphonomethyl) phosphorothiolate **1** [^{31}P NMR : δ = 19.7 ppm and δ = 23.2 ppm, 2 d, $^{3}J_{PP}$ = 36 Hz, prepared by sodium borohydride reduction of methyl (diisopropylphosphonomethane) dithioate and *in situ* phosphonylation[15]], was deprotonated with butyllithium (1.5 equivalents) in THF at -35°C. The reaction was monitored by ^{31}P NMR (in C_6D_6, H_3PO_4 as external standard). The carbanion (**A**) was not observed by NMR but rearranged immediately, *via* a [1,2] sigmatropic shift, into the thiolate anion (**B**) (^{31}P NMR : δ = 21.7 ppm, s) (Scheme 2). This reaction was complete within 5 minutes in the NMR cell. Further protonation between -60°C and -30°C gave the tetraisopropyl (mercaptomethylene)diphosphonate **2** (^{31}P NMR : δ = 16.0 ppm, s, 100%), isolated in 82% yield. Derivatives **3 - 6** were obtained by *in situ* methylation, allylation, or acylation of the thiolate intermediate, in 56 to 82% yield (Scheme 2). In preference to methyl or ethyl groups, the O-isopropyl substituents have been chosen to avoid any dealkylation of the phosphonate function.[16] The protonation is the key-step to get the thiol in good yield, and the temperature must be carefully controlled during this step. Lithium salt of thiol **2** was stable at -40°C, but rising progressively the temperature of the reaction mixture to room temperature partly induced a desulfuration with formation of the methylene diphosphonate carbanion (iPrO)$_2$P(O)CH⁻P(O)(OiPr)$_2$ detected by NMR (^{31}P NMR : δ = 41 ppm, s). This signal appeared at -5°C, and accounted for 35 % of the mixture after 5 mn at +5°C ; its proportion climbed to 64 % at +35°C. The loss of sulfur, which is the reverse reaction of the

addition of sulfur to a carbanion, is plausible, due to the strong electroattractive effects of the two phosphono groups, and this reversibility has been already mentioned for α-mercapto ketones in basic medium.[17] The facility of this (S-phosphono)-phosphorothiolate → mercaptodiphosphonate isomerisation, compared to the easy reverse rearrangement in oxygenated series, may be rationalized by consideration of bond energies : (P-C : 62 Kcal ; P-S : 55 Kcal ; P-O : 84 Kcal).[18]



R = iPr ; **3** : R' = Me (76%) ; **4** : R'= undecyl (56%) ; **5** : R' = allyl (82%); **6** : R' = acetyl (64%)

Scheme 2

CONCLUSION

We have described the first phosphorothiolate → mercaptophosphonate, [1,2]-sigmatropic, rearrangement, which allows the preparation of a new (mercaptomethylene) diphosphonate. This rearrangement is the reverse of the one usually observed in the oxygenated series. It offers a convenient route for the synthesis of new sulfur-substituted methylene diphosphonic acid derivatives.

EXPERIMENTAL

General Methods : The ^{1}H NMR spectra were recorded with a "Bruker AC 250" spectrometer at 250.13 MHz in $CDCl_3$, using TMS as internal standard. The ^{13}C NMR spectra were recorded with a "Bruker AC 250" spectrometer at 62.89 MHz, in $CDCl_3$ with TMS as internal standard (proton decoupled, J_{CP} given). The ^{31}P NMR spectra were recorded with a "Bruker WP 80 SY" spectrometer at 32.44 MHz with H_3PO_4 as external standard. Chemical shifts are given in δ (ppm) and coupling constants in Hz; conventional abbreviations are used. The infrared spectra were recorded with a "Perkin-Elmer16 PC" spectrometer on the liquid film; ν (cm^{-1}) are given, and the following abbreviations are used : (s) strong, (vs) very strong, (m) medium, (w) weak, (vw) very weak. Mass spectra were recorded with a "Nermag R 10 10 H" spectrometer in electronic impact at 70 eV ; m / z and relative abundance are given.

Synthesis of Diisopropyl (S-diisopropylphosphonomethyl)phosphorothiolate 1 : This compound was prepared by the method we previously reported for the synthesis of the diisopropyl (S-diethylphosphonomethyl) phosphorothiolate analogue.[15] Thus, the dithioester $(iPrO)_2P(O)C(S)SCH_3$ was reduced by excess $NaBH_4$ in

refluxing acetonitrile, and treated with $ClP(O)(OiPr)_2$ [19] at 20°C. Usual work-up and column chromatography (silicagel Merck 60M, eluent : petroleum ether / ethyl acetate) gave 76% of **1** as a pale yellow liquid. Analysis : $C_{13}H_{30}O_6P_2S$: calc. % : S 8.51; obs. % : S 8.76. ^1H NMR ($CDCl_3$ / TMS) : 1.36 (overlapping d, 24H); 3.04 (d d, $^2J_{HP}$ = 15.0 and $^3J_{HP}$ = 9.8, 2H); 4.75 and 4.76 (2 sept d, $^3J_{HH} \approx {}^3J_{HP} \approx 6.2$, 4H). ^{13}C NMR ($CDCl_3$ / TMS) : 23.6 (overlapping d); 25.3 (d d, $^1J_{CP}$ = 123 and $^2J_{CP}$ = 4) ; 71.7 and 73.1 (2 d, $^2J_{CP}$ = 6.6 and 6.3). ^{31}P NMR ($CDCl_3$ / H_3PO_4) : 19.7 (d, $^3J_{PP} \approx 36$); 23.2 (d, $^3J_{PP} \approx 36$). IR (NaCl) ν (cm^{-1}) : 2980 (vs); 2934 (s); 2876 (m); 1468 (m); 1454 (m); 1386 (m); 1376 (m); 1356 (m); 1256 (vs and broad, $\nu_{P=O}$); 1180 (m); 1142 (m); 1106 (m); 986 (vs and broad, $\nu_{P\text{-}O\text{-}C}$); 938 (m); 898 (m); 886 (m); 814 (w); 772 (m). Mass : m / z (%) : 376 (0.6) $M^{+\cdot}$; 290 (11); 271 (13); 247 (17); 233 (25); 232 (12); 213 (24); 212 (12); 210 (19); 209 (50); 208 (71); 193 (22); 192 (31); 191 (91); 170 (22); 139 (10); 129 (11); 128 (77); 127 (18); 126 (11); 124 (13); 115 (15); 114 (14); 113 (26); 110 (100, $P(OH)(O)SCH_2^{+\cdot}$); 109 (11); 99 (15); 98 (14); 97 (54); 91 (24); 86 (50); 84 (80); 83 (19); 82 (24); 81 (13); 80 (21); 65 (35); 59 (30); 58 (11).

Synthesis of Tetraisopropyl (mercaptomethylene)diphosphonate 2 : Under N_2 and at -40°C, BuLi (1.3 to 2.0 eq., 1.6 M solution in n-hexane, ACROS) was added to a solution of phosphorothiolate **1** (150 mg, 0.4 mmol) in dry THF (5 ml). The reaction mixture was stirred between -40°C and -30°C for 30 to 45 min. Then trifluoroacetic acid (2.6 to 4.0 eq.) was added all at once at -60°C and the reaction mixture was stirred for 1 to 1.5 hours, allowing the temperature to rise to -30°C. Extraction with ether (15 ml), washing with water (3 x 15 ml), drying over Na_2SO_4, elimination of the solvent under diminished pressure, gave crude **2** as a pale yellow liquid with 82% yield. Analysis : $C_{13}H_{30}O_6P_2S$: calc. % : C 41.48; H 8.03; S 8.51; obs. % : C 41.76; H 8.10; S 8.72. ^1H NMR ($CDCl_3$ / TMS) : 1.37 and 1.39 (2 d, J = 6.0, 24H); 2.41 (d t, $^3J_{HH} \approx {}^3J_{HP} \approx 9.5$, SH); 3.05 (t d, $^2J_{HP}$ = 21.2 and $^3J_{HH}$ = 9.5, 1H); 4.83 sept d, $^3J_{HH} \approx {}^3J_{HP} \approx 6.3$, 4H). ^{13}C NMR ($CDCl_3$ / TMS) : 24.0 (m); 31.3 (t, $^1J_{CP}$ = 140); 72.7 (m). ^{31}P NMR ($CDCl_3$ / H_3PO_4) : 15.9 (s). IR (NaCl) ν (cm^{-1}) : 2980 (vs); 2934 (s); 2874 (m); 2736 (w); 2514 and 2500 (vw, ν_{SH}) ; 1468 (m); 1454 (m); 1386 (s); 1374 (s); 1254 (vs, $\nu_{P=O}$); 1118 (m); 1142 (m); 1104 (m); 987 (vs and broad, $\nu_{P\text{-}O\text{-}C}$); 938 (m); 888 (m); 836 (m); 742 (m). Mass m / z (%) : 376 (7) $M^{+\cdot}$; 334(3); 292 (5); 250 (12); 235 (8); 209 (22); 208 (68); 191 (12); 128 (27); 127 (26); 110 (22); 86 (12); 84 (17); 65 (10); 51 (21); 49 (68); 47 (18); 45 (17); 44 (10); 43 (100, $C_3H_7^+$); 42 (13); 41 (50).

Synthesis of (alkylthiomethylene)diphosphonates 3 - 6 : The same procedure as described for synthesis of thiol **2** was used, hydrolysis being replaced by alkylation (with iodomethane, or 1-bromoundecane, or allyl bromide respectively), or acylation with acetyl chloride, at -30°C for 3 hours. Then the mixture was stirred during an additional 15 hours, allowing the temperature to rise at room temperature. Extraction with ether and usual work-up led to crude compounds, which were purified by Kugelrohr - distillation under 0.02 mmHg. Compounds **3-6** were obtained as pale yellow liquids, with 56 to 82 % yields (we already reported about similar diphosphonates [3]).

Tetraisopropyl (methylthiomethylene)diphosphonate 3 : Yield = 76 %. (RN : 128396-09-8).[3] Analysis : $C_{14}H_{32}O_6P_2S$: calc. % : C 43.06; H 8.26; S 8.21; obs. % : C 43.21; H 8.30; S 8.18. ^1H NMR ($CDCl_3$ / TMS) : 1.37 and 1.38 (2 d, $^3J_{HH}$ = 6.2, 24H); 2.40 (s, 3H); 2.79 (t, $^2J_{HP}$ = 22.0, 1H); 4.84 (sept d, $^3J_{HH} \approx {}^3J_{HP} \approx 6.2$, 4H). ^{13}C NMR ($CDCl_3$ / TMS) : 17.9 (t, $^3J_{CP} \approx 3$,); 24.1 (m); 40.0 (t, $^1J_{CP}$ =140.0); 72.3 and 72.4 (2 d, $^2J_{CP}$ = 3.5). ^{31}P NMR ($CDCl_3$ / H_3PO_4) : 16.0 (s). IR (NaCl) ν (cm^{-1}) : 2978 (vs); 2932 (s); 2874

(s); 2734 (m); 1468 (m); 1452 (m); 1386 (s); 1374 (s); 1318 (w); 1250 (vs, $\nu_{P=O}$) ; 1178 (m); 1142 (m); 1104 (m); ≈ 980 (vs and broad, ν_{P-O-C}); 938 (m); 886 (m); 842 (m); 770 (m); 744 (m). Mass m /z (%) : 392 (100, $MH_2^{+\cdot}$); 391 (11, MH^+); $M^{+\cdot}$ is absent; 350 (11); 346 (9); 345 (19); 304 (30); 262 (41); 220 (15); 219 (14); 205 (12); 177(80); 176 (19); 160 (9); 159 (19); 158 (15); 145 (10); 142 (25); 141 (34); 123 (16); 65 (10); 61 (10); 59 (15); 45 (13); 43 (84); 42 (14); 41 (40).

Tetraisopropyl (undecylthiomethylene)diphosphonate 4 : Yield = 56 %. Analysis : $C_{24}H_{52}O_6P_2S$: calc. % : C 54.31; H 9.87; S 6.04; obs. % : C 54.57; H 10.05; S 6.22. ^1H NMR ($CDCl_3$ / TMS) : 0.87 (t, $^3J_{HH} \approx 6.5$, 3H); 1.26 (m, 16H); 1.36 and 1.37 (2 d, $^3J_{HH} \approx 6.0$, 24H); 1.59 (qt, $^3J_{HH} \approx 7.4$, 2H); 2.81 (t, $^3J_{HH} \approx 7.4$, 2H); 2.87 (t, $^2J_{HP} = 21.8$, 1H); 4.84 (sept d, $^3J_{HH} \approx {}^3J_{HP} \approx 6.2$, 4H). ^{13}C NMR ($CDCl_3$ / TMS) : 14.2 (s); 22.8 (s); 24.1 (m); 29.4 (m); 32.0 (s); 34.7 (s); 38.7 (t, $^1J_{CP} = 141.0$); 72.3 and 72.4 (2 d, $^2J_{CP} \approx 3.4$ and $^2J_{CP} \approx 3.5$). ^{31}P NMR ($CDCl_3$ / H_3PO_4) : 16.3 (s). IR (NaCl) ν (cm^{-1}) : 2978 (s); 2958 (s); 2926 (s); 1468 (m); 1456 (m); 1386 (m); 1374 (m); 1254 (vs, $\nu_{P=O}$) ; 1178 (m); 1142 (m); 1104 (m); 992 (vs, ν_{P-O-C}); 936 (m); 886 (m); 842 (m); 772 (m); 732 (m). Mass m /z (%) : 530 (26, $M^{+\cdot}$); 343 (25); 342 (49); 341 (49); 302 (53); 301 (37); 277 (12); 261 (64); 257 (21); 256 (91); 219 (100, $[P(OH)_2(O)]_2CHSC^{+\cdot}$); 218 (23); 209 (31); 208 (16); 207 (13); 203 (11); 191 (12); 177 (95); 176 (30); 175 (9); 159 (18); 129 (19); 127 (14); 99 (12); 97 (11); 96 (13); 83 (11); 69 (15); 57 (18); 55 (23); 43 (55); 41 (22).

Tetraisopropyl (allylthiomethylene)diphosphonate 5 : Yield = 82 %. Analysis : $C_{16}H_{34}O_6P_2S$: calc. % : C 46.14; H 8.22; S 7.69; obs. % : C 46.27; H 8.30; S 7.92. ^1H NMR ($CDCl_3$ / TMS) : 1.37 and 1.38 (2 d, $^3J_{HH} \approx 6.0$, 24H); 2.93 (t, $^2J_{HP} = 21.3$, 1H); 3.44 (d, $^3J_{HH} = 7.4$, 2H); 4.82 (sept d, $^3J_{HH} \approx {}^3J_{HP} \approx 6.2$, 4H). ≈ 5.16 and ≈ 5.18 (2 d, $^3J_{HH} \approx 10$ and $^3J_{HH} \approx 17.5$, 2H); 5.75 (d d t, $^3J_{HH} \approx 10$ and $^3J_{HH} \approx 17.5$, and $^3J_{HH} \approx 7.4$, 1H). ^{13}C NMR ($CDCl_3$ / TMS) : 23.9 and 24.0 (2 d, $^3J_{CP} = 2.8$); 36.0 (t, $^1J_{CP} = 141.0$); 36.6 (s); 72.2 and 72.3 (2 d, $^2J_{CP} \approx 3.4$); 119.4 (s); 132.9 (s). ^{31}P NMR ($CDCl_3$ / H_3PO_4) : 16.5 (s). IR (NaCl) ν (cm^{-1}) : 3080 (w, $\nu_{CH=CH_2}$); 2978 (vs); 2934 (m); 2876 (m); 1634 (w, $\nu_{C=C}$); 1468 (m); 1452 (m); 1434 (m); 1386 (s); 1374 (m); 1252 (vs, $\nu_{P=O}$); 1178 (m); 1142 (m); 1104 (s); 1078 (w); 984 (vs, ν_{P-O-C}); 936 (m); 898 (m); 888(m); 840 (m); 764 (m); 740 (m). Mass m /z (%) : 417 (9, MH^+); 416 (42, $M^{+\cdot}$); 374 (15); 343 (10); 332 (7); 302 (21); 260 (29); 230 (16); 218 (46); 217 (18); 176 (100, $C[P(OH)_3]_2^{+\cdot}$); 175 (44); 166 (18); 159 (11); 158 (12); 157 (14); 127 (34); 85 (31); 45 (24); 43 (79); 41 (100, $CH_2{=}CHCH_2^+$); 39 (44).

Tetraisopropyl (acetylthiomethylene)diphosphonate 6 : Yield = 64 %. Analysis : $C_{15}H_{32}O_7P_2S$: calc. % : C 43.05; H 7.70; S 7.66; obs. % : C 43.22; H 7.99; S 7.78. ^1H NMR ($CDCl_3$ / TMS) : 1.33 and 1.34 (2 d, $^3J_{HH} = 5.8$, 24H); 2.42 (s, 3H); 4.19 (t, $^2J_{HP} = 21.5$, 1H); 4.79 (m, 4H). ^{13}C NMR ($CDCl_3$ / TMS) : 23.9 (m); 29.7 (s); 35.7 (t, $^1J_{CP} = 141,1$); 72.5 and 72.55 (2 d, $^2J_{CP} = 3.3$ and $^2J_{CP} = 3.1$); 191.7 (s). ^{31}P NMR ($CDCl_3$ / H_3PO_4) : 14.7 (s). IR (NaCl) ν (cm^{-1}) : 2980 (vs); 2934 (s); 2876 (m); 1704 (vs, $\nu_{C=O}$); 1546 (m); 1510 (m); 1468 (m); 1454 (m); 1386 (m); 1374 (m); 1358 (m); 1256 (vs, $\nu_{P=O}$); 1178 (m); 1142 (m); 1104 (s); 983 (vs, ν_{P-O-C}); 886 (m); 844 (m); 772 (m); 742 (m). Mass m /z (%) : 418 (9, $M^{+\cdot}$); 376 (3); 219 (16); 218 (7); 212 (8); 209 (16); 208 (52); 203 (15); 177 (26); 166 (41); 159 (15); 127 (16); 96 (21); 86 (27); 85 (12); 84 (49); 83 (11); 71 (38); 69 (15); 65 (20); 59 (15); 51 (16); 49 (47); 47 (10); 45 (16); 43 (100, CH_3CO^+ and $C_3H_7^+$); 41 (30).

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