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Convenient Synthesis of Bisphosphonomethylphosphoric Acid

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ABSTRACT: *The reaction of phosgene or triphosgene with trimethylsilyl dialkylphosphites led to bisdialkylphosphonomethyl-dialkylphosphates in good yields. The cleavage of the allyl ester was carried out under mild conditions using the Wilkinson catalyst.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:111–113, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10105

INTRODUCTION

Several bisphosphonates have proved to be effective in the treatment of clinical disorders such as Paget's disease of bone, myeloma, and bone metastasis [1,2]. Medronic acid (methylenebisphosphonic acid) derivatives are also used as inhibitors of bone resorption for the treatment of osteoporosis [2,3]. They are selectively taken up and absorbed to mineral surfaces in bone, where they interfere with the action of osteoclasts. A better inhibition of bone resorption might be obtained through an increase of the adsorption to the mineral surfaces in bone. For this reason it became of interest to synthesize the phosphate of medronic acid shown in Scheme 1. This molecule presents two phosphonate groups and one phosphate group, which may increase the presence of the molecule at the sites of resorption. Herein, we describe the synthesis of bisphosphonomethylphosphoric acid **1** *via* the allyl ester **2**.

RESULTS AND DISCUSSION

Bisphosphonomethylphosphoric acid **1** has not been described in the literature. A bisdialkylphosphonomethyl-dialkylphosphate was first mentioned by Quimby [4] as isopropyl ester. It was considered as an intermediate in the reaction of sodium diisopropyl phosphite with phosgene in toluene for the synthesis of tetrasodium carbonyldiphosphonate, but it has not been isolated in a pure state. Bisdialkylphosphonomethyl-dialkylphosphate was also mentioned [5] (a) as a by-product in the reaction of tetraethyldiazomethylenebisphosphonate with diethyl phosphite [6] and (b) in a form of methyl ester in the reaction of dihydroxymethylenebisphosphonate with dimethyl phosphite [7].

The bisdiallylphosphonomethyl-diallylphosphate has likewise not been reported in literature. Although allyl esters are rarely used in phosphorous chemistry because of their sensitivity toward bases, e.g. BuLi, LDA... [8], an allyl ester seemed to be the derivative of choice for the further deprotection leading to the bisphosphonomethylphosphoric acid **1**.

We chose to synthesize bisdiallylphosphonomethyl-diallylphosphate starting from diallyl phosphite **3**, which could be prepared in large quantities following the procedure described by

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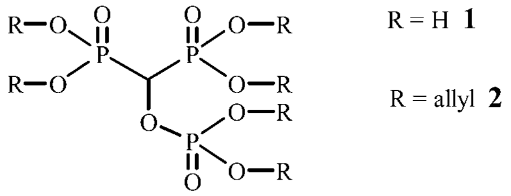
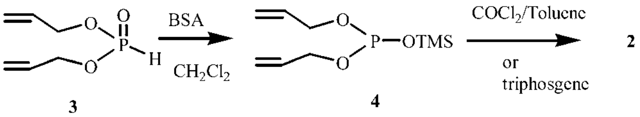


SCHEME 1 Bisphosphonomethylphosphoric acid **1** and its allyl ester **2**.



SCHEME 2 Synthesis of bisdiallylphosphonomethyl-diallylphosphate **2**.

Kennedy [9]. The reactivity of diallyl phosphite **3** was then enhanced by trimethylsilylation with BSA (bis(trimethylsilyl)acetamide) or trimethylsilyl chloride. Trimethylsilyl diallylphosphite **4** obtained by the reaction of BSA with diallyl phosphite **3** was not isolated but was immediately reacted with a solution of phosgene in toluene to give a colorless oil, which corresponds to compound **2** (Scheme 2). Its ^{31}P NMR spectrum (Table 1) is indicative of a phosphate-bisphosphonate moiety.

The use of triphosgene instead of phosgene led to the same results; although, the triphosgene reaction was easier to carry out. Compound **2** was obtained in good yield, showing no dependence on the proportion of phosgene/phosphite used. It is sensitive to oxidation and must be stored under inert atmosphere at low temperature.

We applied the same procedure to the synthesis of other bisdialkylphosphonomethyl-dialkylphosphates (Table 1). These esters were also characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy, and mass spectrometry.

The reactivity of trimethylsilyl dialkylphosphite with phosgene or triphosgene was different from the reactivity of trialkyl phosphites and no chlorination was observed [10]. Indeed, the trialkyl phosphites gave a corresponding dialkylchlorophosphate whereas the trimethylsilyldialkylphosphite led to the bisdialkylphosphonomethyl-dialkylphosphate.

The hydrolysis of bisdialkylphosphonomethyl-dialkylphosphate **5, 6** with refluxing hydrochloric acid resulted in the cleavage of the compound to give a methanehydroxybisphosphonate [4]. In order to preserve the phosphate-bisphosphonate structure the cleavage of the ester should be carried out under neutral conditions, which is usually done with allyl esters employing the Wilkinson catalyst chlorotris(triphenylphosphine)rhodium [11]. This catalyst has been successfully employed to obtain the expected bisphosphonomethyl-phosphoric acid in quantitative yield from its allyl ester.

CONCLUSION

In this article we described a convenient synthesis of bisphosphonomethyl-phosphoric acid **1** *via* the bisdiallylphosphonomethyl-diallylphosphate **2**. For the first time these compounds are fully described in the literature. The cleavage of the allyl ester, carried out under very mild conditions using Wilkinson's catalyst, led to the expected bisphosphonomethylphosphoric acid **1**.

EXPERIMENTAL

Materials

Chemicals were purchased from Aldrich and used as received. Diallyl-*H*-phosphonate was not commercially available and was prepared according to procedure described by Kennedy [9].

Merck silica gel 60 F_{254} (0.25 mm) plates were employed for analytical TLC. Compounds were revealed by UV, iodine, 1% aqueous potassium permanganate, and molybdenum blue. Merck silica gel 60H was used for silica gel column chromatography.

^{1}H and ^{13}C NMR were recorded on Bruker AC200 and WP200SY spectrometers, respectively. Mass spectra were recorded on a JEOL DX 100 spectrometer. The matrix used was *m*-nitrobenzylic alcohol (NOBA). Microanalysis were performed in the analytical department of the CNRS (Vernaison, Rhône).

TABLE 1 NMR Data of the Central Moiety of Bisphosphonomethylphosphoric Acid and Esters

	R	$\delta\ ^{1}H$	$\delta\ ^{13}C$	$\delta\ ^{31}P_{phosphate}$	$\delta\ ^{31}P_{phosphonate}$	$^{3}J_{PP}$ *(Hz)*
1	H	4.88	69.7	2.3	13.6	
2	Allyl	5.13	69.1	0.58	15.08	14.0
5	Ethyl	5.01	68.7	0.24	14.67	13.8
6	Isopropyl	4.81	70.4	−1.45	13.20	14.0

Bis-diallylphosphonomethyl-diallylphosphate **2**

N,*O*-bis(trimethylsilyl)acetamide (1.8 ml, 6.1 mmol) was added to a solution of 1.1 ml of diallyl phosphite **3** (2.1 mmol) in 10 ml of methylenechloride, under nitrogen atmosphere and at room temperature. After 4 h of stirring, 1.1 ml of phosgene (20%) in toluene (7.4 mmol) was added dropwise at 0°C. Then the reaction was stirred overnight at room temperature. The solvents were removed under reduced pressure and the residual oil was purified by column chromatography (silica gel 50:50, ethyl acetate/petroleum ether 70:30 and 80:20) to give 0.77 g of bis-diallylphosphonomethyl-diallylphosphate as a colorless oil in 73% yield. ^{1}H NMR ($CDCl_3$/200 MHz): δ (ppm): 4.60 (m, 4H, CH_2—O—P); 5.13 (td, $^{2}J_{HP} = 16.5$ Hz, $^{3}J_{HP} = 13.0$ Hz, 1H, —CH); 5.30 (m, 12H, CH_2=CH—); 5.92 (m, 6H, CH_2=CH—). ^{13}C NMR ($CDCl_3$/400 MHz): δ (ppm): 68.5 (d, $^{2}J_{CP} = 2.8$ Hz, CH_2—O—$P_{phosphonate}$); 69.1 (td, $^{1}J_{CP} = 156.4$ Hz, $^{2}J_{CP} = 8.4$ Hz, CH), 69.1 (d, $^{2}J_{CP} = 4.9$ Hz, CH_2—O—$P_{phosphate}$); 118.7 (s, CH_2=$CH_{phosphate}$); 119.0 (s, CH_2=$CH_{phosphonate}$); 132.9 (m, CH_2=CH). ^{31}P NMR ($CDCl_3$/250 MHz): δ (ppm): 0.58 (t, $^{3}J_{PP} = 14.0$ Hz, 1P); 15.08 (d, $^{3}J_{PP} = 14.0$ Hz, 2P). MS (Fab$^+$/NOBA) $m/z = 535$ [M + Na]$^+$, 513 [M + H]$^+$. Calcd. for $C_{19}H_{31}O_{10}P_3$ (512.4): C, 44.54; H, 6.10; P, 18.14; found: C, 44.32; H, 6.07; P, 18.04.

Bis-diethylphosphonomethyl-diethylphosphate **5**

In the same manner as for **2**, 1 ml of diethylphosphonate and 4.1 ml of phosgene (20%) in toluene were used to give **5** in 98% yield. ^{1}H NMR ($CDCl_3$/200 MHz): δ (ppm): 1.31 (t, $^{3}J_{HH} = 7.1$ Hz, 6H, $CH_{3\,phosphate}$); 1.33 (t, $^{3}J_{HH} = 7.1$ Hz, 6H, $CH_{3\,phosphonate}$); 4.19 (m, 12H, CH_2—O—P); 5.01 (td, $^{2}J_{HP} = 16.7$ Hz, $^{3}J_{HP} = 13.0$ Hz, 1H, —CH). ^{13}C NMR ($CDCl_3$/400 MHz): δ (ppm): 16.35 (d, $^{3}J_{CP} = 7.2$ Hz, $CH_{3\,phosphate}$); 16.72 and 16.79 (2d, $^{3}J_{CP} = 3.4$ Hz, $CH_{3\,phosphonate}$); 64.21 (d, $^{2}J_{CP} = 2.5$ Hz, CH_2—O—$P_{phosphonate}$); 64.87 (d, $^{2}J_{CP} = 6.1$ Hz, CH_2—O—$P_{phosphate}$); 68.68 (td, $^{1}J_{CP} = 156.8$ Hz, $^{2}J_{CP} = 8.3$ Hz, CH). ^{31}P NMR ($CDCl_3$/200 MHz): δ (ppm): 0.24 (t, $^{3}J_{PP} = 13.8$ Hz, 1P); 14.67 (d, $^{3}J_{PP} = 13.8$ Hz, 2P). MS (Fab$^+$/NOBA): $m/z = 463$ [M + Na]$^+$, 441 [M + H]$^+$. Calcd. for $C_{13}H_{31}O_{10}P_3$ (440.3): C, 35.46; H, 7.10; P, 21.10; found: C, 35.26; H, 7.06; P, 20.97.

Bis-diisopropylphosphonomethyl-diisopropylphosphate **6**

In the same manner as for **2**, 1 ml of diisopropylphosphonate and 2 ml of phosgene (20%) in toluene were used to give **6** in 94% yield. ^{1}H NMR ($CDCl_3$/200 MHz): δ (ppm): 1.27 (m, 36H, CH_3); 4.77 (m, 6H, CH—O—P); 4.81 (td, $^{2}J_{HP} = 15.8$ Hz, $^{3}J_{HP} = 13.2$ Hz, 1H, —CH). ^{13}C NMR ($CDCl_3$/400 MHz): δ (ppm): 24.2 (m, CH_3); 70.4 (td, $^{1}J_{CP} = 159.1$ Hz, $^{2}J_{CP} = 8.0$ Hz, CH); 73.8 (m, CH—O—P). ^{31}P NMR ($CDCl_3$/200 MHz): δ (ppm): −1.45 (t, $^{3}J_{PP} = 14.0$ Hz, 1P); 13.20 (d, $^{3}J_{PP} = 14.0$ Hz, 2P). SM (Fab$^+$/NOBA): $m/z = 547$ [M + Na]$^+$, 525 [M + H]$^+$; 273 [$(HO)_2PO$—$OCH[PO(OH)_2]_2$ + H]$^+$. Calcd. for $C_{19}H_{43}O_{10}P_3$ (524.5): C, 43.51; H, 8.56; P, 17.72; found: C, 43.32; H, 8.51; P, 17.59.

Bisphosphonomethylphosphoric Acid **1**

To a solution of 0.50 g (9.76 mmol) of **2** in 10 ml of a mixture acetonitrile/water (85:15), was added 0.054 g (0.059 mmol) of chlorotris(triphenylphosphine)rhodium(I). The reaction was refluxed for 3 h. The acetonitrile was removed and water was added. The aqueous layer was washed twice with methylenechloride and then freeze-dried to give 0.260 g of **1** as an yellow oil in 97% yield. ^{1}H NMR (D_2O/200 MHz): δ (ppm): 4.88 (s, 1 H, CH). ^{13}C NMR (D_2O/400 MHz): δ (ppm): 69.7 (td, $^{1}J_{CP} = 146.6$ Hz, $J_{CP} = 8.3$ Hz, CH). ^{31}P NMR (D_2O/250 MHz): δ (ppm): 2.3 (br s, 1P); 13.6 (br s, 2P). MS (ESI$^-$): $m/z = 270.9$ [M − H]$^-$, 292.8 [M − 2H + Na]$^-$, 190.9 [HO—$CH[PO(OH)_2]_2$—H]$^-$, 252.8 [M—H_2O—H]$^-$. Calcd. for $CH_7O_{10}P_3$, H_2O (290.0): C, 4.14; H, 3.13; P, 32.04; found: C, 4.09; H, 3.16; P, 30.12.

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