New Efficient Synthesis of 1-Hydroxymethylene-1,1-Bisphosphonate Monomethyl Esters

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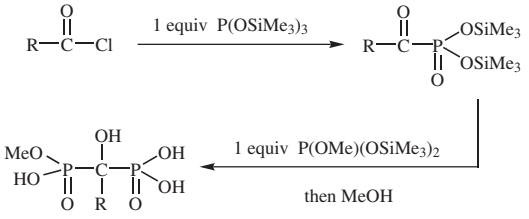
Abstract: A new efficient procedure for the synthesis of 1-hydroxymethylene-1,1-bisphosphonate monomethyl esters in three steps from acid chlorides is reported here.

Key words: 1-hydroxymethylene-1,1-bisphosphonates, α-ketophosphonates, bis(silylated) phosphite, Arbuzov reaction

Derivatives of 1-hydroxymethylene-1,1-bisphosphonates (HMBPs) have gained considerable interest in recent years because of their biological properties and medical applications.[1–3] They are an important class of products used in the treatment of a variety of diseases showing an abnormal calcium metabolism such as Paget's disease, osteoporosis and metastatic bone diseases.[4–6] More recently, HMBPs have been found to have an effect on treatment of metastatic cancer.[7] It has been reported that they inhibit bone metastases proliferation in prostate and breast cancers.[8–10] These compounds, characterized by a P-C-P linkage, are stable structural analogues of pyrophosphate and are completely resistant to enzymatic hydrolysis. However, the major drawback in the efficacy of these products is their poor oral bio-availability (only 3–7% of the drug is metabolized).[11] This results from their low lipophilicity due to their high ionization at physiological pH values. Moreover, absorption of HMBPs is further reduced by their strong complexation of calcium and other divalent metal cations in the intestinal lumen.[11] To circumvent these problems, a prodrug strategy was considered that would deliver bisphosphonates with an improved gastrointestinal absorption. Only few reports about the design of bisphosphonate prodrugs have been published in the literature.[12,13] Among them, Ezra et al. have shown that the introduction of a dipeptide as the side chain in bisphosphonate increased the specificity of the drug significantly.[14] Another interesting approach is the modification of the phosphonic acid function itself, by introducing an ester group. Thus, by masking the negative charges of HMBPs with suitable bioreversible substituents, the lipophilicity of bisphosphonates could be enhanced and the complexation with divalent cations decreased. Bisphosphonate prodrugs should then release bisphosphonic acids via enzymatic and/or chemical hydrolysis. HMBP tetraesters could be the best prodrugs. Unfortunately, these derivatives are not stable at physiological pH as they rearrange into phosphonophosphate pentaesters.[15] For this reason, synthesis of HMBP partial esters has been investigated. Turhanen et al. reported a synthetic method to prepare such compounds, by using regioselective dealkylation of HMBP tetraesters by different metal halides or trimethylsilyliodide.[16] Recently, our laboratory described a one-pot synthesis of HMBP di-and trimethylesters.[17] HMBP *P*,*P*′-diesters were synthesized from acid chlorides and two equivalents of methyl bis(trimethylsilyl) phosphite whereas HMBP *P*,*P*-diesters and trimethylesters were prepared by reaction of one equivalent of tris(trimethylsilyl) phosphite or methyl bis(trimethylsilyl) phosphite, respectively, with α-ketophosphonates. These last intermediates were preferred to acid chlorides in order to avoid a second attack of the phosphite on the carbonyl of the acid chloride.

Concerning the synthesis of HMBP monomethyl esters, a similar strategy was considered. Initial attempts employed acid chlorides and one equivalent of tris(trimethylsilyl) phosphite without solvent in order to obtain the bis(silylated) α-ketophosphonate (Scheme 1).[18] Addition of one equivalent of methyl bis(trimethylsilyl) phosphite and methanolysis gave the expected HMBP monomethyl esters with satisfactory crude yields (44% and 62%, respectively, for R = CH_3 and R = *i*-Pr). However, although the reaction was carried out at –20 °C, the major HMBP monomethyl ester was obtained as a mixture with the corresponding bisphosphonic acid and HMBP *P*,*P*′-dimethyl ester; these three compounds being difficult to separate. Bisphosphonic acid was formed due to the addition of tris(trimethylsilyl) phosphite on silylated α-ketophosphonate whereas HMBP dimethyl ester resulted from the reaction between methyl bis(trimethylsilyl) phosphite and the unreacted acid chloride. Consequently, a new procedure reported herein was investigated using bis(silylated) α-ketophosphonates (prepared in two steps from acid chlorides) and methyl bis(trimethylsilyl) phosphite.



Scheme 1

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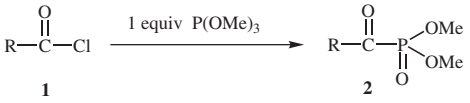
The first step of the synthesis consisted of an Arbuzov reaction between the acid chloride **1** and trimethylphosphite in order to furnish the corresponding α-ketophosphonate **2** (Scheme 2). The reaction, realized without solvent under argon, was exothermic and carried out at –10 °C during the addition of acid chloride. After being warmed to room temperature, the reaction mixture was stirred for two hours. The end of the reaction was easily monitored by ^{31}P {^{1}H} NMR (appearance of a peak with a chemical shift about 0 ppm, different from the starting product at δ = 141.0 ppm) or by IR spectroscopy (disappearance of the acid chloride signal about 1800 cm^{-1}).

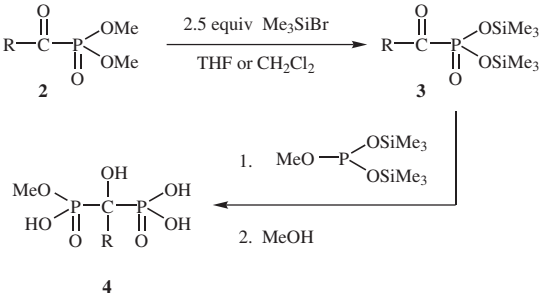


Scheme 2

Table 1 shows the different alkyl or aryl α-ketophosphonate dimethyl esters **2a–f** obtained in excellent yields from 74% to 90% (entries 1–6). We indicate here the purification method used for each α-ketophosphonate **2a–f** and its characteristic chemical shift in ^{31}P {^{1}H} NMR in $CDCl_3$ solution. We note that these compounds, kept cold under argon, are stable for several months.

The same reaction conditions (no solvent, temperature about –10 °C, then r.t. for 2 h) were applied to phenylacetyl chloride **1g**. As reported previously,[19] a mixture of the desired α-ketophosphonate **2g** as the minor product along with its corresponding enolic form as the major product was obtained. We modified the solvent and temperature conditions as shown in Table 1 (entries 8–10) in order to try to push the reaction towards formation of the α-ketophosphonate. Attempts were carried out in distilled THF or dichloromethane at low temperature (–70 °C) and gave the same results as previously. By using trimethyl phosphite, the corresponding enolic form of **2g** was always obtained as the major compound whatever the temperature. No more purification was attempted and another method for the synthesis of the HMBP monomethyl ester **2g** was subsequently investigated.

Next, α-ketophosphonates **2a–f** were silylated via an Arbuzov reaction. Thus, addition of 2.5 equivalents of freshly distilled trimethylsilyl bromide to a cooled solution of the appropriate α-ketophosphonate **2** in distilled THF or dichloromethane under argon was carried out (Method A, Scheme 3). The reaction was exothermic and the temperature had to be maintained below 10 °C. The bis(silylated) α-ketophosphonate **3** was obtained, usually after five hours at room temperature; the end of the reaction being monitored by ^{31}P {^{1}H} NMR. After evaporation of volatile fractions and solvent under reduced pressure, the bis(silylated) intermediate **3** was treated with one equivalent of methyl bis(trimethylsilyl) phosphite[20] at 0 °C under argon. The reaction mixture was stirred overnight, furnishing HMBP monomethyl esters **4** after methanolysis. After vacuum evaporation of volatile fractions, the crude compounds **4** were purified as indicated in Table 2. Oils **4a** and **4b** were purified by washes with diethyl ether (entries 11 and 12) or by precipitation in diethyl ether for products **4c** and **4f** (entries 13 and 16) or methanol for products **4d** and **4e** (entries 14 and 15). HMBP monomethyl esters **4** were synthesized very efficiently both in aliphatic or aromatic series with good yields.



Scheme 3 Synthesis of monomethyl esters **4**, Method A

Because of the presence of two stereogenic centers, four stereoisomers were expected. However, the two diastereoisomers were not distinguished by NMR spectroscopy. Indeed, the ^{31}P {^{1}H} NMR spectra of HMBP monomethyl esters **4** showed the presence of only two different doublets with equal $^{2}J_{P\text{-}P}$ coupling constants. The ^{31}P {^{1}H} NMR chemical shifts and $^{2}J_{P\text{-}P}$ coupling constants were sensitive to the substituent R on the central carbon. They were, respectively, about 20–22 ppm and 36–43 Hz for aliphatic compounds **4a–c** (entries 11–13) and about 16–18 ppm and 26–31 Hz for aromatic compounds **4d–f** (entries 14–16). The chemical shift differences between these two doublets were very low (about only 1–2 ppm) because of the presence of only one methyl ester group. Use of coupled ^{31}P NMR spectroscopy allowed us to assign the two different signals of phosphorus atoms of HMBP monomethyl esters **4**. The chemical shift of phosphonic acid fragment was always higher. Moreover, the ^{13}C {^{1}H} NMR spectra showed a characteristic signal about δ = 70–80 ppm (dd) with $^{1}J_{C\text{-}P}$ coupling constants about 140–145 Hz for the central carbon.

In order to synthesize HMBP monomethyl ester **4g** (R = $PhCH_2$) and to avoid the formation of the enol as described previously, we used tris(trimethylsilyl) phosphite instead of trimethyl phosphite. In the first procedure, as indicated in Scheme 1, $P(OMe)_3$ was applied to phenylacetyl chloride **1g**. Nevertheless, the reaction carried out at very low temperature to avoid a second attack of the tris(trimethylsilyl) phosphite on the carbonyl of acid chloride. Thus, one equivalent of tris(trimethylsilyl) phosphite was added dropwise at –70 °C to phenylacetyl chloride **1g** in dichloromethane (Method B, Scheme 4). After 30 minutes at this temperature, ^{31}P {^{1}H} NMR spectroscopy indicated the disappearance of tris(trimethylsilyl) phosphite (δ = 114.0 ppm) and the formation of the intermediate bis(silylated) α-ketophosphonate **3g** about –20 ppm. Under these conditions, the formation of the enolic form was not observed. Compound **3g** was not isolated but directly

Table 1 Synthesis of α-Ketophosphonate Dimethyl Esters **2**[23]

Entry	Compound	R	Solvent	Temp	Purification method	Yield (%)	^{31}P {^{1}H} NMR [($CDCl_3$, δ (ppm)]
1	**2a**	Me	–	–10 °C then r.t.	Distillation	86	–0.6
2	**2b**	*i*-Pr	–	–10 °C then r.t.	Distillation	86	–0.3
3	**2c**	$C_{15}H_{31}$	–	–10 °C then r.t.	No purification	89	–0.4
4	**2d**	Ph	–	–10 °C then r.t.	Distillation	74	–0.9
5	**2e**	*p*-MeOPh	–	–10 °C then r.t.	Distillation	89	1.8
6	**2f**	*p*-BrPh	–	–10 °C then r.t.	Extraction in Et_2O	90	0.4
7	**2g**	$PhCH_2$	–	–10 °C then r.t.	–	Nd[a]	–0.7
8	**2g**	$PhCH_2$	THF	–70 °C then r.t.	–	Nd[a]	–0.7
9	**2g**	$PhCH_2$	THF	–70 °C	–	Nd[a]	–0.7
10	**2g**	$PhCH_2$	CH_2Cl_2	–70 °C	–	Nd[a]	–0.7

[a] Nd = not determined.

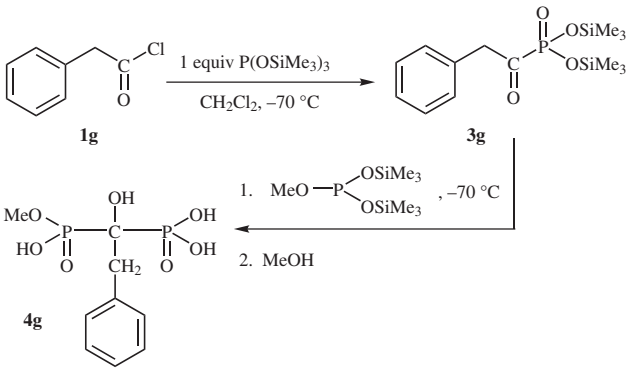
Table 2 Synthesis of 1-Hydroxymethylene-1,1-bisphosphonate Monomethyl Esters **4**[24]

Entry	Compound	R	Method	Purification method	Yield (%)	^{31}P {^{1}H} NMR [D_2O or $CDCl_3$, δ (ppm)][a]
11	**4a**	Me	A	Washes with Et_2O	75	20.6, d; 21.8, d, $^{2}J_{P\text{-}P}$ = 36.2 Hz
12	**4b**	*i*-Pr	A	Washes with Et_2O	73	20.6, d; 21.3, d, $^{2}J_{P\text{-}P}$ = 37.7 Hz
13	**4c**	$C_{15}H_{31}$	A	Precipitation in Et_2O	48	20.0, d; 21.6, d, $^{2}J_{P\text{-}P}$ = 43.2 Hz
14	**4d**	Ph	A	Precipitation in MeOH	88	17.0, d; 17.9, d, $^{2}J_{P\text{-}P}$ = 26.6 Hz
15	**4e**	*p*-MeOPh	A	Precipitation in MeOH	80	17.2, d; 18.1, d, $^{2}J_{P\text{-}P}$ = 30.8 Hz
16	**4f**	*p*-BrPh	A	Precipitation in Et_2O	84	16.3, d; 16.9, d, $^{2}J_{P\text{-}P}$ = 26.8 Hz
17	**4g**	$PhCH_2$	B	Reverse phase chromatography	47	18.8, d; 20.3, d, $^{2}J_{P\text{-}P}$ = 29.4 Hz

[a] ^{31}P {^{1}H} NMR spectra were realized in D_2O for products **4a**,**b** and **4d**–**g** and in $CDCl_3$ for product **4c**.

used without further purification. One equivalent of methyl bis(trimethylsilyl) phosphite[20] was then added dropwise at –70 °C. The reaction mixture was stirred at this temperature for 45 minutes before methanolysis. After vacuum evaporation of volatile fractions, HMBP monomethyl ester **4g** was obtained in 47% yield and purified by reverse phase column chromatography using C-18 resin (Polygoprep 60-130, Macherey-Nagel; see Table 2, entry 17).

To conclude, we have developed a new and efficient synthesis of HMBP monomethyl esters from different aliphatic or aromatic acid chlorides via corresponding α-ketophosphonates. Nevertheless, an alternative method using tris(trimethylsilyl) phosphite had to be considered in case of phenylacetyl chloride to avoid enol formation. These procedures will be applied to other related systems and should have applications in biology[21] including the synthesis of nucleoside-5′-(1-hydroxymethylene-1,1-bisphosphonates).[22]



Scheme 4 Synthesis of monomethyl ester **4g**, Method B

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(23) **Typical Procedure for the Synthesis of α-Ketophosphonate Dimethyl Esters 2.**
The adequate acid chloride **1** (50 mmol) was added dropwise at –10 °C under argon to trimethylphosphite (5.9 mL, 50 mmol). The reaction mixture was then stirred at r.t. for 2 h (the end of the reaction was ascertained by $^{31}P\{^1H\}$ NMR or IR spectroscopy). The crude product was purified as indicated in Table 1 to furnish the corresponding α-ketophosphonate dimethyl ester **2**.
Compound **2a**: ^1H NMR (200 MHz, $CDCl_3$): δ = 2.45 (d, 3 H, $^3J_{P\text{-}H}$ = 5.0 Hz, CH_3C=O), 3.83 (d, 6 H, $^3J_{P\text{-}H}$ = 10.6 Hz, OCH_3). ^{31}P NMR $\{^1H\}$ (80.9 MHz, $CDCl_3$): δ = –0.6 (s). ^{13}C NMR $\{^1H\}$ (50.3 MHz, $CDCl_3$): δ = 29.9 (CH_3C=O), 52.6 (OCH_3), 202.1 (*C*=O). IR (H_2O): 1040, 1060 (P-O), 1270 (P=O), 1703 (C=O) cm^{-1}. Anal. Calcd for $C_4H_9O_4P$: C, 31.59; H, 5.96; P, 20.37. Found: C, 31.70; H, 5.92; P, 20.33.
Compound **2d**: ^1H NMR (200 MHz, $CDCl_3$): δ = 3.58 (d, 6 H, $^3J_{P\text{-}H}$ = 10.8 Hz, OCH_3), 7.17 (dd, 2 H, $^3J_{H\text{-}H}$ = 7.4 Hz and $^3J_{H\text{-}H}$ = 7.4 Hz, *H m*-C_6H_5), 7.33 (d, 1 H, $^3J_{H\text{-}H}$ = 7.4 Hz, *H p*-C_6H_5), 7.92 (d, 2 H, $^3J_{H\text{-}H}$ = 7.4 Hz, *H o*-C_6H_5). ^{31}P NMR $\{^1H\}$ (80.9 MHz, $CDCl_3$): δ = –0.9 (s). ^{13}C NMR $\{^1H\}$ (50.3 MHz, $CDCl_3$): δ = 53.0 (OCH_3), 127.8 (*p*-C_6H_5), 128.3 (*o*-C_6H_5), 129.0 (*m*-C_6H_5), 133.7 (C_6H_5-C=O), 202.1 (*C*=O). IR (H_2O): 1040, 1067 (P-O), 1270 (P=O), 1667 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{11}O_4P$: C, 50.48; H, 5.18; P, 14.46. Found: C, 50.39; H, 5.20; P, 14.51.
(24) **Typical Procedure for the Synthesis of 1-Hydroxymethylene-1,1-bisphosphonate Monomethyl Esters 4.**
Method A: To α-ketophosphonate dimethyl ester **2** (5 mmol) in 4 mL of distilled THF or CH_2Cl_2 at 0 °C under argon was added dropwise trimethylsilyl bromide (1.65 mL, 12.5 mmol). The reaction was exothermic and the temperature had to be maintained below 10 °C during the addition. The reaction mixture was stirred at r.t. for 5–6 h (the end of the reaction was controlled by $^{31}P\{^1H\}$ NMR) and evaporation of volatile fractions (0.01 Torr) at 50 °C gave bis(silylated) α-ketophosphonate **3**. Methyl bis(trimethylsilyl) phosphite (1.2 g, 5 mmol) was then added dropwise to **3** at 0 °C under argon. The reaction mixture was stirred overnight at r.t. and methanolysis for 2 h led to 1-hydroxymethylene-1,1-bisphosphonate monomethyl esters **4**. After reduced pressure evaporation of volatile fractions, the crude compound **4** was purified as indicated in Table 2.
Method B [(preparation of 1-hydroxymethylene-1,1-bisphosphonate monomethyl ester (**4g**)]: To phenyl acetyl chloride **1g** (0.66 mL, 5 mmol) in 25 mL of distilled CH_2Cl_2 at –70 °C under argon was added dropwise tris(trimethylsilyl) phosphite (1.76 mL, 5 mmol). The reaction mixture was stirred at –70 °C for 30 min and methyl bis(trimethylsilyl) phosphite (1.2 g, 5 mmol) was then added dropwise at the same temperature. After stirring at –70 °C for 45 min, methanolysis for 2 h led to 1-hydroxymethylene-1,1-bisphosphonate monomethyl ester (**4g**). After vacuum evaporation of volatile fractions, the crude compound **4g** was purified by reverse phase column chromatography using C-18 resin (Polygoprep 60-130, Macherey-Nagel) and obtained with 47% yield.
Compound **4a**: ^1H NMR (200 MHz, D_2O): δ = 1.44 (dd, 3 H, $^3J_{P\text{-}H}$ = 16.0 Hz and $^3J_{P\text{-}H}$ = 16.0 Hz, CH_3C-OH), 3.58 (d, 3 H, $^3J_{P\text{-}H}$ = 9.8 Hz, OCH_3). ^{31}P NMR $\{^1H\}$ (80.9 MHz, D_2O): δ = 20.6 [d, 1 P, $^2J_{P\text{-}P}$ = 36.2 Hz, *P*(O)(OH)(OMe)], 21.8 [d, 1 P, $^2J_{P\text{-}P}$ = 36.2 Hz, *P*(O)$(OH)_2$]. ^{13}C NMR $\{^1H\}$ (50.3 MHz, D_2O): δ = 21.5 (CH_3C-OH), 55.8 (OCH_3), 72.6 (dd, $^1J_{C\text{-}P}$ = 152.4 Hz and $^1J_{C\text{-}P}$ = 152.4 Hz, *C*OH). IR (H_2O): 1008, 1053, 1125 (P-O), 945, 1049 (*P*-*O*-CH_3), 1190 (P=O) cm^{-1}. Anal. Calcd for $C_3H_{10}O_7P_2$: C, 16.37; H, 4.58; P, 28.15. Found: C, 16.47; H, 4.53; P, 28.19.
Compound **4d**: ^1H NMR (200 MHz, D_2O): δ = 3.53 (d, 3 H, $^3J_{P\text{-}H}$ = 4.0 Hz, OCH_3), 7.33 (d, 1 H, $^3J_{H\text{-}H}$ = 7.6 Hz, *H p*-C_6H_5), 7.38 (dd, 2 H, $^3J_{H\text{-}H}$ = 7.6 Hz and $^3J_{H\text{-}H}$ = 7.6 Hz, *H m*-C_6H_5), 7.71 (d, 2 H, $^3J_{H\text{-}H}$ = 7.6 Hz, *H o*-C_6H_5). ^{31}P NMR $\{^1H\}$ (80.9 MHz, D_2O): δ = 17.0 [d, 1 P, $^2J_{P\text{-}P}$ = 26.6 Hz, *P*(O)(OH)(OMe)], 17.9 [d, 1 P, $^2J_{P\text{-}P}$ = 26.6 Hz, *P*(O)$(OH)_2$]. ^{13}C NMR $\{^1H\}$ (50.3 MHz, D_2O): δ = 56.8 (OCH_3), 79.6 (dd, $^1J_{C\text{-}P}$ = 144.6 Hz and $^1J_{C\text{-}P}$ = 144.6 Hz, *C*OH), 129.2 (*o*-C_6H_5), 131.0 (*p*-C_6H_5), 131.4 (*m*-C_6H_5), 139.3 (C_6H_5-C=O). IR (H_2O): 1035, 1077, 1094 (P-O), 960, 1054 (*P*-*O*-CH_3), 1200 (P=O) cm^{-1}. Anal. Calcd for $C_8H_{12}O_7P_2$: C, 34.06; H, 4.29; P, 21.96. Found: C, 34.21; H, 4.32; P, 21.91.