Heteroatom Chemistry
Volume 20, Number 6, 2009

# Synthesis of α-Hydroxy-methylenebisphosphonates by the Microwave-Assisted Reaction of α-Oxophosphonates and Dialkyl Phosphites under Solventless Conditions

Alajos Grün,[1,2] István Gábor Molnár,[1] Béla Bertók,[3] István Greiner,[3] and György Keglevich[1]

[1]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*

[2]*Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*

[3]*Gedeon Richter Plc., H-1475 Budapest 10, PO Box 27, Hungary*

*Received 26 May 2009; revised 24 July 2009*

ABSTRACT: *The synthesis of hydroxy-methylenebisphosphonates (**2a–c**) by the addition of dialkyl phosphite to the carbonyl group of the corresponding α-oxophosphonate (**1a–c**) was studied under microwave irradiation (MW) and solventless conditions in the presence of dialkylamine as the catalyst. After optimization, products **2a** and **2b** were obtained selectively and in good yields avoiding the formation of the phosphonate-phosphate by-product (**3a** and **3b**) that is the result of a rearrangement. The MW-assisted synthesis of hydroxybisphosphonates (**2a** and **2b**) offers complete conversions and a chemoselectivity of 100% as compared to the not so efficient thermal reaction. At the same time, the phenyl-substituted methylenebisphosphonate **2c** could be obtained in only 75% selectivity.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:350–354, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20558

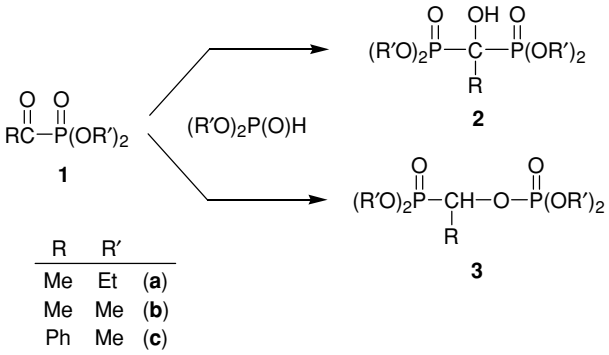
*Correspondence to:* György Keglevich; e-mail: keglevich@mail.bme.hu.

Contract grant sponsor: Hungarian Scientific Research Fund.
Contract grant number: OTKA T067679.



## *INTRODUCTION*

More than 50 years ago, McConnel and Coover claimed that the reaction of α-oxophosphonates (**1**) with dialkyl phosphites carried out in the presence of a base gave 1-substituted-1-hydroxybisphosphonates (**2a**) (Scheme 1) [1]. The α-oxophosphonate (**1a**) was added dropwise to the solventless equimolar mixture of diethyl phosphite and diethylamine with stirring whereupon the temperature rose to 70°C. The product (**2a**) was identified by boiling point, refractive index, elemental analysis, and IR spectral data. Several years later, Fitch and Moedritzer confuted the above results, stating that reproduction of the experiment provides the corresponding phosphonate-phosphate (**3a**) formed by rearrangement (Scheme 1) [2]. There were two signals at $\delta_P$ −1.3 and 20.2 in the $^{31}P$ NMR spectrum of the product isolated. The IR spectrum of the product described in [1] is identical to that of the phosphonate-phosphate (**3a**) described in [2]. It was also observed that if the reaction mixture was not heated above 80°C, the bisphosphonate (**2a**) characterized by a $\delta_P$ shift of 20.8 could be prepared by crystallization at 0°C. No rearrangement was observed by heating **2a** at 124°C for 10 min. On an attempted distillation




SCHEME 1

of **2a**, however, quantitative isomerization of **2a** to phosphonate-phosphate **3a** took place. Bisphosphonate **2a** was prepared by adding a catalytic amount of NaOEt (in ethanol) to the equimolar mixture of oxophosphonate **1a** and diethyl phosphite. The temperature rose to 72°C. On cooling at 0°C, product **2a** crystallized from the mixture. In the light of the above observations, it is probable that McConnel and Coover initially obtained the expected bisphosphonate (**2a**) that underwent isomerization on heating in an oil bath at 170°C. Finally, Nicholson and Vaughn described an exact procedure for the preparation of bisphosphonate **2c** by adding dimethyl benzoylphosphonate dropwise to the stirred solution of dimethyl phosphite and 0.05 equivalent of dibutylamine in diethyl ether at 0°C. The product (**2c**) precipitated could be separated by filtration [3].

It can be seen that the synthesis of hydroxybisphosphonates **2** from α-oxophosphonate and dialkyl phosphite can be best accomplished in the presence of base as the catalyst, such as diethylamine, dibutylamine, or NaOEt. The use of a solvent may promote the selectivity, and the temperature should be kept below 100°C. Consequently, the bisphosphonates cannot be purified by distillation at reduced pressure.

α-Oxophosphonates may be prepared by the Arbuzov reaction of carboxylic acid chlorides and trialkyl phosphites [3,4]. In most cases, the reaction takes place at as low as 0–35°C. The oxophosphonate can be purified by distillation in vacuum.

The reaction of acid chlorides with 2 equivalents of diethyl phosphite leads also to hydroxybisphosphonates [5]. In these cases, the formation of the by-product by rearrangement is inevitable even in the presence of a base.

In this paper, the microwave-assisted and solventless accomplishment of the addition reaction under discussion together with some comparing experiments is described. The optimum conditions are also surveyed.

## *RESULTS AND DISCUSSION*

The reaction of diethyl acetylphosphonate (AP) **1a** with diethyl phosphite (DEP) was chosen as the model to be studied in detail. Formation of the two possible products, tetraethyl 1-hydroxy-ethylidenebisphosphonate (BP) **2a** and phosphonate-phosphate (PP) **3a**, and the conversion of the starting acetylphosphonate **1a** were monitored by $^{31}$P NMR spectroscopy and/or GC. Using a column of 100°C, no isomerization of compound **1** occurred.

Carrying out the reaction of **1a** and DEP in diethyl ether in the presence of 20% of diethylamine at 0°C for 8 h, 95% of BP **2a** and 5% of PP **3a** were formed (Table 1, entry 1). Hence, it is true that the primary product of McConnel and Coover may have been BP **2a**.

We wished to study the effect of the presence and quantity of the catalyst in solventless reactions. To shorten the reaction times, a reaction temperature of 120°C was chosen. Using 5%, 25%, and 50% of diethylamine, the conversion was complete after 20 min and the ratio of the BP and the PP was 87:13, 20:80, and 0:100, respectively (Table 1, entries 2–4).

Performing the reaction in the absence of any catalyst, the conversion was only 58% after 20 min and the ratio of the BP (**2a**) and PP (**3a**) was 83:17 (Table 1, entry 5).

Using dibutylamine instead of diethylamine in a quantity of 5%, 10%, 25%, and 50%, the relative quantity of BP **2a** and PP **3a** was 94:6, 91:9, 36:64, and 25:75, respectively, but in the first and second case, the conversion was not complete (Table 1, entries 6–9). The application of longer reaction times in the presence of 5% of dibutylamine did not help in attaining complete conversion (Table 1, entries 10 and 11). It can be seen that under thermal conditions the use of dibutylamine is more advantageous than that of diethylamine, as the proportion of BP **2a** was, in all cases, somewhat higher (Table 1, entries 2 vs. 6, 3 vs. 8, and 4 vs. 9). Applying the secondary amine in 5%–10%, in all cases the BP **2a** predominated (Table 1, entries 2, 6, and 7).

Just to try another simple accomplishment, the reaction was carried out under solid–liquid phase transfer catalytic conditions using $K_2CO_3$ as the base, acetonitrile as the solvent, and triethylbenzylammonium chloride (TEBAC) as the catalyst. In boiling acetonitrile, the reaction time was 8 h and only the rearranged product (**3a**) was found to have been formed (Table 1, entry 12).

**TABLE 1** Results of the Reaction of **1a** with 1 Equivalent of $(EtO)_2P(O)H$ under Different Conditions

| | *Conditions* | | | | *Result* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Catalyst* | *Temperature (°C)* | *Time* | *Solvent* | *Conversion (%)* | **2a** *(%)* | **3a** *(%)* | | *Yield (%)* | *Entry* |
| DEA (20%) | 0 | 8 h | Ether | 100 | 95 | 5 | a | | 1 |
| DEA (5%) | 120 | 20 min | – | 100 | 87 | 13 | a | 71 | 2 |
| DEA (25%) | 120 | 20 min | – | 100 | 20 | 80 | a | | 3 |
| DEA (50%) | 120 | 20 min | – | 100 | 0 | 100 | b | | 4 |
| – | 120 | 20 min | – | 58 | 83 | 17 | b | | 5 |
| DBA (5%) | 120 | 20 min | – | 92 | 94 | 6 | b | 83 | 6 |
| DBA (10%) | 120 | 20 min | – | 95 | 91 | 9 | b | | 7 |
| DBA (25%) | 120 | 20 min | – | 100 | 36 | 64 | a | | 8 |
| DBA (50%) | 120 | 20 min | – | 100 | 25 | 75 | b | | 9 |
| DBA (5%) | 120 | 40 min | – | 94 | 91 | 9 | b | | 10 |
| DBA (5%) | 120 | 90 min | – | 94 | 83 | 17 | b | | 11 |
| TEBAC (10%) | $K_2CO_3$/MeCN/$\Delta$/8 h | | | 100 | 0 | 100 | a | | 12 |

Abbreviations: DEA: Diethylamine; DBA: dibuthylamine.
[a]Determined on the basis of relative $^{31}P$ NMR intensities.
[b]Determined by GC.

From among the solventless reactions mentioned above, the ones giving the best results (Table 1, entries 2 and 6) were repeated and the expected product, BP **2a**, was separated by column chromatography (in 71% and 83% yield, respectively).

It seemed to be interesting to study the reaction of AP **1a** with DEP under microwave (MW) conditions. In the first experiments carried out at 120°C, the ratio of BP **2a** and PP **3a** was ca. 4:1. After an irradiation of 20 min, the conversion was only 45%, but extending the reaction time to 1 h, the conversion still remained incomplete (69%) (Table 2, entries 1 and 2). After an irradiation of 1.5 h, the conversion was almost quantitative (98%), but in this case, the proportion of **2a** over **3a** changed to 65:35 (3:1, Table 2, entry 3).

The use of diethylamine as the catalyst led to a dramatic change. Adding diethylamine in a quantity of 5%, 10%, 25%, and 50% to the reaction mixtures, product compositions (BP (**2a**)/PP (**3a**)) of 100:0, 90:10, 53:47, and 7:93 could be observed, in all cases

**TABLE 2** Result of the Reaction of **1a** with 1 Equivalent of $(EtO)_2P(O)H$ under MW and Solventless Conditions

| | *Conditions* | | | *Result* | | | | |
|---|---|---|---|---|---|---|---|---|
| *Catalyst* | *Temperature (°C)* | *Time (min)* | *Conversion (%)* | **2a** *(%)* | **3a** *(%)* | | *Yield (%)* | *Entry* |
| – | 120 | 20 | 45 | 79 | 21 | b | | 1 |
| – | 120 | 60 | 69 | 81 | 19 | b | | 2 |
| – | 120 | 90 | 98 | 65 | 35 | a | | 3 |
| DEA (5%) | 120 | 20 | 100 | 100 | 0 | a | 81 | 4 |
| DEA (10%) | 120 | 20 | 100 | 90 | 10 | a | | 5 |
| DEA (25%) | 120 | 20 | 100 | 53 | 47 | a | | 6 |
| DEA (50%) | 120 | 20 | 100 | 7 | 93 | a | | 7 |
| DBA (5%) | 120 | 20 | 100 | 100 | 0 | a | 76 | 8 |
| DBA (10%) | 120 | 20 | 100 | 82 | 18 | b | | 9 |
| DBA (25%) | 120 | 20 | 98 | 27 | 72 | a | | 10 |
| DBA (50%) | 120 | 20 | 100 | 0 | 100 | a | | 11 |
| DEA (5%) | 60 | 30 | 100 | 100 | 0 | a | | 12 |
| DEA (5%) | 80 | 30 | 100 | 100 | 0 | a | | 13 |
| DEA (5%) | 100 | 20 | 100 | 100 | 0 | a | | 14 |
| DBA (25%) | 60 | 30 | 100 | 69 | 31 | a | | 15 |
| DBA (25%) | 80 | 30 | 100 | 51 | 49 | b | | 16 |
| DBA (25%) | 100 | 20 | 100 | 35 | 65 | b | | 17 |

Abbreviations: DEA: Diethylamine; DBA: dibuthylamine.
[a]Determined on the basis of relative $^{31}P$ NMR intensities.
[b]Determined by GC.

with complete conversion of the AP (**1a**) (Table 2, entries 4–7).

Replacing diethylamine by dibutylamine, the tendency regarding the ratio of products remained the same, but from the point of view of the desired product (**2a**), the relative proportions were somewhat unfavorable. Using 5%, 10%, 25%, and 50% of dibutylamine, the BP (**2a**) to PP (**3a**) ratios were 100:0, 82:18, 27:72, and 0:100, respectively (Table 2, entries 8–11). It is interesting that while under thermal conditions the use of dibutylamine seemed to be advantageous, under MW irradiation the use of diethylamine is more efficient from the point of view of selectivity.

Then, the effect of temperature was investigated in MW-assisted reactions. Using 5% of diethylamine and applying conditions of 60°C/30 min, 80°C/30 min, and 100°C/20 min, the conversion was in all cases quantitative and BP **2a** was the only product (Table 2, entries 12–14). Applying 25% of dibutylamine as the catalyst, the proportion of BP **2a** decreased with the increase of the temperature (Table 2, entries 15–17, 10).

Finally, we wished to see whether the optimized MW conditions can be used in the synthesis of other related compounds (**2b** and **2c**) as well. It was found that dimethyl acetylphosphonate (**1b**) reacts with dimethyl phosphite at 120°C/20 min, 100°C/30 min, and 60°C/45 min in the presence of 5% of diethylamine to afford the expected tetramethyl 1-hydroxyethylidenebisphosphonate **2b** in complete conversions and in ca. 85% isolated yields.

As regard the MW-assisted reaction of dimethyl benzoylphosphonate (**1c**) and dimethyl phosphite, the maximum selectivity for the formation of tetramethyl 1-hydroxy-benzylidenebisphosphonate **2c** was achieved at 60°C/1.5 h in the presence of 5% of diethylamine. In this case, the ratio of bisphosphonate **2c** and rearranged product **3c** was 7:3. Moreover, this reaction was found to be quite sensitive to the parameters applied. At 100°C, in the presence of 5% of diethylamine, the ratio of **2c** to **3c** was 1:3. Carrying out the reaction at 60°C, but using 10% of diethylamine, only the rearranged compound (**3c**) was formed.

It was interesting to find that heating α-oxophosphonate **1a** at 160°C for 3 h in the absence of diethyl phosphite, rearranged product **3a** was formed in a 43% conversion. At the same time, MW irradiation of **1a** at 120°C/20 min gave only bisphosphonate **2a** in a conversion of 15%. The use of 5% diethylamine as the catalyst was helpful, as in this case the conversion to **2a** was 58% under similar conditions. It is obvious that some of the oxophosphonate (**1a**) serves as the precursor for diethyl phosphite. This interesting reaction is to be studied further.

It can be concluded that after optimization, the MW-assisted solventless reaction of α-oxophosphonates (**1a–c**) with dialkyl phosphates gives the corresponding 1-hydroxy-methylenebisphosphonates (**2a–c**) in a higher (in most cases quantitative) selectivities and in complete conversions, as compared to the thermal variations.

## *EXPERIMENTAL*

The $^{31}P$, $^{13}C$, and $^{1}H$ NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% $H_3PO_4$ or TMS. The couplings are given in hertz. Mass spectrometry was performed on a ZAB-2SEQ instrument.

The MW-assisted reactions were carried out in a CEM Discover microwave reactor equipped with a pressure controller using ca. 30 W irradiation.

All products were liquids.

### *Diethyl Acetylphosphonate (**1a**)*

Triethyl phosphite (0.05 mol, 8.3 g) was added dropwise to acetyl chloride (0.05 mol, 3.9 g) at 0°C on intensive stirring. After all of the triethyl phosphite had been introduced, the reaction mixture was allowed to warm up to room temperature. Vacuum distillation of the crude product afforded 5.5 g (61%) of the acetylphosphonate (**1a**) [1]; bp: 86–88°C/6 Torr (bp [1]: 62–65°C/1.5 Torr); $^{31}P$ NMR ($CDCl_3$) $\delta$ 2.9.

*Dimethyl acetylphosphonate* (**1b**) was prepared similarly using trimethyl phosphite. Yield: 40%; bp: 82°C/6 Torr (bp [6]: 90–91°C/10 Torr); $^{31}P$ NMR ($CDCl_3$) $\delta$ −0.95.

*Dimethyl benzoylphosphonate* (**1c**) was prepared similarly using trimethyl phosphite and benzoyl chloride. Yield: 80%; bp: 154–156°C/8 Torr (bp [3]: 130–134°C/3 Torr); $^{31}P$ NMR ($CDCl_3$) $\delta$ −0.85 ($\delta_P$ [3] −1.0).

### *Tetraethyl(1-hydroxyethylidene)-bisphosphonate (**2a**) [3]*

A solution of diethyl phosphite (5.5 mmol, 0.76 g) and diethylamine (1 mmol, 0.074 g) in diethyl ether (15 mL) was cooled to 0°C, and diethyl acetylphosphonate **1a** (5.5 mmol, 1.0 g) in diethyl ether (5 mL) was added dropwise with intensive stirring. The reaction mixture was stirred further for 8 h at 0°C, then it was allowed to warm up to room temperature. The solvent was evaporated to afford 1.7 g (91%) of bisphosphonate **2a** [3] in a purity of 95%.

$^{31}$P NMR ($CDCl_3$) $\delta$ 20.3; $\delta_P$ [2] 20.8. $^{13}$C NMR 16.4 (t, $J = 2.7$ Hz, $CH_2CH_3$), 20.1 (t, $J = 1.1$ Hz, $CCH_3$), 63.6 (m, $CH_2CH_3$), 71.4 (t, $J = 156.1$ Hz, $CCH_3$). $^1$H NMR 1.31 (12H, t, $J = 6.9$ Hz), 1.62 (3H, t, $J = 16.2$ Hz), 4.20 (9H, bs).

### *Reaction of diethyl acetylphosphonate and diethyl phosphite (**2a**) under heating (General Procedure)*

Diethyl acetylphosphonate (0.55 mmol, 0.099 g), diethyl phosphite (0.55 mmol, 0.076 g), and diethylamine or dibuthylamine (catalyst) were measured in a small flask that was placed in a preheated bath of 120°C. The mixture, after complete reaction, was purified by flash column chromatography (silica gel, 3% methanol in chloroform) to give a mixture of the two isomers (**2a** and **3a**). The details are listed in Table 1.

### *Reaction of diethyl acetylphosphonate and diethyl phosphite (**2a**) under microwave conditions (General Procedure)*

Diethyl acetylphosphonate (0.55 mmol, 0.099 g), diethyl phosphite (0.55 mmol, 0.076 g), and diethylamine or dibuthylamine (catalyst) were measured in a microwave tube that was placed in a microwave reactor equipped with a pressure controller. The mixture, after complete reaction, was purified by flash column chromatography (silica gel, 3% methanol in chloroform) to provide a mixture of two possible products (**2a** and **3a**). Experimental details are given in Table 2.

*Tetramethyl(1-hydroxyethylidene)-bisphosphonate* **2b** was prepared according to the general procedure reacting dimethyl 1-oxoethylphosphonate **1b** and dimethyl phosphite at 120°C/20 min in the presence of 5% of diethylamine. Yield: 85%. $^{31}$P NMR ($CDCl_3$) $\delta$ 22.3, $\delta_P$ [3] 22.0.

*Tetramethyl hydroxybenzylylidenebisphosphonate* (**2c)** was prepared according to the general procedure reacting dimethyl benzoylphosphonate **1c** and dimethyl phosphite at 60°C/1.5 h in the presence of 5% of diethylamine. Yield: 55%. $^{31}$P NMR ($CDCl_3$) $\delta$ 18.4, $\delta_P$ [3] 18.0.

*Diethyl 1-(diethylphosphono)ethyl phosphate* (**3a**) was obtained from experiment 4 of Table 1 in 85% yield after column chromatography (silica gel, 3% methanol in chloroform).

$^{31}$P NMR ($CDCl_3$) $\delta$ −1.2 (d, $J = 32.4$ Hz), 20.3 (d, $J = 32.4$ Hz); $\delta_P$ [2] −1.9 and 19.9.

The other phosphonate-phosphates (**3b** and **3c**) were identified from unoptimized reactions (**3b**: $^{31}$P NMR ($CDCl_3$) $\delta$ 1.0 (d, $J = 27.6$), 22.4 (d, $J = 27.6$) and **3c**: $^{31}$P NMR ($CDCl_3$) $\delta$ 1.4 (d, $J = 32.6$), 18.9 (d, $J = 32.8$)). The NMR data are in accord with those described in the literature [7].

## *REFERENCES*

[1] McConnel, R. L.; Coover, H. W. J Am Chem Soc 1956, 78, 4450.
[2] Fitch, S. J.; Moedritzer, K. J Am Chem Soc 1962, 84, 1876.
[3] Nicholson, D. A.; Vaughn, H. J Org Chem 1971, 36, 3843.
[4] Berlin, K. D.; Taylor, H. A. J Am Chem Soc 1964, 86, 3862.
[5] Ruel, R.; Bouvier, J.-P.; Young, R. N. J Org Chem 1995, 60, 5209.
[6] Al'fonsov, V. A. Izv Akad Nauk SSSR, Ser Khim 1985, 2619.
[7] Tromelin, A.; Elmanouni, D.; Burgada, R. Phosphorus Sulfur Silicon 1986, 27, 301.