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Solid–Liquid Two-Phase Alkylation of Tetraethyl Methylenebisphosphonate under Microwave Irradiation

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ABSTRACT: *Optimum conditions for the solid–liquid phase alkylation of tetraethyl methylenebisphosphonate are dependent on the nature of the alkyl halide. The benzylation with benzyl bromide takes place efficiently in boiling acetonitrile in the presence of potassium carbonate and a phase transfer catalyst. The ethylation with ethyl iodide was best accomplished under solventless microwave conditions in the presence of cesium carbonate and in the absence of an onium salt. The analogous propylation and butylation were complicated by the formation of mixed esters.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 22:11–14, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20648

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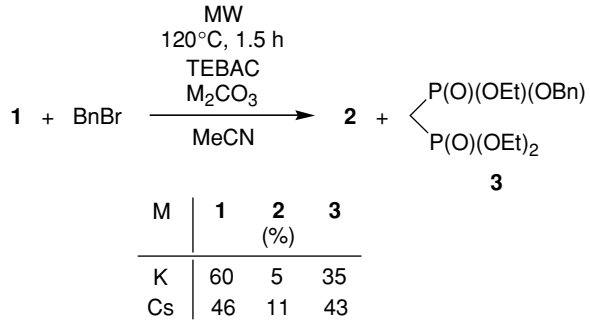
INTRODUCTION

gem-Bis(phosphonic acids) are important drugs used in the treatment of osteoporosis as they inhibit bone resorption [1]. The corresponding alkyl esters can be hydrolyzed to the related acids [2]. A representative method for the preparation of C-substituted methylene bisphosphonates involves the Michael addition of simple Grignard reagents to the corresponding ethenylidenebisphosphonate [3]. Another possibility for the synthesis of methylenebisphosphonates involves the reaction of alkylphosphonates with chlorophosphates via the corresponding lithiated intermediate [4].

Bisphosphonates form a special group of CH-acidic compounds, for which the anions, generated with suitable bases, may undergo alkylation. Surprisingly, such alkylations of methylene bisphosphonates carried out under different conditions are not obviously a method of choice. Forming the potassium salt of the bisphosphonate by reacting it with potassium in xylene followed by alkylation led to "rather unsatisfactory yields" [5]. When sodium hydride was used as the base, the alkylation was more efficient as indicated by the yield of 58% [6].

The use of phase transfer catalysis would be an up-to-date method [7]. During the solid–liquid phase alkylation of a variety of common CH acidic compounds, it was found that the phase transfer catalyst can be substituted by microwave (MW) irradiation; moreover, there was no need to use any solvent [8,9]. It seemed to be interesting to see what the situation is in this respect with bisphosphonates. For this purpose, we wished to study the effect of MW on the solid–liquid phase alkylation of bisphosphonates in the presence and in the absence of a phase transfer catalyst.



M	1	2 (%)	3
K	60	5	35
Cs	46	11	43

SCHEME 2

RESULTS AND DISCUSSION

In the first experiment, tetraethyl methylenebisphosphonate **1** was alkylated with benzyl bromide in the presence of potassium carbonate and triethylbenzylammonium chloride (TEBAC) in acetonitrile at reflux. Completion of the benzylation to afford benzyl-methylenebisphosphonate **2** required 40 h. The isolated yield of compound **2** was 83% after column chromatography (Scheme 1). No bisbenzylated product could be detected in the crude mixture.

Carrying out the reaction under similar conditions but with MW irradiation and at 120°C, the conversion was 40% after 1.5 h and along with the benzyl-methylenebisphosphonate **2** (5%), a monobenzyl triethyl ester (**3**) (5%) was also present. Replacing potassium carbonate by cesium carbonate, the conversion was 54% and the reaction mixture contained 11% of the *C*-benzylated product (**2**) and 43% of the monobenzyl triethyl ester (**3**) along with the unreacted starting material (46%) (Scheme 2).

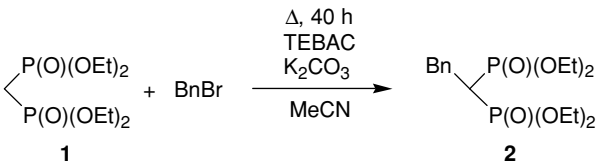
By-product **3** was isolated from the reaction mixture by column chromatography. In respect of the model reaction under discussion, the solventless accomplishment was not appropriate.

The formation of the by-product **3** can be explained by assuming that water is released in the reaction of hydrogen halide (formed in the alkylation) with alkali carbonate under the circumstances of the reaction that may lead to the partial hydrolysis of the tetraethyl ester or the alkyl halide. Then, either the acid function may react with the alkyl halide or the ester itself with the alcohol to furnish mixed ester **3**.

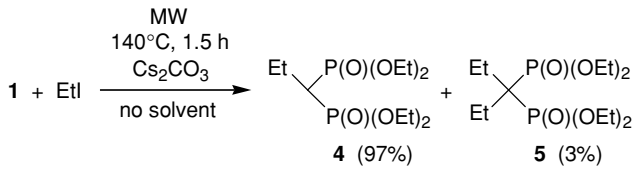
It can be seen that due to a side reaction, the use of MW irradiation is not helpful in the solid–liquid phase benzylation of tetraethyl methylenebisphosphonate (**1**). In this case, the phase transfer catalyzed thermal accomplishment remains the method of choice providing the expected product (**2**) in good yield (~90%), but in a rather slow reaction.

Then, the alkylation of methylenebisphosphonate **1** was investigated with ethyl iodide at 140°C under MW irradiation, in the presence of cesium carbonate without the use of any solvent. After a reaction time of 1.5 h, the conversion was complete and the *C*-ethyl methylenebisphosphonate **4** was obtained in 80% yield. In a small amount (~3%), the bisalkylated by-product (**5**) was also present in the reaction mixture (Scheme 3).

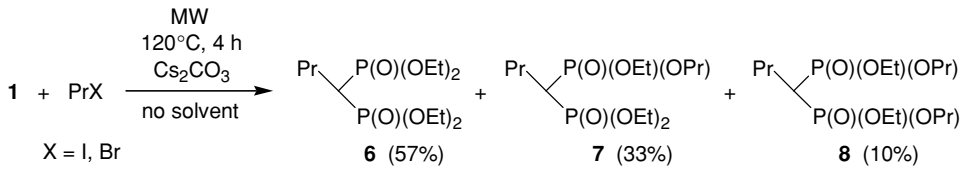
At 120°C, the conversion was not complete, but reacting the crude mixture so obtained with a second portion of ethyl iodide (as in the first "round"), the ethylation became complete. It is important to note that in the case of the MW-promoted reaction of methylenebisphosphonate **1** with ethyl iodide, there was no need to use phase transfer catalyst. This means that the situation is similar to that experienced in the case of classical CH acidic compounds by us as mentioned above [8,9]. According to this, the **1** → **4** conversion is another example, when MW



SCHEME 1



SCHEME 3



SCHEME 4

irradiation may substitute a phase transfer catalyst in a solid–liquid phase alkylation.

Next, methylenebisphosphonate **1** was reacted with propyl bromide at 120°C in the presence of cesium carbonate. After an irradiation of 4 h, a mixture was formed consisting of C-propyl bisphosphonate **6** (57% δ_P ($CDCl_3$) 25.0, $(M + H)^+_{found}$ = 331.1429, $C_{12}H_{29}O_6P_2$ requires 331.1439), and by-products deriving from transesterification, such as triethyl propyl ester **7** (33%) and diethyl dipropyl ester **8** (10%). The situation was quite similar when propyl iodide was used instead of the bromide (Scheme 4).

Mixed esters **7** and **8** may be formed similarly as **3** (see above).

Disregarding the details, the alkylation with butyl bromide took place analogously.

The use of phase transfer catalyst in the alkylation with propyl halide led to complex mixtures. On the one hand, the conversion was not complete; on the other hand, extensive decomposition of the products (**6–8**) could be observed. It can be seen that the use of a phase transfer catalyst in the propylation of methylenebisphosphonate **1** is surely harmful.

Products **2–4** were obtained in pure form by column chromatography and were characterized by ^{31}P, ^{13}C, and ^1H NMR spectral data, as well as MS. Methylenebisphosphonates **2** and **4** were described earlier [3,4], but only **2** was characterized adequately.

It can be concluded that the MW technique offers advantage in the alkylation of methylenebisphosphonates only when the alkyl groups of the two reactants are identical. The advantage is that there is no need for a phase transfer catalyst and the reaction time becomes much shorter.

EXPERIMENTAL

General

The ^{31}P, ^{13}C, and ^1H 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 MW reactor equipped with a pressure controller using ca. 30 W irradiation.

Tetraethyl Phenylethylidenebisphosphonate **2**

The mixture of 0.50 g (1.74 mmol) of bishosphonate **1**, 0.74 g (1.74 mmol) of K_2CO_3, 0.10 g (0.44 mmol) of TEBAC, and 0.25 mL (2.08 mmol) of benzyl bromide in 7 mL of acetonitrile was stirred under reflux for 40 h. Then the solid phase was removed by filtration, washed with 5 mL of acetonitrile, and the combined organic phases concentrated on vacuum. The crude product so obtained was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.54 g (83%) of product **2**.

^{31}P NMR ($CDCl_3$) δ: 23.9; ^{13}C NMR ($CDCl_3$) δ: 16.2 (d, $J = 6.7$, CH_3), 31.1 (t, $J = 4.8$, CH_2Ph), 39.0 (t, $J = 132.5$, CH), 62.3 (d, $J = 6.8$, OCH_2), 62.5 (d, $J = 6.8$, OCH_2), 126.4 (s, $C_{4'}$), 128.1, 128.8 (2s, $C_{2'}$, $C_{3'}$), 139.4 (t, $J = 7$, $C_{1'}$); ^1H NMR ($CDCl_3$) δ: 1.26 (t, $J = 8.2$, 6H, CH_3), 1.28 (t, $J = 7.2$, 6H, CH_3), 2.66 (tt, 1H, $J_1 = 24$, $J_2 = 6$, CH), 3.25 (dt, $J_1 = 16.5$, $J_2 = 6$, 2H, CH_2Ph), 4.04–4.18 (m, 8H, OCH_2), 7.18–7.28 (m, 5H, Ph); $[M + H]^+_{found}$ = 379.1427, $C_{16}H_{29}O_6P_2$ requires 379.1439. The NMR spectral data are identical with those reported earlier [3].

Triethyl, Benzyl Methylidenebisphosphonate **3**

0.50 g (1.74 mmol) of bishosphonate **1**, 0.57 g (1.74 mmol) of Cs_2CO_3, 0.10 g (0.44 mmol) of TEBAC, 0.25 mL (2.08 mmol) of benzyl bromide, and 5 mL of acetonitrile was measured in a tube that was irradiated at 120°C applying 10 W under pressure control. After a reaction time of 1.5 h, the mixture was filtrated and the organic phase evaporated. The reaction was repeated two times, and the combined crude mixtures were subjected to column chromatography (as above) to furnish 0.21 g (34%) of compound **3**.

^{31}P NMR ($CDCl_3$) δ: 20.1 (d, $J = 6.9$), 20.9 (d, $J = 6.9$); ^{13}C NMR ($CDCl_3$) δ: 16.39 (t, $J = 3.5$, CH_3), 16.44 (d, $J = 3.2$, CH_3), 25.7 (t, $J = 136$, PCH_2P), 62.7

(d, $J = 6.5$, OCH_2CH_3), 68.1 (d, $J = 6$, OCH_2Ph), 128.1, 128.7 (2s, $C_{2'}$, $C_{3'}$), 128.5 (s, $C_{4'}$), 128.6 (d, $J = 51$, $C_{1'}$); ^{1}H NMR ($CDCl_3$) δ: 1.24–1.34 (m, 9H, CH_3), 2.46 (t, $J = 21$, 2H, PCH_2P), 4.06–4.19 (m, 6H, OCH_2CH_3), 5.14 (d, $J = 8.5$, 2H, CH_2Ph), 7.33–7.43 (m, 5H, Ph); MS.

Tetraethyl Propylidenebisphosphonate **4**

The mixture of 0.50 g (1.74 mmol) of bishosphonate **1**, 0.57 g (1.74 mmol) of Cs_2CO_3, and 0.17 mL (2.08 mmol) of ethyl iodide was irradiated in a tube at 140°C applying 10 W under pressure control. After a 1.5 h reaction time, the resulting mass was taken up in 25 mL of ethyl acetate and the solid phase was removed by filtration. The filtrate was evaporated, and the residue obtained purified by column chromatography (as above) to afford 0.44 g (80%) of product **4**.

^{31}P NMR ($CDCl_3$) δ: 24.9, δ_P: [4] 21.2; ^{13}C NMR ($CDCl_3$) δ :14.1 (t, $J = 6.9$, CH_2), 16.4 (d, $J = 1.9$, CH_3), 16.5 (d, $J = 1.9$, CH_3), 19.3 (t, $J = 5.2$, CH_3), 38.4 (t, $J = 132.5$, CH), 62.4 (d, $J = 6.9$, OCH_2), 62.6 (d, $J = 6.9$, OCH_2); ^{1}H NMR ($CDCl_3$) δ: 1.16 (t, $J = 7.5$, 3H, CH_3), 1.34 (t, $J = 7$, 12H, CH_3), 1.91–2.10 (m, 2H, CH_2), 2.21 (tt, $J_1 = 24$, $J_2 = 5.7$, 2H, CH), 4.13–4,23 (m, 8H, OCH_2); $[M]^+_{found} = 316.1194$, $C_{17}H_{26}O_6P_2$ requires 316.1205.

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