Facile and High-Yielding Preparation of \( \alpha \)-Acetoxyphosphonates from \( \alpha \)-Hydroxyphosphonates Assisted by Microwave Irradiation

Habib Firouzabadi,\* Nasser Iranpoor, Sara Sobhani, Zohreh Amoozgar

Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran
Fax +98(711)2280926; E-mail: Firouzabadi@chem.susc.ac.ir; E-mail: Iranpoor@chem.susc.ac.ir

Received 16 March 2004

Abstract: A convenient and eco-friendly procedure is described for the efficient preparation of a variety of \( \alpha \)-acetoxyphosphonates from their corresponding \( \alpha \)-hydroxyphosphonates using acetic anhydride under microwave irradiation in the absence of solvent.

Key words: hydroxyphosphonates, solvent-free, \( \alpha \)-acetoxyphosphonates, acetic anhydride, microwave irradiation

\( \alpha \)-Acetoxyphosphonates are considered as important and valuable phosphorus compounds for the synthesis of optically active \( \alpha \)-hydroxyphosphonates. Enzymatic systems have been introduced for the enantioselective hydrolysis of racemic \( \alpha \)-acetoxyphosphonates.\(^1\) Chiral and nonracemic \( \alpha \)-hydroxyphosphonates are useful precursors for a variety of \( \alpha \)-substituted phosphonates, especially for \( \alpha \)-aminoephosphonic acids which in recent years have received considerable attention owing to their potential activities as analogues of \( \alpha \)-amino acids\(^{1b,2} \) in medical, bioorganic and organic chemistry.

A literature survey reveals that practical and high yielding methods for the synthesis of pure \( \alpha \)-acetoxyphosphonates are rare. The reactions of aldehydes and ketones with acyl phosphites is reported for the preparation of \( \alpha \)-acetoxyphosphonates at 120 °C to produce the desired products in low yields.\(^3\) The other reported procedures for this purpose include direct acetylation of \( \alpha \)-hydroxyphosphonates\(^4\) with ketene catalyzed by \( \text{BF}_3 \cdot \text{OEt}_2 \) or \( \text{H}_2\text{SO}_4 \).\(^5\) These protocols suffer from usually low yields, requiring rather high temperatures (70–80°C) and long reaction times (10–15 h).\(^6\) Acetylation of \( \alpha \)-hydroxyphosphonates with \( \text{Ac}_2\text{O} \) or \( \text{AcCl} \) in the presence of \( \text{Et}_3\text{N} \) or pyridine was conducted at room temperature in 1–18 hours, providing products in yields ranging from low to excellent.\(^{b,c,7} \) In another reported procedure, \( \text{AcCl} \) was used for direct acetylation of \( \alpha \)-trimethylsilylhydroxyphosphonates at a rather high temperature (120 °C) to produce \( \alpha \)-acetoxyphosphonates in moderate yields (55–70%).\(^8\)

Recently, the application of microwave irradiation has gained popularity in organic synthesis\(^9\) particularly in chemical reactions, which are carried out under solvent-free conditions. Combination of solvent-free conditions and microwave irradiation leads to noticeable reductions in reaction times, enhancement of the efficiency of the reaction, sometimes their selectivity plus several other advantages could be considered as an eco-friendly approach that is termed green chemistry.\(^{9b,10} \)

We have recently paid attention to the chemistry of diethyl \( \alpha \)-hydroxyphosphonates and introduced new methods for their direct transformation to other derivatives.\(^11\) In this article, we present a new solventless procedure in which microwave irradiation is employed for the direct acetylation of various types of \( \alpha \)-hydroxyphosphonates \( 1a–o \) to provide the corresponding \( \alpha \)-acetoxyphosphonates \( 2a–o \). As shown in Table 1, various types of diethyl \( \alpha \)-hydroxy(phenylmethyl)phosphonates \( 1a–k \) were cleanly converted into their corresponding diethyl \( \alpha \)-acetoxyphosphonates \( 2a–k \) in excellent yields (90–98%). Diethyl \( \alpha \)-hydroxy-2-naphthyl-, 3-pyridyl-, alkyl- and aryl-\( \beta,\gamma \)-unsaturated phosphonates \( 1l–o \) were also acetylated efficiently giving the corresponding diethyl \( \alpha \)-acetoxyphosphonates \( 2l–o \) in 91–97% yields.

As shown in Table 1, various types of diethyl \( \alpha \)-hydroxy(phenylmethyl)phosphonates \( 1a–k \) were cleanly converted into their corresponding diethyl \( \alpha \)-acetoxyphosphonates \( 2a–k \) in excellent yields (90–98%). Diethyl \( \alpha \)-hydroxy-2-naphthyl-, 3-pyridyl-, alkyl- and aryl-\( \beta,\gamma \)-unsaturated phosphonates \( 1l–o \) were also acetylated efficiently giving the corresponding diethyl \( \alpha \)-acetoxyphosphonates \( 2l–o \) in 91–97% yields.

In all the reactions we have reported in this paper cleavage of C–P bond of the phosphonates were not detected and the conversion of the substrates to their corresponding acetoxy compound was clean and quantitative. Workup of the reaction mixture is very easy and gives highly pure liquid products, which do not need further purification (detected by TLC and their spectral data).

Consequently, in this paper, we have described a high yielding, convenient and environmentally friendly procedure for the efficient preparation of a variety of \( \alpha \)-acetoxyphosphonates from \( \alpha \)-hydroxyphosphonates using acetic anhydride under microwave irradiation. This method is superior with respect to the other reported methods, which use corrosive \( \text{BF}_3 \cdot \text{OEt}_2 \), \( \text{H}_2\text{SO}_4 \) and \( \text{AcCl} \) and require purification of the acetoxy products from pyridine and \( \text{Et}_3\text{N} \), a tedious and time consuming process. High-yielding, solventless and mild reaction conditions, short reaction times and easy workup make this new protocol a
Table 1 Solventless Acetylation of Diethyl α-Hydroxyphosphonates 1a–o to Diethyl α-Acetyloxyphosphonates 2a–o with Ac₂O Using Microwave Irradiation

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Molar ratio of Ac₂O/2 (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₆H₅</td>
<td>1:1</td>
<td>98</td>
</tr>
<tr>
<td>b</td>
<td>4-CH₂C₆H₄</td>
<td>1:1</td>
<td>94</td>
</tr>
<tr>
<td>c</td>
<td>3-CIC₆H₄</td>
<td>1:3</td>
<td>95</td>
</tr>
<tr>
<td>d</td>
<td>2,6-(CH₂)₂C₆H₄</td>
<td>1:2</td>
<td>90</td>
</tr>
<tr>
<td>e</td>
<td>2-CIC₆H₄</td>
<td>1:2</td>
<td>94</td>
</tr>
<tr>
<td>f</td>
<td>4-ClC₆H₄</td>
<td>1:2</td>
<td>97</td>
</tr>
<tr>
<td>g</td>
<td>4-O₂NC₆H₄</td>
<td>1:4</td>
<td>95</td>
</tr>
<tr>
<td>h</td>
<td>2,6-Cl₂C₆H₄</td>
<td>1:3</td>
<td>92</td>
</tr>
<tr>
<td>i</td>
<td>2-O₂NC₆H₄</td>
<td>1:2</td>
<td>94</td>
</tr>
<tr>
<td>j</td>
<td>3-O₂NC₆H₄</td>
<td>1:3</td>
<td>92</td>
</tr>
<tr>
<td>k</td>
<td>4-O₂NC₆H₄</td>
<td>1:4</td>
<td>95</td>
</tr>
<tr>
<td>l</td>
<td>2-naphthyl</td>
<td>1:2</td>
<td>91</td>
</tr>
<tr>
<td>m</td>
<td>3-pyridyl</td>
<td>1:4</td>
<td>97</td>
</tr>
<tr>
<td>n</td>
<td>PhCH=CH</td>
<td>1:3</td>
<td>91</td>
</tr>
<tr>
<td>o</td>
<td>CH₂CH=CH</td>
<td>1:3</td>
<td>90</td>
</tr>
</tbody>
</table>

*Yields refer to isolated products.

**300 W, 5 min.

*700 W, 5 min.

useful method for the preparation of diethyl α-acetyloxyphosphonates.

Chemicals were purchased from Merck and Fluka Chemical Companies. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-200. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. The purity of the products and the progress of the reactions were accomplished by TLC on silica gel polygram SILG UV254 plates.

Diethyl α-Acetyloxyphosphonates 2; General Procedure

A mixture of 1 (0.218–0.342 g, 1 mmol) and Ac₂O (0.342–0.57 g, 3–5 mmol) was irradiated in a microwave oven at 400 or 700 W for 5 min (Table 1). The reaction progress was monitored by TLC analysis. After complete conversion of the starting material, Et₂O (10 mL) was added to the reaction mixture and the solution was washed with sat. NaHCO₃ (3 × 10 mL) and H₂O (3 × 10 mL). The organic layer was separated and dried (Na₂SO₄) and filtered. Evaporation of the filtrate resulted in highly pure 2 in 90–98% yields.

2a

IR (neat): 1745 cm⁻¹ (C=O).

1H NMR (CDCl₃/TMS): δ = 1.17–1.29 (m, 6 H, 2 OCH₂CH₃), 2.16 [s, 3 H, 3 O(O)CH₃], 3.86–4.13 (m, 4 H, 2 OCH₂CH₃), 6.15 (d, 1 H, JₚH = 13.6 Hz, CH₃), 7.35 (d, JₚH = 7.1 Hz, 3 H, C₆H₅), 7.50 (d, JₚH = 7.3 Hz, 2 H, C₆H₅).

2b

IR (neat): 1751 cm⁻¹ (C=O).

1H NMR (CDCl₃/TMS): δ = 1.14–1.27 (m, 6 H, 2 OCH₂CH₃), 2.10 [s, 3 H, 3 O(O)CH₃], 2.58–2.83 (m, 4 H, 2 OCH₂CH₃), 5.93 (d, 1 H, JₚH = 13.4 Hz, CH₃), 7.09 (d, JₚH = 7.5 Hz, 2 H, C₆H₅), 7.30 (d, JₚH = 7.1 Hz, 2 H, C₆H₅).

2c

IR (neat): 1750 cm⁻¹ (C=O).

1H NMR (CDCl₃/TMS): δ = 1.22–1.40 (m, 6 H, 2 OCH₂CH₃), 2.19 [s, 3 H, 3 O(O)CH₃], 3.84 (s, 3 H, 4-CH₃Ar), 3.96–4.28 (m, 4 H, 2 OCH₂CH₃), 6.13 (d, 1 H, JₚH = 13.08 Hz, CH₂), 6.94 (d, 2 H, JₚH = 8.0 Hz, C₆H₅), 7.48 (d, JₚH = 8.0 Hz, 2 H, C₆H₅).

2d

IR (neat): 1745 cm⁻¹ (C=O).

1H NMR (CDCl₃/TMS): δ = 1.15–1.35 (m, 6 H, 2 OCH₂CH₃), 2.18 [s, 3 H, 3 O(O)CH₃], 4.02–4.16 (m, 4 H, 2 OCH₂CH₃), 6.12 (d, 1 H, JₚH = 13.9 Hz, CH₃), 7.29–7.69 (m, 4 H, C₆H₅).

2e

IR (neat): 1743 cm⁻¹ (C=O).

1H NMR (CDCl₃/TMS): δ = 1.60–1.85 (m, 6 H, 2 OCH₂CH₃), 2.18 [s, 3 H, 3 O(O)CH₃], 4.02–4.16 (m, 4 H, 2 OCH₂CH₃), 6.12 (d, 1 H, JₚH = 13.9 Hz, CH₃), 7.29–7.69 (m, 4 H, C₆H₅).

2f

IR (neat): 1743 cm⁻¹ (C=O).

1H NMR (CDCl₃/TMS): δ = 1.60–1.85 (m, 6 H, 2 OCH₂CH₃), 2.18 [s, 3 H, 3 O(O)CH₃], 4.02–4.16 (m, 4 H, 2 OCH₂CH₃), 6.12 (d, 1 H, JₚH = 13.9 Hz, CH₃), 7.29–7.69 (m, 4 H, C₆H₅).
1H NMR (CDCl₃/TMS): δ = 1.20–1.28 (m, 6 H, 2 OCH₂CH₃), 2.15 [s, 3 H, OC(O)CH₃], 3.94–4.00 (m, 4 H, 2 OCH₂CH₃), 5.97 (d, 1 H, Jₚ,...
(m, 1 H, CH), 6.19–6.30 (m, 1 H, =CH), 6.75 (d, 1 H, 2 OCH3), 5.53–5.66 (m, 2 H, =CH), 5.88–5.99 (m, 1 H, =CH).

13C NMR (CDCl3/TMS): δ = 16.74–16.90 (2 OCH3CH3), 21.24 [OC(O)CH3], 63.64–63.84 (2 OCH3CH3), 69.76 (d, 1 JCP = 171.4 Hz, CH), 120.53 (d, 1 JCP = 120.5 Hz, =CH), 127.14, 127.16, 127.78–129.22, 135.49–135.69 (C6H5), 136.07 (=CH), 169.65 [d, 1 JCP = 8.1 Hz, OC(O)CH3].

IR (neat): 1751 cm–1 (C=O).

MS (70 eV): m/z = 312 (M+).

Acknowledgment

We are thankful to Iran TWAS Chapter Based at ISMO and the Shiraz University Research Council for the support of this work.

References


