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### Iodine-Catalyzed, Efficient Synthesis of $\alpha$ -Hydroxy Phosphonates in Water

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## IODINE-CATALYZED, EFFICIENT SYNTHESIS OF $\alpha$ -HYDROXY PHOSPHONATES IN WATER

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*An efficient and simple synthesis of  $\alpha$ -hydroxy phosphonates from aldehydes and triethylphosphite in the presence of iodine in water has been developed. Environmentally benign reaction conditions, high yield, and easily available catalyst are important features of this method.*

*Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements to view the free supplemental file.*

**Keywords** Aldehydes;  $\alpha$ -hydroxy phosphonates; iodine; triethylphosphite; water

### INTRODUCTION

$\alpha$ -Hydroxy phosphonates have been found to possess widespread biological and pharmaceutical activities.<sup>1,2</sup> These compounds are useful precursors for the preparation of  $\alpha$ -functionalized phosphonates such as  $\alpha$ -amino,<sup>3</sup>  $\alpha$ -acetoxy,<sup>4</sup>  $\alpha$ -keto,<sup>5</sup> and  $\alpha$ -halophosphonates.<sup>6</sup> The synthesis of  $\alpha$ -hydroxy phosphonates from aldehydes and dialkylphosphites or trialkylphosphites promoted by various catalysts such as  $\text{Al}_2\text{O}_3$ ,<sup>7</sup>  $\text{KF}/\text{Al}_2\text{O}_3$ ,<sup>8</sup>  $\text{NEt}_3$ ,<sup>9</sup>  $\text{LiClO}_4$ ,<sup>10</sup>  $\text{Al}(\text{salalen})$  complex,<sup>11</sup> phosphates,<sup>12</sup> oxalic acid,<sup>13</sup> Amberlyst-15,<sup>14</sup>  $\text{Na}_2\text{CO}_3$  or  $\text{CaO}$ ,<sup>15</sup>  $\text{HCl}$ ,<sup>16,17</sup> and  $\text{MgO}$ <sup>18</sup> has been reported. However, some of these methods suffer from the low yields and the use of expensive and commercially unavailable catalysts. Therefore, the development of a convenient and environmentally benign method for the preparation of  $\alpha$ -hydroxy phosphonates is still desirable.

With the increasing public concern over environmental pollution, it is of great importance for chemists to come up with new approaches that are less hazardous to human health and environment. The use of environmentally benign solvents like water and the use of

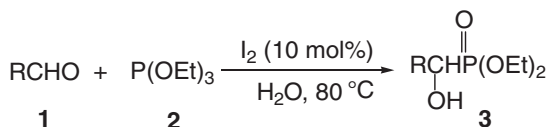
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solvent-free reactions represent very powerful green chemical technology procedures from both the economical and synthetic points of view. Water has many potential advantages as a solvent for organic reactions because of its low cost, safety, and environmental concern.<sup>19–21</sup>

In recent years, the use of molecular iodine as a relatively inexpensive and easily available catalyst has received considerable attention for various organic transformations.<sup>22–29</sup> In continuation to our work in studying iodine-catalyzed reactions,<sup>30–32</sup> we report in this article an efficient procedure for the preparation of  $\alpha$ -hydroxy phosphonates from aldehydes and triethylphosphite using iodine as a catalyst in water at 80°C (Scheme 1).



Scheme 1

## RESULTS AND DISCUSSION

Initially, in order to establish the optimum conditions for the synthesis of  $\alpha$ -hydroxy phosphonates, different amounts of iodine were examined. Using the reaction of benzaldehyde with triethylphosphite as a model, we investigated the effect of the amount of iodine on the reaction. It was found that 10 mol% of iodine is sufficient to promote the reaction to completion in 93% yield. Increasing the amount of catalyst did not enhance the yield of the product. In the absence of iodine, only a low yield (18%) of the product was obtained within 180 min. Although the reaction of benzaldehyde and triethylphosphite occurred both in the presence and in the absence of molecular iodine, iodine catalyzed the reaction efficiently and improved the reaction yield in a short time. In addition, in the present conversion, iodine has been found to be more efficient than the conventional Lewis acids such as  $\text{ZnCl}_2$ ,  $\text{SnCl}_2$ ,  $\text{FeCl}_3$ , and  $\text{AlCl}_3$  in terms of yield and reaction time.

Then, in order to examine the effect of temperature, the amount of iodine was kept constant at 10 mol%. The reaction was monitored at different temperatures. When the reaction was carried out at room temperature, the yield was not satisfactory (56%). After the temperature was elevated to 80°C, the yield increased to 93%. However, while increasing the temperature continuously, the yield did not obviously change.

To demonstrate the generality of this method, other aldehydes were also used to react with triethylphosphite in the presence of iodine (10 mol%) in water at 80°C, and the results are summarized in Table I. As shown in Table I, in all cases, the reactions proceeded smoothly to produce  $\alpha$ -hydroxy phosphonates in good to excellent yields. Aromatic aldehydes containing electron-withdrawing groups such as chloro and nitro proceeded at faster rates than those containing electron-donating groups such as methoxy and methyl (Table I, entries 2–9). Moreover,  $\alpha,\beta$ -unsaturated aldehydes such as cinnamaldehyde (entry 10) and heteroaromatic aldehydes (entries 11 and 12) also reacted with triethylphosphite smoothly to generate the desired products in high yields, but for longer reaction times. Aliphatic aldehydes reacted with triethylphosphite to give the corresponding products in excellent yields (entries 13–15). However, in a similar manner, ketones and triethylphosphite did not react under these reaction conditions.

**Table I** Iodine-catalyzed synthesis of  $\alpha$ -hydroxy phosphonates in water<sup>a</sup>

Entry	R	Product	Time (min)	Yield <sup>b</sup> (%)
1	C <sub>6</sub> H <sub>5</sub>	<b>3a</b>	30	93
2	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3b</b>	50	87
3	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	60	86
4	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3d</b>	20	96
5	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3e</b>	20	92
6	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3f</b>	15	92
7	4-ClC <sub>6</sub> H <sub>4</sub>	<b>3g</b>	45	89
8	2-ClC <sub>6</sub> H <sub>4</sub>	<b>3h</b>	30	91
9	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3i</b>	15	97
10	C <sub>6</sub> H <sub>5</sub> CH = CH	<b>3j</b>	120	83
11	2-Furyl	<b>3k</b>	60	92
12	2-Thienyl	<b>3l</b>	60	89
13	CH <sub>3</sub>	<b>3m</b>	30	93
14	CH <sub>3</sub> CH <sub>2</sub>	<b>3n</b>	30	92
15	(CH <sub>3</sub> ) <sub>2</sub> CH	<b>3o</b>	30	90

<sup>a</sup>All the reactions were carried out with 10 mol% iodine in water at 80°C.<sup>b</sup>Isolated yield.

Iodine is capable of bonding with the carbonyl oxygen increasing the reactivities of parent carbonyl compounds. As shown in Scheme S1 (available online in the Supplemental Materials), we propose a likely mechanism based on analogous reports in the literature.<sup>14</sup> The reaction may proceed by initial coordination of iodine with the carbonyl group, which facilitates the formation of intermediate **4**. Subsequent hydrolysis of the intermediate **4** through the intermediates **5** and **6** gives the desired product **3**.

In conclusion, iodine was found to be an efficient catalyst for the synthesis of  $\alpha$ -hydroxy phosphonates from aldehydes and triethylphosphite in water. The present method has the advantages of environmentally benign reaction conditions, easy workup, and high yields.

## EXPERIMENTAL

All solvents were dried by standard procedures. The benzaldehyde was distilled prior to use. All other reagents were commercially available products and were used without further purification. Melting points were determined on an XT4A electrothermal apparatus equipped with a microscope and are uncorrected. NMR spectra were recorded on a Bruker Avance 400 spectrometer in CDCl<sub>3</sub> with TMS as an internal standard. Low-resolution MS analyses were measured on a Bruker Esquire 3000 spectrometer using the ESI (electrospray ionization) technique. IR spectra were recorded on a Nicolet FTIR-750 spectrometer.

### General Procedure for the Synthesis of $\alpha$ -Hydroxy Phosphonates

A mixture of aldehyde **1** (1 mmol), triethylphosphite **2** (1 mmol), and iodine (10 mol%) in H<sub>2</sub>O (2 mL) was stirred and heated at 80°C for the appropriate time (Table I). After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, and CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added. Then it was washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> followed by brine solution and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL).

The combined organic phase was dried over anhydrous  $\text{MgSO}_4$ . Removal of the solvent under reduced pressure afforded the crude product 3, which was further purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (V:V, 4:1) as eluent.

All the products are known compounds. The spectroscopic and physical data for all compounds correspond to those given in the literature.<sup>16–18</sup>

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