Amberlyst-15 as a Heterogeneous Reusable Catalyst for the Synthesis of α-Hydroxy Phosphonates in Water

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Abstract: An efficient and simple synthesis of α-hydroxy phosphonates has been achieved via reaction of aldehydes with trimethylphosphite in the presence of Amberlyst-15 in water. The reaction is highly selective with excellent yields under mild conditions.

Key words: α-hydroxy phosphonates, Abramov reaction, water, Amberlyst-15, nucleophilic addition

One of the fundamental and challenging goals to scientists is to perform organic reactions in water, because water is an environmentally friendly and safe medium, although widely accepted as a contaminant in organic synthesis.[1] Recently, water and aqueous reaction media attracted much interest not only for the viewpoint of green chemistry, but also for unique physical and chemical properties of water.[2] Water also exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[3] There is no doubt that the use of water as a reaction medium could have an outstanding impact on chemical synthesis, including at a process scale. In addition, water is a weak electrolyte at room temperature but dissociates to a greater extent on increasing the temperature, resulting in higher concentrations of H_3O^+ and OH^- at neutral conditions, which can catalyze chemical reactions.[4]

On the other hand, there has been considerable interest in phosphorus–carbon [P–C] bond-forming reactions.[5] α-Hydroxy phosphonates which are easily prepared from commercially available materials, have received attention both as substrates for the preparation of other α-substituted phosphonates and because of their potential biological activity.[6] These compounds show antiviral,[7a] antibacterial,[7b] antivaccinia,[7c] anticancer,[7d] pesticides,[7e] renin inhibitors,[7f] HIV-protease,[7g] anti-HIV activities,[7h,i] and enzyme inhibitor properties.[7j] Much of this activity has been attributed to the relatively inert nature of the C–P bond and to the physical and structural similarity of phosphonic and phosphinic acids to the biologically important phosphate ester and carboxylic acid functional groups.[8] Furthermore, α-hydroxy phosphonates are also useful precursors for the preparation of α-functionalized phosphonates, such as α-amino,[9] α-keto,[10] α-halo,[11] and α-acetoxyphosphonates.[12]

The synthesis of α-hydroxy phosphonates has been investigated in the presence of Lewis acids,[13] alumina,[14] potassium fluoride on alumina,[15] lithium perchlorate in diethyl ether,[16] cesium fluorides,[14] guanidine hydrochloride,[17] quaternary ammonium hydroxide ion exchange resin,[18] (*R*)-Al(salalen) complex,[19] L-prolineamide,[20] and titanium alkoxides.[21] An alternative method is the reaction of trialkylphosphites with aldehydes in the presence of hydrogen chloride via Arbusov-like reaction of oxonium salts derived from aldehydes or ketones.[22]

Surprisingly, we found very few reports describing the reaction of trialkylphosphites with aldehydes or ketones, despite the fact that trialkylphosphites are obviously much better nucleophiles than dialkylphosphonates, and they are certainly P-nucleophiles because of their free electron pairs located only on the phosphorus atom.[22]

Trialkylphosphites undergo the Abramov reaction only under forcing conditions, but the replacement of one alkoxy residue on phosphorus with a trialkylsiloxy group increases greatly the reactivity of the resulting silyl phosphite ester towards unsaturated organic substrates.[23]

However, these methods have some disadvantages. For example, it was found that in all studied cases, which included aliphatic and aromatic aldehyde or ketone, the hydroxy phosphonates decompose to the starting carbonyl compounds.[24] In addition, the yields are not always good and mixtures of products are sometimes obtained. Hence, there is a need to develop a convenient, environmentally benign, and feasible method for the synthesis of α-hydroxy phosphonates.

In recent years, the use of solid acidic catalyst has attracted considerable attention.[25] In this regard, Amberlyst-15 possesses unique properties such as environmental compatibility, nontoxic, reusability, non-corrosive, selectivity, chemical and physical stability and can be used over a prolonged period. Owing to the numerous advantages associated with this cheap and no hazardous catalyst, Amberlyst-15 has been explored as a powerful catalyst for various organic reactions.[26]

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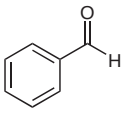
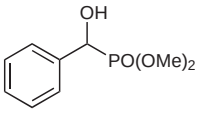
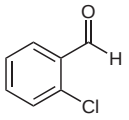
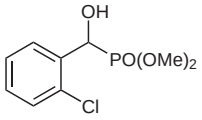
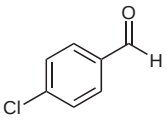
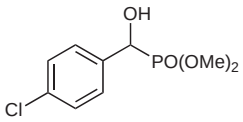
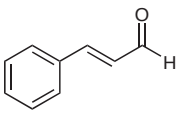
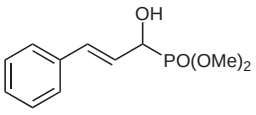
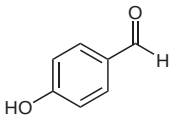
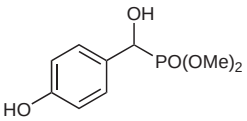
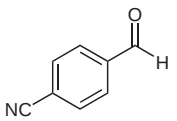
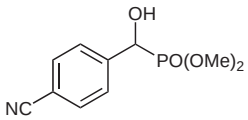
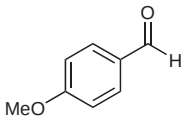
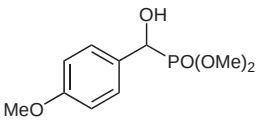
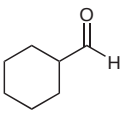
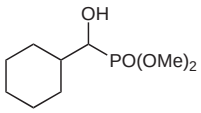
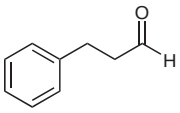
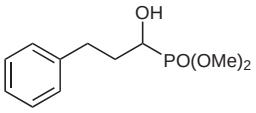
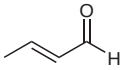
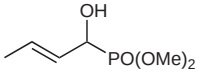
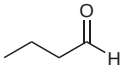
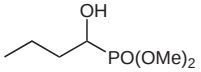
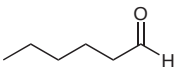
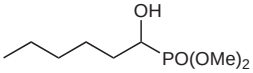
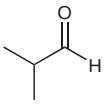
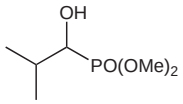
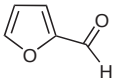
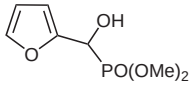
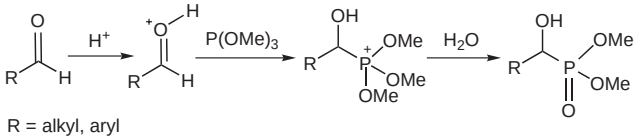
Table 1 Synthesis of α-Hydroxy Phosphonates from Various Aldehydes

Entry	Aldehyde	Product[a]	Time (min)	Yield (%)[b]
1			90	95
2			180	85
3			225	74
4			150	80
5			90	94
6			105	65
7			110	89
8			120	85
9			90	95
10			170	75
11			120	92
12			120	90
13			120	88
14			110	80

[a] All the products are known compounds and were characterized by their IR, ^{1}H NMR spectra and comparison with the authentic samples.
[b] All yields refer to isolated products.

We report here a new method for the preparation of α-hydroxy phosphonates from a mixture of aldehydes and trimethylphosphite in the presence of Amberlyst-15 in water at 50 °C and the results are summarized in Table 1.[27] When we treated benzaldehyde with trimethylphosphite in water at 50 °C for 4 hours in the absence of Amberlyst-15, only a low yield (<40%) of dimethyl 1-hydroxy-1-phenylmethylphosphonate was obtained, so implying the role of Amberlyst-15 in this reaction.

We assume that the solid acid catalyst generates hydronium ion in water that activates the carbonyl group, which consequently undergoes nucleophilic attack by trialkylphosphite (Scheme 1).



Scheme 1

As shown in Table 1, the reaction of a mixture of aliphatic or aromatic aldehydes and trimethylphosphite in the presence of Amberlyst-15 in water at 50 °C, afforded the desired products in good to high yields, after a typical reaction time of about 1–4 hours. α,β-Unsaturated aldehydes also selectively afforded the corresponding α-hydroxy phosphonates in good yield, with no byproduct formation. The catalyst can be regenerated simply by filtration and reused several times without losing its activity.

This reaction has been performed in different organic solvents such as diethyl ether, CH_2Cl_2, $CHCl_3$, MeCN, THF, dioxane, and methanol in the presence of Amberlyst-15 in water at 50 °C and a low yield (<50%) of the α-hydroxy phosphonates was obtained. In a similar manner, the mixture of ketones and trimethylphosphite does not react under these reaction conditions.

In summary, we have developed a protocol for the synthesis of α-hydroxy phosphonates in the presence of Amberlyst-15 in aqueous media.

Experimental convenience, more economic, environmentally benign, good yields, and relatively clean reaction conditions without any byproducts make this method an attractive and a useful protocol. In many cases the products just crystallize directly out of the reaction mixture and crude products are obtained in a high purity.

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(27) **Typical Procedure**
A solution of benzaldehyde (0.107 g, 1 mmol), trimethylphosphite (0.136 g, 1.1 mmol), and Amberlyst-15 (0.1 g) in H_2O (2 mL) was placed in a round-bottomed flask equipped with a magnetic stirrer and was heated at 50 °C. The stirring was continued for 1.5 h. After completion of the reaction as indicated by TLC, the reaction mixture was treated with aq sat. $NaHCO_3$ solution followed by brine and the product was extracted three times with 5 mL CH_2Cl_2, dried over anhyd $MgSO_4$, and concentrated to give an oily residue, which was crystallized to give 0.216 g (95%) of dimethyl 1-hydroxy-1-phenylmethylphosphonate.

Spectral Data for Selected Products

Dimethyl 1-Hydroxy-1-phenylmethylphosphonate[19] **(Table 1, Entry 1)**
IR: 3260 (OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.6 (d, *J* = 10.3 Hz, 3 H), 3.6 (d, *J* = 10.3 Hz, 3 H), 5.0 (d, 1 H, *J* = 13.2 Hz), 6.0 (s, OH), 7.3–7.5 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.7 (d, J_{CP} = 7.5 Hz), 54.2 (d, J_{CP} = 7.5 Hz), 69.1 (d, J_{CP} = 164.0 Hz), 128.8, 129.4, 131.1, 133.8 (d, J_{CP} = 2.9 Hz).

Dimethyl 1-Hydroxy-1-(4-chlorophenyl)methylphosphonate[19] **(Table 1, Entry 3)**
IR: 3290 (OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.6–3.7 (m, 6 H), 5.1 (d, *J* = 13.4 Hz, 1 H), 6.2 (s, OH), 7.4 (d, *J* = 8.5 Hz, 2 H), 7.5 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.7 (d, J_{CP} = 7.1 Hz), 54.2 (d, J_{CP} = 7.5 Hz), 69.1 (d, J_{CP} = 161.1 Hz), 128.8, 129.4, 133.1 (d, J_{CP} = 3.9 Hz), 138.2.

Dimethyl 1-Hydroxy-3-phenyl-2-propenylphosphonate[28] **(Table 1, Entry 4)**
IR: 3255 (OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.8 (d, J_{PH} = 10.3 Hz, 3 H), 3.8 (d, J_{PH} = 10.3 Hz, 3 H), 4.7 (s, OH), 6.4 (d, *J* = 15.9, 6.2 Hz, J_{PH} = 5.6 Hz, 1 H), 6.8 (d, *J* = 15.6, 1.5 Hz, J_{PH} = 4.9 Hz, 1 H), 7.3–7.2 (m, 3 H), 7.4–7.4 (m, 2 H). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 53.7 (d, J_{PC} = 7.4 Hz), 53.9 (d, J_{PC} = 7.1 Hz), 69.2 (d, J_{PC} = 161.0 Hz), 128.4, 127.8, 126.5, 123.5 (d, J_{PC} = 4.3 Hz), 132.2 (d, J_{PC} = 13.0 Hz), 136.1 (d, J_{PC} = 2.9 Hz).

Dimethyl 1-Hydroxybutylphosphonate[17] **(Table 1, Entry 11)**
IR: 3312 (OH) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.0 (t, 3 H), 1.8–1.1 (m, 4 H), 2.7 (m, 1 H), 3.7 (d, $^3J_{PH}$ = 5.4 Hz, 3 H), 3.8 (d, $^3J_{PH}$ = 5.4 Hz, 3 H), 3.9 (s, OH). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 13.8 (d, $^4J_{PC}$ = 19.1 Hz, CH_3), 19.9 (d, $^3J_{PC}$ = 11.8 Hz, CH_2), 29.0 (d, $^2J_{PC}$ = 7.4 Hz, CH_2), 51.1 (d, $^2J_{PC}$ = 7.3 Hz, OCH_3), 52.2 (d, $^2J_{PC}$ = 7.3 Hz, OCH_3), 56.8 (d, $^1J_{PC}$ = 136.8 Hz, OCH_3).

Dimethyl 1-Hydroxy-2-methylpropylphosphonate[17] **(Table 1, Entry 13)**
IR: 3313 (OH) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 0.8 (m, 3 H), 1.9 (m, 1 H), 3.6 (m, 1 H), 3.6 (d, $^3J_{PH}$ = 4.4 Hz, 3 H), 3.7 (d, $^3J_{PH}$ = 4.4 Hz, 3 H), 4.8 (s, O H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 17.4 (d, $^4J_{PC}$ = 7.0 Hz, CH_3), 19.4 (d, $^3J_{PC}$ = 9.5 Hz, CH_2), 29.9 (d, $^2J_{PC}$ = 8.0, CH), 52.4 ($^2J_{PC}$ = 6.5 Hz, OCH_3), 52.6 ($^2J_{PC}$ = 6.5 Hz, OCH_3), 73.2 ($^1J_{PC}$ = 148.4 Hz, CH).

Dimethyl 1-Hydroxy-1-furylmethylphosphonate[17] **(Table 1, Entry 14)**
^1H NMR (90 MHz, $CDCl_3$): δ = 1.3 (s, OH), 3.7 (d, $^3J_{PH}$ = 5.8 Hz, 3 H), 3.9 (d, $^3J_{PH}$ = 5.8 Hz, 3 H), 5.0 (d, $^2J_{PH}$ = 13.5 Hz, 1 H), 6.4–6.6 (m, 2 H), 7.4 (s, 1 H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 53.6 (d, $^2J_{PC}$ = 2.7 Hz, OCH_3), 53.9 (d, $^2J_{PC}$ = 2.7 Hz, OCH_3), 64.2 (d, $^1J_{PC}$ = 167.8 Hz, CH), 109.3 (d, $^3J_{PC}$ = 6.4 Hz, C), 110.7 (s, CH), 142.8 (d, $^3J_{PC}$ = 1.8 Hz, CH), 149.9 (s, CH).

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