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An organocatalyzed facile and rapid access to α-hydroxy and α-amino phosphonates under conventional/ultrasound technique

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ABSTRACT

In the present work, successful implementation of ultrasound irradiation for the rapid synthesis of α-hydroxy and α-amino phosphonates under solvent-free conditions is demonstrated. Use of a novel catalyst (i.e., camphor sulfonic acid) in combination with ultrasound technique is reported for the first time. Comparative study for the synthesis of α-hydroxy and α-amino phosphonates using conventional as well as ultrasonication method is discussed.

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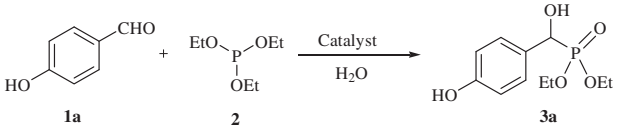
Emerging area of green chemistry demands ecofriendly organic chemical processes, considering the increasing environmental pollution and its drastic impact on living systems.[1] Hence, significance of greener pathways in organic synthesis is ever-growing in order to attain the sustainability. For many chemical operations, a major adverse effect to the environment is consumption of energy for heating and cooling. To overcome such problems, it is highly desirable to develop efficient routes that utilize alternative energy resources.[2] Ultrasound technique has increasingly been used in organic synthesis.[3–6] There is still lot of scope to exploit the applications of ultrasonication in organic transformations and synthesis of bioactive molecules.

From organic and polymer synthesis to biology and biochemistry, molecules containing phosphonate moiety are attracting an enormous interest of organic chemists for the structural modifications and synthetic developments of phosphonate derivatives,[7] particularly the α-functionalized analogs.[8] Within the α-functionalized phosphonates, α-hydroxy phosphonates are important compounds, since, α-hydroxyphosphonic acids and their esters possess a special place as they are endowed with a wide range of biologic/pharmacological actions: from antibacterial, neuroactive, and anticancer drugs to enzymes inhibitors and pesticides.[9] Moreover, they are useful precursors for the preparation of other types of α-functionalized phosphonates.[10] Among them, an important one is α-amino phosphonates. α-Amino phosphonates constitute significant class of compounds in pharmaceutical chemistry with potential biologic effects.[11,12]

One of the most attractive routes for the synthesis of these compounds involves the reaction of aldehyde with alkyl phosphite and reaction of aldehyde with primary amine and alkyl phosphite to get α-hydroxy and α-amino phosphonates, respectively. Several catalysts have been used for the synthesis of α-hydroxy phosphonates[13,14] and α-amino phosphonates.[15,16] Moreover, to the best of our knowledge, there is only single report on the use of a common catalyst[14f] for the synthesis of both α-hydroxy and α-amino phosphonates.

Interest in the field of organocatalysis has increased spectacularly in the last few years.[17] Camphor sulfonic acid (CSA) is achieving enormous significance in organic synthesis as this catalyst is used in the synthesis of chromans,[18a] ligands,[18b] and pseudoglycosides,[18c] as an auxillary,[19a] and in some polymerization reactions.[19b] In continuation of our endeavor[20] toward the development of ecofriendly synthetic protocols, it was thought worthwhile to disclose new and expeditious route for the synthesis of α-hydroxy and α-amino phosphonates under conventional/ultrasound technique using camphor sulfonic acid as an organocatalyst.



1a 2 3a

Scheme 1. Standard model reaction.

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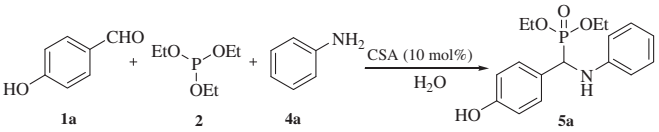
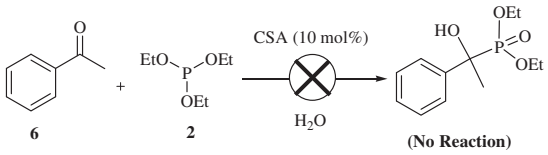
Table 1
Screening of catalysts[a]

Entry	Catalyst	Catalyst conc. (mol %)	Time (min)	Yield[b] (%)
1	*p*TSA	10	40	72
2	Sulfanilic acid	10	40	59
3	EDTA·2Na (in water (1 mL))	10	60	47
4	L-proline	10	30	78
5	CSA	10	30	91
6	CSA[c]	2.5, 5, 10, 15	30	55, 68, 90, 90

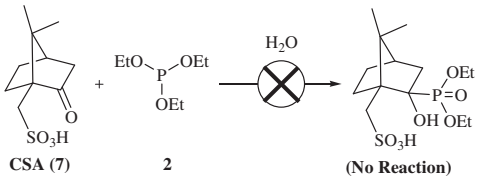
[a] Reactions and conditions: **1a** (1 mmol) and **2** (1 mmol) at rt under solvent free conditions.
[b] Isolated yields.
[c] Respective yields under different concentrations of this catalyst are given.



Scheme 2. Reaction for the synthesis of α-amino phosphonate (**5a**).



Scheme 3. Reaction of acetophenone with triethyl phosphite.



Scheme 4. Reaction of camphor sulfonic acid (CSA) with triethyl phosphite.

In our initial experiments, the reaction of *p*-hydroxy benzaldehyde and triethyl phosphite was performed under solvent-free and catalyst-free conditions (Scheme 1). Unfortunately, even after 60 min, the reaction was not initiated and only starting materials were recovered. Therefore it was thought that for initiation of the reaction intervention of catalyst is necessary. Hence, some well known acid catalysts such as *p*TSA, sulfanilic acid and EDTA·2Na salt were tested to activate the reaction mass.

When *p*TSA was used as a catalyst for the reaction, desired product was obtained in 72% yield (Table 1, entry 1), whereas, sulfanilic acid failed to deliver the product in more than 59% yield (Table 1, entry 2). In case of EDTA·2Na only 47% product yield was obtained (Table 1, entry 3). In order to improve the yield some organocatalysts like L-proline and camphor sulfonic acid (CSA) were also examined. To our surprise, reaction in the presence of CSA was found to proceed rapidly affording 90% yield (Table 1, entry 5). L-proline also delivered the product in good yield (Table 1,

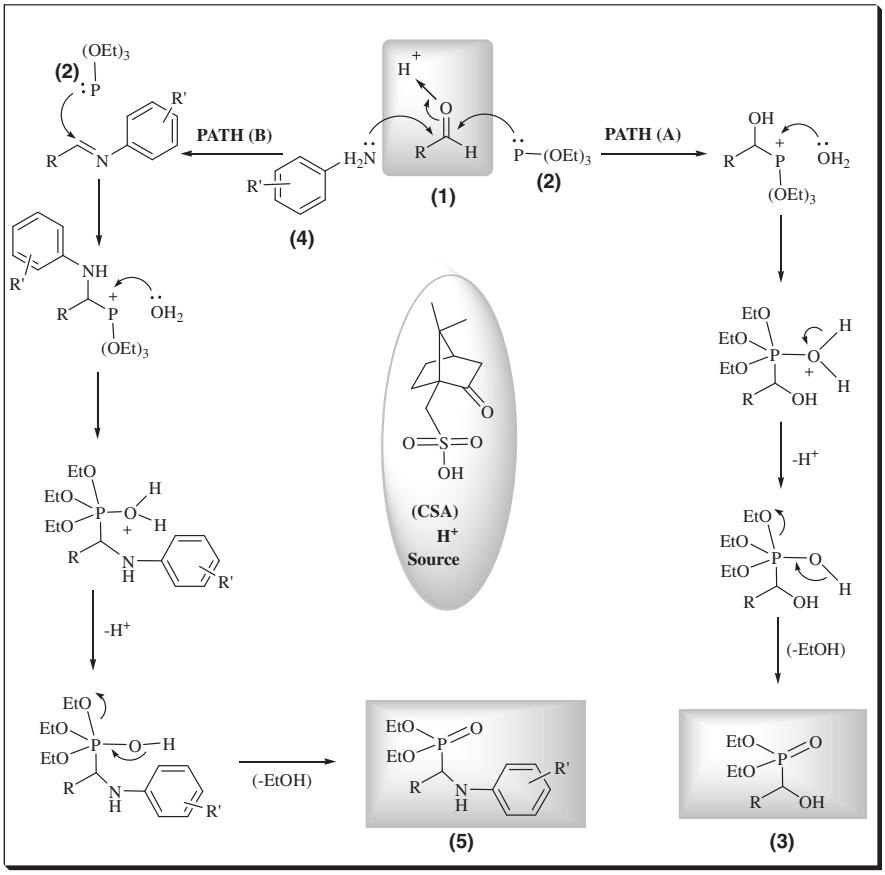
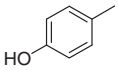
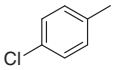
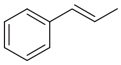
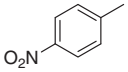
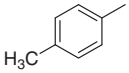
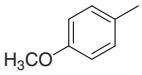
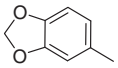
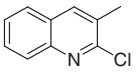
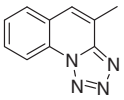


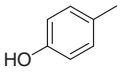
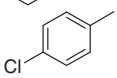
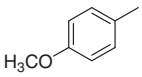
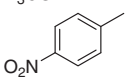
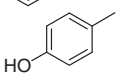
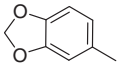
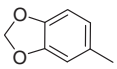
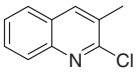
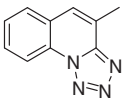
Figure 1. Proposed mechanism for the synthesis of α-functionalized phosphonates.

Table 2
Synthesis of α-hydroxy phosphonates[a]

Compound	R	Time (min)	Yield[b] (%)
		A/B	**A/B**
3a		40/10	90/92
3b		30/08	91/93
3c		30/10	92/91
3d		40/12	84/85
3e		30/08	91/92
3f		40/10	88/90
3g		35/12	85/85
3h		45/12	89/91
3i		60/15	85/87
3j		60/15	87/86
3k[c]		60/20	83/86
3l[c]		60/20	88/89

[a] Reactions and conditions: **1** (1 mmol), **2** (1 mmol) and CSA (0.1 mmol) at rt under solvent free conditions.
[b] Isolated yields.
[c] For these aldehydes ethanol as a solvent (5 mL) was used to homogenize the reaction mixture; **A** = conventional method and **B** = ultrasound method.

Table 3
Synthesis of α-amino phosphonates[a]

Compound	R	R′	Time (min)	Yield[b] (%)
			A/B	**A/B**
5a		H	45/12	89/91
5b		H	30/10	91/91
5c		H	45/10	85/83
5d		H	50/15	86/87
5e		H	30/08	92/93
5f		4-CH_3	30/08	89/90
5g		4-CH_3	45/15	91/89
5h		H	50/15	87/87
5i		H	60/20	83/85
5j		4-CH_3	50/15	88/89
5k[c]		H	70/20	83/87
5l[c]		4-F	75/20	82/83

[a] Reactions and conditions: **1** (1 mmol), **2** (1 mmol), **4** (1 mmol) and CSA (0.1 mmol) at rt under solvent free conditions.
[b] Isolated yields.
[c] For these aldehydes ethanol as a solvent (5 mL) was used to homogenize the reaction mixture; **A** = conventional method and **B** = ultrasound method.

entry 4). Therefore, considering the effective catalytic activity of CSA and for exploitation of its applications in organic transformations, CSA was preferred as a catalyst of choice for subsequent optimization studies.

To determine the exact requirement of catalyst for the reaction, we investigated the model reaction using different concentrations of CSA such as 2.5, 5, 10, and 15 mol %. During this, formation of the product was observed in 55%, 68%, 90%, and 90% yield, respectively (Table 1, entry 6). This indicated that 10 mol % of CSA was sufficient to carry out the reaction smoothly.

In further set of experiments, reaction of *p*-hydroxy benzaldehyde, aniline and triethyl phosphite was carried out under optimized reaction conditions (Scheme 2). During this study, formation of corresponding α-amino phosphonate analog was observed in good yield. It clarified that achieved optimum conditions were equally applicable for the synthesis of α-hydroxy as well as α-amino phosphonate.

Since CSA is having carbonyl group in its structure, one may speculate possibility of the reaction of CSA with triethyl phosphite. To confirm this, initially, acetophenone was reacted with triethyl phosphite in the presence of CSA as a catalyst (Scheme 3) and in another experiment CSA itself was reacted with triethyl phosphite (Scheme 4). However, in both cases initiation of the reaction was not observed even after 60 min and starting materials were quantitatively recovered. This study revealed that, in the presence of CSA, only aldehydes react to give α-hydroxy phosphonates and not ketones. In this way, possibility of the side reaction of CSA has been ruled out.

Considering the well established applications of ultrasound to promote variety of chemical reactions, we next attempted to carry out the model reaction using optimized reaction conditions under ultrasound irradiation with a view to explore whether, (i) the reaction could be expedited and, (ii) the product yield could be enhanced. Assistance of ultrasound irradiation did not bring about any significant improvement in the product yield (92%). It is worth noting here, that the reaction time reduced significantly (10 min) as compared to conventional method (40 min).

The difference in the reaction times may be due to the specific effects of ultrasound. The effect observed on the reaction is due to the phenomenon of acoustic cavitation.[3–6] The collapse of cavitation bubbles result in the formation of very reactive chemical species having short lifetime which facilitates the rapid synthesis of α-functionalized phosphonates derivatives.

Schematic representation depicting possible mechanism for CSA catalyzed synthesis of α-hydroxy and α-amino phosphonates is rationalized with the help of Figure 1.

Having established the optimum experimental conditions for obtaining the best yields of α-functionalized phosphonate derivatives, wide range of aldehydes were treated with triethyl phosphite to get α-hydroxy phosphonates and different aldehydes were reacted with substituted anilines and triethyl phosphite for synthesizing α-amino phosphonates under conventional and ultrasound method.[23] Notably, all the substrates were observed to be well tolerated under optimized conditions furnishing the product in good to excellent yields. All the results are compiled in Table 2 and 3. Formation of the desired product was confirmed by comparing their physical constant, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data with reported compounds.[13–16,21]

In summary, an efficient, greener and expeditious synthetic protocol for α-functionalized phosphonates has been developed. This technique overcomes some of the problems associated with excessive or wasteful heating. Remarkable advantages of this synthetic strategy over others are- (i) use of non-classical energy source (ultrasonication) which offers better energy balance in comparison with those of classical performance, (ii) reduced reaction times, (iii) non-toxic and economically viable catalyst, (iv) omission of solvents, (v) ambient reaction temperature, and (vi) simplified work-up procedure. Present work is the first report on the combined use of ultrasound irradiation and camphor sulfonic acid for organic transformation.

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23. *Typical experimental procedure*:
preparation of α-hydroxy phosphonates. Conventional method: a mixture *p*-hydroxy benzaldehyde **1a** (1 mmol), triethyl phosphite **2** (1 mmol) and CSA (0.1 mmol) was stirred vigorously at rt under solvent-free conditions for 40 min. Reaction progress was monitored by TLC (ethyl acetate/*n*-hexane: 1:9). After 40 min, 10 mL water was added to the reaction mass and stirred again for 5 min to obtain the solid product. Reaction mass containing product was poured on crushed ice and product was collected by simple filtration, washed with water and dried. The crude product (**3a**) was recrystallized from ethanol to obtain pure product.
Ultrasound method: a mixture *p*-hydroxy benzaldehyde **1a** (1 mmol), triethyl phosphite **2** (1 mmol) and CSA (0.1 mmol) under neat conditions was subjected to ultrasound irradiation for 10 min. Reaction progress was monitored by TLC (ethyl acetate/*n*-hexane: 1:9). After 10 min, 10 mL water was added to the reaction vessel and irradiated again for 2–3 min to obtain the solid product. Reaction mass containing product was poured on crushed ice and product was collected by simple filtration, washed with water and dried. The crude product (**3a**) was recrystallized from ethanol to obtain pure product.
Preparation of α-amino phosphonates. Conventional method: a mixture *p*-hydroxy benzaldehyde **1a** (1 mmol), aniline **4a** (1 mmol), triethyl phosphite **2** (1 mmol) and CSA (0.1 mmol) was stirred vigorously at rt under solvent free conditions for 45 min. Reaction progress was monitored by TLC (ethyl acetate/*n*-hexane: 1:9). After 45 min, 10 mL water was added to the reaction mass and stirred again for 5 min to obtain the solid product. Reaction mass containing product was poured on crushed ice and product was collected by simple filtration, washed with water and dried. The crude product (**5a**) was recrystallized from ethanol to obtain pure product.
Ultrasound method: a mixture *p*-hydroxy benzaldehyde **1a** (1 mmol), aniline **4a** (1 mmol), triethyl phosphite **2** (1 mmol) and CSA (0.1 mmol) under neat conditions was subjected to ultrasound irradiation for 12 min. Reaction progress was monitored by TLC (ethyl acetate/*n*-hexane: 1:9). After 12 min, 10 mL water was added to the reaction vessel and irradiated again for 2–3 min to obtain the solid product. Reaction mass containing product was poured on crushed ice and product was collected by simple filtration, washed with water and dried. The crude product (**5a**) was recrystallized from ethanol to obtain pure product.