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An Efficient Synthesis of α -Hydroxy Phosphonates Catalyzed by Phenylboronic Acid at Ambient Temperature Condition

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Abstract: We have developed an effective approach for the synthesis of α -hydroxy phosphonates catalyzed by phenylboronic acid as an efficient catalyst. The reaction was carried out at ambient temperature condition by reaction of aromatic aldehyde and triethyl phosphite in solvent ethanol catalyzed by phenylboronic acid as catalyst. This method offers several advantages such as excellent yields (87-94%), mild reaction condition, environmentally benign and simple work-up.

Keywords: α -Hydroxy phosphonates; phenylboronic acid; aromatic aldehyde; triethyl phosphite.

Introduction

Phosphonate moiety having hydroxy groups have attracted significant attention due to their importance in biologically processes [1] and wide range of their applications [2]. α -Hydroxy phosphonates work as an inhibitor of diverse group of enzymes containing Renin [3a] and HIV-protease [3b]. Moreover, α -hydroxy phosphonates used as attractive precursors in the synthesis of various α -substituted phosphonates and phosphonic acids such as α -aminophosphonates and α -aminophosphonic acids which have both medicinal and synthetic significance. α -Hydroxy phosphonates have been applied for the synthesis of 1,2-diketones

[4], α -halophosphonates, halosubstituted alkenes and alkynes [5], α -ketophosphonates [6]. Recently α -hydroxy allylic phosphonates were used in the synthesis of (-)-Enterolactone and cyclopentenones [7].

Several protocols have been developed for the synthesis of α -hydroxy phosphonates [8]. These methods are based on the reaction of aldehydes or ketones with dialkyl phosphonates in presence of several bases such as potassium fluoride on alumina [9], piperizine [10], MgO [11], TMG [12], DBU [13]. There are some disadvantages over the use of base for the activation of dialkyl phosphonates. Some acid catalysts like niobium(V)chloride [14] have been

also employed for the synthesis of α -hydroxy phosphonates in the Abramov reaction. However, few reports have been developed by the reaction of trialkyl phosphite with aldehydes or ketones in the presence of acid catalysts such as sulphamic acid [15], ammonium metavanadate [16], amberlyst-[17] hydrochloric acid [18] and pyridine 2,6-dicarboxylic acid [19].

As a continuation of our interest in the development of an efficient method using arylboronic acids as a catalyst [20-23], herein we describe a convenient synthesis of α -hydroxy phosphonates starting from aromatic aldehyde and triethyl phosphite using phenylboronic acid as a catalyst at ambient temperature condition.

Experimental

All solvents were used as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (80–120 mesh). Melting points were determined in open capillary tube and are uncorrected. The purity of the compounds has been checked by TLC. ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in CDCl_3 solvent and TMS as an internal standard. Mass spectra were taken on Polaris-Q Thermoscientific GC-MS.

General procedure for synthesis of α -hydroxy phosphonates (3a-l): Aromatic aldehyde (1 mmol) and triethyl phosphite (1.5 mmol) were mixed in solvent ethanol (15 mL). A Catalytic amount of phenylboronic acid (20 mol %) was added and reaction mixture was stirred at room temperature for appropriate time (Table 3). After completion of reaction indicated by thin layer chromatography (pet ether: ethyl acetate 8:2), the reaction mixture was diluted with 10 mL water and extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained product was purified by column

chromatography using silica gel mesh 80-120 to afford the pure product.

Diethyl (4-chlorophenyl)(hydroxy) methylphosphonate (3a): ^1H NMR(300 MHz, CDCl_3): δ 1.22 (t, 3H), 1.26 (t, 3H), 4.18 (m, 4H), 4.78 (d, 1H, $J = 11.2$ Hz), 6.02 (s, 1H, -OH), 7.18 (d, 2H, $J = 7.8$ Hz, Ar-H), 7.52 (d, 2H, $J = 7.8$ Hz, Ar-H); ^{13}C NMR(300 MHz, CDCl_3): δ 135.8, 133.0, 130.2, 129.4, 76.2, 66.2, 18.2; GC-MS, m/z: 279 (M+); Elemental Analysis: Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{ClO}_4\text{P}$: C, 47.41; H, 5.79; Found C, 47.43; H, 5.76.

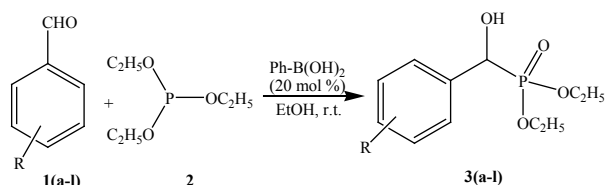
Diethyl hydroxy(phenyl)methylphosphonate (3d): ^1H NMR(300 MHz, CDCl_3): δ 1.20 (t, 3H), 1.28 (t, 3H), 4.15-4.26 (m, 4H), 4.9 (d, 1H, $J = 10.8$ Hz), 6.10 (s, 1H, -OH), 6.94-7.735 (m, 5H, Ar-H); ^{13}C NMR(300 MHz, CDCl_3): δ 139.4, 132.5, 130.2, 128.0, 72.5, 65.4, 21.0; GC-MS, m/z: 245 (M+); Elemental Analysis: Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{O}_4\text{P}$: C, 54.10; H, 7.02. Found C, 54.12; H, 7.05.

Diethyl hydroxy(4-nitrophenyl) methylphosphonate (3f): ^1H NMR(300 MHz, CDCl_3): δ 1.28 (t, 3H), 1.35 (t, 3H), 4.24-4.35 (m, 4H), 5.01 (d, 1H, $J = 10.2$ Hz), 6.20 (s, 1H, -OH), 7.42 (d, 2H, $J = 7.0$ Hz, Ar-H), 7.92 (d, 2H, $J = 7.2$ Hz, Ar-H); ^{13}C NMR(300 MHz, CDCl_3): δ 151.2, 145.4, 133.2, 125.0, 74.8, 68.2, 22.4; GC-MS, m/z: 290 (M+); Elemental Analysis: Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_6\text{P}$: C, 45.68; H, 5.58; N, 4.84; Found C, 45.72; H, 5.62; N, 4.81.

Diethyl (4-fluorophenyl)(hydroxy) methylphosphonate (3g): ^1H NMR(300 MHz, CDCl_3): δ 1.24-1.35 (m, 6H), 4.15-4.23 (m, 4H), 4.85 (d, 1H, $J = 10.6$ Hz), 6.12 (s, 1H, -OH), 7.18 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.80 (d, 2H, $J = 8.4$ Hz, Ar-H); ^{13}C NMR(300 MHz, CDCl_3): δ 157.4, 138.0, 130.2, 121.0, 74.0, 65.2, 20.6; GC-MS, m/z: 263 (M+); Elemental Analysis: Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{FO}_4\text{P}$: C, 50.39; H, 6.15; Found C, 50.36; H, 6.19.

Results and Discussion

As part of our interest to develop efficient synthetic protocols in organic synthesis using arylboronic acids, herein we report phenylboronic acid catalyzed convenient synthesis of α -hydroxy phosphonates in superior yields through the reaction of aromatic aldehydes and triethyl phosphite at ambient temperature (**Scheme 1**).



Scheme 1: Phenylboronic acid catalyzed synthesis of α -hydroxy phosphonates

The study was initiated with solvent optimization for a model reaction of 4-chloro benzaldehyde and triethyl phosphite. The model reaction was investigated by employing different solvents in presence of 10 mol % phenylboronic acid at ambient temperature and results are summarized in Table 1. In optimization study, it was found that the reaction offered good results in solvent ethanol. The reaction afforded 76 % product yield within reaction time 45 minutes (Table 1, Entry 2). In the solvent methanol and water, product yield was observed 60 % and 52 % respectively (Table 1, Entry 1 & 3 respectively). Moreover, the model reaction in solvent acetonitrile offered 60 % yield in reaction time 70 minutes. In non-polar solvent dichloromethane and chloroform, the desired product was obtained in lower yield with extended reaction time (Table 1, Entry 5 & 6 respectively).

Table 1: Optimization of solvents on synthesis of α -hydroxy phosphonates^a

Entry	Phenylboronic acid (mol %)	Solvent	Time (min)	Yield (%) ^b
1	10	MeOH	60	60

2	10	EtOH	45	76
3	10	H ₂ O	85	52
4	10	CH ₃ CN	70	60
5	10	DCM	120	38
6	10	CHCl ₃	90	41

^aConditions: 4-Chlorobenzaldehyde (1 mmol), triethyl phosphite (1.5 mmol), phenylboronic acid (10 mol %) at room temperature. The progress of reaction was monitored by thin layer chromatography. ^bIsolated yield

Furthermore for optimization of catalytic amount, we also screened the effect of catalytic loading on the model reaction of 4-chloro benzaldehyde and triethyl phosphite for giving the excellent yield of desired product. The results are given in Table 2. The model reaction in presence of catalytic loading 5 mol% and 12 mol% afforded 58 % and 78 % yield respectively (Table 2, Entry 1 & 3 respectively). Improvement in results was observed when reaction was carried out in presence of 15 mol% of catalyst which gives 84% product yield (Table 2, Entry 4). Moreover we have noted that 20 mol% of catalyst gives excellent results for the formation of desired product. The reaction was completed within 40 minutes and offered the product **3a** in excellent yield 94% (Table 2, Entry 5). To examine the impact of phenylboronic acid as catalyst, reaction was carried out in the absence of catalyst. We noticed that, less amount of yield was observed after 130 minutes (Table 2, Entry 7).

Table 2: Effect of catalytic loading on synthesis of α -hydroxy phosphonates^a

Entry	Phenylboronic acid (mol %)	Time (min)	Yield (%) ^b
1	5	65	58
2	10	45	76
3	12	45	78
4	15	40	84

5	20	40	94
6	25	40	92
7	-	130	38

^aConditions: 4-Chlorobenzaldehyde (1 mmol), triethyl phosphite (1.5 mmol), phenylboronic acid (mol %), EtOH, room temperature. The progress of reaction was monitored by thin layer chromatography. ^bIsolated yield

In order to study the generality of this protocol with optimized condition, a variety of aromatic aldehydes were applied. The results are shown in Table 3. Aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the corresponding products in higher yields.

Table 3: Synthesis of α -hydroxy phosphonates catalyzed by phenylboronic acid

Entry	R	Product	Reaction time (min)	M. P. (°C)	Yield (%)
1	4-Cl	3a	40	65-67	94
2	4-OCH ₃	3b	45	122-124	88
3	4-CH ₃	3c	35	94-96	89
4	-H	3d	60	76-78	87
5	3-NO ₂	3e	45	82-84	90
6	4-NO ₂	3f	50	87-88	88
7	4-F	3g	40	63-65	87
8	3,4(OCH ₃) ₂	3h	50	128-130	92
9	4-CN	3i	55	75-77	90
10	4-Br	3j	45	64-66	94
11	2-NO ₂	3k	40	112-114	89
12	2-Cl	3l	35	73-75	92

^aConditions: Aromatic aldehyde (1 mmol), triethyl phosphite (1.5 mmol), phenylboronic acid (20 mol

%), EtOH (15 mL), room temperature. The progress of reaction was monitored by thin layer chromatography.

^bIsolated yield

Conclusion:

In conclusion, we have developed a convenient and useful approach for the synthesis of α -hydroxy phosphonates catalyzed by phenylboronic acid in solvent ethanol under ambient temperature condition. Some of the noteworthy advantages of this protocol are mild reaction condition, simple work-up, use of benign reaction solvents, cost efficiency and excellent yields of α -hydroxy phosphonates.

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