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Short Communication

$Cd(ClO_4)_2 \cdot xH_2O$ as a novel catalyst for the synthesis of α-aminophosphonates under solvent-free conditions

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ABSTRACT

In this paper, we report cadmium perchlorate hydrate to be an novel, expeditious catalyst for the three-component one-pot reaction of an amine, an aldehyde and a H-phosphonate diesters in open air without any solvent, leads to α-aminophosphonates in excellent yields. To the best of our knowledge this finding is the first example of a cadmium perchlorate hydrate catalyzed Kabachnik-Fields reaction.

1. Introduction

Phosphorus compounds constitute an important class of organic compounds with diverse biological activities and possess a wide range of application [1], owing to their biological and physical properties as well as their utility as synthetic intermediates [2–6]. The activity of α-aminophosphonates as antibiotics, antitumor agents, pharmacogenic agents and herbicidal is reported in literature [7–11]. A more detailed discussion of the mechanism of the Kabachnik-Fields reaction, its synthetic potential and the biological activity of the α-aminophosphonates was well documented [12].

There are many report available using addition of phosphorous nucleophiles to imines is a general synthetic method for the preparation of α-aminophosphonates via two steps [13–16]. Catalytic synthetic methods attract a special attention because they play impressive role in many organic reaction. Over the last few years we observed there are many acid catalysts were used in synthetic organophosphorus chemistry. Typically Bronsted acid or Lewis acids like $In(OTf)_3$, $ZnCl_2$, CdI_2/benzene, CdI_2/microwave have been used [17–21]. Some loss of advantage of these reported catalyst because of their long reaction time, comparative more tedious work up purification procedure and most of the reported methods require strictly anhydrous conditions. Very recently Zirconium(IV) Compounds have been reported as an effective catalyst for the synthesis of α-aminophosphonates without any activator or base [22].

In this paper, we report the use of $Cd(ClO_4)_2 \cdot xH_2O$ as a novel, efficient catalyst for the preparation of α-aminophosphonates via a three-component system, composing of aldehydes/ketones, amines, and dimethylphosphite/diethylphosphite under solvent-free condition (Scheme 1). We eventually achieved excellent yields in very short duration at milder condition. Solvent-free reaction condition has been demonstrated to be an efficient technique for various organic reactions. It often leads to a remarkable decrease in reaction time, increased yields, easier workup procedure. Our model of studies indicated that this reaction proceeds with catalytic amount of catalyst with short reaction time (20 to 55 min) and easy work up procedure are the some of the advantages of this protocol.

In search for an effective catalyst and the best operative experimental conditions, we have selected 4-chlorobenzaldehyde, 4-nitroaniline as an electron-deficient amine and dimethylphosphite. For this model reaction, we have tested various acids and metal catalysts. The best results were obtained in using 5 mol% of $Cd(ClO_4)_2 \cdot xH_2O$ at rt for 2 h (yields 94%) and at 40 °C for 20 min (96%) under neat conditions (Table 1).

2. Experimental

2.1. General

Solvents were purified by conventional methods and distilled under nitrogen, prior to use. Dimethylphosphite/diethylphosphite and $Cd(ClO_4)_2 \cdot xH_2O$ were obtained from Aldrich. The progress of the reactions was monitored by thin layer chromatography (TLC) on

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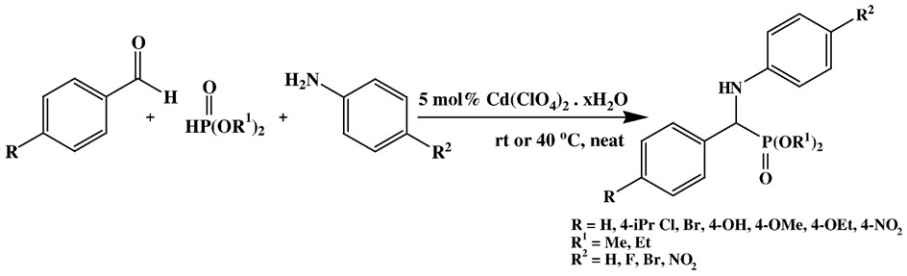


Scheme 1. $Cd(ClO_4)_2{\cdot}xH_2O$ catalyzed **s**ynthesis of α-aminophosphonates.

250 μm silica plates using 8:2 n-hexane and ethyl acetate mixture as an eluent. All the ^1H and ^{13}C NMR spectra of the synthesized compounds were recorded on Jeol JNM ECP 400 NMR spectrometer at 294 K. The ^1H and ^{13}C NMR spectra were measured respectively 0.03 M and 0.05 M solutions in $CDCl_3$ with TMS as internal reference in 5 mm NMR tubes. The ^1H and ^{13}C chemical shift values are given in δ scale (ppm) and referred to TMS, (^{13}C, via the solvent signal of $CHCl_3$ at 77.16 ppm). Coupling constants *J* are reported in Hz.

2.2. General procedure for the preparation of α-aminophosphonates using $Cd(ClO_4)_2{\cdot}xH_2O$

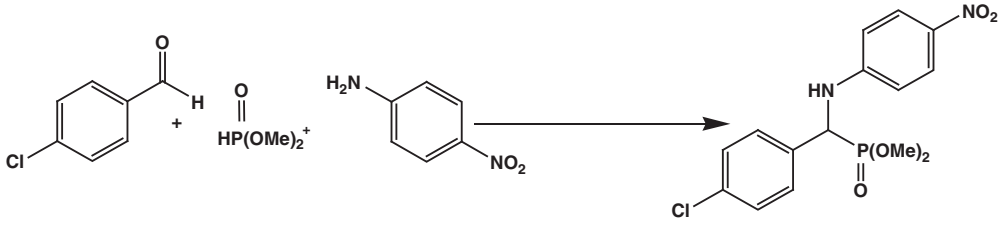
In a typical experiment, to a mixture of aldehyde (1 mmol), amine (1 mmol), and dimethylphosphite/diethylphosphite (1.2 mmol) was added $Cd(ClO_4)_2{\cdot}xH_2O$ (5.0 mol%) and stirred at room temperature to 40 °C for the appropriate reaction time. The progress of the reaction was monitored by TLC. When the reaction was completed, plenty of water was added to the reaction mixture then filtered and washed with hexane in order to get the solid crude product. And obtained crude solid was recrystallized in the mixture of chloroform and hexane to afford the pure product without further column purification.

3. Results and discussion

In order to explore the scope and the limitations of this novel method, we investigated the reaction using several electron-donating methoxy, ethoxy, hydroxy and isopropyl and electron-withdrawing nitro, bromo and chloro substituted benzaldehydes as well as amine with H-dialkylphosphonate $HP(O)(OR^1)_2$ (R^1: Me, Et) under solvent-free conditions at 40 °C (Table 2). It was observed that, excellent yields were obtained with electron withdrawing substituent on aromatic benzaldehyde and aromatic amine. The reaction was compatible with various functional groups such as Cl, Br, F, OMe, OEt, NO_2, OH, do not interfere by competitive complex formation with the catalyst.

The reaction of 4-chlorobenzaldehyde, 4-nitroaniline and dimethyl phosphite in presence of different catalyst was considered as the model reaction. In our present study we screened different catalyst and condition. Surprisingly, the best result obtained in using 5 mol% $Cd(ClO_4)_2{\cdot}xH_2O$ at room temperature in 2 h, afforded a high yield of

Table 1
Effect of various catalysts and solvent condition on the synthesis of α-aminophosphonates **13**[a].



Entry	Catalyst (5 mol%)	Solvent	Temp (°C)	Time (h)	Yield[b](%)
1	Cu-Sn (200 mesh)	Toluene	90	12	65
2	Cu-Sn (200 mesh)	Neat	90	4	85
3	Amberlite-IR-15	Toluene	90	24	70
4	Amberlite-IR-15	neat	90	7	75
5	$ZnCl_2$ SiO_2	MeCN	80	5	60
6	$ZnCl_2$ SiO_2	neat	80	5	73
7	$ZnCl_2$ SiO_2	neat	80	1	78
8	$MgCl_2{\cdot}4H_2O$	MeCN	80	3	52
9	$MgCl_2{\cdot}4H_2O$	neat	80	1	74
10	$Cd(ClO_4)_2{\cdot}xH_2O$	MeCN	rt	5	78
11	$Cd(ClO_4)_2{\cdot}xH_2O$	MeCN	80	2	84
12	$Cd(ClO_4)_2{\cdot}xH_2O$	EtOH	rt	6	70
13	$Cd(ClO_4)_2{\cdot}xH_2O$	EtOH	80	3	82
14	$Cd(ClO_4)_2{\cdot}xH_2O$	H_2O	100	4	78
15	$Cd(ClO_4)_2{\cdot}xH_2O$	PEG-400	100	4	75
16	$Cd(ClO_4)_2{\cdot}xH_2O$	neat	rt	2	94
17	$Cd(ClO_4)_2{\cdot}xH_2O$	neat	40	20 min	96
18	$Cd(ClO_4)_2{\cdot}xH_2O$	neat	60	20 min	96
19	$Cd(ClO_4)_2{\cdot}xH_2O$ (10 mol%)	neat	40	20 min	97
20	$Cd(ClO_4)_2{\cdot}xH_2O$ (20 mol%)	neat	40	20 min	97

[a] 4-Chlorobenzaldehyde (1 mmol) was treated with 4-nitroaniline (1 mmol) and Dimethyl phosphite (1.2 mmol) in the presence of the catalyst 5 mol% (except entry 19, 20) under solvent-free conditions (except entry 1, 3, 5, 8, 10, 11, 12, 13, 14, and 15).
[b] Isolated yields.

Table 2
Synthesis of diversified α-aminophosphonates derivatives in presence of 5 mol% Cd $(ClO_4)_2{\cdot}xH_2O$ via Scheme 1.

Entry[a]	Aldehyde/Ketone	R^1	R^2	Time (min)	Yield[b] (%)
1	R = H	Me	H	45	92
2	R = H	Me	4-NO_2	30	96
3	R = 4-MeO	Me	4-F	55	87
4	R = 4-MeO	Me	4-Br	50	91
5	R = 4-EtO	Me	NO_2	35	90
6	R = 4-EtO	Me	4-Br	30	96
7	R = 4-OH	Me	4-Br	50	94
8	R = 4-OH	Me	4-F	45	90
9	R = 4-OH	Me	4-NO_2	40	94
10	R = 4-OH	Et	4-NO_2	15	96
11	R = 4-Cl	Me	4-F	20	94
12	R = 4-Cl	Me	4-Br	30	98
13	R = 4-Cl	Me	4-NO_2	20	96
14	R = 4-Cl	Et	4-Br	10	97
15	R = 4-Cl	Et	4-NO_2	25	96
16	R = 4-Br	Me	4-Br	20	93
17	R = 4-Br	Me	4-NO_2	40	91
18	R = 4-*iso*-Pr	Me	4-NO_2	50	96
19	R = 4-NO_2	Me	4-NO_2	50	87
20	Cylohexanone	Me	4-NO_2	40	82
21	2-Pentanone	Me	H	55	79
22	Butyraldehyde	Me	H	360	53
23	Butyraldehyde	Me	4-NO_2	270	67
24	Butyraldehyde	Et	4-Cl	360	52
25	Cyclohexanecarboxaldehyde	Me	4-NO_2	40	78
26	Isobutyraldehyde	Me	H	180	72

[a] All reaction condition: aldehydes (1 mmol), amine (1 mmol), $HP(O)(OMe)_2$/ $HP(O)(OEt)_2$ (1.2 mmol) and $Cd(ClO_4)_2{\cdot}xH_2O$ (5 mol%) at 40 °C.
[b] Isolated yields.

96% in 20 min at 40 °C. However, no improvement in the yield beyond this duration and increase in amount of catalyst (see Table 1 entry 17). To see effect of solvent for improvement of yield we screen different solvents such as MeCN, EtOH, PEG-400 and aqueous medium, it is observed that under solvent condition required longer times (2–6 h) to afford comparable yields. A careful analysis of Table 1 reveals the fact that, the reaction afforded only 30–82 % yield in the presence of different catalysts such as $Y(O_2CCH_3)_3{\cdot}xH_2O$, $Zn(O_2CCH_3)_2{\cdot}2H_2O$, $ZnCl_2{\cdot}SiO_2$ and $MgCl_2{\cdot}4H_2O$. It is interesting to report that with use of $Y(O_2CCH_3)_3{\cdot}xH_2O$ and $Zn(O_2CCH_3)_2{\cdot}2H_2O$ conversion rate of intermediate imine to product is very poor in neat as well as under solvent condition. When $ZnCl_2\,SiO_2$ heterogeneous catalyst and $MgCl_2{\cdot}4H_2O$ used as catalyst under neat condition, they showed good improvement in the yield of reaction, but promising results were obtained with $Cd(ClO_4)_2{\cdot}xH_2O$ in lesser time with better yield.

In order to elucidate the role of $Cd(ClO_4)_2{\cdot}xH_2O$, a controlled reaction was carried out with $Cd(ClO_4)_2{\cdot}xH_2O$ with different mole, temperature and solvent condition. Reaction takes long time to complete, when $Cd(ClO_4)_2{\cdot}xH_2O$ was used under solvent condition. We observed reaction proceeding with high yield in less time when diethyl phosphite used as nucleophile in place of dimethyl phosphite nucleophile. In terms of catalyst loading, 5 mol% was sufficient and mandatory for completion of reaction. However no significant improvement was observed with 10 or 20 mol% of $Cd(ClO_4)_2{\cdot}xH_2O$. Once, the reaction conditions were optimized using $Cd(ClO_4)_2{\cdot}xH_2O$, a variety of aromatic/aliphatic aldehydes as well as aliphatic ketone and different substituted anilines, were coupled with $HP(O)(OMe)_2$/ $HP(O)(OEt)_2$ and substituted anilines to produce desired product.

Therefore, the advantages of our present methodology using of $Cd(ClO_4)_2{\cdot}xH_2O$ include: (i) use of solvent free condition (ii) anhydrous condition need not to be maintained (iii) no base or any additional activator as well as additive required. However, there is not a single report on the use of cadmium perchlorate hydrate as a catalyst for the synthesis of α-aminophosphonates. All the compounds are well reported which were further characterized by their spectral techniques (^1H and ^{13}C NMR) and synthesized compounds are in good agreement with the literature compounds, which were further provided as supplementary information.

A plausible mechanism of the reaction has been proposed on the basis of formation of a Schiff base as intermediate [23, 24], which has been isolated and characterized by NMR spectroscopy. After formation of Schiff base followed by the nucleophilic attack of phosphite on imino carbon, subsequent shifting of hydrogen atom leads to the formation of α-aminophosphonates (Scheme 2).

4. Conclusion

In conclusion, we have developed a new method for the synthesis of α-aminophosphonates by a three-component one-pot reaction using commercially available $Cd(ClO_4)_2{\cdot}xH_2O$ as efficient catalyst. This methodology using $Cd(ClO_4)_2{\cdot}xH_2O$ is simple, novel and highly efficient catalyst, which afford α-aminophosphonates in good to excellent yields under mild and solvent free conditions. Cleaner conversion, solvent-free, higher yields, very short duration, avoidance of the tedious work-up procedure as well as the simplicity of operation are some of the advantages of this protocol.

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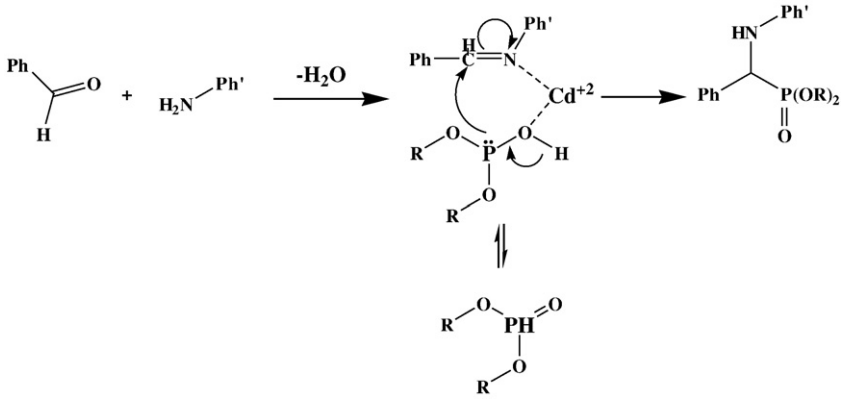
Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.10.025.



Scheme 2. Postulated mechanism for the one-pot synthesis of α-aminophosphonates promoted by $Cd(ClO_4)_2{\cdot}xH_2O$.

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