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Facile One-Pot Synthesis of α-Amino Phosphonates Using Lanthanide Chloride as Catalyst

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ABSTRACT: *An efficient preparation of α-amino phosphonates by the one-pot condensation of aldehydes, amines, and dialkyl phosphites using catalytic amounts of lanthanide chloride under mild conditions is successfully developed. Moreover, the catalyst is water-tolerant and could be recovered and reused.* Heteroatom Chem 17:389–392, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20219

INTRODUCTION

α-Amino phosphonates are an important class of compounds widely used in biochemical and pharmaceutical fields. Therefore, the development of efficient methodologies for the synthesis of α-amino phosphonates has attracted continuous attention. A variety of synthetic methods, mainly including Lewis acid-catalyzed addition reaction of phosphites with imines, have been reported [1–4]. Among these, the Lewis acid-catalyzed one-pot reaction starting from aldehyde, amine, and dialkyl phosphite is, without doubt, the most direct and efficient one that avoids the isolating of imine as an intermediate. Several Lewis acids were recently reported to be the effective catalysts for this one-pot reaction. These are rare earth triflates [5,6], indium(III) chloride [7], scandium tris(dodecyl sulfate) [8], and SmI_2 (samarium diiodide) as well [9]. Obviously, Lewis acids available in this reaction are quite few because most traditional Lewis acids such as $ZnCl_2$ and $MgBr_2$ will react with the water generated at the stage of imine formation resulting their deactivation. In consideration of the wide range of pharmacological property of α-amino phosphonates, it is still necessary to develop new Lewis acid-type catalyst, which is simple, low-cost, efficient, especially, stable and functions well in the presence of water, for this three-component reaction.

Lanthanide chlorides are normally considered to have weaker Lewis acidity than the corresponding lanthanide triflates that had found increasing applicability as Lewis acid catalysts for numerous organic reactions [10]. However, lanthanide chlorides are more readily available and economical than the latter. In the course of our investigation of lanthanide catalyzed C—N bond-forming reactions [11–13], we focused on lanthanide chlorides and tested their catalytic activity for the one-pot reaction of aldehyde, amine, and dialkyl phosphite. Surprisingly, we found that lanthanide chlorides not only show high activity but also can be recovered and reused without loss of efficiency. Herein, we wish to report the results.

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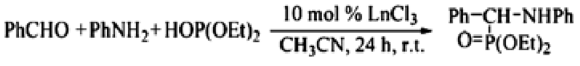
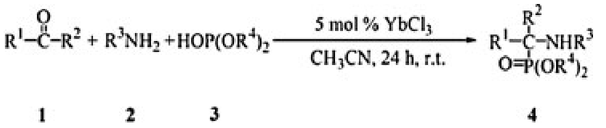


$$\mathrm{PhCHO + PhNH_2 + HOP(OEt)_2 \xrightarrow[\mathrm{CH_3CN,\ 24\ h,\ r.t.}]{10\ mol\ \%\ LnCl_3} \underset{O{=}P(OEt)_2}{Ph{-}CH{-}NHPh}}$$

SCHEME 1



$$\underset{1}{\mathrm{R^1{-}\overset{\overset{O}{\|}}{C}{-}R^2}} + \underset{2}{\mathrm{R^3NH_2}} + \underset{3}{\mathrm{HOP(OR^4)_2}} \xrightarrow[\mathrm{CH_3CN,\ 24\ h,\ r.t.}]{\mathrm{5\ mol\ \%\ YbCl_3}} \underset{4}{\mathrm{R^1{-}\underset{O{=}P(OR^4)_2}{\overset{R^2}{C}}{-}NHR^3}}$$

SCHEME 2

RESULTS AND DISCUSSION

The reaction of benzaldehyde, aniline, and diethyl phosphite was first tested using 10 mol% ytterbium chloride as catalyst in acetonitrile at room temperature for 24 h (Scheme 1). The reaction went smoothly and the corresponding α-amino phosphonate was really obtained in almost quantitative yield (Table 1, entry 1). It is observed that the lanthanide elements have great effect on the reaction activity and the results were summarized in Table 1. The active order is $\mathrm{YbCl_3} \sim \mathrm{YCl_3} > \mathrm{GdCl_3} \sim \mathrm{SmCl_3} > \mathrm{NdCl_3} \sim \mathrm{ErCl_3} > \mathrm{LaCl_3}$, which is in contrast to the order of their ionic radius. It means that the smaller the ionic radius of lanthanide metal, the stronger the electrophilicity and the Lewis acidity. Among the tested lanthanide trichlorides, $\mathrm{YbCl_3}$ shows the highest catalytic activity. The reaction with $\mathrm{YbCl_3}$ gave the yield still as high as 93% even the amount of $\mathrm{YbCl_3}$ decreased from 10 mol% to 5 mol% (entries 1 and 2). The halide anion also shows remarkable effect on the catalytic activity. The yield with $\mathrm{SmCl_3}$ is 86%, while 67% for $\mathrm{SmI_3}$ (entries 6 and 7).

In order to understand the catalytic behavior of lanthanide chloride in detail, the reactions with several aldehydes, amines, and dialkyl phosphites were also examined with 5 mol% $\mathrm{YbCl_3}$ in $\mathrm{CH_3CN}$ (Scheme 2). All the reactions gave the corresponding α-amino phosphonates in moderate to excellent yields and a summary of this study was listed in Table 2. As can be seen from the table, most of the aromatic and heteroaromatic aldehydes, but *p*-nitrobenzaldehyde, reacted with aromatic amines providing the corresponding products in excellent yields (entries 5–8). The reaction with *p*-nitrobenzaldehyde (entry 9) gave rather low yield. The reason for this may lie in the competitive coordination of $-\mathrm{NO_2}$ with lanthanide cation. It was noticed that the reactions involving aromatic aldehyde with linear primary amines and benzylamine could also give the yields more than 90% (entries 1, 2, and 4). However, the reaction involving steric bulky amine such as tertiary butylamine led to the corresponding α-amino phosphonate in relatively lower yield (entry 3). The similar steric effect can also be observed in the reaction of benzaldehyde, aniline with diisopropyl phosphite (entry 13). Surprisingly, the reaction involving diphenyl phosphite gave the corresponding product in almost quantitative yield within a relatively shorter time (entry 14). Aldehydes are more reactive than ketone. For example, the reaction of aniline, diethyl phosphite with acetophenone gave the desired product in 63% yield using 10 mol% $\mathrm{YbCl_3}$ (entry 12), while quantitative yield with benzaldehyde (entry 5). It is worth mentioning that sensitive functional groups such as Cl, $\mathrm{NO_2}$, and carbon–carbon double bond remained unchanged during the reaction process, although the reaction involving α,β-unsaturated aldehyde (entry 10) afforded the corresponding product in moderate yield.

Compared with $\mathrm{SmI_2}$ [9], $\mathrm{YbCl_3}$ works well in no need of heating and water absorber, and gives relatively higher yields with lower catalyst loading.

Normally, most traditional Lewis acids are extremely moisture sensitive and easily decomposed or deactivated in the presence of even a small amount of water. So, their use as catalysts in organic synthesis has been seriously limited. However, the present reaction catalyzed by lanthanide chlorides can proceed without any water absorber, $\mathrm{MgSO_4}$ or 4 Å molecular sieves, as additive. Accordingly,

TABLE 1 $\mathrm{LnCl_3}$-Catalyzed Reaction of Benzaldehyde, Aniline, and Diethyl Phosphite[a]

Entry	*Catalyst*	*Yield[b] (%)*
1	$\mathrm{YbCl_3}$	99[c]
2	$\mathrm{YbCl_3}$	93[d]
3	$\mathrm{YbCl_3{\cdot}H_2O}$	92[d] (92)[d,e]
4	$\mathrm{YCl_3}$	95
5	$\mathrm{GdCl_3}$	87
6	$\mathrm{SmCl_3}$	86
7	$\mathrm{SmI_3}$	67
8	$\mathrm{NdCl_3}$	77
9	$\mathrm{ErCl_3}$	73
10	$\mathrm{LaCl_3}$	58
11	$\mathrm{SmI_2}$	60[f]

[a] Typical reaction conditions: $\mathrm{PhCHO{:}PhNH_2{:}\ HOP(OEt)_2 = 1{:}1.1{:}1.2}$, 10 mol% $\mathrm{LnCl_3}$ relative to PhCHO (concentration of $\mathrm{LnCl_3} = 0.05$ M in solvent), room temperature, 24 h.
[b] Yield determined by HPLC.
[c] Isolated yield.
[d] 5 mol% $\mathrm{YbCl_3}$ used.
[e] Yield of the second-cycle reaction.
[f] 10 mol% $\mathrm{SmI_2}$ relative to PhCHO (concentration of $\mathrm{SmI_2} = 0.05$ M in solvent), 80°C, 24 h, 4 Å molecular sieves.

TABLE 2 One-Pot Synthesis of α-Amino Phosphonates Catalyzed by $YbCl_3$[a]

Entry	*R^1*	*R^2*	*R^3*	*R^4*	*Product*	*Isolated yield (%)*
1	Ph	H	*n*-C_6H_{13}	Et	**4a**	96
2	Ph	H	*n*-Bu	Et	**4b**	90
3	Ph	H	*t*-Bu	Et	**4c**	68
4	Ph	H	$PhCH_2$	Et	**4d**	92
5	Ph	H	Ph	Et	**4e**	93 (99[b])
6	Ph	H	*p*-ClPh	Et	**4f**	96
7	*p*-CH_3Ph	H	Ph	Et	**4g**	97
8	2-Furyl	H	Ph	Et	**4h**	89
9	*p*-NO_2Ph	H	Ph	Et	**4i**	28 (55[b])
10	PhCH=CH	H	Ph	Et	**4j**	55
11	$PhCH_2$	H	$PhCH_2$	Et	**4k**	78
12	Ph	Me	Ph	Et	**4l**	63[b]
13	Ph	H	Ph	*i*-Pr	**4m**	79
14	Ph	H	Ph	Ph	**4n**	98[c]

[a] Typical reaction conditions: aldehyde or ketone:amine:dialkyl phosphite = 1:1.1:1.2, 5 mol% $YbCl_3$ relative to carbonyl compound (concentration of $YbCl_3$ = 0.025 M in CH_3CN), room temperature, 24 h.
[b] 10 mol% $YbCl_3$ used.
[c] The reaction time is 5 h.

the reaction of benzaldehyde, aniline, and diethyl phosphite catalyzed by hydrated lanthanide chloride, $YbCl_3{\cdot}H_2O$, was tested. The reaction proceeded highly efficiently (Table 1, entry 3), indicating that lanthanide chloride is stable towards water and the activity of H_2O-coordinated $YbCl_3$ as a Lewis acid is retained. Thus, although various kinds of Lewis acid-promoted reactions must be carried out under strict anhydrous conditions to preserve the activity of Lewis acid, lanthanide chlorides can be expected to be new "friendly" Lewis acid catalyst and probably have much wider applications in various Lewis acid-catalyzed reactions.

Encouraged by above-mentioned result, we examined the catalytic activity of $YbCl_3$ recovered after the reaction was completed. Under usual quenching condition, almost quantitative of Yb(III) was recovered from the aqueous layer, and it can be reused without loss of efficiency in the second-cycle reaction (Table 1, entry 3). Taking into account the environmental problem induced by treatment of the Lewis acid left in various types of reactions, the reusability of lanthanide chlorides is interesting and available in industry.

In summary, this work demonstrates that lanthanide trichlorides, which are simple, low-cost, and easy available, are efficient catalysts for the one-pot reactions of aldehydes, amines, and dialkyl phosphites affording α-amino phosphonates under mild and convenient conditions. In view of their water-tolerance and reusability, the present catalyst represents an ideal "friendly" Lewis acid catalyst and would be widely used in organic synthesis.

EXPERIMENTAL

General Remarks

All the manipulations were conducted under dry Ar atmosphere with flame-dried glassware. Lanthanide chlorides were synthesized according to the method described by Taylor and Carter [14]. The aldehydes, ketone, amines, and acetonitrile were distilled from CaH_2 prior to use. Dialkyl and diphenyl phosphites were prepared by the reported procedure [15,16].

^1H NMR spectra were obtained from a Varian INOVA-400 spectrometer using TMS as the internal reference. Elemental analyses were determined on a CARLO ERBA EA1110-CHNS-O. Mass spectra (MS) data were obtained from a Micromass GCT-TOF instrument. HPLC analyses were performed by a Waters-515 liquid chromatograph.

General Procedure

A mixture of aldehyde (2 mmol), amine (2.2 mmol), dialkyl phosphite (2.4 mmol), and ytterbium chloride (0.1 mmol) in acetonitrile (4 mL) was well stirred at room temperature for 24 h. Then acetonitrile was removed under reduced pressure. Water was added to the residue, and the mixture was extracted with hexane/dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by chromatography on silica gel using acetone–petroleum ether 1:7 as eluent to afford α-amino phosphonate. The recovered catalyst was obtained from the aqueous layer after removing water. The spectral and physical data of the known compounds (**4a, 4b, 4c, 4k, 4l, 4m** [9], **4d, 4e, 4g,**

4h, 4i, 4j [5], **4n** [17]) were identical with those reported in the literature. The structure of the new compound was determined by ^{1}H NMR, MS, and elemental analysis.

Spectral and Analytical Data of Phosphonate **4f**

^{1}H NMR ($CDCl_3$) δ (ppm): 1.09–1.12 (t, 3H, $J = 7.4$ Hz, CH_3), 1.27–1.31 (t, 3H, $J = 7.4$ Hz, CH_3), 3.60–4.17 (m, 4H, $2CH_2$), 4.69 (d, 1H, $J = 23.6$ Hz, Ar-C—H), 6.50–7.44 (m, 9H, Ar-H); MS (EI): m/z 353 (M^+); Anal. Calcd for $C_{17}H_{21}ClNO_3P$: C, 57.71; H, 5.98; N, 3.96. Found: C, 58.00; H, 6.04; N, 3.76.

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