Tetrahedron Letters 53 (2012) 3897–3899

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient one-pot synthesis of α-aminophosphonates from aldehydes and ketones catalyzed by ytterbium(III) triflate

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ARTICLE INFO

Article history:
Received 9 April 2012
Revised 8 May 2012
Accepted 14 May 2012
Available online 26 May 2012

Keywords:
Aldehyde
Ketone
α-Aminophosphonate
Ytterbium(III) triflate

ABSTRACT

An efficient three component one-pot synthesis of N-silylated α-aminophosphonates and α,α-disubstituted α-aminophosphonates was developed using $Yb(OTf)_3$ as a catalyst at room temperature under mild conditions.

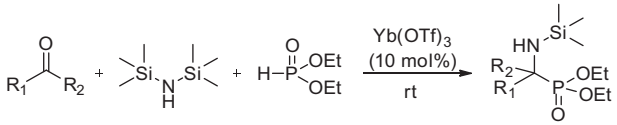
α-Aminophosphonates and their derivatives represent an important class of compounds that perform increasing applications in chemical industries. Their synthesis has received great attention due to their potent biological activities. Most mammalian cells contain some enzymes that hydrolyze phosphate groups. Phosphonates are important because of their stability with such enzymes and their negligible mammalian cell toxicity.[1] Their use in medicinal chemistry as enzyme inhibitors,[2] antitumors,[3] antibacterials,[4] and anti-HIV agents[5] has been well documented. Phosphonates also serve as building blocks in the synthesis of pharmaceutically useful compounds.[6]

Different methodologies have been developed for preparing phosphonates, including one-pot reaction from methyleneaziridines,[7a] DDQ-mediated direct oxidative phosphonylation of amines under metal-free conditions,[7b] and lithium amide-induced phosphonyl migration from nitrogen to carbon in terminal aziridines.[7c] One of the most important ways to synthesize α-aminophosphonates involves nucleophilic addition of phosphites to imines. This reaction can be promoted by several types of catalysts, including non-ionic surfactant Triton X-100,[8a] Fe_3O_4, and CeO_2 nanoparticles,[8a,b] β-cyclodextrin,[8c] NBS,[8d] base catalysts,[9] heteropoly acids,[10a] heterogeneous catalysts,[10b,c] ion exchange resins Amberlite-IR 120,[10d] solid acids montmorillonite KSF,[10e] Brønsted acids,[10f–h] and Lewis acids.[11]

Lewis acid-catalyzed one-pot synthesis of α-aminophosphonates is the most simple and efficient of the reported synthesis methods. However, some Lewis acids such as $ZnCl_2$ and $MgBr_2$ are deactivated by water released at an intermediate stage.[12]

Due to its high reactivity, easy handling, and inertness toward air and water, $Yb(OTf)_3$ has been used as an efficient Lewis catalyst in organic transformations.[13] The reaction of N-silylated imines generated in situ with phosphites has been thought to afford N-silylated α-aminophosphonates, which readily deprotect to α-aminophosphonates. In this Letter, we report an efficient one-pot synthesis of N-silylated α-aminophosphonates from aldehydes or ketones using hexamethyldisilazane and diethyl phosphite in the presence of $Yb(OTf)_3$ (Scheme 1).

The study began with a three component reaction of benzaldehyde with 1,1,1,3,3,3-hexamethyldisilazane and diethyl phosphite in CH_2Cl_2 in the presence of 10 mol % $Yb(OTf)_3$. The reaction proceeded smoothly at room temperature affording the desired product in excellent yield (Table 1, entry 1). A comparable product yield in CH_3CN (entry 3) was noted, while yield was slightly reduced when the reaction was performed in THF (entry 2). The reaction had relatively low yield and a longer reaction time in EtOAc and $CHCl_3$ (entries 4 and 5). For further studies, CH_2Cl_2 was selected as the solvent. A reaction using $Sc(OTf)_3$ was not as efficient as using $Yb(OTf)_3$ (entry 6). To study the effect of nucleophiles,



Scheme 1. Synthesis of α-aminophosphonates.

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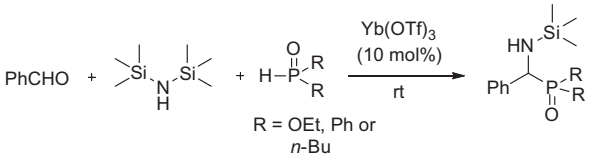
http://dx.doi.org/10.1016/j.tetlet.2012.05.068

Table 1
Synthesis of N-silylated α-aminophosphonates from benzaldehyde under various reaction conditions



Entry	R	Solvent	Time (h)	Yield[a] (%)
1	OEt	CH_2Cl_2	2.5	96
2	OEt	THF	2.5	90
3	OEt	CH_3CN	2.5	96
4	OEt	EtOAc	4	89
5	OEt	$CHCl_3$	12	77
6[b]	OEt	CH_2Cl_2	2.5	43
7	Ph	CH_2Cl_2	2.5	90
8	*n*-Bu	CH_2Cl_2	2.5	92

[a] Isolated yield.
[b] $Sc(OTf)_3$ was used instead of $Yb(OTf)_3$.

diphenylphosphine oxide and dibutylphosphine oxide were also investigated while maintaining other optimized conditions. In both cases, the corresponding products were obtained in comparative yields (entries 7 and 8).

Due to the above observations, a range of aromatic and aliphatic aldehydes and ketones were investigated to determine the method's scope and limitations. The results are summarized in Table 2. A general trend was observed for different aromatic and aliphatic aldehydes. Aromatic aldehydes with an electron-donating group and a moderate electron-withdrawing group afforded high yields (entries 1–3) while aromatic aldehydes with a strong electron-withdrawing group, such as a nitro functionality, gave the desired product in poor yield (entry 4). Reactions with *iso*-butyraldehyde required excess 1,1,1,3,3,3-hexamethyldisilazane and diethyl phosphite to obtain a high yield of the product (entry 5 vs 6). Similarly, *n*-butyraldehyde was converted into the desired product with 87% yield (entry 7). Next, the reactivity of ketones was examined under the present reaction conditions. Successful synthesis of α,α-disubstituted α-amino phosphonates was accomplished by employing ketones in place of aldehydes. Both aromatic and aliphatic ketones reacted well to produce the corresponding phosphonates in good yields. However, longer reaction times were required compared to aldehydes (entry 1 vs 8). Long chained normal and α,β-unsaturated ketones were good substrates for the reaction (entries 9 and 10), whereas the reactivity of a cyclic ketone was low (entry 11). The reaction did not proceed with α,β-unsaturated cyclic ketone and benzophenone (entries 12 and 13). To investigate the catalyst loading effect, the amount of $Yb(OTf)_3$ was increased from 0.1 to 1.0 equiv in the reaction with acetophenone. However, the reaction time and yield were almost the same.

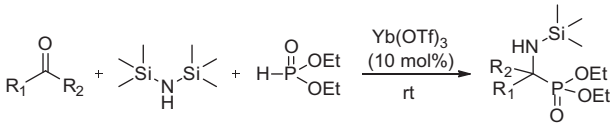
Deprotection of the trimethyl silyl group from N-silylated α-aminophosphonates was accomplished by treating the compound with trifluoroacetic acid in CH_2Cl_2 at room temperature in quantitative yield (Scheme 2). The α-aminophosphonates obtained can be further modified to produce useful biologically active compounds.[14]

In conclusion, an efficient one-pot synthesis of N-silylated α-aminophosphonates and α,α-disubstituted α -aminophosphonates was developed from aldehydes/ketones, hexamethyldisilazane, and diethylphosphite in the presence of $Yb(OTf)_3$ under mild conditions. The protocol's advantage is the formation of α-aminophosphonates with easily removable N-protecting groups.

Typical procedure for one-pot synthesis of N-silylated α-aminophosphonates

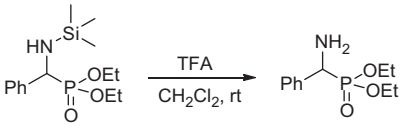
A solution of benzaldehyde (53 mg, 0.5 mmol), 1,1,1,3,3,3-hexamethyldisilazane (121 mg, 0.75 mmol), and diethylphosphite (103 mg, 0.75 mmol) in the presence of $Yb(OTf)_3$ (31 mg, 0.05 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 2.5 h. The reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution, and the product was extracted into ethyl acetate (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and were evaporated under reduced pressure to afford a residue which was purified by silica gel column chromatography (ethyl acetate/hexane, 3:7) to afford the product (151 mg, 96%): ^1H NMR ($CDCl_3$): δ 7.45–7.27 (5H, m), 4.96 (1H, d, J_{PH} = 15.0 Hz), 4.08–3.93 (4H, m), 1.33–1.15 (6H, m), 0.09 (9H, s); ^{31}P NMR ($CDCl_3$): δ 20.4.

Table 2
Synthesis of N-silylated α-aminophosphonates from aldehydes and ketones in the presence of $Yb(OTf)_3$



Entry	Aldehyde/Ketone	$((CH_3)_3Si)_2NH$ (equiv)	$(EtO)_2P(O)H$ (equiv)	Time (h)	Yield[a] (%)
1	*p*-Anisaldehyde	1.5	1.5	2.5	91
2	*p*-*N*-Acetylbenzaldehyde	1.5	1.5	2.5	97
3	*p*-Chlorobenzaldehyde	1.5	1.5	2.5	97
4	*p*-Nitrobenzaldehyde	1.5	1.5	2.5	26
5	*iso*-Butyraldehyde	1.5	1.5	2.5	52
6	*iso*-Butyraldehyde	3.0	3.0	2.5	88
7	*n*-Butyraldehyde	3.0	3.0	2.5	87
8	Acetophenone	3.0	3.0	36	89
9	2-Dodecanone	3.0	3.0	30	75
10	Methylvinylketone	3.0	3.0	30	80
11	Cyclohexanone	3.0	3.0	36	55
12	Cyclohexenone	3.0	3.0	48	0
13	Benzophenone	3.0	3.0	48	0
14[b]	Acetophenone	3.0	3.0	36	87

[a] Isolated yield.
[b] 1.0 equiv of $Yb(OTf)_3$ was used.



Scheme 2. Deprotection of the trimethyl silyl group.

Typical procedure for deprotection of the trimethyl silyl group from N-silylated α-aminophosphonates

To a solution of diethyl phenyl(trimethylsilylamino)methylphosphonate (175 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL) dropwise at 0 °C and the reaction mixture was stirred for 2 h at room temperature. Solvent was removed under reduced pressure and pH was adjusted to 8.0 with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted into ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and were evaporated under reduced pressure to afford a residue which was purified by silica gel column chromatography (ethyl acetate/hexane, 6:4) to afford the product (134 mg, 99%): ^{1}H NMR ($CDCl_3$): δ 7.45–7.26 (5H, m), 5.01 (1H, d, J_{PH} = 15.0 Hz), 4.19–3.65 (4H, m), 1.24 (6H, t, J = 7.2 Hz); ^{31}P NMR ($CDCl_3$): δ 21.8.

Acknowledgment

M.K.M. is grateful for a research fellowship from Yonsei University.

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