

One-Pot Synthesis of α -Amino Phosphonates Using Samarium Diiodide as a Catalyst Precursor

Fan Xu,^[a] Yiqin Luo,^[a] Mingyu Deng,^[a] and Qi Shen*^[a]

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A simple and efficient preparation of α -amino phosphonates under relatively mild conditions by the one-pot reaction of aldehydes with amines and dialkyl phosphites using catalytic amounts of SmI_2 is described.

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Introduction

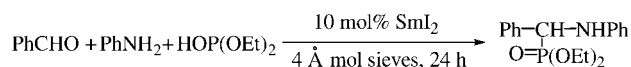
α -Amino phosphonates are an important class of compounds widely used in biochemical and pharmaceutical chemistry. Their synthesis has therefore been the subject of much interest. A variety of methods are available, but the nucleophilic addition reaction of phosphites with imines, usually catalyzed by Lewis acids, is the most direct and efficient one among them. As many imines are unstable or difficult to purify, one-pot reactions (starting from carbonyl compounds, amines and phosphites) have also received attention. Several Lewis acids, such as rare earth triflates,^[1,2] indium(III) chloride^[3] and scandium tris(dodecyl sulfate)^[4] have been found to be the most effective catalysts for this three-component reaction. However, some of them are either expensive or somewhat difficult to prepare.

Recently, the use of SmI_2 (which is both cheap and easily prepared) has received great attention as a precatalyst in organic reactions such as aldol reactions, Michael additions, Diels–Alder reactions and ring-opening reactions.^[5] In earlier reports,^[6,7] we showed that SmI_2 is an efficient Lewis acid-type catalyst for the cyclotrimerization of nitriles and the condensation of amines with nitriles. As a part of our continued studies on SmI_2 -catalyzed C–N bond-forming reactions, the one-pot synthesis of α -amino phosphonates from aldehydes, amines and phosphites was investigated.

Results and Discussion

The reaction of benzaldehyde with aniline and diethyl phosphite was carried out in the presence of 10 mol % SmI_2 and 4-Å molecular sieves under several different conditions

(Scheme 1). The results obtained are summarized in Table 1. The reaction in acetonitrile worked best at 80 °C; the yield decreased at higher or lower temperature (Entries 1–3). The same reaction in dichloromethane gave a slightly higher yield at 45 °C (Entry 7). The order of addition of the three reactants to the SmI_2 solution had no effect on the yield of the product. For example, stirring a mixture of benzaldehyde and aniline in advance resulted in a similar yield to that obtained by mixing the three substrates simultaneously (Entries 2 and 4), probably because of instantaneous imine formation. The reaction proceeded smoothly both with and without molecular sieves, giving the product in similar yields (Entries 2 and 6), indicating that the active species generated from SmI_2 is stable in the presence of the water generated during imine formation. A slight increase in the yield of phosphonate was observed when benzyldieneaniline and diethyl phosphite were used as starting materials (Entry 5).



Scheme 1

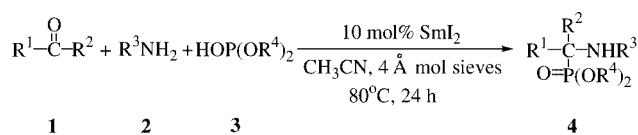
The reactions of several carbonyl compounds with amines and dialkyl phosphites were investigated in the presence of a catalytic amount (10 mol %) of SmI_2 and 4-Å molecular sieves in acetonitrile at 80 °C for 24 h (Scheme 2); the results are listed in Table 2. Most of the reactions proceeded smoothly to give moderate to excellent yields of the corresponding α -amino phosphonates. Only the reactions of 2-furaldehyde (Entry 8), cinnamaldehyde (Entry 9) and a ketone (Entry 12) with aniline and diethyl phosphite gave rather low yields. However, the reactions of aromatic aldehydes with aliphatic amines and diethyl phosphite gave high yields. For example, the reaction of benzaldehyde with ani-

^[a] Department of Chemistry, Suzhou University,
1 Shizi Street, Suzhou 215006, China
Fax: (internat.) + 86-512-65112371
E-mail: qshen@suda.edu.cn

Table 1. Effect of reaction conditions on the SmI₂-catalyzed reaction of benzaldehyde, aniline and diethyl phosphite

Entry ^[a]	Solvent	T (°C)	Additive	Isolated yield (%)
1 ^[b]	CH ₃ CN	60	4-Å mol. sieves	47
2	CH ₃ CN	80	4-Å mol. sieves	60
3	CH ₃ CN	100	4-Å mol. sieves	36
4 ^[c]	CH ₃ CN	80	4-Å mol. sieves	63
5 ^[d]	CH ₃ CN	80	4-Å mol. sieves	74
6	CH ₃ CN	80	—	63
7	CH ₂ Cl ₂	45	4-Å mol. sieves	66

^[a] Typical reaction conditions: PhCHO: PhNH₂: HOP(OEt)₂ = 1:1.1:1.2, 10 mol % SmI₂ relative to PhCHO and 0.05 M SmI₂, 24 h, 4-Å molecular sieves (MS). ^[b] Reaction time was 4 days. ^[c] The mixture of PhCHO and PhNH₂ was stirred for 2 h in the presence of SmI₂, followed by the addition of HOP(OEt)₂. ^[d] Reaction of PhCH=NPh and HOP(OEt)₂.



Scheme 2

Table 2. One-pot synthesis of α -amino phosphonates catalyzed by SmI₂

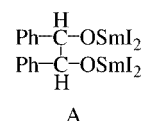
Entry ^[a]	R ¹	R ²	R ³	R ⁴	Product	Isolated yield (%)
1	Ph	H	Ph	Et	4a	60
2	Ph	H	<i>n</i> Bu	Et	4b	88
3	Ph	H	<i>t</i> Bu	Et	4c	91
4	Ph	H	<i>n</i> C ₆ H ₁₃	Et	4d	92
5	Ph	H	C ₆ H ₁₁	Et	4e	96
6	Ph	H	PhCH ₂	Et	4f	92 (93 ^[b])
7	4-CH ₃ Ph	H	Ph	Et	4g	78
8	PhCH=CH	H	Ph	Et	4h	39
9	2-furyl	H	Ph	Et	4i	37
10	4-CH ₃ Ph	H	<i>t</i> Bu	Et	4j	88
11	PhCH ₂	H	PhCH ₂	Et	4k	72
12	Ph	CH ₃	Ph	Et	4l	18 (29 ^[b])
13	Ph	H	Ph	<i>i</i> Pr	4m	42 (59 ^[c])

^[a] Typical reaction conditions: aldehyde or ketone/amine/dialkyl phosphite 1:1.1:1.2, 10 mol % SmI₂ relative to the carbonyl compound (concentration of SmI₂ 0.05 M in CH₃CN), 80 °C, 24 h, 4-Å mol. sieves. ^[b] Solvent CH₂Cl₂, 45 °C. ^[c] 80 °C, 3 days.

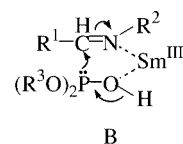
line and diethyl phosphite gave the corresponding phosphonate in 60 % yield, but when benzylamine was used, the yield of product was 92 % (Entries 1 and 6). When diisopropyl phosphite was used instead of diethyl phosphite, the yield of phosphonate decreased (Entries 1 and 13). This might be due to a steric effect.

The change in the color of the reaction mixture from dark blue to yellow and the formation of the solid imine is observed immediately after the addition of the mixture of amine and aldehyde to the solution of SmI₂. This observation suggests that a Sm^{III} species,^[5,8] supposedly the active species for this one-pot reaction, is generated during the reaction of SmI₂ with aldehyde or amine. In order to

obtain more information on the possible Sm^{III} species, aniline and benzaldehyde were separately mixed with SmI₂ in THF. The color change from dark blue to yellow was only observed in the latter case. This indicates that the active species may be the pinacol–Sm^{III} complex A (Scheme 3) previously observed in the SmI₂-mediated reduction of aldehydes to pinacols.^[9,10] To confirm this, the reaction of benzaldehyde, aniline and diethyl phosphite was carried out using a 1:1 mixture of SmI₂ and benzaldehyde as a catalyst (10 mol %). Indeed, the reaction proceeded smoothly to give product **4a** in a similar yield (58%) as that obtained with SmI₂ alone (Table 2, Entry 1). Due to both the Lewis acidic nature of the metal center and its potential for a high coordination number, coordination of nitrogen and oxygen is highly favorable. The nucleophilic addition could then proceed via a transition state B, once the phosphite is added to the reaction mixture (Scheme 4).



Scheme 3



Scheme 4

In conclusion, samarium diiodide has been found to be an efficient precatalyst in the one-pot synthesis of α -amino phosphonates from aldehydes, amines and phosphites under mild conditions, giving moderate to excellent yields depending on the structure of the three reactants.

Experimental Section

General Remarks: All manipulations were conducted under an atmosphere of dry Ar with flame-dried glassware. SmI₂ was synthesized by stirring a mixture of Sm metal and I₂ in THF at room temperature for several hours.^[11] Aldehydes, amines and acetonitrile were distilled from CaH₂ prior to use. CH₂Cl₂ was heated at reflux over P₂O₅ for several hours and then distilled. Dialkyl phosphites were prepared according to the literature method.^[12] ¹H NMR spectra were obtained on a Varian INOVA-400 spectrometer using tetramethylsilane as an internal reference. Elemental analyses were determined on a Carlo Erba EA1110-CHNS-O analyzer. Mass spectra were recorded on a Micromass GCT instrument.

Typical Procedure: A mixture of aldehyde (2 mmol), amine (2.2 mmol), phosphite (2.4 mmol) and samarium diiodide (10 mol %) in acetonitrile (4 mL) was stirred with 4-Å molecular sieves (250 mg) at the desired temperature for the given time. The acetonitrile was removed under reduced pressure, water was added to the residue, and the mixture extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, concentrated in

vacuo and purified by chromatography on silica gel (eluant: acetone/petroleum ether 1:7) to afford the α -amino phosphonate. All new compounds were fully characterized by ^1H NMR, MS and elemental analysis.

Phosphonate 4b: ^1H NMR (400 MHz, CDCl_3): δ = 0.86 (t, J = 7.2 Hz, 3 H, CH_3), 1.14 (t, J = 7.2 Hz, 3 H, CH_3), 1.28 (t, J = 7.2 Hz, 3 H, CH_3), 1.32–1.47 [m, 4 H, $(\text{CH}_2)_2$], 2.41–2.56 (m, 2 H, NCH_2), 3.80–4.09 (m, 5 H, NCH and $2 \times \text{OCH}_2$), 7.27–7.43 (m, 5 H, ArH) ppm. MS (EI): m/z = 299 [M^+]. $\text{C}_{15}\text{H}_{26}\text{NO}_3\text{P}$: calcd. C 60.18, H 8.76, N 4.68; found C 60.22, H 8.96, N 4.52.

Phosphonate 4c: ^1H NMR (400 MHz, CDCl_3): δ = 1.00–1.78 (m, 15 H, $5 \times \text{CH}_3$), 3.72–4.19 (m, 5 H, NCH and $2 \times \text{OCH}_2$), 7.27–7.46 (m, 5 H, ArH) ppm. MS (EI): m/z = 299 [M^+]. $\text{C}_{15}\text{H}_{26}\text{NO}_3\text{P}$: calcd. C 60.18, H 8.76, N 4.68; found C 59.97, H 8.75, N 4.56.

Phosphonate 4d: ^1H NMR (400 MHz, CDCl_3): δ = 0.86 (t, J = 6.6 Hz, 3 H, CH_3), 1.15 (t, J = 7.2 Hz, 3 H, CH_3), 1.24–1.46 [m, 11 H, $(\text{CH}_2)_4$ and CH_3], 2.40–2.55 (m, 2 H, NCH_2), 3.80–4.12 (m, 5 H, NCH and $2 \times \text{OCH}_2$), 7.28–7.43 (m, 5 H, ArH) ppm. MS (EI): m/z = 327 [M^+]. $\text{C}_{17}\text{H}_{30}\text{NO}_3\text{P}$: calcd. C 62.35, H 9.25, N 4.28; found C 62.32, H 9.33, N 4.15.

Phosphonate 4j: ^1H NMR (400 MHz, CDCl_3): δ = 1.02 (s, 9 H, $3 \times \text{CH}_3$), 1.13 (t, J = 7.1 Hz, 3 H, CH_3), 1.29 (t, J = 7.1 Hz, 3 H, CH_3), 2.33 (s, 3 H, ArCH_3), 3.76–4.17 (m, 5 H, NCH and $2 \times \text{OCH}_2$), 7.12–7.35 (m, 4 H, ArH) ppm. MS (EI): m/z = 313 [M^+]. $\text{C}_{16}\text{H}_{28}\text{NO}_3\text{P}$: calcd. C 61.33, H 9.00, N 4.47; found C 61.41, H 9.16, N 4.42.

Phosphonate 4k: ^1H NMR (400 MHz, CDCl_3): δ = 1.22–1.39 (m, 6 H, $2 \times \text{CH}_3$), 2.93–3.02 (m, 2 H, CH_2), 3.78–3.92 (m, 3 H, NCH and CH_2), 4.07–4.35 (m, 4 H, $2 \times \text{OCH}_2$), 7.18–7.35 (m, 10 H, ArH) ppm. MS (EI): m/z = 347 [M^+]. $\text{C}_{19}\text{H}_{26}\text{NO}_3\text{P}$: calcd. C 65.69, H 7.55, N 4.03; found C 65.82, H 7.87, N 3.57.

Phosphonate 4l: ^1H NMR (400 MHz, CDCl_3): δ = 1.20–1.28 (m, 6 H, $2 \times \text{CH}_3$), 2.00 (s, 3 H, PhCCH_3), 3.93–4.02 (m, 4 H, $2 \times$

OCH_2), 6.39–7.62 (m, 10 H, ArH) ppm. MS (EI): m/z = 333 [M^+]. $\text{C}_{18}\text{H}_{24}\text{NO}_3\text{P}$: calcd. C 64.85, H 7.26, N 4.20; found C 64.71, H 7.41, N 4.13.

Phosphonate 4m: ^1H NMR (400 MHz, CDCl_3): δ = 0.92 (d, J = 5.6 Hz, 3 H, CH_3), 1.22 (d, J = 6.4 Hz, 3 H, CH_3), 1.26 (d, J = 5.6 Hz, 3 H, CH_3), 1.32 (d, J = 6.4 Hz, 3 H, CH_3), 4.41–4.49 (m, 1 H, NCH), 4.66–4.85 (m, 2 H, $2 \times \text{OCH}$), 6.58–7.51 (m, 10 H, ArH) ppm. MS (EI): m/z = 347 [M^+]. $\text{C}_{19}\text{H}_{26}\text{NO}_3\text{P}$: calcd. C 65.69, H 7.54, N 4.03; found C 65.78, H 7.67, N 4.01.

Acknowledgments

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