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# Phosphorus, Sulfur, and Silicon and the Related Elements

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# TiCl<sub>4</sub>-Catalyzed Efficient One-Pot Synthesis of α α-Amino Phosphonates

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# ${\rm TiCl_4}\mbox{-}{\rm Catalyzed}$ Efficient One-Pot Synthesis of $\alpha\mbox{-}{\rm Amino}$ Phosphonates

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 $\alpha$ -Aminophosphonates are synthesized by three-component condensation of aldehydes, amines, and trimethylphosphite in acetonitrile by using TiCl<sub>4</sub> as catalyst. Compared to conventional methods, this new method consistently has advantages, including excellent yields, short reaction times, and mild reaction conditions.

Keywords  $\alpha$ -aminophosphonates; aldehydes; amines; one-pot reaction; TiCl<sub>4</sub>

## INTRODUCTION

Aminophosphates are an important class of biologically active compounds,<sup>1</sup> because of their structural analogy to  $\alpha$ -aminoacids. Hence,  $\alpha$ -aminophosphonates continue to attract increased interest as synthetic targets. Also,  $\alpha$ -aminophosphonates act as peptide mimics,<sup>2</sup> enzyme inhibitors,<sup>3</sup> antibiotics,<sup>4</sup> crop protection agents,<sup>5</sup> and catalytic antibodies.<sup>6</sup> As a result, a variety of synthetic approaches<sup>7</sup> have been developed for the synthesis of  $\alpha$ -aminophosphonates. Of these methods, the nucleophilic addition of phosphates with imines, catalyzed by an acid or a base, is one of the most convenient methods. It is interesting to note that the Lewis acids catalyze the reaction in much milder conditions.<sup>8</sup> Among these, Lewis acids-such as SnCl<sub>2</sub>, SnCl<sub>4</sub>, BF<sub>3</sub>.OEt<sub>2</sub>, and ZnCl<sub>2</sub>/MgBr<sub>2</sub>, have been used for this transformation.<sup>9,10</sup> However, these reactions cannot be carried out in a one-pot operation starting from aldehydes.<sup>10</sup> Recent reagents include ZrCl<sub>4</sub>, <sup>11</sup> lanthanide

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#### SCHEME 1

triflates,<sup>12</sup> InCl<sub>3</sub>,<sup>13</sup> LiClO<sub>4</sub>-TMSCl<sup>14</sup> and Montimorllonite-KSF<sup>15</sup> were used for this transformation. Very recently, a solvent-free reaction between aldehydes, ammonium formate, and dialkylphosphite catalyzed by alumina under microwave conditions was also reported.<sup>16</sup> Most of the previously mentioned procedures employ dimethylphospite as the reagent, with a view to see the migration of a methyl carbonium ion to that of using a dimethyl (trimethyl silyl) phosphite.<sup>17</sup> The present study also aims at the development of a cheaper alternative reagent. Herein we report an efficient and inexpensive protocol for the synthesis of  $\alpha$ -aminophosphonates using a catalytic amount of TiCl<sub>4</sub> under mild reaction conditions (Scheme 1).

The treatment of benzaldehyde, aniline, and trimethylphosphite in the presence of 10 mole percent of TiCl<sub>4</sub> in acetonitrile medium at r.t. resulted in corresponding  $\alpha$ -aminophosphonate. Similarly, various aldehydes and amines were treated with trimethylphosphite to afford corresponding  $\alpha$ -aminophosphonates at an ambient temperature within 10–25 min in high yields 88–93% (Table I). The reaction conditions were very mild, and the  $\alpha$ -aminophosphonates were exclusively formed without the formation of any undesired side products. The present method does not require any additives or promoters<sup>10</sup> for the reaction to proceed.

### **General Experimental Procedure**

To a stirred solution of benzaldehyde (1.06 g, 10 mmol) and aniline (0.93 g, 10 mmol) in acetonitrile (25 mL) was added trimethylphosphite (1.40 g, 10 mmol) and TiCl<sub>4</sub> (0.189 g, 10 mol%). The reaction mixture was stirred at r.t. (Table I) until completion of the reaction as indicated by TLC. The reaction mixture was quenched with cold water and extracted with dichloromethane (2 × 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum, and purified by column chromatography (hexane:ethyl acetate, 80:20) to afford correspondingly pure  $\alpha$ -aminophosphonates in a 93% (0.80 g) yield.

Selected spectral data of **4a**. IR (KBr): 3302 cm<sup>-1</sup> (NH). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 3.42$  (d, 3H, CH<sub>3</sub>), 3.75 (d, 3H, CH<sub>3</sub>), 4.53 (brs, 1H, NH), 4.80 (d, 1H, CH), 6.69–7.45 (m, 10H, Ar-H).

Entry	Aldehyde	Amine	Reaction Time (min)	Yield (%) <sup>b</sup>
4a		NH <sub>2</sub>	10	93
74	ОН	NH <sub>2</sub>	10	
4b	СНО		15	89
4c	Н₃С−∕СНО	NH <sub>2</sub>	10	91
4d	МеО-СНО	NH <sub>2</sub>	15	90
4e	СІ	NH <sub>2</sub>	15	88
4f	СІ	NH <sub>2</sub>	15	90
4g	СНО	NH <sub>2</sub> CH <sub>3</sub>	15	91
4h	СНО	CH <sub>3</sub>	25	89
<b>4i</b>	СНО		10	90
4j	СНО	NH <sub>2</sub>	15	92
4k	Сно	NH <sub>2</sub> Br	15	90

# TABLE I TiCl<sub>4</sub>-Catalyzed Efficient Synthesis of $\alpha\text{-Aminophosphonates}^a$

(Continued on next page)

Entry	Aldehyde	Amine	Reaction Time (min)	Yield (%) <sup>b</sup>		
41	СНО	NH <sub>2</sub>	15	91		
4m	СНО	NH <sub>2</sub>	15	92		

TABLE I TiCl <sub>4</sub> -Catalyzed Efficient Synthesis of
$\alpha$ -Aminophosphonates <sup>a</sup> (Continued)

<sup>*a*</sup>Yields refer to pure products, and all products were characterized by comparison of their physical and spectral data with those of authentic samples.

<sup>b</sup>All α-aminophosphonates are known compounds.

**4d.** IR (KBr): 3316 cm<sup>-1</sup> (NH). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 3.45$  (d, 3H, CH<sub>3</sub>),  $\delta = 3.64$  (d, 3H, CH<sub>3</sub>), 3.78 (d, 3H, OCH<sub>3</sub>), 4.72 (brs, 1H, NH), 6.59 (d, 1H, CH), 6.54–7.11 (m, 9H, Ar-H).

4e. IR (KBr): 3322 cm<sup>-1</sup> (NH). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 3.54$  (d, 3H, CH<sub>3</sub>),  $\delta = 3.72$  (d, 3H, CH<sub>3</sub>), 5.27 (brs, 1H, NH), 5.83 (d, 1H, CH), 6.54–6.63 (d, 2H), 6.65–6.78 (t, 1H), 7.05–7.42 (m, 5H).

### CONCLUSION

We have demonstrated a novel and efficient protocol for the synthesis of  $\alpha$ -aminophosphonates using a catalytic amount of titanium tetrachloride. The method offers several advantages, including high yields of product, very short reaction times, and an inexpensive catalyst, and does not involve any additives to promote the reaction.

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