# Tetrahedron Letters 52 (2011) 863-866

Contents lists available at ScienceDirect

**Tetrahedron Letters** 

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



# One-pot three-component Kabachnik–Fields synthesis of $\alpha$ -aminophosphonates using H-beta zeolite catalyst

V. H. Tillu<sup>a</sup>, D. K. Dumbre<sup>b</sup>, R. D. Wakharkar<sup>a</sup>, V. R. Choudhary<sup>b,\*</sup>

<sup>a</sup> Organic Chemistry Division, National Chemical Laboratory, Pune 411008, India
<sup>b</sup> Chemical Engineering and Process Development Division, National Chemical Laboratory, Pune 411008, India

## ARTICLE INFO

Article history: Received 23 June 2010 Revised 12 November 2010 Accepted 19 November 2010 Available online 24 November 2010

Keywords: Carbonyl compound Primary amine Substituted phosphite H-beta zeolite

# ABSTRACT

One-pot three-component Kabachnik–Fields synthesis of  $\alpha$ -aminophosphonates with high yields from the reaction between carbonyl compound, primary amine, and substituted phosphite can be carried out in a short period, using H-beta zeolite as a reusable catalyst.

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The  $\alpha$ -aminophosphonic acids and  $\alpha$ -aminophosphonates exhibit a wide range of intriguing biological activities. The  $\alpha$ -aminophosphonic acids are potential antibacterial agents besides exhibiting neuro-active characteristics and have been employed as anticancer drugs and pesticides.<sup>1</sup>  $\alpha$ -Aminophosphonic acid containing compounds have demonstrated their ability to modulate biochemical processes by enzyme inhibition. Examples of  $\alpha$ -aminophosphonic acid containing enzyme,<sup>2</sup> D-Ala:D-Ala ligase,<sup>3</sup> HIV-protease,<sup>4</sup> glutamine synthetase,<sup>5</sup> and stromelysin-1 (MMP-3) inhibitors.<sup>6</sup> Besides antagonists in the metabolism of amino acids,  $\alpha$ -aminophosphonic acid containing compounds have also found novel drug delivery applications, for example to stabilize peptide drugs during their intranasal absorption.<sup>7</sup>

 $\alpha$ -Aminophosphonate, the key substrate in the synthesis of  $\alpha$ -aminophosphonic acid, shows a number of interesting activities, such as peptidomimetics, enzyme inhibitors, pharmacogenic agents, herbicides, inhibitors of serine hydrolyses, and inhibitors of UDP-galactopyranose mutate and anti-tumor agents.<sup>8</sup> It is synthesized by the Kabachnik–Fields reaction<sup>9,10</sup> which involves a three-component coupling of a carbonyl, an amine, and a hydrophosphonyl compound.

Among the various synthetic approaches to the synthesis of  $\alpha$ -aminophosphonate, the acid catalyzed nucleophilic addition of phosphites to amines is established as the most useful method.<sup>11</sup>

However this method is not devoid of limitations because many imines are hygroscopic and unstable. The first one-pot synthesis of  $\alpha$ -aminophosphonate was achieved by the in situ generated reaction of phosphite in the presence of lanthanide triflate as the catalyst with imines.<sup>12</sup> Since then a number of methods for the preparation of diverse  $\alpha$ -aminophosphonates, such as nucleophilic amination of  $\alpha$ -hydroxy phosphonate derivatives,<sup>13</sup> electrophilic amination of  $\alpha$ -alkylphosphonamides,<sup>14</sup> hydrogenation of dehydroaminophosphonate,15 Aldol type reactions of (isocyanomethyl) phosphonates with aldehyde,<sup>16</sup> hydrogenation of aziridinylphosphonates,<sup>17</sup> addition of phosphites to sulfimine,<sup>18</sup> and catalyzed Mannich-type one-pot procedure,<sup>19</sup> have been reported. However, these methods suffer from drawbacks, such as long reaction times, low product yields, requirement of the stoichiometric amounts of catalysts, formation of a large amount of waste and/ or use of toxic catalyst.

Use of solid catalysts, such as alumina,<sup>20</sup> and KSF,<sup>21</sup> has also been reported for the synthesis of  $\alpha$ -aminophosphonates. However, the catalyst required was very large and it has a limited reusability. Hence, it is of great practical importance to develop a more efficient and also an environmentally benign method for the synthesis of  $\alpha$ -aminophosphonates. In this Letter, we report a onepot synthesis of  $\alpha$ -aminophosphonates from the reaction between carbonyl compound, primary amine, and substituted phosphite, with a high product yield, using H-beta zeolite as a catalyst in small amounts as per Scheme 1. The catalyst can be easily separated by filtration and reused several times in the reaction.

Results showing the performance of H $\beta$ ,<sup>22</sup> HY,<sup>23</sup>and HM<sup>23</sup> zeolites and also of the H $\beta$  modified by its impregnation with Lewis acid, such as anhydrous InCl<sub>3</sub> and FeCl<sub>3</sub><sup>20-22</sup> in the one-pot



<sup>\*</sup> Corresponding author. Tel.: +91 20 25902318; fax: +91 20 25902612.

*E-mail addresses:* vr.choudhary@ncl.res.in, vrc0001@yahoo.co.in (V.R. Choudhary).

<sup>0040-4039/\$ -</sup> see front matter  $\odot$  2010 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2010.11.105



**Scheme 1.** H-beta zeolite catalyzed synthesis of  $\alpha$ -aminophosphonates.

#### Table 1

Performance of different zeolite catalysts in the Kabachnik–Fields synthesis from indole-3-carboxaldehyde, *p*-anisidine and dibenzyl phoshite

Catalyst	Reaction time (h)	Product yield (%)
Нβ	4	93
НҮ	4	81
InCl <sub>3</sub> /Hβ	4	83
FeCl <sub>3</sub> /Hβ	4	79
HM	5	61
Η β <sup>a</sup>	4	92

<sup>a</sup> Fifth reuse of the catalyst.

synthesis are presented in Table 1. Zeolites are crystalline microporous aluminosilicates. Their porous structure can accommodate a wide variety of cations which can readily be exchanged for other cations. They differ widely in their cations Si/Al ratios, pore shapes and sizes, and channel system (1, 2 or 3 dimensional channels).

Among the different acidic zeolites, the H $\beta$  (H<sup>+</sup>-exchanged beta zeolite) showed the best performance. Moreover, this catalyst showed excellent reusability. Hence the further synthesis of different  $\alpha$ -aminophosphonates was carried out using the H $\beta$  zeolite catalyst. The results of the synthesis are given in Table 2. The preparation and characterization of the H $\beta$ , HY, HM, and InCl<sub>3</sub> (or FeCl<sub>3</sub>)/H $\beta$  zeolite catalysts were reported earlier.<sup>22-24</sup> The typical experimental procedure for the synthesis is given in Ref. 25.

The observed better performance of H $\beta$  zeolite (Table 1) is expected because of its higher concentration of acid sites and three dimensional large size pore system. The impregnation of the H $\beta$  by InCl<sub>3</sub> or FeCl<sub>3</sub> resulted in a decrease in the product yield. This may be due to the blockage of some of the zeolite channels and/ or pore openings by the deposited InCl<sub>3</sub> or FeCl<sub>3</sub> and, thereby, increasing the diffusion resistance for the reaction species/products

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I-beta zeolite catal	yzed Kabachnik-	Fields synthesis	of different	α-aminophos	phonates

Sr. No. 1	Carbonyl compound 2	Amine 3	Product 4	Reaction time (h) 5	Yield (%) 6
1	MeO	MeO NH2	OCH <sub>2</sub> Ph O P OCH <sub>2</sub> Ph CH OCH <sub>2</sub> Ph OCH <sub>2</sub> Ph OCH <sub>2</sub> Ph OCH <sub>2</sub> Ph	1	89
2	O <sub>2</sub> N CHO	O <sub>2</sub> N NH <sub>2</sub>	OCH <sub>2</sub> Ph O P OCH <sub>2</sub> Ph CH O NO <sub>2</sub>	4	76
3	СНО	NH <sub>2</sub>	$O = P O C H_2 P h$	5	90
4	H N CHO	MeO NH2	OCH <sub>2</sub> Ph O P-OCH <sub>2</sub> Ph CH-NH O Me	1	93
5	СНО	NH <sub>2</sub>	$O = \frac{Ph}{P - OCH_2Ph}$	4	91
6	O C	NH <sub>2</sub>	$ \begin{array}{c} O \\ CH_3 \\ P \\ OCH_2Ph \\ NH \\ Ph \end{array} $	2	87

 Table 2 (continued)

Sr. No. 1	Carbonyl compound 2	Amine 3	Product 4	Reaction time (h) 5	Yield (%) 6
7	0	NH <sub>2</sub>	$O \\ \parallel O \\ O \\ C \\ H_2 P \\ O \\ C \\ H_2 P \\ h$	1	93
8	MeO	MeO NH2		1	78
9	СНО	NH <sub>2</sub>	HN O HN O B OMe OMe	2	90
10	СНО	NH <sub>2</sub>	HN O U OMe P OMe	2	91
11	MeO	NH <sub>2</sub>	HN O U OC <sub>2</sub> H <sub>5</sub> MeO OC <sub>2</sub> H <sub>5</sub>	2	90
12	СНО	NH <sub>2</sub>	$HN O O OC_2H_5$ $P O OC_2H_5$	1	89
13	MeO	O <sub>2</sub> N NH <sub>2</sub>		3	87
14	MeO	Br NH <sub>2</sub>	HN O HN O P MeO OC <sub>2</sub> H <sub>5</sub>	4	80
15	MeO	NH <sub>2</sub>	HN O P OC <sub>2</sub> H <sub>5</sub> MeO OC <sub>2</sub> H <sub>5</sub>	3	84

<sup>\*</sup>Dibenzylphosphite is used in entry Nos. 1–7, Dimethylphosphite is used in entry Nos. 8–10, Diethylphosphite is used in entry Nos. 11–15.

in the zeolite. The lowest performance of the HM zeolite is mostly because of its one dimensional channels which are prone to blockage by the large size reaction species. As shown in Table 2, a wide range of structurally different carbonyl compounds and amines were subjected to this procedure and converted into the corresponding  $\alpha$ -aminophosphonates in



Scheme 2. Reaction scheme for the formation of  $\alpha$ -aminophosphonates.

high yields. Both the aromatic and aliphatic aldehydes or ketones react with aromatic or aliphatic amines quite effectively for their conversion to open-chain, cyclic, and aromatic imines and then to the respective  $\alpha$ -aminophosphonates. No difficulty was encountered with the reaction of conjugated aldehydes (entry 7). Sensitive functionalities such as OMe, NO<sub>2</sub>, and C–C double bond are found to be unaffected under the present reaction conditions. The reactions are fast and the products obtained are clean. All the products were characterized by usual spectroscopic methods.

Since  $\alpha$ -hydroxyphosphonates are found to be present in the reaction mixture at room temperature, it is believed that the reaction proceeds via  $\alpha$ -hydroxyphosphonates followed by the substitution of hydroxyl group by amino group. Based on this idea, Fields<sup>10</sup> postulated that  $\alpha$ -aminophosphonates are formed via hemiaminals or imines. The plausible reactions involved in the overall synthesis are shown in Scheme 2.

In conclusion, the present procedure using H $\beta$  zeolite as the catalyst provides an efficient one-pot synthesis of  $\alpha$ -aminophosphonates from the reaction of a carbonyl compound, primary amine, and dibenzyl/dimethyl/diethyl phosphite. The notable advantages of this procedure are (a) operational simplicity, requirement of no additive, and excellent reusability of the catalyst, (b) general applicability to aldehydes and ketones, (c) participation of aromatic as well as aliphatic amines, (d) reaction conditions tolerant to a variety of sensitive functional groups, (e) reduced reaction time, and (f) high product yields. This will be a more practical alternative to existing methodologies for the synthesis of  $\alpha$ aminophosphonous acid from their corresponding dibenzyl  $\alpha$ -aminophosphonates.

# Acknowledgment

V.R.C. and D.K.D. are grateful to the National Academy of Sciences, India, for the NASI Senior Scientist Platinum Jubilee Fellowship and Project Assistantship, respectively.

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- 25. Typical experimental procedure: For the preparation of (4-methoxy-phenylamino)-(tetrahydro-1H-indole-3-yl)-methyl]-phosphonic acid dibenzyl ester uses different catalysts (Table 1): A mixture of indol-3-carboxaldehyde (1 mmol), p-anisidine (1 mmol), dibenzyl phosphite, and catalyst (10% w/w of aldehyde) in acetonitrile was refluxed for 4–5 h.

For the synthesis of different  $\alpha$ -aminophosphonates using H-beta zeolite catalyst (Table 2): A mixture of aldehyde (1 mmol), amine (1 mmol), dibenzyl/ dimethyl/diethyl phosphite, and H $\beta$  (10% w/w of aldehyde) in acetonitrile was refluxed for 4–5 h. The reaction was monitored by TLC.

After completion of reaction, the catalyst was separated by filtration. Then the filtrate was quenched with water followed by extraction with ethyl acetate to give the crude product, which was subsequently purified by column chromatography on silica gel with petroleum ether/ethyl acetate as an eluent. The catalyst was further washed with acetone, dried, and reused. The products are known compounds and their spectroscopic data are given earlier.<sup>8,10,12,14–16,19</sup>