Efficient Synthesis of β-Lactam-Containing α-Aminophosphonates using Fumaric Acid as Mild Catalyst

Vijaya Bhaskar Vangala, Hari Narayan Pati*

Department of Chemistry, Eurofins Advinus Ltd., 21 & 22, Phase II, Peenya Industrial Area, Bengaluru-560058, Karnataka, India

*Dedicated to Professor Virinder S. Parmar on his 70th Birthday

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ABSTRACT

A short and efficient protocol for the synthesis of novel α-aminophosphonate esters containing β-lactam moiety is described. Inexpensive and mild acid catalyst such as fumaric acid was used for the synthesis of α-aminophosphonate esters by reacting N-(4-methoxyphenyl)-2-(substituted) propiolactam-3-carbaldehyde with amine and triethylphosphite in acetonitrile under reflux conditions. α-aminophosphonate esters containing β-lactam hybrids were obtained in moderate to good yield and purity.
Graphical Abstract

Introduction

α-Amino phosphonates are intriguing class of bioactive compounds that share structural similarity with α-amino acids and mimic transition state of active peptides. Prominence of α-amino phosphonate derivatives is particularly due to their proven potential as enzyme inhibitors [1], [4] and [3], antibiotics [2], peptide mimics [6], herbicides [7], and other pharmacological agents [8] and [5]. α-Amino phosphonate derivatives are generally synthesized through various modifications of the original Kabachnik-Fields reaction [9] or Pudovik reaction conditions [10]. In quest of novel compounds with increased pharmacological activity [11] and [12], some of the synthetic efforts dealt with the preparation of hybrid α-amino phosphonate derivatives bearing skeletons such as indoles, thiazoles, pyrazoles, etc. However, to the best of our knowledge, there are no reports of α-amino phosphonate derivatives containing β-lactam skeleton. Several β-lactam derivatives such as cephalosporins, carbapenems, nocardicins and monobactams are known for their anti-microbial activity and pharmacokinetic performance [13]. Additionally, molecules having β-lactam moiety are known for other interesting biological properties, such as cholesterol absorption inhibitors [14], human cytomegalovirus protease inhibitors [15], thrombin inhibitors [16], antitumour [17], anti-HIV [18] and serine-dependent enzyme inhibitors [19] and [20]. In the current article, we wish to report the synthesis of novel hybrid molecules containing α-amino phosphonate analogues bearing substituted β-lactam skeleton.
All chemicals used for the synthesis were of reagent grade and procured from Sigma-Aldrich, Bangalore, India. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ on AS 400 MHz Varian NMR spectrometer using TMS as an internal standard. IR spectra were recorded by using Perkin Elmer Spectrum 100 Series FT-IR spectrometer. Mass spectra were recorded on Agilent 1200 Series LC/MSD VL system. Melting points were determined by using Buchi melting point B-545 instrument and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC) using precoated silica 60 F$_{254}$, 0.25 mm aluminum plates (Merck) and detection was carried out using ultraviolet light followed by developing the plates dipped in a solution of phosphomolybdic acid by heating.

**General procedure for synthesis of β-lactam-containing α-aminophosphonate esters (2a-2l)**

To a solution of N-(4-methoxyphenyl)-3-(substituted) propiolactam-2-carbaldehyde(s) 3a-3d (0.02 mol) in acetonitrile (10 mL) was added successively triethylphosphite (5) (0.02 mol), amine 4a-4d (0.02 mol) and fumaric acid (10 mol%) and the resulting mixture was heated to 70-80 °C for 30 min. The progress of the reaction was monitored by TLC. After cooling the reaction mixture to room temperature, acetonitrile was evaporated under vacuum and the residue was dissolved in CH$_2$Cl$_2$ (20 mL) washed with purified water (10 mL), 5% aq. NaCl solution, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under vacuum to obtain a crude residue which was subjected to column chromatography purification over silica gel (60-120 mesh) using EtOAc/hexane as eluent (1:1) obtained the desired product(s) which were later recrystallized in diisopropyl ether afforded 2a-2l as yellow-white solid(s). Yields of all the isolated products are given in the Table 1.
{1-(4-Methoxy-phenyl)-3-methyl-4-oxo-azetidin-2-yl}-phenylamino-methyl)-phosphonic acid diethyl ester (2a)

The compound 2a was synthesized by following the general procedure produced the desired compound in 45 % as a white solid; M. P.: 153-154 °C; IR (KBr) ν<sub>max</sub>/cm<sup>-1</sup>: 3479, 3295, 3185, 3122, 3042, 2986, 2903, 2834, 2777, 2597, 2047, 1748, 1601, 1535, 1511, 1445, 1382, 1354, 1318, 1296, 1244, 1223, 1159, 1120, 1057, 1028, 912, 829, 796, 752, 701. ¹H NMR (400 MHz, CDCl<sub>3</sub>), δ: 1.10 (t, J=7.2 Hz, 3H), 1.12 (t, J=7.2 Hz, 3H), 1.51 (d, J=7.6 Hz, 3H), 3.57-3.64 (m, 1H), 3.79 (s, 3H), 3.81-4.07 (m, 4H), 4.19-4.28 (m, 1H), 4.51-4.54 (q, J=10.0, 4.4 Hz, 1H), 6.42 (d, J=7.6 Hz, 2H), 6.68 (t, J=7.6 Hz, 1H), 6.86-6.89 (dd, J=6.8, 2.4 Hz, 2H), 7.04 (t, J=7.6 Hz, 2H), 7.26-7.29 (dd, J=6.8, 2.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl<sub>3</sub>), δ: 168.3, 156.4, 146.1, 130.3, 129.2, 119.9, 118.8, 114.2, 113.6, 63.4, 63.3, 62.2, 62.1, 55.5, 55.2, 55.1, 51.5, 50, 47.8, 47.7, 16.3, 16.2, 16, 15.9, 10.0; MS (ESI) m/z: 433.3 (M+1)⁺.

Results and discussion

The β-lactam skeleton is a four-membered cyclic amide framework and is core to many pharmacologically active compounds. It was envisaged that the novel molecules designed by structural integrity of α-amino phosphonate esters and β-lactam functionalities would impart synergistic effect towards antimicrobial properties (Figure 1) and to turn our idea into reality, we set out to synthesize the hybrid molecules by taking 4-formyl-2-azetedinones (3a-c) as the key starting materials. The syntheses of 4-formyl-2-azetedinones (3a-c) were accomplished by following the synthetic protocol reported by Benito and co-workers [21], wherein the substituted acetic acid chlorides were dehydrochlorinated by a base, and in-situ reacted with glyoxal diimines in toluene smoothly underwent cycloaddition, and resulted into the corresponding imine intermediates. Further, acidic work up of those imine intermediate gave rise to the desired racemic cis-aldehydes exclusively with good yields. The cis stereochemical outcome (³J<sub>cis</sub>=6.4 Hz) of racemic products was assigned based on the H₃-H₄ coupling constants of 4-formyl-2-azetedinones (usually ³J<sub>cis</sub>=5.0-6.5 Hz and ³J<sub>trans</sub>=2.0-2.5 Hz), and NOE measurements. In addition to H₃-H₄ cis stereochemical assignment, we have also analyzed earlier in our group by XRD, the relative stereochemistry of the vicinal proton adjacent to β-lactum ring in one of the synthesized analogues of α-hydroxyphophonates [22] and the stereochemical outcome was in alignment with our expectation as cis H₃-H₄ and trans H₄-H₅, respectively. With a similar objective for making α-amino phosphonates in the equivalent manner, we prepared the title compounds using 4-formyl-2-
azetidinones (3a-c), substituted anilines (4a-d) and triethylphosphite in the presence of a mild acid catalyst fumaric acid.

The original syntheses of α-amino phosphonate esters (1) involved the use of aldehyde/ketone, amine and dialkyl/trialkyl phosphites in the presence of an acid or a base under harsh conditions, but those methods were incapable for the synthesis in presence of sensitive functional groups such as β-lactam. Hence, finding the milder reaction conditions was crucial to obtain novel β-lactam containing α-amino phosphonate esters. Cognizant of the sensitivity of β-lactam functionality present in one of the reactants and subsequently in the final products, milder acidic conditions were explored. Initially, trials involving the conversion of N-(4-methoxyphenyl)-2-(substituted) propiolactam-3-carbaldehydes (3a-3c) and aromatic amine to the corresponding imine, followed by treatment of the isolated imine with triethyl phosphate under Pudovik reaction conditions did not yield the required product. During those trials, the unsubstituted aniline 4a and substituted anilines 4b-4d also didn’t yield any success. Similarly, seemingly straightforward trials of one-pot Kabachnik-Fields reaction between N-(4-methoxyphenyl)-2-(substituted) propiolactam-3-carbaldehyde (3a-3c), aromatic amine (4a-4c) and triethyl phosphate in the presence of p-TsOH were attempted, but without success. Hence, we decided to explore Kabachnik-Fields type reaction conditions using mild acidic catalysts.

Scheme 1. Synthesis of α-amino phosphonate ester derivatives of N-4-methoxyphenyl-3-substituted-β-propiolactam (2a-2l)
During our trials probing various mild acidic catalysts with pKa ranging from 2-5, not so advantage was gained from lactic acid and tartaric acid, since the yields of the reactions varied between 10% and 30%. However, when fumaric acid was used under identical reaction conditions, product yields improved moderately greater than 50%. Encouraged by these results, to synthesize a diverse set of analogs (2b-2l), (Scheme 1), we employed fumaric acid as a mild catalyst in the three-component synthesis involving \( N \)-\((4\text{-methoxyphenyl})\)-2-\((\text{substituted})\) propiolactam-3-carbaldehyde (3a-3c), triethyl phosphate and aromatic amines 4a-4c. (Table 1).

**Table 1.** Conversion of \( N \)-(4-methoxyphenyl)-2-\((\text{substituted})\) phenyl propiolactam-3-carbaldehydes (3a-3c) to \( \alpha \)-aminophosphonates (2a-2l) using fumaric acid as catalyst

<table>
<thead>
<tr>
<th>Compound</th>
<th>( R )</th>
<th>( R' )</th>
<th>Yield (%)</th>
<th>Isomer ratio (dr)*</th>
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<tbody>
<tr>
<td>2a</td>
<td>( \text{CH}_3 )</td>
<td>( \text{Ph} )</td>
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<td>100</td>
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<tr>
<td>2b</td>
<td>( \text{CH}_3 )</td>
<td>( \text{Br} )</td>
<td>55</td>
<td>100</td>
</tr>
<tr>
<td>2c</td>
<td>( \text{CH}_3 )</td>
<td>( \text{NO}_2 )</td>
<td>57</td>
<td>50:50</td>
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<tr>
<td>2d</td>
<td>( \text{CH}_3 )</td>
<td>( \text{F} )</td>
<td>58</td>
<td>48:52</td>
</tr>
<tr>
<td>2e</td>
<td>( \text{Ph} )</td>
<td>( \text{Ph} )</td>
<td>60.5</td>
<td>100</td>
</tr>
<tr>
<td>2f</td>
<td>( \text{Ph} )</td>
<td>( \text{Br} )</td>
<td>62</td>
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<tr>
<td>2g</td>
<td>( \text{Ph} )</td>
<td>( \text{NO}_2 )</td>
<td>52</td>
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<tr>
<td>2h</td>
<td>( \text{Ph} )</td>
<td>( \text{F} )</td>
<td>58</td>
<td>50:50</td>
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<tr>
<td>2i</td>
<td>\text{n-CH}_3(\text{CH}_2)_3\text{H}</td>
<td>( \text{Ph} )</td>
<td>70</td>
<td>45:55</td>
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<td>2j</td>
<td>\text{n-CH}_3(\text{CH}_2)_3\text{H}</td>
<td>( \text{Br} )</td>
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<td>\text{n-CH}_3(\text{CH}_2)_3\text{H}</td>
<td>( \text{NO}_2 )</td>
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<td>2l</td>
<td>\text{n-CH}_3(\text{CH}_2)_3\text{H}</td>
<td>( \text{F} )</td>
<td>57.5</td>
<td>48:52</td>
</tr>
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*The diastereomer ratio (rac) was approximately evaluated from the\(^{13}\)C spectral data of the pure/mixture by taking carbonyl carbon signal as reference*
The target compounds (2a-2l) were initially isolated as their racemic diastereomeric mixtures after subjecting their crude compounds to purification by silica gel column chromatography. Further, recrystallization of their isolates in diisopropyl ether produced the products with yields ranging from 45-70%. Overall, the products 2a, 2b, 2e, 2f, 2g and 2k were isolated as their racemic single diastereomers, while others such as 2c, 2d, 2h, 2i, 2j and 2l were isolated as their mixture of diastereomers, analyzed by the interpretation of their respective 1H and 13C NMR spectra (Table 1). Finally, all the compounds (2a-2l) were characterized by IR, 1H NMR, 13C NMR spectroscopy, and mass spectrometry.

Conclusion
Fumaric acid was found to be suitable catalyst for synthesis of novel β-lactam-containing α-aminophosphonates (2a-2l). We believe that streamlining the protocol described in this paper may present a viable alternative to the existing procedures for the synthesis of α-aminophosphonates possessing sensitive functionalities that are unstable in acidic and basic conditions.

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References
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