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Efficient Synthesis of *β*-Lactam-Containing *α*-Aminophosphonates using Fumaric Acid as Mild Catalyst$^{\Phi}$

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$^{\phi}$ 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.

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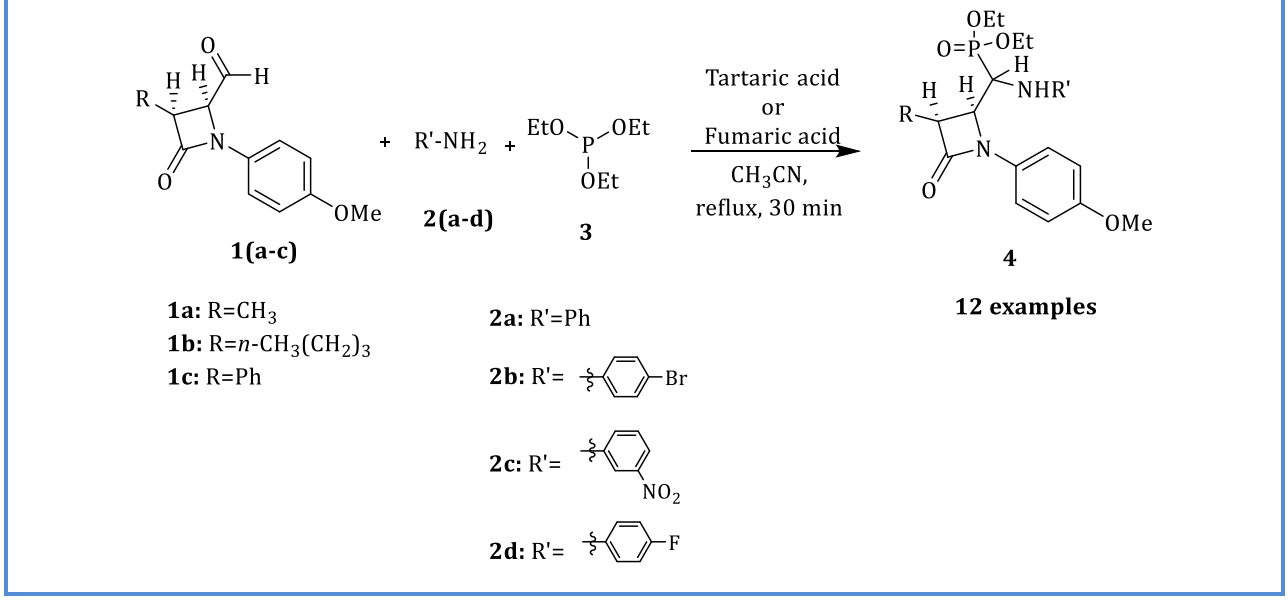
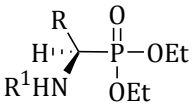
Graphical Abstract



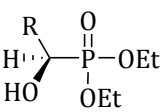
Introduction

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.

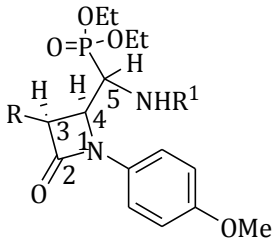


1a

R, R^1 = Alkyl, aryl, hetero aryl



1b



2(a-l)

R = Ph, CH_3, n-$CH_2(CH_2)_3$;
R^1 = Aryl

Figure 1. General structure of *α*-aminophosphonates (**1a**), α-hydroxyphosphonates (**1b**) and *α*-aminophosphonates derived from *N*-(4-methoxyphenyl)-2-(substituted)propiolactam-3-carbaldehyde (**2a-2l**)

Experimental

All chemicals used for the synthesis were of reagent grade and procured from Sigma-Aldrich, Bangalore, India. ^1H 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_2Cl_2 (20 mL) washed with purified water (10 mL), 5% aq. NaCl solution, dried over anhydrous Na_2SO_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)

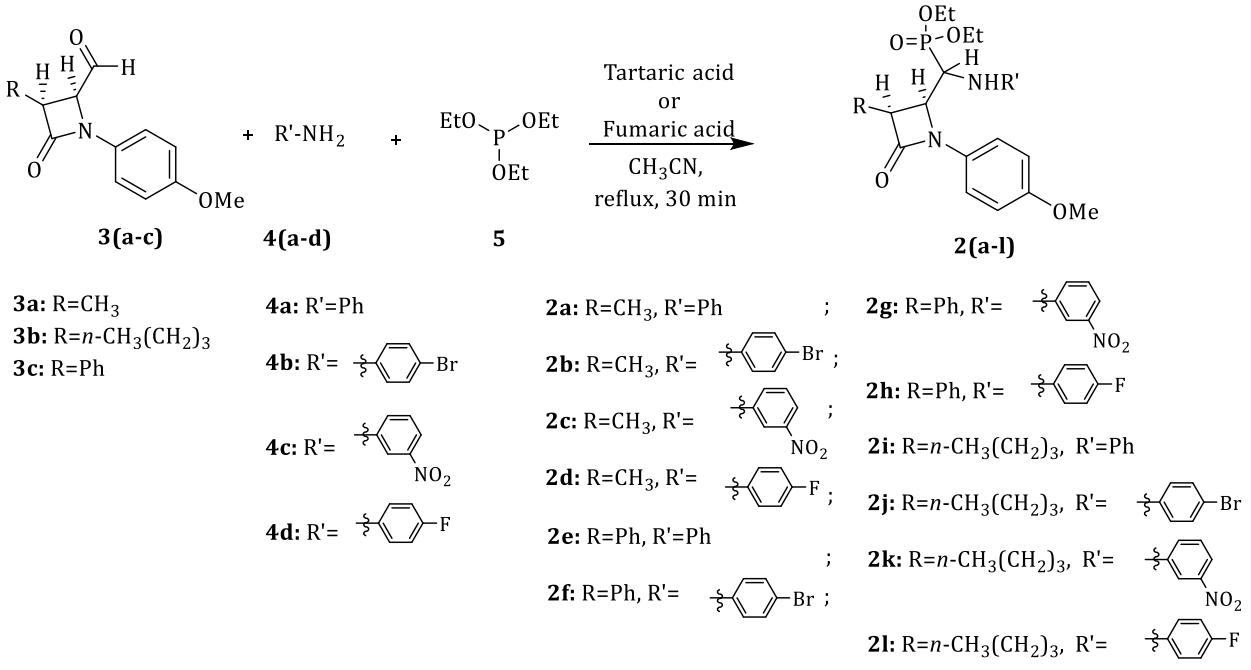
The compound **2a** was synthesized by following the general procedure produced the desired compound in 45 % as a white solid; M. P.: 153-154 °C; IR (KBr) ν_{max}/cm^{-1}: 3479, 3295, 3185, 3122, 3042, 2986, 2903, 2834, 2777, 2597, 2047, 1748, 1601, 1535, 1511, 1445, 1382, 1354, 1318, 1296, 1244, 1223, 1159, 1120, 1057, 1028, 980, 912, 861, 829, 796, 752, 701. ^{1}H NMR (400 MHz, $CDCl_3$), 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). ^{13}C NMR (100 MHz, $CDCl_3$), 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 ($^3J_{cis}$=6.4 Hz) of racemic products was assigned based on the H_3-H_4 coupling constants of 4-formyl-2-azetedinones (usually $^3J_{cis}$=5.0-6.5 Hz and $^3J_{trans}$=2.0-2.5 Hz), and NOE measurements. In addition to H_3-H_4 *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* H_3-H_4 and *trans* H_4-H_5, respectively. With a similar objective for making *α*-amino phosphonates in the equivalent manner, we prepared the title compounds using 4-formyl-2-

azetedinones (**3a-c**), substituted anilines (**4a-d**) and triethylphosphite in the presence of a mild acid catalyst fumaric acid.

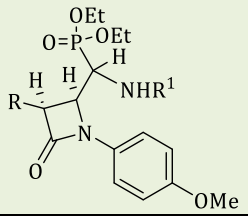
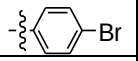
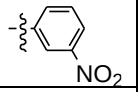
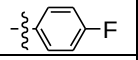
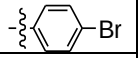
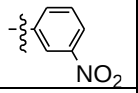
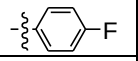
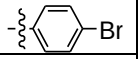
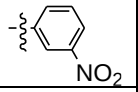
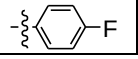
The original syntheses of *α*-amino phosphonate esters (**1**) involved the use of aldehyde/ketone, amine and dialkyl/trialkyl phosphites in the presence of an acid or a base under harsh conditions, but those methods were incapable for the synthesis in presence of sensitive functional groups such as *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 phosphite 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 phosphite 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-methoxyphenyl)-2-(substituted) propiolactam-3-carbaldehyde (**3a-3c**), triethyl phosphite and aromatic amines **4a-4c**. (Table 1).

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

Compound 	**R**	**R'**	**Yield (%)**	**Isomer ratio (dr)***
2a	CH_3-	Ph	45	100
2b	CH_3-		55	100
2c	CH_3-		57	50:50
2d	CH_3-		58	48:52
2e	Ph-	Ph	60.5	100
2f	Ph-		62	100
2g	Ph-		52	100
2h	Ph-		58	50:50
2i	*n*- $CH_3(CH_2)_3$-	Ph	70	45:55
2j	*n*- $CH_3(CH_2)_3$-		65.5	60:40
2k	*n*- $CH_3(CH_2)_3$-		50	100
2l	*n*- $CH_3(CH_2)_3$-		57.5	48:52

*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 ^{1}H and ^{13}C NMR spectra (Table 1). Finally, all the compounds (**2a-2l**) were characterized by IR, ^{1}H NMR, ^{13}C 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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