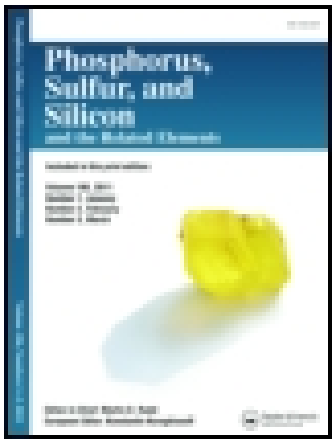

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/gpss20

Bismuth(iii) Chloride Mediated Michaelis-Arbuzov Reaction: A Facile Synthesis of Substituted Arylphosphonates / Phosphinates and Bioactivity Evaluation

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Accepted author version posted online: 13 May 2015.

To cite this article: Ch. Subramanyam, G. Madhava, S. K. Thaslim Basha, S. Rasheed, A. Uday Sankar & C. Naga Raju (2015): Bismuth(iii) Chloride Mediated Michaelis-Arbuzov Reaction: A Facile Synthesis of Substituted Arylphosphonates / Phosphinates and Bioactivity Evaluation, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2015.1043048

To link to this article: http://dx.doi.org/10.1080/10426507.2015.1043048

BISMUTH(III) CHLORIDE MEDIATED MICHAELIS-ARBUZOV REACTION: A FACILE SYNTHESIS OF SUBSTITUTED ARYLPHOSPHONATES / PHOSPHINATES AND BIOACTIVITY EVALUATION

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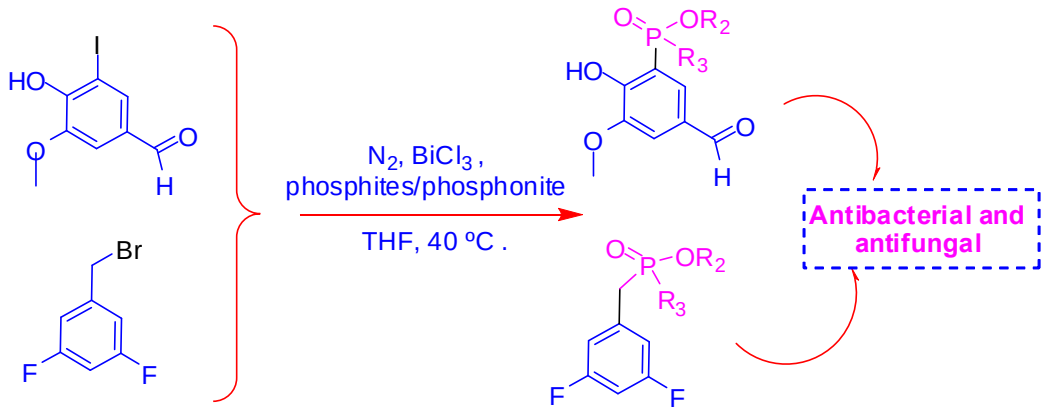
Running head: $BiCl_3$ Catalyzed Synthesis of Substituted Arylphosphonates/Phosphinates

ABSTRACT $BiCl_3$ is economically affordable, less toxic and ecofriendly catalyst. A facile synthesis of substituted arylphosphonates/phosphinates in good yields was achieved using $BiCl_3$ catalyzed *via* Michaelis-Arbuzov reaction. 5-Iodovanillin / 3,5-difluorobenzylbromide was reacted with various phosphites and dimethyl phenylphosphonite in the presence of Lewis acid catalyst $BiCl_3$, under N_2 atmosphere at 40 °C to produce the corresponding arylphosphonates/phosphinates. They were characterized by ^{31}P, ^{1}H and ^{13}C NMR spectroscopy, IR, mass spectrometry and elemental analysis. All title compounds were screened for their *in vitro* antibacterial and antifungal activity. The compounds **5d**, **3b**, **5e, 5b** exhibited good antibacterial activity and the compounds **3a, 3b**, **5a** and **5d** exhibited significant antifungal activity compared to the standard bactericide Norfloxacin and fungicide Griseofulvin.



Keywords Michaelis-Arbuzov reaction, $BiCl_3$, 5-Iodovanillin, 3,5-difluorobenzylbromide, arylphosphonates / phosphinates, antibacterial activity, antifungal activity

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INTRODUCTION

Phosphonates signify a class of stable organophosphorus compounds containing a single carbon-phosphorus (C–P) bond, which makes them resistant to chemical and enzymatic hydrolysis, thermal decomposition[1] and photolysis.[2] They have broad applications in flame retardancy,[3-4] organic synthesis[5] and biological applications.[6-7] Synthetic phosphonates are now widely used as herbicides,[8a] stimulants for the latex production of *Hevea brasiliensis*,[8b] pesticides,[9] detergents,[10] reagents for Wittig-Horner reactions,[11] anti-bacterial,[12] antiviral[13] and antitumor agents.[14] A phosphonate motif is present in biomolecules which can act as inhibitors of certain biosynthetic pathways and can be degraded only by some prokaryotic microorganisms.[15] The high chemical stability of phosphonates, together with their resistance to biodegradation, makes this class of compounds of particular interest for the drug design. Phosphinates are also proved to be superior transition state analogues for the preparation of catalytic antibodies[16-17] and several arylphosphinates have been explored as potential therapeutics.[18]

The Michaelis-Arbuzov rearrangement is one of the most extensively investigated reactions in organophosphorus chemistry and is widely used to prepare phosphonates, phosphinates and phosphine oxides.[19] The mechanism of the Arbuzov reaction has been shown to involve two nucleophilic attacks, i.e., the formation of a quasi-phosphonium salt by the reaction of trialkyl phosphite with an alkyl halide and the dealkylation of this salt, accompanied by rearrangement to a phosphonate.[20] However, due to the resistance of aryl groups to nucleophilic attack, the classic Arbuzov reaction was essentially limited to the preparation of alkyl phosphonates. The synthesis of aryl phosphonates represents one early challenge. In this

regard, the transition-metal catalyzed Arbuzov reaction has gained remarkable success.[21ï25] Tavs extended the classic Arbuzov reaction to the synthesis of dialkyl arylphosphonates by phosphonylation of aryl halides with trialkyl phosphites catalyzed by nickel.[21] Keglevich *et al.* also synthesized arylphosphonates by the microwave-assisted Arbuzov reaction of triethyl phosphite and aryl bromides in the presence of $NiCl_2$ as the catalyst under solvent-free conditions. [26] Rajeshwaran *et al* reported Lewis acid mediated Michaelis-Arbuzov reaction to synthesize arylmethyl and heteroarylmethyl phosphonate esters at room temperature.[27] In recent years, economically affordable ecofriendly catalysts such as Cu(II) salts,[28] Fe (II)/Fe(III) salts,[29] Ni salts and Bi(III) salts[30,31] received some interest in various organic reactions. Recently, bismuth trichloride ($BiCl_3$) has received attention in organic synthesis because of its low toxicity, low cost and relative insensitivity to air and to small amounts of moisture when compared with transition-metal complexes.[32] Hua Li *et al.* developed a Bismuth(III) chloride-catalyzed one-pot Mannich reaction for the synthesis of *β*-aminocarbonyl compounds.[33] Zhan *et al.* reported the $BiCl_3$ catalyzed substitution reaction of propargylic alcohols with carbon and heteroatom-centered nucleophiles such as allyl trimethylsilane, alcohols, aromatic compounds, thiols and amides, leading to the construction of Cï C, Cï O, Cï S and Cï N bonds.[34]

The possibility of broad applications of phosphonates as well as phosphinates and the significance of $BiCl_3$ as an ecofriendly catalyst prompted us to synthesize a series of novel substituted aryl phosphonates/phosphinates catalyzed by Bismuth(III) chloride at 40 °C.

RESULTS AND DISCUSSION

As part of the research programme in the development of new methodologies for the synthesis of bioactive phosphonates and phosphinates, in this letter, we report the synthesis of various substituted 5-formyl-2-hydroxy-3-methoxyphenylphosphonate/phosphinate (**3a-e**) and substituted 3,5-difluorobenzylphosphonate/phosphinate (**5a-e**) in the presence of the efficient catalyst Bismuth(III) chloride. To optimize the reaction conditions, 5-iodovanillin (**1**) and trimethyl phosphite (TMP) (**2a**) were selected as substrates (**Scheme 1**).

Initially, the reaction was performed using 5-iodovanillin (**1**) (1.2 mmol, 0.33 g) and trimethyl phosphite (TMP) (**2a**) (1.8 mmol, 0.21 mL) in ethanol as solvent. Without catalyst under refluxed conditions, it resulted in only trace amounts of the product **3a**. Further, the effect of the reaction was scrutinized with different catalysts (10 mol %) in EtOH to afford dimethyl 5-formyl-2-hydroxy-3-methoxyphenylphosphonate (**3a**) as shown in Table 1, entry 1-5. Remarkably, the good yield of compound **3a** was observed with Bismuth(III) chloride. This result attracted us to explore further the finest reaction conditions. Hence, the same reaction was conducted in different solvents like THF, toluene and DCM (Table 1, entry 6-8). The best result was obtained in THF (Table 1, entry 8). To our interest, the effect of the amount of the catalyst on the reaction conditions was scrutinized by altering the amount of the catalyst (Table 1, entry 9-14). The highest yield was observed at 20 mol% amount of the catalyst (Table 1, entry 12).

After optimization of the reaction conditions, to explore the scope and generality of this method, various trialkyl phosphites (**2b-d**) and dimethyl phenylphosphonite (**2e**) (1.8 mmol) were selected to undergo reaction with 5-iodovanillin (**1**) (1.2 mmol, 0.33 g) under the assigned

conditions to obtain the corresponding substituted 5-formyl-2-hydroxy-3-methoxyphenylphosphonates (**3b-d**) and methyl 5-formyl-2-hydroxy-3-methoxyphenyl(phenyl)phosphinate (**3e**) (**Scheme 2**).

Inspired by the above results, we further extended this process on 3,5-difluorobenzyl bromide (**4**) (1.2 mmol, 0.17 mL) with various alkyl phosphites (**2b-d**) and dimethyl phenylphosphonite (**2e**) (1.8 mmol) to afford the desired substituted 3,5-difluorobenzylphosphonates (**5a-d**) and methyl 3,5-difluorobenzyl(phenyl)phosphinate (**5e**) (**Scheme 3**). The physical data of the synthesized compounds are presented in **Table S2**.

Spectroscopy

The chemical structure of the title compounds **3a-e** and **5a-e** are supported by spectral data (^{31}P, ^{1}H and ^{13}C NMR, IR and LC-MS), elemental analysis. The results are presented in the Experimental section. Characteristic ^{31}P NMR signals were observed in the region 39.2-17.5 ppm for all the compounds (**3a–e**, **5a-e**). In ^{1}H NMR spectra, the signals due to ArH protons were observed in the region 7.92-7.63 ppm. The proton signals at 10.20-9.85 and 9.82-9.37 ppm are assigned to CHO and OH functionalities of **3a-e**. The signal due to P-CH_2 proton signals appeared at 3.63-3.47 ppm for **5a-e**. ^{13}C NMR chemical shifts were observed in the expected regions. IR stretching absorptions for P=O, P-O-C_{alip} were observed in the regions 1242-1230, 1029-1022 cm^{-1} respectively. The absorptions due to OH, P-$C_{aromatic}$ were observed in the regions 3417-3411, 1463-1457 cm^{-1} respectively for **3a-e**. The characteristic absorption due to

P-$C_{aliphatic}$ stretching was observed in the region 736-724 cm^{-1} for **5a-e**. In their mass spectra, M^+ ions were observed for the expected m/z values.

Based on an overview and a literature survey, we propose a possible mechanism for the $BiCl_3$ mediated Michaelis-Arbuzov reaction (Figure S 1 Supplemental Materials). The alkyl halide and Lewis acid catalyst form a complex which enhances the electrophilic nature of the alkyl halide and make it feasible to the S_N2 attack of the lone pair electrons of the phosphorus of trialkyl phosphite and determine the reaction pathway.

Biological activity

Antibacterial activity

The antibacterial activity of the title compounds was assayed against two Gram positive and two Gram negative bacteria by the agar well diffusion method.[35a,35b,35c] All newly synthesized compounds exhibited moderate to good activity against both Gram positive and Gram negative bacteria. Especially **5d**, **3b**, **5e** and **5b** exhibited good antibacterial activity against both Gram positive and Gram negative bacteria when compared to that of standard drugs. The data are presented in Table S 1 (Supplemental Materials).

Antifungal activity

The antifungal activity of the newly synthesized compounds was screened against two fungi, *Aspergillus niger* and *Fusarium oxysporum* by the poison plate technique.[36] All compounds exhibited moderate to good antifungal activity against the two fungi. Especially **3a**,

3b, **5a** and **5d** exhibited better activities than the remaining compounds. The data are presented in **Table S 2**.

EXPERIMENTAL

Materials and methods

All chemicals used were purchased from Sigma-Aldrich and Merck. Solvents were distilled from the appropriate drying agents and stored under N_2. The reactions were monitored by thin layer chromatography (TLC) on Merck precoated silica G_{F254} plates. Melting points were determined in open capillaries on a Guna melting point apparatus and are uncorrected. IR Spectra were recorded as KBr discs on a Nicolet 380 FT-IR spectrophotometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 for ^{31}P NMR. TMS was used as the internal standard for ^{1}H and ^{13}C NMR spectra and H_3PO_4 as the external standard for ^{31}P NMR spectra. Chemical shifts were expressed in ppm. LC-MS spectra were recorded on a SHIMADZU 2010A mass spectrometer. Elemental analysis was performed on Thermo Finnigan Flash 1112 instrument at the University of Hyderabad, Hyderabad. Silica gel (100-200 mesh) was used in column chromatography (CC) for purification of the synthesized compounds. Multiplicities are shown as the abbreviations: s (singlet), d (doublet), t (triplet), m (multiplet) and *J* in Hz. The structures of the products, and sample spectroscopic characterizations for 3d and 5d are shown in Table S 3 and Figures S 2 ï S 5 (Supplemental Materials)

General synthesis of compounds 3a-d

5-Iodovanillin (**1**) (1.2 mmol, 0.33 g) and trimethyl phosphite (**2a**) (1.8 mmol, 0.21 mL) in dry THF (20 mL) were taken in a flat bottomed flask. To this mixture, $BiCl_3$ (20 mol%) was added and the reaction mixture was stirred vigorously at 40 °C under a N_2 atmosphere for 4 h. The progress of the reaction was monitored by TLC (EtOAc: hexane, 2:1). After completion of the reaction, the reaction mixture was filtered to separate the catalyst. The solvent from the filtrate and the byproducts were removed under reduced pressure to get the crude product. The resulting crude product was purified by CC (EtOAc-hexane 1:1 as eluent) to afford pure dimethyl 5-formyl-2-hydroxy-3-methoxyphenylphosphonate (**3a**). The remaining title compounds (**3b-d**) were prepared by adopting the above described procedure.

Methyl 5-formyl-2-hydroxy-3-methoxyphenyl(phenyl)-phosphinate (3e). 5-Iodovanillin (**1**) (1.2 mmol, 0.33 g) was treated with dimethyl phenylphosphonite (**2e**) (1.8 mmol) in dry THF in the presence of $BiCl_3$ as catalyst at 40 °C under N_2 for 4 h. The crude product was purified by CC to obtain pure **3e.**

General Synthesis of 5a-d

3,5-Difluorobenzyl bromide (**4**) (1.2 mmol, 0.17 mL) and trimethyl phosphite (**2a**) (1.8 mmol, 0.21 mL) in dry THF (20 mL) were taken in a flat bottomed flask. To this mixture, $BiCl_3$ (20 mol%) was added and the reaction mixture was stirred vigorously at 40 °C under N_2 for 4 h. The progress of the reaction was monitored by TLC (EtOAc/hexane, 2:1). After completion of the reaction, the reaction mixture was filtered to separate the catalyst. The solvent from the filtrate and the byproducts were removed under reduced pressure. The resulting crude product was purified by CC (EtOAc/hexane 1:1 as eluent to afford pure dimethyl 3,5-

difluorobenzylphosphonate (**5a**). The remaining title compounds (**5b-d**) were prepared by adopting the above described procedure.

Methyl 3,5-difluorobenzyl(phenyl)phosphinate (5e). 3,5-Difluorobenzyl bromide (**4**) (1.2 mmol, 0.17 mL) was reacted with dimethyl phenylphosphonite (**2e**) (1.8 mmol) in dry THF in the presence of $BiCl_3$ as catalyst at 40 °C under N_2 for 4 h. The crude product was purified by CC to obtain pure **5e**.

The synthetic protocol for the compounds (**3a-e**) and (**5a-e**) is shown in **Scheme 2 Scheme 3**.

Physical, analytical and spectral data of 3a-e and 5a-e

Dimethyl 5-formyl-2-hydroxy-3-methoxyphenylphosphonate (3a). Semi solid, Yield 75%. ^{31}P NMR: δ 21.5; ^{1}H NMR: δ 10.20 (s, 1H, CHO), 9.85 (s, 1H, OH), 7.76 (s, 1H, ArH), 7.35 (s, 1H, ArH), 3.79 (s, 3H, OCH_3), 3.40 (s, 6H, OCH_3); ^{13}C NMR: δ 192.1 (C-7), 154.7 (C-3), 147.8 (C-2), 133.0 (C-5), 126.9 (C-6), 125.1 (C-1), 117.8 (C-4), 56.4 (C-8), 54.1 (C-9, C-9N), IR: 3417 (OH), 1463 (P-C_{ar}), 1240 (P=O), 1028 (P-O-C_{alip}); LCMS *m/z*, (%): 261 (100) $[M+H]^+$. Calcd. for $C_{10}H_{13}O_6P$ (260); C, 46.16; H, 5.04%; found: C, 46.10; H, 5.09%.

Diethyl 5-formyl-2-hydroxy-3-methoxyphenylphosphonate (3b). Semi solid, Yield 80%. ^{31}P NMR: δ 22.3; ^{1}H NMR: δ 10.12 (s, 1H, CHO), 9.82 (s, 1H, OH), 7.82 (s, 1H, ArH), 7.42 (s, 1H, ArH), 4.01 (m, 4H, O$\underline{CH_2}CH_3$), 3.75 (s, 3H, OCH_3), 1.15 (t, 6H, $OCH_2\underline{CH_3}$); ^{13}C NMR: δ 190.2 (C-7), 153.5 (C-3), 152.1 (C-2), 131.3 (C-5), 127.4 (C-6), 117.3 (C-1), 116.2 (C-4), 61.6 (C-9, C-9N), 56.3 (C-8), 16.2 (C-10, C-10N), IR: 3415 (OH), 1460 (P-C_{ar}), 1238 (P=O),

1027 (P-O-C_{alip}); LCMS *m/z* (%): 289 (100) $[M+H]^+$. Calcd. for $C_{12}H_{17}O_6P$ (288): C, 50.00; H, 5.94%), found: C, 50.05; H, 5.89%.

Diisopropyl 5-formyl-2-hydroxy-3-methoxyphenylphosphonate (3c). Semi solid, Yield 77%. ^{31}P NMR: δ 20.3; ^{1}H NMR: δ 10.03 (s, 1H, CHO), 9.78 (s, 1H, OH), 7.83 (s, 1H, ArH), 7.41 (s, 1H, ArH), 4.52 (m, 2H, O<u>CH</u>$(CH_3)_2$), 3.80 (s, 3H, OCH_3), 1.21 (t, 12H, OCH(<u>CH_3</u>)$_2$); ^{13}C NMR: δ 191.5 (C-7), 159.9 (C-3), 135.4 (C-2), 127.7 (C-5), 126.5 (C-6), 120.6 (C-1), 117.6 (C-4), 71.6 (C-9, C-9), 56.5 (C-8), 23.9 (C-10, C-10, C-10, C-10); IR: 3415 (OH), 1458 (P-C_{ar}), 1235 (P=O), 1026 (P-O-C_{alip}); LCMS *m/z* (%): 317 (100) $[M+H]^+$. Calcd. for $C_{14}H_{21}O_6P$ (316): C, 53.16; H, 6.69%; found: C, 53.10; H, 6.62%.

Dibutyl 5-formyl-2-hydroxy-3-methoxyphenylphosphonate (3d). Semi solid, Yield 78%. ^{31}P NMR: 17.5; ^{1}H NMR: δ 9.94 (s, 1H, CHO), 9.75 (s, 1H, OH), 7.88 (s, 1H, ArH), 7.41 (s, 1H, ArH), 3.95 (m, 4H, O<u>CH_2</u>$CH_2CH_2CH_3$), 3.89 (s, 3H, OCH_3), 1.62 (m, 4H, OCH_2<u>CH_2</u>CH_2CH_3), 1.34 (m, 4H, OCH_2CH_2<u>CH_2</u>CH_3), 1.05 (t, 6H, $OCH_2CH_2CH_2$<u>CH_3</u>); ^{13}C NMR: δ 190.1 (C-7), 152.1 (C-3), 147.3 (C-2), 134.7 (C-5), 130.0 (C-6), 115.5 (C-1), 112.8 (C-4), 79.3 (C-9 & C-9), 54.6 (C-8), 32.4 (C-10, C-10), 19.5 (C-11, C-11), 14.4 (C-12, C-12); IR: 3413 (OH), 1457 (P-C_{ar}), 1232 (P=O), 1024 (P-O-C_{alip}); LCMS *m/z,* (%): 345 (100) $[M+H]^+$; Calcd. For $C_{16}H_{25}O_6P$ (344): C, 55.81; H, 7.32; found: C, 55.73; H, 7.26%.

Methyl 5-formyl-2-hydroxy-3-methoxyphenyl(phenyl)phosphinate (3e). Semi solid, Yield 71%. ^{31}P NMR: δ 31.2; ^{1}H NMR: δ 9.85 (s, 1H, CHO), 9.37 (s, 1H, OH), 7.92-7.41 (m, 7H, Ar-H), 3.80 (s, 3H, OCH_3), 3.47 (s, 3H, $POCH_3$); ^{13}C NMR: δ 191.8 (C-7), 157.8 (C-3), 151.6 (C-2), 135.8 (C-10), 132.2 (C-5), 131.2 (C-12, C-12), 128.4 (C-6), 124.5 (C-1), 121.5 (C-13), 118.4 (C-11, C-11), 112.6 (C-4), 56.0 (C-8), 52.9 (C-9); IR: 3411 (OH), 1458 (P-C_{ar}), 1230

(P=O), 1025 (P-O-C_{alip}); LCMS *m/z* (%): 307 (100) $[M+H]^+$. Calcd. for $C_{15}H_{15}O_5P$ (306): C, 58.83; H, 4.94%; found: C, 58.88; H, 4.89%.

Dimethyl 3,5-difluorobenzylphosphonate (5a). Semi solid, Yield 76%. ^{31}P NMR: δ 28.2; ^1H NMR: δ 6.71-6.65 (m, 3H, ArH), 3.61 (d, J = 6.5 Hz, 2H, PCH_2), 3.49 (s, 6H, OCH_3); ^{13}C NMR: ŭ 165.6 (C-3, C-5), 133.8 (C-1), 112.4 (C-2, C-6), 103.4 (C-4), 53.9 (C-7), 29.7 (C-8, C-8); IR: 1242 (P=O), 1029 (P-O-C_{alip}), 735 (P-C_{alip}); LCMS *m/z* (%): 237 (100) $[M+H]^+$. Calcd. for $C_9H_{11}F_2O_3P$ (236): C, 45.77; H, 4.69%; found: C, 45.85; H, 4.62%.

Diethyl 3,5-difluorobenzylphosphonate (5b). Semi solid, Yield 79%. ^{31}P NMR: δ 25.0; ^1H NMR: δ 6.82-6.73 (m, 3H, ArH), 3.94 (m, 4H, O$\underline{CH_2}CH_3$), 3.63 (d, J = 6.4 Hz, 2H, PCH_2), 1.28 (t, J = 5.6 Hz, 6H, $OCH_2\underline{CH_3}$); ^{13}C NMR: δ 166.1 (C-3, C-5), 140.6 (C-1), 114.2 (C-2, C-6), 104.7 (C-4), 66.6 (C-8, C-8); 38.9 (C-7), 16.3 (C-9, C-9); IR: 1238 (P=O), 1028 (P-O-C_{alip}), 728 (P-C_{alip}); LCMS *m/z* (%): 265 (100) $[M+H]^+$. Calcd. for $C_{11}H_{15}F_2O_3P$ (264): C, 50.01; H, 5.72%; found: C, 50.08; H, 5.67%.

Di-isopropyl-3,5-difluorobenzylphosphonate (5c): Semi solid, Yield 73%. ^{31}P NMR: δ 25.3; ^1H NMR: δ 6.92-6.70 (m, 3H, ArH), 4.20 (m, 2H, O$\underline{CH}(CH_3)_2$), 3.54 (d, J= 6.0 Hz, 2H, PCH_2), 1.10 (d, J = 5.8 Hz, 12H); ^{13}C NMR: δ 164.3 (C-3, C-5), 136.9 (C-1), 113.3 (C-2, C-6), 102.7 (C-4), 70.6 (C-8, C-8); 33.4 (C-7), 24.5 (C-9, C-9, C-9, C-9); IR: 1233 (P=O), 1024 (P-O-C_{alip}), 727 (P-C_{alip}); LCMS *m/z* (%): 293 $[M+H]^+$. Calcd. for $C_{13}H_{19}F_2O_3P$ (292): C, 53.42; H, 6.55%; found: C, 53.50; H, 6.60%.

Dibutyl 3,5-difluorobenzylphosphonate (5d): Semi solid, Yield 75%. ^{31}P NMR: δ 21.8; ^1H NMR: δ 6.89-6.73 (m, 3H, ArH), 3.99 (m, 4H, O$\underline{CH_2}CH_2CH_2CH_3$), 3.56 (d, J = 6.2 Hz, 2H,

PCH_2), 1.63 (m, 4H, $OCH_2\underline{CH_2}CH_2CH_3$), 1.35 (m, 4H, $OCH_2CH_2\underline{CH_2}CH_3$), 1.10 (t, 6H, $OCH_2CH_2CH_2\underline{CH_3}$); ^{13}C NMR: δ 164.3 (C-3, C-5), 136.1 (C-1), 112.5 (C-2, C-6), 102.4 (C-4), 79.1 (C-8, C-8′), 34.5 (C-7), 32.6 (C-9, C-9′), 19.7 (C-10, C-10′), 14.6 (C-11, C-11′); IR: 1230 (P=O), 1022 (P-O-C_{alip}), 724 (P-C_{alip}); LCMS *m/z* (%): 321 $[M+H]^+$. Calcd. for $C_{15}H_{23}F_2O_3P$ (320): C, 56.25; H, 7.24%; found: C, 56.31; H, 7.29%.

Methyl 3,5-difluorobenzyl(phenyl)phosphinate (5e): Semi solid, Yield 77%. ^{31}P NMR: δ 39.2; ^{1}H NMR: δ 7.48-6.63 (m, 8H, ArH), 3.84 (d, J = 6.4 Hz, 2H, PCH_2), 3.47 (s, 3H, $POCH_3$); ^{13}C NMR: δ 166.1 (C-3, C-5), 136.2 (C-9), 134.5 (C-1), 132.0 (C-11, C-11′), 129.1 (C-12), 128.5 (C-10, C-10′), 113.8 (C-2, C-6), 104.7 (C-4), 50.3 (C-8), 28.9 (C-7); IR: 1237 (P=O), 1029 (P-O-C_{alip}), 736 (P-C_{alip}); LCMS *m/z* (%): 283 (100) $[M+H]^+$. Calcd. for $C_{14}H_{13}F_2O_2P$ (282): C, 59.58; H, 4.64%; found: C, 59.52; H, 4.68%.).

Statistical analysis

Data of antimicrobial activity were expressed as means ± S.D. of three replicates. On the basis of the calculated value by using ANOVA method, it has been observed that the difference below 0.05 level (P<0.05) were considered as statistically significant.

CONCLUSION

In conclusion, we have synthesized a series of novel alkyl substituted aryl phosphonates/phosphinates by Michaelis-Arbuzov rearrangement at 40 °C with high yields by the reaction of an aryl halide with various trialkyl phosphites and dimethyl phenylphosphonite in the presence of inexpensive, economically affordable and ecofriendly catalyst, Bismuth(III)

chloride which has proved to be a superior catalyst in this reaction. The majority of the newly synthesized compounds exhibited good antibacterial and antifungal activity when compared to the standard drug.

ACKNOWLEDGMENT

The authors G. Madhava and S. K. Thaslim Basha acknowledge the University Grants Commission for the award of Senior Research Fellow (SRF). Also, the authors express their thanks to Hyderabad Central University and Osmania University for providing instrumentation facilities for recording the spectra.

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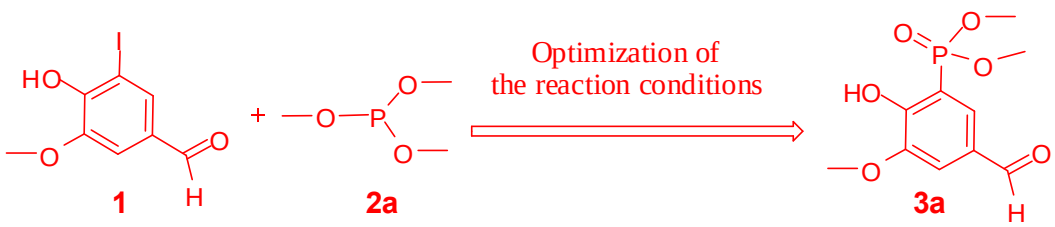
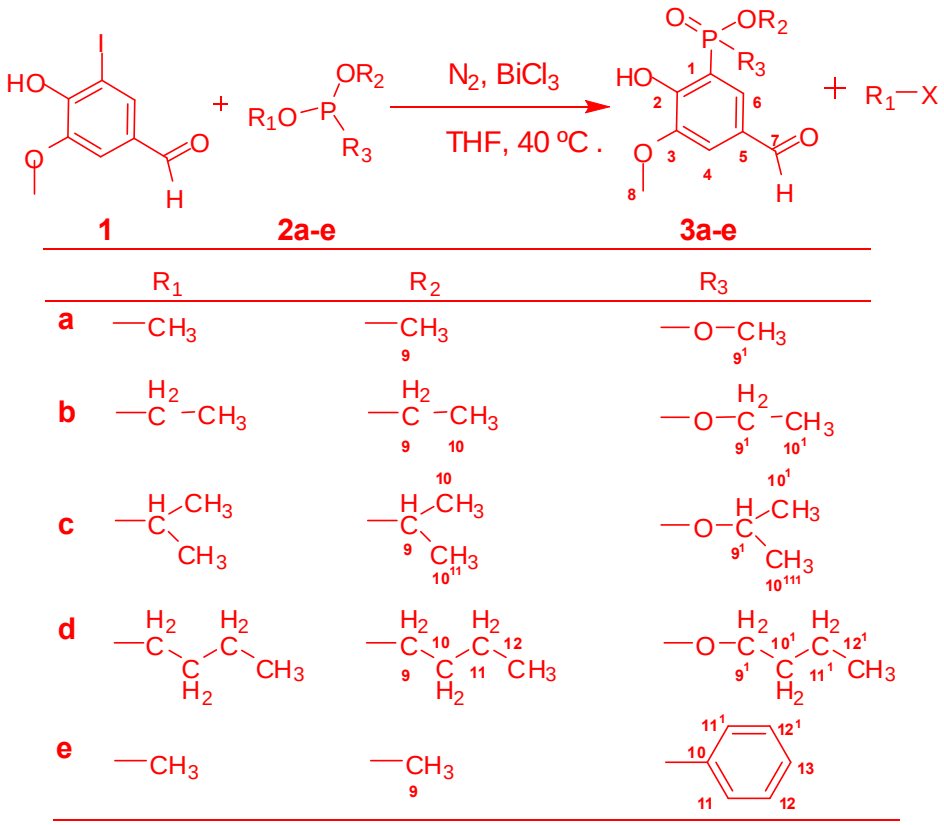
Table 1. Optimization of reaction conditions for the synthesis of **3a**[a]

Entry	Catalyst (mol%)	Solvent	Time	Temperature	Yield (%)[b]
1	No Catalyst	EtOH	24h	reflux	Trace
2	Et_3N	EtOH	24h	reflux	30
3	BF_3·Et_2O (10)	EtOH	6h	55	58
4	$CeCl_3$·$7H_2O$ (10)	EtOH	5h	50	56
5	$BiCl_3$ (10)	EtOH	5h	40	63
6	$BiCl_3$ (10)	Toluene	5h	40	62
7	$BiCl_3$ (10)	DCM	5h	40	63
8	$BiCl_3$ (10)	THF	4h	40	68
9	$BiCl_3$ (12.5)	THF	4h	40	69
10	$BiCl_3$ (15)	THF	4h	40	70
11	$BiCl_3$ (17.5)	THF	4h	40	72
12	$BiCl_3$ (20)	THF	4h	40	75
13	$BiCl_3$ (22.5)	THF	4h	40	75
14	$BiCl_3$ (25)	THF	4h	40	75

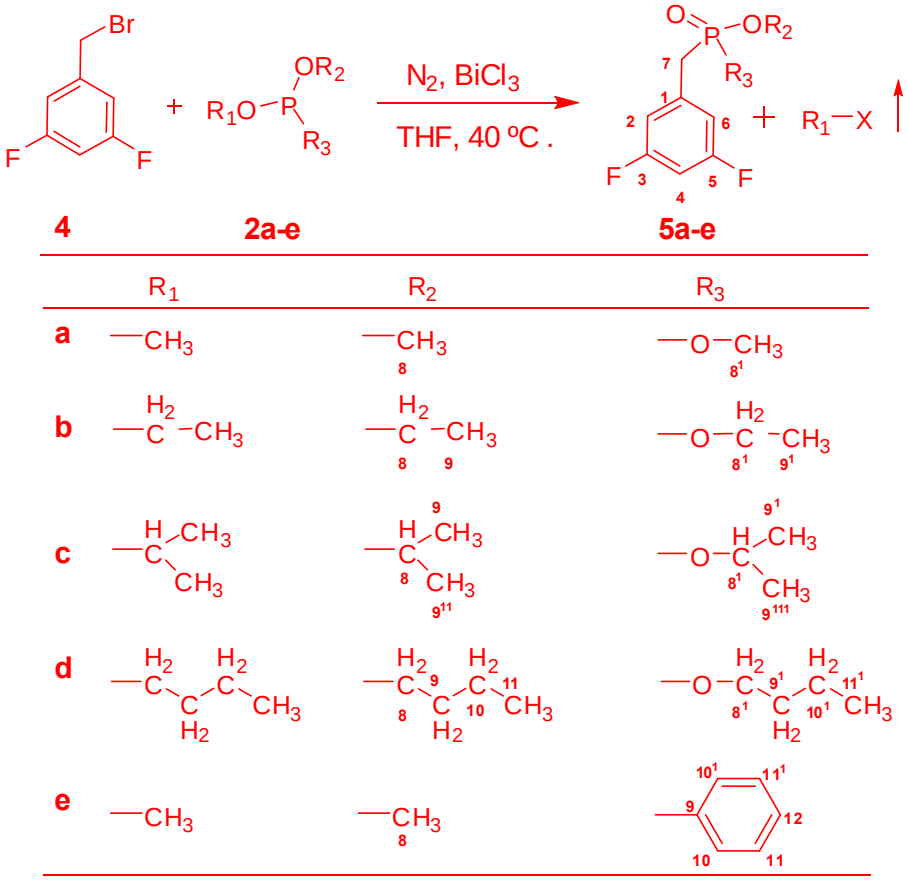
[a] The reaction was performed using 5-iodovanillin (1.2 mmol) and trimethyl phosphite (1.8 mmol); [b]Isolated yields.



Scheme 1: Model reaction for the optimization of the reaction conditions



Scheme 2: Synthesis of substituted 5-formyl-2-hydroxy-3-methoxyphenylphosphonates (**3a-d**)/phosphinate (**3e**)



Scheme 3: Synthesis of substituted 3,5-difluorobenzylphosphonates (**5a-d**)/phosphinate (**5e**).