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Highly efficient one-pot multi-component synthesis of α-aminophosphonates and bis-α-aminophosphonates catalyzed by heterogeneous reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) at ambient temperature and their antitubercular evaluation against *Mycobactrium Tuberculosis*†

Shafeek A. R. Mulla,*[a] Mohsinkhan Y. Pathan,[a] Santosh S. Chavan,[a] Suwara P. Gample[b] and Dhiman Sarkar[b]

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A highly efficient one-pot multi-component reaction (MCR) protocol over DTP/SiO_2 has been developed for the synthesis of α-aminophosphonate derivatives (**4a–x**) in excellent yields. The α-aminophosphonate derivatives were for the first time evaluated for their antitubercular activity against the *M. tuberculosis* H37Ra (MTB) strain. An evaluation of the data on the cytotoxicity and antimicrobial activity shows that **4n** and **4v** are promising antitubercular agents.

Introduction

The synthesis of α-aminophosphonates has become the center of interest among world researchers due to their wide spectrum of biological and/or medicinal activities and structural analogy to natural α-amino acids and α-aminophosphoric acids. They have achieved a significant importance as a key moieties having wide applications not only in agriculture but also in biological/medicinal chemistry, as anti-cancer agents,[1a–c] inhibitors of synthase,[1d] HIV protease,[1e] antibiotics,[1f] enzyme inhibitors,[1g] anti-thrombotic agents,[1h] cytotoxicity,[1c] antibacterial activity,[1i] antifungal activity,[1j] antiproliferative activity,[1j] inhibitors of protein tyrosine phosphatases,[1k] herbicides, fungicides,[1l] insecticides,[1m] plant growth regulators,[1n] and as substrates in the synthesis of phosphonopeptides. Owing to the potential importance of α-aminophosphonate derivatives as a key moieties in life sciences, pharmaceuticals, agriculture, world-wide efforts have made in the last few decades by researchers and various protocols have been developed for their synthesis using various catalysts such as $SnCl_4$,[2] $SnCl_2$,[3] $ZnCl_2$,[4] $BF_3 \cdot OEt_2$,[5] $InCl_3$,[6] $Mg(ClO_4)_2$,[7] $M(OTf)_3$,[8] $AlCl_3$,[9] CF_3CO_2H,[10] Montmorillonite Clay-MW,[11] TiO_2,[12] scandium (tris-dodecyl sulfate),[13] I_2,[14] Nano Fe_3O_4,[15] EAN,[16] H-beta zeolite,[17] Nano ZnO,[18] AIKIT-5,[19] $ZrOCl_2 \cdot 8H_2O$,[20] $SbCl_3/Al_2O_3$,[21] and Amberlyst-15,[22] which have been reported in the literature. The acid[2–10,20] catalyzed synthesis of α-aminophosphonates by the nucleophilic addition reaction of phosphite to amines is convenient and the most preferred method, however, its practical approach is limited since the water formed during the course of the reaction either deactivates or decomposes the acid catalyst. Even though significant improvements and/or developments using either homogeneous or heterogeneous catalysts have been achieved, almost all of the methods reported so far lack general applicability and commercial scale implementation, and suffer from one or more limitations such as the use of excess or stoichiometric quantity, moisture sensitive, toxic, corrosive, expensive catalysts, which are non-recoverable and/or recoverable with tedious separation procedures involving lots of toxic waste generation besides a long reaction time, high temperature and low yield for the desired product.

As α-aminophosphonate derivatives are the key constituent and structural backbone of many pharmaceutical and agricultural compounds, the development of more general and cost effective, one-pot multi-component protocols for their synthesis under much milder, more efficient, environment friendly conditions using recyclable, eco friendly catalysts is still a possibility to explore. As part of our continuous efforts to develop a green, ecofriendly, general and cost effective protocol for the organic transformation using DTP/SiO_2[23a] and recyclable catalysts,[23b–f] we report herein a highly efficient, cost effective,

[a]*Chemical Engineering & Process Development Division, National Chemical Laboratory, Dr Homi Bhabha Road, Pune-411008, Maharashtra, India. E-mail: sa.mulla@ncl.res.in; Fax: +91-20-25902676; Tel: +91-20-25902316*

[b]*Combi. Chem. Bio. Resource Center, Organic Chemistry Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India*

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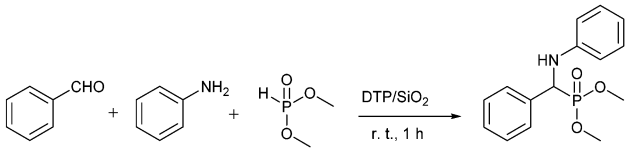
general, and much milder one-pot multi-component protocol for the synthesis of α-aminophosphonate and bis-α-aminophosphonate derivatives in excellent yields *via* a one-pot three component condensation of various aldehydes, amines and di or tri alkyl phosphites using a heterogeneous reusable silica supported dodecatungstophosphoric acid catalyst at ambient temperature in a short reaction time (Scheme 1).

TB is a chronic infectious disease[24] and a serious threat to the public health worldwide. The world health organization (WHO) declared[25] TB as an international public health crisis and appealed to develop the anti-TB drug or vaccine, which could be licensed by 2020. Even though α-aminophosphonate derivatives, which are constituents of various potent drugs,[1a–k] and their bioevaluation for anticancer activity are well reported,[1a–c] surprisingly its antitubercular (TB) activity has not been reported so far. Therefore, herein we report for the first time the preliminary results on the antitubercular activity of α-aminophosphonate derivatives against the *Mycobactrium Tuberculosis* H37Ra (MTB) strain.

To develop a one-pot multi-component protocol for synthesis of α-aminophosphonate derivatives, benzaldehyde (10 mmol), aniline (10 mmol), and dimethylphosphite (10 mmol), catalyzed by 50 mg (0.35 mol%) 20% DTP/SiO_2 catalyst in a 5 ml solvent at ambient temperature for 1 h was selected as a model reaction to optimize the reaction conditions. Initially, the screening of different solvents such as methanol, ethanol, dichloromethane, acetonitrile, dimethylformamide and water were performed. However, the acetonitrile solvent gives the desired α-aminophosphonate product in a 98% yield (Table 1, entry 4) whereas methanol, ethanol and dichloromethane give 74%, 78%, and 40% yields, respectively (Table 1, entries 1–3). The formation of the desired product was not observed using dimethylformamide or water as the solvent (Table 1, entry 5, 6) and also in the absence of catalyst in an acetonitrile solvent (Table 1, entry 7). The promising results using acetonitrile as a solvent over a DTP/SiO_2 catalyst allowed us to further optimize the DTP loading and catalyst loading, and the results in Table 1 (entry 8–11) reveal that the catalyst with 20% DTP loading and 50 mg catalyst shows excellent catalytic activity (Table 1, entry 4).

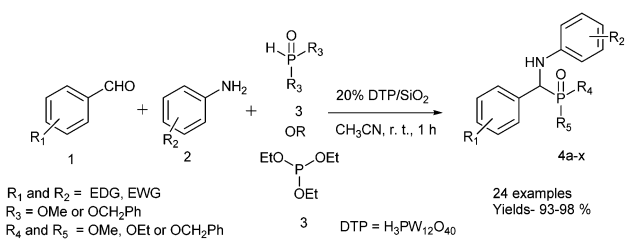
The excellent yield, using 20% DTP/SiO_2 in an acetonitrile solvent, motivated us to investigate the scope of the one-pot multi-component protocol for the synthesis of the α-aminophosphonate and bis-α-aminophosphonate derivatives from various substituted aldehydes, amines and di or tri alkyl phosphites in the presence of a DTP/SiO_2 catalyst at optimized reaction conditions. To establish the general applicability, a variety of substituted aldehydes, substituted amines and di/tri alkyl phosphites were subjected for a three-component condensation (Kabachnik-Fields) reaction. Interestingly, a wide range of aryl/heteroaromatics aldehydes. and amines possessing various electron donating and electron withdrawing functional groups reacted smoothly with di or tri alkyl phosphites over a DTP/SiO_2 catalyst at ambient temperature for 1 h to give the desired products in excellent yields (Table 2, entries **4a–x**). The aromatic/heteroaromatics aldehydes such as benzaldehyde, 4-methoxy benzaldehyde, 4-chloro benzaldehyde, 4-methyl benzaldehyde, 2,5-dimethoxy benzaldehyde and furfural reacted well with aniline/3-chloroaniline/2,4,6-trimethylaniline/1-naphthylamine/4-nitroaniline/4-methoxyaniline and dimethylphosphite to produce the corresponding α-aminophosphate in excellent yields (Table 2, entries **4a–o**). To further elaborate the scope of a one-pot multi-component protocol over a DTP/SiO_2 catalyst, the substituted aromatic amines such as aniline, 3-chroloaniline and 1-naphthylamine reacted smoothly with benzaldehyde/3,4,5-trimethoxybenzaldehyde/4-chloro benzaldehyde/4-methylbenzaldehyde/4-methoxy benzaldehyde, and dibenzylphosphite/triethylphosphite to obtain the corresponding α-aminophosphonate in an excellent yield (Table 2, entries **4p–u**). The excellent performance of the DTP/SiO_2 catalyst for the synthesis of α-aminophosphonate derivatives from the various combinations of aryl/heteroaromatics aldehydes/substituted aldehydes, amines/substituted amines and di or tri alkyl phosphites made us excited to investigate the dimer formation of α-aminophosphonates. Amazingly, benzaldehyde/4-methoxyaldehyde (20 mmol) reacted very well with dimethyl phosphite/triethylphosphite (20 mmol) and 4-amino aniline

Table 1 Optimizations of the reaction conditions for the synthesis of α-aminophosphonate[a]



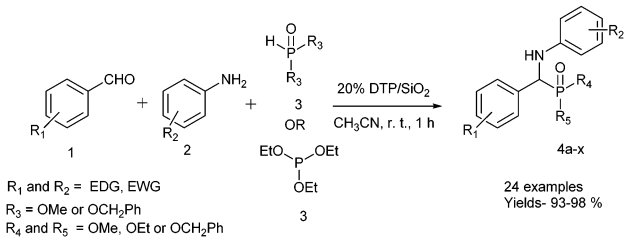
Entry	Solvent	Catalyst	Yield[b] (%)
1	Methanol	DTP/SiO_2	74
2	Ethanol	DTP/SiO_2	78
3	Dichloromethane	DTP/SiO_2	40
4	Acetonitrile	DTP/SiO_2	98
5	Dimethylformamide	DTP/SiO_2	N.R.
6	Water	DTP/SiO_2	N.R.
7	Acetonitrile	—	N.R.
8	Acetonitrile	DTP/SiO_2 (25 mg)	84
9	Acetonitrile	DTP/SiO_2 (100 mg)	98
10[c]	Acetonitrile	10% DTP/SiO_2	76
11[d]	Acetonitrile	30% DTP/SiO_2	98

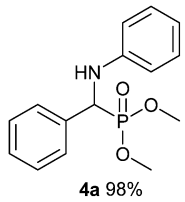
[a] Reaction conditions: benzaldehyde (10 mmol), aniline (10 mmol), dimethylphosphite (10 mmol), catalyst 20% DTP/SiO_2: 25–100 mg (0.18–0.7 mol% of DTP) in 5 ml solvent, room temperature 1 h. [b] Isolated yields after column chromatography. [c] 50 mg = 0.17 mol%. [d] 50 mg = 0.52 mol%.

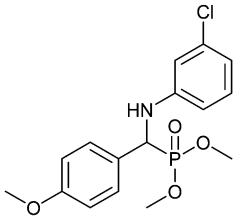


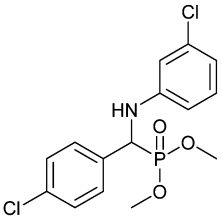
Scheme 1 The synthesis of α-aminophosphonate derivatives *via* a one-pot three-component condensation reaction.

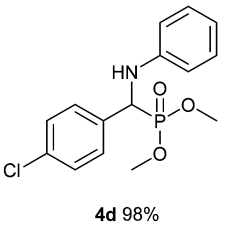
Table 2 The substrate scope for the one-pot three-component condensation reaction for the synthesis of α-aminophosphonate derivatives[a,b]

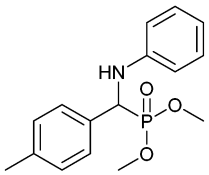


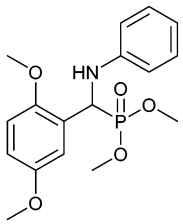

4a 98%

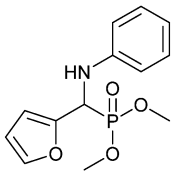

4b 98%
12.8[e]

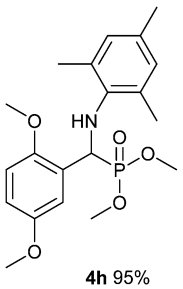

4c 97%
8.7[e]

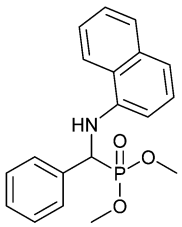

4d 98%

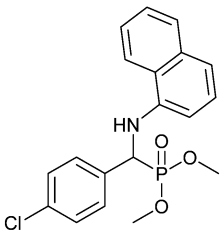

4e 98%

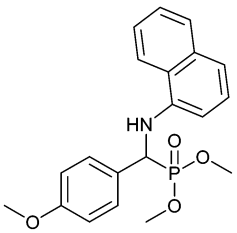

4f 97%

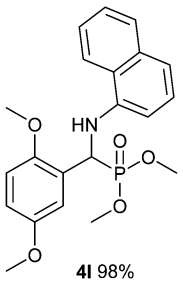

4g 97%

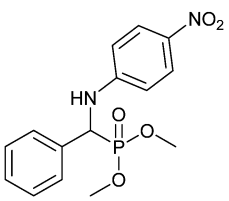

4h 95%

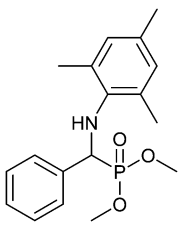

4i 98%

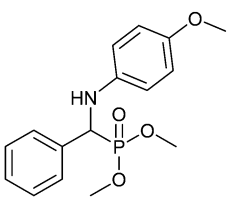

4j 97%


4k 98%


4l 98%


4m 95%


4n 97%
8.62[d]


4o 98%

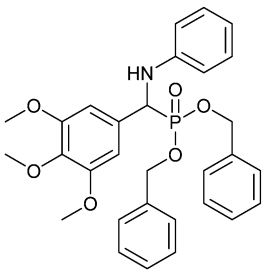
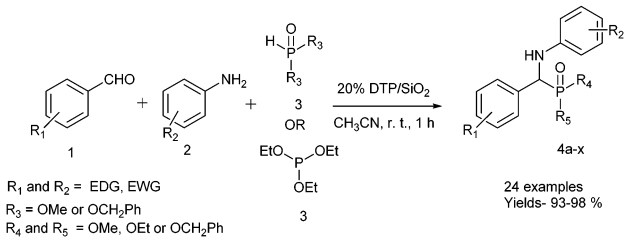
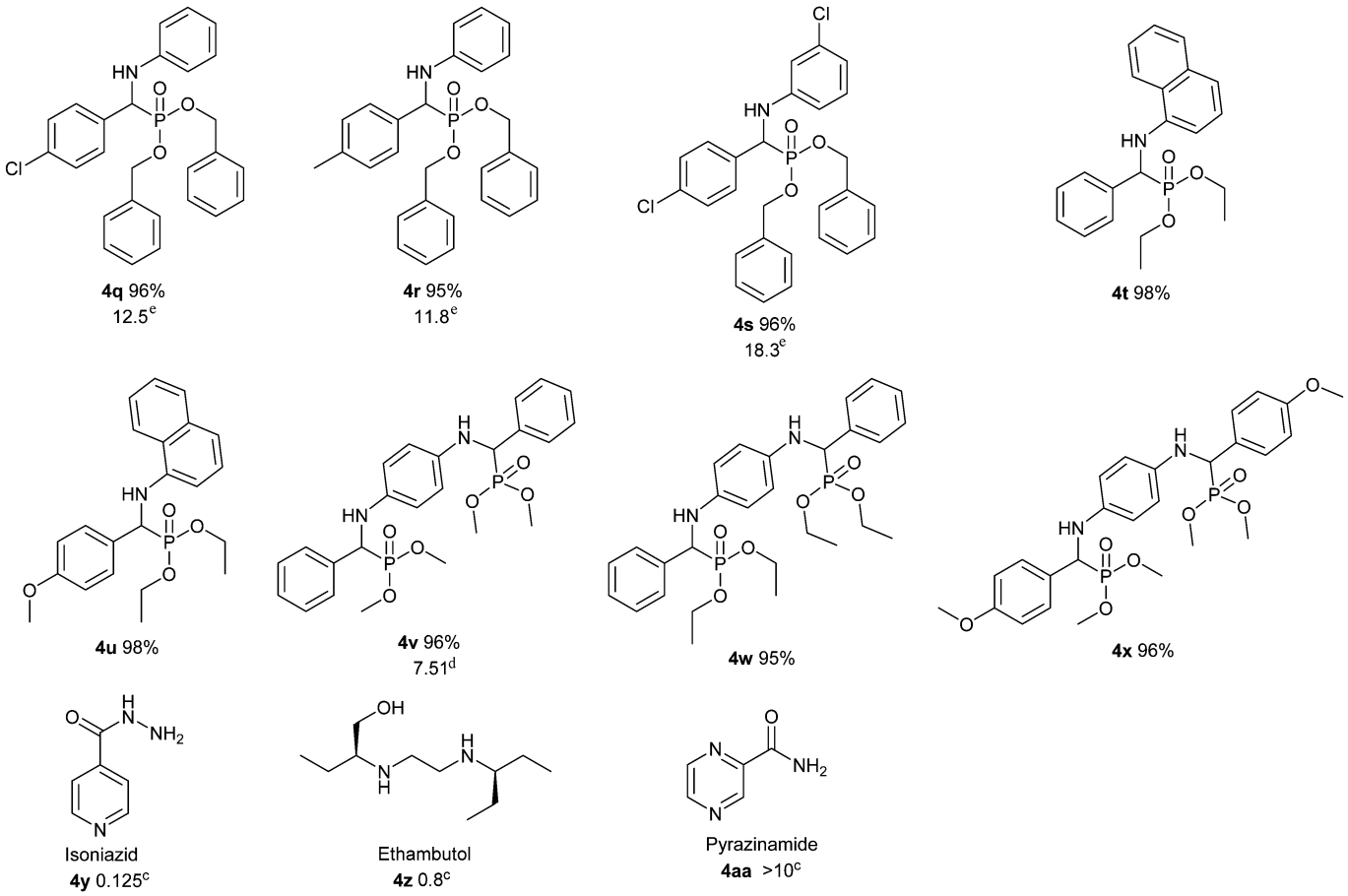

4p 93%
19[e]

Table 2 (*Contd.*)



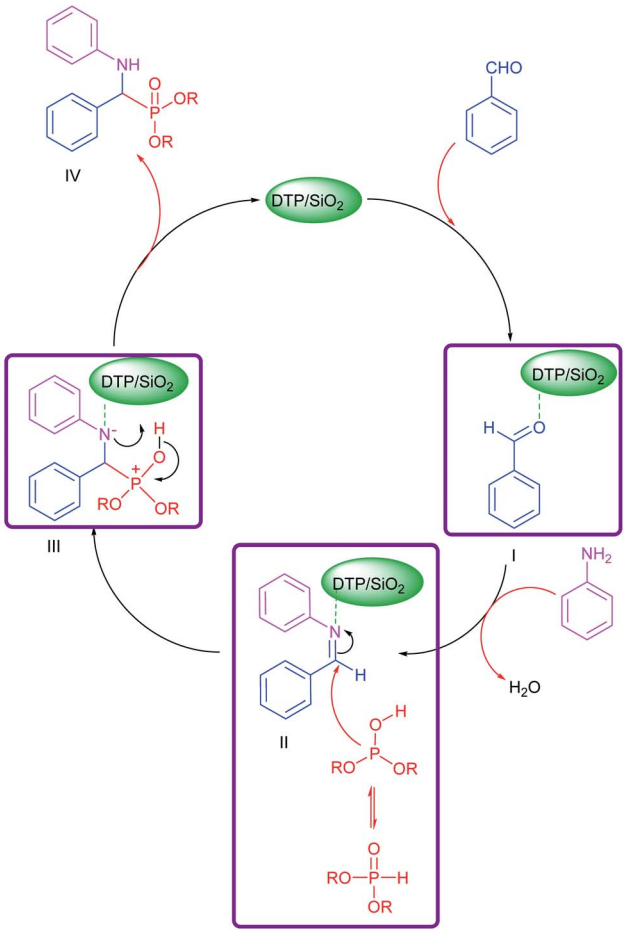


[a] Reaction conditions: aldehyde (10 mmol), amine (10 mmol), phosphite (10 mmol), DTP/SiO_2 (50 mg) in 5 ml CH_3CN, room temperature 1 h. [b] Isolated yields after column chromatography. [c] IC_{90} for stander drugs. [d] IC_{50} against M. tuberculosis H37Ra for antitubercular activity. [e] IC_{50} against THP 1 cell line for cytotoxicity.

(10 mmol) to provide the corresponding bis-α-aminophosphonate as a dimer in a high yield (Table 2 entries **4v–x**). The results in Table 2 clearly reveal that the one-pot three-component condensation reactions over the DTP/SiO_2 catalyst show a remarkable and excellent performance irrespective to the presence of an electron donating/electron withdrawing groups on the aromatic/heterocyclic aldehydes and/or amines and hence the one-pot three-component protocol is highly effective, promising, and general for the synthesis of α-aminophosphonate and bis-α-aminophosphonate derivatives.

As per earlier literature,[5,23a–c] a probable mechanism is shown in Scheme 2 for the synthesis of α-aminophosphonate. The mechanism involves the activation of the carbonyl group of aldehyde by DTP/SiO_2 (I) followed by the nucleophilic addition of amine to afford the imine (II) by the removal of water. The subsequent activation of imine (II) by DTP/SiO_2 facilitated the addition of phosphite to give an activated phosphonium intermediate (III), which then gave the desired product IV (Scheme 2).

The recyclability and recovery of the DTP/SiO_2 catalyst was investigated for the synthesis of α-aminophosphonates by a one-pot three-component condensation of benzaldehyde and aniline with dimethyl phosphite as a model substrate in an acetonitrile solvent at room temperature for 1 h, and the results are provided in Table 3. The DTP/SiO_2 catalyst was recovered quantitatively from reaction mixture by filtration and reused several times without the loss of catalytic activity (Table 3,



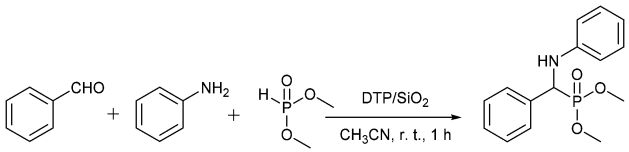
Scheme 2 A possible mechanism for the synthesis of α-aminophosphonates over a DTP/SiO_2 catalyst.

entries 2–6). The isolated yield obtained for the product at the end of the 5th recycle (Table 3, entry 6) is very much consistent with the fresh DTP/SiO_2 catalyst (Table 3, entry 1). The consistent catalytic activity of the recovered and reused DTP/SiO_2 catalyst indicates that the reused catalyst shows an excellent performance for the synthesis of α-aminophosphonates.

All of the synthesized α-aminophosphonate and bis-α-aminophosphonate derivatives (**4a–x**) were screened using 100 μg ml^{-1} concentrations for their *in vitro* antitubercular activity against the *M. tuberculosis* H37Ra (ATCC 25177) strain by XTT reduction menadione assay. As shown in Fig. 1, the **4e**, **4f**, **4g**, **4i**, **4j**, **4n**, **4o** and **4v** α-aminophosphonate derivatives exhibited inhibition. However, only the **4n** and **4v** derivatives exhibited more than 90% inhibition, and they were further screened using various concentrations for their *in vitro* antitubercular activity to achieve IC_{50} which is compared with standard drugs such as isoniazid, ethambutol and pyrazinamide (Table 2, entry **4y–aa**).

The **4n** and **4v** α-aminophosphonate derivatives exhibited half maximal concentration (IC_{50}) values of 8.62 and 7.51 μg ml^{-1} (Table 2 entry **4n** and **4v**), respectively, which indicate that the compounds are promising antitubercular agents. These findings inspired us to evaluate their cytotoxicity. Hence, all of

Table 3 The recyclability of DTP/SiO_2[a]



Cycles	Yield[b] (%)
1	98
2	98
3	97
4	98
5	96
6	97

[a] *Reaction conditions*: Benzaldehyde (10 mmol), aniline (10 mmol), dimethylphosphite (10 mmol), 20% DTP/SiO_2 in 5 ml CH_3CN, room temp. 1 h. [b] Isolated yields after column chromatography.

the α-aminophosphonate derivatives (**4a–x**) were evaluated for their cytotoxicity using a THP 1 (Human acute monocytic leukemia cell line) *in vitro* MTT assay. Surprisingly, the **4n** and **4v** compounds were found to be non active towards cytotoxicity. However, a few compounds, **4b**, **4c**, **4p**, **4q**, **4r** and **4s** (Table 2), showed a good cytotoxicity.

The selectiveness of the **4n** and **4v** compounds towards antitubercular activity made us enthusiastic to evaluate these compounds for their antimicrobial activity. **4n** and **4v** were evaluated for their antimicrobial activity against gram-negative (*Escherichia coli*) and gram-positive (*Staphylococcus aureus* and *Bacillus*) bacteria (Table 4). Miraculously, **4n** and **4v** show no antibacterial activity towards gram-negative and gram-positive bacteria. The evaluation data on cytotoxicity using the THP 1 (Human acute monocytic leukemia) cell line (Table 2), antimicrobial activity against gram-positive and gram-negative

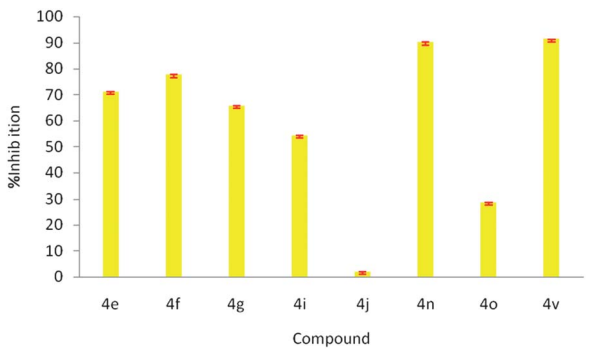


Fig. 1 The analysis of the antitubercular activity of compounds using an XTT Reduction menadione assay. 100 μg ml^{-1} of the compounds were added to 2 M tuberculosis culture at 0 days after inoculation. The cell growth was estimated by monitoring the extent of the XTT reduction after 8 days of incubation with respect to the DMSO vehicle control and media as a blank. The percent inhibition of the compounds is as shown in a graph. Further details are provided in the ESI.† The results are the average of three identical experiments ± the standard deviation.

Table 4 The antibacterial screening of **4n** and **4v** against gram-positive and gram-negative bacteria

Compounds	Concentration ($\mu g\ ml^{-1}$)	% Inhibition		
		E. coli	*S. aureus*	*Bacillus*
4n	100	0.8	35	87.3
4v	100	10.1	−10.3	2.5

bacteria (Table 4) clearly shows that **4n** and **4v** are highly selective towards antitubercular activity against the *M. tuberculosis* H37Ra (MTB) strain and were found to be promising antitubercular agents for further drug discoveries.

Conclusions

In conclusion, a novel, environment friendly, highly efficient, cost effective, one-pot multi-component protocol has been developed for the efficient synthesis of α-aminophosphonate derivatives in excellent yields *via* a one-pot three-component condensation of various substituted aldehydes, substituted amines and di or tri alkyl phosphites using an ecofriendly, heterogeneous, reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) catalyst at ambient temperature in a short reaction time. The one-pot multi-component condensation reactions (MCR) over the DTP/SiO_2 catalyst show a remarkable and excellent performance irrespective of the presence of electron donating/electron withdrawing groups on the aromatic/heterocyclic aldehydes and/or amines and hence the one-pot three-component protocol is highly effective, promising and general for the synthesis of α-aminophosphonate and bis-α-aminophosphonate derivatives.

The catalyst was recycled several times without the loss of catalytic activity. These α-aminophosphonate derivatives were evaluated for the first time for the antitubercular activity against the *M. tuberculosis* H37Ra (MTB) strain by using an XTT reduction menadione assay (XRMA) protocol. However, the **4n** and **4v** α-aminophosphonate derivatives exhibited half maximal concentration (IC_{50}) values of 8.62 and 7.51 $\mu g\ ml^{-1}$ (Table 2 entry **4n** and **4v**), respectively. An evaluation of the data on the cytotoxicity and antimicrobial activity shows that **4n** and **4v** are highly selective towards antitubercular activity against the *M. tuberculosis* H37Ra (MTB) strain and were found to be promising antitubercular agents for further drug discoveries.

Experimental section

All chemicals and reagents were procured from Sigma Aldrich, S.D. Fine chemical and commercial suppliers and used without further purification. The products were characterized using ^1H NMR, ^{13}C NMR spectra. The NMR spectra of the product were obtained using a Bruker AC-200 MHz spectrometer with TMS as the internal standard. Column chromatography was performed on silica gel, Merck grade 60–120 mesh size. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F_{254}).

General experimental procedure for the 20% DTP/SiO_2 mediated synthesis of α-aminophosphonates

The reaction mixture of aldehyde (10 mmol), amine (10 mmol) and di/tri alkyl phosphite (10 mmol) was stirred in a 10 ml round bottom flask containing 5 ml acetonitrile solvent in the presence of 50 mg DTP/SiO_2 catalyst at room temperature for 1 h. The completion of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (10 ml) and the catalyst was recovered by filtration. The filtrate was washed with aqueous $NaHCO_3$ and then with water followed by the separation of an aqueous layer and organic layer. The organic layer is dried over anhydrous Na_2SO_4 and concentrated in a vacuum to give the crude product. The crude product was purified by silica gel column chromatography using a 70 : 30 ratio of pet ether : ethyl acetate to afford the pure α-amino phosphonate. The products obtained were characterized by NMR.

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