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Original article

$CeCl_3{\cdot}7H_2O$-SiO_2: Catalyst promoted microwave assisted neat synthesis, antifungal and antioxidant activities of α-diaminophosphonates

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ABSTRACT

$CeCl_3{\cdot}7H_2O$ supported on silica ($CeCl_3{\cdot}7H_2O$-SiO_2) is used as a heterogeneous, efficient and recyclable catalyst for a three component one-pot reaction of an amine, aldehydes and diethyl phosphite to synthesize α-diaminophosphonate derivatives under microwave irradiation exploiting neat reaction conditions. Ten α-diaminophosphonates (**6a–j**) of 4,4′-sulfonyldianiline (Dapsone) (**3**) were synthesized and structural elucidation was confirmed by spectral data. Antifungal and antioxidant activities were evaluated include minimum inhibitory concentrations and IC_{50} values, respectively of the titled compounds. Compounds **6h**, **6i** exhibited promising antioxidant activity at lower IC_{50} values 53.7 μg/mL, 53.2 μg/mL, respectively as compared with standard IC_{50} value 51.6 μg/mL.
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1. Introduction

α-Aminophosphonates are important biologically active compounds and structural analogs of natural amino acids [1], and have received wide attention in medicinal, bioorganic, and agricultural chemistry. Many of these derivatives have applications as antibiotics [2], herbicides [3], fungicides, plant growth regulators [4], anti-thrombotic agents [5], peptidases and proteinases [6], and enzyme inhibitors [7]. They can also suppress the growth of various tumors and viruses [8]. Moreover, some aminophosphonic acids inhibit bone resorption, delay the progression of bone metastases, exert direct cytostatic effects on a variety of human tumor cells and have found clinical applications in the treatment of bone disorders and cancer [9]. The inert nature of the C–P bond in α-aminophosphonates as well as physical and structural similarity of phosphonic acid and phosphinic acid (see Fig. 1) to the biologically important phosphate ester and carboxylic acid functionalities attributed a great deal of these activities [10].

In the last few decades, research has been made for the development of new methodologies for their synthesis due to outstanding biological importance of α-aminophosphonate derivatives. The traditional Lewis acid-catalyzed addition of diethyl phosphite to aldimines has provided a useful method for preparation of α-aminophosphonates [11]. However, these reactions cannot proceed smoothly due to formation of water during one-pot three component reactions. Recently, some new Lewis acid catalysts were reported as effective catalysts for one-pot reactions [12–23]. It is clear that some synthetic transformations are more difficult using conventional conditions and may require long reaction time and low yield. Moreover, it is necessary to prevent waste generation by avoiding the use of auxiliary substances such as solvents and additional reagents and minimizing the energy requirement in synthetic pathways/processes. There has been increasing influence of green approaches in both medicinal chemistry and research based chemistry organizations. Recently, chemical transformations involving eco-friendly reagents such as solid supported catalysts and those assisted by microwaves under solvent-free conditions have gained popularity because these methods are not only valuable for ecological and economic reasons but also simplicity of procedure and high yield. Further, lanthanide halides, particularly Ce(III) salts, are of great research interest due to their low toxicity, ease of handling, low cost, stability in air and water and recoverability. In silica supported inorganic catalysts, SiO_2 was originally introduced as only a support in the beginning. Then, kinetic studies revealed that it not only acts as a carrier to increase the surface area but also enhances the rate of reaction.

By considering all these advantages, we developed a simple three component one-pot procedure under microwave assisted neat reaction conditions for the synthesis of α-diaminophosphonates **6a–j** of Dapsone using silica supported $CeCl_3{\cdot}7H_2O$ and screened for their antifungal and antioxidant activities.

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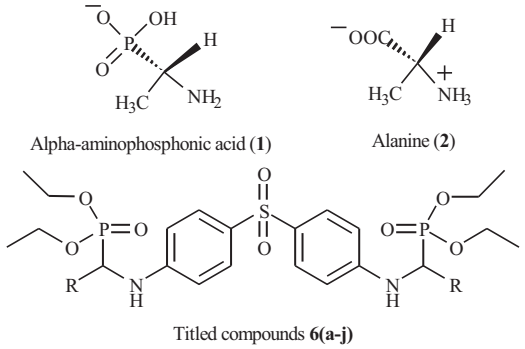


Fig. 1. Biological active phosphorus compounds.

2. Experimental

2.1. General procedure

2.1.1. Conventional method

Dapsone (**3**) (1 mmol, 248 mg), 3-nitrobenzaldehyde (**4c**) (1.1 mmol, 167 mg), diethylphosphite (**5**) and the catalyst, $CeCl_3{\cdot}7H_2O$-SiO_2 (12 mol%), were placed into a 50 mL flat-bottomed flask. The reaction mixture was stirred vigorously at 80 °C. The progress of the reaction was monitored by TLC in 30 min of intervals. After completion of the reaction, dichloromethane (DCM, 15 mL) was added to the reaction mixture and filtered-off to recover the catalyst and washed with DCM (2 × 10 mL) to remove strains on the catalyst. The combined organic layer was concentrated under reduced pressure and pure product **6c** was obtained using column chromatography eluting with ethylacetate:hexane in a ratio of 4:6. The catalyst was dried and reused for future reactions.

2.1.2. Microwave conditions

The mixture of Dapsone (**3**) (1 mmol, 248 mg), 3-nitrobenzaldehyde (**4c**) (1.1 mmol, 167 mg), diethylphosphite (**5**) and the catalyst, $CeCl_3{\cdot}7H_2O$-SiO_2 (12 mol%) was placed into a 50 mL flat-bottomed flask. The reaction mixture was irradiated under microwave radiations using catalyst systems (CATA-4R), % power is 65% and 465 W. After completion of the reaction (monitored by TLC), DCM (15 mL) was added to the reaction mixture. The catalyst was filtered and washed with DCM (5 mL) to recover it. The combined filtrates and washings were concentrated under reduced pressure, followed by purification on column chromatography using ethylacetate:*n*-hexane in the ratio of 4:6 as an eluent to afford pure tetraethyl[4,4′-sulfonylbis(4,1-phenylene)bis(azanediyl)]bis[(3-nitrophenyl)methylene]diphosphonate (**6c**). The filtered residue catalyst was dried under vacuum and reused for the next reaction. This same procedure was adopted for preparing the remaining title products.

2.1.3. Tetraethyl[4,4′-sulfonylbis(4,1-phenylene)bis(azanediyl)]bis[(3-nitrophenyl)methylene]diphosphonate (**6c**)

Pale orange solid, yield 96%, mp 140–142 °C; IR (KBr, cm^{-1}): ν_{max} 3282 (–N–H, str), 2983 (–C–H, str), 1595 (Ar–C–C–, str), 1352 (–NO_2, str), 1300 (–SO_2, str), 1284 (C–N, str), 1238 (–P=O, str), 1022 (P–C–O–, str); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, 6H, J = 5.6 Hz, –O–CH_2–C$\underline{H_3}$), 1.13 (t, 6H, J = 5.6 Hz, –O–CH_2–C$\underline{H_3}$), 3.79–3.84 (m, 2H, –O–C$\underline{H_2}$–CH_3), 3.93–3.96 (m, 2H, –O–C$\underline{H_2}$–CH_3), 4.02–4.07 (m, 4H, –O–C$\underline{H_2}$–CH_3), 5.47 (dd, 2H, J = 7.6, 12.4 Hz, –P–CH–NH), 6.88 (d, 2H, J = 8.0 Hz, –CH–NH), 7.44–7.46 (d, 4H, J = 8.0 Hz, Ar–H), 7.47–7.94 (m, 8H, Ar–H), 8.11 (d, 4H, J = 7.0 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1 (C_8, C_{13}), 148.1 ($C_3{}^1$, $C_3{}^{11}$), 139.4 ($C_1{}^1$, $C_1{}^{11}$), 135.1 ($C_6{}^1$, $C_6{}^{11}$), 130.2 (C_1, C_3), 129.9 ($C_5{}^1$, $C_5{}^{11}$), 128.7 (C_6, C_{10}, C_{11}, C_{15}), 123.3 ($C_2{}^1$, $C_2{}^{11}$), 123.0 ($C_4{}^1$, $C_4{}^{11}$), 113.2 (C_7, C_9, C_{12}, C_{14}), 62.9 (C_{25}, C_{28}, C_{31}, C_{34}), 53.6 (C_{18}, C_{19}), 16.4 (C_{26}, C_{29}, C_{32}, C_{35}); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.9; MS (+ mode) (m/z): 791 ($M+H^+$).

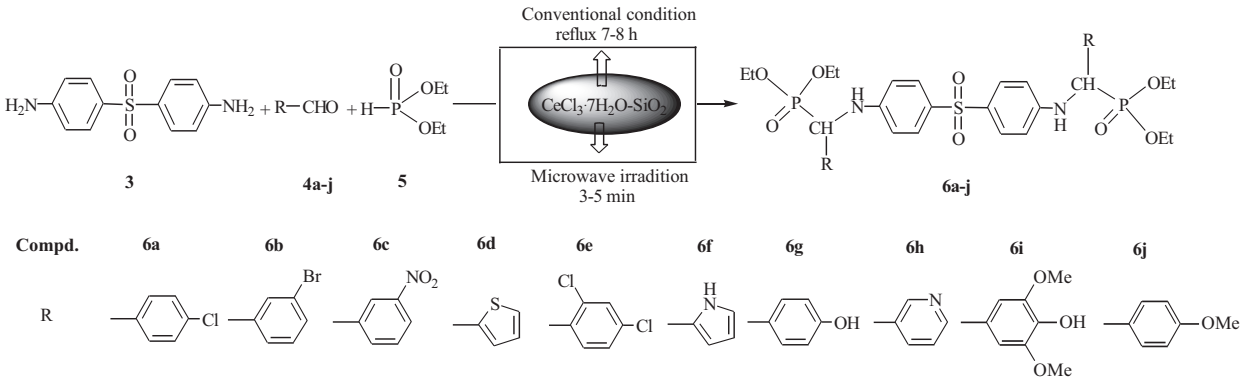
2.2. Recycling of $CeCl_3{\cdot}7H_2O$-SiO_2 catalyst

The catalyst is inserted residue obtained ($CeCl_3{\cdot}7H_2O$-SiO_2) by filtration of reaction mixture was washed with 10 mL of DCM two or three times to remove the strains and tars, then dried in an oven at 90 °C for 2 h. The catalyst was reused up to five cycles with slight decrease of catalytic activity.

3. Results and discussion

Herein, we report a three component reaction of diamine (Dapsone) (**3**) substituted aryl/heteroaryl aldehydes (**4a–j**) and diethylphosphite (**5**), which led to the formation of tetraethyl[4,4′-sulfonylbis(4,1-phenylene)bis(azanediyl)]bis[(substituted aryl/heteroaryl)methylene]diphosphonates (**6a–j**) using heterogeneous solid support catalyst, $CeCl_3{\cdot}7H_2O$-SiO_2 under solvent-free conditions in conventional and microwave irradiation methods as depicted in Scheme 1.

To optimize the experimental conditions, the reaction of 4,4′-sulfonyldianiline (**3**), 3-nitrobenzaldehyde (**4c**) and diethyl phosphite (**5**) was considered as a model reaction. The progress of the reactions was investigated without catalyst and with different catalysts in EtOH under conventional conditions (Table 1, entries 1–8). Overall, $CeCl_3{\cdot}7H_2O$-SiO_2 (10 mol%) achieved the best results (Table 1, entry 8) to synthesize **6c** when compared to other catalysts. Further, $CeCl_3{\cdot}7H_2O$-SiO_2 was investigated in different solvents like THF, Toluene, CH_3CN (Table 1, entries 9–11) besides solvent-free conditions by keeping the temperature at 80 °C



Scheme 1. Synthesis of α-diaminophosphonates (**6a-j**) in the presence of $CeCl_3{\cdot}7H_2O$-SiO_2.

Table 1
Effect of the different catalysts on Kabachnik–Fields reaction for the synthesis of compound **6c**.

Entry	Catalyst (mol%)	Solvent	Time	Yield (%)	Entry	Catalyst (mol%)	Solvent	Time	Yield (%)
1	No catalyst	EtOH[a]	24 h	Trace	12	$FeCl_3$ (10)	Neat[a] (80 °C)	8 h	73
2	Et_3N	EtOH[a]	24 h	30	13	$FeCl_3$ (10)	Neat[b]	7 min	81
3	$FeCl_3$ (10)	EtOH[a]	18 h	67	14	$AlCl_3$ (10)	Neat[a] (80 °C)	8 h	70
4	$AlCl_3$ (10)	EtOH[a]	18 h	65	15	$AlCl_3$ (10)	Neat[b]	7 min	80
5	$CuCl_2$ (10)	EtOH[a]	16 h	68	16	$CuCl_2$ (10)	Neat[a] (80 °C)	8 h	72
6	$ZnCl_2$ (10)	EtOH[a]	18 h	68	17	$CuCl_2$ (10)	Neat[b]	7 min	80
7	$CeCl_3{\cdot}7H_2O$ (10)	EtOH[a]	14 h	70	18	$ZnCl_2$ (10)	Neat[a] (80 °C)	8 h	76
8	$CeCl_3{\cdot}7H_2O$-SiO_2 (10)	EtOH[a]	15 h	73	19	$ZnCl_2$ (10)	Neat[b]	6 min	87
9	$CeCl_3{\cdot}7H_2O$-SiO_2 (10)	THF[a]	15 h	78	20	$CeCl_3{\cdot}7H_2O$-SiO_2 (10)	Neat[a] (80 °C)	7 h	82
10	$CeCl_3{\cdot}7H_2O$-SiO_2 (10)	Toluene[a]	15 h	63	21	$CeCl_3{\cdot}7H_2O$-SiO_2 (10)	Neat[b]	5 min	91
11	$CeCl_3{\cdot}7H_2O$-SiO_2 (10)	CH_3CN[a]	15 h	69					

[a] Reactions were carried out under conventional conditions.
[b] Reactions were carried out under microwave irradiation conditions.

Table 2
Effect of $CeCl_3{\cdot}7H_2O$-SiO_2 catalyst loading for synthesis compound **6c**.

Entry	Amount of catalyst (%)	Conventional		Microwave	
		Time (h)	Yield (%)	Time (min)	Yield (%)
1	7	9	75	9	87
2	8	9	78	8	90
3	9	8	80	7	91
4	10	7	82	5	91
5	11	7	86	5	94
6	12	7	90	4	96
7	13	7	90	4	96

Table 3
The effect of the reusability of the catalyst $CeCl_3{\cdot}7H_2O$-SiO_2 to synthesize compound **6c**.

Entry	Reusability	Conventional		Microwave	
		Time (h)	Yield (%)	Time (min)	Yield (%)
1	1	7	90	4	96
2	2	7	90	4	95
3	3	7	85	4	91
4	4	7	84	4	91
5	5	7	82	4	89

(Table 1, entry 20). It was observed that high yield was obtained in solvent-free condition (Table 1, entry 20). The model reaction was also tested with different catalysts $FeCl_3$, $AlCl_3$, $CuCl_2$ and $ZnCl_2$ under neat reaction conditions (Table 1, entries 12, 14, 16, 18). In comparison of catalytic activity, $CeCl_3{\cdot}7H_2O$-SiO_2 progressed the reaction most effectively with high yields (Table 1, entry 20). Again, the same reaction was run for microwave irradiation (CATA-4R, % power is 70% and 490 W), which led to the excellent yield 91% in the presence of $CeCl_3{\cdot}7H_2O$-SiO_2 in very short reaction time (5 min) (Table 1, entry 21) as compared with other catalysts (Table 1, entries 13, 15, 17, 19). Also, the effect of a catalytic amount of $CeCl_3{\cdot}7H_2O$-SiO_2 (Table 2, entries 1–7) was examined in conventional as well as in microwave conditions. The reaction was stimulated effectively in the catalytic amount of $CeCl_3{\cdot}7H_2O$-SiO_2, 12 mol% (Table 2, entry 6) and excess addition of the catalyst does not affect the reaction.

The reusability of this heterogeneous catalyst was also inspected in both the methods. After each run, the reaction mixture was filtered and the residual catalyst was washed with CH_2Cl_2 to remove tars from the catalyst surface and re-used up to four cycles to synthesize compound **6c** (Table 3, entry 1–5), with slight decrease of catalytic activity. To establish the generality, various active aldehydes were used to synthesize titled α-aminophosphonates (**6a–j**) using 12 mol% of the catalyst under assigned conditions (Table 3). Based on the experimental results, new analogs were prepared in excellent yields with electron deficient aldehydes as compared with electron rich aldehydes, and the catalyst is very tolerant toward various substituents including halides, alkoxy and nitro groups (Table 4).

The structures of the designed compounds were confirmed by spectral data (see Supporting information). IR spectra showed intensive bands in the region of 3240–3390 cm^{-1} of the –NH str, 1310–1355 cm^{-1} of the $-SO_2$ asym. str and 1220–1246 cm^{-1} of the –P═O str confirmed the functionalities in the desired compounds (**6a–j**). ^1H NMR spectra showed chemical shift values in the region of δ 1.02–1.17 as triplet, δ 3.56–4.30 as multiplet due to $-O-CH_2-CH_3$ of phosphate functionality. Doublet of doublet was observed at δ 4.58–5.54 due to –CH–P–, δ 5.20–5.68 as singlet/doublet due to –NH–CH– and δ 6.40–8.20 corresponding to aromatic protons confirmed the designed compounds. In ^{31}P NMR spectra, the chemical shifts in the region of δ 20.5–27.3 corresponding to phosphorus confirmed the functional group phosphonate group in the synthesized compounds. In addition, the corresponding carbon chemical shift values in ^{13}C NMR spectra and the molecular ion peaks, fragmented ion peaks in mass spectra have given further evidence to elucidate the structures of the synthesized compounds (**6a–j**).

The titled α-diaminophosphonates (**6a–j**) were screened for their antibacterial activity against strains such as *Staphylococcus aureus* (ATCC-19433), *Bacillus cereus* (ATCC-11778) and *Escherichia coli* (ATCC-25922) using disk diffusion method at 200 μg/mL. All the tested compounds did not exhibit good activity. Antifungal activity of the synthesized compounds was also examined against fungi such as *Aspergillus niger* (MTCC 1881), *Fusarium oxysporum*

Table 4
Physical data of the synthesized α-diaminophosphonates (**6a–j**) under neat reaction conditions.

Entry	Conventional		Microwave		Mp (°C)	Entry	Conventional		Microwave		Mp (°C)
	Time (h)	Yield (%)	Time (min)	Yield (%)			Time (h)	Yield (%)	Time (min)	Yield (%)	
6a	7.5	89	4	92	169–171	**6f**	7.5	86	4	90	106–108
6b	8.0	88	4	91	189–191	**6g**	7.5	86	4	91	128–130
6c	7.0	90	4	96	140–142	**6h**	8.0	87	5	90	140–142
6d	7.5	86	5	90	170–172	**6i**	8.0	86	5	91	114–116
6e	7.0	89	5	91	108–110	**6j**	8.0	84	4	91	118–120

Table 5
Antifungal zone of inhibition of the synthesized compounds (**6a-j**).

Compd.	Zone of inhibition (mm)[a]					
	A. niger (MTCC-1881)	MIC	*F. oxysporum* (MTCC-1755)	MIC	*A. foetidus* (NCIM-505)	MIC
6a	24.50	12	22.50	14	21.5	16
6b	22.25	14	20.0	16	21.25	18
6c	13.0	45	15.75	50	14.75	45
6d	19.50	30	17.0	30	16.25	34
6e	17.0	35	22.50	18	18.50	16
6f	20.50	25	19.50	20	21.0	30
6g	20.50	25	18.0	27	15.75	36
6h	18.25	37	19.0	30	18.0	34
6i	21.75	20	16.0	35	17.25	30
6j	19.0	30	21.50	20	20.5	24
Ketocon-azole	28.0	04	26.0	05	27.0	05

[a] Antifungal activity of the titled compounds was tested at conc. 200 μg/mL.

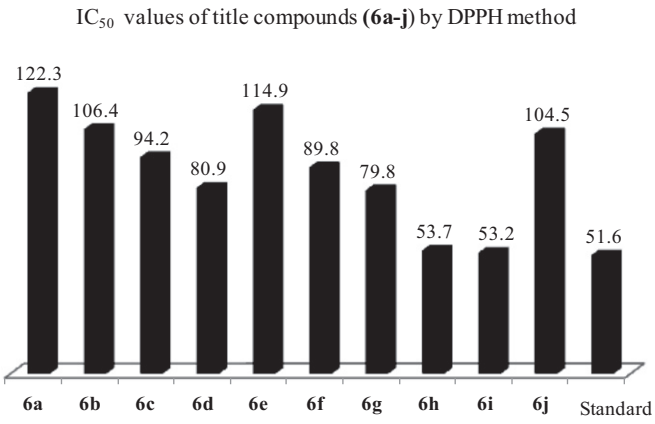


Fig. 2. Antioxidant IC_{50} values of α-diaminophosphonates (**6a-j**) by DPPH method.

(MTCC 1755) and *Aspergillus foetidus* (NCIM-505) using agar disk-diffusion method [24]. Ketoconazole was used as the standard and results were presented in Table 5. All the compounds showed moderate to excellent antifungal activity. Among the compounds **6a**, **6b** and **6f** exhibited excellent activity against all the tested fungi. Compounds **6e**, **6i** and **6j** are shown good inhibition against *F. oxysporum*, *A. niger* and *F. oxysporum* and *A. foetidus*. Further, the antioxidant activity of the synthesized α-diaminophosphonates (**6a–j**) were screened *in vitro* using DPPH [25], NO [26] and H_2O_2 [27] methods and results are presented in Table S1, Table S2 and Table S3, respectively (see Supporting information). Compounds **6h**, **6i** showed significant antioxidant activity among all the tested compounds in all the methods and showed lower IC_{50} values (Fig. 2).

4. Conclusion

We herein reported the synthesis of α-diaminophosphonate derivatives of Dapsone in the presence of heterogeneous catalyst, $CeCl_3{\cdot}7H_2O$-SiO_2 under solvent-free microwave assisted irradiation conditions in short reaction time with good to excellent yields. The presented procedure has many advantageous: (i) heterogeneous catalyst is reusable, cheap, readily available, eco-friendly, versatile and does not need any special precautions for preparation and simple handling and storage, (ii) short reaction times, (iii) avoidance of harmful organic solvents, (iv) simple work-up procedure, (v) tolerance toward various functional groups including halides, alkoxy and nitro groups. The synthesized compounds' *in vitro* antifungal and antioxidant activities were evaluated and results showed that the synthesized compounds have significant antifungal activity and antioxidant properties. Finally, the developed procedure is environmentally benign and the new compounds are more efficacious against fungi and as antioxidants.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.04.037.

References

[1] M.A. Phillips, R. Fletterick, W.J. Rutter, Arginine 127 stabilizes the transition state in carboxypeptidase, J. Biol. Chem. 265 (1990) 20692–20698.
[2] F.R. Atherton, C.H. Hassal, R.W. Lambert, Synthesis and structure–activity relationship of antibacterial phosphonopeptides incorporating (1-aminoethyl)phosphonic acid and (aminomethyl)phosphonic acid, J. Med. Chem. 29 (1986) 29–41.
[3] L. Maier, Synthesis and properties of 1-amino-2-arylethylphosphonic acid and phosphinic acids as well as phosphine oxides, Phosphorus, Sulfur Silicon Relat. Elem. 53 (1990) 43–67.
[4] L. Maier, H. Spoerri, Organic phosphorus compounds 96.1 resolution of 1-amino-2-(4-fluorophenyl)ethylphosphonic acid as well as some di- and tripeptides, Phosphorus, Sulfur Silicon Relat. Elem. 61 (1991) 69–75.
[5] J.H. Meyer, P.A. Barlett, Macrocyclic inhibitors of penicillopepsin. 1: design, synthesis, and evaluation of an inhibitor bridged between P1 and P3, J. Am. Chem. Soc. 120 (1998) 4600–4609.
[6] D.J. Miller, S.M. Hammond, D. Anderluzzi, et al., Aminoalkylphosphinate inhibitors of d-Ala-d-Ala adding enzyme, J. Chem. Soc. Perkin Trans. 1 (1998) 131–142.
[7] M.C. Allen, W. Fuhrer, B. Tuck, et al., Renin inhibitors: synthesis of transition-state analog inhibitors containing phosphorus acid derivatives at the scissile bond, J. Med. Chem. 32 (1989) 1652–1661.
[8] (a) J. Oleksyszyn, J.C. Powers, Irreversible inhibition of serine proteases by peptide derivatives of (α-aminoalkyl)phosphonate diphenyl esters, Biochemistry 30 (1991) 485–493;
(b) D. Green, G. Patel, S. Elgendy, et al., The facile synthesis of O,O-dialkyl 1-aminoalkanephosphonates, Tetrahedron Lett. 34 (1993) 6917–6920.
[9] (a) D.M. Mizrahi, T. Waner, Y. Segall, α-Amino acid derived bisphosphonates. Synthesis and anti-resorftive activity, Phosphorus, Sulfur Silicon Relat. Elem. 173 (2001) 1–25;
(b) J.R. Green, Anti-tumor potential of bisphosphonates, Med. Klin. 95 (2000) 23–28.
[10] S.C. Fields, Synthesis of natural products containing a C–P bond, Tetrahedron 55 (1999) 12237–12273.
[11] (a) J. Zon, Asymmetric addition of tris(trimethylsilyl) phosphite to chiral aldimines, Pol. J. Chem. 55 (1981) 643–646;
(b) S. Laschat, H. Kunz, Carbohydrates as chiral templates: stereoselective synthesis of (R)- and (S)-α-aminophosphonic acid derivatives, Synthesis 1 (1992) 90–95;
(c) J.S. Yadav, B.V.S. Reddy, K. Sarita Raj, et al., Zr^{4+}-catalyzed efficient synthesis of α-aminophosphonates, Synthesis 15 (2001) 2277–2280.

[12] B.C. Ranu, A. Hajra, U. Jana, General procedure for the synthesis of α-aminophosphonates from aldehydes and ketones using indium(III) chloride as a catalyst, Org. Lett. 1 (1999) 1141–1143.
[13] Z.P. Zhan, J.P. Li, Bismuth(III) chloride-catalyzed three-component coupling: synthesis of α-aminophosphonates, Synth. Commun. 35 (2005) 2501–2504.
[14] Z. Rezaei, H. Firouzabadi, N. Iranpoor, et al., Design and one-pot synthesis of α-aminophosphonates and bis(α-aminophosphonates) by iron(III) chloride and cytotoxic activity, Eur. J. Med. Chem. 44 (2009) 4266–4275.
[15] F. Xu, Y.Q. Luo, J.T. Wu, Q. Shen, H. Chen, Facile one-pot synthesis of α-aminophosphonates using lanthanide chloride as catalyst, Heteroat. Chem. 17 (2006) 389–392.
[16] A. Manjula, B.V. Rao, P. Neelakantam, One-pot synthesis of α-aminophosphonates: an inexpensive approach, Synth. Commun. 33 (2003) 2963–2969.
[17] S. Ambica, S.C. Kumar, M.S. Taneja, et al., One-pot synthesis of α-aminophosphonates catalyzed by antimony trichloride adsorbed on alumina, Tetrahedron Lett. 49 (2008) 2208–2212.
[18] R. Ghosh, S. Maiti, A. Chakraborty, et al., In(OTf)3 catalysed simple one-pot synthesis of α-aminophosphonates, J. Mol. Catal. A: Chem. 210 (2004) 53–57.
[19] S. Sobhani, Z. Tashrifi, One-pot synthesis of primary 1-aminophosphonates: coupling reaction of carbonyl compounds, hexamethyldisilazane, and diethyl phosphite catalyzed by Al(OTf)3, Heteroat. Chem. 20 (2009) 109–115.
[20] S. Sobhani, Z. Tashrifi, Al(OTf)3 as an efficient catalyst for one-pot synthesis of primary diethyl 1-aminophosphonates under solvent-free conditions, Synth. Commun. 39 (2008) 120–131.
[21] N. Azizi, M.R. Saidi, Lithium perchlorate-catalyzed three-component coupling: a facile and general method for the synthesis of α-aminophosphonates under solvent-free conditions, Eur. J. Org. Chem. (23) (2003) 4630–4633.
[22] L. Shen, S. Cao, N.J. Liu, et al., Ytterbium(III) perfluorooctanoate catalyzed one-pot, three-component synthesis of fully substituted pyrazoles under solvent-free conditions, Synlett 9 (2008) 1341–1344.
[23] A.J. Abbas, N. Mahshid, A.D. Mohammad, $CeCl_3{\cdot}7H_2O$-catalyzed one-pot Kabachnik–Fields reaction: a green protocol for three-component synthesis of α-aminophosphonates, Heteroat. Chem. 21 (2010) 397–403.
[24] (a) A.W. Bauer, M.M. Kirby, J.C. Sherris, et al., Antibiotic susceptibility testing by a standardized single disk method, Am. J. Clin. Pathol. 45 (1966) 493–496;
(b) National Committee for Clinical Laboratory Standards, Methods for Dilution, Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard M7-A5, 5th ed., NCCLS, Wayne, PA, 2000, p. 30;
(c) G.H. Bonjar Shahidi, Evaluation of antibacterial properties of iranian medicinal-plants against *Micrococcus luteus*, *Serratia marcescens*, *Klebsiella pneumonia* and *Bordetella bronchoseptica*, Asian J. Plant Sci. 3 (2004) 82–86.
[25] (a) M. Burits, F. Bucar, Antioxidant activity of *Nigella* sativa essential oil, Phytother. Res. 14 (2000) 323–328;
(b) M. Cuendet, K. Hostettmann, O. Potterat, Iridoid glucosides with free radical scavenging properties from *Fagraea blumei*, Helv. Chim. Acta 80 (1997) 1144–1152.
[26] (a) L.C. Green, D.A. Wagner, J. Glogowski, et al., Analysis of nitrate, nitrite, and [15N] nitrate in biological fluids, Anal. Biochem. 126 (1982) 131–138;
(b) L. Marcocci, J.J. Maguire, M.T. DroyLefaix, et al., The nitric oxide scavenging property of *Ginkgo biloba* extract EGb 761, Biochem. Biophys. Res. Commun. 201 (1994) 748–755.
[27] R.J. Ruch, S.J. Cheng, J.E. Klaunig, Prevention of cytotoxicity and inhibition of intercellular communication by antioxidant catechins isolated from Chinese green tea, Carcinogenesis 10 (1989) 1003–1008.