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ORIGINAL ARTICLE

Heterogeneous catalyst SiO_2–$LaCl_3{\cdot}7H_2O$: characterization and microwave-assisted green synthesis of *α*-aminophosphonates and their antimicrobial activity

S. K. Thaslim Basha[1] · Reddi Mohan Naidu Kalla[2] · M. Varalakshmi[3] · H. Sudhamani[1] · Rama Moorthy Appa[4] · Sung Chul Hong[4] · Chamarthi Naga Raju[1]

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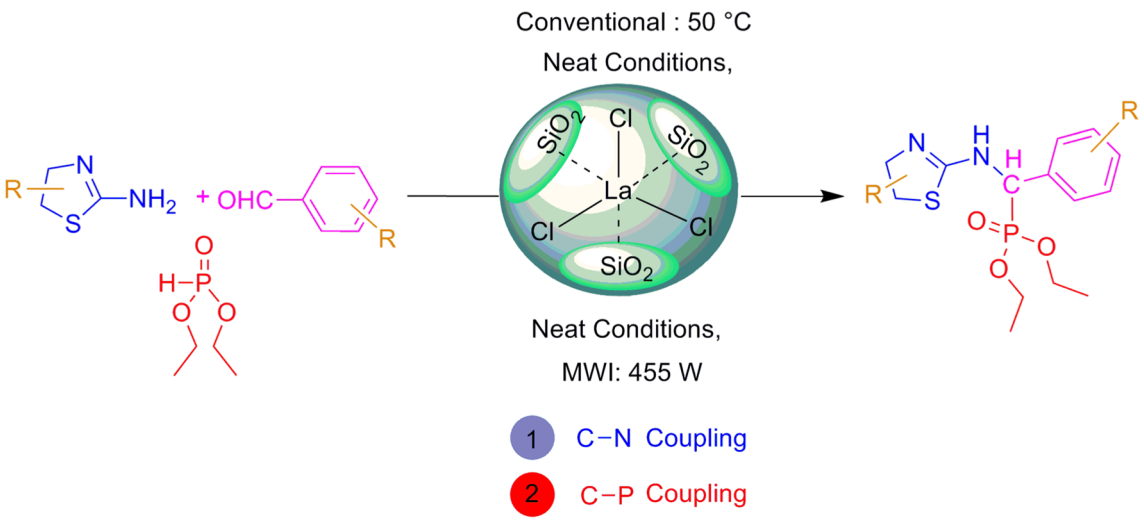
Abstract

Silica-supported lanthanum (III) chloride (SiO_2–$LaCl_3{\cdot}7H_2O$) was prepared and characterized by infrared spectroscopy, X-ray diffraction analysis, scanning electron microscope, energy-dispersive X-ray spectroscopy, thermogravimetric analysis and differential thermal analysis techniques. The catalytic activity of this silica-supported lanthanum (III) chloride was investigated in a one-pot three-component Kabachnik-Fields reaction. A library of new α-aminophosphonates was prepared employing various benzothiazole and thiadiazole amines, different substituted aldehydes and diethylphosphite under solvent-free conditions using conventional/microwave methods with good to excellent yields (85–97%). The advantages of this catalyst are that it is environmentally benign, economically inexpensive, and easy to prepare, gives high yields and high purity is less time-consuming, offers easy purification is reusable and enables products to be obtained by simple recrystallization without column chromatography.

Graphical Abstract



Keywords Novel α-aminophosphonates · Heterogeneous catalyst · Sustainable method · Microwave condition · Recyclability · Anti-microbial activity

Extended author information available on the last page of the article

Introduction

The immense intention of organic chemists in terms of public concern and economy has been focused on the development of greener and more economically competitive processes, which is an important factor in synthetic chemistry [1] for the efficient synthesis of organic molecules, intermediates and biologically active compounds with potential applications. Solid-supported Lewis acid catalysts are unique and have gained expanded widespread importance over the last decade. Particularly, silica and SiO_2 as supports have gained considerable interest because kinetic studies have disclosed that SiO_2 not only acts as a carrier to increase the surface area as intended but also enhances the rate of reaction. Hence, chemists have focused on the expansion of silica-supported catalysts and exploration of their efficacy in organic synthesis.

In recent years, lanthanum (III) chloride has been widely used as a catalyst for many organic transformations due to its easy handling, reusability, simple work-up procedure, inexpensiveness and moisture stability [2]. Recently, $LaCl_3$ was used for the synthesis of benzimidazoles under mild reaction conditions [3], the synthesis of imidazo-fused polyheterocycles via a one-pot three-component Groebke-Blackburn-Bienayme reaction [4] and the preparation of aryl or heteroaryl phosphonates in high yields by the Michaelis-Arbuzov reaction [5]. In addition, heterogeneous catalysts in solvent-free reactions have received great interest in organic synthesis due to several advantages such as operational simplicity, non-toxicity, reusability, inexpensiveness, ready availability and ease of isolation after completion of the reaction [6].

The Kabachnick-Fields reaction is one of the most important nitrogen-carbon-phosphorus bond (–N–C–P–) forming reactions in organic synthesis. It is widely used for the synthesis of many biologically and synthetically active α-aminophosphonates that mimic naturally occurring α-amino acids in living organisms and are involved in enzyme inhibition and metabolic regulation [7]. Many of these α-aminophosphonate and their derivatives have a broad spectrum of biological applications such as potent anticancer [8], antibiotic [9], antitumor [10], herbicidal [11], enzyme inhibition [12], pesticidal [13] and antimicrobial activities [14].

Owing to their wide applications, numerous methodologies have been developed for the synthesis of α-aminophosphonates using various catalysts such as Bronsted and Lewis acids [15], heteropoly acids [16], catalyst-free [17], ionic liquids [18], silica-supported catalysts[19–28] and nanocatalysts [29] in conventional, microwave and ultrasound methods [30]. Among these catalysts, heterogeneous silica-supported catalysts were effectively used for the synthesis of α-aminophosphonates such as $TaCl_5$–SiO_2 [19], polyphosphoricacid/SiO_2 [20], $HClO_4$/SiO_2 [21], Fe_2O_3·SiO_2–PA [22], $CeCl_3$·$7H_2O$–SiO_2 [23], nano-BF_3·SiO_2 [24], $ZnCl_2$/SiO_2 [25], TiO_2·SiO_2 [26], SiO_2–OSO_3H [27] and silica-supported dodecatungstophosphoric acid (DTP/SiO_2) [28]. However, silica-supported catalysts were found to be efficacious in most circumstances and achieved significantly good outcomes, but there were some limitations associated with long reaction times, the use of expensive catalysts, moisture-sensitive catalysts, high temperatures and solvents required for the purification of compounds. Hence, a better synthetic procedure for the synthesis of α-aminophosphonates is still warranted.

By considering the above stated applications of α-aminophosphonates, in continuous efforts on the development of new methodologies and efficient catalytic activity of lanthanum (III) chloride, herein, we prepared a new silica-supported catalyst, SiO_2–$LaCl_3$·$7H_2O$, and developed an efficient, green procedure for the synthesis of a library of α-aminophosphonates under neat conditions by conventional as well as microwave methods using this catalyst. To the best of our knowledge, this is the first report of the synthesis of α-aminophosphonates in the presence of SiO_2–$LaCl_3$·$7H_2O$ under microwave and conventional conditions.

Results and discussion

Characterization of SiO_2–$LaCl_3$·$7H_2O$ catalyst

A heterogeneous catalyst, silica–supported lanthanum (III) chloride (SiO_2–$LaCl_3$·$7H_2O$), was prepared and characterized by fourier transform-infrared spectroscopy (FT-IR), X-ray diffraction analysis (XRD), scanning electron microscope (SEM), energy-dispersive X-ray spectroscopy (EDS), thermogravimetric analysis (TGA), and differential thermal analysis (DTA) techniques. The FT-IR correlation spectra for pure $LaCl_3$·$7H_2O$ and silica-supported lanthanum (III) chloride are presented in Fig. 1. The FT-IR spectrum of pure $LaCl_3$·$7H_2O$ shows absorption bands at 3280 cm^{-1} and 1616 cm^{-1} due to O–H stretching and O–H bending vibrations, respectively. The SiO_2–$LaCl_3$·$7H_2O$ spectrum demonstrated that the O–H stretching and bending bands appeared at 3359 cm^{-1} and 1633 cm^{-1} with a slight increase in the absorbance due to the adherence of silica, whereas the Si–O stretching band position slightly decreased from 1100 to 1068 cm^{-1}. The elemental composition of the catalyst was confirmed by EDS analysis, and it was estimated that 246 mg of $LaCl_3$ was supported on 1.0 g of silica-supported lanthanum (III) chloride, as shown in Fig. 2.

Figure 3a shows the X-ray diffraction pattern of the prepared SiO_2–$LaCl_3$·$7H_2O$ compound. As observed in Fig. 3a,

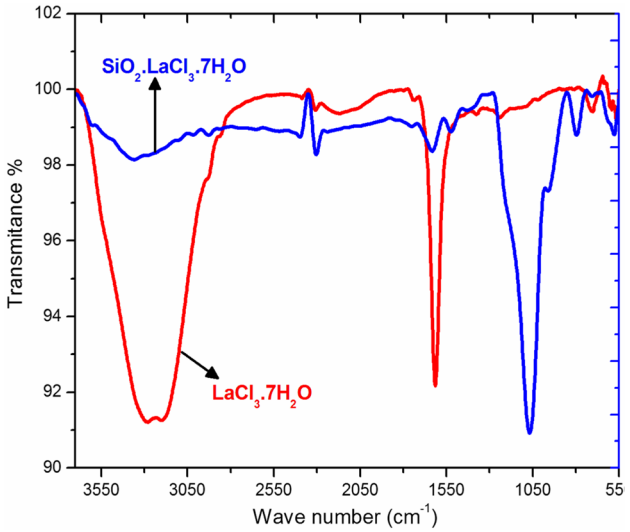


Fig. 1 FT-IR spectra for pure $LaCl_3{\cdot}7H_2O$ and silica-supported lanthanum (III) chloride

the intense diffraction peaks indexed to the (100), (101) and (201) planes appearing at $2\theta = 13.6°$, 24.5° and 34.4°, respectively, coincide with the standard XRD data for $LaCl_3$ with a hexagonal structure (JCPDS Card No. 75-1890). This result confirmed the existence of $LaCl_3$ in the pure phase. In addition, the diffraction angle appeared at approximately 23°, which indicates the SiO_2 structure. Figure 3b shows the SEM image of SiO_2–$LaCl_3{\cdot}7H_2O$, which indicates that the particles have nearly hexagonal structures, which confirms the XRD results.

The thermal stability of the catalyst was evaluated by TGA and DTA (Fig. 4). The DTA graph shows an endothermic transition at approximately 100–110 °C, which is due to the loss of water molecules in the catalyst [32]. Furthermore, the graph does not show any transition up to 450 °C, after which another endothermic peak begins to appear, which may be due to the loss of bonded chloride groups. Thus, it can be inferred that the catalyst is stable up to 450 °C. The TGA curve provided further information about the thermal stability of the catalyst. The TGA curve showed a weight loss of 30% at approximately 100–110 °C, which can be attributed to the loss of water molecules present in SiO_2–$LaCl_3{\cdot}7H_2O$ [33]. The catalyst did not show any further weight loss up to 450 °C. This observation confirms that the catalyst is stable up to this temperature, as also shown by the DTA results. A further weight loss of 18% at 450 °C is attributed to the decomposition of chloride groups from the surface of the catalyst. Thus, DSC and TGA analyses showed that the catalyst can tolerate temperatures up to 450 °C.

Application of catalyst for the synthesis of α-aminophosphonates

Recently, our research group used $LaCl_3{\cdot}7H_2O$ for the synthesis of aryl and heteroaryl phosphonates by a C–P coupling reaction [5], with high yields. The results obtained

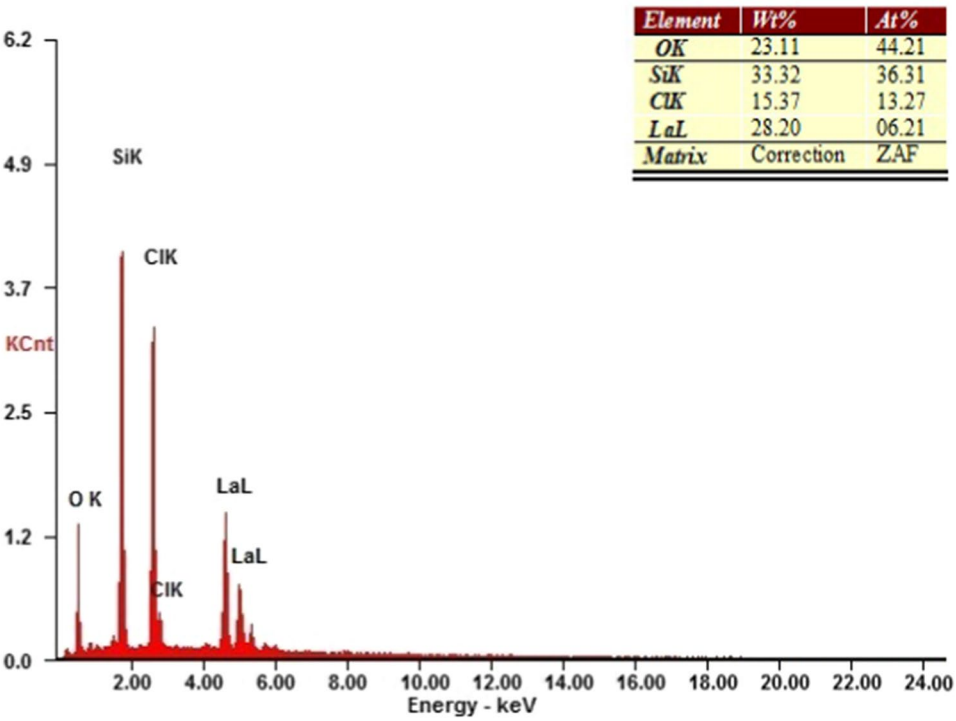


Fig. 2 EDS analysis of silica-supported lanthanum (III) chloride

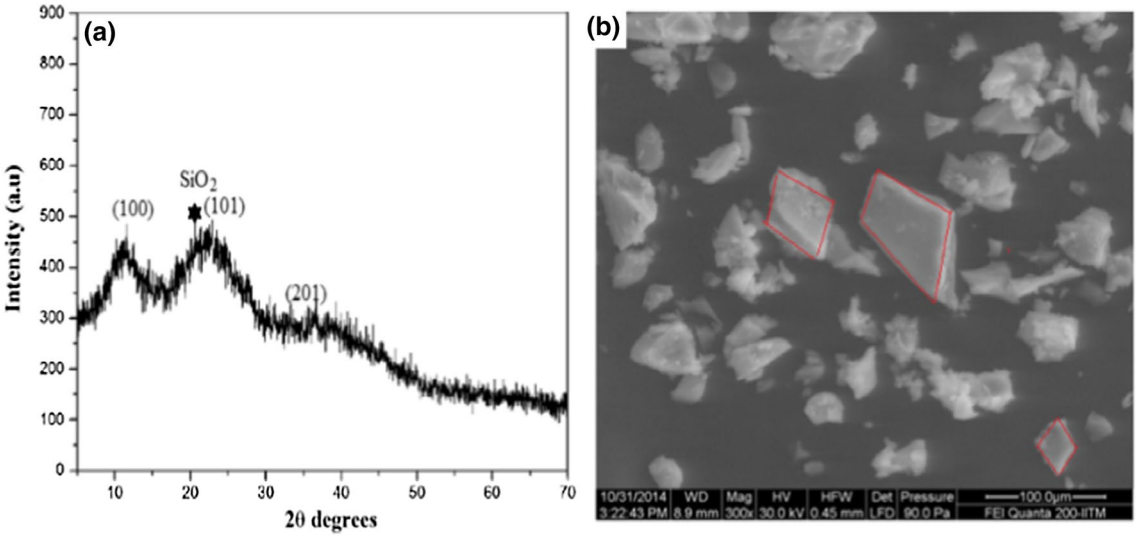


Fig. 3 **a** X-ray diffraction studies of the catalyst. **b** SEM image of the catalyst

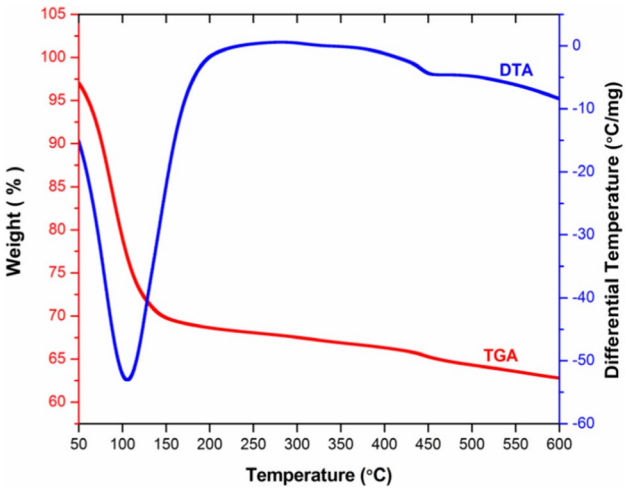
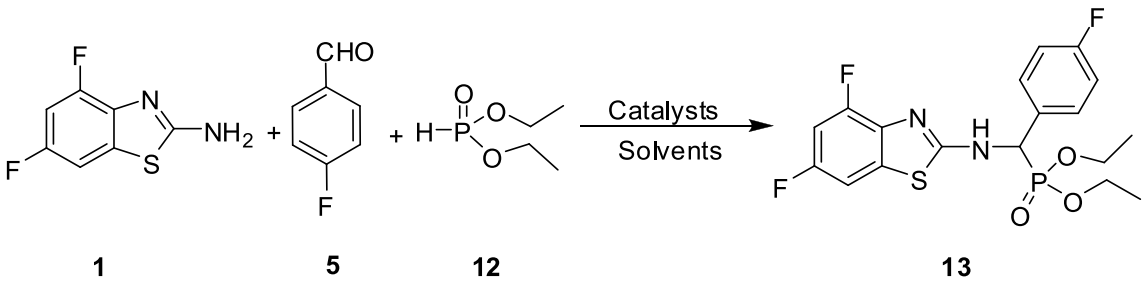


Fig. 4 Thermal analysis of silica-supported lanthanum (III) chloride

for the $LaCl_3{\cdot}7H_2O$ catalyst encouraged further study, so we prepared a new heterogeneous catalyst, silica-supported $LaCl_3{\cdot}7H_2O$, and characterized it. Several successful attempts have been reported by our group for the preparation of α-aminophosphonates using Lewis acid catalysts [8] and silica-supported Lewis acid catalysts [23–25]. To determine the catalytic activity of the prepared catalyst, silica-supported $LaCl_3{\cdot}7H_2O$ was used, adopting this catalyst in a one-pot three-component Kabachnick-Fields reaction for the preparation of α-aminophosphonates. At the outset, the substances 2-amino-4,6-difluorobenzothiazole, 4-fluorobenzaldehyde and diethylphosphite were selected as models to run the reaction, and the reaction is depicted in Scheme 1.

The model reaction progressed in ethanol using 15 mol% heterogeneous catalyst SiO_2–$LaCl_3{\cdot}7H_2O$; surprisingly, a high quantity of the product (89%) was obtained (Table 1, entry 1). It is well known that the rate of reaction also influences the solvent; hence, subsequent efforts were needed for the optimization of the solvent. The model reaction was run in different solvents such as dichloromethane, toluene, dioxane, acetonitrile, tetrahydrofuran, water and solvent-free



Scheme 1 Model reaction to optimize the reaction conditions

Table 1 Optimization of solvent and catalyst for the synthesis of compound **13***

Entry	Catalyst (15 mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	SiO_2–$LaCl_3{\cdot}7H_2O$	Ethanol	50	3.0	89
2	SiO_2–$LaCl_3{\cdot}7H_2O$	DCM	50	5.0	72
3	SiO_2–$LaCl_3{\cdot}7H_2O$	Toluene	Reflux	5.0	75
4	SiO_2–$LaCl_3{\cdot}7H_2O$	Dioxane	Reflux	5.0	70
5	SiO_2–$LaCl_3{\cdot}7H_2O$	Acetonitrile	Reflux	5.0	77
6	SiO_2–$LaCl_3{\cdot}7H_2O$	THF	Reflux	5.0	74
7	SiO_2–$LaCl_3{\cdot}7H_2O$	Water	Reflux	5.0	50
8	SiO_2–$LaCl_3{\cdot}7H_2O$	Solvent-free	50	2.5	95
9	$LaCl_3{\cdot}7H_2O$	Solvent-free	60	3.5	85
10	$ZnCl_2$	Solvent-free	60	5.0	76
11	SiO_2–$ZnCl_2$	Solvent-free	60	4.5	84
12	$ZnBr_2$	Solvent-free	60	5.0	73
13	SiO_2–$ZnBr_2$	Solvent-free	60	4.0	83
14	$CeCl_3{\cdot}7H_2O$	Solvent-free	60	5.0	78
15	SiO_2–$CeCl_3{\cdot}7H_2O$	Solvent-free	60	3.5	88

*Isolated yield of diethyl(4,6-difluorobenzo[d]thiazol-2-ylamino)(4-fluorophenyl)methylphosphonate

conditions, and the results are summarized in Table 1 (entries 2–8). As given in the table, a promising yield (95%) was obtained under solvent-free conditions compared with the use of solvents; therefore, the solvent-free conditions were optimized.

To explore the efficacy of the SiO_2–$LaCl_3{\cdot}7H_2O$ catalyst, the model reaction was examined under solvent-free conditions in different catalysts such as $LaCl_3{\cdot}7H_2O$, $ZnCl_2$, $ZnBr_2$, $CeCl_3{\cdot}7H_2O$, SiO_2–$ZnCl_2$, SiO_2–$ZnBr_2$ and SiO_2–$CeCl_3{\cdot}7H_2O$ (Table 1, entries 9–15). It was observed that the product diethyl(4,6-difluorobenzo[*d*]thiazol-2-ylamino)(4-fluorophenyl)methyl phosphonate (13) was obtained in better yield when the reaction progressed in the presence of SiO_2–$LaCl_3{\cdot}7H_2O$ catalyst than with other examined catalysts, and moderate yields were obtained in the presence of an unsupported Lewis acid catalyst.

The catalytic amount of the SiO_2–$LaCl_3{\cdot}7H_2O$ catalyst in the conventional method was determined by varying the quantity of the catalyst (Table 2, entries 1–6). The results indicated that a loading of 12.5 mol% was sufficient to obtain the optimum yield for the product, and a promising yield for the product was not obtained when utilizing more than 12.5 mol% catalyst. The reusability of the catalyst was also examined for up to five cycles (Table 2, entries 7–10), and the data revealed that until three cycles, considerable yield variation was not observed, and later, the catalytic activity decreased slowly.

To our delight and as in our earlier reports on microwaves, the model reaction was carried out under microwave conditions at 490 W under neat conditions and using 12.5 mol% catalyst. The reaction was completed within 8 min and afforded 95% of the product. To determine the effect of the microwave power on the catalyst, the reaction

Table 2 Determination of catalyst amount under conventional conditions*

Entry	SiO_2–$LaCl_3{\cdot}7H_2O$	Time (h)	Yield (%)
1	2.5 mol%	3.0	75
2	5 mol%	3.0	78
3	7.5 mol%	3.0	80
4	10 mol%	3.0	86
5	15.0 mol%	3.0	95
6	12.5 mol%	3.0	95
7	2nd run	3.0	93
8	3rd run	3.0	91
9	4th run	3.0	87
10	5th run	3.0	81

*Model reaction was carried out at 50 °C

was screened at 700, 560, 455, 420 and 350 W using 12.5 mol% of SiO_2–$LaCl_3{\cdot}7H_2O$ catalyst. As given in the table, the reaction effectively progressed in the microwave oven at a power of 455 W with a high yield (96%) (Table 3, entry 4), and a low yield for the product was observed along with impurities when using a high power; however, in the case of applying a low amount of power, the starting materials were observed. Therefore, we decided to use 455 W of power in the microwave oven. Additionally, the amount of catalyst was optimized by adopting a power of 455 W and varying the amount of catalyst. As shown in Table 3, an increase in the amount of catalyst from 2.5 to 10 mol% led to the formation of the desired product with a yield as high as 97% (entries 7–10). Upon further catalyst loading (10–15 mol%), no significant improvement in the yield was observed. These results indicated that a

Table 3 Effect of microwave oven power (W) and amount of catalyst on the yield of compound **13***

Entry	SiO_2–$LaCl_3{\cdot}7H_2O$	Microwave oven power (W)	Time (min)	Yield (%)
1	12.5 mol%	700	5	84
2	12.5 mol%	560	7	89
3	12.5 mol%	490	8	95
4	12.5 mol%	455	8	96
5	12.5 mol%	420	8	95
6	12.5 mol%	350	8	88
7	2.5 mol%	455	8	83
8	5.0 mol%	455	8	87
9	7.5 mol%	455	8	90
10	10.0 mol%	455	5	97
11	15.0 mol%	455	5	97
12	2nd run	455	5	97
13	3rd run	455	5	96
14	4th run	455	8	95
15	5th run	455	8	95
16	6th run	455	8	92
17	7th run	455	10	90
18	8th run	455	10	90

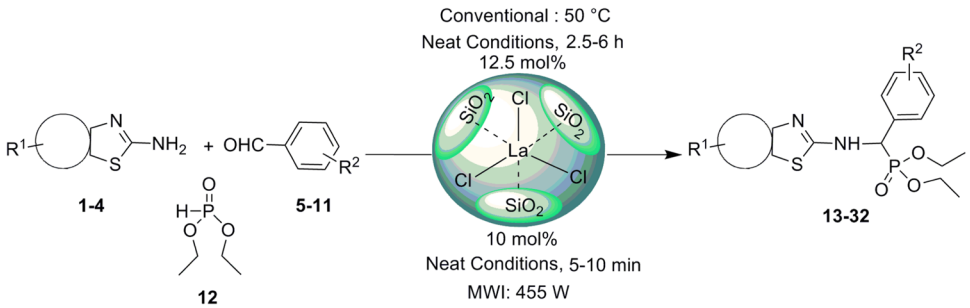
*The model reaction was performed under neat condition at 10.0 mol % of SiO_2.$LaCl_3{\cdot}7H_2O$

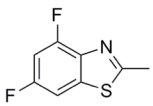
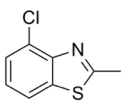
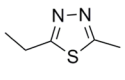
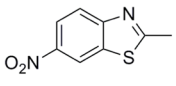
loading of 10 mol% was sufficient to effectively maintain the reaction. In addition, reusability of the catalyst was initially examined until five cycles, but we did not observe a promising yield variation for the product. Then, three cycles were evaluated again (Table 3, entry 12–18), and some deviation in the yield of the product was observed. Hence, we can reuse the catalyst in a microwave oven for five cycles.

After optimization of the reaction conditions, we investigated the scope and limitations of the catalyst in both conventional and microwave methods using various amines such as substituted benzothiazole amines **(1–3)** and 5-ethyl-1,3,4-thiadiazol-2-amine **(4)**, aryl aldehydes **(5–11)** and diethylphosphite **(12)**, as shown in Scheme 2. The experimental results (Table 4) indicated that this catalyst was efficient for the three-component one-pot synthesis of α-aminophosphonates. From the results, it was concluded that SiO_2–$LaCl_3{\cdot}7H_2O$ is able to catalyze the synthesis of α-aminophosphonates in conventional as well as microwave methods. However, the microwave method shows the advantages of high product yields, low reaction time, low catalyst loading and reusability of the catalyst (up to 8 cycles).

Results on the primary antimicrobial activity of the title compounds are presented in Tables 5 and 6. The compounds **17, 26, & 32** with a di fluoro and nitro substitution at aromatic aldehydes condense with respective amines showed enhanced antibacterial activity against *Bacillus subtilis* (MTCC-441), *Staphylococcus aureus* (MTCC-737), *Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-741) bacteria. Whereas compounds **17, 18 & 32** showed good antifungal activity against following fungi such as *Aspergillus niger, Aspergillus flavus, Candida albicans, Candida non-albicans.* The remaining targeted compounds shows moderate antimicrobial activity. The compounds which is having mono fluoro, chloro and nitro shows less activity compared to di substitution.

Scheme 2 Synthesis of α-aminophosphonates using SiO_2–$LaCl_3{\cdot}7H_2O$



Entry	1	2	3	4
R^1				

Entry	5	6	7	8	9	10	11
R^2	4-F	4-Cl	3-NO_2	4-Cl, 3-NO_2	3,4-F_2	2,4-Cl_2	4-OH, 3-NO_2

Table 4 Synthesized α-aminophosphonates **(13–32)**

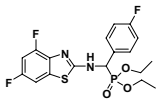
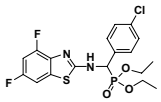
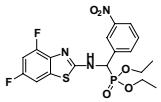
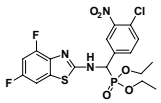
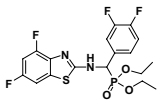
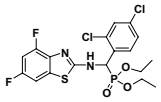
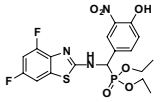
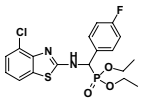
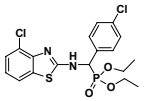
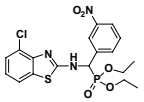
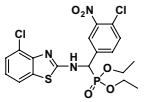
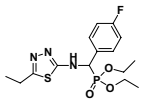
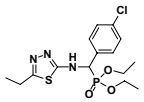
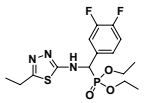
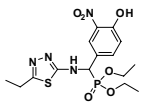
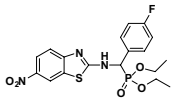
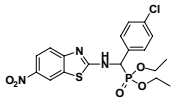
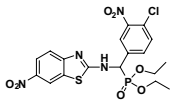
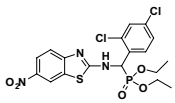
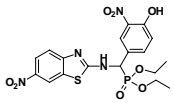
Compound	Precursors	Product	Time (min)[a]/h[b]	Yield (%)[a/b]	Melting point (°C)
13	1 + 5		5/2.5	97/95	196–198
14	1 + 6		8/3.0	95/91	209–211
15	1 + 7		6/3.5	90/88	181–183
16	1 + 8		10/4.0	91/87	175–177
17	1 + 9		8/3.0	95/90	172–174
18	1 + 10		9/3.5	92/89	157–159
19	1 + 11		10/6.0	89/86	207–209
20	2 + 5		5/2.5	96/92	158–160
21	2 + 6		6/3.0	97/93	130–132
22	2 + 7		8/5.0	92/90	135–137
23	2 + 8		10/4.5	88/85	140–142
24	3 + 5		8/4.0	90/92	134–136
25	3 + 6		8/4.0	93/90	149–151
26	3 + 9		10/5.0	90/86	113–115

Table 4 (continued)

Compound	Precursors	Product	Time (min)[a]/h[b]	Yield (%)[a/b]	Melting point (°C)
27	3 + 11		10/6.0	89/87	142–144
28	4 + 5		7/3.0	92/90	214–216
29	4 + 6		5/2.5	94/90	198–200
30	4 + 8		10/6.0	87/85	249–251
31	4 + 10		7/4.0	87/85	140–142
32	4 + 11		8/5.5	90/86	163–165

[a]Microwave conditions

[b]Conventional conditions

As number of substitution, and nitrogen atoms increases, the activity also increases. The obtained results are more potent than that of reported α-aminophosphonates.

The reusability of the catalyst was evaluated in conventional as well as microwave methods. After completion of the reaction, the heterogeneous catalyst SiO_2–$LaCl_3{\cdot}7H_2O$ was filtered off and washed with dichloromethane (3 × 5 mL) to remove the organic stain particles adhered to the catalyst. The recovered catalyst was dried in a vacuum oven at 60 °C at 760 mm Hg pressure for 1 h. From the results, it was observed that the catalyst recovered from the conventional method exhibited good efficacy up to 3 cycles. From the 4th cycle, the yield decreased, whereas in the microwave method, the catalyst was reused up to the 5th cycle, after which the yield decreased.

Experimental methods

General

Chemicals were purchased from Merck and Sigma-Aldrich and used without further purification. Microwave irradiation was carried out in a microwave oven with a catalyst system (CATA-4R). The melting points for the compounds were determined in open capillary tubes with a Guna melting pointing apparatus and were uncorrected. Infrared spectra were recorded on a Bruker ALPHA interferometer instrument. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with a Bruker 400 MHz instrument in $CDCl_3$; TMS was used as an internal standard for proton and carbon NMR spectroscopy. The chemical shift and coupling constant are expressed in ppm and Hz, respectively. Mass spectra were recorded via ESI–MS in positive mode, and elemental analyses were carried out with a FLASH EA Thermo Finnigan 1112 instrument. SEM and EDS were performed with FEI Quanta 200 and Quanta 400 scanning electron microscopes. TGA and DTA were performed with an SDT Q600V20.9 Build-20 instrument.

Synthesis of diethyl(4,6-difluorobenzo[d] thiazol-2-ylamino)(4-fluorophenyl)methyl phosphonate (13)

Conventional method

A mixture of 2-amino-4,6-difluourobenzothiazole **(1)** (186 mg, 1 mmol), 4-fluoro benzaldehyde **(5)** (124 mg, 1 mmol), diethylphosphite **(12)** (207 mg, 1.5 mmol) and 12.5 mol% SiO_2–$LaCl_3{\cdot}7H_2O$ was placed into a 50 mL round-bottom flask without solvent. The mixture was stirred for 2.5 h at 50 °C. After completion of the reaction, the reaction mixture was cooled, 10 mL of DCM was added, and the mixture was filtered to remove the

Table 5 In vitro antibacterial activity and MIC of synthesized compounds (**13–32**)

Entry	Compd	*Bacillus subtilis* (MTCC-441)	*Staphylococcus aureus* (MTCC-737)	*Escherichia coli* (MTCC-443)	*Pseudomonas aeruginosa* (MTCC-741)
1	**13**	11.5 ± 0.26	9.2 ± 0.14	9.6 ± 0.10	10.4 ± 0.24
2	**14**	10.0 ± 0.23	11.2 ± 0.21	8.1 ± 0.22	10.0 ± 0.14
3	**15**	9.0 ± 0.20	8.0 ± 0.18	8.2 ± 0.15	8.8 ± 0.14
4	**16**	12.5 ± 0.10	12.1 ± 0.22	10.5 ± 0.29	11.0 ± 0.12
5	**17**	15.5 ± 0.18	14.2 ± 0.15	13.5 ± 0.12	15.0 ± 0.18
6	**18**	8.2 ± 0.12	8.9 ± 0.21	7.5 ± 0.25	9.0 ± 0.21
7	**19**	10.8 ± 0.12	9.6 ± 0.16	9.2 ± 0.15	11.2 ± 0.15
8	**20**	12.5 ± 0.30	11.2 ± 0.15	11.2 ± 0.19	12.1 ± 0.24
9	**21**	11.5 ± 0.24	10.2 ± 0.12	10.8 ± 0.24	12.0 ± 0.16
10	**22**	8.0 ± 0.14	8.2 ± 0.17	6.5 ± 0.08	7.1 ± 0.25
11	**23**	10.8 ± 0.20	9.6 ± 0.16	10.4 ± 0.15	11.8 ± 0.12
12	**24**	13.5 ± 0.20	13.8 ± 0.18	12.5 ± 0.14	11.2 ± 0.26
13	**25**	9.4 ± 0.12	8.5 ± 0.22	8.6 ± 0.20	9.8 ± 0.18
14	**26**	15.1 ± 0.25	13.8 ± 0.09	13.2 ± 0.14	14.5 ± 0.19
15	**27**	12.0 ± 0.14	10.8 ± 0.18	11.4 ± 0.12	12.2 ± 0.15
16	**28**	12.5 ± 0.25	11.2 ± 0.12	11.9 ± 0.18	13.5 ± 0.06
17	**29**	11.4 ± 0.20	9.6 ± 0.15	9.4 ± 0.18	11.2 ± 0.22
18	**30**	10.2 ± 0.21	11.5 ± 0.15	8.2 ± 0.10	12.1 ± 0.03
19	**31**	12.8 ± 0.14	12.5 ± 0.20	12.8 ± 0.22	13.2 ± 0.20
20	**32**	13.2 ± 0.14	13.4 ± 0.15	13.2 ± 0.16	13.6 ± 0.15
21	**std**	16.4	16.5	16.0	16.8
22	**DMSO**	–	–	–	–

Compd	Minimum inhibition concentration of chemical compounds (μg)			
	Bacillus subtilis (MTCC-441)	*Staphylococcus aureus* (MTCC-737)	*Escherichia coli* (MTCC-443)	*Pseudomonas aeruginosa* (MTCC-741)
13	12.5	12.5	12.5	12.5
14	50	50	50	50
15	12.5	12.5	25	12.5
16	25	25	25	25
17	6.25	6.25	6.25	6.25
18	> 50	> 50	> 50	> 50
19	25	25	25	25
20	25	25	25	25
21	50	50	50	50
22	> 50	> 50	> 50	> 50
23	12.5	12.5	12.5	12.5
24	25	> 25	25	25
25	> 50	> 50	> 50	> 50
26	6.25	6.25	6.25	6.25
27	12.5	12.5	12.5	12.5
28	> 6.25	> 6.25	> 6.25	> 6.25
29	25	25	25	25
30	25	25	> 25	25
31	> 12.5	25	25	25
32	12.5	12.5	12.5	12.5
std	3.125	6.25	6.25	6.25

Standard: Streptomycin

*Zone of inhibition at 100 μg/mL

#Mean of triplicaton

Table 6 In vitro antifungal activity and MIC of synthesized compounds **(13–32)**

Entry	Compd	*Aspergillus niger*	*Aspergillus flavus*	*Candida albicans*	*Candida non-albicans*
1	**13**	10.6 ± 0.28	9.6 ± 0.24	9.2 ± 0.12	9.3 ± 0.14
2	**14**	14.0 ± 0.18	14.0 ± 0.18	13.0 ± 0.12	13.2 ± 0.14
3	**15**	12.5 ± 0.30	11.7 ± 0.12	10.9 ± 0.12	9.9 ± 0.50
4	**16**	11.5 ± 0.18	10.2 ± 0.35	10.8 ± 0.19	9.6 ± 0.28
5	**17**	13.2 ± 0.20	13.4 ± 0.25	12.6 ± 0.22	12.4 ± 0.22
6	**18**	15.4 ± 0.24	15.2 ± 0.12	14.5 ± 0.14	15.0 ± 0.20
7	**19**	12.3 ± 0.51	11.2 ± 0.15	10.3 ± 0.25	11.0 ± 0.17
8	**20**	10.8 ± 0.22	10.6 ± 0.20	8.3 ± 0.15	8.6 ± 0.12
9	**21**	7.5 ± 0.14	8.9 ± 0.18	6.5 ± 0.29	8.2 ± 0.19
10	**22**	12.2 ± 0.24	12.5 ± 0.12	10.0 ± 0.16	8.0 ± 0.12
11	**23**	7.2 ± 0.14	6.9 ± 0.41	7.1 ± 0.28	6.5 ± 0.32
12	**24**	11.5 ± 0.26	11.2 ± 0.18	12.1 ± 0.13	10.4 ± 0.12
13	**25**	10.2 ± 0.15	9.3 ± 0.17	8.5 ± 0.24	9.1 ± 0.29
14	**26**	14.2 ± 0.22	12.3 ± 0.12	10.2 ± 0.20	10.6 ± 0.14
15	**27**	10.8 ± 0.20	9.0 ± 0.20	8.0 ± 0.12	7.8 ± 0.16
16	**28**	11.5 ± 0.18	12.2 ± 0.14	8.4 ± 0.18	8.8 ± 0.12
17	**29**	8.9 ± 0.15	8.1 ± 0.41	7.2 ± 0.32	8.8 ± 0.33
18	**30**	12.4 ± 0.14	11.5 ± 0.18	10.8 ± 0.12	10.4 ± 0.12
19	**31**	8.2 ± 0.14	7.6 ± 0.25	8.1 ± 0.24	6.2 ± 0.19
20	**32**	14.5 ± 0.14	13.2 ± 0.15	13.5 ± 0.21	12.9 ± 0.28
21	**std**	16.1	16.0	16.2	16.2
22	**DMSO**	–	–	–	–

Compd	Minimum inhibition concentration of chemical compounds (µg)			
	Aspergillus niger	*Aspergillus flavus*	*Candida albicans*	*Candida non-albicans*
13	12.5	12.5	12.5	12.5
14	25	25	25	25
15	50	50	50	50
16	25	25	25	25
17	25	25	25	25
18	3.125	3.125	6.25	6.25
19	50	50	50	50
20	25	25	25	25
21	50	50	50	50
22	12.5	12.5	12.5	12.5
23	6.25	6.25	6.25	6.25
24	> 12.5	> 12.5	> 12.5	> 12.5
25	25	25	25	25
26	50	50	50	50
27	6.25	6.25	6.25	6.25
28	12.5	12.5	12.5	12.5
29	6.25	6.25	6.25	6.25
30	> 12.5	> 12.5	> 12.5	> 12.5
31	12.5	12.5	12.5	12.5
32	3.125	3.125	3.125	3.125
std	3.125	3.125	6.5	6.5

Standard: Ampotericin

*Zone of inhibition at 100 µg/mL

Table 6 (continued)

[#]Mean of triplicaton

catalyst with SiO_2–$LaCl_3$ as the residue. The organic layer was washed with water (2 × 5 mL), and the water layer was discarded. The combined organic mixture was washed with brine solution (5 mL) and dried with anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure, and the product was obtained as a white solid. The crude product was recrystallized from diethylether:methanol (9:1) to obtain the pure compound diethyl(4,6-difluorobenzo[*d*]thiazol-2-ylamino)(4-fluorophenyl)methylphosphonate **(13).** The same protocol was adopted for the synthesis of the remaining title compounds **14–32**.

Microwave method

2-Amino-4,6-difluorobenzothiazole **(1)** (186 mg, 1 mmol), 4-fluorobenzaldehyde **(5)** (124 mg, 1 mmol), diethylphosphite **(12)** (207 mg, 1.5 mmol) and 10 mol% SiO_2–$LaCl_3$ were placed into a flat-bottom flask. The reaction mixture was irradiated with microwaves using a catalyst system (CATA-4R) at 450 W. The progress of the reaction was monitored by TLC (3:2; *n*-hexane:ethyl acetate) every 1.0 min. After completion of the reaction, the reaction mixture was dissolved in 10 mL of DCM and filtered to remove the catalyst as a residue. The organic layer was washed with water (2 × 5.0 mL), and the water layer was discarded. The combined organic mixture was washed with brine solution (5 mL) and dried with anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure, and the product was obtained as a white solid. The solid was washed with cold water, air-dried and recrystallized from diethylether:methanol (9:1) to obtain the pure compound diethyl(4,6-difluorobenzo[*d*]thiazol-2-ylamino)(4-fluorophenyl)methylphosphonate **(13).** The same procedure was adopted for the synthesis of the remaining α-aminophosphonates **14–32**.

Preparation of SiO_2–$LaCl_3 \cdot 7H_2O$

Lanthanum (III) chloride heptahydrate (6 mmol, 2.23 gm) and silica gel (3.6 gm) were placed into a 50 mL round-bottom flask containing 20 mL of methanol. The mixture was heated for 2.0 h at reflux temperature (65–70 °C). The mixture was cooled, and the solvent was removed under reduced pressure. The product was dried in a vacuum oven for 3.0–4.0 h at 60 °C.

Antibacterial activity

The in vitro antibacterial activity of the α-aminophosphonates/phosphinates were screened against two Gram-positive bacterial stains, *Bacillus subtilis, Staphylococcus aureus* and two Gram-negative bacterial stains, *Pseudomonas aeruginosa, Escherichia coli* using agar well diffusion method [29]. Stock solution was prepared by dissolving 1 mg of the test compounds in 1 mL of dimethylsulphoxide (DMSO) and further diluted to prepare 100 µg/mL concentrations. The antibiotic Streptomycin was used as standard for comparing activity of the tested compounds. Freshly prepared Mueller Hinton Agar medium (20 mL) was poured in each petri plate. After solidification of the medium, 24 h old bacterial culture containing approximately 10^5–10^6 colony forming units (CFU) per mL was spread on the surface of the medium and 5–8 mm wells were created on the surface of the culture plates with sterile metallic borer and 1 mL of test compounds were loaded in each well and incubated at 37 °C for 24 h. The inhibition of the test pathogens by the synthesized compounds around the wells was measured to determine the antibacterial (zone of inhibition) activity of the samples under the study. The experiments were conducted in triplicate and average tabulated as final result.

Antifungal activity

Antifungal activity was screened against four fungal pathogens, *Candida albicans, Candida non-albicans, Aspergillus niger and Penicillium chrysogenum.* Antifungal activity was determined using the disc diffusion method [30] according to the National Committee for Clinical Laboratory Standards (NCCLS), 2003. Standard drug, Ampotericin B was used as negative control and DMSO was used as positive control. Stock solutions of the test compounds and standard drug was prepared in DMSO (Merck) was used as solvent control. All the fungal stains were grown pre-warmed Mueller–Hinton agar (MHA) is seeded throughout the plate evenly. The test compound were prepared in DMSO (100 µg/mL) were pipetted (10 µL) onto the sterile paper discs (6 mm diameter) and placed onto the surface of inoculated agar plates. Plates were inverted and incubated for 37 °C in incubator for 72 h. The zone of inhibition was measured in mm for activity of test compound. The experiment was repeated thrice and maintained for each test compound at every 24 h interval. After the incubation period, the diameter of inhibition zone was

measured and documented as an indicator for the activity of the compounds.

Resazurin based microtitre dilution assay

Resazurin based microtitre dilution assay was performed in 96 well plates under aseptic conditions [31]. A volume of 100 µL of test materials in 10% (v/v) Dimethyl sulphoxide (DMSO) or sterile water (usually a stock concentration 25 mg/ml for crude extracts) added into the first row of the plate. To all wells of plate 50 µL of nutrient broth and 50 µL of normal saline was added. Serial dilutions were performed using a multichannel pipette such that each well had 100 µL of the test material in serially descending concentrations. Tips were discarded after use. 10 µL of resazurin indicator solution was added in each well. Finally 10 µL of bacterial suspension was added to each well to achieve a concentration of 5×10^6 CFU/ml. Each plate was wrapped loosely with cling film to ensure that bacteria did not become dehydrated. Each plate had a set of controls: a column with a broad-spectrum antibiotic as positive control (usually tetracycline in serial dilution).

The plates were prepared in triplicate and placed in an incubator set at 37 °C for 18–24 h. The colour change was then assessed visually. Any colour change from purple to pink or colorless was recorded as positive. The lowest concentration at which colour change occurred was taken as the MIC value. The average of three values was calculated and that was the MIC for the test material.

Conclusion

A heterogeneous catalyst, SiO_2–$LaCl_3 \cdot 7H_2O$, was prepared, its structure was characterized by FT-IR, XRD, SEM, and EDS analyses, and its stability was determined by TGA and DTA. The catalytic activity of the SiO_2–$LaCl_3 \cdot 7H_2O$ catalyst was tested for application in a one-pot three-component Kabachnik-Fields reaction for the synthesis of α-aminophosphonates. The reaction conditions were optimized by conventional as well as microwave methods, and a library of α-aminophosphonates was prepared under solvent-free conditions by varying the numerous benzothiazole and thiadiazole amines and substituted benzaldehydes. The protocol has several advantages such as high tolerance to temperature, easy preparation, easy recovery, reusability of the catalyst, neat reaction conditions, environmental benignity, short reaction time, excellent product yield, product purity, no need for tedious column chromatography and generality to produce a library of compounds.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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Authors and Affiliations

S. K. Thaslim Basha[1] · Reddi Mohan Naidu Kalla[2] · M. Varalakshmi[3] · H. Sudhamani[1] · Rama Moorthy Appa[4] · Sung Chul Hong[4] · Chamarthi Naga Raju[1]

✉ Reddi Mohan Naidu Kalla
reddinaidu.svu@gmail.com

✉ Sung Chul Hong
sunghong@sejong.ac.kr

✉ Chamarthi Naga Raju
rajuchamarthi10@gmail.com

[1] Organic Division, Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India

[2] Department of Science and Humanities, Sri Venkateswara Engineering College, Karakambadi Road, Tirupati, Andhra Pradesh 517507, India

[3] Centre of Applied Sciences, Department of Basic Sciences and Humanities, Sree Vidyanikethan Engineering College, A. Rangampet, Tirupati, Andhra Pradesh 517502, India

[4] HMC, Department of Nanotechnology and Advanced Materials Engineering, Sejong University, 209 Neungdong-ro, Gwangjin-gu, Seoul 143-747, Republic of Korea