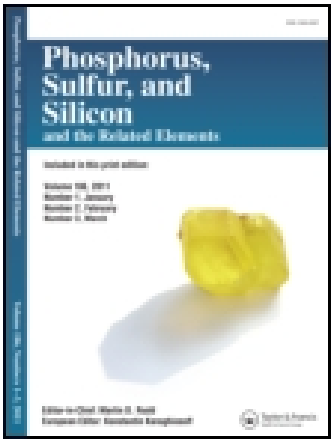

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$CeCl_3 \cdot 7H_2O$ Catalyzed, Microwave-Assisted High-Yield Synthesis of α-Aminophosphonates and their Biological Studies

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$CeCl_3 \cdot 7H_2O$ CATALYZED, MICROWAVE-ASSISTED HIGH-YIELD SYNTHESIS OF α-AMINOPHOSPHONATES AND THEIR BIOLOGICAL STUDIES

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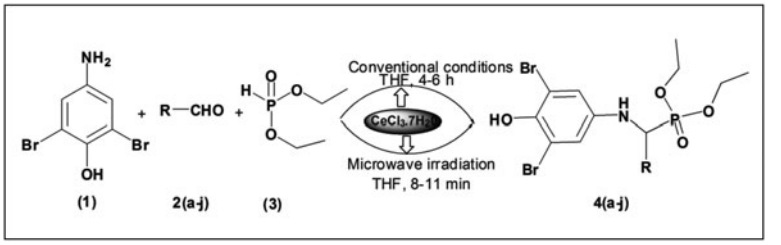
GRAPHICAL ABSTRACT



Abstract *A new class of diethyl(3,5-dibromo-4-hydroxyphenylamino) (substituted phenyl/heterocyclic) methylphosphonates* ***4(a–j)*** *has been synthesized by one-pot three component simultaneous reaction (Kabachnik–Fields) of 4-amino-2,6-dibromophenol* ***1****, substituted heterocyclic/phenyl aldehydes* ***2(a–j)****, and diethylphosphite* ***3*** *using a Lewis acid catalyst, $CeCl_3 \cdot 7H_2O$ (5 mol%) under microwave irradiation as well as conventional conditions. It was observed that microwave irradiation method is more facile, efficient, and advantageous with respect to reaction time and yields. The structures of all the synthesized compounds were supported by analyzing IR, $^1H/^{13}C/^{31}P$ NMR, and mass spectral data. The synthesized compounds were screened for their in vitro antimicrobial and antioxidant activities.*

Keywords α-Aminophosphonates; Lewis acid catalyst ($CeCl_3 \cdot 7H_2O$); microwave irradiation; antimicrobial and antioxidant activities

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INTRODUCTION

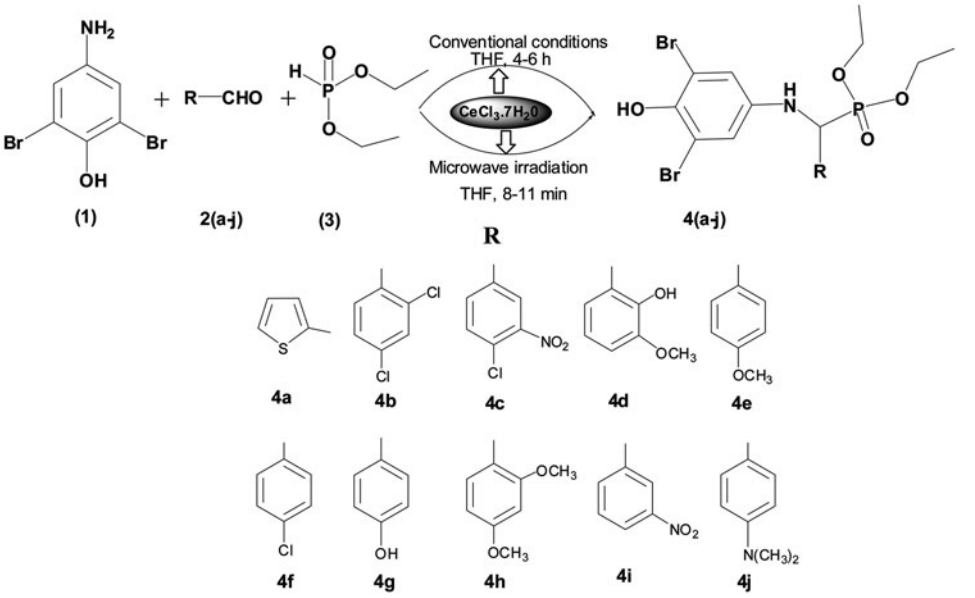
Phosphorus functionalized organic molecules have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties[1] and offer fascinating possibilities for structural, synthetic, and mechanistic study.[2] As mimics of natural amino acids and of low mammalian toxicity, the α-aminophosphonates and derivatives are currently attracting a great deal of interest in industrial as well as in medicinal chemistry.[3] They are also found to be effective in inhibiting test-tube growth of malarial parasite[4] *plasmodium falciparum*, and it has same effect as related types of single-celled parasites such as Toxoplasma that causes opportunistic infections in AIDS patients.[5] Also, these derivatives have shown various biological activities such as antifungal activity,[6] antibacterial activity,[7] antitumor effects,[8] antiviral activity,[9] enzymes inhibitors such as rennin, HIV protease, serine protease,[10] PTP1B inhibitors,[11] herbicides,[12] and pharmacological agents.[13] The marine red algae of the family Rhodomelaceae are known to contain high concentration of bromophenols with a diversity of molecular structures. Some of the bromophenols previously isolated from this family have shown significant nitrite scavenging, glucosidase inhibition, and antioxidant activities.[14]

Several methodologies have reported in the literature to synthesize α-aminophosphonate (–P-C-N bond) derivatives by Pudovik reaction as well as other pathways such as Mannich-type reactions and Kabachnik–Fields. Among them, Kabachnik–Fields reaction is a powerful one-pot three component (amine, aldehyde, phosphite) reaction to synthesize α-aminophosphonate derivatives.[15] Several Lewis acid catalysts, such as $InCl_3$,[16] $BiCl_3$,[17] $FeCl_3$,[18] $YbCl_3$,[19] and $SbCl_3$,[20] have been used to promote this reaction easily and efficiently. Recently, Jafari et al.[21] reported three component synthesis of α-aminophosphonates using Cerium (III) chloride heptahydrate catalyst under solvent-free conditions. Although the described procedures worked nicely in many cases, they are associated with one or more shortcomings, such as long reaction time, low yield, lack of generality, require stoichiometric amount of toxic catalyst, moisture sensitive catalyst, the use of an expensive or less easily available catalysts, generate large amount of waste, and vigorous reaction conditions.

$CeCl_3 \cdot 7H_2O$ has emerged as a potential catalyst for effecting various organic transformations due to its high catalytic ability, water tolerance, economic availability, and being a "eco-friendly" reagent.[22] Moreover, microwave chemistry can provide access to synthetic transformations that may be prohibitively long or low yielding using conventional heating. As part of our research program, we synthesized a series of new diethyl(3,5-dibromo-4-hydroxyphenylamino) (substituted phenyl/heterocyclic) methylphosphonates **4(a–j)** in tetrahydrofuran (THF) solvent under microwave irradiation conditions as well as conventional conditions using $CeCl_3 \cdot 7H_2O$. Optimum yields of α-aminophosphonate derivatives were obtained under microwave irradiation. The antibacterial and antifungal activities of titled compounds were investigated against corresponding pathogens and some of the compounds showed significant activity against microorganisms. Also, the antioxidant activity of the synthesized compounds was examined; **4c**, **4d**, **4g**, and **4i** exhibited potent antioxidant activity.

RESULTS AND DISCUSSION

The synthesis of new α-aminophosphonate derivatives was carried out effectively in the presence of $CeCl_3 \cdot 7H_2O$ under microwave irradiation and conventional conditions as depicted in Scheme 1.



Scheme 1 Synthesis of α-aminophosphonates **4(a–j)** in the presence of $CeCl_3 \cdot 7H_2O$.

4-Amino-2,6-dibromophenol (**1**), 4-chloro-3-nitrobenzaldehyde (**2c**), and diethylphosphite (**3**) were selected as materials for optimization of the reaction conditions. The three component Kabachnik–Fields reaction was examined with these models in different solvents, such as ethanol (EtOH), THF, toluene, dimethylformamide (DMF), and acetonitrile (ACN) using 5 mol% of $CeCl_3 \cdot 7H_2O$ at 50–65°C to synthesize compound **4c** and the yields are shown in Table 1. The reaction in THF solvent gave the highest yield (88%) of **4c** (Table 1, entry 2) as compared with other solvents. To establish the generality of the reaction, various aldehydes were examined in the presence of 5 mol% of $CeCl_3 \cdot 7H_2O$ in THF solvent to afford the corresponding α-aminophosphonates **4(a–f)** (Table 2). To reduce the reaction time and improve the yields, the model reaction was tested under microwave irradiation [CATA-4R, Power (70%) Watts (490)] using 5 mol% of $CeCl_3 \cdot 7H_2O$ catalyst in THF solvent. A high yield (Table 2, entry 3) (94%) was observed in a short reaction time (8 min). This optimized procedure was applied for the synthesis of all the title compounds that were already prepared under conventional conditions and the results are summarized in Table 2. The reusability of the catalyst was also examined up to

Table 1 Solvent effect on the synthesis of α-aminophosphonates using $CeCl_3 \cdot 7H_2O$ (5 mol%)

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	Ethanol	60	6	75
2	THF	65	3	88
3	Toluene	80	6	70
4	DMF	85	5	78
5	ACN	50	7	69

Table 2 Synthesis of α-aminophosphonates using $CeCl_3 \cdot 7H_2O$ (5 mol%) under conventional and microwave irradiation conditions

		Conventional conditions		Microwave irradiation		
Entry	Compd	Time (h)	Yield (%)	Time (min)	Yield (%)	mp (°C)
1	**4a**	3.5	84	10	90	118–120
2	**4b**	4	81	11	89	183–185
3	**4c**	3	88	8	94	145–147
4	**4d**	4	83	10	89	178–180
5	**4e**	4	84	11	90	129–131
6	**4f**	3.5	84	9	91	135–137
7	**4g**	3.5	85	9	90	137–139
8	**4h**	3.5	82	9	90	178–180
9	**4i**	3	85	8	92	131–133
10	**4j**	3.5	83	10	91	112–114

two cycles to synthesize compound **4c** and gave the corresponding yields 80% and 76% in conventional conditions and 90% and 87% in microwave conditions.

A reasonable pathway for the reaction of an amine and an aldehyde with diethylphosphite using $CeCl_3 \cdot 7H_2O$ catalyst in THF is presented in Figure 1, in which $CeCl_3 \cdot 7H_2O$ exhibits dual activity: one action is in situ generation of imine and the second action is to

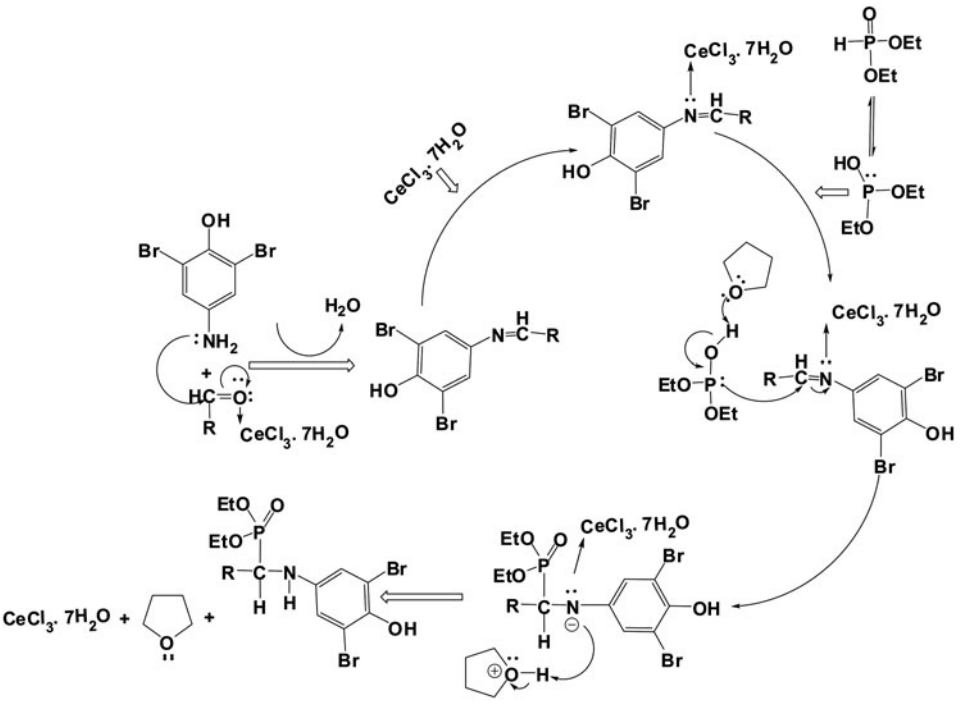


Figure 1 The plausible mechanism for synthesis of α-aminophosphonates in the presence of $CeCl_3 \cdot 7H_2O$ catalyst.

enhance the activity of imine, and to bring the diethylphosphite substrate close to the imine by the template effect.[21,23]

The structures of the title compounds **4(a–j)** were confirmed by analytical and spectral data (see Experimental section). The IR absorption bands appeared in the region of 3400–3520, 3200–3380, and 1210–1260 cm^{-1} of the –O-H, -N-H, and -P=O stretches, respectively. In ^{1}H NMR spectra, the chemical shifts appeared in the region of 1.00–1.30, 3.50–4.20, 4.50–5.40, 6.00–6.93, and 6.50–8.50 of the $–CH_3$, $-OCH_2$, -CHP-N-, -NH-CH, and aromatic protons, respectively. Further, the structural confirmation of the designed compounds **4(a–j)** was confirmed by the corresponding ^{13}C NMR chemical shift values and molecular ions, fragmentation ion peaks in the mass spectra.

The synthesized compounds in the present paper were screened for their antibacterial activity (Table S1, Supplemental Materials) against the growth of *Staphylococcus auerus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* by employing cup-plate agar diffusion method,[24] and streptomycin was used as standard drug. The antifungal activity was tested (Table S2, Supplemental Materials) against fungi such as *Trichoderma harzanium, Aspergillus flavus*, and *Aspergillus niger* by using agar disc-diffusion method,[25] and bovastin was used as reference drug. Minimum inhibitory concentrations of the synthesized compounds against tested strains were also investigated by using micro-broth dilution method.[26] Antioxidant activity of the titled compounds was also tested using 1,1-diphenylpicrylhydrazyl (DPPH)[27] (Table S3) and nitric oxide (NO) (Table S4) method.[28]

CONCLUSION

We have prepared biologically active α-aminophosphonate derivatives in excellent yields in short reaction times by a one-pot, three component reaction using $CeCl_3 \cdot 7H_2O$ as a catalyst under microwave irradiation as well as conventional conditions in THF solvent. In vitro antimicrobial activity includes minimum inhibition concentrations (MICs) against the growth of selected microorganisms and antioxidant activity was examined. Most of the compounds exhibited potent to moderate activity against the tested pathogens. It is concluded that the present method might be useful for the synthesis of α-aminophosphonate derivatives in short reaction time with high yields in small scale and the title compounds may be act as reference compounds or intermediates for further synthesis of potent chemotherapeutic agents in future.

EXPERIMENTAL

All chemicals were purchased from Merck, Aldrich and S. D. Fine-chem. (India) for use without further purification. Solvents were distilled from the appropriate drying agents and degassed before use. Melting points were determined in open capillaries on Guna melting point apparatus and are uncorrected. IR spectra were recorded on JASCO FT-IR 5300 using KBr discs. ^{1}H NMR, ^{31}P NMR, and ^{13}C NMR spectra were recorded on Bruker AV-400 spectrometer. Mass spectra were recorded on an API 3000 mass spectrometer (Positive mode). The progress of the reactions was monitored by thin layer chromatography (TLC) on Merck silica plates. Results are presented as chemical shift δ in ppm, multiplicity, J values in Hertz (Hz), number of protons, and proton's position. Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), and m (multiplet).

Synthesis of α-Aminophosphonates Under Conventional Conditions

4-Amino-2,6-dibromophenol (**1**) (264.87 mg, 1 mmol), 4-chloro-3-nitrobenz aldehyde (**2c**) (144.99 mg, 1 mmol), and diethylphosphite (**3**) (0.162 mL, 1.2 mmol) were dissolved in THF (10 mL) and stirred for 5 min to obtain a homogeneous solution. To this reaction mixture, the catalyst $CeCl_3 \cdot 7H_2O$ (5 mol%) was added and the mixture was refluxed at 60°C for 3 h. After completion of the reaction (checked by TLC), the reaction mixture was filtered to remove the catalyst. The filtrate was evaporated under vacuum and the resulting crude material was purified by chromatography on small silica gel column using 30% ethyl acetate and *n*-hexane as an eluent to afford diethyl(4-chloro-3-nitrophenyl) (3,5-dibromo-4-hydroxyphenylamino)methylphosphonate **4c** (88%).

Pale yellow solid, yield: 94%, mp: 145–147°C. FT-IR (KBr) (ν_{max} cm^{-1}): 3423 (-OH, str), 3029 (-NH, str), 1503 (-N=O, str), 1235 (-P=O, str), 1018 (-P-O-C, str); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, $J = 7.2$ Hz, 3H, $-CH_3$), 1.18 (t, $J = 6.8$ Hz, 3H, $-CH_3$), 3.85–4.10 (m, 4H, $-OCH_2$), 5.35 (dd, $J = 13.2$ Hz, $J = 10.8$ Hz, 1H, -P-CH-N), 6.52 (d, $J = 8.4$ Hz, 1H, -NH-CH), 7.08 (s, 2H, Ar-H), 7.79–7.85 (m, 2H, Ar-H), 8.21 (s, 1H, Ar-H), 8.90 (s, 1H, Ar-OH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 16.3 (C_{15}, C_{17}), 62.5 (C_{14}, C_{16}), 62.04 (C_7), 113.1 (C_3, C_5), 116.8 (C_2, C_6), 124.7 (C_9), 125.8 (C_{11}), 132.3 (C_{12}), 134.0 (C_{13}), 135.1 (C_8), 142.6 (C_4), 142.8 (C_1), 147.0 (C_{10}); ^{31}P NMR (DMSO-d_6, 200 MHz): δ 22.7. MS (positive mode) (*m*/*z*): 571 ($M + H^+$), 573 ($M + 2{+}H^+$), 575 ($M + 4{+}H^+$), 577 ($M + 6 + H^+$).

Reusability of the Active Catalyst

After completion of the reaction, the reaction mixture was cooled and filtered-off to remove the catalyst. The residue, $CeCl_3 \cdot 7H_2O$ was washed with dichloromethane (DCM; 3×10 mL) to remove the tars and then dried in an oven at 60°C for 2 h. The catalyst was reused up to two cycles without loss of catalytic activity.

Synthesis of α-Aminophosphonates Under Microwave Irradiation Conditions

A mixture of 4-amino-2,6-dibromophenol (**1**) (264.87 mg, 1 mmol), 4-chloro-3-nitrobenzaldehyde (**2c**) (144.99 mg, 1 mmol), and diethylphosphite (**3**) (0.162 mL, 1.2 mmol) was dissolved in a 50 mL beaker containing THF (5 mL). The reaction mixture was irradiated with microwave radiation using 4R Catalyst micro oven at Power cycling 70%, Watts 490. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was filtered to remove the catalyst. The filtrate was evaporated under vacuum and the resulting crude material was purified by column chromatography using 30% ethyl acetate and *n*-hexane as an eluent to afford diethyl(4-chloro-3-nitrophenyl)(3,5-dibromo-4-hydroxyphenylamino)methylphosphonate **4c** (94%).

The characterization data for the other synthesized compounds can be found in the Supplemental Materials.

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