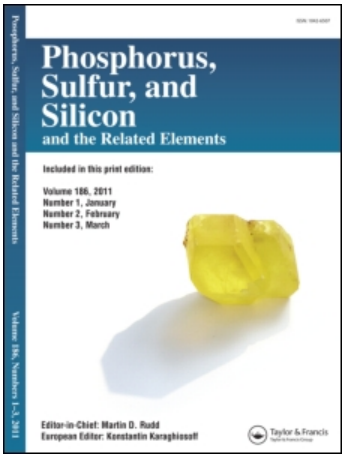


## Phosphorus, Sulfur, and Silicon and the Related Elements

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# Green Synthesis of Aminobisphosphonates Under Microwave Irradiation

G. Chandra Sekhar Reddy[a]; M. Veera Narayana Reddy[a]; N. Bakthavatchala Reddy[a]; C. Suresh Reddy[a]
[a] Department of Chemistry, Sri Venkateswara University, Tirupati, India

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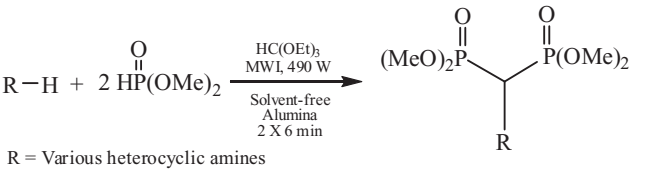
# GREEN SYNTHESIS OF AMINOBISPHOSPHONATES UNDER MICROWAVE IRRADIATION

**G. Chandra Sekhar Reddy, M. Veera Narayana Reddy, N. Bakthavatchala Reddy, and C. Suresh Reddy**
*Department of Chemistry, Sri Venkateswara University, Tirupati, India*

## GRAPHICAL ABSTRACT




R = Various heterocyclic amines

**Abstract** *A simple, efficient, and environmentally benign green chemical method has been developed for the synthesis of aminobisphosphonates by reacting aliphatic/aromatic 2°-amines, dimethylphosphite, and triethylorthoformate by microwave irradiation under solvent-free conditions, in the presence of an alumina solid support. The advantages of this method are less reaction time, simple work-up, and excellent yields.*

*Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

**Keywords** Aminobisphosphonates; green synthesis; microwave irradiation; solvent-free



## INTRODUCTION

Recent developments in organophosphorus chemistry have been in the area of bisphosphonates (BPs) and bisphosphonic acids,[1] due to their diverse pharmacological properties. Their activities are attributed to the core carbon–phosphorus (P—C—P) and hydroxy bisphosphonate (P—C(OH)—P) structure. They are chemically stable analogues of naturally occurring endogenous metabolites and inorganic pyrophosphates with P—O—P bonding. They are metabolically more stable, they cannot be hydrolysed by phosphatases,[1] and they constitute an important class of biologically active compounds. A number of aminobisphosphonates or aminomethyl-bisphosphonates (N—BPs) in their zwitterionic forms (Figure 1) represent an important class of drugs currently used in the treatment of bone diseases such

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Address correspondence to C. Suresh Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati-517 502, India. E-mail: csrsvu@gmail.com

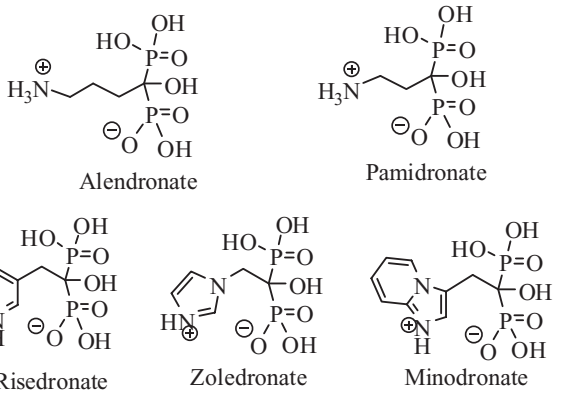



**Figure 1** Zwitterionic forms of some aminobisphosphonates.

as Paget's disease, myeloma, bone metastases, osteoporosis,[2] and hypercalcemia due to malignancy.[3]

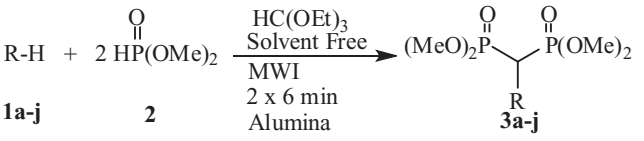
Bioactivity of BPs is also largely decided by the structure of the side chain and the nature of the functional groups connected with the methylene bisphosphonate moiety. Derivatives with an amino functional side chain at the $\alpha$-carbon of BPs are very active and physiologically potent compounds.[2] The length of the side chain is again relevant, with the highest activity being found with a side chain of three carbons, as present in alendronate. Cyclic geminal bisphosphonates are also observed to be very potent, especially those containing a nitrogen atom in the ring. The most active compounds described so far are zoledronate and minodronate, which belong to this class of cyclic bisphosphonates. These compounds function primarily by adsorbing to bone and inhibiting the synthesis of enzyme farnesyl diphosphate in osteoclasts, consequently resulting in decreased levels of protein prenylation.[4] BPs have also been found to exhibit antiparasitic activity.[5] They stimulate human $\gamma\delta$ T cells,[6] and this property is of current interest because of their use as vaccines for a variety of B cell malignancies.[7]

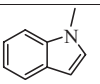
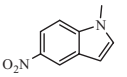
The conventional (oil bath) synthetic methodologies of N—BPs have a large number of problems,[8–10] and so there is a need to develop an alternate synthetic approach for these biologically important compounds. One of the advances in this area where substantial progress has been made is the microwave-assisted solid-support synthesis.[11,12]

We report in this article a novel green chemical method (Scheme 1) for the synthesis of amino-bisphosphonates (**3a–j**). The same compounds were prepared by the conventional techniques (Table 1) to compare and evaluate the results with respect to the green synthetic procedure. The spectral data and gas-chromatographic retention times of the compounds obtained by both the techniques were identical.

## RESULTS AND DISCUSSION

N—BPs were synthesized by stirring the mixture of aliphatic/aromatic 2°-amines, triethylorthoformate, and diethylphosphites (**2**) on solid support, alumina ($Al_2O_3$), by microwave irradiation (MWI) for 12 min in two intervals. The $Al_2O_3$ is separated by filtration of the reaction mixture dissolving in the chloroform.




| Entry | R | Entry | R |
|---|---|---|---|
| **1a & 3a** |  | **1f &3f** |  |
| **1b & 3b** |  | **1g & 3g** |  |
| **1c & 3c** |  | **1h & 3h** |  |
| **1d & 3d** |  | **1i & 3i** |  |
| **1e & 3e** |  | **1j & 3j** |  |

**Scheme 1** Synthesis of aminobisphosphonates (**3a–j**).

To ascertain the merits of MWI on the reaction, comparative studies were carried out by manipulating the reaction in an oil-bath without changing other conditions. The results show that MW heating has advantages over the oil-heat method in terms of shorter reaction times, ease of manipulation, higher yields, and lower costs (i.e., they can be solvent-free). The rate enhancement in such reactions is due to rapid superheating of the solvent. Currently the methods are solvent-free; thus irradiation is performed in the presence of

**Table 1** Used conditions and results in synthesis of **3a–j**

| | Time | | Yield (%) | |
|---|---|---|---|---|
| Entry | MWI (min) | Oil bath (h) | MWI | Oil bath |
| **3a** | 2 × 6 | 3 | 90 | 58 |
| **3b** | 2 × 6 | 3 | 82 | 30 |
| **3c** | 2 × 6 | 3 | 89 | 54 |
| **3d** | 2 × 6 | 3 | 87 | 48 |
| **3e** | 2 × 6 | 3 | 84 | 34 |
| **3f** | 2 × 6 | 4 | 84 | 34 |
| **3g** | 2 × 6 | 4 | 86 | 43 |
| **3h** | 2 × 6 | 4 | 85 | 38 |
| **3i** | 2 × 6 | 4 | 86 | 43 |
| **3j** | 2 × 6 | 4 | 88 | 52 |

alumina mineral support reactants. In these cases the rate enhancement in such reactions can be due to simple thermal effects (high localized temperatures may be reached) or specific microwave effects.

The title compounds **3a–j** exhibited characteristic IR absorption bands in the regions 3010–3023, 2966–2986, 1240–1260, and 1010–1046 $cm^{-1}$ for C—$H_{aromatic}$, C—$H_{aliphatic}$, P=O, and P–O–C, respectively.[13] The $^1H$ NMR spectral data of **3a–j** showed characteristic peaks at $\delta$ 6.58–8.92 and 1.41–2.65 as multiplets for all aromatic and aliphatic hydrogens, respectively. The methoxy group protons of the dimethylphosphite moiety resonated as two distinct doublets in the range of $\delta$ 3.48–3.70, indicating their non-equivalency.[14] The P—CH—N hydrogens showed a triplet at $\delta$ 4.32–4.50 ($^2J_{PH} = 21.8$ Hz) by coupling with phosphorus.[15] In the $^{13}C$ NMR of **3a**, **3b**, **3d**, **3f**, and **3g**, all the aromatic carbons resonated at $\delta$ 97.9–145.6. The "PCH" $\alpha$-carbons resonated as doublet at $\delta$ 54.9–56.1($^1J_{PC} = 163.4$ Hz). The methoxy carbon on phosphorus resonated as doublet in the region of $\delta$ 55.6–56.8 ($^2J_{PC} = 6.5$ Hz) by coupling with phosphorus.[14] Other carbon chemical shifts appeared in the expected region. $^{31}P$ resonance signals appeared within the region 18.75–19.85 ppm for all title compounds.[15] The compounds **3a**, **3b**, **3d**, **3f**, and **3g** gave $M^{+\bullet}$ ions peaks corresponding to their molecular weights.



## EXPERIMENTAL

### Synthesis of Tetramethyl (1H-Indol-1-yl) Methylene Diphosphonate (3a)

***MWI method.*** Indole (**1a**) (0.005 mol), dimethylphosphite (0.01 mol), triethylorthoformate (0.005 mol), and 1 equiv. of $Al_2O_3$ were sufficiently mixed and exposed to MWI in the CATA-4R—Scientific Microwave oven (Catalyst Systems) at 490 W in ambient pressure. The reaction mixtures were heated successively for 6 min periods followed by a 2 min cooling interval between irradiations. This method was designed to avoid overheating of reactants, according to the procedure of Varma and Dahiya,[16] and the reaction mixtures were stirred continuously to maintain the homogeneity of the irradiating field throughout the intermittent reaction. By monitoring with TLC, the reaction was stopped after 12 min. Then chloroform (2 × 5 mL) was added to the container, and $Al_2O_3$ was separated by filtration. The solvent was evaporated in a rotary evaporator, and the residue was recrystallized from ethyl acetate to afford pure **3a** as a white solid, 1.56 g (yield, 90%), mp 118–120 °C.

***Oil-heat method.*** Indole (**1a**) (0.005 mol), dimethylphosphite (0.01 mol), and triethylortho-formate (0.01 mol) were sufficiently mixed and heated in an oil-bath (90 °C). TLC monitoring showed completion of the reaction after 3 h. The excess triethylorthoformate was removed on a rotary evaporator, and the crude product was washed repeatedly with petroleum ether and water. It was purified by column chromatography on 60–120 mesh silica gel using ethyl acetate:hexane (1:3) as eluent, and the solvent was evaporated in a rotary evaporator. The residue was recrystallized from ethyl acetate to afford pure **3a** as a white solid, 1.00 g (yield, 58%), mp 118–120 °C. This procedure was applied successfully for the preparation of other compounds (**3b–j**). All the compounds were characterized by IR, $^1H$, $^{13}C$, and $^{31}P$ NMR, mass spectral, and elemental analytical data.

### Physical, Analytical, and Spectral Data for the Compounds 3a–j

**Tetramethyl (1H-indol-1-yl)methylenediphosphonate (3a).** White solid, yield: 90%, mp: 115–117 °C; IR (KBr)($\nu_{max}$ $cm^{-1}$); 1254 (P=O), 3020 (C—$H_{aromatic}$),

2979 & 2967 (C—$H_{aliphatic}$), 1046 (P—O—C); $^1$H NMR ($\delta$ ppm): 6.85–7.82 (m, 6H, Ar-H), 4.42 (t, 1H, $^2J_{PH}$ = 21.8 Hz, PCH), 3.65 (d, 6H, $^3J_{PH}$ = 10.3 Hz, 2 × $OCH_3$), 3.52 (d, 6H, $^3J_{PH}$ = 9.2 Hz, 2 × $OCH_3$); $^{13}$C NMR ($\delta$ ppm): 130.2 (C-2), 98.7 (C-3), 130.8 (C-3a), 116.8 (C-4), 113.9 (C-5), 118.2 (C-6), 102.8 (C-7), 132.7 (C-7a), 54.9 (d, $^1J_{PC}$ = 163.4 Hz, PCH), 55.6 (d, $^2J_{PC}$ = 6.5 Hz, $OCH_3$); $^{31}$P NMR ($\delta$ ppm): 19.52; LCMS: (m/z) 347 ($M^{+\bullet}$). Anal.calcd for $C_{13}H_{19}NO_6P_2$: C, 44.97; H, 5.52; N, 4.03. Found: C, 44.93; H, 5.49; N, 4.00.

**Tetramethyl (5-nitro-1H-indol-1-yl)methylenediphosphonate (3b).** White solid, yield: 82%, mp: 120–122 °C; IR (KBr)($\nu_{max}$ cm$^{-1}$); 1245 (P=O), 3010 (C—$H_{aromatic}$), 2975 & 2966 (C—$H_{aliphatic}$), 1016 (P—O—C); $^1$H NMR ($\delta$ ppm): 6.85–8.92 (m, 5H, Ar-H), 4.41 (t, 1H, $^2J_{PH}$ = 21.7 Hz, PCH), 3.70 (d, 6H, $^3J_{PH}$ = 7.3 Hz, 2 × $OCH_3$), 3.63 (d, 6H, $^3J_{PH}$ = 7.3 Hz, 2 × $OCH_3$); $^{13}$C NMR ($\delta$ ppm): 130.4 (C-2), 97.9 (C-3), 129.8 (C-3), 145.6 (C-4), 133.8 (C-5), 113.9 (C-6), 104.2 (C-7), 144.9 (C-7), 55.15 (d, $^1J_{PC}$ = 163.5 Hz, PCH), 55.9 (d, $^2J_{PC}$ = 6.5 Hz, $OCH_3$); $^{31}$P NMR ($\delta$ ppm): 20.15; LCMS: (m/z) 392 ($M^{+\bullet}$). Anal.calcd for $C_{13}H_{18}N_2O_8P_2$: C, 39.81; H, 4.63; N, 7.14. Found: C, 39.77; H, 4.60; N, 7.10.

**Tetramethyl (1H-benzo[d]imidazol-1-yl)methylenediphosphonate (3c).** White solid, yield: 89%, mp: 112–114 °C; IR (KBr)($\nu_{max}$ cm$^{-1}$); 1248 (P=O), 3019 (C—$H_{aromatic}$), 2980 & 2972 (C—$H_{aliphatic}$), 1021 (P—O—C); $^1$H NMR ($\delta$ ppm): 7.18–8.02 (m, 5H, Ar-H), 4.42 (t, 1H, $^2J_{PH}$ = 21.6 Hz, PCH), 3.58 (d, 6H, $^3J_{PH}$ = 10.2 Hz, 2 × $OCH_3$), 3.51 (d, 6H, $^3J_{PH}$ = 9.2 Hz, 2 × $OCH_3$); $^{31}$P NMR ($\delta$ ppm): 19.87. Anal.calcd for $C_{12}H_{18}N_2O_6P_2$: C, 41.39; H, 5.21; N, 8.04. Found: C, 41.36; H, 5.18; N, 8.00.

**Tetramethyl (1H-pyrrol-1-yl)methylenediphosphonate (3d).** White solid, yield: 87%, mp: 110–112 °C; IR (KBr)($\nu_{max}$ cm$^{-1}$); 1251 (P=O), 3019 (C—$H_{aromatic}$), 2978 & 2969 (C—$H_{aliphatic}$), 1016 (P—O—C); $^1$H NMR ($\delta$ ppm): 6.75–7.15 (m, 4H, Ar-H), 4.41 (t, 1H, $^2J_{PH}$ = 21.5 Hz, PCH), 3.55 (d, 6H, $^3J_{PH}$ = 10.3 Hz, 2 × $OCH_3$), 3.49 (d, 6H, $^3J_{PH}$ = 9.2 Hz, 2 × $OCH_3$); $^{13}$C NMR ($\delta$ ppm): 127.6 (C-2&5), 98.2 (C-3&4), 54.3 (d, $^1J_{PC}$ = 163.4 Hz, PCH), 56.3 (d, $^2J_{PC}$ = 6.3 Hz, $OCH_3$); $^{31}$P NMR ($\delta$ ppm): 18.90; LCMS: (m/z) 297 ($M^{+\bullet}$). Anal.calcd for $C_9H_{17}NO_6P_2$: C, 36.37; H, 5.77; N, 4.71. Found: C, 36.33; H, 5.72; N, 4.67.

**Tetramethyl (1H-imidazol-1-yl)methylenediphosphonate (3e).** White solid, yield: 84%, mp: 122–124 °C; IR (KBr)($\nu_{max}$ cm$^{-1}$); 1244 (P=O), 3023 (C—$H_{aromatic}$), 2981 & 2973 (C—$H_{aliphatic}$), 1014 (P—O—C); $^1$H NMR ($\delta$ ppm): 6.58–7.68 (m, 3H, Ar-H), 4.41 (t, 1H, $^2J_{PH}$ = 21.6 Hz, PCH), 3.58 (d, 6H, $^3J_{PH}$ = 10.3 Hz, 2 × $OCH_3$), 3.51 (d, 6H, $^3J_{PH}$ = 9.2 Hz, 2 × $OCH_3$); $^{31}$P NMR ($\delta$ ppm): 19.75. Anal.calcd for $C_8H_{16}N_2O_6P_2$: C, 32.23; H, 5.41; N, 9.40. Found: C, 32.20; H, 5.38; N, 9.38.

**Tetramethyl pyrrolidin-1-ylmethylenediphosphonate (3f).** White solid, yield: 84%, mp: 109–111 °C; IR (KBr)($\nu_{max}$ cm$^{-1}$); 1243 (P=O), 3017 (C—$H_{aromatic}$), 2975 & 2967 (C—$H_{aliphatic}$), 1022 (P—O—C); $^1$H NMR ($\delta$ ppm): 2.25–2.51 (m, 4H, $NCH_2$), 1.87–2.04 (m, 4H, $CCH_2$), 4.39 (t, 1H, $^2J_{PH}$ = 21.3 Hz, PCH), 3.53 (d, 6H, $^3J_{PH}$ = 10.3 Hz, 2 × $OCH_3$), 3.48 (d, 6H, $^3J_{PH}$ = 9.2 Hz, 2 × $OCH_3$); $^{13}$C NMR ($\delta$ ppm): 56.8 (C-2&5), 21.2 (C-3&4), 56.1 (d, $^1J_{PC}$ = 163.4 Hz, PCH), 56.2 (d, $^2J_{PC}$ = 6.3 Hz, $OCH_3$); $^{31}$P NMR ($\delta$ ppm): 18.86; LCMS: (m/z) 301 ($M^{+\bullet}$). Anal.calcd for $C_9H_{21}NO_6P_2$: C, 35.89; H, 7.03; N, 4.65. Found: C, 35.85; H, 7.00; N, 4.61.

**Tetramethyl piperidin-1-ylmethylenediphosphonate (3g).** White solid, yield: 86%, mp: 123–125 °C; IR (KBr)($\nu_{max}$ cm$^{-1}$); 1254 (P=O), 3022 (C—$H_{aromatic}$), 2984 & 2976 (C—$H_{aliphatic}$), 1026 (P—O—C); $^1$H NMR ($\delta$ ppm): 2.40–2.63 (m, 4H, $NCH_2$),

1.41–1.52 (m, 6H, $CCH_2$), 1.25–1.48 (m, 6H, $CCH_2$), 4.32 (t, 1H, $^2J_{PH} = 20.8$ Hz, PCH), 3.52 (d, 6H, $^3J_{PH} = 10.3$ Hz, $2 \times OCH_3$), 3.48 (d, 6H, $^3J_{PH} = 9.2$ Hz, $2 \times OCH_3$); $^{13}$C NMR ($\delta$ ppm): 52.8 (C-2&6), 23.8 (C-3&5), 23.2 (C-4), 55.7 (d, $^1J_{PC} = 163.5$ Hz, PCH), 56.8 (d, $^2J_{PC} = 6.3$ Hz, $OCH_3$); $^{31}$P NMR ($\delta$ ppm): 18.75; LCMS: (m/z) 315 ($M^{+\bullet}$). Anal.calcd for $C_{10}H_{23}NO_6P_2$: C, 38.10; H, 7.35; N, 4.44. Found: C, 38.06; H, 7.32; N, 4.40.

**Tetramethyl morpholinomethylenediphosphonate (3h).** White solid, yield: 85%, mp: 119–121 °C; IR (KBr)($\nu_{max}$ $cm^{-1}$); 1247 (P=O), 3015 (C−$H_{aromatic}$), 2986 & 2972 (C−$H_{aliphatic}$), 1023 (P−O−C); $^1$H-NMR ($\delta$ ppm): 2.51–2.65 (m, 4H, $NCH_2$), 3.40–3.54 (m, 4H, $OCH_2$), 4.43 (t, 1H, $^2J_{PH} = 21.5$ Hz, PCH), 3.54 (d, 6H, $^3J_{PH} = 10.2$ Hz, $2 \times OCH_3$), 3.50 (d, 6H, $^3J_{PH} = 9.2$ Hz, $2 \times OCH_3$); $^{31}$P NMR ($\delta$ ppm): 19.85. Anal.calcd for $C_9H_{21}NO_7P_2$: C, 34.08; H, 6.67; N, 4.42. Found: C, 34.05; H, 6.64; N, 4.38.

**Tetramethyl thiomorpholinomethylenediphosphonate (3i).** White solid, yield: 86%, mp: 114–116 °C; IR (KBr)($\nu_{max}$ $cm^{-1}$); 1256 (P=O), 3021 (C−$H_{aromatic}$), 2980 & 2969 (C−$H_{aliphatic}$), 1020 (P−O−C); $^1$H NMR ($\delta$ ppm): 2.57–2.63 (m, 4H, $NCH_2$), 2.45–2.65 (m, 4H, $SCH_2$), 4.44 (t, 1H, $^2J_{PH} = 21.2$ Hz, PCH), 3.55 (d, 6H, $^3J_{PH} = 10.3$ Hz, $2 \times OCH_3$), 3.48 (d, 6H, $^3J_{PH} = 9.2$ Hz, $2 \times OCH_3$); $^{31}$P NMR ($\delta$ ppm): 19.82. Anal.calcd for $C_9H_{21}NO_6P_2S$: C, 32.43; H, 6.35; N, 4.20. Found: C, 32.39; H, 6.31; N, 4.16.

**Tetramethyl (4-methylpiperazin-1-yl)methylenediphosphonate (3j).** White solid, yield: 87%, mp: 130–132 °C; IR (KBr)($\nu_{max}$ $cm^{-1}$); 1251 (P=O), 3019 (C−$H_{aromatic}$), 2983 & 2974 (C−$H_{aliphatic}$), 1023 (P−O−C); $^1$H NMR ($\delta$ ppm): 2.29–2.60 (m, 8H, $NCH_2$), 2.15 (s, 3H, $NCH_3$), 4.50 (t, 1H, $^2J_{PH} = 21.1$ Hz, PCH), 3.55 (d, 6H, $^3J_{PH} = 10.3$ Hz, $2 \times OCH_3$), 3.50 (d, 6H, $^3J_{PH} = 9.2$ Hz, $2 \times OCH_3$); $^{31}$P NMR ($\delta$ ppm): 19.84. Anal.calcd for $C_{10}H_{24}N_2O_6P_2$: C, 36.37; H, 7.32; N, 8.48. Found: C, 36.33; H, 7.28; N, 8.43.



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