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One-Pot Synthesis of 1-Aminophosphinic Acids Using 50% Hypophosphorus Acid under Microwave Irradiation

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Dedicated to Professor Habib Firouzabadi on the occasion of his 65 birthday and also his retirement

A simple and efficient method has been developed for the synthesis of α-aminophosphinic acids from hypophosphorus acid under solvent–free conditions using microwave irradiation. α-Aminophosphinic acids were obtained in high yield under mild conditions by reaction of hypophosphorus acid with aldehydes in the presence of amines under microwave irradiation.

Keywords: Addition reaction, Aldehydes, Amines, 1-Aminophosphinic acids, Microwave-assisted

INTRODUCTION

Phosphinic acids are of growing importance in biological processes [1]. In recent years, the synthesis of α-substituted phosphoryl derivatives (phosphonic and phosphinic acids) has attracted considerable attention, due to their potential biological activities with broad application as enzyme inhibitors, antimetabolites and antibiotics. Among the α-functionalized phosphinic acids, α-aminoalkylphosphinic derivatives have potential biological activities such as anti-bacterial, herbicidal and fungicidal [2-4]. 1-Aminoalkylphosphinic acids, the phosphinic acid analogues of 1-amino carboxylic acids, are important compounds that exhibit a variety of interesting and useful properties. In contrast to the widely studied 1-aminoalkylphosphonic acid derivatives [5-8], relatively few papers have been reported on the chemistry of 1-aminoalkylphosphinic acids, although there are evidences that α-aminophosphinic acids are pharmacologically active compounds.

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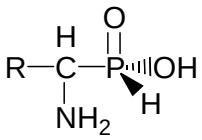
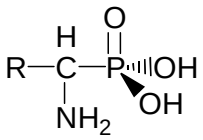


1-aminoalkylphosphinic acid



1-aminoalkylphosphonic acid

Many effective methods for the preparation of 1-aminoalkylphosphonic acids have been developed, but few synthetic routes to 1-aminoalkylphosphinic acids have been reported which involve Manich-type reaction of amines with aldehydes in the presence of anhydrous hypophosphorus acid and prolonged heating of anhydrous hypophosphorus acid in the presence of a Schiff's base. Addition of hypophosphorus acid to structurally diverse imines appears to be a general method for the preparation of *N*-substituted 1-aminoalkanephosphinic acids [9]. However there are problems with drastic reaction conditions, anaerobic and anhydrous conditions, long reaction times and severe side reactions. On the other hand the key step in one-pot synthesis of 1-aminoalkyl phosphinic acid is the nucleophilic addition of an

amine to a carbonyl compound followed by the addition of hyphophosphorus acid as nucleophile to the resulting imine. Formation of 1-hydroxyalkylphosphinic acids frequently accompanies the formation of 1-aminoalkylphosphinic acids [10].

As part of our efforts to explore the utility of microwave-assisted reactions for the synthesis of organophosphorus compounds [11], we report here a one-pot method for the preparation of α-aminoalkylphosphinic acids from a mixture of aldehyde and amine in the presence of hypophosphorus acid in solvent-free conditions under microwave irradiation.

EXPERIMENTAL

General

All chemicals were commercial products and distilled or recrystallized before use. All melting points were obtained by a Buchi 510 and are uncorrected. NMR spectra were taken with a 250 Brucker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to $CHCl_3$ (δ=7.26) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are recorded relative to the $CDCl_3$ resonance (δ=77.0). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ=0) with broad-band ^{1}H decoupling. A kitchen-type microwave was used in all experiments. Silica gel column chromatography was carried out with Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC.

General Procedure for the One-Pot Synthesis of 1-Aminophosphinic Acids 3: 10 mmol of hypophosphorus acid (50% solution) was added to 10 mmol of amine and the mixture was irradiated under microwave for 2 min (a kitchen-type Samsung microwave oven, model number CE290DN, was used in all experiments). Aldehyde (12 mmol) was added to reaction mixture and the mixture irradiated under microwave for 1-6 min. 30 mL of 50% sodium hydroxide (30 mL, 5%) was added dropwise to reaction mixture and extracted with ether (3x50 ml) until the ether layer appeared completely colorless. The aqueous portion was fed from residual ether by heating. After cooling, 3N hydrochloric acid was added dropwise to the aqueous solution with rapid stirring until no further precipitate appeared. The precipitated phosphininc acid was filtered and redissolved in aqueous sodium hydroxide, the solution again extracted with ether, and the phosphinic acid reprecipitated by adding to aqueous hydrochloric acid as shown above. After filtration, washing with water, and drying *in vacuo* over phosphorus pentoxide (58-79% yield) a white solid was obtained. All products gave satisfactory spectral data in accord with the assigned structures.

Anilino(phenyl)methylphosphinic acid (**3a)**.
White solid; mp 150-152 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 4.78 (1H, d, J_{HP}=19.7 Hz, -CHP), 6.48 (1H, t, *J*=7.2 Hz), 6.65 (2H, d, *J*=8.2), 6.91 (2H, t, *J*=7.2 Hz), 6.90 (1H, d, J_{HP}=550 Hz), 7.20-7.50 (m, 5H); ^{31}P NMR (DMSO/H_3PO_4): 26.26; ^{13}C NMR (DMSO/TMS-62.9 MHz): 57.5 (d, J_{CP}=98.7 Hz, C-P), 113..9, 117.4, 127.5.8-129.2 (aromatic), 136.5, 147.6 (d, J_{CP}=13.5 Hz). IR (KBr): 3650-2120 (-NH_3), 2356 (P-H), 1187 (P=O), 1055-930 (P-O) cm^{-1}; Anal. Calcd for $C_{13}H_{14}NO_2P$. C, 63.1; H, 5.7; N, 5.7. Found: C, 62.8; H, 5.4; N, 5.5.

Anilino(4-methylphenyl)methylphosphinic acid (**3b)**:
White solid; mp 106-109 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 2.34 (s, 3H), 4.74 (1H, d, J_{HP}=19.3 Hz, -CHP), 6.50 (1H, t, *J*=7.2 Hz), 6.68 (2H, d, *J*=8.2), 6.89 (1H, d, J_{HP}=540 Hz), 6.95 (2H, t, *J*=7.2 Hz), 7.09 (2H, d, *J*=5.5 Hz), 7.32 (2H, d, *J*=6.2); ^{31}P NMR (DMSO/H_3PO_4): 26.13 ; ^{13}C NMR (DMSO/TMS-62.9 MHz): 21.1, 57.3 (d, J_{CP}=98.7 Hz, C-P), 113.9, 117.2, 128.4, 128.5, 129.1, 133.6, 136.7 (d, J_{CP}=3.1 Hz), 147.8 (d, J_{CP}=13.2 Hz). IR (KBr): 3650-2120 (-NH_3), 1171 (P=O), 2357 (P-H), 1055-950 (P-O) cm^{-1}; Anal. Calcd for $C_{13}H_{14}NO_2P$. C, 64.3; H, 6.2; N, 5.4. Found: C, 64.0; H, 6.0; N, 5.3.

Anilino(1-naphthyl)methylphosphinic acid (**3c)**:
White solid; mp 140-143 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 5.31 (1H, d, J_{HP}=19.7 Hz, -CHP), 6.48 (1H, t, *J*=7.2 Hz), 6.65 (2H, d, *J*=8.2), 6.91 (2H, t, *J*=7.2 Hz), 7.05 (1H, d, J_{HP}=550 Hz), 7.42-7.90 (m, 6H), 8.45 (1H, d, *J*=8.3 Hz); ^{31}P NMR (DMSO/H_3PO_4): 25.34 ; ^{13}C NMR (DMSO/TMS-62.9 MHz): 53.4 (d, J_{CP}=98.6 Hz, C-P), 113.8, 117.4, 124.3, 125.8-129.2 (aromatic), 132.1 (d, J_{CP}=4.0 Hz), 133.0, 133.8, 147.6 (d, J_{CP}=13.5 Hz). IR (KBr): 3650-2020 (-NH_3), 1172 (P=O),

1055-960 (P-O) cm^{-1}; Anal. Calcd for $C_{17}H_{16}NO_2P$. C, 68.7; H, 5.4; N, 4.7. Found: C, 68.5; H, 5.1; N, 4.5.

(4-isopropylphenyl)[(3-nitrophenyl)amino]methylphosphinic acid (**3d**):
White solid; mp 100-103 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 1.06 (6H, d, *J*=6.8 Hz), 2.80 (1H, sep, *J*=6.8 Hz), 4.78 (1H, d, J_{HP}=19.7 Hz, -CHP), 6.83 (1H, d, J_{HP}=531.5 Hz), 6.90-7.65 (m, 8H); ^{31}P NMR (DMSO/H_3PO_4): 23.54; ^{13}C NMR (DMSO/TMS-62.9 MHz): 24.2, 24.3, 33.5, 57.6 (d, J_{CP}=95.2 Hz, C-P), 107.4, 111.1, 119.6, 119.7, 126.6, 128.3, 130.2, 133.8, 149.0, 149.5 (d, J_{CP}=12.8 Hz). IR (KBr): 3650-2120 (-NH_3), 2365 (P-H), 1201 (P=O), 980 (P-O) cm^{-1}; Anal. Calcd for $C_{16}H_{19}N_2O_4P$. C, 57.5; H, 5.7; N, 8.4. Found: C, 57.3; H, 5.4; N, 8.2.

(3-Fluorophenyl)[(3-nitrophenyl)amino]methylphosphinic acid (**3e**):
White solid; mp 90-93 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 5.08 (1H, d, J_{HP}=19.7 Hz, -CHP), 6.96 (1H, d, J_{HP}=547.8 Hz), 6.97-7.70 (m, 8H); ^{31}P NMR (DMSO/H_3PO_4): 24.35; ^{13}C NMR (DMSO/TMS-62.9 MHz): 55.6 (d, J_{CP}=97.5 Hz, C-P), 107.7, 111.8, 114.6, 114.9, 115.3, 119.9, 124.6, 130.4 130.6 (d, J_{CP}=7.6 Hz), 139.1, 148.9, 149.1 (d, J_{CP}=13.2 Hz). IR (KBr): 3650-2060 (-NH_3), 2365 (P-H), 1160 (P=O), 983 (P-O) cm^{-1}; Anal. Calcd for $C_{13}H_{12}FN_2O_4P$. C, 50.3; H, 3.9; N, 9.0. Found: C, 50.0; H, 3.8; N, 8.8.

(4-Chlorophenyl)[(3-nitrophenyl)amino]methylphosphinic acid (**3f**):
White solid; mp 130-134 °C;^{1}H NMR (DMSO/TMS-250 MHz): 4.77 (1H, d, J_{HP}=19.0 Hz, -CHP), 6.85 (1H, d, J_{HP}=529.8 Hz), 6.95-8.10 (m, 8H); ^{31}P NMR (DMSO/H_3PO_4): 21.51; ^{13}C NMR (DMSO/TMS-62.9 MHz): 57.7 (d, J_{CP}=93.7 Hz, C-P), 107.4, 111.2, 119.7, 128.1-132.1 (aromatic), 136.1, 138.2, 149.3 (d, J_{CP}=12.6 Hz); IR (KBr): 3650-2150 (-NH_3), 1201 (P=O), 1055-930 (P-O) cm^{-1}; Anal. Calcd for $C_{13}H_{12}ClN_2O_4P$. C, 47.8; H, 3.7; N, 8.6. Found: C, 47.6; H, 3.6; N, 8.6.

(3-Methoxyphenyl)[(4-bromophenyl)amino]methylphosphinic acid (**3g**):
White solid; mp 140-144 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 3.70 (s, 3H), 4.78 (1H, d, J_{HP}=19.3 Hz, -CHP), 6.70-7.30 (m, 8H), 6.92 (1H, d, J_{HP}=545 Hz); ^{31}P NMR (DMSO/H_3PO_4): 25.87; ^{13}C NMR (DMSO/TMS-62.9 MHz): 55.42, 57.4 (d, J_{CP}=98.8 Hz, C-P), 108.2, 112.8, 114.5, 115.9, 120.8, 129.7, 131.7, 137.9, 147.3 (d, J_{CP}=13.8 Hz), 159.7; IR (KBr): 3650-2120 (-NH_3), 2344 (P-H), 1163 (P=O), 1050-930 (P-O) cm^{-1}; Anal. Calcd for $C_{14}H_{15}NO_3P$. C, 60.8; H, 5.5; N, 5.1. Found: C, 60.5; H, 5.4; N, 4.9.

2-Naphthyl[(4-nitrophenyl)amino]methylphosphinic acid (**3h**):
White solid; mp 120-123 °C;
^{1}H NMR (DMSO/TMS-250 MHz): 5.16 (1H, d, J_{HP}=18.0 Hz, -CHP), 6.88 (1H, d, *J*=8.7 Hz), 6.80 (1H, d, J_{HP}=550 Hz), 7.42-8.10 (m, 1H); ^{31}P NMR (DMSO/H_3PO_4): 23.42; ^{13}C NMR (DMSO/TMS-62.9 MHz): 57.7 (d, J_{CP}=95.7 Hz, C-P), 126.2-128.3 (aromatic), 1325.8, 133.2, 133.8, 137.2, 154.3 (d, J_{CP}=13.5 Hz). IR (KBr): 3650-2100 (-NH_3), 2370 (P-H), 1183 (P=O), 1055-920 (P-O) cm^{-1}; Anal. Calcd for $C_{17}H_{15}N_2O_4P$. C, 59.6; H, 4.4; N, 8.2. Found: C, 59.6; H, 4.2; N, 8.0.

[(4-Methoxyphenyl)amino)](2-methylphenyl)methylphosphinic acid (**3i**):
White solid; mp 118-121 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 2.45 (s, 3H), 3.55 (s, 3H), 4.84 (1H, d, J_{HP}=20.5 Hz, -CHP), 5.80-6.30 (br, NH), 6.49-6.69 (4H, m), 7.02 (1H, d, J_{HP}=550 Hz), 7.05-7.30 (m, 3H), 7.40-7.60 (m, 1H); ^{31}P NMR (DMSO/H_3PO_4): 25.89; ^{13}C NMR (DMSO/TMS-62.9 MHz): 53.4 (d, J_{CP}=98.6 Hz, C-P), 113.8, 117.4, 124.3, 125.8-129.2 (aromatic), 132.1 (d, J_{CP}=4.0 Hz), 133.0, 133.8, 147.6 (d, J_{CP}=13.5 Hz). IR (KBr): 3650-2050 (-NH_3), 1185 (P=O), 1055-930 (P-O) cm^{-1}; Anal. Calcd for $C_{13}H_{12}FN_2O_4P$. C, 65.4; H, 6.6; N, 5.1. Found: C, 65.1; H, 6.5; N, 5.1.

[(4-Methoxyphenyl)amino)](4-fluorophenyl)methylphosphinic acid (**3j**):
White solid; mp 117-120 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 3.53 (s, 3H), 4.76 (1H, d, J_{HP}=19.0 Hz, -CHP), 6.50-7.60 (m, 8H), 6.95 (1H, d, J_{HP}=524 Hz); ^{31}P NMR (DMSO/H_3PO_4): 25.99; ^{13}C NMR (DMSO/TMS-62.9 MHz): 55.6, 57.4 (d, J_{CP}=99.4 Hz, C-P), 114.8, 115.1, 115.2, 115.5, 130.5, 132.9, 141.3 (d, J_{CP}=14.5 Hz), 151.9. IR (KBr): 3650-2120 (-NH_3), 2318 (P-H), 1170 (P=O), 1050-920 (P-O) cm^{-1}; Anal. Calcd for $C_{14}H_{15}FNO_3P$. C, 60.2; H, 5.4; N, 5.0. Found: C, 60.0; H, 5.3; N, 4.7.

(3-Methylphenyl)(1-naphthylamino)methylphosphinic acid (**3k)**:
White solid; mp 155-158 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 2.34 (s, 3H), 4.85 (1H, d, J_{HP}=20.5 Hz, -CHP), 6.20-8.40 (m, 11H), 7.05 (1H, d, J_{HP}=549 Hz); ^{31}P NMR (DMSO/H_3PO_4): 26.8; ^{13}C NMR (DMSO/TMS-62.9 MHz): 21.5, 58.2 (d, J_{CP}=96.9 Hz, C-P), 106.1, 117.7, 121.8, 124.0, 124.6, 125.0, 125.5, 126.3, 126.8, 128.5, 128.7, 134.3, 136.6, 136.7, 137.8 (d, J_{CP}=4.0 Hz), 142.7 (d, J_{CP}=13.2 Hz). IR (KBr): 3650-2150 (-NH_3), 2353 (P-H), 1160 (P=O), 1050-950 (P-O) cm^{-1}; Anal. Calcd for $C_{18}H_{18}NO_2P$. C, 69.4; H, 5.8; N, 4.5. Found: C, 69.2; H, 5.8; N, 4.4.

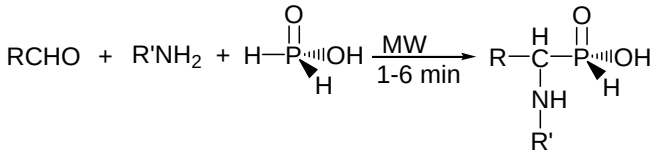
(3-Methoxyphenyl)(1-naphthylamino)methylphosphinic acid (**3l)**:
White solid; mp 160-163 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 3.63 (s, 3H), 4.93 (1H, d, J_{HP}=20.5 Hz, -CHP), 5.20-5.80 (br, NH), 6.42-8.40 (m, 11H), 7.03 (1H, d, J_{HP}=550 Hz), 7.42-7.90 (m, 6H); ^{31}P NMR (DMSO/H_3PO_4): 26.72;^{13}C NMR (DMSO/TMS-62.9 MHz): 55.4, 58.5 (d, J_{CP}=98.5 Hz, C-P), 106.1, 112.8, 114.3, 117.7, 120.6, 122.0, 122.0, 124.0, 124.9, 126.2, 126.8, 129.8, 134.3, 138.4, 142.7 (d, J_{CP}=13.5 Hz), 159.8; IR (KBr): 3650-2020 (-NH_3), 2360 (P-H), 1176 (P=O), 1055-960 (P-O) cm^{-1}; Anal. Calcd for $C_{18}H_{18}NO_3P$. C, 66.0; H, 5.5; N, 4.3. Found: C, 65.7; H, 5.4; N, 4.0.

1-Anilino-3-phenyl-prop-2-enylphosphinic acid (**3m):**
White solid; mp 118-120 °C; ^{1}H NMR (DMSO/TMS-250 MHz): 4.49 (1H, dd, J_{HH}=6.2 J_{HP}=19.2 Hz, -CHP), 6.23-7.45 (m, 12 H), 6.91 (1H, d, J_{HP}=540 Hz); ^{31}P NMR (DMSO/H_3PO_4): 25.74; ^{13}C NMR (DMSO/TMS-62.9 MHz): 55.9 (d, J_{CP}=100.6 Hz, C-P), 113.8, 117.4, 124.1, 126.7, 128.1, 129.1, 129.3, 132.2, 132.4, 136.7 (d, J_{CP}=3.8 Hz), 14.3, 147.7 (d, J_{CP}=10.6 Hz). IR (KBr): 3650-2120 (-NH_3), 2350 (P-H), 1196 (P=O), 1065-950 (P-O) cm^{-1}; Anal. Calcd for $C_{15}H_{16}NO_2P$. C, 65.9; H, 5.9; N, 5.1. Found: C, 65.7; H, 5.7; N, 4.9.

RESULTS AND DISCUSSION

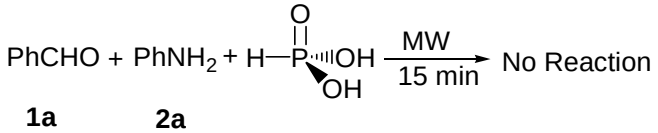
The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques [12]. Syntheses which normally requires for periods, can be achieved conveniently and very rapidly in a microwave oven. The three-component reaction of benzaldehyde **1a**, aniline **2a** and hyphophosphorus acid was selected as a model reaction for the one-pot synthesis of 1-aminophosphinic acid **3a** under microwave irradiation. As shown in Table 1, a mixture of aniline (**2a**) and benzaldehyde (**1a**) in the presence of hyphophosphorus acid under microwave irradiation, afforded the desired product (**3a**) in 79% yield. Other mixtures of amines and aldehydes also reacted with hypophosphorus acid under microwave irradiation to give desired compounds in good yields (Table 1). The strong electron withdrawing property of the nitro group in *p*-nitroaniline decreases the nucleophilicity of the amine group. As shown in Table 1, a mixture of *p*-nitroaniline and β-naphthaldehyde in the presence of hyphophosphorus acid under microwave irradiation, afforded the desired product in 66% yield. The reactions were clean with no tar formation.

These results prompted us to extend this process to phosphorus acid. Initially we carried out the reaction of benzaldehyde **1a** with anililine **2a** in the presence of phosphorus acid under microwave irradiation (Scheme 2). Unfortunately, the reaction failed and no product was detected after 15 min irradiation.



1 **2** **3**

Scheme 1



1a **2a**

Scheme 2

CONCLUSION

In summary, we reported here a one-pot method for the preparation of α-aminoalkylphosphinic acids from a mixture of aldehyde and amine in the presence of hypophosphorus acid

Table 1. One-pot synthesis of 1-aminophosphinic acids under microwave irradiation

Entry	R-	R'	Reaction Time (min)	Yield[a] (**3**)	^{31}P NMR (δppm)
a	C_6H_5-	C_6H_5-	5	79	26.26
b	*p*-$CH_3C_6H_4$-	C_6H_5-	1	65	26.13
c	1-$C_{10}H_7$-	C_6H_5-	1	75	25.34
d	*p*-$(CH_3)_2CHC_6H_4$-	*m*- $O_2NC_6H_4$-	5	62	23.54
e	*m*-FC_6H_4-	*m*- $O_2NC_6H_4$-	4	69	24.35
f	*p*-ClC_6H_4-	*m*- $O_2NC_6H_4$-	5	62	21.51
g	*m*-$CH_3OC_6H_4$-	*p*- BrC_6H_4-	4	77	25.87
h	2-$C_{10}H_7$-	*p*- $O_2NC_6H_4$-	6	66	23.42
i	*o*-$CH_3C_6H_4$-	*p*-$CH_3OC_6H_4$-	2	71	25.89
j	*p*-FC_6H_4-	*p*-$CH_3OC_6H_4$-	1	58	25.99
k	*m*-$CH_3C_6H_4$-	1-$C_{10}H_7$-	1	65	26.80
l	*m*-$CH_3OC_6H_4$-	1-$C_{10}H_7$-	1	70	26.72
m	Ph-CH=CH-	C_6H_5-	2	78	25.74

[a] Isolated Yields

under solvent-free conditions using microwave irradiation. A simple work-up, rapid reaction rates, mild reaction conditions, good yields, relatively clean reactions with no tar formation make this method an attractive and also a useful contribution to present methodologies. Indeed, a wide range of aldehydes and amines were converted to corresponding α-aminophosphinic acids using this method.

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