

Synthesis of Cyclic Aminomethylphosphonates and Aminomethyl-Arylphosphinic Acids by an Efficient Microwave-Mediated Phospha-Mannich Approach

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ABSTRACT: Microwave-assisted condensation of 1,3,2-dioxaphosphinane 2-oxide (**1**), paraformaldehyde and secondary amines including 5- and 6-membered *N*-heterocycles at 55°C gave cyclic aminomethylphosphonates (**2**), whereas an analogous reaction involving dibenzo[*c,e*][1,2]oxaphosphinane 2-oxide (**3**) resulted in the corresponding aminomethyl-2-(2'-hydroxybiphenyl)phosphinic acids (**4**) as a consequence of a hydrolytic ring opening following the condensation. © 2008 Wiley Periodicals, Inc. *Heteroatom Chem* 19:207–210, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20387

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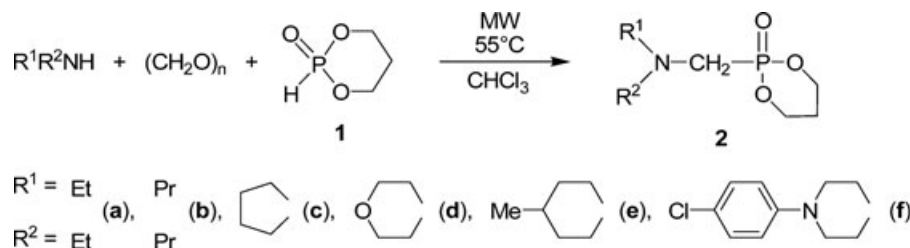
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INTRODUCTION

The Kabachnik–Fields reaction [1,2] involving the condensation of a ternary system comprising a $>\text{P}(\text{O})\text{H}$ reactant, an aldehyde or ketone, and a secondary or primary amine is an important method for the synthesis of compounds of type $>\text{NC}(\text{R}^1)(\text{R}^2)\text{P}(\text{O})<$, such as aminophosphonates [3–6] that forms an important class of biologically active compounds. The green chemical aspects of the Kabachnik–Fields reaction also received considerable attention [4,6].

In our laboratory, the microwave promoted, solvent-free synthesis of phosphono- and phosphinoylmethylated *N*-heterocycles has been elaborated [7]. In this paper, we introduce aminomethylphosphonic and phosphinic derivatives based or related on 6-membered P-heterocycles.

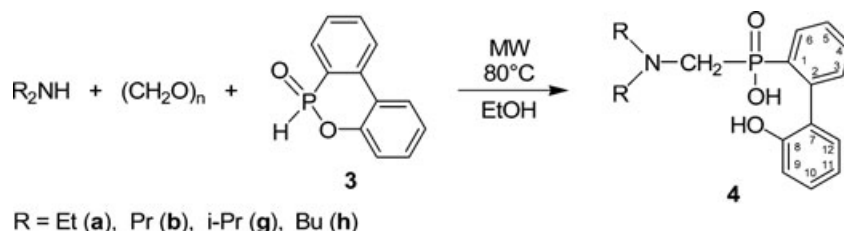
On the basis of our previous experiences with cyclic $>\text{P}(\text{O})\text{H}$ species [8,9], it was a challenge for us to convert them to the corresponding aminomethyl derivatives. 1,3,2-Dioxaphosphinane



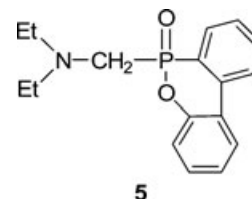
SCHEME 1

2-oxide **1** reacted easily with paraformaldehyde and secondary amines including pyrrolidine, morpholine, piperidine-, and piperazine derivatives at 55°C in chloroform under microwave to afford the corresponding aminomethylphosphonates **2a–f** (Scheme 1). After purification by column chromatography, products **2a–f** were obtained in 54%–72% yields and were characterized by ^{31}P , ^{13}C , and ^1H NMR, as well as mass spectral data.

The next cyclic $>\text{P}(\text{O})\text{H}$ species was dibenzo[*c,e*][1,2]oxaphosphinane oxide **3** that was reacted with paraformaldehyde and secondary amines at 80°C in dry ethanol, again under microwave. Instead of the desired aminomethyl-dibenzo-oxaphosphorine oxides, aminomethyl-2-(2'-hydroxybiphenyl)phosphinic acids **4a,b,g,h** were obtained (Scheme 2). Compounds **4** were formed by opening of the oxaphosphinane ring of the primary product (e.g., **5**) via hydrolysis. The water bringing about the hydrolytic ring opening is derived from the primary Mannich condensation. Products **4a,b,g,h** were purified by recrystallization and were identified on the basis of ^{31}P , ^{13}C , and ^1H NMR, as well as mass spectrometry. Carrying out the condensation in chloroform instead of ethanol, the ring opening was somewhat suppressed and the presence of the aminomethyldibenzo-oxaphosphinane oxide (e.g., **5**) could be detected by ^{31}P NMR and FAB, but it was not possible to prevent the predominant ring opening. The ratio of **4a** and **5** was ca. 75:25 on the basis of relative ^{31}P NMR intensities.



SCHEME 2



In summary, new aminomethyl cyclic phosphonates and hydroxybiphenylphosphinic acids were synthesized by the microwave-assisted condensation of a cyclic or acyclic secondary amine, paraformaldehyde, and the $\text{P}(\text{O})\text{H}$ derivative of the corresponding P-heterocycle.

EXPERIMENTAL

The ^{31}P , ^{13}C , and ^1H NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. Mass spectrometry was performed on a ZAB-2SEQ instrument. The reactions were carried out in a 300-W CEM Discover focused microwave reactor under isothermic conditions.

General Procedure for the Preparation of Aminomethyl[1,3,2]dioxaphosphinane 2-Oxides (**2a–f**)

A mixture of [1,3,2]dioxaphosphinane 2-oxide **1** [10] (0.21 g, 1.7 mmol), paraformaldehyde (0.05 g,

1.7 mmol), and secondary amine (1.7 mmol) in 2 mL of chloroform was stirred at 55°C in a microwave reactor for 20 min. Volatile components including water were removed in vacuo. Column chromatography (silica gel, 3% methanol in chloroform) of the residue afforded the product (**2a–f**) as an oil.

The following products were thus prepared:

2a: Yield, 72%; ^{31}P NMR (CDCl_3) δ 21.5; ^{13}C NMR (CDCl_3) δ 11.6 (CH_3), 26.6 ($^3J = 8.4$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 48.6 ($^3J = 8.8$, NCH_2CH_3), 49.0 ($^1J = 159.7$, PCH_2), 67.2 ($^2J = 7.5$, OCH_2); ^1H NMR (CDCl_3) δ 1.08 (t, $J = 7.0$, 6H, CH_3), 2.06–2.15 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.69–2.78 (m, 4H, NCH_2CH_3), 3.03 (br d, $^2J_{\text{PH}} = 10.0$, 2H, PCH_2), 4.33–4.46 (m, 2H, OCH_2), 4.46–4.58 (m, 2H, OCH_2); ($\text{M} + \text{H}$) $^+_{\text{found}} = 208.1084$, $\text{C}_8\text{H}_{19}\text{NO}_3\text{P}$ requires 208.1102.

2b: Yield: 55%; ^{31}P NMR (CDCl_3) δ 19.6; ^{13}C NMR (CDCl_3) δ 11.3 (CH_3), 19.7 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 26.2 ($^3J = 8.2$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 49.9 ($^1J = 157.9$, PCH_2), 57.0 ($^3J = 8.0$, NCH_2CH_2), 66.3 ($^2J = 7.3$, OCH_2); ^1H NMR (CDCl_3) δ 0.90 (t, $J = 7.5$, 6H, CH_3), 1.40–1.55 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.00–2.18 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.54 (m, 4H, NCH_2CH_2), 2.99 (d, $^2J_{\text{PH}} = 9.9$, 2H, PCH_2), 4.30–4.42 (m, 2H, OCH_2), 4.45–4.58 (m, 2H, OCH_2); ($\text{M} + \text{H}$) $^+_{\text{found}} = 236.1398$, $\text{C}_{10}\text{H}_{23}\text{NO}_3\text{P}$ requires 236.1416.

2c: Yield: 49%; ^{31}P NMR (CDCl_3) δ 20.9; ^{13}C NMR (CDCl_3) δ 23.9 (NCH_2CH_2), 26.7 ($^3J = 7.9$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 51.2 ($^1J = 161.8$, PCH_2), 56.2 ($^3J = 10.7$, NCH_2CH_2), 66.6 ($^2J = 7.0$, OCH_2); ^1H (CDCl_3) NMR δ 1.75–1.85 (m, 4H, NCH_2CH_2), 2.00–2.16 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.65–2.75 (m, 4H, NCH_2CH_2), 3.05 (d, $^2J_{\text{PH}} = 12.0$, 2H, PCH_2), 4.30–4.42 (m, 2H, OCH_2), 4.49–4.61 (m, 2H, OCH_2); ($\text{M} + \text{H}$) $^+_{\text{found}} = 206.0937$, $\text{C}_8\text{H}_{17}\text{NO}_3\text{P}$ requires 206.0946.

2d: Yield: 50%; ^{31}P NMR (CDCl_3) δ 19.8; ^{13}C NMR (CDCl_3) δ 26.8 ($^3J = 8.1$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 54.3 ($^1J = 160.6$, PCH_2), 55.4 ($^3J = 10.1$, $\text{OCH}_2\text{CH}_2\text{N}$), 66.8 ($^2J = 7.1$, POCH_2), 67.1 ($\text{OCH}_2\text{CH}_2\text{N}$); ^1H NMR (CDCl_3) δ 2.03–2.15 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.65 (t, $^3J_{\text{HH}} = 4.8$, 4H, $\text{OCH}_2\text{CH}_2\text{N}$), 2.89 (d, $^2J_{\text{PH}} = 11.4$, 2H, PCH_2), 3.71 (t, $J_{\text{HH}} = 4.5$, 4H, $\text{OCH}_2\text{CH}_2\text{N}$), 4.29–4.43 (m, 2H, OCH_2), 4.47–4.61 (m, 2H, OCH_2); ($\text{M} + \text{H}$) $^+_{\text{found}} = 222.0880$, $\text{C}_8\text{H}_{17}\text{NO}_4\text{P}$ requires 222.0895.

2e: Yield: 54%; ^{31}P NMR (CDCl_3) δ 19.8; ^{13}C NMR (CDCl_3) δ 21.7 (CH_3), 26.5 ($^3J = 8.1$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 30.0 (CH), 34.4 (CHCH_2), 54.3 ($^1J = 159.6$, PCH_2), 55.7 ($^3J = 9.6$, NCH_2), 67.3 ($^2J = 7.3$, OCH_2); ^1H NMR (CDCl_3) δ 0.90 (d, $J = 6.4$, 3H, CH_3), 1.18–1.28 and 1.58–1.64 (m, 4H, CHCH_2), 1.29–1.40 (m, 1H, CH), 2.02–2.16 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.21 (br t, $J = 11.6$, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 2.89 (d, $^1J_{\text{PH}} = 10.2$, 2H, PCH_2), 2.97 (br d, $J = 11.5$, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 4.38–4.56

(m, 4H, OCH_2); ($\text{M} + \text{H}$) $^+_{\text{found}} = 234.1245$, $\text{C}_{10}\text{H}_{21}\text{NO}_3\text{P}$ requires 234.1259.

2f: Yield: 64%; ^{31}P NMR (CDCl_3) δ 19.1; ^{13}C NMR (CDCl_3) δ 26.5 ($^3J = 8.3$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 49.1 (ArNCH_2), 52.6 ($^1J = 159.7$, PCH_2), 54.7 ($^3J = 10.0$, $\text{CH}_2\text{NCH}_2\text{P}$), 67.0 ($^2J = 7.2$, OCH_2), 117.3 (CHCN), 124.5 (ClC), 128.9 (ClCCH), 149.7 (NC); ^1H NMR (CDCl_3) δ 2.10–2.10 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.65 (t, $^3J_{\text{HH}} = 5.0$, 4H, $\text{CH}_2\text{NCH}_2\text{P}$), 2.97 (d, $^2J_{\text{PH}} = 11.5$, 2H, PCH_2), 3.19 (t, $^3J_{\text{HH}} = 5.5$, 4H, $\text{ArNCH}_2\text{CH}_2\text{N}$), 4.35–4.44 (m, 2H, OCH_2), 4.47–4.59 (m, 2H, OCH_2), 6.82 (d, $J_{\text{HH}} = 9.0$, 2H, Ar), 7.20 (d, $J_{\text{HH}} = 9.0$, 2H, Ar); ($\text{M} + \text{H}$) $^+_{\text{found}} = 331.0956$, $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_3\text{P}$ requires 331.0978.

General Procedure for the Preparation of Aminomethyl-2-(2'-hydroxybiphenyl)phosphinic Acids **4a,b,g,h**

A mixture of dibenzooxaphosphinane oxide **3** (0.20 g, 0.93 mmol), paraformaldehyde (0.03 g, 1.0 mmol), and secondary amine (1.0 mmol) in 2 mL of ethanol was reacted under microwave conditions at 80°C for 1.5 h. Volatile components including water were removed in vacuo to give phosphinic acid (**4a,b,g,h**) as a solid.

The following products were thus prepared:

4a: Yield, 98%; mp. 176°C–178°C after recrystallization from ethyl acetate–pentane; ^{31}P NMR (CDCl_3) δ 15.1; ^{13}C NMR (CDCl_3) δ 7.8 (CH_3), 47.9 ($^3J = 4.4$, NCH_2CH_3), 50.8 ($^1J = 91.3$, PCH_2), 121.2 (Ar),^a 122.5 (Ar),^a 127.2 ($J = 11.3$, Ar),^b 129.6 (Ar),^a 130.9 (Ar),^a 131.2 ($J = 2.4$, Ar),^b 131.7 ($J = 7.6$, Ar),^b 132.1 ($J = 11.1$, Ar),^b 134.2 ($^2J = 3.0$, C_2), 135.5 ($^1J = 129.2$, C_1), 141.9 ($^3J = 10.3$, C_7), 154.9 (C_8),^a tentative assignment for C_9 , C_{10} , C_{11} and C_{12} ,^b tentative assignment for C_3 , C_4 , C_5 , and C_6 ; ^1H NMR (CDCl_3) δ 0.97–1.15 (m, 6H, CH_3), 2.66–2.76 (m, 2H, PCH_2), 2.93–3.18 (m, 4H, NCH_2CH_3), 7.04 (t, $J = 7.5$, 1H, ArH), 7.11 (d, $J = 6.5$, 1H, ArH), 7.14 (d, $J = 8.5$, 1H, ArH), 7.23 (dd, $J_1 = 7.0$, $J_2 = 5.0$, 1H, ArH), 7.33 (t, $J = 7.0$, 1H, ArH), 7.43 (t, $J = 7.5$, 1H, ArH), 7.51 (t, $J = 7.5$, 1H, ArH), 8.08 (dd, $J_1 = 7.5$, $J_2 = 12.5$, 1H, ArH); ($\text{M} + \text{H}$) $^+_{\text{found}} = 320.1402$, $\text{C}_{17}\text{H}_{23}\text{NO}_3\text{P}$ requires 320.1416. Performing the above reaction at 55°C for 40 min in 2 mL of chloroform led to a mixture of **4a** (75%) and **5** (25%).

5: ^{31}P NMR (CDCl_3) δ 33.8; ($\text{M} + \text{H}$) $^+_{\text{found}} = 302.1278$, $\text{C}_{17}\text{H}_{21}\text{NO}_2\text{P}$ requires 302.1310.

4b: Yield, 56%; mp 156°C–158°C after crystallization from ethylacetate–hexane; ^{31}P NMR (CDCl_3) δ 14.9; ^{13}C NMR (CDCl_3) δ 10.7 (CH_3), 16.1 (CH_3CH_2), 52.0 ($^1J = 90.8$, PCH_2), 55.6 (br signal, NCH_2CH_2), 121.5 (Ar),^a 121.7 (Ar),^a 127.4 ($J = 11.3$, Ar),^b 129.7 (Ar),^a 131.1 (Ar),^a 131.5 ($J = 1.8$, Ar),^b 131.9 ($J = 8.0$,

Ar),^b 132.2 ($J = 11.5$, Ar),^b 133.7 ($^2J = 3.0$, C₂), 134.9 ($^1J = 130.7$, C₁), 141.6 ($^3J = 10.5$, C₇), 154.2 (C₈),^atentative assignment for C₉, C₁₀, C₁₁, and C₁₂,^btentative assignment for C₃, C₄, C₅, and C₆; ¹H NMR (CDCl₃) δ 0.68–0.85 (m, 6H, CH₃), 1.37–1.58 (m, 4H, CH₂CH₃), 2.67–2.98 (overlapping signals, 6H, NCH₂ + PCH₂), 6.98–7.52 (m, 8H, ArH), 8.05 (dd, $J_1 = 7.5$, $J_2 = 11.5$, 1H, OH), 10.40 (br s, 1H, OH); (M + H)⁺_{found} = 348.1709, C₁₉H₂₇NO₃P requires 348.1729.

4g: Yield: 59%; ³¹P NMR (CDCl₃) δ 13.3; ¹³C NMR (CDCl₃) δ 17.8 (br s, CH₃), 46.0 ($^1J = 87.3$, PCH₂), 55.7 (NCH), 121.2 (Ar),^a 122.2 (Ar),^a 127.1 ($J = 11.5$, Ar),^b 129.6 (Ar),^a 130.8 (Ar),^a 131.0 ($J = 2.3$, Ar),^b 131.5 ($J = 7.7$, Ar),^b 131.8 ($J = 11.1$, Ar),^b 134.0 ($^2J = 3.0$, C₂), 135.3 ($^1J = 132.1$, C₁), 141.2 ($^3J = 10.3$, C₇), 154.2 (C₈),^atentative assignment for C₉, C₁₀, C₁₁, and C₁₂,^btentative assignment for C₃, C₄, C₅, and C₆; ¹H NMR (CDCl₃) δ 1.12–~ 1.20 (m, 6H, CH₃), 1.21 (d, $J = 6.6$, 6H, CH₃), 2.52–2.64 (septet, $J = 7.7$, 2H, CH), 3.54–3.64 (m, 2H, PCH₂), 6.98–7.50 (m, 8H, Ar), 8.03 (dd, $J_1 = 7.6$, $J_2 = 11.5$, 1H, OH), 10.43 (br s, 1H, OH); (M + H)⁺_{found} = 348.1724, C₁₉H₂₇NO₃P requires 348.1729.

4h: Yield: 61%; mp. 152°C–154°C; ³¹P NMR (CDCl₃) δ 14.5; ¹³C NMR (CDCl₃) δ 13.5 (CH₃), 19.8 (CH₂CH₂), 24.2 (CH₂CH₂), 51.4 ($^1J = 92.3$, PCH₂), 52.9 (br s, NCH₂CH₂), 121.1 (Ar),^a 122.8 (Ar),^a 127.0 ($J = 11.2$, Ar),^b 129.5 (Ar),^a 130.7 (Ar),^a 131.0 ($J = 2.4$, Ar),^b 131.7 ($J = 7.5$, Ar),^b 132.1 ($J = 11.1$, Ar),^b 134.3 ($^2J = 2.9$, C₂), 135.6 ($^1J = 128.4$, C₁), 141.9 ($^3J = 10.3$, C₇), 155.0 (C₈),^atentative assignment for C₉, C₁₀, C₁₁, and C₁₂,^btentative assignment for C₃, C₄, C₅, and C₆; ¹H NMR (CDCl₃) δ 0.84 (br s, 6H,

CH₃), 0.98–1.80 (m, 8H, CH₂), 2.71–3.08 (overlapping signals, 6H, NCH₂ + PCH₂), 6.98–7.52 (m, 8H, Ar), 8.03 (dd, $J_1 = 7.4$, $J_2 = 12.3$, 1H, OH), 10.3 (br s, 1H, OH); (M + H)⁺_{found} = 376.2018, C₂₁H₃₁NO₃P requires 376.2042.

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