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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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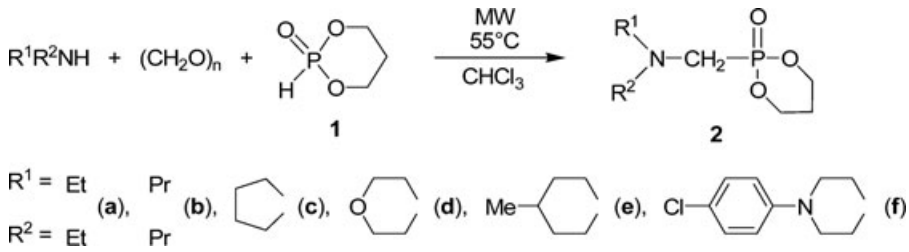
INTRODUCTION

The Kabachnik–Fields reaction [1,2] involving the condensation of a ternary system comprising a >P(O)H reactant, an aldehyde or ketone, and a secondary or primary amine is an important method for the synthesis of compounds of type of >NC(R^1)(R^2)P(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.

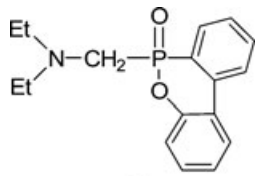
On the basis of our previous experiences with cyclic >P(O)H species [8,9], it was a challenge for us to convert them to the corresponding aminomethyl derivatives. 1,3,2-Dioxaphosphinane



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 ^{1}H NMR, as well as mass spectral data.

The next cyclic >P(O)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 aminomethyldibenzooxaphosphorine 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 ^{1}H 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 aminomethyldibenzooxaphosphinane 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.



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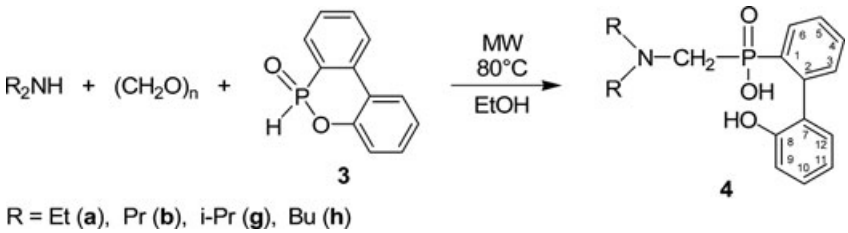
In summary, new aminomethyl cyclic phosphonates and hydroxybiphenylphosphinic acids were synthesized by the microwave-assisted condensation of a cyclic or acyclic secondary amine, paraformaldehyde, and the P(O)H derivative of the corresponding P-heterocycle.

EXPERIMENTAL

The ^{31}P, ^{13}C, and ^{1}H 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 isotermic 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,



SCHEME 2

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 ($^3J = 8.4$, $CH_2CH_2CH_2$), 48.6 ($^3J = 8.8$, NCH_2CH_3), 49.0 ($^1J = 159.7$, PCH_2), 67.2 ($^2J = 7.5$, OCH_2); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, $J = 7.0$, 6H, CH_3), 2.06–2.15 (m, 2H, $CH_2CH_2CH_2$), 2.69–2.78 (m, 4H, NCH_2CH_3), 3.03 (br d, $^2J_{PH} = 10.0$, 2H, PCH_2), 4.33–4.46 (m, 2H, OCH_2), 4.46–4.58 (m, 2H, OCH_2); $(M + H)^+_{found} = 208.1084$, $C_8H_{19}NO_3P$ 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 ($CH_2CH_2CH_3$), 26.2 ($^3J = 8.2$, $CH_2CH_2CH_2$), 49.9 ($^1J = 157.9$, PCH_2), 57.0 ($^3J = 8.0$, NCH_2CH_2), 66.3 ($^2J = 7.3$, OCH_2); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, $J = 7.5$, 6H, CH_3), 1.40–1.55 (m, 4H, $CH_2CH_2CH_3$), 2.00–2.18 (m, 2H, $CH_2CH_2CH_2$), 2.54 (m, 4H, NCH_2CH_2), 2.99 (d, $^2J_{PH} = 9.9$, 2H, PCH_2), 4.30–4.42 (m, 2H, OCH_2), 4.45–4.58 (m, 2H, OCH_2); $(M + H)^+_{found} = 236.1398$, $C_{10}H_{23}NO_3P$ 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 ($^3J = 7.9$, $CH_2CH_2CH_2$), 51.2 ($^1J = 161.8$, PCH_2), 56.2 ($^3J = 10.7$, NCH_2CH_2), 66.6 ($^2J = 7.0$, OCH_2); ^{1}H ($CDCl_3$) NMR δ 1.75–1.85 (m, 4H, NCH_2CH_2), 2.00–2.16 (m, 2H, $CH_2CH_2CH_2$), 2.65–2.75 (m, 4H, NCH_2CH_2), 3.05 (d, $^2J_{PH} = 12.0$, 2H, PCH_2), 4.30–4.42 (m, 2H, OCH_2), 4.49–4.61 (m, 2H, OCH_2); $(M + H)^+_{found} = 206.0937$, $C_8H_{17}NO_3P$ requires 206.0946.

2d: Yield: 50%; ^{31}P NMR ($CDCl_3$) δ 19.8; ^{13}C NMR ($CDCl_3$) δ 26.8 ($^3J = 8.1$, $CH_2CH_2CH_2$), 54.3 ($^1J = 160.6$, PCH_2), 55.4 ($^3J = 10.1$, OCH_2CH_2N), 66.8 ($^2J = 7.1$, $POCH_2$), 67.1 (OCH_2CH_2N); ^{1}H NMR ($CDCl_3$) δ 2.03–2.15 (m, 2H, $CH_2CH_2CH_2$), 2.65 (t, $^3J_{HH} = 4.8$, 4H, OCH_2CH_2N), 2.89 (d, $^2J_{PH} = 11.4$, 2H, PCH_2), 3.71 (t, $J_{HH} = 4.5$, 4H, OCH_2CH_2N), 4.29–4.43 (m, 2H, OCH_2), 4.47–4.61 (m, 2H, OCH_2); $(M + H)^+_{found} = 222.0880$, $C_8H_{17}NO_4P$ 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 ($^3J = 8.1$, $CH_2CH_2CH_2$), 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); ^{1}H 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, $CH_2CH_2CH_2$), 2.21 (br t, $J = 11.6$, 2H, CH_2CH_2N), 2.89 (d, $^1J_{PH} = 10.2$, 2H, PCH_2), 2.97 (br d, $J = 11.5$, 2H, CH_2CH_2N), 4.38–4.56 (m, 4H, OCH_2); $(M + H)^+_{found} = 234.1245$, $C_{10}H_{21}NO_3P$ requires 234.1259.

2f: Yield: 64%; ^{31}P NMR ($CDCl_3$) δ 19.1; ^{13}C NMR ($CDCl_3$) δ 26.5 ($^3J = 8.3$, $CH_2CH_2CH_2$), 49.1 ($ArNCH_2$), 52.6 ($^1J = 159.7$, PCH_2), 54.7 ($^3J = 10.0$, CH_2NCH_2P), 67.0 ($^2J = 7.2$, OCH_2), 117.3 ($CHCN$), 124.5 (ClC), 128.9 ($ClCCH$), 149.7 (NC); ^{1}H NMR ($CDCl_3$) δ 2.10–2.10 (m, 2H, $CH_2CH_2CH_2$), 2.65 (t, $^3J_{HH} = 5.0$, 4H, CH_2NCH_2P), 2.97 (d, $^2J_{PH} = 11.5$, 2H, PCH_2), 3.19 (t, $^3J_{HH} = 5.5$, 4H, $ArNCH_2CH_2N$), 4.35–4.44 (m, 2H, OCH_2), 4.47–4.59 (m, 2H, OCH_2), 6.82 (d, $J_{HH} = 9.0$, 2H, Ar), 7.20 (d, $J_{HH} = 9.0$, 2H, Ar); $(M + H)^+_{found} = 331.0956$, $C_{14}H_{21}N_2O_3P$ 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; ^{1}H 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); $(M + H)^+_{found} = 320.1402$, $C_{17}H_{23}NO_3P$ 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; $(M + H)^+_{found} = 302.1278$, $C_{17}H_{21}NO_2P$ 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 ($^2J = 3.0$, C_2), 134.9 ($^1J = 130.7$, C_1), 141.6 ($^3J = 10.5$, C_7), 154.2 (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; ^{1}H NMR ($CDCl_3$) δ 0.68–0.85 (m, 6H, CH_3), 1.37–1.58 (m, 4H, CH_2CH_3), 2.67–2.98 (overlapping signals, 6H, NCH_2 + PCH_2), 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); $(M + H)^+_{found} = 348.1709$, $C_{19}H_{27}NO_3P$ requires 348.1729.

4g: Yield: 59%; ^{31}P NMR ($CDCl_3$) δ 13.3; ^{13}C NMR ($CDCl_3$) δ 17.8 (br s, CH_3), 46.0 ($^1J = 87.3$, PCH_2), 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 ($^2J = 3.0$, C_2), 135.3 ($^1J = 132.1$, C_1), 141.2 ($^3J = 10.3$, C_7), 154.2 (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; ^{1}H NMR ($CDCl_3$) δ 1.12– $\sim$ 1.20 (m, 6H, CH_3), 1.21 (d, $J = 6.6$, 6H, CH_3), 2.52–2.64 (septet, $J = 7.7$, 2H, CH), 3.54–3.64 (m, 2H, PCH_2), 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); $(M + H)^+_{found} = 348.1724$, $C_{19}H_{27}NO_3P$ requires 348.1729.

4h: Yield: 61%; mp. 152°C–154°C; ^{31}P NMR ($CDCl_3$) δ 14.5; ^{13}C NMR ($CDCl_3$) δ 13.5 (CH_3), 19.8 (CH_2CH_2), 24.2 (CH_2CH_2), 51.4 ($^1J = 92.3$, PCH_2), 52.9 (br s, NCH_2CH_2), 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 ($^2J = 2.9$, C_2), 135.6 ($^1J = 128.4$, C_1), 141.9 ($^3J = 10.3$, C_7), 155.0 (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; ^{1}H NMR ($CDCl_3$) δ 0.84 (br s, 6H, CH_3), 0.98–1.80 (m, 8H, CH_2), 2.71–3.08 (overlapping signals, 6H, NCH_2 + PCH_2), 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); $(M + H)^+_{found} = 376.2018$, $C_{21}H_{31}NO_3P$ requires 376.2042.

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