A Convenient Synthesis of *N*-Alkylaminomethanephosphonic and *N*-Alkylaminomethylphosphinic Acids

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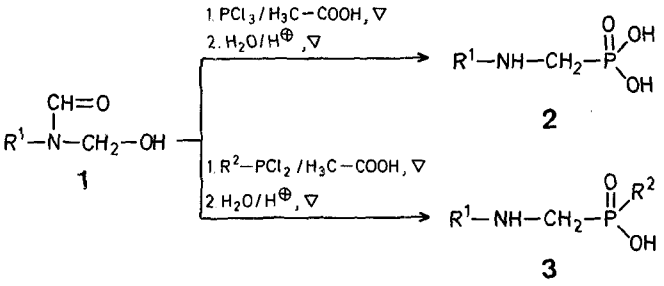
Two general synthetic routes lead to *N*-alkylaminomethanephosphonic acids **(2)**; the first one uses Mannich-type reactions of primary amines with formaldehyde and phosphorous acid[1], and the second one involves condensation reactions of corresponding primary amines with chloromethanephosphonic acids[2,3].

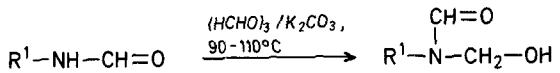
One of the limitations of the first method is that primary amines when treated with 1 equivalent of formaldehyde and phosphorous acids, yield mixtures of mono- and bis-methanephosphonic acids. The disadvantage of the second procedure is that long reaction times and ion exchange are required to separate the desired products. Moreover, both methods are not applicable for the preparation of the yet unknown[4] *N*-alkylaminomethylphosphinic acids **(3)**.

In this communication we present convenient synthetic routes leading to *N*-alkylaminomethanephosphonic acids **(2)**, and their phosphinic acid derivatives **(3)** via reaction of *N*-alkyl-*N*-hydroxymethylformamides **(1)** with either phosphorus trichloride or alkyl- or aryldichlorophosphines in glacial acetic acid solution.



The general procedure is an extension of the preparation of aminomethanephosphonic acid starting from *N*-hydroxymethylamides and phosphorus trichloride as described previously[5,6].

The preparation of *N*-alkyl-*N*-hydroxymethylformamides **(1)** represents the key problem in our synthetic approach. Böhme et al.[7] reported that some of these compounds may be prepared from *N*-alkylacetamides or from *N*-alkylbenzamides and paraformaldehyde in the presence of dry potassium carbonate at high temperatures. Unfortunately, we were not able to obtain *N*-hydroxymethylamides in yields higher than 30% using the method given in Ref.[7]. However, we found, that *N*-hydroxymethylation proceeds smoothly and with good yields when *N*-alkylformamides **(4)** were used instead of *N*-alkylacetamides or *N*-alkylbenzamides.



Melting points were determined using a Boethius apparatus and were not corrected. The I.R. spectra were taken on a Perkin Elmer 621 instrument. ^{1}H-N.M.R. spectra were recorded with a Tesla BS 467 instrument operating at 60 MHz.

Table. *Compounds* **2** *and* **4** *prepared*

Product No.	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (D_2O)[b] δ [ppm]
2a	CH_3	—	55	272–274° (C_2H_5OH/H_2O)	274.5–275.5°[8]	—	—
2b	C_2H_5	—	57	273–275° (acetone/H_2O)	260°[9]	—	—
2c	*n*-C_3H_7	—	65	267–270° (C_2H_5OH/H_2O)	260–262°[3]	—	—
2d	*n*-C_4H_9	—	54	248–250° (acetone/H_2O)	235–237°[3]	—	—
2e	$C_6H_5CH_2$	—	64	270–272° (H_2O)	265–266°[3]	—	—
3a	CH_3	CH_3	65	268–270° (acetone/H_2O)	$C_3H_{10}NO_2P$ (123.1)	*3410, 3200–2000,* 1630, 1480, 1300, 1140, 1040	*1.70* (d, 3H, J = 14 Hz); 3.13 (s, 3H); 3.48 (d, 2H, J = 10 Hz)
3b	CH_3	C_6H_5	58	248–250° (acetone/H_2O)	$C_8H_{12}NO_2P$ (185.2)	3490, 3260–2200, 1600, 1410, 1210, 1140, 1110	3.01 (s, 3H); 3.64 (d, 2H, J = 10 Hz); 7.83–8.25 (m, 5H)
3c	C_2H_5	CH_3	80	232–233° (acetone/H_2O)	$C_4H_{12}NO_2P$ (137.1)	3410, 3130–1800, 1630, 1480, 1300, 1150, 1060	1.61 (t, 3H); 1.70 (d, 3H, J = 14 Hz); 3.47 (d, 2H, J = 10 Hz); 3.50 (q, 2H)
3d	C_2H_5	C_6H_5	55	252–255° (acetone/H_2O)	$C_9H_{14}NO_2P$ (199.2)	3320, 3160–2000, 1630, 1445, 1180, 1130, 1060	1.46 (t, 3H); 3.36 (q, 2H); 3.53 (d, 2H, J = 10 Hz); 7.75–8.25 (m, 5H)
3e	*n*-C_3H_7	CH_3	65	232–234° (acetone/H_2O)	$C_5H_{14}NO_2P$ (151.1)	3420, 3200–1800, 1630, 1490, 1300, *1180, 1140, 1060*	1.28 (t, 3H); 1.70 (d, 3H, J = 14 Hz); 1.71–2.36 (m, 2H); 3.43 (t, 2H); 3.45 (d, 2H, J = 10 Hz)

Table. (Continued)

Product No.	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (D_2O)[b] δ [ppm]
3f	n-C_3H_7	C_6H_5	61	244–246° (acetone/H_2O)	$C_{10}H_{16}NO_2P$ (213.2)	3400, 3160–2000, 1630, 1435, 1180, 1130, 1060	1.15 (t, 3H); 1.53–2.25 (m, 2H); 3.26 (t, 2H); 3.55 (d, 2H, J = 10 Hz); 7.7–8.25 (m, 5H)
3g	n-C_4H_9	CH_3	53	242–245° (acetone/C_2H_5OH)	$C_6H_{16}NO_2P$ (165.2)	3410, 3300–2000, 1630, 1460, 1300, 1180, 1150, 1060	1.23 (t, 3H); 1.73 (d, 3H, J = 14 Hz); 1.33–2.24 (m, 4H); 3.47 (t, 2H); 3.48 (d, 2H, J = 10 Hz)
3h	n-C_4H_9	C_6H_5	58	248–251° (acetone/C_2H_5OH)	$C_{11}H_{18}NO_2P$ (227.2)	3340, 3140–2000, 1610, 1470, 1435, 1170, 1130, 1060	1.08 (t, 3H); 1.33–1.91 (m, 4H); 2.78 (t, 2H); 3.13 (d, 2H, J = 10 Hz); 7.75–8.25 (m, 5H)
3i	$C_6H_5CH_2$	CH_3	65	243–245° (H_2O)	$C_9H_{14}NO_2P$ (199.2)	3420, 3150–1800, 1620, 1480, 1135, 1060	1.56 (d, 3H, J = 14 Hz); 2.93 (d, 2H, J = 10 Hz); 4.06 (s, 2H); 7.66 (s, 5H)
3j	$C_6H_5CH_2$	C_6H_5	75	267–269°[c]	$C_{14}H_{16}NO_2P$ (261.3)	3420, 3160–1700, 1600, 1480, 1435, 1130, 1050, 1020	3.05 (d, 2H, J = 10 Hz); 3.78 (s, 3H); 7.33 (s, 5H); 7.6–8.25 (m, 5H)

[a] Satisfactory microanalyses obtained: N ±0.33, P ±0.33.

[b] Details of the ^{1}H-N.M.R. spectra will be published elsewhere[10].

[c] Product dissolved in 5% aqueous sodium hydroxide solution, precipitated with 5% hydrochloric acid, filtered, and washed with hot ethanol.

***N*-Alkyl-*N*-hydroxymethylformamides (1); General Procedure:**

A mixture of *N*-alkylformamide **4** (0.2 mol), paraformaldehyde (6 g, 0.2 mol) and anhydrous potassium carbonate (0.2 g) is heated at 90–110°C until all paraformaldehyde is dissolved (1–1.5 h). After cooling to room temperature, chloroform is added to the mixture, followed by filtration. The solvent is removed under reduced pressure to give the product **1** as an oil. This crude product is used directly without further purification in the subsequent condensation step.

***N*-Alkylaminomethanephosphonic Acids (2) and *N*-Alkylaminomethylphosphinic Acids (3); General Procedure:**

N-Alkyl-*N*-hydroxymethylformamide **1** (0.2 mol) in glacial acetic acid (30 ml) is added slowly under stirring and cooling (cold water) to phosphorus trichloride or alkyl- or aryldichlorophophine (0.18 mol). After stirring for 15 min, the mixture is heated under reflux for 30 min, treated with 20% hydrochloric acid (40 ml) and refluxed for another 30 min. Volatile products are evaporated in vacuo, the remaining residue is dissolved in ethanol (25–50 ml), and treated with propylene oxide until precipitation ceases. The precipitate is filtered, washed with acetone, and dried. In certain cases, the product is isolated as an oil in which case crystallisation from acetone/water or ethanol/water is advisable (Table).

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