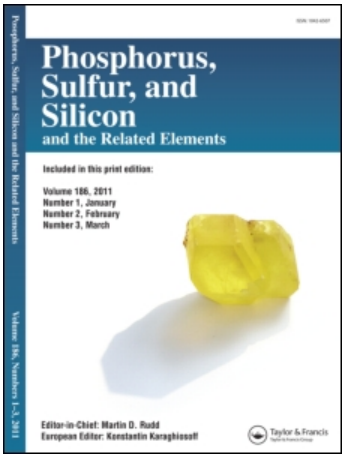

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ORGANIC PHOSPHORUS COMPOUNDS 98.[1] SYNTHESIS AND PROPERTIES OF N-METHYLAMINOMETHYLPHOSPHONIC ACID AND DERIVATIVES

Ludwig Maier[a]
[a] Division Agro, Ciba-Geigy AG, Basel, Switzerland

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ORGANIC PHOSPHORUS COMPOUNDS 98.[1] SYNTHESIS AND PROPERTIES OF N-METHYLAMINOMETHYLPHOSPHONIC ACID AND DERIVATIVES

LUDWIG MAIER
Ciba-Geigy AG, Division Agro, CH-4002 Basel, Switzerland

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High yield syntheses of N-methylaminomethylphosphonic acid, **4**, are achieved by the interaction of diisopropylphosphite and trimethylhexahydro-s-triazine, followed by hydrolysis, or by heating methylamine and chloromethylphosphonic acid in aqueous solution to 150° and finally by debenzylation of N-methyl-N-benzylaminomethylphosphonic acid with H_2 in the presence of Pd/C as catalyst.

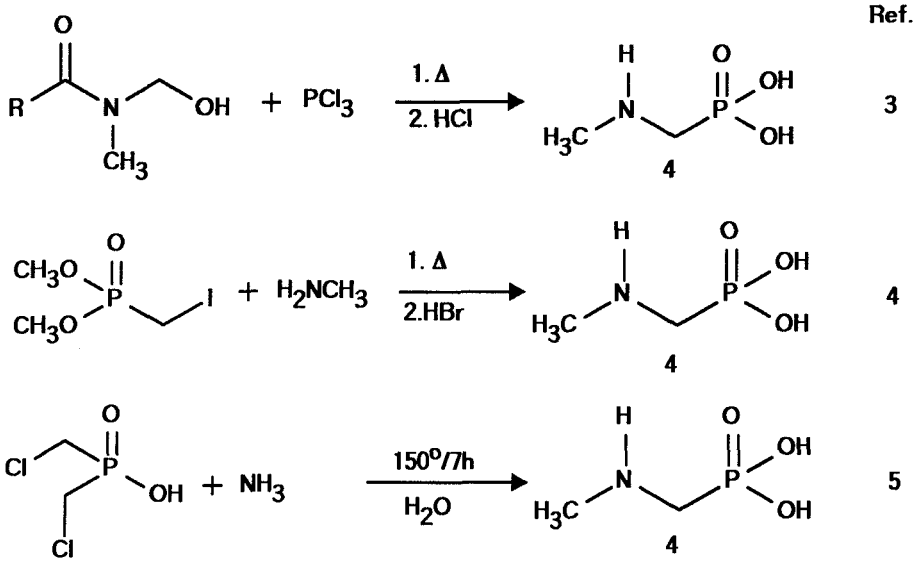
The syntheses of N-methylaminomethylphosphonates, **5**, -thiophosphonates, **6**, and of N-methylaminomethyl-methylphosphinic acid, **7**, are also reported.

N-Methylaminomethylphosphonic acid, **4**, is a strong chlorosis agent and exhibits herbicidal activity, whereas N-methylamino-methyl-methylphosphinic acid, **7**, is inactive.

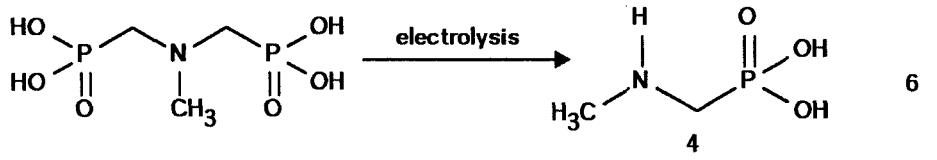
Key words: N-Methylaminomethylphosphonate; N-methylaminomethylthiophosphonate; N-methylaminomethylphosphonic acid; N-methylaminomethyl-methylphosphinic acid.

INTRODUCTION

N-Methylaminomethylphosphonic acid, **4**, was reported by us to be an active herbicide and chlorosis agent.[2] Previously several methods have been reported for its preparation as shown in Scheme I below:



SCHEME I



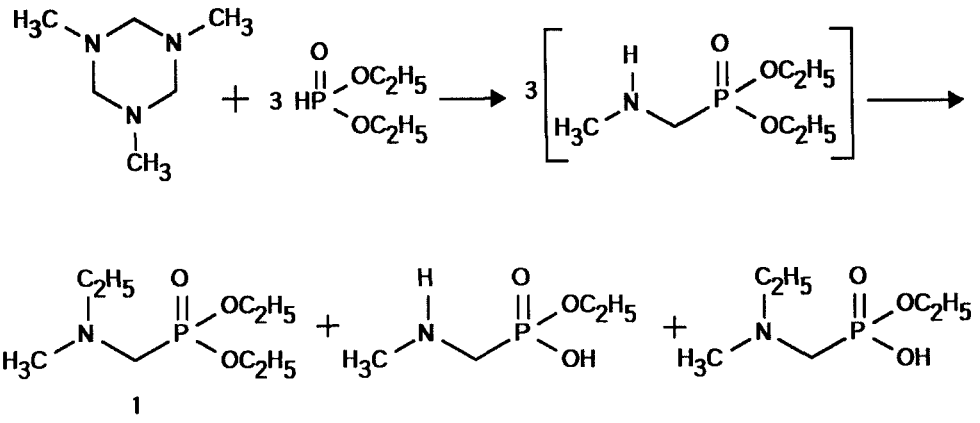
SCHEME I *(Continued)*

However, none of the procedures is directly applicable for large scale preparation. In the following we shall describe procedures which allow the synthesis of **4** in kilogram quantities.

RESULTS AND DISCUSSION

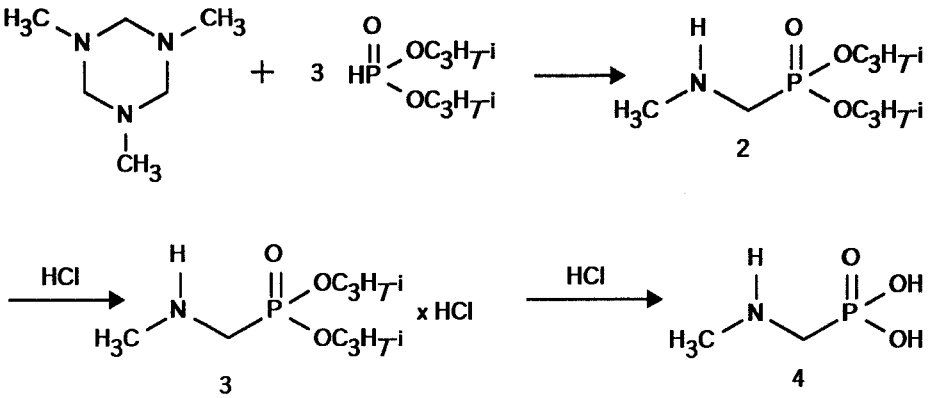
Attempts to prepare N-methylaminomethylphosphonates by the interaction of trimethylhexahydro-s-triazine and secondary phosphites[7] were not successful initially.

Thus when a mixture of trimethylhexahydro-s-triazine and dimethylphosphite was heated, it started to fulminate strongly, when the temperature reached 80°C. On the other hand, when a mixture of diethylphosphite and trimethylhexahydro-s-triazine was heated at a temperature of 110°C for a period of 4 hrs, two layers were observed. Distillation of the upper layer yielded O,O-diethyl-N-methyl-N-ethyl-aminomethylphosphonate, **1**, in 15.6% yield. The lower layer exhibited OH groups in the ^{1}H-NMR spectrum and showed a very complex spectrum. These results suggest, that the following reaction had occurred (Scheme II):

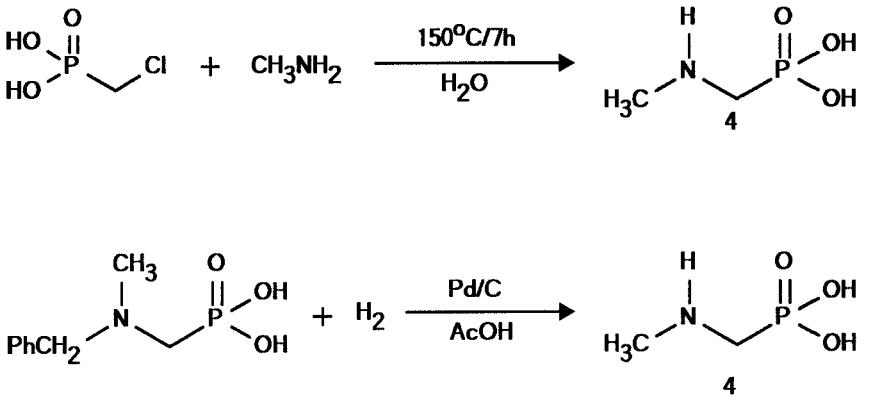


SCHEME II

The alkylation reaction on nitrogen can be avoided when phospites with secondary alkyl groups are used in this Mannich type reaction,[8] e.g., when diisopropylphosphite was heated with trimethylhexahydro-s-triazine a 69% yield of O,O-diisopropyl-N-methylaminomethylphosphonate was isolated by thin layer distillation in the vacuum (Scheme III):



SCHEME III



SCHEME IV

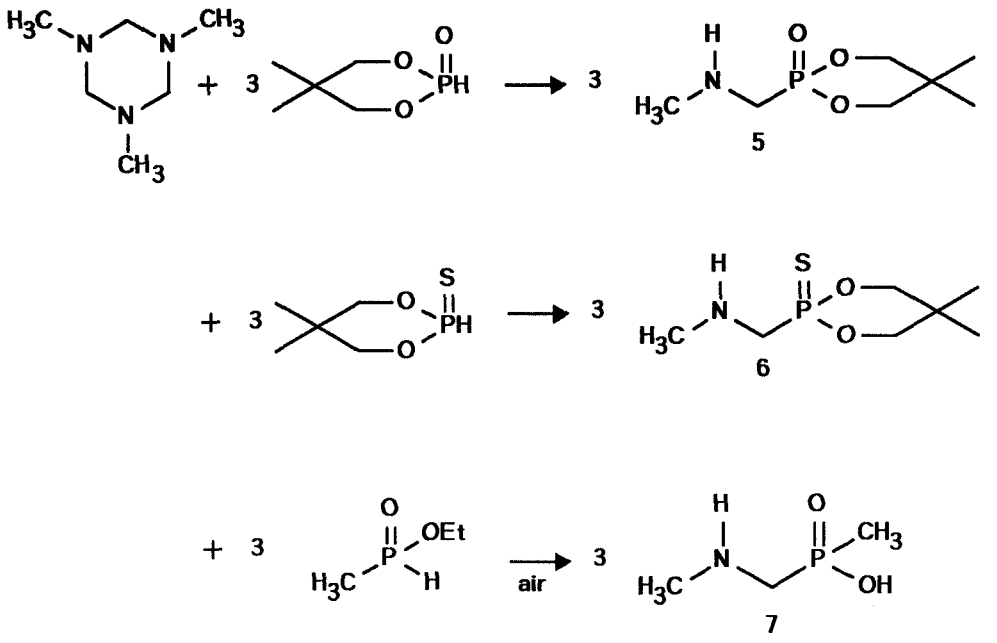
An even higher yield was obtained (72.6%) when the phosphonate was isolated as the hydrochloride, **3**. Hydrolysis of either **2** or **3** with HCl under reflux produced N-methylaminomethylphosphonic acid, **4**, in 90% yield.

Other methods for the preparation of **4** involve the interaction of chloromethylphosphonic acid and methylamine at 150°C under pressure and the debenzylation of N-benzyl-N-methylaminomethylphosphonic acid with H_2 in the presence of Pd/C as catalyst (Scheme IV). Both procedures give **4** in about 50% yield.

Finally the Mannich type reaction is also suitable for the preparation of cyclic N-methylaminomethylphosphonate **5**, cyclic N-methylaminomethylthionophosphonate **6**, and N-methylaminomethyl-methylphosphinic acid **7** (Scheme V).

BIOLOGICAL ACTIVITY

N-Methylaminomethylphosphonic acid, **4**, is a herbicide with post-emergent activity against mono- and dicotyledonous weeds. Symptoms become evident 2–3 weeks



SCHEME V

after application, taking the form of severe chlorosis which results in almost total destruction of the green parts of the plant. The phosphinic acid **7** however, is inactive.

EXPERIMENTAL

Phosphorus NMR-spectra were recorded using a Bruker WP 80 spectrometer at 32.28 MHz (ref. 85% H_3PO_4), and ^{1}H-NMR spectra were recorded with a Varian EM 360 spectrometer at 60 MHz or a Bruker WM 250/250 MHz spectrometer (ref. $(CH_3)_4Si$). The chemical shifts are reported in ppm, with negative values being upfield of the standard, and positive downfield. All the reactions were run under an atmosphere of argon.

1. O,O-Diethyl-N-methyl-N-ethyl-aminomethylphosphonate, **1.** A mixture of 43.0 g (0.33 mol) of trimethylhexahydro-s-triazine and 138.1 g (1 mol) of diethylphosphite is heated at a temperature of 110°C for a period of four hours. Two layers are observed after the reaction period, a waxy lower layer and a liquid upper layer. Upon distillation, the liquid layer yields 16.1 g of **1**, a colorless liquid, b.p. 130°C/0.05 torr.

^{1}H-NMR (in $CDCl_3$) δ: 1.1 (t, $\underline{CH_3}CH_2N$, 3H); 1.36 (t, $\underline{CH_3}CH_2O$, 6H); 2.43 (s, NCH_3, 3H); 2.53 (q, CH_2N) and 2.8 (d, J10, CH_2P) (4H); 4.13 (qui, OCH_2, 4H).

^{31}P-chem.shift (in $CDCl_3$) 24.9 ppm.

2. O,O-Diisopropyl-N-methyl-aminomethylphosphonate, **2.** A mixture of 830 g (5 mol) of diisopropylphosphite and 213 g (1.67 mol) of trimethylhexahydro-s-triazine is stirred for 16 h at 110°C. Fractional distillation yields 290.3 g (28%) of **2**, a clear liquid, b.p. 72–75°C/0.45 torr.

The substance decomposed partially during distillation; therefore it is more advantageous to isolate the ester in the form of the hydrochloride or by thin layer distillation as described below.

^{1}H-NMR (in $CDCl_3$) δ: 1.3 (d, CH_3 + NH, 13H); 2.17 (d, J2, NCH_3, 3H); 2.27 (d, J12, CH_2P, 2H); 4.23 (m, OCH, 2H).

^{31}P-chem shift (in $CDCl_3$) 24.18 ppm.

$C_8H_{20}NO_3P$ (209.23) calc.: C 45.93 H 9.64 N 6.7 P 14.81%
found: C 45.79 H 9.52 N 6.8 P 14.43%

Thin layer distillation of 323 g of crude **2** gave 217 g (69.3%) **2**, b.p. 130°C/0.2 torr, n_D^{20} = 1.4262.

3. O,O-Diisopropyl-N-methylaminomethylphosphonate · HCl, **3.** To 8.61 g (0.067 mol) of trimethylhexahydro-s-triazine are added 33.23 g (0.2 mol) of diisopropylphosphite and the mixture is heated with stirring to 100–110°C for 4 h. Then diethyl ether is added and gaseous HCl introduced; thereby 35.7 g (72.6%) of **3** precipitate, m.p. 128–131°C (dec.).
^{1}H-NMR (in DMSO-D_6) δ: 1.45 (d, CH_3, 12H); 2.73 (s, NCH_3, 3H); 3.55 (d, J13, CH_2P, 2H); 4.83 (m, OCH, 2H); 8.5 (s., NH + HCl).

4. N-Methylaminomethylphosphonic acid, **4.**

a) From ester **2.** A mixture of 20.92 g (0.1 mol) of **2** and 200 ml of HCl conc. is refluxed for 8 h and the clear solution evaporated on a rotavapor. The oily residue is dissolved in water and ethanol added until the solution becomes turbid. After several hours standing the crystalline product is filtered and dried to give 10.3 g (82.4%) of **4**, m.p. 265–270°C (dec.). In a large scale experiment 1110 g of **2** and 3000 mol of HCl conc. gave 511.6 g (90.5%) of **4**, m.p. 270–272°C (dec.); **4** · i-$C_3H_7NH_2$ m.p. 268–271°C (dec.); 4 · t-$C_4H_9NH_2$ m.p. 261—267°C (dec.).
^{1}H-NMR (in D_2O) δ: 2.55 (s, NCH_3, 3H); 2.9 (d, J13, CH_2P, 2H); 4.8 (s, OH, NH).

$C_2H_8NO_3P$ (125.06) calc.: C 19.21 H 6.45 N 11.20 P 24.77%
found: C 19.21 H 6.32 N 11.07 P 24.50%

b) From chloromethylphosphonic acid and methylamine. To an aqueous solution of 39 g (0.3 mol) of chloromethyl-phosphonic acid in 150 ml of water is added in an autoclave 50 g of methylamine and the mixture heated for 7 h at 150°C and 25 bar. Work-up as described for other alkylaminomethylphosphonic acids[9] gave 20.2 g (53.8%) of **4**, m.p. 280–285°C (dec.).

c) From N-benzyl-N-methylaminomethylphosphonic acid. To an aqueous solution of 251.6 g (1 mol) of $PhCH_2N(CH_3)CH_2PO_3H_2HCl$ (obtained from $PhCH_2NHCH_3$, CH_2O, H_3PO_3, H_2O and HCl[10]) in 500 ml of H_2O is added 500 ml of acetic acid and 25 g of Pd/C (5%) and the mixture hydrogenated at 25°C. Usual work-up gave 56.35 g (45%) of **4**, m.p. 273–276°C (dec.)

5. 2-(N-Methylaminomethyl)-5,5-dimethyl-1,3,2-dioxaphosphorane-2-oxide, **5.** A mixture of 46 g (0.31 mol) of 5,5-dimethyl-1,3,2-dioxaphosphorane and 13 g (0.1 mol) of trimethylhexahydro-s-triazine is heated with stirring to 110°C for 2 h and then fractionally distilled to give 24 g (42%) of **5**, a clear liquid, b.p. 135–140°C/0.1 torr.
^{1}H-NMR (in $CDCl_3$) δ: 0.91 and 1.12 (s, CH_3 6H); 1.79 (s, NH, 1H); 2.43 (d, J1.5, NCH_3, 3H); 3.0 (d, J12, PCH_2, 2H): 4.0 (m, OCH_2, 4H).

$C_7H_{16}NO_3P$ (193.18) calc.: C 43.52 H 8.35 N 7.25 P 16.03%
found: C 44.17 H 8.79 N 6.72 P 15.0%

6. 2-(N-Methylaminomethyl)-5,5-dimethyl-1,3,2-dioxaphosphorane-2-sulfide, **6.** From 16.6 g (0.1 mol) of 5,5-dimethyl-1,3,2-dioxaphosphorane-2-sulfide and 4.2 g of trimethylhexahydro-s-triazine as described under 5 is obtained 17 g (81%) of **6**, b.p. 80°C/0.05 torr.
^{1}H-NMR (in $CDCl_3$) δ: 0.95 and 1.25 (s, CH_3, 6H); 1.6 (s, NH, 1H); 2.55 (d, J2, NCH_3, 3H); 3.27 (d, J7, CH_2P, 2H); 3.5–4.6 (m, OCH_2, 4H).

$C_7H_{16}NO_2PS$ (209.24) calc.: C 40.18 H 7.71 N 6.70 S 15.32 P 14.81%
found: C 40.19 H 7.97 N 6.41 S 15.57 P 14.78%

7. N-Methylaminomethyl-methylphosphinic acid, **7.** A mixture of 21.61 g (0.2 mol) of O-ethyl-methylphosphonite and 8.61 g of trimethylhexahydro-s-triazine is heated for 4 h at 110°C. On standing over night 0.2 g of **7** precipitate. These are filtered and air is bubbled through the filtrate in order to hydrolyse all the ester. Thereby another 9.4 g of crude **7** precipitate. Recrystallization of crude **7** from water/acetone gives 6.8 g (27.6%) of pure **7**, m.p. 266–268°C (dec.).
^{1}H-NMR (in D_2O) δ: 1.38 (d, J14, PCH_3, 3H); 2.77 (s, NCH_3, 3H); 3.13 (d, J9, CH_2P, 2H); 4.8 (s, NH + OH).
^{31}P-chem. shift (in D_2O) 29.48 ppm

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