A Convenient Synthesis of 2-Phosphonomethylacrylic Acid and its Triethyl Ester

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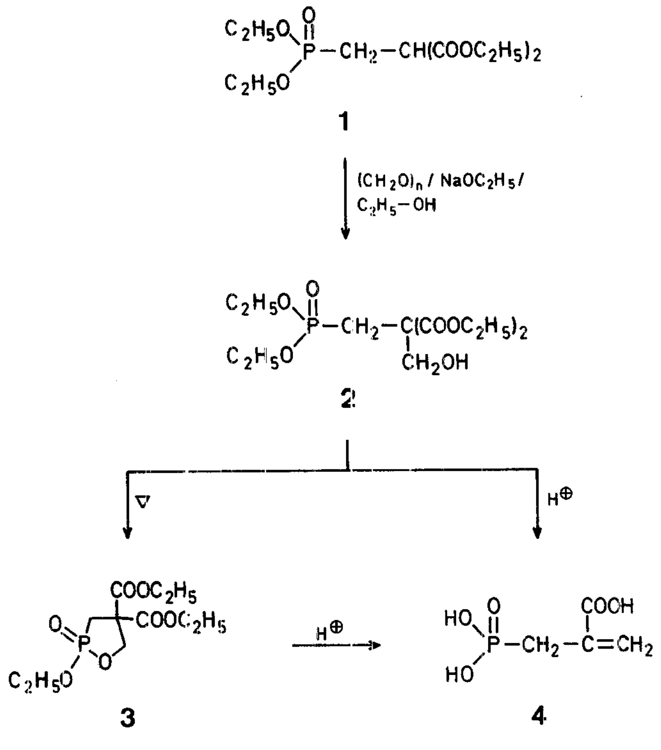
As part of a programme on the synthesis of substituted 3-phosphonopropanoic acids for screening as corrosion inhibitors, we required quantities of 2-phosphomonomethylacrylic acid (**4**) as an intermediate. Compound **4** has attracted attention as an isostere of phosphoenolpyruvic acid and several syntheses are reported in the recent literature[1,2]. None of these, however, are suitable for production of larger quantities of **4**.

Ivanov and colleagues[3] isolated the oxaphospholane **3** as a minor byproduct in the formation of the malonate **1** from diethyl malonate, triethyl phosphite, and excess paraformaldehyde, and described its hydrolysis to **4**. We have found that acid hydrolysis of **2**, an intermediate in the formation of **3**, readily gives acid **4**.



Scheme A

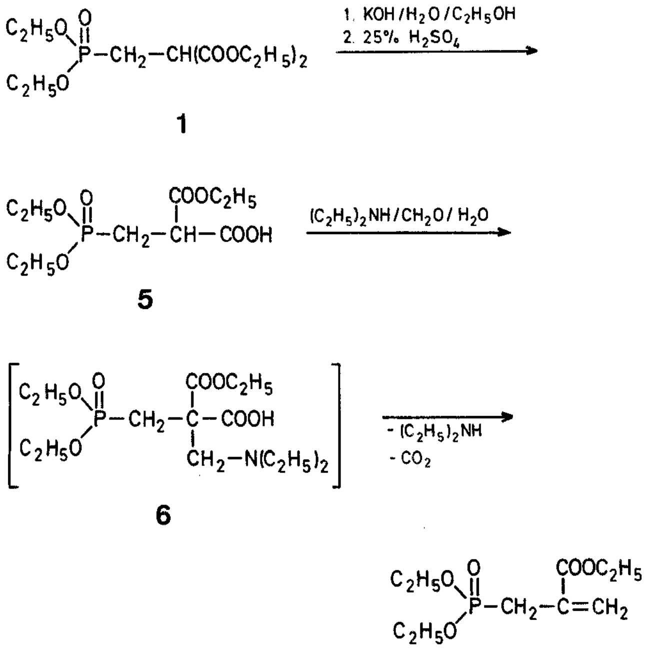
Thus, an equimolar mixture of the malonate **1** and paraformaldehyde, when treated with a catalytic quantity of sodium ethoxide, gives **2** which is not isolated but immediately hydrolysed with 18% hydrochloric acid to give pure 2-phosphonomethylacrylic acid (**4**) in 58% overall yield. Since **1** can be readily prepared in kilogram quantities[4], this represents a very convenient, one-pot synthesis of **4**. Alternatively, distillation of **2** with loss of ethanol gives **3** (b.p. 126°/0.06 torr) in 85% yield. Acid hydrolysis of **3** gives **4** in 55% yield (Scheme **A**).

The malonate **1** also proves to be a useful intermediate for the synthesis of the triethyl ester **7**. Careful saponification of **1** furnishes the acid **5**; reaction of this malonic monoester with diethylamine and formaldehyde gives the Mannich condensation product **6** which spontaneously eliminates carbon dioxide and diethylamine[5] to give triethyl 2-phosphonomethylacrylate (**7**) in 55% yield (Scheme **B**). Literature routes[6-11] to esters of **4** involve the use of relatively inaccessible starting materials.

^{31}P-N.M.R. spectra were measured on a Jeol FX 60 instrument at 24.15 MHz.

2-Phosphonomethylacrylic Acid (4):

The malonate **1**[4] (310 g, 1.0 mol) and paraformaldehyde (30 g, 1.0 mol) are stirred together and a saturated solution of sodium ethoxide in ethanol is added slowly in 5 ml portions until no further exothermic reaction occurs (about 20 ml required). Stirring is con-



Scheme B

tinued for 1 h. To the resulting clear solution is added 18% hydrochloric acid (1500 ml). The solution is stirred at reflux temperature for 16 h, cooled, and evaporated to dryness in vacuo (thorough drying is important at this stage to obtain reproducible yields). The product is triturated with acetone, filtered, washed with acetone, and air-dried to give **4**; yield: 97 g (58%); m.p. 179–181 °C (Lit. m.p. 118–120 °C[1]; 148–150 °C[3], 168–170 °C[2]); the ^{1}H-N.M.R. spectrum is identical with that previously reported[1].

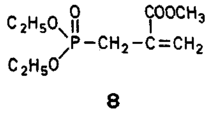
^{31}P-N.M.R. (H_2O/85% H_3PO_4, ext.): $\delta = 24.3$ ppm (tt, $J_{P-CH_2} = 22$ Hz, $J_{P-C=CH_2} = 6$ Hz).

Triethyl 2-Phosphonomethylacrylate (7):

The malonate **1**[4] (310 g, 1.0 mol) is dissolved in 70% aqueous ethanol (1000 ml) and stirred at 15–20 °C while a solution of potassium hydroxide (56 g, 1.0 mol) in 70% ethanol (500 ml) is added dropwise over 8 h. The solution is stirred overnight at room temperature and the solvent evaporated in vacuo below 40 °C. The resulting liquid is extracted with ether (200 ml) and the ether extract discarded. The aqueous solution is neutralised with 25% sulphuric acid, with cooling, and then saturated with sodium chloride. The product is extracted with ether (5 × 150 ml), the extracts combined, dried with magnesium sulphate, and evaporated to give crude **5**. This viscous oil is stirred at 0 °C and diethylamine (74 g, 1.0 mol) added at such a rate that the temperature remains below 20 °C. 40% Formalin (90 ml) is then added dropwise over 30 min (gas evolution) and the mixture stirred overnight. The resulting solution is saturated with sodium chloride, acidified to pH 1 with 4 normal sulphuric acid, and extracted with ether (3 × 250 ml). The ether extracts are combined, dried with magnesium sulphate, and distilled to give **7**; yield: 138 g (55%); b.p. 106–108 °C/0.2 torr; the ^{1}H-N.M.R. spectrum is identical to that previously reported[2].

^{31}P-N.M.R. (CCl_4/H_3PO_4, ext.): $\delta = 25.0$ ppm (m, $J_{P-CH_2} = 22$ Hz; $J_{P-OCH_2} = 8.5$ Hz, $J_{P-C-C=CH_2} = 5.5$ Hz).

Up to 5% of an impurity is sometimes present. This is partially separated by fractional distillation and found to be the partial methyl ester **8** (G.L.C.-M.S., ^{1}H-N.M.R.), probably formed by transesterification with methanol present in the aqueous formaldehyde.



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