## A Simple Synthesis of Dialkyl 1-Formylalkanephosphonates

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1-Formylalkanephosphonates play an important part in synthesis[1], for example as precursors of $\alpha,\beta$-unsaturated aldehydes[2], and have since come to be used as intermediates in the synthesis of aminoalkanephosphonates[3]. The classical methods of synthesis of 1-formylalkanephosphonates consist of the formation and subsequent acidic cleavage either of a phosphonylated alkane diethylacetal (Arbuzov reaction) or of a phosphonylated ethoxyalkene (Razumov reaction); the two methods are complementary[4]. These traditional methods have several advantages, however, they are not attractive for our purpose since they require several steps and, consequently, the yields are only moderate.

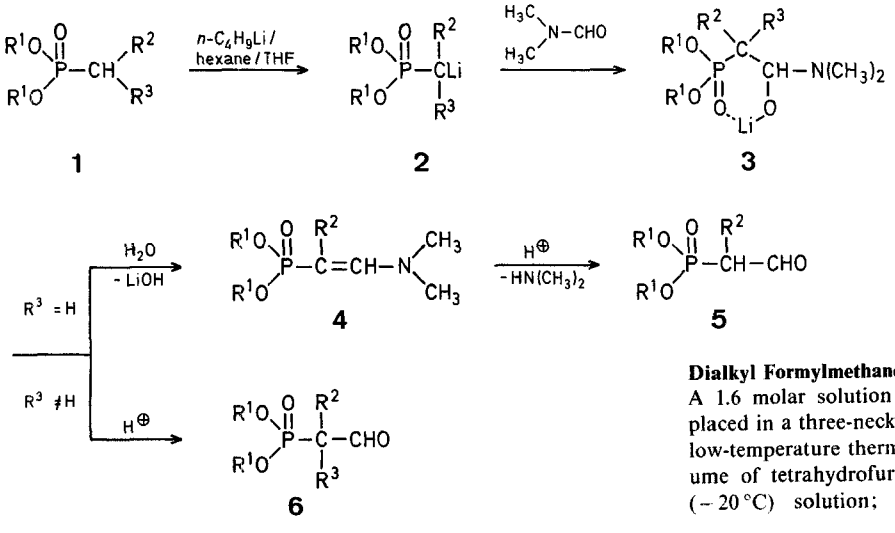
Now we report that the reaction of *O,O*-dialkyl $\alpha$-lithioalkanephosphonates **2** with dimethylformamide affords a method of wide applicability for the preparation of 1-formylalkanephosphonates **5** or **6** on a large scale in one step from the parent phosphonates[5] **1**. The overall process consists in the reaction of **2** with dimethylformamide followed by a short acidic hydrolysis of the resulting lithium $\beta$-aminoalkoxide **3**.

When dimethylformamide is added to the $\alpha$-lithioalkanephosphonate **2** in tetrahydrofuran at $-60\,^{\circ}C$ the lithiated $\beta$-aminoalkoxide **3** is formed rapidly with complete consumption of the reagent **2**.

On allowing the reaction mixture to reach room temperature intermediate **3** remains stable and does not undergo spontaneous elimination to form the enaminophosphonate **4**. The reaction solution shows, in the $^{31}P$-N.M.R. spectrum, a single signal corresponding to **3** in a chelated form (Table 1). The ready formation of a six-membered chelate ring prohibits the release of the aldehyde under the reaction conditions, thus protecting it from further reactions with the organolithium reagent. As frequently, the *O,O*-dimethyl methanephosphonate **(1a)** is an exception and the lithiated $\beta$-aminoalkoxide derived therefrom partially decomposes at room temperature to give a mixture of alkoxide **3a** and enaminophosphonate **4a**.

Elimination forming the enaminophosphonate **4** occurred readily when the lithiated $\beta$-aminoalkoxide **3** is treated *in situ* with water. We first observe precipitation of lithium hydroxide and then its dissolution. At this stage, in basic medium, the enaminophosphonate **4** can be extracted, characterized by spectroscopy and/or G.L.C., and distilled. This has only been performed for the example of **4c**. If the reaction mixture is treated by aqueous acid until acidic pH, the enaminophosphonate **4** is hydrolyzed to form the 1-formylalkanephosphonate **5** which is isolated in near quantitative yield without any traces of side products.

We have found that $\alpha$-unsubstituted 1-formylalkanephosphonates **5a, b, c** can be distillated only with difficulty and give large amounts of polycondensation products. In contrast, $\alpha$-substituted formylalkanephosphonates **5d, e, f,** and **6** are more easily distilled. We have also found that the crude formylalkanephosphonates give, in solution, a mixture of enol and aldehyde forms, especially $\alpha$-substituted formylphosphonate, which disappeared in the distilled product to the benefit of the aldehyde. Diethyl phenylmethanephosphonate has been tested under these conditions and is recovered mainly unaltered after the overall process, essentially for retrocondensation reasons. Table 2 summarizes the results for a number of products and Table 3 the $^1H$-N.M.R. data.




**Dialkyl Formylmethanephosphonates 5a–c; General Procedure:**
A 1.6 molar solution of butyllithium in hexane (0.10 mol + 5%) is placed in a three-necked flask equipped with stirrer, addition funnel, low-temperature thermometer, and nitrogen-inlet tube. An equal volume of tetrahydrofuran (~65 ml) is added to the stirred, cooled (−20 °C) solution; then the dialkyl methanephosphonate (**1**;

$R^1 = CH_3$, 12.4 g; $R^1 = C_2H_5$, 15.2 g; $R^1 = i\text{-}C_3H_7$, 18.0 g; 0.1 mol) in tetrahydrofuran (25 ml) is added dropwise at −60 °C. After 10 min, a solution of dimethylformamide (8.0 g, 0.110 mol) in tetrahydrofuran (25 ml) is then added at −60 °C. The solution is warmed to room temperature and 20% hydrochloric acid is added until pH 1. The two phases system is stirred for a few minutes at room temperature and then decanted. The aqueous solution is extracted with dichloromethane (3 × 40 ml). The combined organic layers are dried with magnesium sulfate, the solvent is removed under reduced pressure, and the product distilled. The yields of crude product are practically quantitative and the crude products as well as the distilled products show the same spectra ($^1$H-N.M.R. or $^{31}$P-N.M.R.). They can be used just as they are for synthetic purposes.

**Dialkyl 1-Formylalkanephosphonates 5d–e; General Procedure:**
A 1.6 molar solution of butyllithium in hexane (0.1 mol +5%) is placed in a three-necked flask fitted with stirrer, addition funnel, and nitrogen-inlet tube. An equal volume of tetrahydrofuran (~65 ml) is added to the stirred and cooled (−20 °C) solution; then, the dialkyl methanephosphonate (**1**; $R^1 = C_2H_5$, 15.2 g; $R^1 = i\text{-}C_3H_7$, 18.0 g; 0.1 mol) in tetrahydrofuran (25 ml) is added dropwise at −60 °C. After 10 min, the alkyl iodide ($R^2 = CH_3$, 15 g; $R^2 = C_2H_5$, 16.5 g; 0.105 mol) in tetrahydrofuran (25 ml) is added dropwise at −60 °C and the mixture is allowed to warm slowly to room temperature. After 30 min at room temperature the mixture is cooled to −45 °C and a solution of butyllithium (0.1 mol +5%) in hexane is added. Stirring is continued for 20 min at −45 °C, dimethylformamide (8.0 g, 0.110 mol) in tetrahydrofuran (25 ml) is added and the procedure described above is followed. Instead of *in situ* alkylation of dialkyl methanephosphonate, we can use the previously prepared dialkyl ethane- or propanephosphonate[5] described in the literature and available on a large scale.

**Diethyl 2-Formyl-2-propanephosphonate (6; $R^1 = C_2H_5$, $R^2 = R^3 = CH_3$):**
The procedure described above is followed. The diethyl ethanephosphonate[4] is first metallated at −45 °C in tetrahydrofuran during 25 min, alkylated with methyl iodide at −45 °C, and then metallated a second time at −45 °C during 35 min before adding dimethylformamide.

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**Table 1.** $^{31}$P-N.M.R. Data for Compounds **3** and **4**

| | $R^1$ | $R^2$ | $R^3$ | $^{31}$P-N.M.R. (THF) of **3**, $\delta$ [ppm] | $^{31}$P-N.M.R. ($CDCl_3$) of **4**, $\delta$ [ppm] |
|---|---|---|---|---|---|
| **a** | $CH_3$ | H | H | +37.5 | +28.6 |
| **b** | $C_2H_5$ | H | H | +35.1 | +25.6 |
| **c** | $i\text{-}C_3H_7$ | H | H | +33.6 | +23.4[a] |
| **d** | $C_2H_5$ | $CH_3$ | H | +38.0 | +28.6 |
| **e** | $i\text{-}C_3H_7$ | $CH_3$ | H | +36.1 | +25.8 |
| **f** | $C_2H_5$ | $C_2H_5$ | H | +37.9 | +28.9 |
| **g** | $C_2H_5$ | $CH_3$ | $CH_3$ | +38.1 | — |

[a] Compound **4c** was isolated by distillation; yield: 55%; b.p. 128–131 °C/1.5 torr.

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**Table 2.** Dialkyl 1-Formylalkanephosphonates **5a–f** and **6**

| Product No. | $R^1$ | $R^2$ | $R^3$ | Yield [%][a] | b.p. [°C]/torr | | $^{31}$P-N.M.R. ($CDCl_3$) $\delta$ [ppm] | | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | found | reported | enol | aldehyde | |
| **5a** | $CH_3$ | H | — | 52 (97) | 106–110°/3 | 87–89°/1[4a] | — | +18.9 | 3.05 (dd, 2H, $J$=22 Hz, 3 Hz); 3.75 (d, 6H, $J$=11 Hz); 9.60 (dt, 1H, $J$=1.7 Hz, 3 Hz) |
| **5b** | $C_2H_5$ | H | — | 53 (98) | 76–79°/0.3 | 82–83°/0.1[4a] | — | +16.1 | 1.30 (t, 6H, $J$=7 Hz); 3.00 (dd, 2H, $J$=22 Hz, 3 Hz); 4.10 (q, 4H, $J$=7 Hz, 7 Hz); 9.60 (dt, 1H, $J$=1.5 Hz, 3 Hz) |
| **5c** | $i\text{-}C_3H_7$ | H | — | 51 (98) | 94–98°/2 | 85–87°/0.8[4a] | +16.3 | +14.0 | 1.30 (d, 12H, $J$=6 Hz); 3.00 (dd, 2H, $J$=22 Hz, 3 Hz); 4.70 (d hept, 2H, $J$=8 Hz, 6 Hz); 9.60 (t, 1H, $J$=3 Hz) |
| **5d** | $C_2H_5$ | $CH_3$ | — | 86 (97) | 93–96°/2 | 85–87°/0.8[4a] | +24.1 | +20.2 | 1.30 (t, 6H, $J$=7 Hz); 1.30 (dd, 3H, $J$=18 Hz, 7 Hz); 3.05 (dqd, 1H, $J$=27.5 Hz, 7 Hz, 1.7 Hz); 4.10 (q, 4H, $J$=7 Hz, 7 Hz); 9.70 (dd, 1H, $J$=0.7 Hz, 1.7 Hz) |
| **5e** | $i\text{-}C_3H_7$ | $CH_3$ | — | 88 (98) | 98–102°/2 | 102–103°/0.7[4a] | +21.2 | +18.1 | 1.30 (d, 12H, $J$=6 Hz); 1.30 (dd, 3H, $J$=17.5 Hz, 7 Hz); 3.00 (dqd, 1H, $J$=28 Hz, 7 Hz, 1.7 Hz); 4.7 (d hept, 2H, $J$=8 Hz, 6 Hz); 9.70 (dd, 1H, $J$=0.7 Hz, 1.7 Hz) |
| **5f** | $C_2H_5$ | $C_2H_5$ | — | 78 | 96–99°/2 | 83–84°/0.5[4a] | +24.5 | +19.2 | 0.90 (dt, 3H, $J$=3 Hz, 7 Hz); 1.25 (t, 6H, $J$=7 Hz); 1.3–2.4 (m, 2H); 2.5–3.1 (dm, 1H, $J$=25 Hz); 4.10 (q, 4H, $J$=7 Hz, 7 Hz); 9.60 (d, 1H, $J$=3 Hz) |
| **6** | $C_2H_5$ | $CH_3$ | $CH_3$ | 79 | 88–91°/2 | 62°/0.4[4d] | — | +23.7 | 1.30 (t, 6H, $J$=7 Hz); 1.35 (d, 6H, $J$=16 Hz); 4.15 (q, 4H, $J$=7 Hz, 7 Hz); 9.60 (d, 1H, $J$=1.5 Hz) |

[a] Value in brackets is yield of crude product.

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