## A Direct Synthesis of Diethyl 1-Alkyl-2-oxoalkanephosphonates

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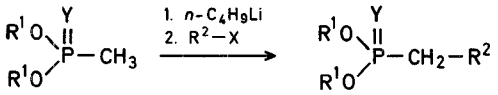
1-Substituted 2-oxoalkanephosphonates are extremely useful intermediates in the synthesis of certain olefins from aldehydes and ketones and especially in the synthesis of enones and cycloenones[1]. Recently Heathcock et al. have offered a new route to the important perfumery agent *cis*-jasmone from 2,5-diketophosphonates[2].

Generally, 1-substituted 2-oxoalkanephosphonates are prepared in two steps. In the first step[3], the reaction of an α-lithiated alkanephosphonate with an ester leads to the corresponding 2-oxoalkanephosphonate; in the second step[4] the alkylation of the sodium or potassium enolates of these 2-oxoalkanephosphonates with reactive alkyl halides gives the 1-monoalkylated products.

We now wish to report that 1-substituted 2-oxoalkanephosphonates can be obtained in good yield by a one-step process under mild reaction conditions.

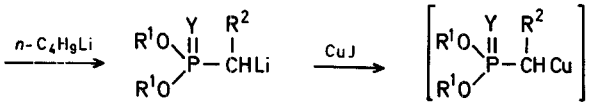
*O,O'*-Dialkyl α-lithio alkanephosphonates have been found to undergo exchange reactions with copper(I) halides to give solutions of the corresponding α-copper(I) derivatives. These α-copper(I)alkanephosphonates were allowed to react with a variety of acyl halides.

Thus *O,O'*-diethyl 1-methyl 2-oxopropanephosphonate has been obtained efficiently in 87% overall yield by sequential "one-pot" methylation and acylation of *O,O'*-diethyl methanephosphonate.

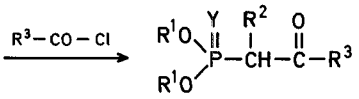


**1a** $R^1 = CH_3$, $Y = O$
**b** $R^1 = C_2H_5$, $Y = O$
**c** $R^1 = CH_3$, $Y = S$

**2**



**3** **4**



**5a-j**

In one flask, starting with *O,O'*-diethyl methanephosphonate, we accomplished the following sequence of operations: (a) addition of *n*-butyllithium at −65°, (b) reaction with methyl iodide at −70 to 25°, (c) addition of *n*-butyllithium at −60°, (d) addition of copper(I) iodide at −35°, and storage at this temperature for 1 h to perform the Li→Cu exchange, (e) reaction with acetyl chloride; Table 1 summarizes the results for a number of products.

We have found that with normal alkyl halides, iodides give more satisfactory results than bromides; with reactive halides, (allylic) bromides are superior to chlorides. We have also found that diethyl alkanephosphonates are preferable to dimethyl alkanephosphonates since diethyl alkanephosphonates are more stable in basic media; however dimethyl methanephosphonothioate is preferable to diethyl methanephosphonothioate since the copper(I) derivatives of the former are more reactive, essentially for sterics reasons.

This direct procedure can efficiently supplement the two methods previously described by Grieco and Heathcock.

**Preparation of Dialkyl 1-Alkyl-2-oxoalkanephosphonates (5); General Procedure:**

Under a nitrogen atmosphere, butyllithium (0.05 mol + 10%) in hexane (~1.8 M) is added at −10° to tetrahydrofuran (30 ml) followed by dropwise addition of the dialkyl methanephosphonate (0.05 mol) in tetrahydrofuran (20 ml) with stirring between −70° and −60°. After 10 min stirring, the alkyl halide (0.055 mol) in tetrahydrofuran (15 ml) is added at −70° and the reaction mixture allowed to warm to room temperature (15 min) before being cooled again at −60°. A new addition of butyllithium (0.05 mol + 10%) in hexane is made at −60°. After 30 min stirring, copper(I) iodide (0.05 mol + 10%) is added and the reaction mixture allowed to warm to −35° to −30° during 60 min. To the resultant black solution, acyl halide (0.055 mol) in ether (50 ml) is added at −40° and the mixture kept at this temperature two hours before being allowed to warm to room temperature over night. Water (50 ml) is added. The solution is filtered on Celite, washed with dichloromethane (2 × 50 ml), filtered, and washed again (50 ml). The combined organic layers are dried with magnesium sulfate, the solvent is removed under reduced pressure, and the product purified by distillation in vacuo.

**Table 1.** Preparation of Dialkyl 1-Alkyl-2-oxoalkanephosphonates (**5**, Y = O) and 1-Alkyl-2-oxoalkanephosphonothioates (**5**, Y = S)

| | $R^1$ | Y | $R^2$-X | $R^3$ | Yield [%][a] | b.p./torr | Microanalyses | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | $CH_3$ | O | $H_3C$-J | $CH_3$ | 67 | 78–80°/0.5 | $C_6H_{13}O_4P$ | calc. | C 40.00 | H 7.27 |
| | | | | | | | (180.13) | found | 39.38 | 7.28 |
| **5b** | $C_2H_5$ | O | $H_3C$-J | $CH_3$ | 87 | 85–88°/1 | Lit.[4,5] b.p. 65°/0.5 torr, 88°/0.1 torr | | | |
| **5c** | $C_2H_5$ | O | $C_2H_5$—Br | $CH_3$ | 75 | 87–90°/1 | $C_9H_{19}O_4P$ | calc. | C 48.65 | H 8.56 |
| | | | $C_2H_5$—J | | 90 | | (222.21) | found | 48.77 | 8.53 |
| **5d** | $C_2H_5$ | O | $H_2C$=CH—$CH_2$—Br | $CH_3$ | 75 | 105–108°/1 | $C_{10}H_{19}O_4P$ | calc. | C 51.28 | H 8.12 |
| | | | | | | | (234.24) | found | 50.95 | 8.18 |
| **5e** | $C_2H_5$ | O | $H_2C$=C($CH_3$)—$CH_2$—Cl | $CH_3$ | 58 | 115–118°/1 | $C_{11}H_{21}O_4P$ | calc. | C 53.22 | H 8.47 |
| | | | | | | | (248.25) | found | 52.84 | 8.47 |
| **5f** | $C_2H_5$ | O | $(H_3C)_2C$=CH—$CH_2$—Cl | $CH_3$ | 60 | 117–120°/1 | Lit.[4] b.p. 125°/1 torr | | | |
| **5g** | $C_2H_5$ | O | $H_3C$—J | *i*-$C_4H_9$ | 70 | 98–102°/1 | $C_{11}H_{23}O_4P$ | calc. | C 52.79 | H 9.26 |
| | | | | | | | (250.27) | found | 53.61 | 9.36 |
| **5h** | $C_2H_5$ | O | $H_3C$—J | *n*-$C_5H_{11}$ | 84 | 103–106°/1 | $C_{12}H_{25}O_4P$ | calc. | C 54.54 | H 9.47 |
| | | | | | | | (264.30) | found | 54.88 | 9.27 |
| **5i** | $C_2H_5$ | O | $H_2C$=CH—$CH_2$—Br | *n*-$C_5H_{11}$ | 65 | 130–132°/1 | $C_{14}H_{27}O_4P$ | calc. | C 57.91 | H 9.37 |
| | | | | | | | (290.33) | found | 57.16 | 9.47 |
| **5j** | $CH_3$ | S | $H_3C$—J | $CH_3$ | 56 | 75–76°/1 | $C_6H_{13}O_3PS$ | calc. | C 36.73 | H 6.68 |
| | | | | | | | (196.19) | found | 37.12 | 6.77 |

[a] Yield of isolated product.

**Table 2.** $^1$H-N.M.R. Data for Tetrachloromethane Solutions of Some Compounds **5**

| Compound | $\delta$ [ppm] |
|---|---|
| **5a** | 1.45 (d.d, 3H), 2.46 (t, 3H), 3.34 (d.q, 1H), 3.98 (d, 6H) |
| **5b** | 1.2 (d.d, 3H), 1.28 (t, 6H), 2.2 (s, 3H), 3.0 (d.q, 1H), 4.0 (d.q, 4H) |
| **5c** | 0.93 (t, 3H), 1.3 (t, 6H), 2.26 (s, 3H), 2.9 (m, 1H), 4.0 (d.q, 4H) |
| **5d** | 1.27 (t, 6H), 2.2 (s, 3H), 2.98 (m, 1H), 4.0 (d.q, 4H), 4.95 (m, 2H), 5.55 (m, 1H) |
| **5f** | 1.33 (t, 6H), 1.67 (s, 6H), 2.92 (m, 1H), 4.0 (d.q, 4H), 4.95 (t, 1H) |
| **5j** | 1.33 (d.d, 3H), 2.23 (s, 3H), 3.22 (d.q, 1H), 3.66 (d, 6H) |

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