A Facile and General, One-pot Synthesis of 2-Oxoalkane Phosphonates from Diethylphosphonocarboxylic Acid Chlorides and Organometallic Reagents

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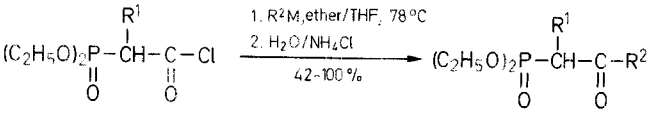
An efficient and general method for the preparation of 2-oxoalkane phosphonates **2** is described. Diethylphosphono-2-alkanoyl chlorides are used to introduce directly the 2-oxophosphonate 1-substituted synthons on Grignard or cuprate reagents.

2-Oxoalkane phosphonates are very interesting compounds which are known for their application to metal solvent extraction[1], in particular for the extraction of uranium(VI)[2]. Approaches to the synthesis of these products are reviewed in older surveys or papers[3,4].

Some years ago, work in our group has resulted in a unique route to 2-oxoalkane phosphonate by direct conversion of aldehydes *via* the diethyl α-lithiochloromethane phosphonate anion[5]. Other synthetic methods include the alkylation of 2-oxopropyl phosphonate[6] and the condensation of a lithiated or cuprated phosphonate anion with a carbonyl precursor (carboxylic acid chloride[7,8], amide or ester[9]).

We report here the use of the diethylphosphonoacetic acid chloride **1** ($R^1 = H$) and some α-branched derivatives **1** ($R^1 = CH_3$, C_6H_5, SC_6H_5) to introduce the 2-oxophosphonate synthon on an organometallic reagent (Scheme **A**).

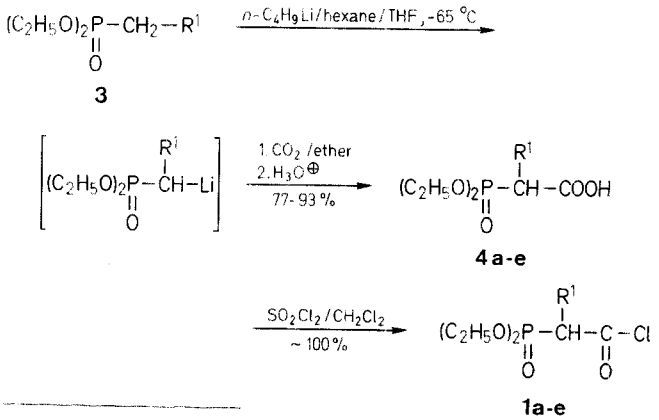


1a-e **2a-k**

M = MgX or 0.5 CuLi

Scheme **A**

Previously the α-substituted diethylcarboxylic methane phosphonates **4** ($R^1 = CH_3$, C_6H_5, SC_6H_5, Cl) were prepared from **3** by a route described by us in precedent papers in the cases where $R^1 = H$ or Cl[10,11] (Scheme **B**).



3 **4a-e** **1a-e**

1,4	R^1
a	H
b	CH_3
c	C_6H_5
d	SC_6H_5
e	Cl

Scheme **B**

Table 1. Preparation of α-branched derivatives of diethylcarboxymethanephosphonate **4** and corresponding carboxylic acid chlorides **1**

Product[a]	Yield [%][b]	Molecular Formula[c]	^{1}H-N.M.R. (CCl_4) δ [ppm]
4a	75–85	$C_6H_{13}O_5P$[d] (196.1)	1.3 (t, 6H, J = 6.7 Hz); 2.9 (d, 2H, J = 21.3 Hz); 3.6–4.5 (m, 4H); 11.7 (s, 1H)
4b	82–85	$C_7H_{15}O_5P$ (210.2)	1.0–1.7 (m, 9H); 2.4–3.5 (dq, 1H, J = 23.3 Hz); 3.7–4.5 (m, 4H); 11.1 (s, 1H)
4c	78–93	$C_{12}H_{17}O_5P$ (272.2)	1.10 (t, 3H, J = 6Hz); 1.17 (t, 3H, J = 6Hz); 3.5–4.6 (m, 5H); 7.0–7.7 (m, 5H); 12.0 (s, 1H)
4d	73–77	$C_{12}H_{17}O_5PS$ (304.3)	1.26 (t, 6H, J = 6.7 Hz); 3.7–4.9 (m, 5H); 7.0–7.7 (m, 5H); 12.6 (s, 1H)
4e	87–91	$C_6H_{12}ClO_5P$[d] (230.6)	1.35 (t, 6H, J = 6.7 Hz); 4.37 (dq, 4H, J_{PH} = 7.0 Hz, J_{HH} = 6.7 Hz); 4.55 (d, 1H, J = 17Hz); 11.7 (s, 1H)
1a	~100	$C_6H_{12}ClO_4P$ (214.6)	1.38 (t, 6H, J = 6.7 Hz); 3.5 (d, 2H, J = 21.3 Hz); 3.9–4.6 (dq, 4H, J_{PH} = 7.0 Hz, J_{HH} = 6.7 Hz)
1b	~100	$C_7H_{14}ClO_4P$ (228.6)	1.1–1.8 (m, 9H); 3.2–4.7 (m, 5H)
1c	~100	$C_{12}H_{16}ClO_4P$ (290.7)	1.13 (t, 3H, J = 8.0 Hz); 1.25 (t, 3H, J = 8.0 Hz); 3.5–4.4 (m, 4H); 4.7 (d, 1H, J = 23 Hz); 7.1–7.7 (m, 5H)
1d	~100	$C_{12}H_{16}ClO_4PS$ (322.8)	1.0–1.6 (m, 6H); 3.7–4.8 (m, 5H); 7.0–7.9 (m, 5H)
1e	~100	$C_6H_{11}ClO_4P$ (213.6)	1.37 (t, 6H, J = 7.0 Hz); 3.8–4.6 (m, 4H); 5.1 (d, 1H, J = 17 Hz)

[a] The I.R. spectra were in good accord with the proposed structures.
[b] Yield of crude product.
[c] The microanalyses of products **4** were in satisfactory agreement with the calculated values: C ±0.30, H ±0.19, Cl ±0.25. The microanalysis of the carboxylic acid chlorides **1** could not be effected because these products slowly decompose, but I.R. and ^{1}H-N.M.R. spectra were in good agreement with the structure.
[d] Previously described by us[10,11].

Direct conversion of **4** into carboxylic acid chloride **1** is achieved with quantitative yields by treatment with sulfuryl chloride in dichloromethane. Crude carboxylic acid chlorides **1** are used for the next step because these compounds decompose partially on distillation (Table 1).

Grignard reagents and organocuprates react with carboxylic acid chlorides **1** to give 2-oxoalkane phosphonates **2** with moderate to good yields (Table 2). It should be noted that 2-oxoalkane phosphonates were also obtained even with Grignard reagents. These results indicate a good stabilization for the intermediate magnesium alcoholate by intramolecular chelation or an *in situ* deprotonation of free 2-oxoalkane phosphonates. Moreover, the carboxylic acid chlorides **1** do not behave similarly to to alkyldiethylphosphonoacetates which are only deprotonated by Grignard reagents[12].

The reaction gives better yields with organocuprates than with organomagnesium compounds. In general the yields of **2** are better when the carboxylic acid chlorides **1** are α-substituted. Moreover steric crowding in organocuprates did not appreciably affect the yields of **2**.

However, when organocuprates are used, α-chlorocarboxylic acid chlorides **1** (R^1 = Cl) give only 2-oxoalkane phosphonates without chlorine in α-position. With Grignard reagents this compound **1** (R^1 = Cl) gives a mixture of unidentified products.

Finally, the synthesis of 2-oxoalkane phosphonates **2** via the α-substituted or unsubstituted diethylphosphonoacetic acid chloride and organocuprates reagents complements the existing methods, in particular the reaction between dialkyl-1-lithioalkane phosphonates and carboxylic acid chlorides[7].

All operations are carried out in carefully dried apparatus under an argon atmosphere and anhydrous solvents are used.

α-Substituted Diethylcarboxymethanephosphonates 4; General Procedure:

A 1.5 molar solution of *n*-butyllithium (70 ml, 0.104 mol) in ether or in hexane is added to tetrahydrofuran (70 ml) at −65 °C, followed by the dropwise addition with stirring at −65 °C of a solution of α-substituted diethylmethanephosphonate **3** (0.1 mol) in tetrahydrofuran (20 ml). The mixture is stirred at −65 °C for 30 min and is poured with stirring into a Dewar containing a saturated dry ice/ether solution (200 ml). After 5 min the mixture is poured into a beaker and allowed to warm to room temperature during 2 h with stirring. Water (100 ml) is added, the organic layer is washed with 10% aqueous sodium carbonate solution (2 × 25 ml) and the aqueous layers are combined before washing with ether (2 × 50 ml). The aqueous layer is acidified to pH 1 with 2 molar sulfuric acid saturated with sodium chloride, and extracted with dichloromethane (3 × 50 ml). After drying with magnesium sulfate the solvent is removed under vacuum to leave crude **4** as an oil (Table 1).

α-Substituted Diethylphosphonoacetic Acid chlorides 1; General Procedure:

A solution of α-substituted diethylcarboxymethanephosphonate **4** (0.05 mol) in dichloromethane (20 ml) is added with stirring to freshly distilled sulfurylchloride (11.9 g, 0.1 mol) in dichloromethane (80 ml). Stirring is continued for 2 h at room temperature (for R^1 = H) or for 5 h at room temperature (for R^1 = CH_3). For R^1 = Cl, C_6H_5 or SC_6H_5 the mixture is refluxed for 3 h. The mixture is concentrated under reduced pressure to give a crude brown oil which is used in the next step, yield: ~100% (Table 1).

Preparation of 2-Oxoalkanephosphonates 2 from Organocuprates Reagents; General Procedure:

An ether-tetrahydrofuran solution of lithium or magnesium dialkyl cuprate (0.03 mol in 100 ml of solvent) is prepared according to the standard procedure. Diethylphosphonoacetic acid chloride **1** (R^1 = H) or α-branched derivative **1** (R^1 = CH_3, C_6H_5, SC_6H_5) (0.015 mol) in ether (15 ml) is added dropwise at −78 °C. The solution acquires a red colour. The mixture is allowed to warm to −40 °C and becomes yellow within a few min. After 90 min stirring at −40 °C, an aqueous saturated ammonium chloride solution

Table 2. Reaction of organometallic reagents with carboxylic acid chlorides **1** to give 2-oxoalkanephosphonates **2**

Organometallic Reagent	Product No.[a]	R^1	R^2	Yield [%]	bp/torr [°C]	Molecular Formula[b] or Lit. b.p. [°C]/torr	^{1}H-N.M.R. (CCl_4) δ[ppm]
$(CH_3)_2CuLi$ CH_3MgBr	**2a**	H	CH_3	55 50	76–81/0.1	88–90/0.5[7]	1.3 (t, 6H, J = 6.7 Hz); 2.2 (s, 3H); 3.0 (d, 2H, J = 2.3 Hz); 3.7–4.4 (m, 4H)
$(C_2H_5)_2CuLi$ C_2H_5MgBr	**2b**	H	C_2H_5	59 62	79–85/0.05	90–93/0.5[7]	1.0 (t, 3H, J = 7.3 Hz); 1.3 (t, 6H, J = 7.3 Hz); 2.6 (q, 2H, J = 7.3 Hz); 3.0 (d, 2H, J = 23 Hz); 3.7–4.4 (m, 4H)
$(nC_4H_9)_2CuLi$	**2c**	H	nC_4H_9	65	103–106/0.05	$C_{10}H_{21}O_4P$ (236.2)	3.0 (d, 2H, J = 23 Hz); 3.7–4.4 (m, 4H); 0.7–1.8 (m, 7H); 1.3 (t, 6H, J = 6.7 Hz); 2.6 (t, 2H, J = 6.7 Hz)
$(CH_3)_2CuLi$	**2d**	CH_3	CH_3	62	70–78/0.1	90–92/0.2[9]	1.1 (d, 3H, J = 6.8 Hz); 1.3 (t, 6H, J = 6.8 Hz); 2.27 (s, 3H); 2.7–3.6 (dq, 1H, J_{PH} = 25 Hz, J_{HH} = 6.8 Hz); 3.6–4.4 (m, 4H)
$(C_2H_5)_2CuLi$	**2e**	CH_3	C_2H_5	76	80–85/0.05	$C_9H_{19}O_4P$ (222.22)	0.7–1.7 (m, 12H), 2.0–3.6 (m, 3H); 3.7–4.4 (m, 4H)
$(nC_4H_9)_2CuLi$	**2f**	CH_3	nC_4H_9	73	87–95/0.1	$C_{11}H_{23}O_4P$ (250.3)	0.7–1.9 (m, 16H); 2.4–2.8 (m, 2H); 2.7–3.6 (dq, 1H, J_{PH} = 25 Hz, J_{HH} = 7 Hz); 3.6–4.4 (m, 4H)
$(iC_3H_7)_2CuMgBr$ iC_3H_7MgBr	**2g**	CH_3	iC_3H_7	67 42	73–77/0.05	$C_{10}H_{21}O_4P$ (236.2)	0.9–1.2 (m, 15H); 2.7–3.3 (m, 1H); 2.7–3.7 (dq, 1H, J_{PH} = 24 Hz, J_{HH} = 7 Hz); 3.7–4.4 (m, 4H)
$(tC_4H_9)_2CuMgBr$	**2h**	CH_3	tC_4H_9	66	74–79/0.1	$C_{11}H_{23}O_4P$ (250.3)	1–1.6 (m, 18H); 3.2–4.4 (dq, 1H, J_{HH} = 7 Hz); 3.6–4.4 (m, 4H)
$(CH_3)_2CuLi$	**2i**	C_6H_5	CH_3	75	118–123/0.05	$C_{13}H_{19}O_4P$ (270.3)	1.1 (t, 3H, J = 6.6 Hz); 1.2 (t, 3H, J = 6.6); 2.22 (s, 3H); 3.55–4.75 (m, 5H); 7.0–7.7 (m, 5H)
$(C_2H_5)_2CuLi$	**2j**	C_6H_5	C_2H_5	94	123–126/0.05	$C_{14}H_{21}O_4P$ (284.3)	0.7–1.4 (m, 9H); 2.6 (q, 2H, J = 7.3 Hz); 3.7–4.4 (m, 4H); 4.4 (d, 1H, J = 23 Hz); 7.0–7.7 (m, 5H)
$(C_2H_5)_2CuLi$	**2k**	SC_6H_5	C_2H_5	100	146–153/0.1	$C_{14}H_{21}O_4PS$ (316.3)	0.7–1.6 (m, 9H); 2.1–4.4 (m, 7H); 7.0–7.7 (m, 5H)

[a] The I.R. spectra were in good accord with the proposed structure.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.33, H ±0.20 (exception: **2k**, C 53.82, H 7.08).
[c] Yield of crude product.

(50 ml) is added and the product is extracted by dichloromethane (3 × 30 ml). The combined organic layer is washed with diluted aqueous ammonia solution until the ammonia solution of the last washing is colourless. The organic layer is dried with magnesium sulfate, the solvent is removed under reduced pressure and the product is purified by vacuum distillation (Table 2).

Preparation of 2-Oxoalkanephosphonates 2 from Grignard Reagents; General Procedure:

A 1.6 molar solution of the Grignard reagent (0.04 mol, 25 ml) in diethylether is added dropwise with stirring to the carboxylic acid chloride **1** (0.02 mol) in ether (50 ml) at −78 °C. A viscous yellow-grey precipitate forms. The mixture is stirred at −70 °C for 30 min and then quenched with an aqueous saturated ammonium chloride solution (50 ml) at −70 °C. The product is extracted with dichloromethane (3 × 30 ml) and the combined organic layer is dried with magnesium sulfate. The solvent is evaporated under reduced pressure and the residual oil is further purified by distillation (Table 2).

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