A Direct Conversion of Aldehydes into 2-Oxoalkanephosphonates via the Diethyl α-Lithiochloromethanephosphonate Anion

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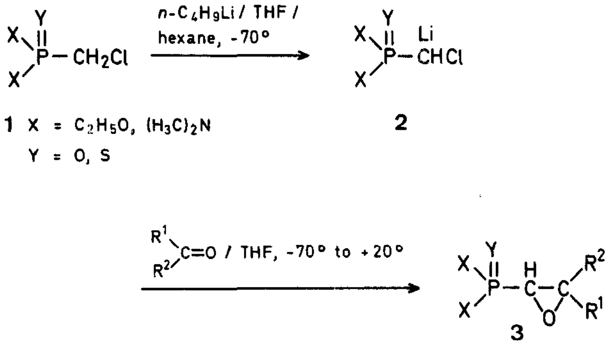
Addition of a carbonyl compound, aldehyde or ketone, to the lithium derivative of dialkyl chloromethanephosphonate **2** in a mixture of tetrahydrofuran and hexane, at low temperature results in the almost immediate formation of a 1-chloro-2-hydroxyalkanephosphonate which leads on warming to epoxyalkanephosphonates[1] **3**.



1 X = C_2H_5O, $(H_3C)_2N$
Y = O, S

2

3

The reactions of the α-lithiochloromethanephosphonate carbanion with aldehydes, instead of an epoxide synthesis, can

0039-7881/78/0932-0682 $ 03.00

Table. Diethyl 2-Oxoalkanephosphonates, Diethyl 2-Oxoalkanephosphonothioates, *N,N,N',N'*-Tetramethyl-2-oxoalkanephosphonic Diamides

Product	X	Y	R	Base[a]	Yield [%]	b.p./torr or m.p. (solvent)	Molecular formula	^{1}H-N.M.R. (CCl_4) δ [ppm]
5a	C_2H_5O	O	i-C_3H_7	$(i$-$C_3H_7)_2NLi$	89	94–98°/0.5[5]	$C_9H_{19}O_4P$ (222.2)	—[5]
5b	C_2H_5O	O	i-C_4H_9	$(i$-$C_3H_7)_2NLi$	90	98–100°/0.5[5,8]	$C_{10}H_{21}O_4P$ (236.3)	—[5]
5c	C_2H_5O	O	n-C_4H_9	$(i$-$C_3H_7)_2NLi$	92	113–117°/0.5[5,7]	$C_{10}H_{21}O_4P$ (236.3)	[5]
5d	C_2H_5O	O	C_7H_{15}	$(i$-$C_3H_7)_2NLi$	88	125–129°/0.1[6]	$C_{13}H_{27}O_4P$ (278.3)	—[5]
5e	C_2H_5O	O	$H_3C-CH=CH$	$(i$-$C_3H_7)_2NLi$	(85)[c]	—[b,5]	$C_9H_{17}O_4P$ (220.2)	—[5]
5f	C_2H_5O	O	C_6H_5	n-C_4H_9Li	41	150–155°/0.9[5,6]	$C_{12}H_{17}O_4P$ (256.2)	—[5]
5g	C_2H_5O	O	C_6H_5	$(i$-$C_3H_7)_2NLi$	68	150–155°/0.9[5,6]	$C_{12}H_{17}O_4P$ (256.2)	—
5h	C_2H_5O	O	4-$Cl-C_6H_4$	n-C_4H_9Li	40	165–170°/1[5]	$C_{12}H_{16}ClO_4P$ (290.7)	—[5]
5i	C_2H_5O	O	4-$H_3CO-C_6H_4$	$(i$-$C_3H_7)_2NLi$	70	155–160°/0.8[5]	$C_{13}H_{19}O_5P$ (286.3)	—[5]
5j	C_2H_5O	O	3,4-$O-CH_2-O-C_6H_3$	$(i$-$C_3H_7)_2NLi$	65	47–48° (ether/pentane)	$C_{13}H_{17}O_6P$ (300.3)[f]	1.3 (t, 6H); 3.35 (d, 2H); 4.0 (d. q, 4H); 5.95 (s, 2H); 6.73 (m, 1H); 7.45 (m, 2H)
5k	C_2H_5O	O	4-$(H_3C)_2N-C_6H_4$	$(i$-$C_3H_7)_2NLi$	76	>150°/0.5[e]	$C_{14}H_{22}NO_4P$ (299.3)[f]	1.23 (t, 6H); 3.0 (s, 6H); 3.25 (d, 2H); 3.95 (d. q, 4H); 6.43 (m, 2H); 7.73 (m, 2H)
5l	C_2H_5O	O	2-thienyl	$(i$-$C_3H_7)_2NLi$	72	155–160°/1[5]	$C_{10}H_{15}O_4PS$ (262.3)	[5]
5m	C_2H_5O	S	i-C_3H_7	$(i$-$C_3H_7)_2NLi$	58	84–87°/0.7	$C_9H_{19}O_3PS$ (238.3)[f]	0.98 (d, 6H); 1.2 (t, 6H); 2.8 (m, 1H); 3.1 (d, 2H); 4.0 (d. q, 4H)
5n	$(H_3C)_2N$	O	i-C_3H_7	$(i$-$C_3H_7)_2NLi$	76	97–100°/0.5	$C_9H_{21}N_2O_2P$ (220.3)[f]	1.05 (d, 6H); 2.53 (d, 12H); 2.90 (m, 1H); 2.93 (d, 2H)
5o	$(H_3C)_2N$	O	C_6H_5	$(i$-$C_3H_7)_2NLi$	88	—[d,9]	$C_{12}H_{19}N_2O_2P$ (254.3)	2.45 (d, 12H); 3.4 (d, 2H); 7.13 (m, 3H); 7.83 (m, 2H)
5p	$(H_3C)_2N$	O	2-thienyl	$(i$-$C_3H_7)_2NLi$	87	[d]	$C_{10}H_{17}N_2O_2PS$ (260.3)	2.53 (d, 12H); 3.4 (d, 2H); 7 (m, 1H); 7.5 (m, 1H); 7.85 (m, 1H)

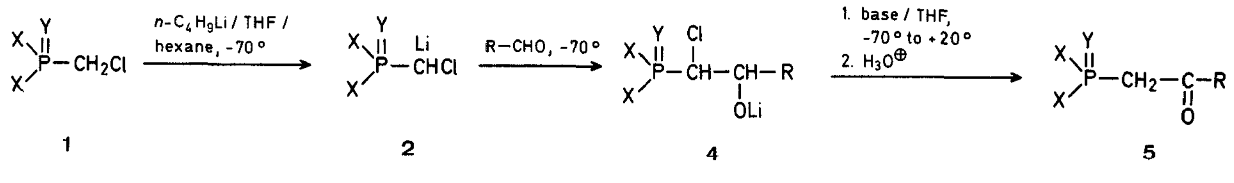
[a] Second equivalent of base; first one is always n-butyllithium.
[b] Polymerises on distillation.
[c] Product partially polymerised.
[d] Decomposes on distillation.
[e] Oil partially decomposed on distillation.
[f] New compound; gave satisfactory microanalyses (C ±0.4%, H ±0.18%, N ±0.03%).

take a different course if the so-formed alkoxide anion is further treated at low temperature with 1 equivalent of strong base.

Under these conditions after warming[2] and hydrolysis we do not recover an epoxyalkanephosphonate but instead a 2-oxoalkanephosphonate **5** is formed.

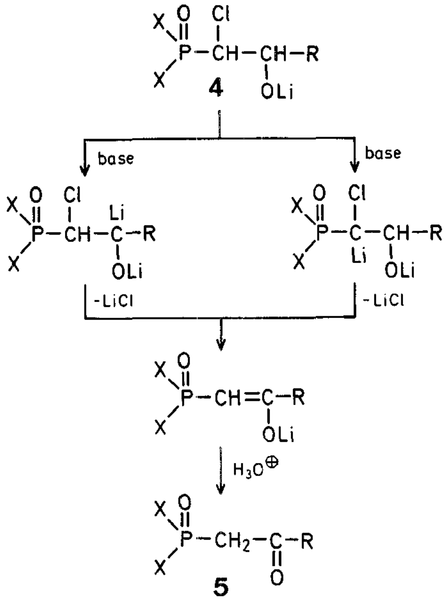
Synthesis of 2-oxoalkanephosphonates by reaction of a 1-chloro-2-hydroxyalkanephosphonate with base is not a standard route and to explain this new synthesis we suggest the two following mechanisms:

- in the first one we assume the formation of a carbanion in the β-position, itself favoured by a β-elimination reac-



tion; the enol phosphonate which results is converted into the 2-oxoalkanephosphonate;

- in the second one the hydrogen in the α-position is abstracted and the so formed carbanion gives an α-elimination simultaneous to a migration of hydrogen[10] leading to an enol phosphonate as above.



Our aim has been to study the limits of the process. The procedure can be applied to:

- a wide range of aldehydes, aliphatic as well as aromatic, however unsaturated aldehydes (e.g. crotonaldehyde) yield partially polymerised 2-oxoalkanephosphonates;
- esters or amides of α-chloromethanephosphonic acids ($X=RO$ or R_2N);
- esters of α-chloromethanephosphonothioic acid ($Y=S$);
- unsubstituted α-chloromethanephosphonic acids only; formation of an α-substituted 2-oxoalkanephosphonate failed (favourable to the second mechanism).

The choice of the base initiating elimination is very important and depends on the phosphonate substituent (X).

We have found that esters of 1-chloro-2-hydroxyalkanephosphonates ($X=RO$) in the presence of butyllithium are subjected to *P*-substitution. Nucleophilic attack at phosphorus by butyllithium can be a major reaction and we isolated a 2-oxoalkanephosphonate mixed with a large amount of the butylation products[4]. Thus, it is better with phosphonate esters to substitute for butyllithium hindered bases such as lithium diisopropylamide. Use of *t*-butyllithium failed; it provides poor yield of 2-oxoalkanephosphonate soiled with side-products.

In contrast, with phosphonamides ($X=R_2N$) attack on the phosphorus atom is avoided and invariably we used two equivalents of butyllithium or the couple butyllithium/lithium diisopropylamide.

Results are summarized in Table I. All the compounds (except **5j**, **5k**, **5m**, **5n**) have been compared (physical data, ^{1}H-N.M.R. and I.R. spectra) to samples obtained by another way[5,6,7,8].

Diethyl 2-Oxoalkanephosphonates 5 ($X=C_2H_5O$, $Y=O$); General Procedure:

A 1.45 molar solution of *n*-butyllithium in hexane (0.054 mol + 5%) is placed in a three-necked flask equipped with a stirrer, an addition funnel, a low temperature thermometer, and a nitrogen inlet tube. An equal volume of tetrahydrofuran (~40 ml) is added to the cooled (−20°) solution. Subsequently diethyl chloromethanephosphonate (10 g, 0.054 mol) in tetrahydrofuran (10 ml) is added dropwise at −70°. After 10 min, the clear reaction mixture becomes turbid and the carbonyl compound (0.054 mol) in tetrahydrofuran (10 ml) is added at −75° to −70°. The mixture slowly becomes clear. After 30 min, lithium diisopropylamide (0.054 mol + 5%) (previously prepared by addition at 0° of *n*-butyllithium to diisopropylamine dissolved in tetrahydrofuran) is added at −70°. Stirring is continued for 3 h at −70° and then the mixture is slowly allowed to warm to room temperature within a few hours (overnight). At room temperature the mixture is slowly hydrolysed with 2 normal sulfuric acid so that it becomes neutral and the aqueous solution extracted with dichloromethane (3 × 50 ml). The combined organic layers are dried with magnesium sulfate, the solvent is removed under reduced pressure, and the product is purified by vacuum distillation.

A similar procedure is used when $X=C_2H_5O$, $Y=S$; when $X=(CH_3)_2N$, $Y=O$ the procedure is the same, especially for metallation, except that the second equivalent of base can be *n*-butyllithium or lithium diisopropylamide and hydrolysis is performed with water (40 ml).

Dedicated to Professor Henri Normant on the occasion of his 71th birthday.

Received: March 30, 1978

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[2] If the addition of the base at low temperature was followed by hydrolysis we recovered the 1-chloro-2-hydroxyalkanephosphonate; at low temperature the elimination reaction is very slow.

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[4] Purification of β-ketophosphonate is simple in the case R = Ar; the ethereal solution of the crude is washed three times with a five per cent aqueous solution of sodium hydroxide and the enolate so formed put in acidic medium to generate the β-ketophosphonate which is then extracted which ether.

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