Alkylation of Diethyl 2-Oxoalkanephosphonates

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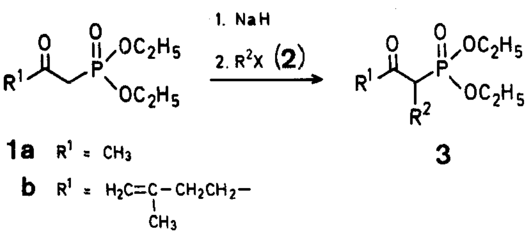
2-Oxoalkanephosphonates are useful intermediates for the synthesis of α,β-unsaturated ketones *via* the Horner-Wittig reaction[1]. These compounds are generally prepared by addition of a lithiated alkyl phosphonate to an ester[2,3]. Since two equivalents of phosphonate anion must be used to achieve complete conversion of the ester to the 2-oxoalkanephosphonate, this process is practical only when the phosphonate is inexpensive and easily removable from the product (e.g. dimethyl methanephosphonate). Grieco has offered an alternative synthesis of 3-substituted 2-oxoalkanephosphonates *via* alkylation of the dianion of dimethyl 2-oxopropanephosphonate (**1**)[4]. Our need for several 1-substituted 2-oxoalkanephosphonates for the synthesis of cycloenones led us to investigate the 1-alkylation of 2-oxoalkanephosphonates[5], and our results are summarized in the Table.



1a $R^1 = CH_3$
b $R^1 = H_2C{=}C(CH_3){-}CH_2CH_2{-}$
c $R^1 = (H_3C)_2C{=}CH{-}CH_2CH_2{-}$

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Alkylation of the sodium enolates in tetrahydrofuran with reactive halides (allylic, acetylenic, and bromo esters) gives good yields of mono-alkylated materials. Normal alkyl halides (e.g., pentyl iodide) fail to react with sodium enolates under the conditions described for the reactive halides and higher temperatures and prolonged reaction times lead to extensive decomposition. We have also found that diethyl phosphonates are preferable, since dimethyl phosphonates often undergo demethylation under the reaction conditions by reaction with the halide ion formed in the alkylation.

The more reactive potassium enolates[6] also give good yields with reactive halides. Although satisfactory yields are obtained with methyl and ethyl iodide, only elimination is observed when the potassium enolate of **1a** is treated with pentyl iodide, isopropyl iodide, or 1-bromo-3-butene.

This alkylation procedure should prove to be complementary to Grieco's dianion alkylation method in the preparation of substituted 2-oxoalkanephosphonates for the synthesis of enones and cycloenones. The two procedures can be combined in a one-step process, but we obtained higher yields by isolating the initial dianion alkylation product before proceeding with the 1-alkylations described here.

Method A: Alkylation of Sodium Enolates; Diethyl 1-(3-Methyl-2-butenyl)-2-oxopropanephosphonate:

Phosphonate **1a** (4.85 g, 25 mmol) in tetrahydrofuran (5 ml) is added slowly to a suspension of sodium hydride (25 mmol) in tetrahydrofuran (50 ml) at 0° and the mixture is allowed to stir at room temperature for 1 h. 4-Bromo-2-methyl-2-butene (4.5

Table. 1-Alkylations of 2-Oxoalkanephosphonates

Phosphonate	Alkylating Agent **2**	Method[a]	Reaction time	Yield (%)[b]	B.p.	Analyses			
1a	$(H_3C)_2C{=}CH{-}CH_2Br$	A	18h	82	125°/1 torr	$C_{12}H_{23}O_4P$ (262.3)	calc. / found	C 54.96 / 55.21	H 8.77 / 9.01
1a	$C_2H_5OOC{-}CH_2Br$	A	11h	67	130°/1 torr	$C_{11}H_{21}O_6P$ (280.3)	calc. / found	C 47.14 / 46.98	H 7.50 / 7.43
1a	$H_2C{=}C(CH_3){-}CH_2Cl$	A	72h	55	115°/0.8 torr	$C_{11}H_{21}O_4P$[d]	calc. / found	248.1184 / 248.1181	
1a	H_3CCH_2J	B	72h	72	90°/1 torr	$C_9H_{19}O_4P$[d]	calc. / found	222.1020 / 222.0981	
1a	$H_3C{-}J$	B	10h	68	65°/0.5 torr	$C_8H_{17}O_4P$ (208.2)	calc. / found	C 46.15 / 45.97	H 8.17 / 8.15
1a	$H_2C{=}CH{-}CH_2Br$	A	48h	68	105°/0.7 torr	$C_{10}H_{19}O_4P$[d]	calc. / found	234.1020 / 234.1010	
1a	$C_6H_5{-}CH_2Br$	A	48h	61	120°/0.3 torr	$C_{14}H_{21}O_4P$[d]	calc. / found	284.1177 / 284.1115	
1a	$H_3C{-}C(Cl){=}CH{-}CH_2Cl$	A	72h	35	130°/1 torr	$C_{11}H_{20}ClO_4PCl$[d]	calc. / found	247.1099($M^{\oplus}-Cl$) / 247.1144	
1b	$H_3C{-}C{\equiv}C{-}CH_2Br$	A	36h	75	160°/0.5 torr	—	—		
1c	$H_3COOC{-}CH_2CH_2CH_2{-}C{\equiv}C{-}CH_2J$	B	1h	89	—[c]	$C_{20}H_{33}O_6P$[e]	calc. / found	400 / 400	

[a] Method A refers to alkylation of the sodium enolate; Method B to the potassium enolate.
[b] Yield of distilled material.
[c] Purified by silica gel chromatography.
[d] By high resolution mass spectrometry.
[e] By low resolution mass spectrometry.

g, 30 mmol) is added and the solution is stirred for 18 h at room temperature. The mixture is poured into 5% hydrochloric acid and extracted with chloroform. The chloroform solution is dried (magnesium sulfate) and evaporated. Distillation of the residue gives the alkylated 2-oxoalkanephosphonate as a colorless oil; yield: 5.38 g (82%); b.p. 125°/1 torr.

$C_{12}H_{23}O_4P$	calc.	C 54.96	H 8.77
(262.3)	found	55.21	9.01

I.R. (film): $\nu_{max} = 1715, 1250\ cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 1.70$ (s, 6H), 2.25 (s, 3H), 3.23 (m, 1H), 5.03 ppm (t, 1H).

Mass spectrum: $m/e = 262$.

Method B: Alkylation of Potassium Enolates (General Procedure): Phosphonate **1** (10 mmol) is added slowly to a suspension of potassium hydride in tetrahydrofuran (25 ml) at 0°. The potassium salt precipitates as a white solid. After stirring at room temperature for 15 min, the alkylating agent is added and the precipitate goes into solution. The reaction is complete within an hour. Work-up is the same as for method A.

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