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Synthesis of γ-ketophosphonates via aerobic hydroacylation of vinyl phosphonates

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ABSTRACT

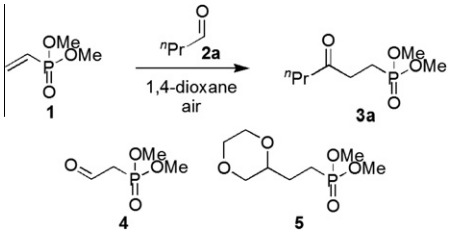
γ-Ketophosphonates are commonly employed as non-hydrolysable phosphate mimetics and as tools in synthesis. The synthesis of γ-ketophosphonates under mild conditions via interception of acyl radicals generated by aldehyde auto-oxidation is described.

γ-Ketophosphonates, and their corresponding phosphonic acids, have been established as useful tools in both synthetic chemistry[1–6] and in biology as non-hydrolysable phosphate mimetics.[7,8] For example, γ-ketophosphonates have been successfully employed as non-hydrolysable mimetics for dihydroxyacetone phosphate,[9] as inhibitors of phosphoglycerate kinase[10] and as β-lactamase inhibitors.[11]

Although alternative methods have been developed for the preparation of γ-ketophosphonates,[12–16] the most commonly employed approach is based around conjugate addition to an enone.[6,17,18] In recent years, the development of catalytic methods to prepare unsymmetrical ketones via the hydroacylation of alkenes has received a great deal of attention.[19,20] In addition, the formation of unsymmetrical ketones via acyl radical mediated carbon–carbon bond formation has been widely investigated.[21–29] However, radical approaches often require noxious precursors or chain carriers that are toxic and/or complicate the purification of reaction products.[30,31] Although alternative methods have been developed for radical alkene hydroacylation, they have not been widely employed.[32,33]

Recently, we described methods for the hydroacylation of electron-deficient alkenes bearing sulfonate, sulfone and ester substituents with simple alkyl aldehydes via interception of the acyl radicals generated during aldehyde auto-oxidation.[34–36] Herein, we report the application of this approach to the synthesis of γ-ketophosphonates via the aerobic hydroacylation of vinyl phosphonates with both simple and, notably, functionalised aldehydes.

We began investigations focusing on the hydroacylation of dimethyl vinyl phosphonate (**1**) with butanal (**2a**) (5 equiv) in 1,4-dioxane at 20 °C, and were pleased to observe formation of γ-ketophosphonate **3a**, albeit in very low yield, <5% by ^{1}H NMR at 15% conversion of **1**, after 144 h (Scheme 1). In addition, careful examination of the crude ^{1}H NMR spectrum indicated the formation of aldehyde **4** and phosphonate **5**. Consistent with previous studies, reaction between vinyl phosphonate **1** and butanal (**2a**) was suppressed completely by addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (10 mol %), clearly indicative of a radical mechanism for the hydroacylation of vinyl phosphonate **1**.[36]



Scheme 1. Hydroacylation of vinyl phosphonate **1** with butanal (**2a**).

Table 1
Optimisation of the reaction of vinyl phosphonate **1** with butanal (**2a**)[a]

Entry	*T* (°C)	[**1**][b] (mol dm^{-1})	% Conv. **1**	**3a**:**4**:**5**[c]	Yield **3a**[d] (%)
1	20	1.00	15	—	<5
2	40	1.00	60	—	35
3	60	5.00	100	1:0.27:0.07	61
4	60	2.00	100	1:0.19:0.08	67
5	60	1.00	100	1:0.18:0.09	70
6	60	0.50	100	1:0.16:0.10	60
7	60	0.25	100	1:0.10:0.14	55
8	80	1.00	100	—	69

[a] Conditions: **1** (1 mmol), **2a** (5 mmol), 1,4-dioxane (see Table 1), 24 h.
[b] Concentration of **1** refers to initial concentration of **1** in 1,4-dioxane before the addition of **2**.
[c] Determined by integration of the ^{1}H NMR spectrum relative to pentachlorobenzene as an internal standard.
[d] Isolated yield.

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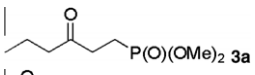
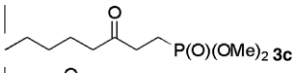
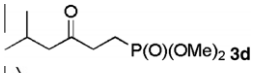
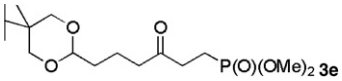
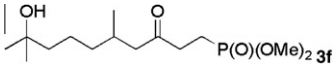
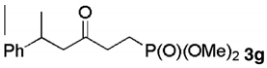
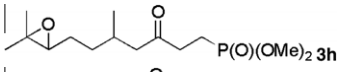
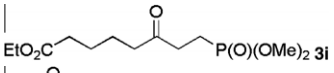
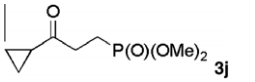
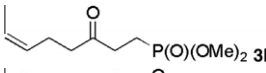
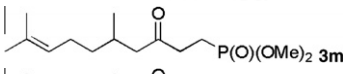
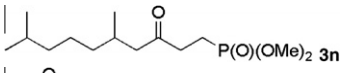
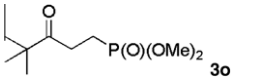
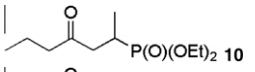
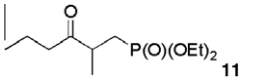
Despite the low yield for the hydroacylation of vinyl phosphonate **1** with butanal (**2a**) (Scheme 1), we were sufficiently encouraged to embark upon an optimisation study focusing on temperature and concentration to attempt to control exposure of the reaction to molecular oxygen, hence to ameliorate formation of aldehyde **4** and phosphonate **5** (Table 1). Gratifyingly, increasing the reaction temperature had a marked impact on the yield of ketophosphonate **3a** with the optimal yield, 70%, afforded at 60 °C and a concentration of 1.00 mol dm^{-3} (Table 1, entry 5); heating to higher temperatures did not affect the yield significantly (Table 1, entry 8). We attribute the improved yield of ketophosphonate **3a** to the lower concentration of dissolved molecular oxygen at elevated temperatures promoting acyl radical trapping by vinyl phosphonate **1** in preference to molecular oxygen. This is supported by the lower conversions of vinyl phosphonate **1** observed at lower temperatures (Table 1, entries 1 and 2) compared to those achieved at 60 and 80 °C (Table 1, entries 5 and 8).

The lower yields observed for the hydroacylation of vinyl phosphonate **1** with butanal (**2a**) at higher (Table 1, entries 3 and 4) and lower concentrations (Table 1, entries 6 and 7) than the optimal 1.00 mol dm^{-3} could be rationalised by the increased formation of aldehyde **4** and phosphonate **5**, respectively (Scheme 2). We anticipate that aldehyde **4** is formed from reaction of peracyl radical **6**, formed during the auto-oxidation of aldehyde **2a** to its corresponding acid **7**, with vinyl phosphonate **1** via peracyl ester **9**. Thus, at high surface area:volume ratio, that is, high reaction concentrations (Table 1, entries 3 and 4), increased exposure to air promotes trapping of acyl radical **8** by molecular oxygen to give a peracyl radical **6**, and hence aldehyde **4**, rather than vinyl phosphonate **3a**, thus lowering the yield of ketophosphonate **3a** and decreasing the **3a**:**4** ratio. Although the formation of aldehyde **4** is suppressed at low reaction concentrations (Table 1, entries 6 and 7), unsurprisingly, an increased **3a**:**5** ratio was observed due to reaction of vinyl phosphonate **1** with the solvent; consequently lowering the yield of ketophosphonate **3a**.

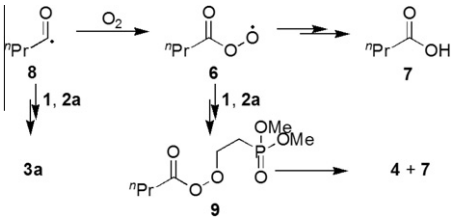
We then sought to evaluate aldehyde scope in the hydroacylation of vinyl phosphonate **1**. Hence, we selected aldehydes with a range of auto-oxidation rates[13] and aldehydes bearing a range of functional groups to emphasise the mild nature of the reaction conditions (Table 2). To our delight, hydroacylation of vinyl phosphonate **1** under optimised conditions (Table 1, entry 5) was shown to be tolerant of aldehydes bearing acetal, alcohol, aryl, epoxide and ester functionalities (Table 2, entries 5–9); exemplifying the mild, orthogonal nature of our reaction conditions. Also encouraging was the success of cyclopropyl- and cyclohexyl-carboxaldehydes (Table 2, entries 10 and 11) as well as β-branched aldehydes (Table 2, entries 4, 6, 8 and 14). Consistent with a radical mechanism was the poor tolerance of our methodology to aldehydes bearing alkenes (Table 2, entries 12 and 13). Although reaction of vinyl phosphonate **1** with β-citronellal proceeded with 100% conversion of vinyl phosphonate **1** (Table 2, entry 13), no clear evidence for the formation of the corresponding hydroacylation product **3m** or other low molecular weight products resulting from radical addition to vinyl phosphonate **1** was apparent, presumably due to polymerisation under the reaction conditions. However, the corresponding reduced aldehyde could be employed successfully to afford **3n** in good yield (Table 2, entry 14). Upon reaction of vinyl phosphonate **1** with pivaldehyde (**2o**) none of the desired ketophosphonate **3o** could be isolated. However, dimethyl (3,3-dimethylbutyl)phosphonate, corresponding to the addition of a *tert*-butyl radical to **1**, was isolated in 46% yield (Table 2, entry 15). Indeed, complete decarbonylation of pivaldehyde and trapping of the intermediate *tert*-butyl radical with **1** could be achieved in a 68% yield at 100 °C.

We then took the opportunity to explore the efficiency of α- and β-substituted vinyl phosphonates in aerobic hydroacylation. Unfortunately, although reaction of α-methyl vinyl phosphonate with butanal (**2a**) proceeded with 100% conversion of the vinyl phosphonate in 16 h, none of the desired γ-ketophosphonate **10**

Table 2
Aldehyde scope in the hydroacylation of vinyl phosphonates[a]

Entry	Product	Yield (%)[b]
1		70
2		68[c]
3		72
4		65
5		71
6		74
7		68
8		62[d]
9		67
10		57
11		60
12		20[d]
13		0
14		68
15		0[e]
16		0
17		60[d,f]

[a] Conditions: **1** (1 mmol), **2** (5 mmol), 1,4-dioxane (1 mL), 60 °C, 24 h.
[b] Isolated yield unless otherwise stated.
[c] 10 equiv of acetaldehyde used.
[d] Determined by integration of the ^{1}H NMR spectrum relative to pentachlorobenzene as an internal standard.
[e] Dimethyl (3,3-dimethylbutyl)phosphonate isolated in 46% yield.
[f] 80% conversion of diethyl *E*-1-propenylphosphonate.



Scheme 2. Proposed mechanism for the formation of aldehyde **4**.

was isolated (Table 2, entry 16), presumably due to telomerisation of the more electron-rich α-phosphonyl radical. In contrast, reaction of β-methyl vinyl phosphonate with **2a** gave the corresponding β-methyl-γ-ketophosphonate **11** in 60% yield, at 80% conversion of vinyl phosphonate, after 120 h at 60 °C.

In summary, we have successfully applied the aerobic hydroacylation of the electron-deficient alkenes to the synthesis of γ-ketophosphonates; an important functional motif in synthesis, biosynthesis and biology. In addition, we have highlighted both the robust and mild nature of this synthetic approach for the synthesis of unsymmetrical ketones employing aldehydes bearing a range of functional groups, such as alcohol, ester, acetal and epoxide, which is a significant advance on aldehyde scope compared to those previously reported.[13–15]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.083.

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