

The Preparation of Acyl Phosphonates by the Heterogeneous Oxidation of 1-Hydroxy Phosphonates

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Abstract: The oxidation of hydroxy phosphonates to acyl phosphonates using three heterogeneous systems, MnO_2 , KMnO_4 and CrO_2 , was investigated. The best results were obtained with CrO_2 in refluxing acetonitrile.

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Acyl phosphonates have a number of properties that make them attractive as reagents or intermediates for synthesis. These properties have stimulated a recent resurgence of interest in the chemistry of such compounds.¹⁻⁶ For several years it has been known that the carbonyl of an acyl phosphonate is activated towards attack by nucleophiles and that the carbon-phosphorus bond is readily cleaved.⁷ This property makes acyl phosphonates potentially useful acylating agents, but also susceptible to hydrolysis and difficult to handle.⁷ Recently it has been shown that acyl phosphonates can serve as precursors for α , α -difluorophosphonates by reaction with DAST,¹ scalemic hydroxy phosphonates via asymmetric reduction,² and as substrates for stereoselective aldol,³ Mukaiyama,⁴ and hetero Diels Alder reactions.⁵

Acyl phosphonates are usually prepared by a Michaelis-Arbuzov reaction between a trialkyl phosphite and an acid chloride.⁸ The Michaelis-Arbuzov reaction works well for the less complex aroyl and alkanoyl chlorides where purification by distillation is possible. However, there has been less success in the preparation of α,β -unsaturated acyl phosphonates where multiple addition products are often observed,^{9a,b} and for thermally or acid sensitive compounds.^{9c} An alternative method for the preparation of acyl phosphonates is the oxidation of the stable, easily prepared hydroxy phosphonate.¹⁰ Although there have been sporadic reports on the oxidation of hydroxy phosphoryl compounds, the reaction conditions tend to work well with isolated examples but are not often general for a range of substrates. Burke *et al.* reported the successful oxidation of di-*tert*-butyl benzylic α -hydroxy phosphonates using 10 equiv. MnO_2 in refluxing PhMe.^{1b} A variety of other oxidizing agents, including PCC, PDC, DDQ, and Swern oxidation were also found to yield the acyl phosphonates.^{1b,c,e} Unfortunately, methyl or benzyl phosphonate esters were incompatible with the reported reaction conditions due to a competing retro-Pudovik reaction of the hydroxy phosphonate. In addition, Evans and Gordon showed that MnO_2 could also oxidize benzyloxy phosphorinanes in CH_2Cl_2 in a 95 % yield.¹¹

As part of an ongoing study in the use of phosphonates and phosphoramides in asymmetric synthesis,¹² we needed a mild method for the cleavage of the phosphorus-carbon bond, and acyl phosphonates appeared to be ideal for this purpose. Consequently, we required a reliable method to transform hydroxy phosphonates into

acyl phosphonates. The ideal oxidant for the formation of acyl phosphonates would be heterogeneous since, as long as high conversions are achieved, the workup involves a simple filtration to remove the metal oxides and evaporation of the solvent. We wish to report an examination of three heterogeneous oxidation systems for the conversion of hydroxy phosphonates to acyl phosphonates.¹³

Scheme 1

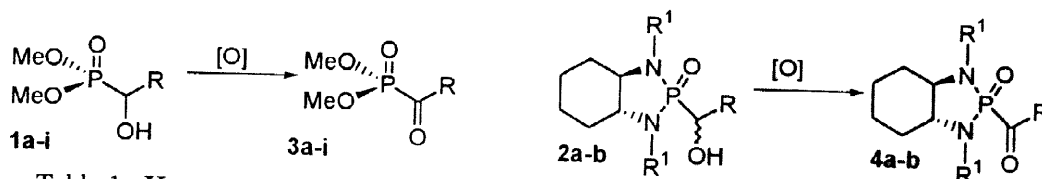


Table 1. Heterogeneous Oxidation of 1-Hydroxy Phosphonates and Phosphonamides

Entry #	Compd. #	Substrate R (and R ¹)	Compound Class	Oxidant	Conditions (time, hr)	Result (% conv.) ^a
1	1a		Allylic Phosphonate	MnO ₂	A (24)	30
2				MnO ₂	B (2.5)	50
3				MnO ₂	C (0.5)	65
4				CrO ₂	D (8)	100 ^c
5	1b		Allylic Phosphonate	MnO ₂	A (24)	60
6				MnO ₂	C (0.2)	72
7				CrO ₂	D (22)	100
8	1c		Allylic Phosphonate	MnO ₂	A (24)	73
9				MnO ₂	C (0.5)	87
10	2a		Allylic Phosphonamide	MnO ₂	A (0.7)	93
11				MnO ₂	B (0.2)	95
12				CrO ₂	D (20)	80 ^d
13	2b		Allylic Phosphonamide	MnO ₂	D (0.7)	93
14	1d		Benzylic Phosphonate	KMnO ₄	E (1)	79
15				KMnO ₄	F (1)	81
16				CrO ₂	D (12)	100 ^e
17	1e		Benzylic Phosphonate	KMnO ₄	E (1)	95
18				CrO ₂	D (20)	100
19	1f		Benzylic Phosphonate	CrO ₂	D (20)	100 ^b
20	1g		Cyclopropylmethyl Phosphonate	CrO ₂	D (10)	100
21	1h		Aliphatic Phosphonate	CrO ₂	D (30)	85 ^e
22	1i		Aliphatic Phosphonate	CrO ₂	D (30)	50

Reaction conditions: A) Stir in CH₂Cl₂ with 30 equiv. of MnO₂ at room temperature; B) sonicate using a cleaning bath in CH₃CN with 30 equiv. of MnO₂ at room temperature; C) Sonicate using a 400 watt Ace Glass high intensity ultrasonic processor and probe in CH₃CN with 30 equiv. of MnO₂ (pulsed 5 sec. on and 1.5 sec. off); D) Reflux in acetonitrile with 20-30 equiv. of CrO₂; E) stir in CH₂Cl₂:PhMe, 2:1, with 7 equiv. of powdered KMnO₄ at room temperature; F) sonicate using a cleaning bath in CH₂Cl₂:PhMe, 2:1, with 7 equiv. of powdered KMnO₄ at room temperature.

Notes: a) determined by ¹H and ³¹P NMR spectroscopy, material recovery was usually >85%; b) the Boc group was lost during the oxidation, c) only the acyl phosphonate was observed by ³¹P, ¹H and ¹³C NMR spectroscopy; d) some decomposition to cinnanaldehyde was observed; e) some hydrolysis occurred (≤20%), probably during workup.

It is well known that MnO_2 is an extremely useful reagent for the oxidation of α,β -unsaturated and benzylic alcohols to the corresponding carbonyl compounds.¹⁴ Unfortunately, MnO_2 oxidations are often difficult to reproduce due to the inconsistency between batches of oxidant and a gradual degradation of performance on standing. However, it was reported that the application of ultrasound to heterogeneous oxidation reactions can overcome some of these problems.¹⁵ Kimura employed sonochemistry to successfully activate MnO_2 of low activity during the oxidation of cinnamyl alcohol.¹⁵

Allylic hydroxy phosphonate **1a** was treated with 30 equiv. of MnO_2 in CH_2Cl_2 for 24 hours. ^1H and ^{31}P NMR spectra of the crude product indicated a 30% conversion to the acyl phosphonate (Table 1, entry 1). However, the conversion varied considerably with the batch of MnO_2 used.¹⁶ Cleaning bath sonication of a similar mixture in CH_3CN resulted a maximum of 50% conversion, but again the yield could vary. In comparison, sonication with a high intensity probe (at below 40 °C) resulted in a highly reproducible, improved conversion (65%, entry 3) in less than 30 mins. These observations held true for other allylic hydroxy phosphonates (**1b** and **1c**). Surprisingly, the allylic hydroxy phosphoramides **2a** and **2b** were more easily oxidized than the corresponding phosphonate **1a** and high conversions were realized with MnO_2 without the aid of sonication (entries 10 and 13).

While KMnO_4 is typically thought of as a solution phase oxidant, Yamawaki reported that the solid suspended in benzene or hexane and sonicated would oxidize alcohols.¹⁷ Treatment of benzylic hydroxy phosphonates **1d** and **1e** with powdered KMnO_4 in $\text{CH}_2\text{Cl}_2:\text{PhMe}$ resulted in a clean conversion to the corresponding acyl phosphonate (entries 14 and 17, respectively). Unfortunately, the allylic hydroxy phosphonates decomposed with KMnO_4 and aliphatic hydroxy phosphonates were unreactive.

Magtrieve™ was recently introduced as a reusable, magnetically retrievable form of CrO_2 , capable of oxidizing aliphatic alcohols in a heterogeneous system.¹⁸ Treatment of allylic hydroxy phosphonate **1a** with magtrieve™ in refluxing acetonitrile resulted in quantitative conversion to the unsaturated acyl phosphonate **3a**. Similarly, allylic hydroxy phosphonate **1b**, benzylic hydroxy phosphonates **1d** and **1e** and cyclopropylmethyl hydroxy phosphonate **1g** were cleanly converted to the corresponding acyl phosphonates. A clean oxidation was also observed with the heterocyclic hydroxymethyl phosphonate **1f**, however, the Boc group was also removed during the reaction. The aliphatic phosphonates proved more resistant to oxidation than the other phosphonates examined. However, prolonged treatment of hydroxy phosphonates **1h** and **1i** with 30 equiv. of Magtrieve™ added in portions every 4-5 hours resulted in good conversions to the corresponding acyl phosphonates (85 and 50%, respectively).

In summary, three heterogeneous oxidizing agents MnO_2 , KMnO_4 , and CrO_2 , were investigated. Of the three systems examined, CrO_2 (Magtrieve™) was superior and consistently gave good conversions with a range of structurally different hydroxy phosphonates.

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