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The *in situ* oxidation–Wittig reaction of α-hydroxyketones

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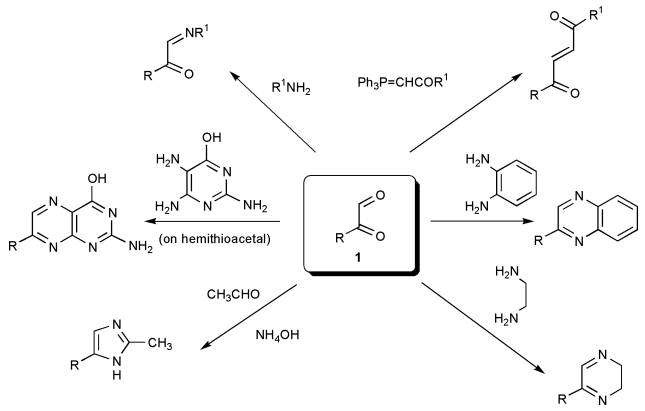
***In situ* oxidation–Wittig methodology has been applied to α-hydroxyketones avoiding the problems normally associated with α-ketoaldehydes; the procedure is practically simple, and in many cases gives high yields of the product γ-ketocrotonates; the procedure has also been successfully utilised with ethyl glycolate and glycolaldehyde dimer.**

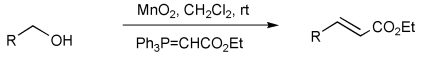
α-Ketoaldehydes **1** are potentially valuable synthetic intermediates.[1–6] For example, they have been used to prepare γ-oxygenated crotonates,[1–3] quinoxalines,[3] dihydropyrazines,[3] imidazoles,[4] pteridines,[5] and α-ketoimines[3] as shown in Scheme 1. However, the synthetic utility of α-ketoaldehydes **1**



Scheme 1

is limited, particularly for alkyl examples, by the hyper-reactivity[1] of the aldehyde carbonyl group. This reactivity results in facile hydration, aerial oxidation and polymerisation.[1] The situation is further complicated by the fact that the oxidation of α-hydroxyketones, often carried out using cupric acetate,[4] can lead to carbon–carbon bond cleavage when other oxidants are employed.[7] To avoid these problems, the hemithioacetals[5] and acetals[6] derived from α-ketoaldehydes **1** have been developed as synthetic equivalents, and indirect methods of generation have been employed (*e.g.* the oxidation of α-diazoketones).[3] There is also one example in which a terminal 1,2-diol has been oxidised to an α-ketoaldehyde using the Swern conditions and then a stabilised Wittig reagent added to the reaction mixture.[1]

We have recently developed a number of one-pot transformations based on manganese dioxide-mediated alcohol oxidation followed by *in situ* trapping of the resulting aldehydes.[8–10] Stabilised phosphoranes (eqn. (1)),[8] non-stabilised phosphoranes,[9] stabilised phosphonate anions[9] and amines[10] have all been utilised. This one-pot, tandem methodology removes the need to isolate the intermediate aldehydes, a particularly useful feature in the case of volatile, toxic or highly reactive aldehydes.



(1)

R = aryl, vinyl, alkynyl, *n*-alkyl *etc.*

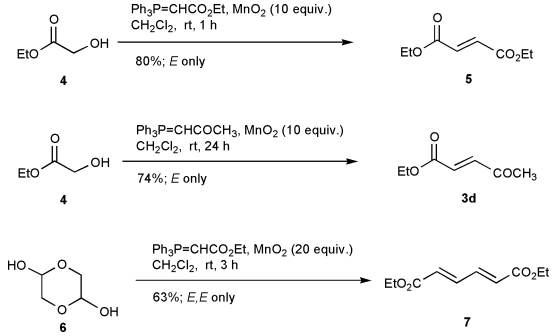
The *in situ* oxidation–trapping approach seemed to be ideally suited to the generation and elaboration of α-ketoaldehydes **1**. We therefore examined the *in situ* oxidation-stabilised Wittig reactions of a range of aromatic and aliphatic α-hydroxyketones **2a**–**2f** (Table 1).[11] Starting alcohols **2a** and **2d** are commercially available; compounds **2b**,[12] **2c**,[12] **2e**[13] and **2f**[12] were readily prepared from the corresponding methyl ketones using published procedures.

Initial studies were carried out using hydroxyacetophenone **2a**. We were delighted to observe that the phenyl substituted γ-ketocrotonate **3a** was obtained in good yield simply by stirring **2a** with manganese dioxide and (carbethoxyethylidene)triphenylphosphorane in dichloromethane for 1 h at rt, followed by filtration and chromatography (entry i). Success was also achieved using the corresponding anisyl and furyl hydroxyketones **2b** and **2c** (entries ii and iii). In all three examples, the reactions were also carried out in refluxing solvent; with the anisyl system this gave a significant rate enhancement.

Given the hyper-reactivity of alkyl-substituted α-ketoaldehydes referred to above, we were particularly interested in reactions of hydroxyacetone **2d**. As can be seen (entries iv–viii), reactions with range of stabilised Wittig reagents proceeded in good to excellent yields. Similar results were obtained using 1-hydroxyheptan-2-one **2e** and cyclohexyl analogue **2f** (entries ix and x). Product **3i** is the ester of (*E*)-4-oxonon-2-enoic acid, an antimicrobial agent isolated from *streptomyces olivaceus*.[14] All of the reactions gave predominantly or exclusively the *E*-alkenyl product, as expected, with the exception of the reaction between hydroxyacetone **2d** and (triphenylphosphoranylidene)acetonitrile (entry viii).

It should be noted that treatment of the α-hydroxyketones with manganese dioxide alone did not produce the corresponding α-ketoaldehydes **1** in an efficient manner: with **2a** and **2e** slow carbon–carbon bond cleavage to give carboxylic acids was observed,[7] whereas **2c** gave a 3 : 1 mixture of starting material and α-ketoaldehyde after stirring with excess manganese dioxide for 4 d at rt. It seems likely that the Wittig reagent traps out small equilibrium quantities of the α-ketoaldehyde before further degradation can occur.

After the success of these studies with α-hydroxyketones we went on to carry out preliminary studies to survey other α-hydroxycarbonyl systems (Scheme 2). We first established that ethyl glycolate **4** also underwent the *in situ* oxidation–Wittig



Scheme 2

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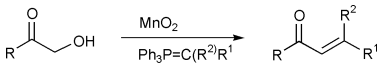
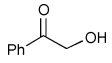
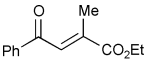
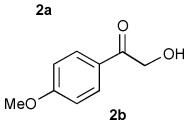
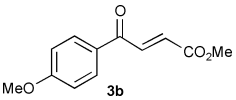
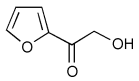
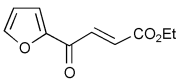
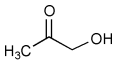
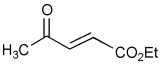
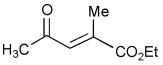
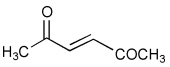
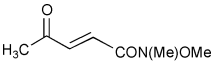
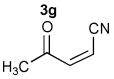
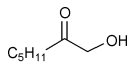
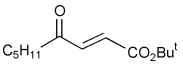
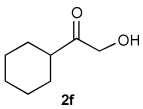
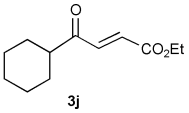
Table 1 *In situ* oxidation–Wittig reactions using α-hydroxyketones



2a-g 3a-3j

Entry	Alcohol	Conditions[a]	Yield	Product
(i)	 **2a**	$Ph_3P{=}C(Me)CO_2Et$ (a) rt, 1 h (b) Δ, 1 h	(a) 70%; *E*:*Z* = 98:2 (b) 78% ; *E* only	 **3a**
(ii)	 **2b**	$Ph_3P{=}CHCO_2Me$ (a) rt, 24 h (b) Δ, 1 h	(a) 44%; *E*:*Z* = 98:2 (b) 67%; *E* only	 **3b**
(iii)	 **2c**	$Ph_3P{=}CHCO_2Et$ (a) rt, 5 min (b) Δ, 1 h	(a) 62%; *E*:*Z* = 91:9 (b) 67%; *E*:*Z* = 94:6	 **3c**
(iv)	 **2d**	$Ph_3P{=}CHCO_2Et$ (a) rt, 24 h	(a)72%; *E* only	 **3d**
(v)	**2d**	$Ph_3P{=}C(Me)CO_2Et$ (a) rt, 1 h (b) Δ, 95 min	(a) 95%; *E* only (b) 83%; *E* only	 **3e**
(vi)	**2d**	$Ph_3P{=}CHCOCH_3$ (a) rt, 22 h (b) Δ, 1 h	(a) 80%; *E* only (b) 79%; *E* only	 **3f**
(vii)	**2d**	$Ph_3P{=}CHCON(Me)OMe$ (a) rt, 24 h (b) Δ, 1 h	(a) 52%; *E* only (b) 100%; *E* only	 **3g**
(viii)	**2d**	$Ph_3P{=}CHCN$ (a) rt, 24 h	(a) 68%; *E*:*Z* = 33:67	 **3h**
(ix)	 **2e**	$Ph_3P{=}CHCO_2Bu^t$ (a) rt, 15 h	(a) 71%; *E* only	 **3i**
(x)	 **2f**	$Ph_3P{=}CHCO_2Et$ (a) rt, 10 min (b) Δ, 1 h	(a) 38%; *E* only (b) 38%; *E* only	 **3j**

[a] Using manganese dioxide (10 equiv.) under nitrogen in dichloromethane; conditions (a) involve stirring at rt, conditions (b) involve heating at reflux.

reaction giving adducts **5** and **3d** in good yield (**3d** was also prepared from hydroxyacetone as shown in Table 1, entry iv).[15] Perhaps more surprisingly, treatment of glycolaldehyde dimer **6** with excess manganese dioxide and (carboethoxymethylene)-triphenylphosphorane gave diethyl *E,E*-muconate **7** in 63% yield.

To summarise, we have shown that *in situ* oxidation–Wittig methodology can be applied to α-hydroxyketones and related compounds, avoiding the problems normally associated with α-ketoaldehydes. The procedure is practically simple, and in many cases gives high yields of the adducts. We are currently extending and applying the chemistry described in this paper, and investigating the suitability of the other transformations shown in Scheme 1 to these *in situ* oxidation–trapping conditions.

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