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Two carbon homologated α,β-unsaturated aldehydes from alcohols using the *in situ* oxidation–Wittig reaction

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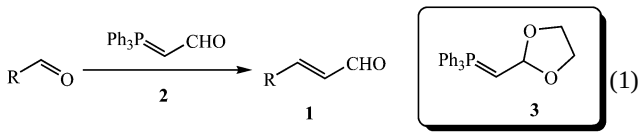
The *in situ* oxidation–Wittig reaction, followed by subsequent hydrolysis, has been applied to the conversion of primary alcohols into α,β-unsaturated aldehydes. This conversion, which proceeds *via* the intermediacy of the homologated unsaturated dioxolanes, gives good to excellent yields with a range of benzylic alcohols and heterocyclic methanols.

α,β-Unsaturated aldehydes **1** are extremely important compounds, particularly as synthetic intermediates[1,2] and as finished products in the flavour and fragrance industry.[3] Numerous methods are available for their preparation[1,2] although most involve redox functional group transformations rather than carbon–carbon bond formation. In principle, the directed aldol approach devised by Trippett and Walker[4] utilising a two carbon homologation of the corresponding aldehyde with formylmethylenetriphenylphosphorane **2** seems attractive (eqn. 1). However, the scope of this process is limited to more reactive aldehydes[5] (presumably due to the products **1** reacting further), and it has not found widespread use. Cresp *et al*. subsequently introduced the use of the related dioxolane reagent **3**,[5] generated *in situ* from phosphonium salt **4** and lithium methoxide in methanol–DMF; the unsaturated dioxolane products were then readily hydrolysed and isomerised with aqueous acid to afford a range of *trans*-α,β-unsaturated aldehydes.



(1)

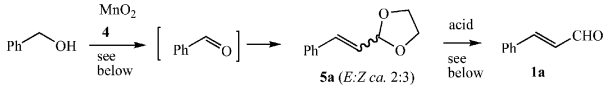
We have recently developed a number of one-pot transformations based on the manganese dioxide-mediated oxidation of primary alcohols followed by *in situ* trapping of the resulting aldehydes.[6,7] This one-pot, tandem methodology, which removes the need to isolate the intermediate aldehydes (a particularly useful feature in the case of volatile, toxic or highly reactive aldehydes), works well using a range of Wittig reagents.[6] Recently, we reported an oxidation-Wittig sequence which converts alcohols into the two carbon homologated α,β-unsaturated Weinreb amides which can be readily reduced to afford α,β-unsaturated aldehydes.[6f] However, to the best of our knowledge, there remains no general procedure for the direct conversion of alcohols into α,β-unsaturated aldehydes. We therefore investigated the extension of the *in situ* oxidation methodology to the preparation of α,β-unsaturated aldehydes **1**. This communication outlines a new one pot MnO_2 oxidation–Wittig trapping sequence with subsequent hydrolysis to afford α,β-unsaturated aldehydes **1** in good to excellent yield over the three step sequence (eqn. 2).

Initial studies were carried out using benzyl alcohol and phosphorane **3**, generated *in situ* from the commercially available dioxolanyl phosphonium bromide **4** (Table 1). Thus, a one-pot MnO_2 oxidation–Wittig reaction afforded the unsaturated dioxolane intermediate **5a** as an *E*–*Z*-mixture. A variety of bases and solvent systems were screened. Use of potassium *tert*-butoxide to facilitate the formation of phosphorane **3** *in situ*, afforded only low yields of the desired acetal (Table 1, entries i and ii). Similarly when phase transfer conditions were employed (entry iii), a disappointing yield of **5a** was obtained.

Gratifyingly, however, the use of organic bases such as DBU resulted in a marked increase in isolated yield (entry iv). Furthermore, switching to the use of the bicyclic guanidine base, 1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)[6d,8] gave an excellent yield (86%) of acetal **5a** after two days at room temperature in DCM. Refluxing conditions were then investigated in a range of solvents. We also established that dilute hydrochloric acid could be employed to hydrolyse acetal **5** with concomitant *Z*–*E*-isomerisation. The optimum conditions (entry vi) involved the use of refluxing THF overnight followed by treatment with dilute hydrochloric acid giving an excellent 82% overall yield of *E*-cinnamaldehyde.

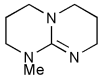
Following these promising results, we proceeded to investigate the scope and limitations of the reaction in refluxing THF, followed by direct hydrolysis, with a range of activated alcohols (Table 2).[9] Normal and electron deficient benzylic alcohols gave good yields of the homologated unsaturated

Table 1 Conversion of benzyl alcohol into cinnamaldehyde **1a**[a]

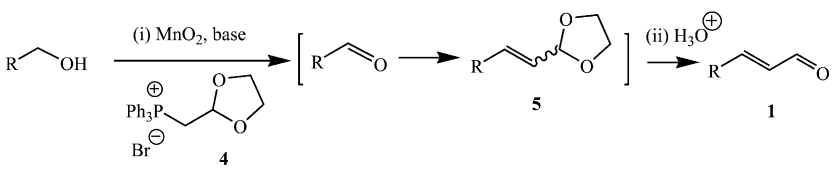


Entry	Base	Conditions	Product (%)
i	KO*t*Bu (1.5 equiv.)	RT, 48 h	**5a**, 10
ii	KO*t*Bu (2.2 equiv.)	RT, 48 h	**5a**, 8
iii	K_2CO_3 + TDA-1[b]	RT, 18 h	**5a**, 33
iv	DBU (2.2 equiv.)	RT, 48 h	**5a**, 47
v	MTBD (2.2 equiv.)	RT, 48 h	**5a**, 86
vi	MTBD (2.2 equiv.)	Δ, 17 h then 10% aq. HCl[c]	**1a**, 82
vii	MTBD (2.2 equiv.)	RT, 3 d then $SnCl_2{\cdot}2H_2O$	**1a**, 54

[a] With MnO_2 (10 equiv.), salt **4** (1.6 equiv.), base (see above), 4 Å mol. sieves and CH_2Cl_2 as solvent unless otherwise stated. [b] TDA-1 [tris(3,6-dioxaheptyl)amine] was used in CH_2Cl_2–satd. aq. K_2CO_3. [c] THF as solvent.



MTBD



(2)

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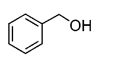
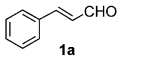
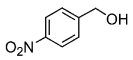
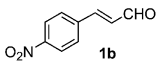
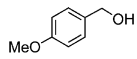
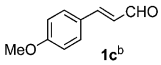
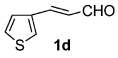
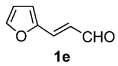
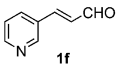
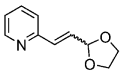
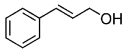
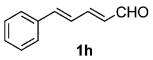
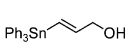
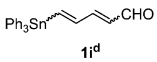
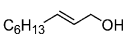
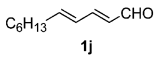
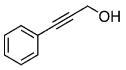
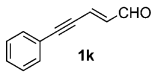
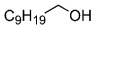
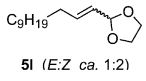
Table 2 *In situ* oxidation-Wittig reaction then hydrolysis to give enals **1**[a]

Entry	Alcohol	Product	Reaction time/h	Isolated yield (%)
i		 **1a**	17	82
ii		 **1b**	9	80
iii		 **1c**[b]	24	33
iv		 **1d**	18	75
v		 **1e**	17	72
vi		 **1f**	3.5	79
vii[c]		 **5g** (*E*:*Z ca.* 1:3)[c]	9	85
viii		 **1h**	5.5	69
ix		 **1i**[d]	20	81
x[e]		 **1j**	23	33
xi		 **1k**	16	43
xii[f]		 **5l** (*E*:*Z ca.* 1:2)	46	12

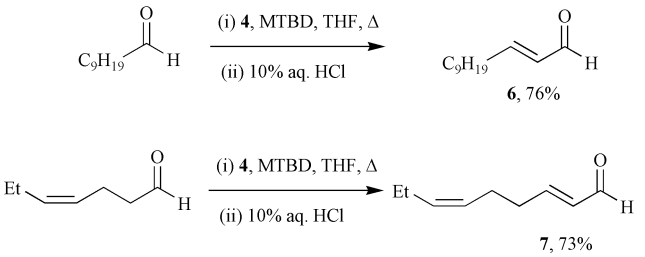
[a] Using manganese dioxide (10 equiv.), salt 4 (1.6 equiv.), MTBD (2.3 equiv.) and 4 A mol. sieves under nitrogen in refluxing THF for the specified time followed by aq. HCl hydrolysis.[9] [b] *p*-Methoxybenzaldehyde was also isolated (*ca.* 50%). [c] Hydrolysis was unsuccessful-see text. [d] As a mixture of isomers. [e] Refluxing dichloroethane as solvent. [f] Refluxing toluene as solvent; hydrolysis was not attempted.

aldehydes **1a** and **1b** (entries i and ii). *p*-Methoxybenzyl alcohol gave a lower yield of **1c** (entry iii), presumably due to the lower reactivity of *p*-methoxybenzaldehyde (which constituted the main by-product of the reaction). We next moved on to heterocyclic examples (entries iv-vii), and thiophene-3-methanol, furan-2-methanol, and pyridine-3-methanol gave the expected *E*-enals **1d–f** in good yields. In the case of pyridine-2-methanol (entry vii), an excellent yield of the intermediate dioxolane **5g** was obtained but, using dilute hydrochloric acid or Lewis acids, attempts to hydrolyse **5g** to the corresponding unsaturated aldehyde were unsuccessful.

Allylic and propargylic examples were also successful (entries viii-xi), although the yields were reduced and solvent optimization was often required. With decanol, however, the dioxolane **5l** was isolated in a paltry 12% yield after refluxing in toluene for 46 hours (entry xii).

The results in Table 2 demonstrate the broad scope of this oxidative methodology covering a structurally diverse group of activated alcohols with many of the yields obtained being comparable, or indeed better, than previously published homologation reactions starting from the corresponding aldehydes.

Although decanol did not react efficiently using this methodology, we have found that aliphatic aldehydes undergo



Scheme 1

Wittig homologation–hydrolysis using the conditions reported herein (**4**, MTBD, THF), to give good yields of *E*-enals as shown in Scheme 1. This is noteworthy as Simoni *et al.* have previously reported that enolisable aldehydes do not give good yields of Wittig products on treatment with phosphonium salts and guanidine bases, possibly due to competing aldol reactions.[8] We presume that phosphorane **3** must be particularly efficient at trapping aliphatic aldehydes under the conditions employed in the present study. Aldehydes **6**[10] and **7**[11] are important flavour and fragrance chemicals,[3] emphasizing the value of this approach.

In summary, we have designed a practical, and in many cases, high yielding synthesis of α,β-unsaturated aldehydes from activated alcohols using an *in situ* MnO_2 oxidation–Wittig reaction followed by acidic hydrolysis. Work is now underway to develop a true one-pot sequence in which the hydrolysis step is carried out without the need for prior removal of the MnO_2. Applications of this methodology in natural product synthesis are also being explored.

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