



A one-pot oxidation/allylation/oxidation sequence for the preparation of β,γ -unsaturated ketones directly from primary alcohols

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ABSTRACT

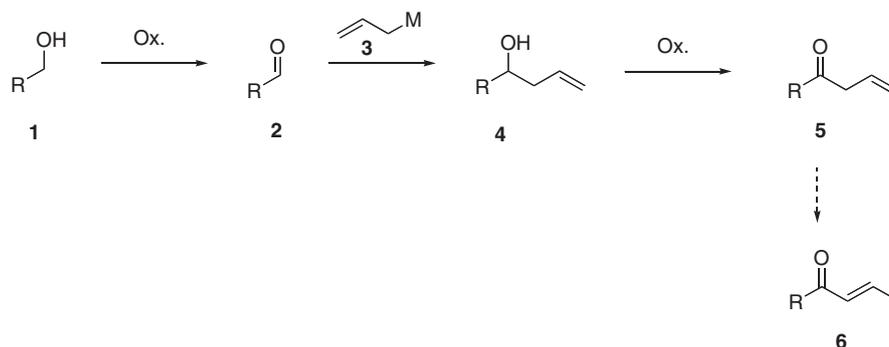
A one-pot oxidation/allylation/oxidation procedure has been developed for the conversion of primary alcohols into β,γ -unsaturated ketones. The methodology has been applied to a range of alcohols, and in some cases, isomerisation to produce the corresponding α,β -unsaturated ketones has been carried out.

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α,β - and β,γ -Unsaturated ketones are important building blocks in organic synthesis.¹ As part of a natural product project, we required a straightforward method of preparing β,γ -unsaturated ketones **5** (R = aryl, hetaryl, alkyl, etc.). Most of the available procedures, such as the Barbier-type allylation of nitriles² and the Hosomi–Sakurai reaction of allyl silanes with acid chlorides,³ proceed from carboxylic acid derivatives,⁴ whereas we wished to use alcohols **1** as simple starting materials.^{5,6} Given our interest in tandem oxidation processes,⁷ the approach outlined in Scheme 1 appeared to present an attractive option. The idea was to oxidise alcohols **1** to aldehydes **2** in the presence of an allylating reagent **3**; by using the oxidant in excess we hoped to achieve the in situ

oxidation of allylic alcohol **4** to produce the target β,γ -unsaturated ketones **5** in a one-pot process. In addition, we anticipated that it would be straightforward to extend this sequence to produce α,β -unsaturated ketones **6** given the numerous methods reported for effecting this type of isomerisation.⁸

Preliminary studies were carried out to assess the viability of a one-pot approach to β,γ -unsaturated ketones using *p*-chlorobenzyl alcohol (**7**), *p*-chlorobenzaldehyde (**8**) and secondary alcohol **9** as test substrates (Scheme 2). The initial oxidation of *p*-chlorobenzyl alcohol **7** was straightforward, as expected, with MnO₂ and Dess–Martin periodinane (DMP) giving the most reliable results.⁹ Many methods are available for the allylation of aldehydes and



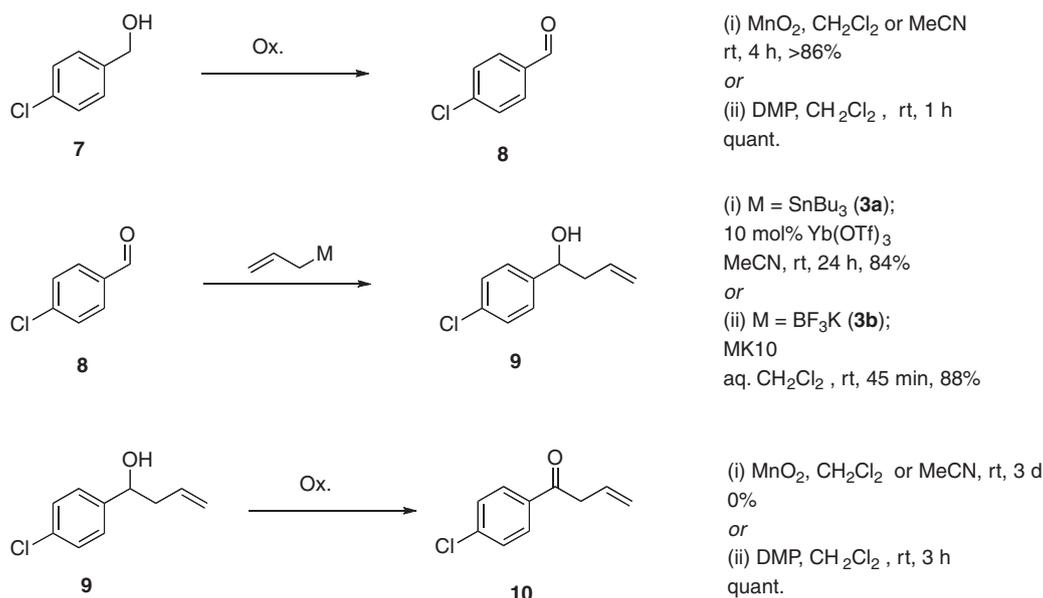
Scheme 1.

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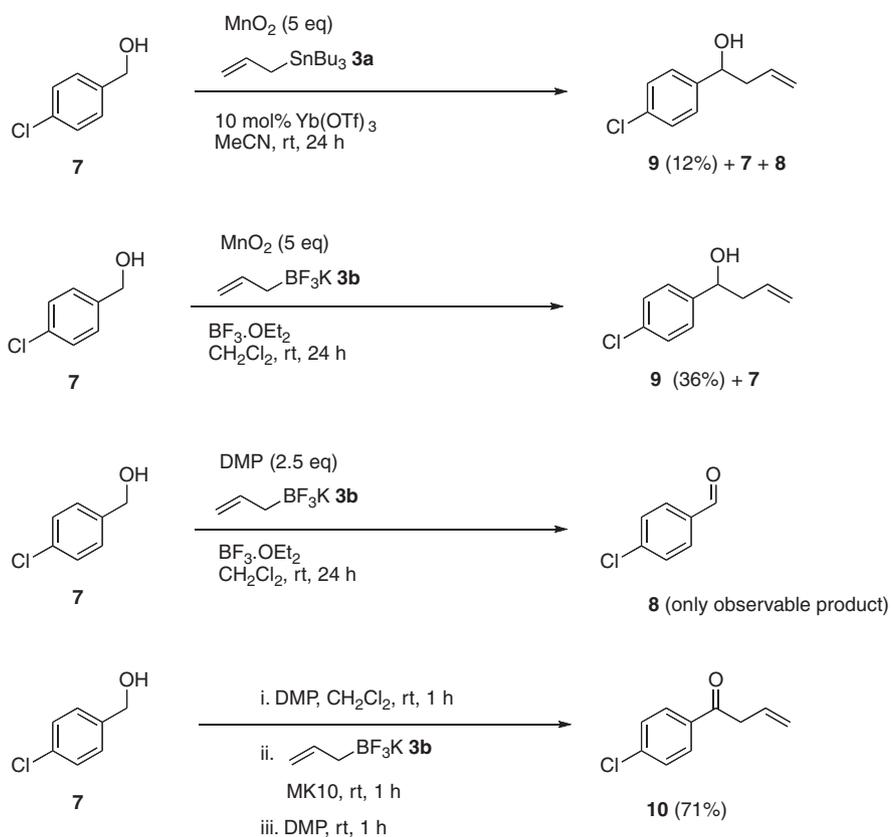
ketones,¹⁰ but in our hands with *p*-chlorobenzaldehyde (**8**), the use of allyl stannane (**3a**) with catalytic Yb(OTf)₃,¹¹ or allyl trifluoroborate (**3b**) with boron trifluoride etherate^{12,13} or Montmorillonite K10 (MK10)¹³ proved the most straightforward giving the allyl alcohol **9** via a practically simple process at room temperature. The final step, the oxidation of the secondary benzylic alcohol **9**, proved more troublesome. No oxidation was observed using

MnO₂ or TPAP/NMO, with DMP being most reliable for the formation of β,γ-unsaturated ketone **10**.¹⁴

Having studied the individual steps, we went on to examine one-pot processes for the three-step sequence (Scheme 3). As can be seen, with MnO₂ as oxidant, it was possible to carry out a tandem oxidation/allylation giving allylic alcohol **9** in low yield, but further oxidation did not occur (as was expected after the



Scheme 2.



Scheme 3.

preliminary studies shown in Scheme 2). Concentrating on the use of DMP as oxidant, the tandem process gave mainly aldehyde **8** with trace amounts of allylated adducts **9** and **10**, at best. We, therefore, developed a sequential process in which DMP oxidation was followed by the addition of allyl trifluoroborate (**3b**) and MK10, and finally additional DMP was added to ensure complete oxidation. In this manner, the required α,β -unsaturated ketone **10** was obtained in a 71% yield by a one-pot procedure.

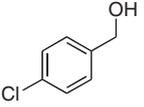
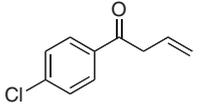
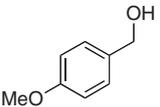
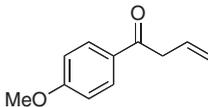
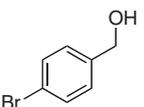
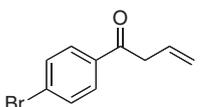
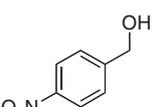
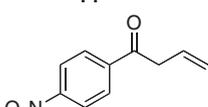
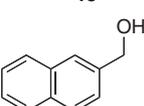
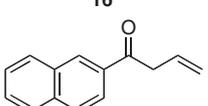
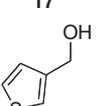
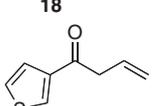
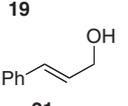
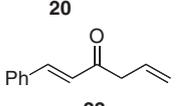
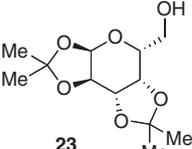
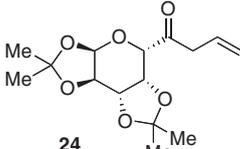
Having established a reliable one-pot procedure for the oxidation/allylation/oxidation route to β,γ -unsaturated ketone **10**, we went on to explore its scope (Table 1). As can be seen, the sequence was successful with a range of electron-rich and electron-poor benzylic alcohols (entries i–iv), with 2-naphthyl-methanol (entry v) and with thiophene-2-methanol (entry vi). In addition to benzylic and related systems, an allylic example proved successful (entry vii), as did an unactivated alcohol (1,2:3,4-di-*O*-isopropylidene-

D-galactopyranose, entry viii). In all cases the yields were good to excellent and the β,γ -unsaturated ketones were usually stable for a day or so, although isomerisation to give the corresponding α,β -unsaturated ketones was observed on prolonged storage.

As mentioned earlier, if conjugated ketones are required, these are easily obtained from the corresponding β,γ -unsaturated ketones. In our hands, DBU in diethyl ether¹⁶ gave the cleanest isomerisation, with α,β -unsaturated ketones **25–27** being isolated in almost quantitative yields, exclusively or predominantly as the *E*-isomers (Scheme 4).

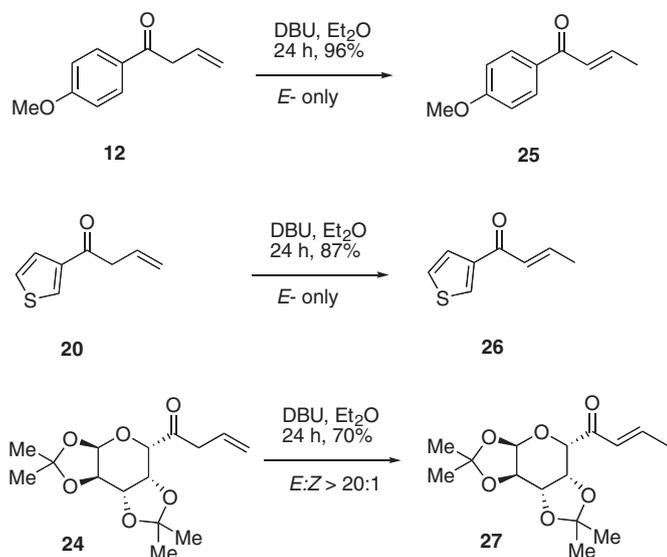
In summary, we have developed a one-pot oxidation/allylation/oxidation procedure for the conversion of primary alcohols into β,γ -unsaturated ketones which involves DMP oxidation followed by the addition of allyl trifluoroborate (**3b**) and Montmorillonite K10 and finally additional DMP. The methodology has been applied to a range of benzylic alcohols, as well as to an allylic and an

Table 1
One-pot oxidation/allylation/oxidation sequence^a

Entry	Substrate	Product	Isolated Yield ^b (%)
i			71 ^{4a}
ii			92 ^{4b}
iii			85 ^{4a,c}
iv			96 ^{4a}
v			75 ^{4d}
vi			76 ^{4e}
vii			67 ^{4f}
viii			75 ¹⁵

^a On a 0.25 mmol scale; (i) DMP (1.5–2.0 equiv), CH₂Cl₂, rt, 1 h; (ii) MK10, **3** (1.5–2.0 equiv), rt, 1 h; (iii) DMP (2.0–2.5 equiv), rt, 1 h.

^b Quenched with sat. aq. NaHCO₃ and sat. aq. Na₂S₂O₃; purified by flash column chromatography.



Scheme 4.

unactivated carbohydrate example. In three examples, base-mediated isomerisation to produce the corresponding α,β -unsaturated ketones has been carried out. We are currently applying this sequence to more complex systems as part of a natural product programme.

Acknowledgements

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15. *Representative experimental procedure*: Galactopyranose derivative **24**: To 1,2:3,4-di-*O*-isopropylidene-*D*-galactopyranose (**23**) (64 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL) at rt under argon was added DMP (209 mg, 0.49 mmol) and the mixture stirred for 1 h. Montmorillonite K10 (50 mg) was then added followed by potassium allyl trifluoroborate (73 mg, 0.49 mmol) and the mixture stirred for 1 h before adding a further portion of DMP (261 mg, 0.62 mmol). After stirring for a further 1 h, the reaction was quenched with sat. aq NaHCO_3 (5 mL) and sat. aq $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and allowed to stir for 1 h before diluting with brine (10 mL) and CH_2Cl_2 (10 mL). The mixture was filtered and then the layers separated. The aqueous portion was further extracted with CH_2Cl_2 (2×5 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (0–5% acetone in CH_2Cl_2) to give the compound **24** (55 mg, 75%) as a colourless micro-crystalline solid, mp 47–49 °C; R_f (CH_2Cl_2) = 0.15; $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 2988, 2936, 1723 (C=O), 1383; $[\alpha]_D^{25}$ –144 (c 0.4, CH_2Cl_2); δ_{H} (400 MHz, CDCl_3) 5.97 (1H, ddt, J = 17.0, 10.5, 7.0, H-8), 5.64 (1H, d, J = 5.0, H-1), 5.20–5.08 (2H, m, H-9), 4.63 (1H, dd, J = 8.0, 2.5, H-3), 4.56 (1H, dd, J = 8.0, 2.0, H-4), 4.35 (1H, dd, J = 5.0, 2.5, H-2), 4.22 (1H, d, J = 2.0, H-5), 3.50 (1H, ddt, J = 18.5, 7.0, 1.5, H-7a), 3.33 (1H, ddt, J = 18.5, 7.0, 1.5, H-7b), 1.49 (3H, s), 1.44 (3H, s), 1.33 (3H, s), 1.30 (3H, s); δ_{C} (100 MHz, CDCl_3) 207.2 (C-6), 130.0 (C-8), 118.7 (C-9), 109.6, 109.0, 96.4 (C-1), 73.5 (C-5), 72.3 (C-4), 70.6 (C-3), 70.4 (C-2), 44.6 (C-7), 25.9, 25.8, 24.8, 24.2; m/z (ESI) 321 $[\text{M}+\text{Na}]^+$; [HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{22}\text{NaO}_6$, 321.1309. Found: $[\text{M}+\text{Na}]^+$, 321.1317 (–2.7 ppm error)]; $[\text{C}_{15}\text{H}_{22}\text{O}_6$ requires C, 60.39; H, 7.43. Found C, 60.35; H, 7.35].
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