The allylic oxidation of unsaturated steroids by tert-butyl hydroperoxide using surface functionalised silica supported metal catalysts

Jorge A. R. Salvador and James H. Clark*

Clean Technology Centre, Chemistry Department, University of York, York, UK YO10 5DD.
E-mail: jhc1@york.ac.uk

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Metal complexes based on Co(n), Cu(n), Mn(n) and V(n) immobilised on mesoporous silica, efficiently catalyse the selective allylic oxidation of unsaturated steroids and valencene, and can be easily recovered and reused.

Introduction

Allylic oxidation is a fundamental organic reaction of significant interest to organic chemists with applications in areas ranging from agricultural products to pharmaceuticals.1,2 The allylic oxidation of steroids is a particularly important subject and has attracted interest over many years. The 5α-steroids can be oxidised to 5-en-7-ones, which are known as inhibitors of sterol biosynthesis and have some use in cancer chemotherapy.3

The allylic oxidation of unsaturated steroids such as 5α-steroids, has traditionally been performed with chromium reagents such as CrO3–pyridine complex,4 CrO3 and 3,5-dimethylpyrazole,5 pyridinium chlorochromate, (PCC),6,7 pyridinium dichromate (PDC),7 sodium chromate,8 sodium dichromate in acetic acid,9 pyridinium fluorochromate,10 and 3,5-dimethylpyrazolium fluorochromate(VI).11 However, the great excess of ecologically and physiologically undesirable chromium reagent and the large volume of solvent required in these procedures, in combination with the difficult work-up and the production of environmentally hazardous chromium residues, causes such procedures to be inconvenient on a commercial scale.

Of greater preparative interest has been the use of copper salts and copper metal have been reported but a difficult separation step is needed to remove the catalyst which cannot easily be recovered and reused.

Hence there is need for a simple, efficient, safe and cost effective procedure for selectivity effecting the allylic oxidation of steroids and especially where the separation stages of the reaction are simple and enable catalyst recycling.

The heterogenisation of inorganic reagents and catalysts useful in organic reactions is a very important area20 and led us to recently report the use of Co(OAc)2·4H2O as catalyst in heterogeneous forms (catalyst 2, Co(OAc)2/SiO2, catalyst 2 and 5) for this type of allylic oxidation reaction.21 In order to ascertain the efficacy of the oxidative system (t-BuOOH/ catalyst 2) a more polar substrate, the steroid 8 was used as substrate leading to the formation of the allylic oxidation product 9 in a very high yield and very high selectivity, (Scheme 1, Table 1).

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Similar oxidation can be performed on valencene 10. Using the catalyst 2, the sesquiterpenoid nootkatone 11, a major contributor to the aroma of grapefruit present in commercial flavourings was the major product (75%), although the catalyst 5 gave the nootkatone in 70% yield, (Table 1).

Results and discussion

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Green Context

The oxidation of naturally occurring alkenes such as steroids and terpenoid compounds can lead to a range of very useful products. Using traditional oxidants is wasteful and alternatives are required. Here, the use of various transition metal salts attached to silica as catalysts in such oxidations is described, with tert-butyl hydroperoxide as primary oxidant. Products are formed in good to excellent yields. This paper demonstrates that the promising results with these catalysts using model compounds can be transferred to bulkier substrates. DJM

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Despite the good yields with the copper catalyst in homogeneous conditions reported in a previous communication\(^1\) the catalyst cannot be easily recovered and reused which encouraged us to use heterogeneous forms of a copper catalyst\(^5\) for this type of allylic oxidation reaction. Using \(\Delta^5\)-steroids\(^8\) and valencene\(^10\) as substrates (Schemes 1 and 2) allylic oxidation products\(^9\),\(^13\)–\(^21\) and \(\mathbf{11}\) were obtained in very high isolated yields, 72–86\% (Table 2). The reactions were generally performed in acetonitrile except for the substrate \(\mathbf{16}\) which required benzene as solvent.

These reactions are very selective compared to those carried out using \(\text{Fe(}\text{acac})_3\) as catalyst reported by Kimura and Muto.\(^17\) Mo(CO)\(_6\) has also been described as a catalyst for this reaction but this led to epoxidation of the cholesteryl acetate under similar oxidative conditions.\(^18\) On the contrary, using manganese catalysts\(^2\) and\(^6\) and vanadium catalyst\(^3\), the allylic oxidation occurs in very good yields (Table 3).

While the product yields of the allylic oxidations are very similar under homogeneous\(^19\) and heterogeneous conditions the easier recovery of the catalyst in heterogeneous conditions,
make these more environmentally friendly processes. Furthermore, using the heterogeneous catalysts 5 and 6, it was possible to reuse the catalyst with only a small reduction in the products yields, under similar experimental conditions (79% for recycled catalyst 5, Table 2, and 77% for recycled catalyst 6, Table 3).

No significant reaction occurs in the absence of catalyst or in the presence of the catalyst support only. The dioxolane group present in the steroid 22 was removed in the presence of the copper catalyst 5 corroborating the previous findings. 24 The catalytic process is also effective for other unsaturated steroids. The substrate 23 gives testosterone benzoate 24 in a yield of 72% (Scheme 3).

The use of 3β-acetoxy-7-nor-androst-5-en-17-one 25 as substrate prepared according to the method of Knof 25 led us to obtain the 5α,6α-epoxide 26 as the major product. The absence of C-7 and the fact that the axial hydrogen at C-4 lies on the more hindered β-face of the molecule reduces the tendency of β-nor-5-enes to undergo allylic oxidative reactions involving bulky reagents that may initially coordinate to the double bond. Thus the axial attack on the π-system of 3β-acetoxy-7-nor-androst-5-en-17-one 25 will be favoured from the less-hindered α-face leading to the formation of the 5α,6α-epoxide 26.

Conclusions

In conclusion, we have discovered an efficient and relatively environmentally friendly method for allylic oxidation of unsaturated steroids and valencene in very good yields and high selectivity. The reaction requires t-BuOOH as oxidant and a supported and easily recoverable and reusable catalyst such as Co(ii), Cu(ii), Mn(ii), and V(ii).
Experimental

The steroids used as substrates were commercially available from Sigma and Aldrich. Reaction solvents were distilled before use according to standard procedures. Kieselgel 60 HF254/Kieselgel 60G was used for TLC analysis. Melting points were determined with a Reichert microscope apparatus and were uncorrected. IR spectra were performed in a JASCO FT/IR-420 spectrophotometer. 1H and 13C NMR were recorded on a Bruker AMX 300 in CDCl3 solution with Me4Si as internal standard.

Allylic oxidation catalyzed by cobalt catalyst (general procedure)

In a typical reaction, to a solution of valencene 10 (0.54 ml/2.45 mmol) in acetonitrile (15 ml) under nitrogen, catalyst 4 (0.06 g/0.025 mmol) and tert-butyl hydroperoxide (ca. 2.4 ml/12 mmol) were added. After 24 h under magnetic stirring at 55 °C, the catalyst was removed by filtration and the solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether. The extract after flash chromatography (light petroleum (bp 40–60 °C)–ethyl acetate) gave nootkatone (0.72 g/2 mmol) in acetonitrile (12 ml) under nitrogen, catalyst 5 (0.015 g/0.006 mmol) and tert-butyl hydroperoxide (ca. 2.4 ml/12 mmol) were added. After 20 h under magnetic stirring at 55 °C, the extract was washed with an aq. saturated solution of NaHCO3, water, dried and evaporated to dryness. The residue was then dissolved in acetone (10 ml) and filtered through a short pad of silica gel. The solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether. The extract was washed with an aq. saturated solution of NaHCO3, water, dried and evaporated to dryness to give 7,17-dioxoandrost-5-en-3-yl acetate 20 (0.06 g/4 mmol) in acetonitrile (12 ml) under nitrogen, catalyst 6 (0.06 g/0.006 mmol) and tert-butyl hydroperoxide (ca. 2.4 ml/12 mmol) added. After 24 h under magnetic stirring at 55 °C, the catalyst was removed by filtration and the solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether. The extract was washed with an aq. saturated solution of NaHCO3, water, dried and evaporated to dryness to give 7,20-dioxopregn-5-en-3-yl acetate 14 (0.72 g/2 mmol) in acetonitrile (12 ml) under nitrogen, catalyst 5 (0.015 g/0.006 mmol) and tert-butyl hydroperoxide (ca. 2.4 ml/12 mmol) were added. After 20 h under magnetic stirring at 55 °C, the catalyst was removed by filtration and the solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether. The extract was washed with an aq. saturated solution of NaHCO3, water, dried and evaporated to dryness to give 7,20-dioxopregn-5-en-3-yl acetate 15 (0.60 g, yield 81%), mp 151–152 °C (MeOH), lit.21,22 153–153.5 °C; IR: 1243, 1630, 1670, 1704, 1726, 2945, 3012 cm−1; 1H NMR (CDCl3, 300 MHz): δ 0.92 (d, J = 6.8 Hz, 3H, 15-H3), 1.20 (s, 3H, 18-H3), 1.23 (s, 3H, 19-H3), 3.84 (m, 1H, 3-CH3CO), 126.44 (C1), 148.87 (C11), 170.82 (C10), 199.79 (C5) (C7).

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References
