Zirconium Alkoxide Catalyzed Oppenauer Oxidation Using Chlortal as the Hydride Acceptor

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A new variation of the Oppenauer oxidation is presented with chlortal as the hydride acceptor and Zr(O-i-Bu)_4 or, for highly reactive carbonyl products, the heterogeneous system SiO_2/Zr(O-i-Pr)_4, as the catalyst. The reaction proceeds under mild conditions (20°C) with a substoichiometric amount of Zr(O-i-Bu)_4 (usually 20%). Primary and secondary alkyl alcohols are converted in high yields to the corresponding carbonyl compounds.

In 1937, Oppenauer showed that steroidal alcohols could be oxidized with acetone in the presence of Al(O-i-Bu)_3 as the catalyst.¹ The reverse process is known as the Meerwein–Ponndorf–Verley (MPV) reaction (reviews²,³). Equation (1) shows the metal alkoxide catalyzed equilibrium of the respective carbonyl/alkyl couples and the cyclic transition state A generally assumed⁴ for the hydride transfer. In Oppenauer oxidations (reviews²,³,⁴) functionalities such as carbon–carbon double and triple bonds, amino groups or halogens are not affected;⁵ this is an advantage compared with many oxygen transferring oxidation processes. Usually, a large excess of acetone or cyclohexanone is used as the hydride acceptor and in many cases, the product has to be removed by continuous distillation to shift the equilibrium towards the product side as shown in Scheme 1.

The MPV-Oppenauer Reaction

However, by selecting a hydride acceptor with a high redox potential (for application in MPV reductions see Lit.⁷) a favourable equilibrium shift towards the product side can theoretically also be established in the Oppenauer oxidation. After intensive experimentation, the commercially available and cheap chlortal (1) was found to be one of the best hydride acceptors in our novel variation of the Oppenauer oxidation. This aldehyde was used previously in the alumina catalyzed oxidation of cyclobutanol⁸ and diols⁹ and it has the additional practical advantage that any excess may be removed by a simple water extraction of the chloral hydrate.

A calculation of the equilibrium situation can be made for the reaction of 1 with cyclohexanol (2) to yield cyclohexanone (3) and trichloroethanol (4) as shown in equation 2. The differences in redox potential between chloral (1, E_0 = 277 mV) and cyclohexanol (4, E_0 = 162 mV) is 115 mV and the application of the Nernst equation [log K = (2/0.0592)(E_0 - E_0)] leads to an equilibrium shift of > 99% in the direction of the products. Thus, high yields can generally be obtained for alcohols with redox potentials up to about 200 mV, particularly if a small excess of chloral is used.

In addition to the hydride acceptor, the right choice of catalyst is also of great importance. As shown for TBHP oxidations⁶ and MPV reductions,⁷ zirconium tetra-tert-butoxide [Zr(O-i-Bu)_4] was a superior catalyst for Oppenauer oxidations in comparison with aluminium alkoxides or other zirconium alkoxides [e.g., Zr(O-i-Pr)_4]. The highly active Zr(O-i-Bu)_4 is monomeric in solution¹⁰ and the ligand exchange is very rapid.¹¹ In contrast to aluminium alkoxides, the zirconium catalyst can therefore be used in substoichiometric amounts (usually 0.2 equiv.). Zr(O-i-Bu)_4 is easily hydrolyzed by water and it is important to remove traces of water by the addition of 3 Å molecular sieves. The solvent used also has some influence: the reaction is fastest in nonpolar solvents such as toluene but chlorinated hydrocarbons which are better solvents for many substrates can also be used.

A number of different saturated primary (5, 6), primary and secondary allylic (7–9), and secondary alcohols (2, 10–15) including steroids (16–19) (Scheme 2) were selected to test the reaction. The results are summarized in Table 1.

The yields are excellent with only a few exceptions. The clean and nearly quantitative conversion of the primary allylic alcohols 7 and 8 (entry 3 and 4, each 99%) are particularly noteworthy; partial conversion of these substrates into epoxides, when TBHP was used as the hydride acceptor, was observed.⁶ The yield is slightly decreased with the sterically hindered substrate menthol (13) (entry
the secondary alcohols 9, 10, and 2, (entries 1, 5, 6, and 8, respectively). Interestingly, in these reactions, side products were detected by GC or TLC (see footnote Table 1) – even at a low reaction temperature ($0^\circ$C, entries 6 and 8). Possibly, aldol type or Tishchenko reactions of the aldehydes derived from the primary alcohols (e.g. octanol) or the highly reactive unhindered ketones derived from the unhindered secondary alcohols may occur in the presence of the basic catalyst Zr(O-t-Bu)$_4$. However, slightly more hindered alcohols such as 2-methylecyclohexanol (12) are oxidized almost quantitatively (entry 9). Other open chain and cyclic saturated secondary alcohols (entries 7, 11, 12) including a number of steroids (entries 13–17) are also oxidized in excellent yields. The only exception is estradiol which forms stable Zr complexes with the phenolic hydroxy group.

A special situation was observed in the case of the allylic epoxide 19 which underwent, in addition to the oxidation at C-17, a base catalyzed epoxide allyl alcohol rearrangement to the dienol 20. The structure of 20 was unambiguously established by COLOC NMR experiments: only one long-range coupling was observed for the vinlyc proton with the quaternary C – OH carbon as postulated for 20.

To overcome the unsatisfactory yields in the cases of reactive oxidation products, a less basic but sufficiently active catalyst had to be used. A good solution to the problem was found by using the heterogeneous silica gel supported zirconium catalyst (SiO$_2$/Zr(O-n-Pr)$_4$) initially prepared by Inada et al.$^{12}$ for MPV reactions. The results of selected experiments with the alcohols 2, 5, 9, and 10 are listed in Table 2.

The heterogeneous catalyst is much less reactive than Zr(O-t-Bu)$_4$, and the reaction times are longer. However, very good yields were obtained at slightly increased catalyst amounts (400 mg, entries 2, 5, 6, and 9) and elevated

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$^a$ Yield as determined by GC.

$^b$ Isolated yield of pure oxo-steroid.

$^c$ Side products as determined by GC: (+) < 4%; + = 4–7%.
temperatures (e.g. 50°C, entries 3, 8). The only exception was observed in the oxidation of the γ-unsaturated alcohol cholesterol that gave a mixture of products.

In summary, a new variation of the Oppenauer oxidation is presented with chloral as the hydride acceptor and Zr(O-t-Bu)₄ or, for highly reactive carbonyl products, the heterogeneous system SiO₂/Zr(O-n-Pr)₄, as the catalyst. The reaction proceeds under mild conditions (20°C) with a stoichiometric amount of Zr(O-t-Bu)₄ (usually 20%). Primary and secondary allylic and saturated secondary allyl alcohols are converted in high yields to the corresponding carbonyl compounds.

For general methods and instrumentation see Lit. 13.

Oxidation of Alcohols with Chloral; General Procedure: A solution of the alcohol (1 mmol, see Table 1) in toluene or CH₂Cl₂ (10 mL) and anhyd chloral (1.2–3 mmol, see Table 1) is treated with powdered, freshly activated molecular sieves (3 Å, 800 mg) and the mixture is stirred for 30 min. The reaction is then started by the addition of Zr(O-t-Bu)₄ (0.1–0.3 mmol, see Table 1) and monitored by means of TLC or GC. After conversion of the starting material, the reaction is quenched by the addition of 10% HCl (5 mL) or H₂O (5 mL). The mixture is filtered, the organic phase is separated and the aqueous phase is extracted with toluene or CH₂Cl₂ (40 mL). The combined organic phases are dried (Na₂SO₄), filtered over Celite (5 g) and the solvent is removed at reduced pressure. If required, the product is purified by column or layer chromatography. For yields and other reaction conditions see Table 1.

Alternatively, the heterogeneous catalyst (SiO₂/Zr(O-n-Pr)₄) as prepared by Inada et al. 12 (100 or 400 mg) and freshly activated molecular sieves (3 Å, 500 mg) are used in the oxidation of the substrates listed in Table 2.

Estra-4,9(10)-diene-3,17-dione: 17β-Hydroxyestra-4,9(10)-diene-3-one (16) (136 mg, 0.50 mmol) is reacted at 20°C as described in the general procedure with chloral (0.098 mL, 1.0 mmol, 2 equiv) and Zr(O-t-Bu)₄ (0.059 mL, 0.15 mmol, 0.3 equiv) in CH₂Cl₂ (10 mL) for 10 h to afford estradiol (103 mg, 76%) which is purified by layer chromatography on silica gel (EtOAc/CH₂Cl₂, 1:1) (Lit. 14 130–131°C; [α]D₂⁰ = −153 (c = 0.12, MeOH) (Lit. 17 [α]D₂⁰ = −154).

H NMR (200 MHz, CDCl₃, δ = 0.96 (s, 3H, 18-H), 1.03–2.94 (m, 18 H), 5.64 (s, 1H, 4-H).
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(13) The nature of the SiO2/Zr(OR) catalyst is not exactly known.