

Oxidative Cleavage of Functionalized Cyclic Olefins with H₂O₂ Using a Peroxotungstate Complex

Mark J. Ford,* Helmut Kohlhepp, Stephen Miller, Sven Riess, Jan Peter Schmidt, and Lothar Wisplinghoff

Bayer CropScience AG, Industriepark Höchst G836, 65926 Frankfurt am Main, Germany

Supporting Information

ABSTRACT: The oxidative cleavage of functionalized cyclic olefins with aqueous hydrogen peroxide was studied. A mild protocol was developed using a readily available diperoxotungstate catalyst that allowed otherwise unstable functionalities to be present during the oxidation. During the optimization of the procedure (3*R**,4*R**)-3-[(benzyloxy)-carbonyl]-4-(ethoxycarbonyl)hexanedioic acid was synthesized on a 400 g scale furnishing the product in 79% yield.

INTRODUCTION

Polycarboxylic acids are important building blocks in the chemical industry. This is particularly true for adipic acid which is prepared by the oxidative cleavage of cyclohexene and finds its use as a raw material of polyesters and 6,6-nylon. Adipic acid is manufactured on a million tons per year scale. Despite increasing environmental concerns, many polyacidic fine chemicals are still manufactured by classical stoichiometric methods that are unacceptable for practical syntheses. Carbon–carbon double bonds cleavage may be achieved through the use of heavy metal oxidants. However, these oxidants typically lead to the formation of large amounts of toxic waste, while known organic stoichiometric oxidants are usually expensive.¹ Nitric acid, the most conventional industrial oxidant, is cheap but unavoidably forms the greenhouse gas nitrous oxide. As a consequence, great attention has been paid to the development of alternative green methods for the preparation of polyacids. Early work by Venturello and Ricci suggested that hydrogen peroxide could be used in the synthesis of polycarboxylic acids from lipophilic olefins.² Their work was greatly expanded by Noyori and co-workers^{3a,b} and has been the focus of green research in oxidation chemistry and industrial technology ever since.⁴ However, the methodologies developed so far showed one great weakness. They did not allow acid sensitive substrates to be used in the oxidative cleavage protocols. Therefore, we had great interest in making this oxidation technology more applicable to a wider range of substrates. For this, we concentrated on a substrate that was previously difficult to cleave oxidatively under the known conditions.

RESULTS AND DISCUSSION

At the onset of our work, there was great interest in the efficient synthesis of dicarboxylic acid **1** (Scheme 3), where the two ester groups are functionally distinct. Starting from readily available 1,2,3,6-*cis*-tetrahydrophthalic anhydride (**3**), cyclohexene-diester **2**

was prepared in near quantitative yield on a 2.5 mol scale (Scheme 1). Here successful alkylative trapping of the intermediate monoester carboxylate salt is crucial to achieving this high yield since otherwise the carboxylate-ester is only present as part of an equilibrating mixture with the starting anhydride.

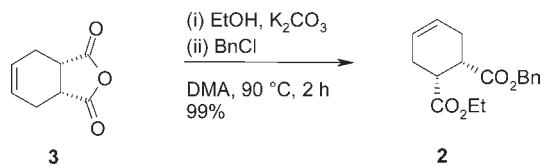
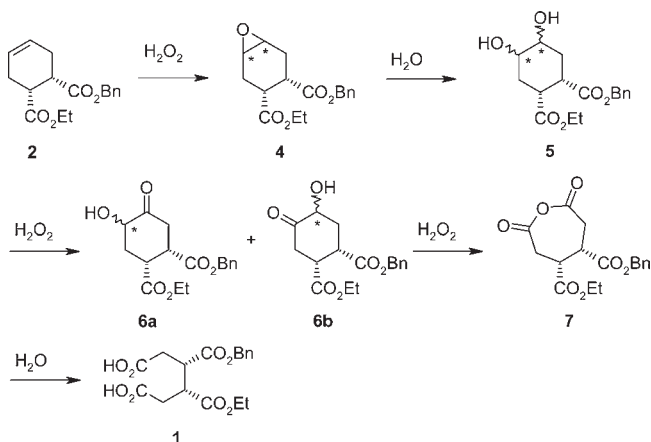
We then went about investigating the oxidative cleavage of the cyclohexene moiety. Heterogeneous oxidation using potassium permanganate (3.15 equiv) gave us access to the desired *bis*-acid **1** in a moderate 64% yield (on a 2 mol scale). However, it was very difficult to isolate the product from the aqueous solvent. In addition, filtration of the manganese dioxide waste product was challenging and the amounts of solid waste generated would have disfavored further scale-up. Changing to catalytic ruthenium(IV) oxide and stoichiometric sodium periodate, we were able to synthesize the target product more efficiently. *Bis*-acid **1** was obtained in a pleasing 90% yield (on a 0.1 mol scale). However, again the use of the stoichiometric oxidant, sodium periodate, was unattractive from an environmental and financial point of view. Additionally, a problematic kinetic behavior of the reaction posed a threat for process safety, and for this reason alone this approach would have been abandoned. This kinetic behavior manifested itself as an unpredictable 3–5 h delayed strongly exothermic oxidation of the dialdehyde which only starts after all of the olefin appears to have been consumed. Encouraged by the ability of ruthenium to catalyze the oxidative cleavage of cyclohexene **2**, we became aware of a report by Che and co-workers in which the catalytic ruthenium(III) species [(*N,N,N'*-trimethyl-1,4,7-triazacyclononane)-(CF₃CO₂)₂Ru(III)(H₂O)]CF₃CO₂ was stoichiometrically reoxidized by aqueous hydrogen peroxide and is reported to oxidatively cleave olefins.⁵ Disappointingly, this catalyst is not easily prepared and in our eyes the reaction protocol would not lend itself to large scale synthesis.

In our search for a robust system, we came across pioneering work by Ishii et al. in which the oxidative cleavage of olefins into carboxylic acids with hydrogen peroxide by tungstic acid is reported.⁶ This work has been carried on by numerous groups in both industry and academia.^{7a–f} Tungstic acid itself cannot oxidize organic substrates in water due to the fact that it is only soluble in water whereas the oxidation substrates are usually immiscible with water. It was found that certain organic acids may form complex catalysts with tungstic acid and enable good catalytic performance in nonoleophilic systems. Jiang and co-workers demonstrated that a large range of organic acids may be employed for this oxidation. Yields were high for cases in which the p*K*_a of the

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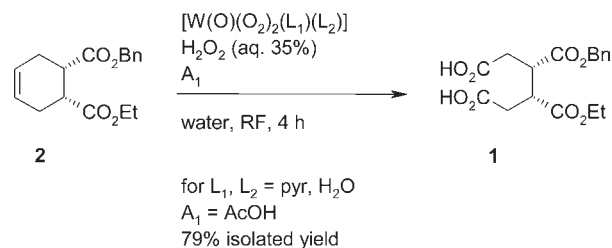
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Scheme 1. Preparation of cyclohexene 2

Scheme 2. Reaction mechanism – in analogy to the proposed reaction pathway for the synthesis of adipic acid by oxidation of cyclohexene with 30% hydrogen peroxide (Noyori *et al.*)^{3a}

acid ligand lay in the range of 1–3.^{7b} However, it was found that neutral or basic ligands inhibited the reaction.

Pleasingly, the procedure described by Jiang *et al.* led to the formation of bis-acid 1 albeit in modest yield. Noyori proposed that the reaction proceeds *via* six steps involving three kinds of oxidation reactions (epoxidation, dehydrogenation, and a Bayer–Villiger oxidation) and two hydrolytic reactions (Scheme 2).^{3a} Clearly, many steps in this scheme are facilitated by (strongly) acidic conditions. Interestingly, in contrast to Noyori's observations, we found that for our substrate the oxidation of cyclohexanediols 5 (four diastereoisomers) was slow (and thus appears for at least one diastereomeric pair to be the rate-limiting step) whereas Noyori reported a possible slow hydrolytic cleavage of the intermediate epoxide: Only at temperatures of 40–50 °C did we see significant accumulation of the epoxide intermediates (two isomers). As under the Noyori conditions, during our rate-limiting step, large amounts of reactant were saponified to ultimately yield 1,2,3,4-butanetetracarboxylic acid and benzoic acid (which is derived from the benzyl alcohol). This is not unexpected at a pH of ~0 in refluxing water. For our substrate, we were in need then of a milder system that would allow us to balance a reaction which progresses through many acid catalyzed reaction steps with an acid sensitive substrate. Catalytic systems of tungstate/cocatalyst for the oxidative cleavage of cyclohexene to adipic acid have been reported as indicated above, but direct catalysis by peroxotungsten complexes has received less attention. Yet, reports by Topich and Shechter indicated that oxidation essentially occurred with peroxotungstate species.^{8,9} Li and co-workers showed that the peroxotungsten complex [W(O)(O₂)₂·Phen]-H₂O was able to catalyze the oxidative cleavage of cyclohexene with hydrogen peroxide in the absence of a cocatalyst and without

Scheme 3. Oxidative cleavage to furnish bis-acid 1^a

^a See ref 11 for details of L₁ and A₁.

organic solvents and a phase transfer catalyst.^{7d} The preparation of their peroxotungsten catalyst was in close analogy to the one described previously by Bhattacharyya *et al.* for the oxidation of simple alcohols, sulfides, and amines.¹⁰ In the search for the optimum system for our substrate 2, we screened a number of ligands L₁ and organic acids A₁ as depicted in Scheme 3.¹¹ Iterating twenty nitrogen heterocyclic ligands (L₁) and eight carboxylic acids (A₁), we found a set of conditions in which L₁ = L₂ = pyridine in the presence of acetic acid (A₁) that allowed smooth oxidative cleavage of our functionalized cyclohexene 2 with minimal saponification side products being formed. It should be noted that the concentration of acetic acid in water in this system was limited to a maximum of 40% since this mixture has no flash point.¹⁵ There is no certainty of the exact nature of the catalytic species because it remained in solution.

However, based on literature reports, it is assumed that whilst L₁ and L₂ in the original freshly prepared catalyst are pyridine it could well be that at least one of these ligands is exchanged for acetic acid or water under the reaction conditions. After optimization, the protocol was finally carried out on a 400 g scale, giving reliable results on upscale.¹⁶

CONCLUSION

An efficient diperoxotungstate catalyzed oxidative cleavage protocol was developed that allowed acid sensitive cyclohexene derivatives to be converted into their *ω*-dicarboxylic acid analogues. The use of heavy metal oxidants and expensive organic oxidants was avoided in favor of readily available hydrogen peroxide. The process was readily scaled up with the target molecule being isolated in good yield and high chemical purity. No attempts have been made to scale the protocol up further. We acknowledge that different substrates to the one used during this optimization might need further optimization of the procedure and might actually favor another ligand/acid combination.¹⁷

EXPERIMENTAL SECTION

General. All reagents and solvents were used directly as purchased from commercial suppliers. Reaction progress was followed by high performance liquid chromatography (HPLC) at 210 nm using an Agilent 1100 series HPLC and a Phenomenex Luna C18(2) (30 mm × 4.6 mm) column. NMR spectra were obtained on a Bruker DRX 400 MHz or Bruker AvanceIII 600 MHz spectrometer.

Catalyst Stock Solution. Tungstic oxide dihydrate (WO₃·2H₂O) was prepared as described by Freedman.¹² Next, the diperoxotungstate species [W(O)(O₂)₂(H₂O)₂] was prepared by dissolving the freshly prepared tungstic oxide dihydrate (22.4 g, 83.6 mmol) in aqueous hydrogen peroxide (35%, 224 mL, 2.56 mol) and stirring the

initial yellow suspension vigorously for 15 min until a colorless solution was obtained.¹³ Now pyridine (13.5 mL, 167 mmol) was introduced until the solution turned a pale yellow. The freshly prepared $[W(O)(O_2)_2(Py)_2]$ was used directly.¹⁴

Benzyl Ethyl (1S*,2R*)-Cyclohex-4-ene-1,2-dicarboxylate (2). 1,2,3,6-*cis*-Tetrahydrophthalic anhydride (3) (95%, 400.4 g, 2.50 mol) and ethanol (460.7 g, 10.0 mol) were dissolved in *N,N*-dimethylacetamide (1.3 L). To this was added at room temperature potassium carbonate (380.1 g, 2.75 mol) whereby the temperature rose to 40 °C with evolution of gas. The suspension was stirred for 15 min until the temperature had dropped to 35 °C when benzyl chloride (97%, 342.6 g, 2.63 mol) was added over 5 min. The final reaction mixture was heated at 90 °C for 2 h before it was allowed to cool to room temperature. Potassium chloride was removed by filtration, and the filtrate was condensed under reduced pressure. The oily residue was dissolved in toluene (1.5 L) and washed with water (3 × 300 mL). The organic solvent was removed *in vacuo* to give the target compound 2 as a colorless liquid (724.9 g, 99%), HPLC purity >99% a/a.

(3R*,4R*)-3-[(Benzoyloxy)carbonyl]-4-(ethoxycarbonyl)hexanedioic Acid (1). Benzyl ethyl (1S*,2R*)-cyclohex-4-ene-1,2-dicarboxylate (2, 400 g, 1.39 mol) and water (400 mL) were placed in a 2 L four-necked flask. The suspension was brought to a boil before glacial acetic acid (320 mL) was added. Over the following 3 h, reagents were added every 15 min: t_0 : 56.0 mL of catalyst solution (CS), t_{15} : 56.0 mL of 35% aqueous hydrogen peroxide (HP), t_{30} : 56.0 mL (HP), t_{45} : 56.0 mL (HP), t_{60} : 56.0 mL (CS), t_{75} : 56.0 mL (HP), t_{90} : 56.0 mL (HP), t_{105} : 56.0 mL (HP), t_{120} : 56.0 mL (CS), t_{135} : 56.0 mL (HP), t_{150} : 56.0 mL (HP), t_{165} : 56.0 mL (HP), t_{180} : 56.0 mL (CS) — the total tungsten added equates to ~4 mol %. The reaction was further stirred at reflux for 1 h at which point the rate of the oxidation had slowed to the point that saponification began to compete with the oxidative cleavage of the diols. The reaction mixture was cooled to 45 °C at which point water (400 mL) and a few product seed crystals were added. Crystallization was complete after stirring at 45 °C for 5 h and then at room temperature overnight. The precipitate was removed by filtration, and the solids were washed with water (2 × 800 mL) and *n*-heptane (640 mL) and dried in the vacuum oven at 35 °C overnight providing the target compound 1 as a colorless powder (388.0 g, 79%, HPLC purity 98.2% a/a, mp: 127–128 °C).

■ ASSOCIATED CONTENT

Supporting Information. ¹H NMR data and HPLC data for cyclohexene 2 and *bis*-acid 1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mark.ford@bayer.com. Telephone: +49 (0)69 305 15797.

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- (11) **Screening:** L₁ = 2,6-lutidine, 2-methylbenzoxazole, 2-phenylbenzimidazole, 2-picoline, 3-chloropyridine, 3-picoline, 4-picoline, 4-*tert*-butylpyridine, benzimidazole, benzoxazole, indazole, *iso*-quinoline, 2-*N*-dimethylbenzimidazole, 2-*N*-dimethylimidazole, *N*-butylimidazole, *N*-methylbenzimidazole, *N*-methylimidazole, *N*-methylpyrazole, pyridine, quinoline, whereby the best results were obtained with pyridine, *N*-methylimidazole, and *N*-methylbenzimidazole. **Screening:** A₁ = Acetic acid ≈ propionic acid ≥ succinic acid > 1,4-phthalic acid ≈ benzoic acid ≈ *iso*-butyric acid > 1,2-phthalic acid > oxalic acid.
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- (17) For example: Synthesis of 3-[(Benzoyloxy)carbonyl]pentan-1,5-dioic acid: A solution of benzyl cyclopent-3-ene carboxylate (1.026 g) in water (1 mL) and acetic acid (0.8 mL) was heated to 100 °C and then treated over 3 h with aqueous hydrogen peroxide (35%) (7 portions) and catalyst solution (4 portions). After a further 1 h the mixture was cooled and the product taken up in ethyl acetate (25 mL). The organic phase was washed with dilute HCl and dilute sodium bisulfate (and checked for the absence of peroxide!) before being dried over sodium sulfate and concentrated *in vacuo*. Purification on silica (Biotage: heptane/ethyl acetate gradient) afforded 1.08 g (80% yield) of the desired product.