A green method of adipic acid synthesis: organic solvent- and halide-free oxidation of cycloalkanones with 30% hydrogen peroxide

Yoko Usui and Kazuhiko Sato*

National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba Central 5, Tsukuba 305-8565, Japan. E-mail: k.sato@aist.go.jp; Fax: +81-29-861-4852; Tel: +81-29-861-4852

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Cyclohexanone and cyclohexanol are oxidized to adipic acid in high yield with aqueous 30% H₂O₂ in the presence of H₂WO₄ as a catalyst under organic solvent- and halide-free conditions. It is important that no solvent is used in order to achieve high reactivity in this heterogeneous reaction. The use of t-buty1 alcohol or dioxane as a solvent (homogeneous conditions) significantly decreases the yield of adipic acid from cyclohexanone. This ketone-to-dicarboxylic acid conversion is applicable to five- to eight-membered cyclic ketones. No operational problems are foreseen for a large-scale version of this green process.

Adipic acid is an important bulk chemical for the production of nylon-6,6.¹ Currently most industrial processes utilize the nitric acid oxidation of cyclohexanone and/or cyclohexanol.² This processing is cost-effective, however, it inevitably leads to nitrous oxide (N₂O) as a stoichiometric waste product.³ N₂O is commonly thought to cause global warming and ozone depletion.⁴ Thus, an environmentally friendly, yet practical procedure for the production of adipic acid from cyclohexanone and/or cyclohexanol is very desirable.⁵

Various oxidants including KMnO₄,⁶,⁷ CrO₃,⁸ and KO₂⁹ have been elaborated for the synthesis of adipic acid from cyclohexanone and cyclohexanol. However, they are hazardous and expensive, and they form equimolar amounts of the deoxygenated compounds as waste products, preventing their use for large-scale reactions. Although air (molecular oxygen) is a clean oxidant, and the catalytic oxidation of cyclohexanone to adipic acid with O₂ has been reported, the reaction requires HMPA or acetic acid as a solvent.¹⁰

Hydrogen peroxide is an ideal oxidant because it has a high oxygen content, and water is the sole theoretical co-product.¹¹ This oxidant has become very inexpensive,¹² and in fact is produced in quantities of ca. 2.4 million metric tons year⁻¹ for use, mainly as a bleach.¹³ H₂O₂ can be a clean oxidant only if it is used in a controlled manner without organic solvents and other toxic compounds.¹⁴,¹⁵

We recently developed methods of performing practical epoxidation, the oxidation of alcohols, and other oxidation reactions with aqueous 30% H₂O₂ under organic solvent- and halide-free conditions.⁵,⁶ These methods give high-yields and are clean, safe, operationally simple, and cost-effective; they therefore meet the primary requirements of contemporary organic synthesis. Although the oxidation of cyclohexanone with H₂O₂ under homogeneous conditions using acetic acid or t-buty1 alcohol as a solvent has been reported, the highest yield of adipic acid was ca. 50%, and the selectivity was relatively low.¹⁷ Here, we report the practical procedures for adipic acid synthesis from the oxidation of cyclohexanone and cyclohexanol with aqueous 30% H₂O₂. These synthetic procedures satisfy the following conditions: (1) they are organic solvent- and halide-free systems; (2) they give a high yield; and (3) they are simple and involve safe manipulation. We also present a green and efficient method for C₅ to C₈ dicarboxylic acid synthesis.

The operation is very simple, even at a hectogram-scale synthesis, as shown in Scheme 1. Cyclohexanone (100 g), 30% H₂O₂ (382 g), and H₂WO₄ (2.50 g) were stirred in open air at 90 °C for 20 h to form adipic acid in > 99% yield (GC analysis). The collection of the crystalline product by filtration followed by drying in air produced a colorless, analytically pure adipic acid in 91% yield (135 g). The aqueous phase of the reaction mixture can be reused with 60% H₂O₂ to give adipic acid in 71% yield.† The oxidation of 100 g of cyclohexanol also produced crystalline adipic acid in 87% yield (127 g).

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Green Context

Clean oxidations are difficult to achieve, but this paper deals with a very efficient route to adipic acid (and other diacids). Aqueous hydrogen peroxide is used with cyclic ketones and a small amount of tungstic acid to directly provide the diacid, which solidifies upon cooling to give the product directly, without the use of promoters or solvents. DJM
achieved through multiple steps involving 4 types of oxidative reactions (two alcohol oxidations, Baeyer–Villiger oxidation, and aldehyde oxidation) and hydrolysis. Since the unproductive decomposition of H₂O₂ does not occur in this catalytic system, only a 3.3 molar amount of H₂O₂ per mol of cyclohexanone (3.0 mol in theory) is necessary for the three oxidation steps (a 4.4 molar amount of H₂O₂ in the case of cyclohexanol). In the course of the oxidation of cyclohexanone (43% conversion), adipic acid was solely formed in 43% yield at 90 °C for 10 h (GC and ¹H NMR analysis). None of the intermediates were observed. The oxidation of ϵ-caprolactone proceeded faster than that of cyclohexanone, to give 83% yield of adipic acid and 17% yield of 6-hydroxyhexanoic acid at 90 °C within 10 h. These results suggest that both Baeyer–Villiger oxidation and the oxidation of 6-hydroxyhexanoic acid in Scheme 2 are slow, but the former is probably the rate-determining step.

Although the reaction utilizes H₂WO₄ as the precatalyst, it is readily oxidized with H₂O₂ to form H₂[WO(O₂)₂(OH)₂], which is soluble in water (eqn. (1)). The pKₐ value is known to be 0.1. When Na₂WO₄ was used instead of H₂WO₄, the oxidation of cyclohexanone and cyclohexanol did not proceed. Since Na₂WO₄ is also readily oxidized with H₂O₂ to form Na₃[WO(O₂)₂(OH)₂], the acidic nature of the catalyst is crucial for the reaction.

\[
\text{H}_2\text{WO}_4 + \text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{W}[\text{O}(\text{O}_2)\text{₂}(\text{OH})\text{₂}] \tag{1}
\]

It is important that no solvent is used in order to achieve high reactivity in this heterogeneous reaction. The use of t-butyl alcohol or dioxane as a solvent (homogeneous conditions) significantly decreases the yield of adipic acid from cyclohexanone (31% with t-butyl alcohol, 52% with dioxane). Several peroxoketals (adducts of H₂O₂ to cyclohexanone) are spontaneously formed from cyclohexanone and H₂O₂ under the homogeneous conditions, whereas such compounds were not observed under our heterogeneous conditions without organic solvent. In our reaction, Baeyer–Villiger oxidation would occur by the reaction of cyclohexanone and H₃[WO(O₂)₂(OH)₂]. The reason why the heterogeneous conditions show high reactivity remains unclear; nonetheless, it is likely that Baeyer–Villiger oxidation of cyclohexanone with H₃[WO(O₂)₂(OH)₂] could be faster than that of peroxoketals.

Table 1 shows the oxidation of five- to eight-membered cycloalkanones and cycloalkanols. A temperature of 90 °C was used as the optimum reaction condition. Lower temperatures decreased the yield of adipic acid from cyclohexanone to < 5% at 60 °C for 20 h. Higher temperatures are not desirable for safety reasons. When 0.05 molar amount of H₂WO₄ was used, adipic acid was obtained in 85% yield within 10 h. Under identical conditions to those used for cyclohexanone, cyclopentanone was converted to glutaric acid in 98% yield. The larger the ring size of the cycloalkanone, the lower was its reactivity. The seven- and eight-membered cycloalkanones need a 0.05 molar amount of the catalyst for completion of the oxidation. This is in accordance with the relative rate of Baeyer–Villiger oxidation with perbenzoic acid, which is known to be slower than that with peroxoketals.

### Table 1: Oxidation of cycloalkanones and cycloalkanols with H₂O₂

<table>
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a Unless otherwise stated, reaction was run using 30% H₂O₂ substrate, and H₂WO₄ in a 330 : 100 : 1 molar ratio at 90 °C for 20 h. b Determined by GC analysis. Based on substrate charged. c Isolated yield after crystallization. d Reaction for 10 h. e Reaction for 10 h. f Reaction for 10 h. g Reaction for 10 h. h Reaction for 10 h.

### Acknowledgement

We would like to thank Prof. R. Noyori for helpful comments and suggestions.

### Notes and references

† Typical procedure (hectogram-scale oxidation of cyclohexanone with H₂O₂ and reuse of the water phase containing the tungsten catalyst): in the first run, a 1-liter, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with 2.50 g (0.01 mol) of H₂WO₄, water (50 mL), and 50 g (0.44 mol) of aqueous 30% H₂O₂. The mixture was heated to 55 °C until a clear solution was obtained, then 100 g (1.02 mol) of aqueous 30% H₂O₂ were added. The mixture was heated at 90 °C for 20 h, and then cooled to room temperature. The homogeneous solution was allowed to stand at 0 °C for 12 h, and the resulting colorless precipitate was separated by filtration and washed with 20 mL of cold water. The product was dried in a vacuum to give 135 g (91% yield) of adipic acid as a colorless solid. Mp 151.0–152.0 °C; ¹H NMR (500 MHz, CDCl₃): δ 2.22 (s, 12H, CH₂), 4.20 (s, 12H, CH₂), 7.20 (s, 12H, CH). The title compound was characterized by ¹H NMR and mass spectrometry.
MHz, CD$_3$OD): δ 1.72 (m, 4H), 2.40 (m, 4H), 5.31 (brs, 2H); $^{13}$C NMR (125 MHz, CD$_3$OD): δ 177.30, 34.57, 25.53; elemental analysis (% calc'd for C$_7$H$_{10}$O$_4$: C 49.31, H 6.90; found: C 49.40, H 6.71. In the second run, a 1-litre round-bottomed flask was charged with the water phase of the first run, which contained the tungsten catalyst, 100 g (1.02 mol) of cyclohexanone, and 191 g (3.37 mol) of aqueous 60% H$_2$O$_2$ were added. This mixture was heated at 90°C for 20 h, and the homogeneous solution was allowed to stand at 0°C for 12 h. The resulting colorless precipitate was separated, washed, and dried in a vacuum to give 106 g (71% yield) of adipic acid.


6. The KMnO$_4$ oxidation of cyclohexanone to adipic acid has been used in a textbook of organic experiments because this transformation is of educational value. For example, see: L. F. Fieser and K. L. Williamson, *Organic Experiments*, Houghton Mifflin Company, Boston, MA, 5th edn., 1998, pp. 254–264.


12. The current price is < 0.7 dollar kg$^{-1}$ (100% H$_2$O$_2$ basis).


15. There is a trend to use H$_2$O$_2$ as an oxidant for large-volume processes such as caprolactam synthesis (Sasitomo Chemical Co.) and propylene oxidation (BASF and Dow Chemical Co.). See: (a) *Samitomo Chemical News Release*, 2000, Oct. 11; (b) *Dow Products and Businesses News*, 2002, Aug. 1.


