

A green process for *O*-heterocyclization of cycloocta-1,5-diene by peroxotungstic species with aqueous H₂O₂

Ruihua Gao,^a Wei-Lin Dai,^{*a} Yingyi Le,^a Xinli Yang,^a Yong Cao,^a Hexing Li^b and Kangnian Fan^a

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The hydroxy- and carbonyl-derivatives of 9-oxabicyclo[3.3.1]nonane have been synthesized through an economic and green catalytic reaction between cycloocta-1,5-diene (COD) and aqueous H₂O₂ with tungstic acid as the catalyst. This process has advantages from the viewpoint of green chemistry, in that the aqueous H₂O₂ is used as the green oxygen donor, the only by-product of H₂O₂ is water and the tungstic acid catalyst can also be easily recovered. The excellent yields of the object products (**1** and **2**) (see Scheme 1) are reached easily under mild reaction conditions.

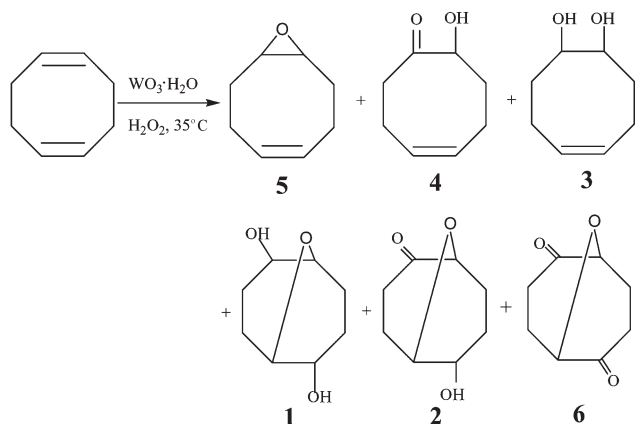
1. Introduction

The γ -butyrolactone structure is a versatile building block in organic synthesis since countless compounds containing this functional group show interesting biological activity.^{1–3} For example, 5-hydroxy- γ -decalactone is a potent cytotoxic agent on different tumour cell lines.⁴ It is commonly accepted that 9-oxabicyclo[3.3.1]nonane-2,6-dioles (**1**) and 2-hydroxy-9-oxabicyclo[3.3.1]nonane-6-one (**2**) are the major starting material for the synthesis of γ -butyrolactones. Therefore, it is of great significance to develop efficient and accessible approaches to affording these products (**1** and **2**). Classical routes to **1** and **2** employ peroxy acid or permanganate as oxidants. For example, Behr *et al.* obtained a 23.3% yield of **1** by using peracetic acid as the oxidant and cycloocta-1,5-diene (COD) as the raw material.⁵ If peracetic acid was replaced by permanganate, a much lower conversion of COD was observed. Moreover, the yield of **1** can reach 70% if performic acid is

used, according to Hegemann *et al.*⁶ However, the performic acid, as well as peracetic acid and permanganate, is an expensive chemical and leads to a large amount of by-products. Therefore, difficult separation of **1** from the products mixture is inevitable in these routes because of the low conversion and selectivity.

Nowadays, the development of environmental friendly techniques is one of the priority goals of chemical research, and this is especially true in the field of the oxidation of organic compounds, where there is an urgent need to replace wasteful and toxic stoichiometric oxidants with “clean” oxygen donors, such as hydrogen peroxide. As we know, the oxidation of organic substrates with hydrogen peroxide is very attractive and has long been studied. Many useful reactions using hydrogen peroxide as oxidant have been developed, such as the epoxidation of olefins and allylic alcohols,^{7–9} olefins to carboxylic acids,¹⁰ oxidation of sulfides to sulfoxides and sulfones¹¹ and oxidative cleavage of carbon–carbon double bonds to aldehydes.^{12–16} It is an effective strategy for the synthesis of these two compounds (**1** + **2**) by the selective oxidation of COD with environmentally benign aqueous H₂O₂. Thus, no noxious substances are needed and no toxic waste is generated in the reaction. However, to the best of our knowledge, no catalytic process has ever been reported so far in this strategy.

Herein we report a green procedure for the *O*-heterocyclization of COD by catalytic oxidation with aqueous H₂O₂. *tert*-Butanol is chosen as the solvent because the *tert*-butanol–H₂O₂ system is stable and safe and has been employed in many oxidation reactions.¹⁶ The reaction is carried out under mild conditions and enjoys good selectivity. Tungstic acid is an inexpensive catalyst and aqueous hydrogen peroxide is a relatively safe and non-polluting oxidant. The tungstic acid catalysts which deposit by adjusting the pH value of the solution to higher than 7 can be easily removed by simple filtration. The products can be easily obtained with high purity through decompressed rectification, due to the big difference in boiling point between the object products and *tert*-butanol. Therefore, the large-scale preparation and industrial manufacture of the hydroxy- or carbonyl-derivatives



Scheme 1 The oxidation products of COD by H₂O₂.

^aDepartment of Chemistry and Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials, Fudan University, Shanghai 200433, P. R. China. E-mail: wldai@fudan.edu.cn; Fax: 86-21-65642978

^bDepartment of Chemistry, Shanghai Normal University, Shanghai 200234, P. R. China. E-mail: Hexing-Li@shnu.edu.cn.; Fax: 86-21-64322272

of 9-oxabicyclo[3.3.1]nonane can be achieved by use of these compounds.

2. Experimental

2.1. Materials

Cycloocta-1,5-diene, 50% aqueous H₂O₂, *tert*-butanol, tungstic acid, 1,4-dioxane, acetonitrile, tetrahydrofuran, methanol, ethanol, *n*-butanol and iso-propanol were of analytical grade and were used as received.

2.2. Catalyst preparation

The novel catalytic system was prepared by a simple method: the required amount of tungstic acid was added into aqueous H₂O₂ at 60 °C. After 2 h pre-reaction, the mixture was used as the catalytic system.

2.3. Catalytic reaction: COD oxidation

The activity test was performed at 35 °C for a set time ranging from 2 to 24 h with magnetic stirring in a closed 25 mL regular glass reactor using 50% aqueous H₂O₂ as oxygen-donor and *t*-BuOH as the solvent. In a typical experiment, 0.108 g of the WO₃·H₂O (0.46 mmol) and 1.4 mL of 50 wt% aqueous H₂O₂ (22.5 mmol) were introduced into the regular glass reactor at 60 °C with vigorous stirring. Then, the reaction was started after the addition of 10 mL of *t*-BuOH and 1.06 mL of COD (7.5 mmol) into the mixture and was kept for 2 h or more. The conversion of H₂O₂ was measured by a standard iodimetric titration method. The quantitative analysis of the reaction products was performed by using a GC method and the identification of different products in the reaction mixture was determined by means of GC-MS on HP 6890GC/5973 MS.

3. Results and discussion

3.1. Products of COD oxidation

According to the GC-MS analysis, the products of COD oxidation, as shown in Scheme 1, consist of the two object products **1** and **2** with small amounts of by-products including **3**, **4** and **5** under the present conditions. All the products are the derivatives from the epoxide of C=C bond and the further oxidation of alcoholic moieties into ketones, such as the conversion of **1** into **2** and the conversion of **2** into 9-oxabicyclo[3.3.1]nonane-2,6-dione (**6**), which can be neglected because of the small amount of it present. It is a surprise to find that there are no cleavage products from one or two C=C bonds. Since the two main products, **1** and **2**, can both be oxidized to the same product— γ -butyrolactones—the total yield of these two products is used to determine the catalytic performance of different catalysts.

3.2. Conversion of COD and H₂O₂ and selectivity of various products over the catalyst

The reaction process is indicated in Fig. 1, which shows a typical plot of COD consumption, and the products formation *versus* time under the reaction conditions. It is shown that a complete conversion of COD is achieved and the selectivity to

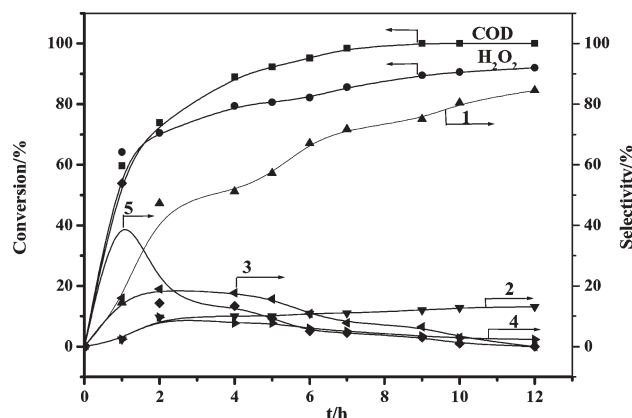


Fig. 1 Conversion of COD and H₂O₂ and selectivity of **1** and **2** over the catalyst (reaction condition: reaction temperature 35 °C, COD 7.5 mmol, H₂O₂ 22.5 mmol, catalyst WO₃·H₂O 0.14 mmol).†

Table 1 Catalytic performances of oxidation of COD over various molar ratios of H₂O₂ to COD^a

H ₂ O ₂ :COD	Conversion (%)		Selectivity (%)		
	COD	H ₂ O ₂	1	2	1 + 2
1:1	71	97	23	1	24
2:1	96	97	67	6	73
2.5:1	98	88	75	11	86
3:1	100	80	79	14	93
4:1	100	80	71	27	98

^a Reaction condition: reaction temperature 35 °C, H₂O₂ 22.5 mmol, catalyst WO₃·H₂O 0.081 mmol, reaction time 24 h, *t*-BuOH 10 mL.

1 and **2** is satisfactorily high. In particular, the curve of **5** with the highest selectivity in the first period declined *versus* time. At the same time, the tendencies of **3** and **4** are similar to **5**. For the main products of **1** and **2**, the selectivity increases with time. Under this reaction condition, the oxidation of COD to **1** and **2** is a very complex process. Some of these steps are similar to those described in refs. 17 and 18. Therefore, a possible reaction scheme can be described (see footnote†).

3.2. COD oxidation with different amount of H₂O₂

Table 1 shows the performance of the selective oxidation of COD over various molar ratios of H₂O₂ to COD. It can be seen that the conversion of COD rises with the increase in molar ratio of H₂O₂ to COD, as does the selectivity to **1** and **2**. Because H₂O₂ is the oxygen donor, the rate of the reaction and the selectivity of products are due to it. The complete consumption of COD cannot be achieved when the ratio is

† Herein, we assume that the process for this reaction, catalysed by tungstic acid, consists of several steps. COD is first oxidized to its oxides, such as 1,5-epoxycyclooctene (**5**), 1,5 diepoxycyclooctane, etc., then **1** is formed *via* hydrolysis of 1,5-diepoxycyclooctane, accompanied by the formation of a by-product **3**, *via* hydrolysis of **5**. Some of these steps are similar to the study of refs. 17 and 18. The step of **1** being formed from 1,5-diepoxycyclooctane is so fast that the diepoxycyclooctane cannot be tested in our experiments. Following above steps, **4** and **2** are respectively formed *via* deep oxidation of **3** and **1**. Finally, **6** is formed by deeper oxidation of **2**, but the amount of **6** is so small that it can be neglected.

lower than 3:1. The selectivity of **1** rises with the increase of the ratio before 3:1, then it decreases at 4:1. However, the selectivity of **2** rises with the increase of the ratio for all the molar ratios. The result shows that **1** and **2** have different trends of selectivity for various molar ratios of H₂O₂ to COD. Thus, different ratios of H₂O₂ to COD can affect the yield of the object products. At the molar ratio of 4:1, the selectivity of the total products reaches 98%, but considering both good catalytic performance and H₂O₂ utility, the 3:1 ratio of the H₂O₂ to COD is needed.

3.3. Catalytic performance with different amounts of WO₃·H₂O

The reaction results as a function of the amounts of WO₃·H₂O catalyst used were also investigated, and are listed in Table 2. It was found that conversion of COD in a fixed reaction period ascends with increasing catalyst dosage, the amounts of which are ranging from 0.013 g (0.055 mmol) to 0.108 g (0.46 mmol). When the amounts are higher than 0.108 g, the conversion of COD in 2 h is the same to 100%. It could thus be suggested that the amounts of active species affect the reaction rate. The higher the amount of peroxotungstic acid, the higher the rate of the consecutive reactions. Entries 1–3 in Table 2 indicate that when COD reaches complete conversion, the total selectivity of (**1** + **2**) with the amount of catalyst is almost the same, ranging from 97 to 99%, but the distributions of **1** and **2** are different from each other (the selectivity of **2** ranges from 5 to 17%). Such a phenomenon can also be seen from entries 4 and 5. This indicates that the amount of catalyst not only affects the rate of the reaction but also affects the distribution of **1** and **2**.

3.4. Effect of solvent on COD oxidation

Solvent plays an important role in the selectivity of the reaction, and hence it was decided to investigate the solvent effect. As shown in Table 3, the maximum selectivity of the object products is formed when the solvent is *tert*-butanol, whereas the use of other alcohols results in a low yield compared with *tert*-butanol. It is important to note here that the by-products in solution using linear alcohols are ethers, which derive from the etherification of the hydroxy derivatives with the corresponding alcoholic solvents. This leads to the

Table 2 The effect of the amounts of catalysts over the reaction^a

Entry	Amount of catalyst/g	COD: catalyst ^b	Time/h	Conversion (%)		Selectivity (%)		
				COD	H ₂ O ₂	1	2	1 + 2
1	0.324	5.40	2	100	98	94	5	99
2	0.216	8.20	2	100	93	82	17	99
3	0.108	16.3	2	100	96	86	11	97
4	0.059	32.6	2	92	80	50	7	57
5	0.059	32.6	12	100	84	85	13	98
6	0.019	101	12	97	80	65	14	79
7	0.019	101	17	98	85	71	17	88
8	0.013	148	12	86	72	46	11	57
9	0.013	148	17	88	76	56	14	70

^a Reaction condition: reaction temperature 35 °C; COD: 7.5 mmol; H₂O₂: 22.5 mmol; *t*-BuOH 10 mL. ^b The molar ratio of COD to catalyst (tungstic acid).

Table 3 The effect of the different solvents over the reaction^a

Solvents	C _{COD} (%)	S ₁ (%)	S ₂ (%)	S ₁₊₂ (%)	S _{other} (%)
Methanol	100	42	30	72	28
Ethanol	100	58	26	84	16
n-Butanol	100	78	6	84	16
2-Propanol	100	81	11	92	8
<i>tert</i> -Butanol	100	86	11	97	3
1,4-Dioxane	93	65	29	94	6
Acetonitrile	100	91	5	96	4
Tetrahydrofuran	100	75	22	97	3

^a Reaction conditions: reaction temperature 35 °C, reaction time 2 h, COD 7.5 mmol, H₂O₂ 22.5 mmol, tungstic acid 0.46 mmol, solvent 10 mL.

conclusion that the *tert*-butanol is the best of its kind, the large alkyl structure of which hinders the formation of ethers. Some other water-soluble solvents, such as 1,4-dioxane, acetonitrile and tetrahydrofuran, which have no tendency to give ethers, were also tested (see Table 3) and the conversion of COD and the selectivity of object products were also high. The nature of the oxidation in these solvents is still under investigation.

Independent experiments were carried out to study the effect of the volume of *tert*-butanol on reaction. Table 4 indicates that there is an optimum volume of *tert*-butanol at which a maximum amount of (**1** + **2**) is formed. Initially, with a decrease in the volume from 20 to 5 mL, the selectivity of object products increases from almost 88 to 98%. This can be explained by the fact that, for the formation of **1** and **2**, the concentration of active oxidizing species is required. The concentration of active oxidizing species formed depends on the concentration of hydrogen peroxide. At 5 mL, large amount of oxidizing species are formed as compared to the case with high volume of *tert*-butanol. It is also found that, without the use of desired amount of organic solvents, this reaction cannot be carried out with high efficiency due to the phase splitting between COD and aqueous H₂O₂. Thus, further studies are under way on the search of new catalysts showing good activity and selectivity without the use of any organic solvents.

Here the ammonium tungstate and sodium tungstate also used were compared with tungstic acid. It was found that the performance of ammonium tungstate was similar to that of tungstic acid. However, the sodium tungstate has no activity for this reaction. It was observed that the pH values of the reaction solution were 0.67, 1.82 and 4.83, respectively, for tungstic acid, ammonium tungstate and sodium tungstate. The different pH values hint that the tungsten species are different in those solutions. Lin *et al.*¹⁹ found that the composition of

Table 4 The effect of volumes of *t*-BuOH on the oxidation of COD^a

Volumes of <i>t</i> -BuOH	Conversion (%)		Selectivity (%)		
	COD	H ₂ O ₂	1	2	1 + 2
5	100	91	78	20	98
10	100	95	86	11	97
15	100	91	83	10	93
20	98	68	80	8	88

^a Reaction conditions: reaction temperature 35 °C, reaction time 2 h, COD 7.5 mmol, H₂O₂ 22.5 mmol, tungstic acid 0.46 mmol.

active tungsten species was affected by the pH value. It can be speculated that the composition of active tungsten species is the inner key to the reaction. However, experiments on the continuous change of the pH value in this reaction by adding alkali were not successful due to the deposition of tungstic species. Detailed work concerning the effect of pH values and the mechanism at molecular level is under way.

4. Conclusions

From this detailed study of *O*-hetero-cyclization of COD by catalytic oxidation with aqueous H₂O₂, the following conclusions can be established. It is possible to oxidize COD to hydroxy- or carbonyl-derivatives of 9-oxabicyclo[3.3.1]nonane at room temperature in the presence of tungstic acid. The reaction rate and selectivity of object products formation are affected by the amount of the tungstic acid and the molar ratio of COD to H₂O₂, as well as the volume ratio of the solvent to reactant. The branched alcohols are recommended as solvents in order to reach good yields of the products. The present method appears to be useful in preparing the hydroxy- or carbonyl-derivatives of 9-oxabicyclo[3.3.1]nonane by oxidation of COD with H₂O₂. It has advantages compared with the other traditional chemical methods. With a high conversion of COD and selectivity of the object products, it is very suitable for the preparation of hydroxy- or carbonyl-derivatives of 9-oxabicyclo[3.3.1]nonane from COD in both the laboratory and industry.

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