## Fe<sub>2</sub>O<sub>3</sub>-Catalyzed Baeyer-Villiger Oxidation of Ketones with Molecular Oxygen in the Presence of Aldehydes

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Abstract: The Fe<sub>2</sub>O<sub>3</sub>-catalyzed oxidation of ketones with molecular oxygen (1 atm) in the presence of an aldehyde at room temperature gives the corresponding lactones or esters highly efficiently.

Baeyer-Villiger oxidation of ketones to lactones or esters is a widely used synthetic method.<sup>1</sup> This oxidative transformation has been performed by using various peroxides such as peracids,<sup>2</sup> hydrogen peroxide,<sup>3</sup> and bis(trimethylsilyl) peroxide;<sup>4</sup> however, catalytic Baeyer-Villiger oxidations of ketones with molecular oxygen are limited to few cases. Aerobic oxidation of cyclohexanone to  $\varepsilon$ -caprolactone in the presence of aldehydes has been studied extensively by using various metal catalysts; however, the reported methods are unsatisfactory with respects to selectivity or conversion.<sup>5</sup> Mukaiyama *et al.* reported that the oxidation of ketones by combined use of molecular oxygen and aldehydes proceeds efficiently in the presence of nickel(II) complexes coordinated with 1,3-diketone such as bis(dipivaloylmethanato)nickel(II).<sup>6</sup>

During the course of our systematic study on cytochrome P-450 type oxidations with metal catalysts,<sup>7</sup> we have found that iron(0)- and ruthenium(III)-catalyzed oxidations of alkanes with molecular oxygen in the presence of an aldehyde and a catalytic amount of an acid give the corresponding ketones.<sup>8</sup> The precise mechanistic study on the iron(0)-catalyzed oxidation led to find highly efficient Baeyer-Villiger oxidation of ketones with molecular oxygen in the presence of Fe<sub>2</sub>O<sub>3</sub> catalyst and an aldehyde (eq 1).

$$\begin{array}{c} O \\ R^{1} \\ \hline \\ R^{2} \\ \hline \\ O_{2}, RCHO \\ \hline \\ O_{2}, RCHO \\ \hline \\ \\ O_{2}, RCHO \\ \hline \\ \\ OR^{2} \end{array}$$
(1)

The catalytic activity of various iron salts was examined for the oxidation of cyclopentanone with molecular oxygen (1 atm) in the presence of benzaldehyde. Fe<sub>2</sub>O<sub>3</sub> has proved to be the most effective catalyst, and the other iron salts such as Fe(OAc)<sub>3</sub>, FeCl<sub>2</sub>•4H<sub>2</sub>O, and iron powder are ineffective. The oxidation of cyclopentanone does not occur without an aldehyde. Benzaldehyde gave the best result among the aldehydes examined, and the effect of aldehydes is in the order of benzaldehyde > heptanal > pivalaldehyde. The aldehydes used were converted into the corresponding acids under the reaction conditions.

The solvent effect is remarkable, and benzene has proved to be an excellent solvent. Other solvents such as acetonitrile, methylene chloride, and ethyl acetate are not effective.

Typically, the oxidation of cyclohexanone is as follows: A mixture of cyclohexanone (981 mg, 10.0 mmol), benzaldehyde (3.18 g, 30.0 mmol), Fe<sub>2</sub>O<sub>3</sub> (16 mg, 0.10 mmol, 1 mol%), and benzene (60 mL) was vigorously stirred at room temperature under oxygen atmosphere (1 atm) for 17 h. The reaction mixture was washed with saturated aqueous NaHCO<sub>3</sub> solution, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. Evaporation followed by column chromatography on silica gel (hexane / ethyl acetate, 3:1) gave  $\varepsilon$ -caprolactone (1.05 g, 9.20 mmol, 92%).

The representative results of the  $Fe_2O_3$ -catalyzed oxidation of various ketones with molecular oxygen (1 atm) in benzene in the presence of benzaldehyde at room temperature are listed in Table 1. Both cyclic and

entry	substrate	conv, <sup>b</sup> %	product <sup>c</sup>	yield, <sup>b</sup> %
1		85	Ļ.	83
2	$\overset{\texttt{l}}{\bigcirc}$	100		98
3	Å	97	Ċ	93 (92) <sup>d</sup>
4	Ů	83	ů.	80
5	С ОСН3	80	COCH3	80
6		)	Aco	(2) 56 <sup>d</sup>
7	(3)		(4)	63 <sup>d</sup>

Table 1. Fe<sub>2</sub>O<sub>3</sub>-Catalyzed Baeyer-Villiger Oxidation of Ketones with Molecular Oxygen in the Presence of Benzaldehyde <sup>a</sup>

<sup>a</sup> The reaction was carried out as described in the text. <sup>b</sup> Determined by GLC analysis based on the starting ketone using internal standards. <sup>c</sup> The structure of the product was determined by GC-MS, IR, NMR spectral data, and elemental analysis. <sup>d</sup> Isolated yield.

acyclic ketones were converted to the corresponding lactones or esters highly efficiently (entries 1-5). 17-Keto steroid (1) was also oxidized to give the corresponding lactone (2) in a moderate yield. It is noteworthy that the oxidation of 2-allylcyclohexanone (3) gave 6-allyl- $\varepsilon$ -caprolactone (4) and 2-(2',3'-epoxypropyl)cyclohexanone in a ratio of 97 : 3.

The oxidation can be rationalized by assuming two pathways shown in Scheme 1. The  $Fe_2O_3$ -catalyzed reaction of an aldehyde with molecular oxygen would give acylperoxy radical (5), which is a key intermediate of autoxidation of aldehyde.<sup>9</sup> The radical 5 abstracts hydrogen from aldehyde to give peracid (6), which undergoes facile reaction with ketone to give 7. Alternatively, the radical 5 reacts with ketone and subsequently with an aldehyde to give 7. The intermediate 7 thus formed would undergo rearrangement to give ester and carboxylic acid.



The present reaction provides a practical and convenient method for synthesis of 4-acyloxy  $\beta$ -lactams, which are key intermediates for the synthesis of thienamycin and 1-methylcarbapenems. Actually, the Fe<sub>2</sub>O<sub>3</sub>-catalyzed aerobic oxidation of 4-benzoyl  $\beta$ -lactam (8), which is readily derived from L-threonine,<sup>10</sup> gave 4-benzovloxy  $\beta$ -lactam (9)<sup>11</sup> with complete retention of configuration in 93% isolated yield (eq 2).



Recently we have found that iron(0)-catalyzed oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde and a catalytic amount of acetic acid gives cyclohexanone highly efficiently.<sup>8</sup> Under the reaction conditions the Baeyer-Villiger oxidation of cyclohexanone to  $\varepsilon$ -caprolactone does not occur. In contrast, in the present Fe<sub>2</sub>O<sub>3</sub>-catalyzed reaction the oxidation of cyclohexane does not occur. We wish to emphasize that completely different catalytic systems, that is, the aerobic oxidation of alkanes to ketones and the aerobic oxidation of ketones to lactones have been explored by using iron catalysts. Interestingly, sequential iron-catalyzed oxidations of cyclohexane with molecular oxygen give  $\varepsilon$ -caprolactone highly efficiently as shown in Scheme 2.

## Scheme 2



Work is actively in progress to apply the method to the other systems. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

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- 11. mp 123–124 °C;  $[\alpha]^{26}_{D}$  +71.4° (*c* 1.03, CHCl<sub>3</sub>) [lit.<sup>12</sup>  $[\alpha]^{25}_{D}$  +69.1° (*c* 1.0, CHCl<sub>3</sub>)]; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta$  0.09 (s, 3 H, SiCH<sub>3</sub>), 0.10 (s, 3 H, SiCH<sub>3</sub>), 0.88 (s, 9 H, *t*-Bu), 1.32 (d, *J* = 6.4 Hz, 3 H, CH<sub>3</sub>), 3.36 (dd, *J* = 1.2 and 3.4 Hz, 1 H, H-3), 4.29 (dq, *J* = 3.4 and 6.4 Hz, 1 H, CH), 6.11 (d, *J* = 1.2 Hz, 1 H, H-4), 6.67 (br-s, 1 H, NH), 7.46 (m, 2 H, ArH), 7.60 (m, 1 H, ArH), 8.04 (m, 2 H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 68 MHz)  $\delta$  –5.2, -4.3, 17.9, 22.3, 25.7, 64.0, 65.4, 75.8, 128.5, 129.1, 129.8, 133.7, 166.4, 166.6.
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(Received in Japan 17 August 1992)