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## Communications

### Baeyer–Villiger Oxidation of Ketones Using Molecular Oxygen and Benzaldehyde in the Absence of Metal Catalysts

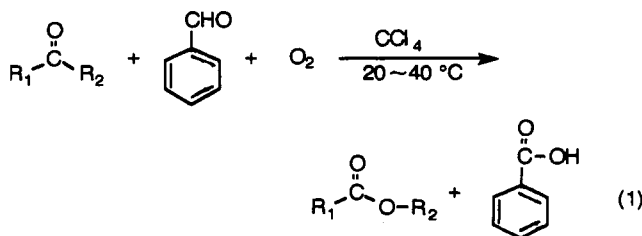
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**Summary:** A combination system of molecular oxygen, benzaldehyde, and carbon tetrachloride oxidizes various ketones to give lactones and esters in high yields at 40 °C, and addition of benzoyl chloride increases yields of the Baeyer–Villiger oxidation products at a lower temperature of 20 °C.

Baeyer–Villiger oxidation of ketones to esters or lactones has been developed by using various reagents, *e.g.*, hydrogen peroxide, peroxy acids, and metal catalysts.<sup>1</sup> Recently, we have found that a combination system of molecular oxygen and aldehydes was an efficient oxidant for both the oxidative cleavage and the epoxidation of olefins.<sup>2,3</sup> Using the above oxidant, here, we wish to report a selective synthesis of lactones or esters from ketones *in the absence of metal catalysts* (eq 1) and that addition



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\* Abstract published in *Advance ACS Abstracts*, May 1, 1994.

(1) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (b) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington, D.C., 1990. (c) Krow, G. R. *Organic Reactions*; John Wiley & Sons: New York, 1993; Vol. 43, p 251.

**Table 1. Effect of Various Aldehydes on Baeyer–Villiger Oxidation of Cyclohexanone and Epoxidation of 2-Octene<sup>a</sup>**

aldehyde	yield of oxidation products <sup>b</sup> /%	
	Baeyer–Villiger Oxidation	epoxidation
PhCHO	78	50
<i>m</i> -ClPhCHO	53	36
<i>p</i> -CH <sub>3</sub> PhCHO	58	32
(CH <sub>3</sub> ) <sub>2</sub> CHCHO	38	94 <sup>c</sup>
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CHO	30	quantitative <sup>c</sup>

<sup>a</sup> Reaction conditions: cyclohexanone or 2-octene, 2 mmol, aldehyde, 6 mmol, 1,2-dichloroethane, 10 mL, 40 °C, 3 h. <sup>b</sup> Yields were determined by GC and based on ketones or olefins used. <sup>c</sup> Cited from ref 3.

of benzoyl chloride remarkably increases yields of the Baeyer–Villiger products. This oxidation system, *in situ* generation of peracids, is a very convenient method for Baeyer–Villiger oxidation, compared with other oxidizing reagents.<sup>4,5</sup>



























A typical procedure of Baeyer–Villiger oxidation of ketones is as follows. Into a three-necked flask with a reflux condenser cooled at –15 °C were placed benzalde-

(2) Kaneda, K.; Haruna, S.; Imanaka, T.; Kawamoto, K. *J. Chem. Soc., Chem. Commun.* 1990, 1467.

(3) Kaneda, K.; Haruna, S.; Imanaka, T.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* 1992, 33, 6827.

(4) For Baeyer–Villiger oxidation using molecular oxygen and aldehydes, see: (a) Yamada, T.; Takahashi, K.; Kato, K.; Takai, T.; Inoki, S.; Mukaiyama, T. *Chem. Lett.* 1991, 641. (b) Murahashi, S.-I.; Oda, Y.; Naota, T. *Tetrahedron Lett.* 1992, 33, 7557. (c) Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* 1993, 58, 6421. (d) Union Carbide Corp. U.S. Patent 3025306, 1962. (e) Knapsack, A. G. U.S. Patent 3483222, 1969. (f) Stamicarbon, N. V. JP Patent Tokkosho 46-12456, 1971. (g) Mitsubishi Kasei Co. JP Patent Tokkosho 47-47896, 1972, and Tokkosho 56-14095, 1981. (h) Mitsubishi, Gasukagaku Co. JP Patent Tokkaihei 5-65245.

Table 2. Baeyer–Villiger Oxidation of Various Ketones Using Benzaldehyde under Oxygen Atmosphere<sup>a</sup>

run	substrate	products	reaction time (h)	convn/%	yield <sup>b</sup> /%
1			5	100	90 (82)
2 <sup>c</sup>			5	83	80
3 <sup>d</sup>			5	77	77
4 <sup>e</sup>			5	0	0
5			5	90	84 (80)
6			5	88	85
7 <sup>c</sup>			5	66	63
8			24	100	quantitative
9		 (ca. 1:1)	5	88	85 (80)
10			24	70	70
11 <sup>f</sup>			17	91	90
12			5	63	63
13			24	60	58

<sup>a</sup> Reaction conditions: ketone, 4 mmol, benzaldehyde, 12 mmol, carbon tetrachloride, 20 mL, O<sub>2</sub> bubbling, 40 °C. <sup>b</sup> Yields were determined by GC and based on ketones used. Isolation yields are in parentheses. <sup>c</sup> 1,2-Dichloroethane was employed instead of carbon tetrachloride. <sup>d</sup> Ethyl acetate was used. <sup>e</sup> Methanol was used. <sup>f</sup> 3-Oxabicyclo[3.2.1]octan-2-one as a regioisomer (6%) was detected in NMR.

hyde (12 mmol) and carbon tetrachloride (17 mL), and oxygen was bubbled into the stirred solution at 40 °C for 30 min. A carbon tetrachloride solution (3 mL) of cyclohexanone (4 mmol) was added, and the resulting mixture was stirred with bubbling of oxygen at 40 °C for 4.5 h. Benzoic acid was removed by successive treatment of the reaction mixture with Na<sub>2</sub>SO<sub>3</sub> and NaHCO<sub>3</sub>. The oxygenation products in carbon tetrachloride solution were then analyzed by GC, and  $\epsilon$ -caprolactone (0.374 g, 82%) was isolated by column chromatography on silica gel (hexane/ethyl acetate, 3:1). The oxidation of cyclohexanone with benzaldehyde at room temperature for 12 h gave 92% of  $\epsilon$ -caprolactone.

We have already reported that both epoxidation and oxidative cleavage of olefins using the system consisting of aldehydes and molecular oxygen were strongly dependent on the kinds of aldehydes used.<sup>2,3</sup> At first, the importance of the aldehyde component in the oxidation system was examined in Baeyer–Villiger oxidation of cyclohexanone as a model substrate. The typical results

are shown in Table 1, together with those in the epoxidation of 2-octene. Baeyer–Villiger oxidation of cyclohexanone with benzaldehyde smoothly occurred to give  $\epsilon$ -caprolactone at 40 °C, and benzoic acid was also formed as a coproduct. Aliphatic aldehydes, e.g., isobutyraldehyde and isovaleraldehyde, having high reactivities for the epoxidation<sup>3</sup> showed lower yields of  $\epsilon$ -caprolactone than benzaldehyde. Notably, the effectiveness of aldehydes is different between the Baeyer–Villiger oxidation and the epoxidation of olefins. In the scrutiny of solvents in the cyclohexanone oxidation with benzaldehyde, it was found that carbon tetrachloride was the best solvent. 1,2-Dichloroethane, ethyl acetate, and benzene were good, while alcohols and acetonitrile were poor solvents for this Baeyer–Villiger oxidation, respectively.

The representative results of Baeyer–Villiger oxidation using the above best combined system of benzaldehyde and carbon tetrachloride under an oxygen atmosphere are shown in Table 2. Monoalkyl-substituted cyclohexanones were converted into the corresponding  $\epsilon$ -caprolactones in high yields; 2-methylcyclohexanone was oxidized into 84% of 6-methylcaprolactone (run 5). 3-Methylcyclohexanone gave a mixture of 5-methylcaprolactone and 3-methylcaprolactone (ca. 1:1, run 9).<sup>6</sup> In the case of menthone,

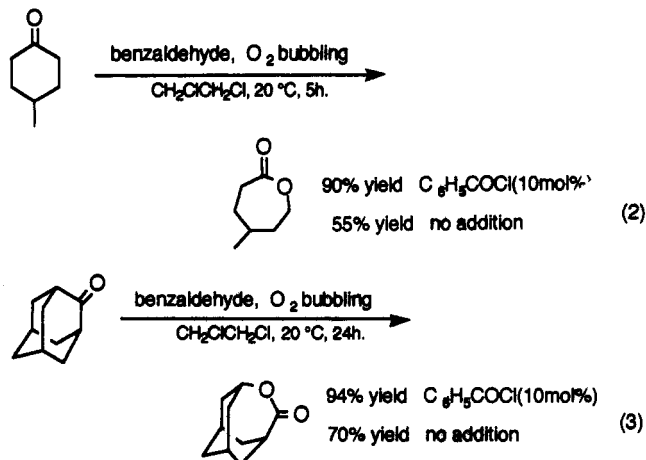
(5) During our study on the above oxidation, Bolm *et al.* have independently found a similar phenomenon on the Baeyer–Villiger oxidation in the absence of metal catalysts; oxidation of 4-methylcyclohexanone with benzaldehyde in 1,2-dichloroethane at 40 °C gave 59% of the corresponding lactone for 21 h: Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* 1993, 34, 3405. Y.I. has already presented the Baeyer–Villiger oxidation of molecular oxygen and aldehydes in the absence of metal catalysts in a Japan patent on July 10, 1992. (Tokuganhei 4-207202).

(6) 5-Methylcaprolactone: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  (ppm) 3.98 (m, 2H), 2.52 (m, 2H), 1.9–1.7 (m, 5H), 0.90 (d,  $J$  = 7.34 Hz, 3H) (Wong, C. F.; Auer, E.; LaLonde, R. T. *J. Org. Chem.* 1970, 35, 517). 3-Methylcaprolactone: 4.15 (m, 2H), 2.57 (m, 2H), 1.9–1.7 (m, 5H), 0.98 (d,  $J$  = 6.6 Hz, 3H).

dialkyl-substituted cyclohexanone, the Baeyer–Villiger oxidation occurred regioselectively *via* migration of the isopropyl-substituted carbon to give 6-isopropyl-3-methylcaprolactone (run 10).<sup>7</sup> Oxidation of cyclopentanone and norcamphor proceeded selectively in spite of slow rates, respectively (runs 11 and 12).<sup>8</sup>

Addition of benzoyl chloride to the above oxidation system could accelerate the Baeyer–Villiger oxidation to give high yields of lactones at a lower temperature of 20 °C. Typical results are shown in eqs 2 and 3. The role of benzoyl chloride might be to promote the yield of perbenzoic acid derived from oxidation of benzaldehyde.<sup>9,10</sup> Notably, an additive of benzoyl chloride does not lead problems in the workup process because of its complete conversion to benzoic acid.

It is conceivable that this Baeyer–Villiger oxidation occurs mainly by an organic peracid generated from the reaction of an aldehyde with molecular oxygen.<sup>11,12</sup> The



three-component system of aldehyde, molecular oxygen, and chlorohydrocarbon plays as a useful monooxygenation-type reagent for both Baeyer–Villiger oxidation of ketones and epoxidation of olefins even *in the absence of metal catalysts*.<sup>3,5</sup> A suitable choice of aldehyde can lead to selective Baeyer–Villiger oxidation and epoxidation, respectively.

**Supplementary Material Available:** General experimental procedures for Baeyer–Villiger oxidation reactions (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) 6-Isopropyl-3-methylcaprolactone: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm) 3.98 (d, d, *J* = 9.16 and 4.39 Hz, 1H), 2.50–3.39 (m, 2H), 1.89–1.77 (m, 4H), 1.58–1.48 (m, 1H), 1.27–1.17 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ (ppm) 174.46, 84.74, 42.69, 37.59, 33.42, 31.06, 30.50, 23.83, 18.28, 17.18 (Alphand, V.; Furstoss, R. *Tetrahedron: Asymmetry* 1992, 3, 379).

(8) In Baeyer–Villiger oxidation of various ketones, perbenzoic acid shows higher reactivity for six-membered ring ketones than five-membered ones: Mateos, J. L.; Menchaca, H. *J. Org. Chem.* 1964, 29, 2026.

(9) There is a report that acyl halides have been used in preparation of peroxy compounds with aldehydes, molecular oxygen, and acid acceptors: Bafford, R. A. U.S. Patent 3580955, 1971.

(10) Another role of benzoyl chloride might be proposed as follows: the benzoyl chloride liberates HCl which catalyzes either the formation of the Criegee intermediate or the collapse of the intermediate. However, addition of small amounts of HCl in place of benzoyl chloride could not improve the yield of lactones. In the case of acid-catalyzed Baeyer–Villiger oxidation, cyclopentanone is oxidized faster than cyclohexanone (Koch, S. S. C.; Chamberlin, A. R. *Synth. Commun.* 1989, 829). Our reaction using benzoyl chloride showed a reverse behavior of the above two ketones. At present, we think that HCl from benzoyl chloride does not play an important role in our oxidation system using benzoyl chloride.

(11) In the case of benzaldehyde, <sup>13</sup>C NMR analysis of the reaction mixture pretreated with oxygen gas showed formation of perbenzoic acid, 168.0 ppm, due to O=C=OOH, in CDCl<sub>3</sub>, whose value was in fair agreement with that of an authentic sample.

(12) Oxygenation of benzaldehyde with molecular oxygen is promoted by Hg lamp and sunlamp: (a) Swern, D.; Findley, T. W.; Scanlan, J. T. *J. Am. Chem. Soc.* 1944, 66, 1925. (b) Reference 5.