Tetrahedron Letters, Vol. 34, No. 21, pp. 3405-3408, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Use of Molecular Oxygen in the Baeyer-Villiger Oxidation The Influence of Metal Catalysts

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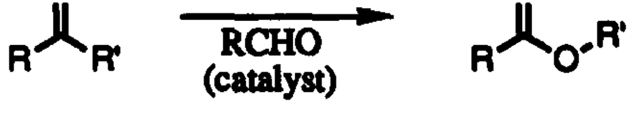
Key Words: Baeyer-Villiger oxidation, Molecular oxygen, Copper catalysts

Abstract: Baeyer-Villiger oxidation of ketones using molecular oxygen and benzaldehyde *in the absence of metal catalysts* afforded lactones in high yields. The catalytic activity of various metal salts has been studied.

Oxidation with molecular oxygen provides an attractive route for the preparation of important synthetic intermediates and oxygen-containing natural products.[1] Several metal catalysts are effective for this purpose and have extensively been studied for alkane oxidations and epoxidations of olefins.[2] *Mukaiyama* et al. found that oxygen transfer from molecular oxygen is readily catalyzed by various metal complexes provided that an aldehyde or an alcohol is present as reductant.[3,4] Studies in several laboratories[5] demonstrated the potential of this metal-catalyzed oxygenation. Two recent communications by *Murahashi* et al., describing the copper-catalyzed oxidation of alkanes and alkenes,[6] and the oxygenation of ketones catalyzed by Fe_2O_3,[7] prompt us to report our results in aerobic oxidative transformations.

During the course of our investigations on oxygen-activation with metal complexes, we tested the ability of several metal salts to catalyze the conversion of ketones to the corresponding lactones (Baeyer-Villiger reaction[8]). Catalytic transformations of this type utilizing molecular oxygen have only been demonstrated in a few cases. These transformations avoid the use of highly oxidized reagents such as peroxides reducing the possibility of side reactions. Nickel(II) complexes coordinated with 1,3-diketones were successfully used by *Mukaiyama* et al.[4] Catalysis by Fe_2O_3 was reported by *Murahashi* and coworkers.[7,9]

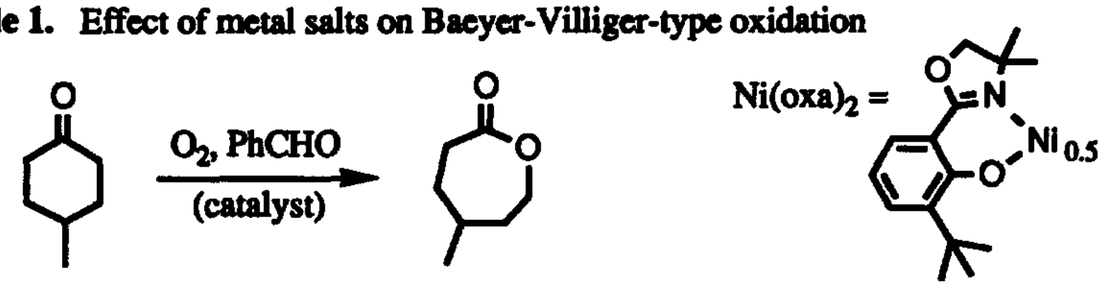


Using the oxygenation of 2-methylcyclohexanone as our model reaction we found several metal salts, in particular copper(II) acetate, to be catalytically highly active. The use of 0.5 mol% of $Cu(OAc)_2 \cdot H_2O$ in the presence of 1.1 equivalents of benzaldehyde afforded the corresponding lactone in 90% yield.[10] Nickel(II) acetate and Ni(II)-naphthenate (3 eq. of aldehyde) also catalyzed this transformation and resulted in the formation of the oxidized product in 80 and 73% yield, respectively. All reactions were performed under an atmospheric pressure of oxygen in 1,2-dichloroethane at room temperature.[11] No ring-opened products were observed.[12] With cobalt(II) and manganese(II) acetate only traces of lactone were formed. Benzyl alcohol, *n*-butanol, and 2-propanol could not be used as reductants [tested with $Ni(OAc)_2{\cdot}4H_2O$]. The addition of water inhibited the catalysis with nickel acetate.

In order to optimize the reaction conditions we next focused on the oxidation of 4-methylcyclohexanone (Table 1). Of major importance was the discovery that *even in the absence of a metal catalyst* the corresponding lactone was formed in high yield.[13,14] Raising the temperature to 40°C, increasing the amount of aldehyde, and use of a sunlamp had positive effects on lactone formation.[15] Thus, by performing the oxidation under an atmospheric pressure of oxygen in the presence of 6 eq. of reductant under light gave 84% of the corresponding lactone. A similar observation had been reported by *Kaneda* et al. in the oxidation of alkenes.[16] In this example the combination of oxygen and an aldehyde resulted in the selective epoxidation of olefins *without* metal catalysts.

The highest yields of lactone were obtained by catalysis with Cu(II)-acetate and $Ni(oxa)_2$.[17] The latter was chosen as a model system for complexes which can easily be obtained in optically active form.[18,19] Reducing the amount of aldehyde to 1 equivalent lowered the product yield. Isovaleraldehyde, which was used as reductant in the nickel catalysis described by *Mukaiyama* et al.[4], was less effective than benzaldehyde and resulted in low conversion of the ketone in the Cu(II)-system (ca. 33%; GC-MS-analysis).

Table 1. Effect of metal salts on Baeyer-Villiger-type oxidation

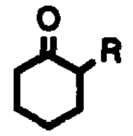
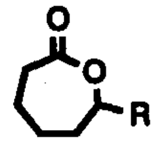
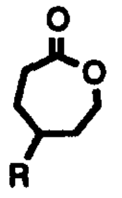
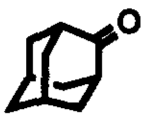
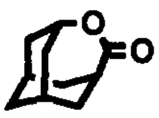
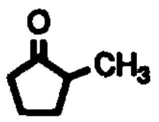
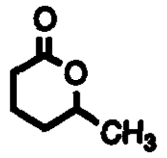
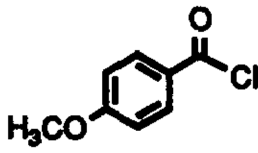
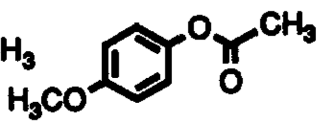


Entry	Catalyst[a)]	(mol%)	Conditions[b)]	Yield (%)
1	$Cu(acetate)_2$	(1)	dark	91
⇨ 2	$Cu(acetate)_2$	(0.2)	dark	94
3	$Cu(acetate)_2$	(1)	dark, 1 eq. PhCHO	65
4	$Ni(acetate)_2$	(1)	dark	84
⇨ 5	$Ni(oxa)_2$	(1)	dark	94
6	—		dark	46
7	—		light	74
⇨ 8	—		light, 6 eq. PhCHO	84
9	—		light, 1 eq. $NaHCO_3$	74
10	—		dark, 40°C[c)]	59
11	—		light, 40°C[c)]	68

[a)] $Cu(OAc)_2{\cdot}H_2O$ and $Ni(OAc)_2{\cdot}4H_2O$ (Fluka) were used. [b)] Unless indicated otherwise: O_2 (1 atm), 3 eq. of PhCHO, r.t., in 1,2-dichloroethane (entry 9: CH_2Cl_2), 21h.[11] [c)] Ketone added to an oxygenated solution of the aldehyde (30 min, 40°C) in 1,2-dichloroethane, 21h.

The oxidation of various cyclic and acyclic ketones was examined applying Cu(II)-acetate and Ni(oxa)$_2$. Representative results are summarized in Table 2.

Table 2. Metal-catalyzed Baeyer-Villiger-type oxidation with molecular oxygen in the presence of benzaldehyde[11]

Entry	Substrate	Product		Yield (%) Cu(acetate)$_2$	Yield (%) Ni(oxa)$_2$
1			R = H		83
2			Me	93 [b]	90 [b]
3			Ph	90	72
4			R = Me	91	74
5			*t*-Bu		76
6				81	91
7				76 [c]	83 [c]
8					40 [b]
9				33	23

[a] Cu(II): 1 mol%, dark; Ni(II): 0.5 mol%. [b] Less than 5% of an isomer were detected. [c] Ratio of regioisomers ca. 6:1 [Cu(II)] and 5:1 [Ni(II)].

With the exception of 2-methylcyclopentanone (entry 8) and cycloheptanone (trace of product) cyclic ketones were readily oxidized and the corresponding lactones were obtained in high yields. In general, good stereoselectivity was observed with the product arrising from preferential migration of the more substituted carbon atom. Oxidation of acyclic ketones proceeded insufficiently and only small amounts of the desired esters were detected by GS-MS (from 5-nonanone) or were isolated in low yield (entry 9).

Synthetic and mechanistic aspects of this valuable transformation are being actively investigated in our laboratory.

Acknowledgement: This research was supported by the Schweizerischen Nationalfonds, the Volkswagen-, and the Ciba-Stiftung. *C.B.* thanks the Freiwillige Akademische Gesellschaft for a Treubel fellowship, *K.W.* is grateful to the Fonds der Basler Chemischen Industrie for a stipend.

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9. For a critical evaluation of transition-metal catalysis for the synthesis of lactones described in patents see ref. 4.
10. The preferential migration of the more substituted center was observed. The minor regioisomer was formed in ≤5% (NMR-analysis).
11. In a typical experiment, the ketone (1 mmol) was added to a suspension of the metal salt (10 µmol, 1 mol%) in 2.5 ml of 1,2-dichloroethane. The reaction flask was flushed with oxygen for 5 min. followed by the addition of benzaldehyde (3 mmol). The reaction mixture was vigorously stirred for 21h at room temperature under an oxygen atmosphere. After diluting with dichloromethane, the mixture was washed with saturated aqueous $NaHCO_3$ and water. Drying over $MgSO_4$ followed by evaporation of the solvent and column chromatography (silica gel, petroleum ether : *tert.*-butylmethyl ether = 5:1) gave the desired lactone.
12. Compare: S. Ito, M. Matsumoto, *J. Org. Chem.* **1983**, *48*, 1135.
13. Prior to use the aldehyde was carefully purified (D. D. Perrin, W. L. F. Amarego, D. R. Perrin, *Purification of Laboratory Chemicals*, 2. ed., Pergamon Press, Oxford, **1980**) and distilled. Washing the reaction flask with 20% nitric acid to remove any traces of metal salts had no influence on product formation.
14. In both the presence and the absence of metal catalyst, benzaldehyde was oxidized to give benzoic acid and phenylformiate (GC- and NMR-analysis).
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(Received in Germany 25 March 1993)