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A Convenient Method for the Preparation of Acetal Carboxylic Acids by Nickel(II) Complex Catalyzed Oxygenation of α-Alkoxy Cyclic Ketones with Molecular Oxygen

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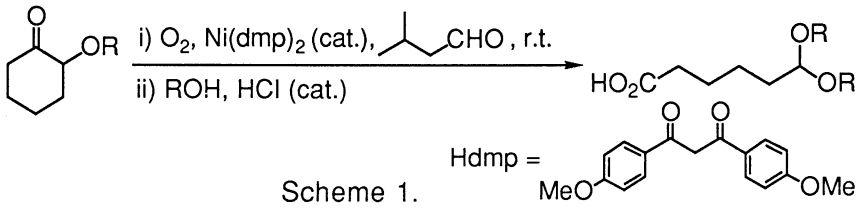
In the presence of a catalytic amount of nickel(II) complex, various α-alkoxy cyclic ketones are smoothly oxygenated into acetal lactones by combined use of molecular oxygen and aldehydes at room temperature under an atmospheric pressure. Successive treatment of formed acetal lactones with hydrogen chloride in alcohols affords the corresponding acetal carboxylic acids in good to quantitative yields.

Selective oxygenation of various organic compounds with molecular oxygen, the abundant oxidant, is one of the most important reactions in organic synthesis. Many research works have been done to develop practical aerobic oxygenation reactions using various transition metal complexes as catalysts. In our previous papers, synthetic methods for the preparation of various types of oxygen-containing compounds from the corresponding olefins using molecular oxygen as an oxidant were developed by choosing suitable combination of transition metal catalysts and organic reductants.[1)]

Oxidation of carbonyl compounds, especially, cyclic ketones, are well known to afford the useful oxygen-containing compounds, such as lactones[2)] or dicarboxylic acids,[3)] and the preparation of lactones from cyclic ketones by the Baeyer-Villiger type oxidation was previously demonstrated by combined use of molecular oxygen and aldehydes in the presence of a catalytic amount of nickel(II) complex.[4)]

In this communication, we would like to describe the convenient oxygenation method for the preparation of acetal carboxylic acids. The oxygenation of α-alkoxy cyclic ketones with combined use of molecular oxygen and aldehydes in the presence of a catalytic amount of nickel(II) complex afforded the corresponding acetal lactones *via* oxygen insertion between carbonyl carbon and α-carbon, and successive treatment with alcohols yielded the corresponding acetal carboxylic acids in good to quantitative yields (Scheme 1).



Scheme 1.

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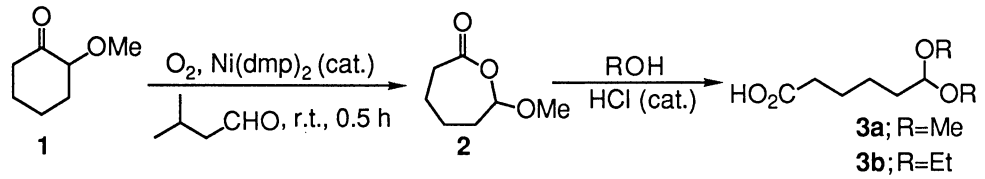
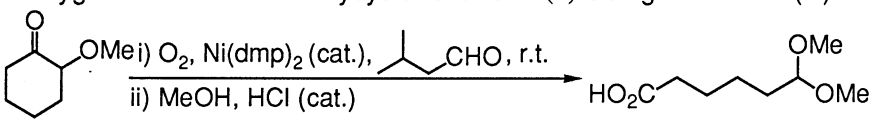
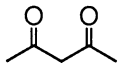
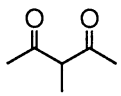
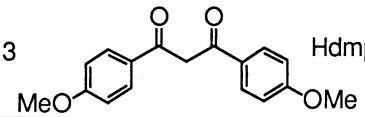


Scheme 2.

In the first place, oxygenation of α-methoxycyclohexanone (**1**) was tried in the presence of isovaleraldehyde and a catalytic amount of bis[1,3-bis(*p*-methoxyphenyl)-1,3-propanedionato]nickel(II) (Ni(dmp)$_2$) in 1,2-dichloroethane under an atmospheric pressure of oxygen at room temperature. α-Methoxycyclohexanone (**1**) was completely consumed after 0.5 h and it was confirmed by GC analysis that 6-methoxy-6-hexanolactone (**2**), acetal lactone,[2,5] was formed in quantitative yield. By the addition of methanol and a catalytic amount of hydrogen chloride into the reaction mixture, 6,6-dimethoxyhexanoic acid (**3a**), acetal carboxylic acid,[6] was obtained in quantitative yield *via* nucleophlic reaction of acetal lactone with methanol. When ethanol was employed as a nucleophile, 6,6-diethoxyhexanoic acid (**3b**) was obtained

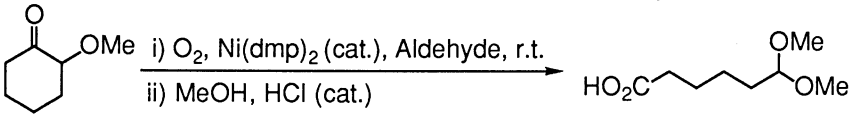
Table 1. Oxygenation of α-Methoxycyclohexanone (**1**) Using Various Ni(II) Complexes[a]



Entry	Ligand (LH)		Conversion /%	Yield /%[b]
1		Hacac	100	84
2		Hmac	100	92
3		Hdmp	100	quant.

a) Reaction conditions; α-methoxycyclohexanone (**1**) 1.0 mmol, nickel(II) complex 1.0 mol%, isovaleraldehyde 3.0 mmol, 1,2-dichloroethane 5.0 ml, r.t., 1 atm O_2, 0.5 h. b) Isolated yield based on starting material.

Table 2. Oxygenation of α-Methoxycyclohexanone (**1**) Using Various Aldehydes[a]



Entry	Aldehyde	Time /h	Conversion /%	Yield /%[b]
1	$(CH_3)_2CHCH_2CHO$	0.5	100	quant.
2	CH_3CH_2CHO	0.5	100	quant.
3	$(CH_3)_2CHCHO$	0.5	100	87
4	$(CH_3)_3CCHO$	1.5	100	90

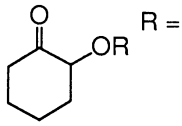
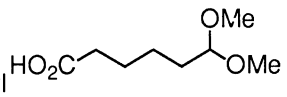
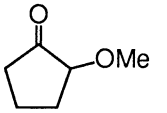
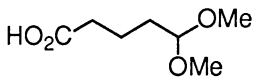
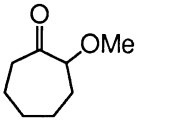
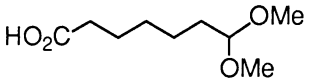
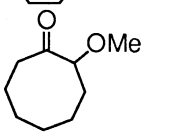
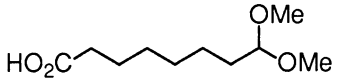
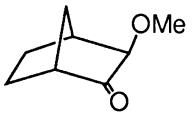
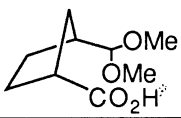
a) Reaction conditions; α-methoxycyclohexanone (**1**) 1.0 mmol, Ni(dmp)$_2$ 1.0 mol%, aldehyde 3.0 mmol, 1,2-dichloroethane 5.0 ml, r.t., 1 atm O_2. b) Isolated yield based on starting material.

in 90% yield as expected. Cyclic acetal carboxylic acid, 6,6-ethylenedioxyhexanoic acid (**3c**), was obtained in 53% yield by employing ethylene glycol (Scheme 2). It was observed that acetal lactone **2** was decomposed by carboxylic acid formed from aldehyde or dicarboxylic acid formed by the over-oxidation during the prolonged reaction time. In order to obtain the acetal lactone **2** without any accompanying by-products, the choice of the adequate reaction time for the oxygenaton of **1** is very important.

In the above reaction, several bis(1,3-diketonato)nickel(II) complexes could be utilized as catalysts (Table 1). Of various ligands screened, nickel(II) complexes coordinated by 1,3-diketones having electron donating substituents, such as Ni(mac)$_2$ or Ni(dmp)$_2$, were found to be effective catalysts to afford 6,6-dimethoxyhexanoic acid (**3a**) in 92% and quantitative yield, respectively, as shown in Entries 2 and 3. Next, several aldehydes were examined by taking the reaction of **1** as a model (Table 2). In the case of employing isovaleraldehyde or propionaldehyde, the acetal carboxylic acid **3a** was obtained in quantitative yield. When aldehydes having secondary or tertiary carbon next to the carbonyl carbon, such as isobutyraldehyde or pivalaldehyde, were employed, **1** was also converted into the acetal carboxylic acid **3a** in 87% or 90% yield, respectively.

The above procedure was successfully applied to the oxidation of various α-alkoxy cyclic ketones as shown in Table 3.[7] Both **1** and α-ethoxycyclohexanone afforded the acetal carboxylic acid **3a** in quantitative yields (Entries 1 and 2). Oxygenation of cyclohexanone having bulky alkoxy group, such as cyclohexyloxy group, at α-position also proceeded to afford the corresponding acetal carboxylic acid **3a** in 62% yield after the treatment with acidic methanol (Entry 3). Various α-methoxy cyclic ketones, such as α-methoxycyclopentanone, α-methoxycycloheptanone, or α-methoxycyclooctanone, were converted into the corresponding acetal carboxylic acids in 91%, 98%, or 53% yield, respectively (Entries 4-6). It is interesting

Table 3. Synthesis of Acetal Carboxylic Acids[a]

Entry	α-Alkoxy cyclic ketone	Acetal carboxylic acid	Yield /%[b]
1	 R = Me		quant.
2	Et		quant.
3	cyclohexyl		62
4			91
5			98
6			53
7			67

a) Reaction conditions; α-alkoxy cyclic ketone 1.0 mmol, Ni(dmp)$_2$ 1.0 mol%, isovaleraldehyde 3.0 mmol, 1,2-dichloroethane 5.0 ml, r.t., 1 atm O_2. b) Isolated yield based on starting material. All products gave satisfactory ^{1}H-NMR and IR spectra.

to point out here that, by the present procedure, even seven or eight membered ring compounds could be smoothly oxygenated, while the aerobic Baeyer-Villiger reaction was not successfully applied to cycloheptanone or cyclooctanone.[4] Cyclopentanecarboxylic acid having acetal group on 3-position could be prepared, when 3-methoxy-2-norbornanone was employed as a starting material (Entry 7).

The typical procedure is described as follows; a mixture of **1** (128 mg, 1.0 mmol), $Ni(dmp)_2$ (6.3 mg, 1.0 mol%), and isovaleraldehyde (258 mg, 3.0 mmol) in 1,2-dichloroethane (5.0 ml) was stirred at room temperature under an atmospheric pressure of oxygen. After 0.5 h, the complete consumption of **1** was confirmed by TLC analysis. Successively, methanol (5.0 ml), and 10% methanol solution of hydrogen chloride (20 mg) was added into the reaction mixture at 0 °C, and stirred at room temperature for 3 h. Then, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/ethyl acetate) to afford the acetal carboxylic acid **3a** (176 mg, quantitative yield).

It is noted that, various α-alkoxy cyclic ketones are effectively converted into the corresponding acetal carboxylic acids *via* C-C bond cleavage between carbonyl carbon and α-carbon in good to quantitative yields by nickel(II) complex catalyzed aerobic oxygenation and successive treatment with acidic alcohol. Thus, the present procedure provides a convenient method for the preparation of acetal carboxylic acids.

References

1) K. Kato, T. Yamada, T. Takai, S. Inoki, and S. Isayama, *Bull. Chem. Soc. Jpn.*, **63**, 179 (1990); T. Yamada, T. Takai, O. Rhode, and T. Mukaiyama, *ibid.*, **64**, 2109 (1991); T. Takai, E. Hata, T. Yamada, T. Mukaiyama, *ibid.*, **64**, 2513 (1991); T. Mukaiyama, T. Yamada, T. Nagata, and K. Imagawa, *Chem. Lett.*, **1993**, 327.

2) G. R. Krow, *Org. React.*, **43**, 251 (1993).

3) It was reported that oxidation of cyclic ketones afforded the corresponding dicarboxylic acids by using several oxidants, such as nitric acid, potassium peroxide, or molecular oxygen and sodium methoxide; E. Boedtker, *J. Pharm. Chim.*, **1932**, 225; M. Lissel and E. V. Dehmlow, *Tetrahedron Lett.*, **1978**, 3689; T. J. Wallace, H. Pobiner, and A. Schriesheim, *J. Org. Chem.*, **30**, 3768 (1965). α-Methylcyclohexanone was also converted into 6-oxoheptanoic acid, ketocarboxylic acid, by molecular oxygen in the presence of a catalytic amount of ferric trichloride; S. Ito and M. Matsumoto, *J. Org. Chem.*, **48**, 1133 (1983).

4) T. Yamada, K. Takahashi, K. Kato, T. Takai, S. Inoki, and T. Mukaiyama, *Chem. Lett.*, **1991**, 641. Recently, aerobic oxygenation of tetrahydrofurans into the corresponding γ-butyrolactones using α-diketone catalyzed by cobalt complex was reported; E. Hata, T. Takai, and T. Mukaiyama, *Chem. Lett.*, **1993**, 1513.

5) Acetal lactones can be prepared by the reaction of α-alkoxy cyclicketones with peroxycarboxylic acid, such as *m*-chloroperbenzoic acid. References are cited in Ref. 2.

6) It was reported that acetal carboxylic acid ester, 6,6-dimethoxyhexanoic acid methyl ester, was obtained by ozonolysis of cyclohexene and appropriate workup procedure; S. L. Schreiber, R. E. Claus, and J. Beagan, *Tetrahedron Lett.*, **23**, 3867 (1982).

7) When α-hydroxycyclohexanone was treated with molecular oxygen in the presence of aldehyde using nickel(II) complex catalyst, adipic acid was directly obtained in 67% yield.

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