Oxovanadium(V)-Induced Ring-Opening Oxygenation of Cyclic Ketones in Alcohol

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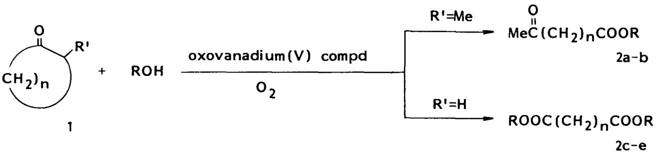
Synopsis. Cyclic ketones underwent ring-opening oxygenation on treatment with $VO(OEt)Cl_2$ in alcohol under oxygen to give the corresponding keto ester or diesters depending on the substituent at 2-position. This system was applicable to a catalytic reaction.

Higher oxidation state species of transition metals induce effective oxidative transformations. Vanadium compounds including oxovanadium ones have been known to be useful in oxidation. Their utilization is, however, limited mostly in acidic water,[1] which reduces the synthetic versatility. We herein describe that oxovanadium(V) ethoxides are sufficiently used in the ring-opening oxygenation reactions of cyclic ketones in alcohol.

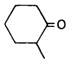
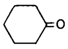
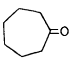
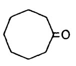
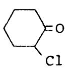
2-Methylcyclohexanone (**1a**) was oxidized to ethyl 6-oxoheptanoate (**2a**) on treatment with the solution of $VO(OEt)_3$ or $VO(OEt)Cl_2$ in ethanol under oxygen. The regioselective bond cleavage between carbonyl carbon and 2-carbon was observed without formation of the regioisomer (Eq. 1). Molecular oxygen was introduced effectively in this system to form the carbonyl function since only a trace amount of the keto ester **2a** was obtained under nitrogen. Reaction in methanol led to the predominant formation of the corresponding methyl ester **2b** with a small amount of **2a**, suggesting that the alkoxyl group is derived from the solvent. The reactivities of vanadium compounds were found to depend on their substituents; $VO(acac)_2$ and $V(acac)_3$ were less active than $VO(OEt)Cl_2$. $VO(OEt)Cl_2$ worked well with cyclohexanone (**1c**) as listed in Table 1, but use of $VO(OEt)_3$ gave a poor yield of diethyl adipate (**2c**) under the same conditions. The similar difference in reactivities was also observed in oxygenation of unsubstituted cyclic ketones such as cycloheptanone (**1d**) and cyclooctanone (**1e**). It is assumed to be due to the high Lewis acidity of $VO(OEt)Cl_2$.



(**1**)

In contrast, substitution with chloro group at 2-position of cyclohexanone resulted in the facile oxidation with either $VO(OEt)_3$ or $VO(OEt)Cl_2$ giving the same diester **2c** as obtained from cyclohexanone (Eq. 2, Table 1).

Table 1. Vanadium-Induced Oxygenation Reactions

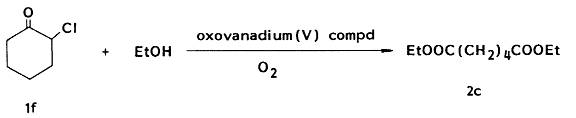
1		Vanadium Compd[a]	ROH, R	Time/h	2	Yield/%
	(**1a**)	$VO(OEt)Cl_2$	Et	3	$Me\overset{O}{\overset{\|}{C}}(CH_2)_4COOEt$ (**2a**)	52
1a		$VO(OEt)Cl_2$	Et	3[b]	**2a**	3
1a		$VO(OEt)_3$	Et	22	**2a**	50
1a		$VO(OEt)_3$	Me	30	$Me\overset{O}{\overset{\|}{C}}(CH_2)_4COOMe$ (**2b**)	60[c]
1a		$VO(acac)_2$	Et	30	**2a**	30
1a		$V(acac)_3$	Et	30	**2a**	19
	(**1c**)	$VO(OEt)Cl_2$[d]	Et	30	$EtOOC(CH_2)_4COOEt$ (**2c**)	64
1c		$VO(OEt)_3$	Et	30	**2c**	3
	(**1d**)	$VO(OEt)Cl_2$	Et	30	$EtOOC(CH_2)_5COOEt$ (**2d**)	40
1d		$VO(OEt)_3$	Et	30	**2d**	Trace
	(**1e**)	$VO(OEt)Cl_2$	Et	20	$EtOOC(CH_2)_6COOEt$ (**2e**)	35
1e		$VO(OEt)_3$	Et	11	**2e**	0
	(**1f**)	$VO(OEt)Cl_2$	Et	3	**2a**	46
1f		$VO(OEt)_3$	Et	11	**2a**	57

a) Vanadium compound (1.0 equiv) was used unless otherwise stated. b) Reaction was carried out under nitrogen. c) The keto ester **2a** was obtained in 7% yield. d) $VO(OEt)Cl_2$ (1.25 equiv) was used.

Table 2. Oxovanadium(V)-Catalyzed Oxygenation Reactions[a)]

1	Oxovanadium Compd/equiv		Time/h	**2**	Yield/%
1a	$VO(OEt)Cl_2$	0.2	10	**2a**	50
1a	$VO(OEt)Cl_2$	0.05	30	**2a**	53
1a	$VO(OEt)_3$	0.2	11	**2a**	3
1c	$VO(OEt)Cl_2$	0.2	60	**2c**	30
1f	$VO(OEt)Cl_2$	0.2	10	**2c**	52

a) Reactions were carried out in ethanol.



(2)

Another interesting feature should be noted that a catalytic system was achieved by use of $VO(OEt)Cl_2$ under oxygen (Eq. 3). Some results are summarized in Table 2, showing that 0.05 mol equiv of $VO(OEt)Cl_2$ were enough for the oxygenation reaction. An active oxovanadium species seems to be regenerated in situ. With $VO(OEt)_3$ employed, however, such a catalytic cycle was not observed under the similar conditions.

$$1 + \mathrm{EtOH} \xrightarrow[O_2]{\text{cat. } VO(OEt)Cl_2} 2 \qquad (3)$$

Although the reaction mechanism has not been elucidated yet, one of the plausible paths is figured out as follows. Oxovanadium(V) ethoxide is assumed to work as a Lewis acid to generate the thermodynamically stable enolate, which is considerd to undergo the similar oxygenation reaction as reported.[1,2)]

The chemistry of transition metal enolates recently draws much attention because it has been scarcely explored despite valuable intermediates in organic syntheses.[3)] Considering oxovanadium(V) ethoxides as Lewis acids with oxidation ability, the above-mentioned ring-opening oxygenation reaction is considered to present such an example.

Experimental

^{1}H NMR spectra were measured on JEOL JNM-FX90Q spectrometer; IR spectra were measured using Hitachi 270-30 spectrometer. Mass spectra were determined by the electron impact method on Hitachi RMV-6E. $VO(OEt)Cl_2$ was prepared from $VOCl_3$ and an equimolar amount of ethanol with bubbling nitrogen into the hexane solution at room temperature and distilled under the reduced pressure (bp 36—38 °C/1 mmHg[†]). $VO(OEt)_3$ was supplied from Shinko Chemical Co., Ltd. Ketones and alcohols were purified according to usual methods.

The Representative Procedure for the Oxovanadium(V)-Induced Oxygenation Reaction of 1. To a solution of 2-methylcyclohexanone (**1a**, 0.224 g, 2.0 mmol) in ethanol (2 mL) was added $VO(OEt)Cl_2$ (0.366 g, 2.0 mmol) at room temperature. The mixture was stirred at reflux under oxygen (1 atm, gasbag) for 3 h. Saturated aqueous $NaHCO_3$ solution (30 mL) was added to the resultant mixture, which was extracted with ether (5×30 mL). The combined ethereal solution was washed with saturated aqueous NH_4Cl solution (10 mL) and then water (10 mL), dried over Na_2SO_4, and concentrated. The yield of ethyl 6-oxoheptanoate (**2a**) was determined by GLC (52% yield, PEG 20M 10%, 2.1 m column, 200 °C). If necessary, the residue was chromatographed on silica-gel column to give **2a**. The reactions of other cyclic ketones and 2-chlorocyclohexanone (**1f**) were carried out in the similar way as mentioned above. The reaction conditions are listed in Table 1. These products were identified by comparison of spectral data with those of the authentic samples.[4)]

The Oxovanadium(V)-Catalyzed Oxygenation Reaction of 1. The amount of $VO(OEt)Cl_2$ was reduced in the catalytic reactions as shown in Table 2. The procedure is similar as described in the stoichiometric reactions.

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References

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2) S. Ito and M. Matsumoto, *J. Org. Chem.*, **48**, 1133 (1984) and references cited therein.

3) T. Hirao, S. Nagata, and T. Agawa, *Tetrahedron Lett.*, **26**, 5795 (1985) and references cited therein.

4) H. Mckennis, Jr. and V. du Vigneaud, *J. Am. Chem. Soc.*, **68**, 832 (1946); A. Müller, *Org. Synth.*, Coll. Vol. II, 535 (1943).

[†] 1 mm Hg=133.322 Pa.