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NOVEL ALLYLIC OXIDATION OF CONJUGATE KETONES WITH $VO(OR)Cl_2$

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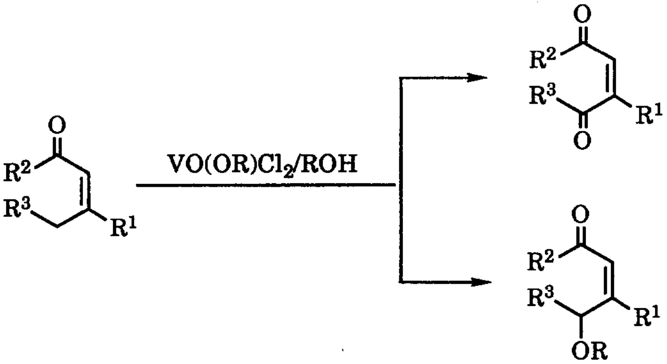
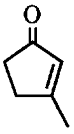
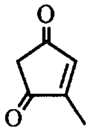
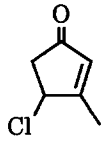
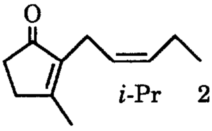
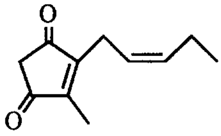
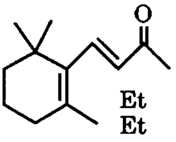
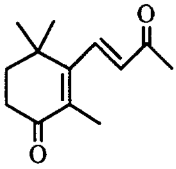
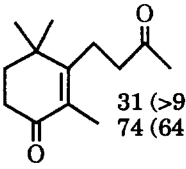
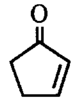
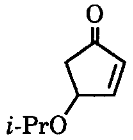
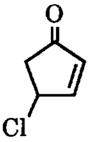
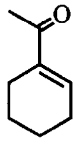
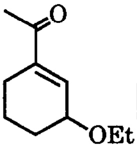
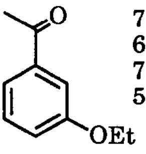
Summary: An oxo group is introduced at the allylic position of 3-methyl-2-cyclopenten-1-one and β-ionone on treatment with $VO(OR)Cl_2$ in ROH. $VO(OR)Cl_2$ induces γ-alkoxylation in the case of 2-cyclopenten-1-one. Reaction of 1-acetyl-1-cyclohexene with $VO(OEt)Cl_2$ results in γ-alkoxylation and/or aromatization to give 1-acetyl-3-ethoxy-1-cyclohexene and the corresponding aromatic.

Oxidative introduction of a functional group provides a versatile tool in synthetic elaboration. A variety of methods have been developed especially by use of transition metal-mediated redox process.[1] Oxygenation or alkoxylation is of importance,[2] but only few methods have been reported for such direct oxidative transformations.[3] Pentavalent vanadium compounds induce oxidation reactions via one-electron transfer.[4] The synthetic demerit that reactions are mostly carried out in acidic aqueous media is solved by employment of readily available $VO(OR)Cl_2$. This oxovanadium compound has been disclosed to be a Lewis acid with oxidative capability to achieve ring-opening oxygenation of alicyclic ketones,[5] dehydrogenative aromatization of α,β-unsaturated cyclohexenones,[6] and oxidative deamination of α-amino acid.[7] We herein report a novel allylic oxidation of conjugate ketones that is induced by $VO(OR)Cl_2$.



An oxo group was introduced regioselectively at γ-position of 3-methyl-2-cyclopenten-1-one (**1a**) on treatment with $VO(OR)Cl_2$ to give 3-methyl-2-cyclopenten-1,4-dione (**2a**).[8] $VO(OPr\text{-}i)Cl_2$ worked better than $VO(OEt)Cl_2$ for this oxidation as shown in Table 1. Running the reaction with 2 equiv of $VO(OPr\text{-}i)Cl_2$ under oxygen was required for a higher yield of **2a**. The

Table 1. VO(OR)Cl_2-induced allylic oxidation of conjugate ketones

ketone	VO(OR)Cl_2 R	equiv	solvent	atmos-phere	reaction conditions[a]	products	yield, %
 **1a**	Et	2	EtOH-CH_2Cl_2[b]	O_2	0 °C 3 h, rt 5h	 **2a**  **3a**	50 (54:46)
	Et	5	EtOH-CH_2Cl_2[b]	N_2	0 °C 5 h		46 (<2:>98)
	i-Pr	2	*i*-PrOH	O_2	0 °C 3 h, rt 5h		40 (>98:<2)
	i-Pr	2	*i*-PrOH	O_2	0 °C 5 h		18 (78:22)
	i-Pr	2	*i*-PrOH	N_2	0 °C 3 h, rt 5h		26 (31:69)
 **1b**	*i*-Pr	2	*i*-PrOH	O_2	0 °C 3 h, rt 5h	 **2b**	20
 **1c**	Et	3	EtOH	O_2	80 °C 5 h	 **2c**  **4c**	31 (>98:<2)
	Et	3	EtOH	N_2	80 °C 5 h		74 (64:36)
 **1d**	*i*-Pr	5	*i*-PrOH-CH_2Cl_2[b]	N_2	0 °C 3 h, rt 5h	 **2d**  **3d**	67 (>98:<2)
	i-Pr	5	*i*-PrOH	O_2	0 °C 3 h, rt 5h		21 (33:67)
 **1e**	Et	2	EtOH	O_2	80 °C 5 h	 **2e**  **5e**	73 (79:21)
	Et	2	EtOH	N_2	80 °C 5 h		60 (82:18)
	Et	3	EtOH	O_2	80 °C 5 h		70 (64:36)
	Et	5	EtOH	O_2	80 °C 5 h		54 (30:70)

[a] rt: room temperature. [b] 10 equiv of ROH was used.

γ-chlorinated ketone **3a** was formed with the yield decrease of **2a** in the reaction under nitrogen. Chlorination also occurred when the mixture was quenched at 0 °C. Thus, use of 5 equiv of $VO(OEt)Cl_2$ under nitrogen resulted in the selective formation of **3a**.

The similar oxygenation reaction of *cis*-jasmone (**1b**) also proceeded with an olefinic moiety intact. The present method is applicable to oxygenation of cyclic olefin bearing an external conjugate carbonyl group. The $VO(OEt)Cl_2$-induced introduction of an oxo group to β-ionone (**1c**) at ε-position was observed to produce the corresponding diketone **2c** although the reaction temperature was elevated. The reaction under nitrogen gave a considerable amount of the reduced diketone **4c** as a by-product, suggesting that **2c** could serve as an hydrogen acceptor.

Contrary to these observations, alkoxylation is a reaction course when 2-cyclopenten-1-one (**1d**) was treated with $VO(OPr\text{-}i)Cl_2$ and 2-propanol under nitrogen. 4-Isopropoxy-2-cyclopenten-1-one (**2d**) was obtained without formation of 2-cyclopentene-1,4-dione. Use of 5 equiv of $VO(OPr\text{-}i)Cl_2$ led to a good yield of **2d**. The reaction under oxygen decreased the yield of **2d** in contrast to the above-mentioned oxygenation of **1a**. $VO(OEt)Cl_2$ in ethanol was found to be less effective.

1-Acetyl-1-cyclohexene (**1e**) also underwent γ-alkoxylation to give 1-acetyl-3-ethoxy-1-cyclohexene (**2e**). It should be noted that the alkoxylation reaction was accompanied by aromatization to 1-acetyl-3-ethoxybenzene (**5e**). The latter formation seems to be due to dehydrogenative oxidation with $VO(OEt)Cl_2$.[6] The **5e**/**2e** ratio was raised with the increased amount of $VO(OEt)Cl_2$.

These allylic oxidation reactions provide a versatile method for direct oxygenation or alkoxylation. The reaction mechanism has not been clarified yet because the mixture contained a paramagnetic species as an intermediate. One of the plausible paths is explained as follows. Considering $VO(OR)Cl_2$ as a Lewis acid,[6] the dienolate seems to be involved at an initial step. One-electron oxidation with $VO(OR)Cl_2$ generates a radical intermediate, which is considered to play an important role in the carbon-oxygen bond formation as reported in the NH_4VO_3-induced hydroxylation.[9] The reaction course to oxygenation[10] or alkoxylation is assumed to depend on the sterically demanding difference at γ-position. Further investigation is now in progress.

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7. Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1990**, *31*, 3917.
8. A representative reaction procedure is as follows. To a solution of 3-methyl-2-cyclopenten-1-one (**1a**, 1.0 mmol) in 2-propanol (10 mmol) was added VO(OPr-*i*)Cl_2 (2.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h and at room temperature for 5 h. Ether (10 mL) and 5% aqueous HCl (2 mL) were added to the reaction mixture. The aqueous layer was extracted with ether. The combined ethereal layers were washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and concentrated. Preparative TLC eluted with ethyl acetate gave **2a**. The yield was determined by glc (1.8 m 10% PEG 20M column, 160 °C) based on **1a** as shown in Table 1.
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10. Introduction of an oxo group at γ-position is presumably explained by one of the following paths; (i) the direct reaction of the oxovanadium dienolate or the corresponding radical intermediate with molecular oxygen, (ii) rearrangement[11] of the oxovanadium dienolate followed by oxidation, (iii) double alkoxylation followed by hydrolysis, or (iv) alkoxylation followed by dehydrogenation and hydrolysis.
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