The Oxidation of β-Alkoxycyclopentenones and β-Alkoxycyclohexenones to α′-Acyloxy Derivatives Using Manganese(III) Acetate in Combination with Carboxylic Acids

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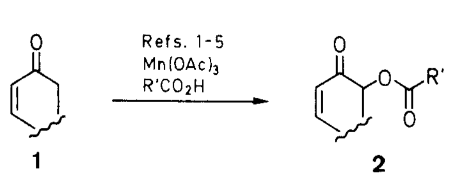
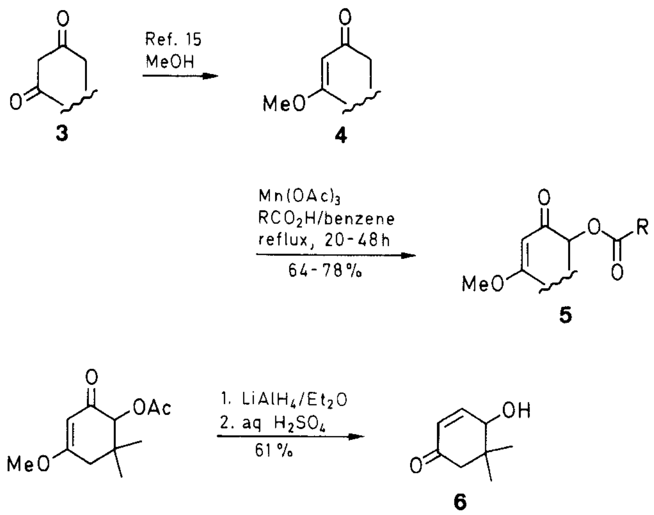
The α′-oxidation of cyclic derivatives of β-alkoxy-α,β-unsaturated ketones using manganese(III) acetate in the presence of various carboxylic acids provided a convenient synthesis of 5-acyloxy-3-alkoxy-2-cyclopentenones and 6-acyloxy-3-alkoxy-2-cyclohexenones.

The oxidation[1-4] of α,β-unsaturated ketones **1** with manganese(III) acetate provided an efficient synthesis of α′-acetoxy-α,β-unsaturated ketones **2** (R′ = CH_3), and the oxidation[5] of **1** using manganese(III) acetate in the presence of an excess of a manganese(II) carboxylate or a carboxylic acid provided a general synthesis of α′-acyloxy-α,β-unsaturated ketones **2** (Scheme **A**). We report here on the extension of the latter oxidation process to cyclic β-alkoxy-α,β-unsaturated ketones **4**, which exhibits the same regiochemical preference for oxidation at the α′-position to afford the α′-acyloxy-β-alkoxy-α,β-unsaturated ketones **5** in good yield (Scheme **B**). These α′-acyloxy-β-alkoxy-α,β-unsaturated ketones **5** are useful intermediates in the synthesis of natural products,[6-14] and general procedures for the synthesis of **5** are either not available or involve multiple steps.



Scheme **A**

The conversion of cyclic β-diketones **3** to the β-alkoxy-α,β-unsaturated ketones **4**[15] and the oxidation of **4** using six equivalents of manganese(III) acetate[16] in combination with twelve equivalents of a carboxylic acid led to the α′-acyloxy-α,β-unsaturated ketones **5** in good yield (Table). As in previous studies,[5] the use of manganese(III) carboxylates other than manganese(III) acetate as the sole oxididant was not successful, suggesting that an initial reaction between the manganese(III) acetate and the carboxylic acid led to an active "mixed" manganese(III) complex having both acetate and other carboxylate ligands. The interaction of the enol or enolate of **4** with this mixed manganese(III) complex presumably furnished the desired product **5**. Since the reduction and hydrolysis of α-acyloxy-β-alkoxy-α,β-unsaturated ketones **5** provided access to γ-hydroxy-α,β-unsaturated ketones as exemplified in the case of 5,5-dimethyl-4-hydroxy-2-cyclohexenone (**6**) (Scheme **B**), this process extended the utility of the manganese(III) oxidation procedure to the oxidation of α,β-unsaturated ketones at either the α′- or γ-positions.



Scheme **B**

All reagents were of commercial quality, and reagent quality solvents were used without further purification. 1,3-Cyclopentanedione (**1a**) and 1,3-cyclohexanedione (**1b**) were purchased from Aldrich Chemical Co. IR spectra were determined on a Philips model PU9700 spectrometer. ^{1}H-NMR spectra were determined on a Bruker AC 80 MHz FT spectrometer. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Elemental analyses were performed at the Middle Eastern Technical University Analysis Center.

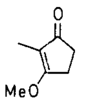
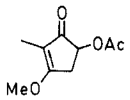
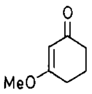
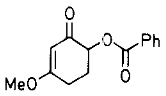
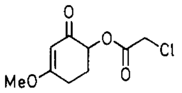
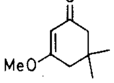
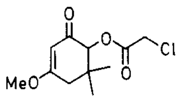
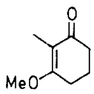
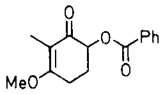
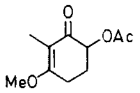
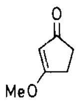
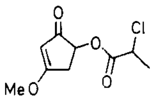
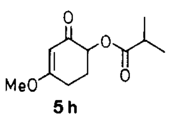
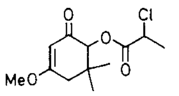
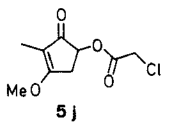
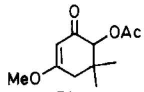
α-Acyloxy-β-alkoxy-α,β-unsaturated ketones 5; General Procedure: A mixture of $Mn(OAc)_3$ (2.68 g, 10 mmol) and a carboxylic acid (30 mmol, Table) in benzene (50 mL) is refluxed for 45 min using a

Dean-Stark apparatus. The mixture is cooled to 25 °C, and β-alkoxy-α,β-unsaturated ketone **4**[15] (2.5 mmol) is added. The mixture is refluxed until the dark brown color disappears (20–48 h). The mixture is cooled to 25 °C, diluted with EtOAc, washed successively with 1 N HCl, sat. $NaHCO_3$ solution, brine, and dried ($MgSO_4$). The crude product is purified by preparative TLC (Merck silica gel F-254 plates, 20 × 20 cm) (Table).

5,5-Dimethyl-4-hydroxy-2-cyclohexenone (6):

To a suspension of $LiAlH_4$ (112 mg, 3 mmol) in anhydrous Et_2O (20 mL) is added 6-acetoxy-5,5-dimethyl-3-methoxy-2-cyclohexenone (1.06 g, 5 mmol) at 25 °C over 30 min. The mixture is refluxed for 2 h, cooled to 0 °C and quenched with water (5 mL) and 10 % aq H_2SO_4 (50 mL). After stirring for 2 h, the organic phase is separated, washed successively with sat. $NaHCO_3$ solution

Table. α′-Acyloxy-α,β-unsaturated Ketones **5** Prepared

Reactants: 4	Reactants: Carboxylic Acid	Reaction Time (h)	Product	Yield (%)	mp (°C)	Molecular Formula[a]	IR (film/KBr) ν (cm⁻¹)	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
 **4a**	none	48	 **5a**	65	oil	$C_9H_{12}O_4$ (184.2)	1730, 1650, 1610	1.52 (s, 3H, CH_3), 2.20 (s, 3H, $COCH_3$), 1.92–2.01 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 5.8 (dd, 1H, J = 6.2, 13.1, CH)
 **4b**	$PhCO_2H$	46	 **5b**	72	oil	$C_{14}H_{14}O_4$ (246.3)	1740, 1650, 1610, 1600	1.71–2.79 (m, 4H, CH_2), 3.62 (s, 3H, OCH_3), 5.41 (s, 1H, H-2), 5.8 (m, 1H, H-6), 7.41–7.72, 7.88–8.31 (m, 5H_{arom})
4b	$ClCH_2CO_2H$	20	 **5c**	70	oil	$C_9H_{11}ClO_4$ (218.6)	1720, 1660, 1610	1.68–2.71 (m, 4H, CH_2), 3.69 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2Cl), 5.42 (s, 1H, H-2), 5.85 (m, 1H, H-6)
 **4c**	$ClCH_2CO_2H$	28	 **5d**	78	69–73	$C_{11}H_{15}ClO_4$ (246.7)	1740, 1660, 1600	1.26, 1.31 (2s, 6H, CH_3), 2.45 (s, 2H, CH_2), 3.65 (s, 3H, OCH_3), 5.42 (s, 1H, H-2), 5.63 (s, 1H, H-6)
 **4d**	$PhCO_2H$	30	 **5e**	78	oil	$C_{15}H_{16}O_4$ (260.3)	1740, 1650, 1600	2.12 (s, 3H, CH_3), 1.78–2.30 (m, 4H, CH_2), 3.66 (s, 3H, OCH_3), 5.62 (m, 1H, H-6), 7.35–7.55, 7.81–8.25 (m, 5H_{arom})
4d	none	26	 **5f**	75	oil	$C_{10}H_{14}O_4$ (198.2)	1730, 1640, 1600	1.61 (s, 3H, CH_3), 2.12 (s, 3H, $COCH_3$), 1.78–2.21 (m, 4H, CH_2), 3.68 (s, 3H, OCH_3), 5.72 (m, 1H, H-6)
 **4e**	MeCH(Cl)CO_2H	30	 **5g**	66	88–89.5	$C_9H_{11}ClO_4$ (218.64)	1780, 1700, 1610	1.72 (d, 3H, J = 7.1, $CHCH_3$), 2.39–2.41 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.25 (q, 1H, J = 6.7, C$\underline{H}CH_3$), 5.20 (s, 1H, H-2), 5.75 (dd, 1H, J = 5.9, 13.4, H-5)
4b	Me_2CHCO_2H	32	 **5h**	68	oil	$C_{11}H_{16}O_4$ (212.3)	1760, 1680, 1620	1.15 [d, 6H, J = 6.2, CH(C$\underline{H}_3)_2$], 1.76–2.61 [m, 5H, CH_2 + C$\underline{H}(CH_3)_2$], 3.68 (s, 3H, OCH_3), 5.25 (m, 1H, H-6), 5.42 (s, 1H, H-2)
4c	MeCHClCO_2H	24	 **5i**	71	oil	$C_{12}H_{17}ClO_4$ (260.7)	1770, 1680, 1610	1.26, 1.32 (2s, 6H, CH_3), 1.74 (d, 3H, J = 6.9, CHC$\underline{H}_3$), 2.25 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.43 (q, 1H, J = 6.8, C$\underline{H}CH_3$), 5.51 (s, 1H, H-6), 5.85 (s, 1H, H-2)
4a	$ClCH_2CO_2H$	30	 **5j**	64	oil	$C_9H_{11}ClO_4$ (218.6)	1770, 1670, 1610	2.15 (s, 3H, CH_3), 2.38–2.41 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.48 (s, 2H, CH_2Cl), 5.58 (dd, 1H, J = 6.1, 13.8, H-5)
4c	none	48	 **5k**	74	oil	$C_{11}H_{16}O_4$ (212.2)	1735, 1640, 1605	1.27, 1.33 (2s, 6H, CH_3), 2.14 (s, 3H, $COCH_3$), 2.43 (s, 2H, CH_2), 3.63 (s, 3H, OCH_3), 5.14 (s, 1H, H-2), 5.61 (s, 1H, H-6)

[a] Satisfactory microanalyses obtained: C ± 0.4, H ± 0.35.

(20 mL), brine, and dried ($MgSO_4$). Evaporation of solvent affords **6** as an oil; yield: 427 mg (61 %).

$C_8H_{12}O_2$	calc.	C 68.55	H 8.68
(140.2)	found	68.72	8.39

IR (film): $\nu = 3620, 1685, 1645\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$): $\delta = 1.05, 1.11$ (2 s, 6 H, CH_3), 2.12 (s, 2 H, CH_2), 3.61 (s, 1 H, OH, exchangeable with D_2O), 4.31–4.38 (m, 1 H, C<u>H</u>OH), 5.85 (d, 1 H, $J = 10$ Hz, H-2), 6.65–6.91 (m, 1 H, H-3).

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