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Manganese(III) acetate based selective oxidation of the tertiary α′-position on various cyclic α,β-unsaturated ketones

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Abstract—We describe the preliminary results of manganese(III) acetate based selective oxidation of various α′-methyl 2-cyclohexenone and 2-cyclopentenone derivatives to afford the corresponding α′-acetoxy-α′-methyl substituted oxidation products in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

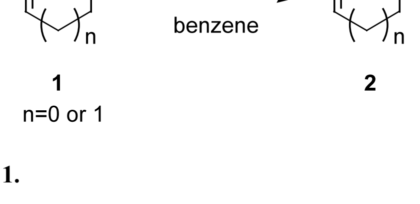
Synthetic methods for the selective oxidation of common functional groups possess a central position in the synthesis of various complex natural products. In particular, α′-hydroxy-α,β-unsaturated cyclic ketones are appealing synthons.[1] In 1976, Williams and Hunter reported that the manganese(III) acetate oxidation of enones affords modest yields of α′-acetoxy enones.[2] Watt et al. reinvestigated this procedure and obtained acceptable yields of the desired α′-acetoxy enones.[3–6] So far, studies on the selective oxidation of cyclic enones in the literature have been concerned with substrates that are unsubstituted at the α′-positions except for one example of a steroidal substrate involving a tertiary α′-position. In this exceptional study, Ahmad et al. reported that they obtained unexpected products other than α′-acetoxyenones with very low yields.[7] However, various naturally occuring compounds such as esters of phorbol and ingenol possess an α′-*tert*-hydroxy-α,β-unsaturated cyclic ketone moiety in their structures.[8] The lack of a selective oxidation method for the α′-*tert*-position of α,β-unsaturated cyclic ketones prompted us toward the development of a new method. In connection with our synthetic studies with manganese(III) acetate,[9–12] we attempted to prepare α′-acetoxy-α′-methyl substituted α,β-unsaturated cyclic ketones via a $Mn(OAc)_3$ acetoxylation method. We describe herein the results obtained from the $Mn(OAc)_3$ oxidation of various α′-methyl α,β-unsaturated cyclic ketones and optimization of the reaction conditions.

2. Results and discussion

α′-Methyl α,β-unsaturated cyclic ketones **1** were prepared from the corresponding α,β-unsaturated cyclic ketones using slightly modified literature procedures[13] and allowed to react with $Mn(OAc)_3$. α′-Methyl α,β-unsaturated cyclic ketones **1** (with benzene as the solvent) underwent a selective oxidation with $Mn(OAc)_3$ to afford products **2**. Characterization of the products revealed the introduction of an acetoxy moiety at the α′-position (Scheme 1). The results are summarized in Table 1.

The reaction presumably proceeds via the formation of the Mn(III) enolate **3**, which loses Mn(II) upon one-electron oxidation to give the α′-keto radical **4**[15] (Scheme 2). The resultant tertiary radical **4** is prone to further oxidation by another equivalent of $Mn(OAc)_3$. The final oxidation step provides α′-acetoxy α′-methyl α,β-unsaturated ketones **2**.

In the next step of this study, 3,6-dimethyl-2-cyclohexenone was chosen as a model compound. The $Mn(OAc)_3$ oxidation was performed in nitrobenzene



Scheme 1.

Keywords: enones; manganese and compounds; oxidation.

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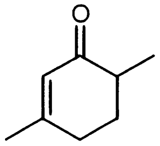
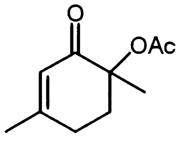
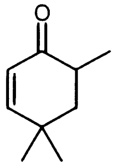
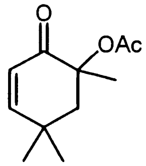
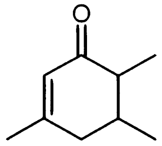
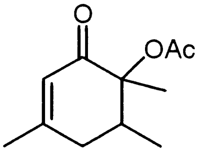
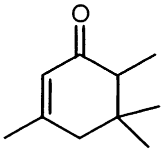
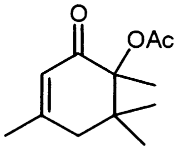
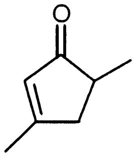
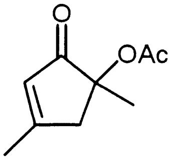
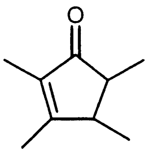
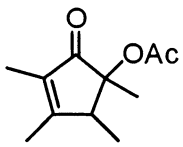
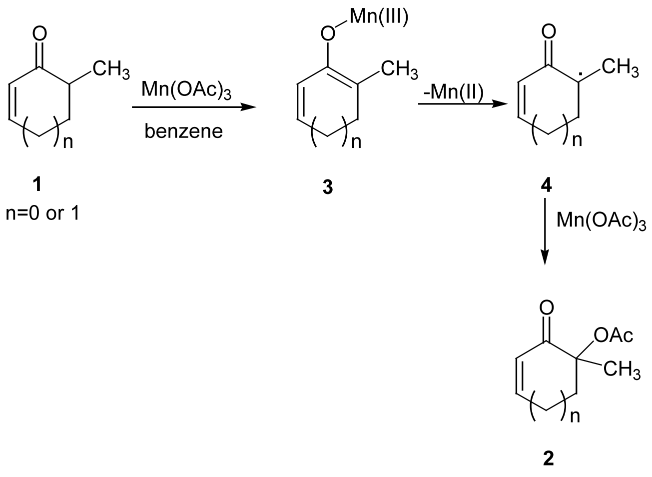
Table 1. Selective oxidation of α′-methyl α,β-unsaturated ketones with $Mn(OAc)_3$ in benzene

Reactant	Product[14]	Yield (%)	Time (h)
		64	10
		78	10
 *cis*/*trans*=1:1	 *cis*/*trans*=3:7	81	12
		76	10
		72	8
 *cis*/*trans*=8:2	 *cis*/*trans*=1:9	68	8



Scheme 2.

which was used to examine the effect of a radical scavenger on the reaction propagation. As expected from the proposed reaction mechanism, no formation of product **2** was observed.

In conclusion, an exciting and synthetically valuable $Mn(OAc)_3$ based oxidation is demonstrated. The applicability of this one-pot oxidation method is attractive for further use in synthesis.

3. Experimental

^1H NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX 400 spectrometers. Chemical shifts are given in ppm from tetramethylsilane. IR spectra were obtained using a Perkin–Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Mass spectra were recorded with a Varian MAT 212.

3.1. General procedure for the $Mn(OAc)_3$ oxidation of β-alkoxy α,β-unsaturated ketones 2

A mixture of $Mn(OAc)_3$ (3.25 g, 14.0 mmol) in benzene (or corresponding solvent) (150 ml) was refluxed for 45 min using a Dean–Stark trap. Then the mixture was cooled to room temperature and the α′-methyl α,β-unsaturated ketone (7.0 mmol) was gradually added. The mixture was allowed to reflux until the dark brown color disappeared and also monitored by TLC. The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase was washed with 1N HCl followed by saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent to afford the product.

3.1.1. $Mn(OAc)_3$ oxidation of 3,5,5,6-tetramethyl-2-cyclohexenone in benzene. $C_{12}H_{18}O_3$ (1.12 g, 76% yield). ^1H NMR: δ 0.79 (s, 3H), 1.02 (s, 3H), 1.36 (s, 3H), 1.77 (s, 3H), 1.79 (d, 1H, $J=18$ Hz), 1.90 (s, 3H), 2.45 (d, 1H, $J=18$ Hz), 5.71 (s, 1H). ^{13}C NMR: δ 16.0, 23.7, 24.8, 26.1, 26.2, 42.8, 46.5, 87.7, 125.5, 158.4, 172.0, 199.1. IR (neat): 1737, 1686 cm^{-1}. MS m/e 210 (2), 150 (28), 128 (28), 86 (100), 82 (32). HRMS (observed): 210.1255, (calculated): 210.1256.

Acknowledgements

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