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Mn(III) acetate-mediated regioselective benzylation of various α , β -unsaturated and β -alkoxy- α , β -unsaturated ketones

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Abstract—We describe herein the results of manganese(III) acetate mediated α' -benzylation of various α,β -unsaturated and β -alkoxy- α,β -unsaturated ketones in moderate yields.

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1. Introduction

The major problem in designing and synthesising complex molecules is the development of reactions which emphasise chemo-, regio-, and stereoselectivity. In defining strategies and reactions to construct complex molecules, regioselectivity is required.¹ Base-induced benzylation plays an important role in the synthesis of some natural compounds, e.g. terpenoids² and the lycorine alkaloid family.³ A wide variety of benzylation reactions are well known in the literature as useful methods for carbon-carbon bond formation, i.e. baseinduced benzylation of ketones⁴ and conversion of α benzyl ketones to α' -benzyl α,β -unsaturated ketones via organoselenium chemistry.5,6 In these studies, the control of regioselectivity is difficult because of the high reaction temperatures required.⁵ Furthermore, the structures of the substrates are limited⁵ and usually high yields of O-benzylated products are obtained when the substrates are β -alkoxy α , β -unsaturated ketones.⁷ These problems encountered during the synthesis of various α' -benzyl α,β -unsaturated ketones prompted us towards the development a new method for the direct benzylation of α,β -unsaturated ketones and β -alkoxy α,β -unsaturated ketones. From our earlier studies, we found that trapping α' -keto radicals obtained from β -alkoxy α , β -unsaturated ketones by benzene,⁸ used as a solvent, is much faster than acetoxylation, affording good yields of tandem oxidation products⁹ and also the direct allylation of various α, β -unsaturated ketones gives good yields of α' -allylated products.¹⁰ We describe herein the results obtained from the Mn(OAc)₃-medi-

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ated α' -benzylation of various α,β -unsaturated ketones and β -alkoxy α,β -unsaturated ketones and the optimisation of the reaction conditions.

2. Results and discussion

As a starting point, we studied the use of manganese(III) acetate as a potential mediator for metal proregioselective α' -benzylation moted of 3-methyl-2-cyclopentenone 1b chosen as a model compound. Reaction of 1b in benzene with 2 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv. of benzyl bromide for 9 h at reflux afforded a 65% yield of 5-benzyl-3-methyl-2cyclopentenone **2b** (Scheme 1). No α' -acetoxylation was observed. In order to increase the yield of the reaction, 3 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ was used, however, the isolated yield of the benzylation product was drastically decreased to 51% and 12% of the α' -acetoxylation product was isolated. Changing the amount of $Mn(OAc)_3 \cdot 2H_2O$ to 1 equiv. decreased the yield of the benzylation product (59%) and no α' -acetoxylation product was observed. Subsequently, a variety of cyclopentenones and cyclohexenones were tested with this metal-mediated benzylation method and selected examples are listed in Table 1.



Scheme 1.

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Table 1. $\alpha'\text{-Benzylation of }\alpha,\beta\text{-unsaturated ketones mediated by }Mn(OAc)_3$





Scheme 2.

As a natural extension of this study, we pursued a complementary investigation aimed at subjecting various β -alkoxy α , β -unsaturated ketones to this reaction. When 3-ethoxycyclohex-2-enone **3c** was stirred with 2 equiv. of Mn(OAc)₃·2H₂O and 1 equiv. of benzyl bromide in benzene for 14 h at reflux, a 42% yield of 6-benzyl-3-ethoxycyclohex-2-enone **4c** was isolated. Subsequently, unsubstituted 3-ethoxycyclopent-2-enone **3a** and 3-ethoxy-2-methylcyclopent-2-enone **3b** were tested with this metal-mediated benzylation method (Scheme 2). The results are listed in Table 2.

In the next step of this study, 3-ethoxycyclohex-2-enone **3c** was chosen as a model compound and the $Mn(OAc)_3 \cdot 2H_2O$ -mediated benzylation reaction was performed in the presence of toluene and cyclohexane as solvents which resulted in a 4 and 6% decrease in yields, respectively. When the reaction was performed in the presence of nitrobenzene which was used to examine the effect of a radical scavenger on the reaction propagation, no product formation was observed.

In conclusion, we have developed a new method for the regioselective α' -benzylation of various α,β -unsaturated ketones and β -alkoxy α,β -unsaturated ketones with

Table 2. α '-Benzylation of β -alkoxy α , β -unsaturated ketones mediated by Mn(OAc)₃



manganese(III) acetate, in one-step, and in moderate yields. The optimisation of the yields is ongoing.

3. Experimental

3.1. General procedure for the $Mn(OAc)_3$ mediated benzylation of α,β -unsaturated ketones 1 and β -alkoxy α,β -unsaturated ketones 3

A mixture of $Mn(OAc)_3 \cdot 2H_2O$ (3.25 g, 14.0 mmol) in benzene (150 ml) was refluxed for 45 min using a Dean–Stark trap. Then the mixture was cooled to room temperature and the α,β -unsaturated ketone (or β alkoxy α,β -unsaturated ketone) (7.0 mmol) and benzyl bromide (1.20 g, 7.0 mmol) were added. The mixture was allowed to reflux until the dark brown colour disappeared and was 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 NaHCO₃ and brine. The organic phase was dried over MgSO₄ and evaporated in vacuo. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent to afford the product.

3.2. 5-Benzyl-3-methylcyclopent-2-enone 2b

(0.85 g, 65%). IR (neat): 3044, 2965, 1695 cm⁻¹. ¹H NMR: δ 2.06 (s, 3H), 2.71 (d, J=19 Hz, 1H), 2.29 (d, J=19 Hz, 1H), 2.51–2.64 (m, 1H), 2.69–2.75 (m, 1H), 3.23 (dd, J=14 and 4 Hz, 1H), 5.92 (s, 1H), 7.15–7.48 (m, 5H). ¹³C NMR: δ 19.8, 36.9, 39.2, 48.1, 126.2, 128.0, 128.5, 129.2, 139.1, 177.2, 210.4. HRMS m/e (observed): 186.1052, (calculated): 186.1045.

3.3. 6-Benzyl-3-ethoxycyclohex-2-en-1-one 4c

(0.68 g, 42%), IR (neat): 3010, 2945, 1675 cm⁻¹. ¹H NMR: δ 1.31 (t, J=7 Hz, 3H), 1.78–1.99 (m, 2H), 2.20–2.53 (m, 4H), 3.25 (m, 1H), 3.95 (q, J=7 Hz, 2H), 5.22 (s, 1H), 7.12 (s, 5H). ¹³C NMR: 15.2, 25.7, 28.1, 36.0, 47.3, 64.1, 103.0, 126.1, 128.3, 129.2, 140.6, 177.2, 201.3. HRMS m/e (observed): 230.1301, (calculated): 230.1306.

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