Manganese-Promoted β -Elimination Reactions: Totally Stereoselective Synthesis of (*E*)- α , β -Unsaturated Esters

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Abstract: Stereoselective β -elimination of 2-bromo-3-hydroxyesters is achieved by using non-preactivated manganese and trimethylsilyl chloride, to yield (*E*)- α , β -unsaturated esters with total diastereoselectivity.

Key words: alkenes, diastereoselectivity, esters, eliminations, manganese

The development of new methods for the stereoselective formation of carbon–carbon double bonds is one of the most demanding subjects in organic chemistry.¹ Our group has reported the preparation of α , β -unsaturated esters with total *E* selectivity from α -halo- β -hydroxyesters promoted by either SmI₂² or CrCl₂.³ Although these methodologies worked obtaining (*E*)- α , β -unsaturated esters in good yield and with total diastereoisomeric excess (de) presented two drawbacks: a) the high cost of these metal halides,⁴ and b) the high sensitivity to air oxidation or moisture of SmI₂ and CrCl₂, and for this reason, these reagents require careful manipulation and storage.

In contrast to Sm(II),⁵ Cr(II)⁶ or other metals, Mn(0) has not yet found such a wide acceptance in organic synthesis, possibly due to the inherent passivity exhibited by this metal, which is coated by an outer shell of oxide.⁷ To overcome this limitation, many approaches have been developed to increase its reactivity and generally the use of Mn(0) has implied the previous preparation of active manganese in processes which are somewhat lengthy and cumbersome.⁸ So, active manganese has been employed in the generation of diverse organomanganese derivatives for synthetic use⁹ including the Reformatsky reaction.¹⁰ However, very scarce synthetic applications of non-activated manganese have been described,¹¹ and to the best of our knowledge, manganese has not been used to date to promote β -elimination reactions.

Motivated from our studies on the preparation of new organometallic reagents derived from active metals, in this paper we report a new general approach for the preparation of α , β -unsaturated esters with total *E* stereoselectivity from 2-bromo-3-hydroxyesters promoted by the cheap manganese. A comparison of this reaction with other β elimination reactions promoted by SmI₂ or CrCl₂ carried

SYNLETT 2006, No. 2, pp 0315–0317 Advanced online publication: 23.12.2005 DOI: 10.1055/s-2005-923592; Art ID: G34005ST © Georg Thieme Verlag Stuttgart · New York out in our laboratory is reported. In addition, a mechanism to explain this β -elimination process is also proposed.

So, when a solution of several 2-bromo-3-hydroxyesters **1** in dry THF was treated with Mn granules (325 mesh, provided by Aldrich, 1.5 equiv), chlorotrimethylsilane (1.75 equiv) and refluxed for five hours, the corresponding α , β -unsaturated esters **2** were isolated, after hydrolysis, with total stereoselectivity and in high yield (Scheme 1).¹²



Scheme 1 Synthesis of (E)- α , β -unsaturated esters 2

The starting materials **1** were easily prepared by reaction of the corresponding lithium enolates of 2-bromoesters (generated by treatment of 2-bromoesters **3** with LDA at -85 °C) with aldehydes at the same temperature (Scheme 2).^{2,3,12}



Scheme 2 Preparation of starting compounds 1

It is noteworthy that although the 2-bromo-3-hydroxyesters **1** were prepared and used as mixtures of diastereoisomers (roughly 1:1), the corresponding α , β -unsaturated esters **2** were obtained with total stereoselectivity.

The diastereoisomeric excess (de) in compounds 2 was determined on the crude reaction products by ¹H NMR spectroscopy (300 MHz). The *E* stereochemistry of the carbon–carbon double bond in products 2 was assigned on the basis of the value of the ¹H NMR coupling constants between the olefinic protons 2a-c. This stereochemistry was also unambiguously confirmed by comparison of NMR data of compounds 2a-h with similar materials previously prepared.¹³

This proposed methodology to obtain α , β -unsaturated esters is general: R^1 and R^2 can be varied widely. So, aliphatic (linear, branched, or cyclic), unsaturated, or aromatic α , β -unsaturated esters can be prepared starting

from the corresponding compounds 1. In turn, structures can be varied starting from the suitable aldehyde or bromoester 3.

When this process was carried out in the absence of TMSCl, no reaction took place. On the other hand, when lower quantities (0.4 equiv with respect to bromohydrin 1) of TMSCl were employed the reaction did indeed proceed although it required a longer time (ca. 12 h). These observations suggest that TMSCl plays some role as manganese activating agent⁷ but does not interfere with the reaction mechanism.

Table 1 Synthesis of α,β -Unsaturated Esters 2 with Mn

Entry	\mathbb{R}^1	\mathbb{R}^2	Yield (%) ^a		
			Mn	SmI_2	$CrCl_2$
2a	C ₇ H ₁₅	Н	82	70	65
2b	Су	Н	85	-	-
2c	p-MeO-C ₆ H ₄	Н	51	-	_
2d	C ₇ H ₁₅	Me	75	75	64
2e	CH ₃ CH(Ph)	$C_{6}H_{13}$	83	87	_
2f	Ph	$C_{6}H_{13}$	90	86	65
2g	MeCH=CH	$C_{6}H_{13}$	78	90	-
2h	PhCH=CH	$C_{6}H_{13}$	91	-	-

^a Isolated yield after column chromatography based on compounds 1; all products were isolated with >98% de, determined by ¹H NMR and/or GC-MS of the crude products 2.

Table 1 also shows results obtained when the β -elimination process took place using SmI₂ or CrCl₂ as a metalating reagent. In general, the yield of the obtained α , β unsaturated esters **2** with the Mn/TMSCl system is higher than when using SmI₂ (entries **2a**, **2d**–**g**) or CrCl₂ (entries **2a**, **2d**, and **2f**). In addition, the reagents utilised to promote this β -elimination reaction, are cheaper than SmI₂ or CrCl₂.

Mechanism: we could surmise that the stereochemistry of this β -elimination reaction is ruled by the thermodynamic stability of the obtained alkene, affording the *E* diastereo-isomer (Scheme 3).



Scheme 3 β -Elimination for the conversion of 1 into 2

Alternatively, and similarly to other β -elimination reactions,^{2,3} we could also propose a mechanism based on a chelation control model (Scheme 4). Thus, metallation of the C–Br bond takes place, and a manganese enolate intermediate is generated.¹⁴ Chelation of the Mn^{II} centre with the oxygen atom of the alcohol group generates a six-

membered ring.¹⁵ Also, this chelation of the Mn^{II} centre with the oxygen atom of the alcohol group increases the ability of the hydroxyl group as a leaving group. Tentatively, we surmise that the chair-like transition state model **A** might be involved, with the R¹ group in an equatorial orientation. As depicted in **B** (Newman projection of **A** through atoms C2 and C3), R¹ and R² show a *cis* relationship. A concerted elimination process as that shown in the tautomeric equilibrium **I** in Scheme 4 afforded the (*E*)- α , β -unsaturated esters **2**. The generation of a Mn-enolate in the presence of an OH group can be rationalised assuming that the elimination process takes place faster than the competing hydrolysis of the C–Mn(II) bond, moreover when the elimination is assumed to go through a rigid chelated transition state.



Scheme 4 Chelation control model for the conversion of 1 into 2

This mechanism would explain the high levels of stereoselectivity shown in this reaction (de >98%). Synthesis of **2** with total stereoselectivity from a mixture of diastereoisomers of **1** could be explained by assuming that after the reaction of **1** with Mn, only one stereoisomer is afforded with the appropriate relative configuration for the coordination of the manganese centre with the oxygen atom from the free alcohol. In this sense, the two starting diastereoisomers **1** are transformed into two enolate enantiomers, which afford a single *E* diastereoisomer through a β -elimination reaction.

When the reaction was performed on α , β -epoxyesters, only starting material was recovered in the reaction outcome. So, a mechanism proceeding via an epoxide must be ruled out.

In conclusion, an efficient, general and very cheap methodology has been developed to synthesise α , β -unsaturated esters with total *E* diastereoselectivity from easily available 2-bromo-3-hydroxyesters promoted by non-preactivated manganese and trimethylsilyl chloride. Attempts to carry out other elimination processes by using the ready available, cheap and stable Mn metal, are currently under investigation in our laboratory.

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- (12) (a) Typical Procedure for Compound 2h.
 - When a solution of **1h** (0.4 mmol, 1 equiv) in dry THF (2.5 mL), in the presence of Mn granules (325 mesh, 0.6 mmol, 1.5 equiv), and TMSCl (0.7 mmol, 1.75 equiv), was refluxed for 5 h, compound **2h** was obtained after hydrolysis with >98 % de and 91% yield. For spectroscopic data of **1h** see ref. 12b.

Compound **2h**: ¹H NMR (300 MHz, CDCl₃): $\delta = 7.52-7.27$ (6 H, m), 7.09 (1 H, dd, J = 15.3, 10.9 Hz), 6.89 (1 H, d, J = 15.3 Hz), 4.26 (2 H, q, J = 7.4 Hz), 2.53 (2 H, t, J = 7.4 Hz), 1.61–1.29 (8 H, m), 1.35 (3 H, t, J = 7.4 Hz), 0.92 (3 H, t, J = 6.1 Hz). ¹³C NMR (75 MHz, CDCl₃): $\delta = 168.1$ (C), 138.9 (CH), 138.1 (C), 136.5 (C), 132.5 (CH), 128.7 (CH), 128.5 (CH), 126.9 (CH), 123.7 (CH), 60.4 (CH₂), 31.5 (CH₂), 29.7 (CH₂), 29.1 (CH₂), 27.0 (CH₂), 22.5 (CH₂), 14.2 (CH₃), 14.0 (CH₃). HRMS: *m*/z calcd for C₁₉H₂₆O₂: 286.1933; found: 286.1904. IR (neat): 2958, 2871, 1461, 1375 cm⁻¹. (b) Concellón, J. M.; Bernad, P. L.; Rodríguez-Solla, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3897.

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