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Synthesis of (*Z*)-α-chloro-α,β-unsaturated esters with complete stereoselectivity promoted by samarium diiodide ☆

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Abstract—Stereoselective β-elimination in α,α-dichloro-β-hydroxyesters **2** was achieved by using samarium diiodide, yielding (Z)-α-chloro-α,β-unsaturated esters **1**. The starting compounds **2** were easily prepared by reaction of the lithium enolate of ethyl dichloroacetate with different aldehydes at −78 °C. A mechanism to explain this process is proposed.
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1. Introduction

α-Chloro-α,β-unsaturated esters (α-chloroacrylates) are useful building blocks in organic synthesis[1] and are attractive starting materials to obtain natural products or pharmaceuticals.[2]

α-Chloro-α,β-unsaturated esters are most often prepared by dehydrohalogenation,[3] rearrangements,[4] alkoxycarbonylation,[5] thermal eliminations[6] or Wittig–Horner condensations[7] and Peterson-type reactions.[8] However, most of these syntheses are limited by their poor stereoselectivity, low yields or involve multi-step transformations. While this paper was being prepared, a synthesis of α-chloro-α,β-unsaturated esters with complete stereoselectivity,[9] which suffers from the use of toxic $CrCl_2$, was described.

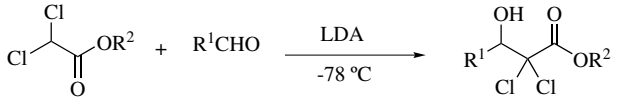
Recently, we have described the first general method to promote β-elimination reactions by using SmI_2 with complete or high stereoselectivity. Thus, we reported the synthesis of (*Z*)-vinyl halides,[10] (*E*)-α,β-unsaturated esters[11] or amides[12] and (*Z*)-vinylsilanes,[13] with total or high stereoselectivity.

Now, we are interested in the use of α-chloro-α,β-unsaturated esters in organic synthesis. For this reason our objective in this work is to describe the synthesis of (*Z*)-α-chloro-α,β-unsaturated esters **1** through a β-elimination reaction of α,α-dichloro-β-hydroxyester promoted by the nontoxic[14] SmI_2.[15] This preparation takes place with complete stereoselectivity.

2. Results and discussion

The starting α,α-dichloro-β-hydroxyesters **2** were easily prepared by reaction of the lithium enolate derived from methyl dichloroacetate (generated by treatment of methyl dichloroacetate **3** with LDA at −78 °C) with various aldehydes **4** at −78 °C[16] (Scheme 1 and Table 1).

With the requisite starting compounds in hand, the initial studies were performed to determine the optimum reaction conditions to prepare unsaturated esters. The best results were obtained by treatment of α,α-dichloro-β-hydroxy esters **2** with a solution of SmI_2 (2.5 equiv) in THF following the conditions shown in Table 1. The



3 4 2

Scheme 1. Synthesis of starting materials **2**.

Keywords: Alkenes; Stereoselection; Eliminations; Samarium; α-Chloro-α,β-unsaturated esters.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.04.101

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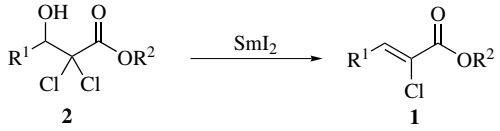
Table 1. Synthesis of starting compounds **2** and α-chloro-α,β-unsaturated esters **1**

Entry	Product[a]	R^1	R^2	% Yield of **2**[b]	*t* (h)[c]	% Yield of **1**[d,e]	% De[f]
1	**a**	*i*-Pr	Me	87	12	73	>98
2	**b**	*n*-C_4H_9	Me	60	4	79	>98
3	**c**	Cyclohexyl	Me	72	12	62	>98
4	**d**	Cyclohexyl	Ph	60	1	83	>98
5	**e**	Cyclohexyl	*i*-Pr	72	1	76	>98
6	**f**	*n*-C_7H_{19}	*i*-Pr	73	1	92	>98
7	**g**	$CH_3CH(Ph)$	Me	87	4	68	>98
8	**h**	$CH_3CH(Ph)$	*i*-Pr	86	1	85	>98
9	**i**	(*E*)-$(C_6H_5)CH{=}CH$	Me	89	12	75	>98
10	**j**	$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2$	Me	93	12	87	>98

[a] All compounds **1** were fully characterized by elemental analysis and spectroscopic methods (IR, ^1H, ^{13}C, and HMRS).
[b] Isolated yield after column chromatography based on compound **3**.
[c] Reaction time to transform **2** into **1**.
[d] All reactions were carried out by using 2.5 equiv of SmI_2 at room temperature.
[e] Isolated yield after column chromatography based on compound **2**.
[f] Diastereoisomeric excess (de) determined by GC–MS and 300 MHz ^1H and ^{13}C NMR analysis of the crude products **1**.



2 **1**

Scheme 2. Synthesis of (*Z*)-α-chloro-α,β-unsaturated esters **1**.

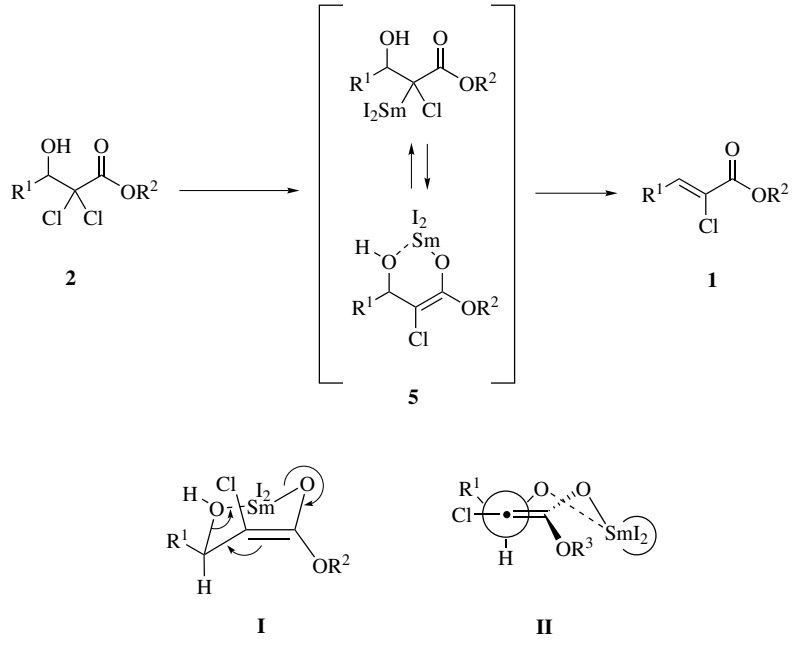
corresponding α-chloro-α,β-unsaturated esters **1**,[17] were isolated, with total stereoselectivity and in good yield by using these reaction conditions (Scheme 2).

The results obtained from subjecting a range of α,α-dichloro-β-hydroxyesters **2** to SmI_2 are summarized in Table 1 and illustrate the generality of the method. Thus, R^1 can be varied and the reaction can be carried out with aliphatic linear, branched, cyclic or unsaturated α,α-dichloro-β-hydroxy esters **2** (Table 1). In addition, the elimination reaction was unaffected by the presence of bulky ($R^2 = i$-Pr) substituents on oxygen (Table 1, entries 5, 6 and 8).[18]

The stereoselectivity of the reaction was determined on the crude reaction products by GC–MS and by ^1H NMR spectroscopy (300 MHz), and only a single stereoisomer was observed.

The *Z* stereochemistry in the double bond C=C of α,β-unsaturated esters **1** was established by NOESY experiments (compounds **1e**, **1f** and **1h**). NOE effects were observed between the olefinic proton and the methylic hydrogens of the alcoholic group (*i*-Pr), showing a *cis* relationship between H_β and $COOR^2$ group.

The β-elimination reaction and the observed configuration of the C=C bond in products **1** may be explained by



2 **5** **1**

I **II**

Scheme 3. Proposed mechanism.

assuming a chelation-control model (Scheme 3). Thus, a two-step reduction of the C–Cl bond in **2** promoted by SmI_2, affords the enolate intermediate **5**, in which the chelation of Sm^{III} centre with both oxygen atoms produces a six-membered ring.[19] Tentatively we propose a transition state model **I** with the R^1 in the equatorial orientation. As depicted in **II** (C2–C3 Newman projection of **I**), R^1 and Cl show a *cis* relationship. Consequently, elimination[20] from **I** affords (*Z*)-α-chloro-α,β-unsaturated esters **1**. No formation of α-chloro-β-hydroxy ester was observed, indicating that the elimination reaction of intermediate **5** is more rapid than its hydrolysis by the proton of the hydroxyl group.

In conclusion, we present a simple and general method for the preparation of (*Z*)-α-chloro-α,β-unsaturated esters **1** with high stereoselectivity from the easily available α,α-dichloro-β-hydroxyesters **2**, with the reaction being promoted by samarium diiodide. A mechanism has been proposed to explain this reaction.

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17. General procedure for the synthesis of compounds **1**: A solution of SmI_2 (1.0 mmol) in THF (12 mL) was added, under a nitrogen atmosphere, to a stirred solution of the corresponding α,α-dichloroester **2** (0.4 mmol) in THF (2 mL) at room temperature and for the time specified in Table 1 (the reaction times were established by TLC). Then, the reaction was quenched with aqueous HCl (20 mL of 0.1 M solution). Usual workup afforded crude α-chloro-α,β-unsaturated esters **1**, which were purified by column flash chromatography over silica gel (20:1, hexane/AcOEt).
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