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Synthesis of (E)- α , β -unsaturated ketones with total or high diastereoselectivity by using samarium diiodide or triiodide

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Abstract—(E)- α , β -Unsaturated ketones are obtained by reaction of α -chloro- β -hydroxy ketones with samarium diiodide or with samarium triiodide with total or high diastereoselectivity and in good yield. © 2003 Elsevier Science Ltd. All rights reserved.

The diastereoselective synthesis of α,β -unsaturated ketones has been extensively developed due to their synthetic applications.¹

Several procedures have been described for the general synthesis of these compounds² such as condensation,³ oxidation,⁴ elimination⁵ and acylation⁶ reactions, and by insertion of carbon monoxide,⁷ among others. However an alternative synthesis of α , β -unsaturated ketones simple, general and highly diastereoselective would still be desirable.

Recently, we have described a new diastereoselective β -elimination reaction promoted by samarium diiodide. In this sense we have reported several obtentions of functionalized alkenes, such as (*Z*)-vinyl halides,⁸ α , β -unsaturated esters,⁹ α , β -unsaturated amides,¹⁰ (*Z*)-vinylsilanes,¹¹ and α , δ -dideuterio- β , γ -unsaturated esters.¹² Here, we wish to report a new preparation of α , β -unsaturated ketones with total diastereoselectivity by treatment of the easily available α -chloro- β -hydroxy ketones with solutions of samarium diodide or triiodide in THF.

Our first attempts were carried out to establish the reaction conditions of the β -elimination process. Thus, several α -chloro- β -hydroxy ketones 1, were treated with a solution of 2.5 equiv. of SmI₂ in THF at room temperature.¹³ However, 3-hydroxy ketones 2 were isolated instead of α , β -unsaturated ketones 3. The same products 2 were obtained performing the reaction at several temperatures and with different amount of

samarium diiodide, and in just a few cases roughly 1:1 mixtures of **2** and **3** were obtained.

Surprisingly, α , β -unsaturated ketones **3** were obtained by using 1 equiv. of SmI₂ (Scheme 1). Thus, when a solution of 1 equiv. of SmI₂ in THF was added to several α -chloro- β -hydroxy ketones **1** at -25°C and then heated at reflux, the corresponding α , β -unsaturated ketones **3** were isolated, after hydrolysis, with total or high diastereoselectivity and in high yield. Transformation was complete after 1 h at reflux.¹⁴

The starting ketones 1a-d were easily obtained by reaction of the corresponding potassium enolate of 4 [generated by treatment of the starting ketone 4 (α -



Scheme 1.



Scheme 2.

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chloroacetophenone or 1-bromopinacolone) with potassium hexamethyldisilazide (KHMDS) at -78°C] with different aldehydes, at temperatures ranging from -78to 25°C; further treatment of the obtained epoxyketones 5 with chlorotrimethylsilane (TMSCl) and dimethylsulphoxide (DMSO),¹⁵ afforded compounds 1a-d (Scheme 2). Compounds 1a-c and 1e can be also obtained by reaction of the potassium or lithium enolate of α -chloroacetophenone 4 (generated from α chloroacetophenone 4 and KHMDS or LDA at -85°C) with different aldehydes and further hydrolysis at $-85^{\circ}C^{16}$ (Scheme 2). Compounds 1f and 1g were prepared by reaction of the ester 6 with bromochloromethyllithium obtaining the 1-bromo-1-chlorohexan-2one 7, which was treated with the corresponding aldehyde in the presence of $Zn/CuBr/Et_2AlCl$ (Scheme 3)¹⁷ yielding the halohydrin as a 1:1 two diastereoisomer mixture.

The diastereoisomeric excess was determined on the crude reaction products by ¹H NMR spectroscopy (300 MHz) and GC–MS, showing the presence of a single diastereoisomer (except compound **3g**). The *E* stereo-chemistry in the double bond C=C of α , β -unsaturated ketones **3** was assigned on the basis of the value of their ¹H NMR coupling constant between the olefinic protons ($J \cong 15$ Hz).

It is noteworthy that although 1:1 mixtures of diastereoisomers 1 were used in some cases, the corresponding α , β -unsaturated ketones 3 were obtained with total diastereoselectivity.

This proposed methodology to obtain α,β -unsaturated ketones is quite general (Table 1): R^1 can be aromatic or aliphatic (linear or branched) and R^2 can be

aliphatic (linear or cyclic) or aromatic, or it can contain other double bonds C=C (entry 7).

The observed results and the stereochemistry of products **3** may be explained (Scheme 4) by assuming two mechanisms for each starting diastereoisomer. In both cases the reaction is initiated by traces of SmI₃, present in the solution of SmI₂ in THF. For the *anti* diastereoisomer, dissociation of SmI₃ produces iodide and cationic species of samarium diiodide(III). Formation of a chelated species between the hydroxyl, Sm^{III}, and oxygen atom of the carbonyl group produces a six-membered ring and increases the ability of the hydroxyl group as a leaving group.¹⁸ Tentatively we propose a chair transition state model **I** with an equatorial R² group (to avoid 1,3-diaxial interactions). Elimination from **I** affords (*E*)- α , β -unsaturated ketones **3**.

For the syn diastereoisomer, iodide (from the SmI_3 dissociation) could substitute the chloro atom, previously to the elimination, to obtain the *anti* diastereoisomer with the appropriate conformation for coordination of the samarium center with the two oxygen atoms. Supporting this substitution reaction, in some cases, iodoacetophenone and aldehyde (retroal-dolic reaction) have been characterized in the crude reaction.

The remaining SmI_2 reacts with the obtained CII or I_2 generating halides of Sm(III), which continue the indicated β -elimination reaction. Indirect support for the proposed mechanism is provided by the observed appearance of I_2 and/or ICl in the crude reaction.

To prove that the β -elimination is promoted by species of Sm(III), the same reaction was carried out by using



Scheme 3.

Table 1. Synthesis of (E)- α , β -unsaturated ketones 2

Entry	Product	R ¹	R ²	SmI ₂		SmI ₃	
				Yield ^a	de ^b	Yield ^a	de ^b
1	3a	Ph	<i>n</i> -C ₄ H ₉	96	>98	72	>98
2	3b	Ph	$n-C_7H_{15}$	98	>98	91	>98
3	3c	Ph	Cyclohexyl	67	>98	72	>98
4	3d	$t-C_4H_9$	$n-C_4H_9$	65	>98	58	>98
5	3e ^c	Ph	Ph	73	>98	80	>98
6	3f	$n-C_4H_9$	Ph	82	>98	70	>98
7	$3g^{d}$	$n-C_4H_9$	(E)-CH=CHPh	76	84	_e	_

^a Isolated yield after column chromatography based on the starting carbonyl compound 1.

^b de determined by 300 MHz ¹H NMR spectroscopy and GC-MS analysis on the crude product.

^c The starting compound 1e was prepared by reaction of the lithium enolate (from 2-chloroacetophenone and lithium diisopropylamide at -85°C)

and benzaldehyde. ^d This elimination reaction was performed at -25° C overnight.

This eminiation reaction was performed at -25 C ov

 $^{\rm e}$ No reaction by using ${\rm SmI}_3$ was carried out.



Scheme 4.

SmI₃ (obtained from metallic samarium and iodine¹⁹). Thus, treatment of ketones **1a–f** with a solution of 1 equiv. of SmI₃ in THF at -25° C for 2 h and later at reflux for 1 h, afforded (*E*)- α , β -unsaturated ketones **3** with total diastereoselectivity²⁰ (Table 1).

When the reaction was carried out by using two equiv. of SmI₂, the metallation of the chloro atom can take place, giving an enolate II, which is hydrolyzed by the proton of the alcohol group (III), yielding, after hydrolysis, the β -hydroxyketone 2.²¹

In conclusion, an easy, simple and general methodology has been developed to synthesize α , β -unsaturated ketones with total *E*-diastereoselectivity from the easily available 2-halo-3-hydroxy ketones, the reaction being promoted by samarium triiodide.

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- 13. α,β -Unsaturated esters or amides were obtained from 2-chloro-3-hydroxyesters or amides and samarium diiodide by using these reaction conditions.
- 14. Over a solution of the starting α -chloro- β -hydroxyketone **1** (0.4 mmol) in dry THF (2 ml) a solution of samarium diiodide [prepared from 0.069 g of Sm (0.4 mmol), 5 ml of dry THF and 0.032 ml of CH₂I₂] was added dropwise at -25°C. The reaction mixture was stirred at the same temperature over 2 h and then heated at reflux for 1 additional hour (the color changed from yellow to orange). The reaction mixture was quenched with 5 ml of 0.1 M HCl and the usual workup gave the crude α , β unsaturated ketone. Purification by flash column chromatography over silica or by distillation afforded the pure compound **3**.
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- 16. When **1a**-**c** were prepared from epoxyketones **4** only the *anti* diastereoisomer was obtained, while both two diastereoisomers, as a mixture roughly 1:1, were isolated when **1a**-**d** were obtained by aldol condensation.
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- 20. 0.4 mmol of the starting ketone were treated with a solution of 0.4 mmol of samarium triiodide (0.069 g of Sm, 5 ml of dry THF and 0.150 g of I₂) at -25° C during 2 h and later heated at reflux by 1 additional hour. The reaction was quenched with 5 ml of 0.1 M HCl, extracted with dichloromethane and concentrated. Purification by flash column chromatography or by distillation yielded the pure enone **3**.
- 21. This intramolecular hydrolysis was previously observed in the transformation of 2-chloro-3-hydroxyesters into α , β -unsaturated esters, in which the double bond C=C is tetrasubstituted: see Ref. 9a.