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Synthesis of 2,3-dideuterioesters from 2-halo-3-hydroxyesters by using metallic samarium and diiodomethane

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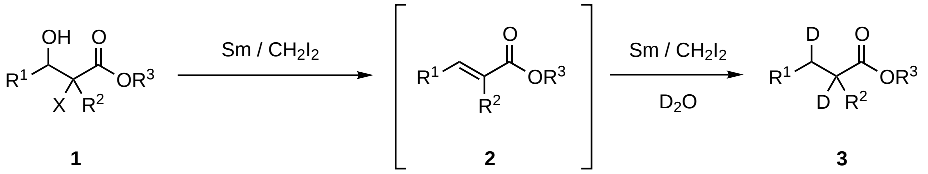
Abstract—2,3-Dideuterioesters are obtained in high yield from 2-chloro-3-hydroxyesters by a sequenced elimination/reduction process promoted by samarium diiodide generated in situ from metallic samarium and diiodomethane. © 2002 Elsevier Science Ltd. All rights reserved.

The synthesis of isotopically labeled compounds is very useful due to their applications in the study of the mechanism of organic reactions as well as in the biosynthesis of many natural compounds.[1] Despite this relatively few methods for the synthesis of 2,3-dideuterioesters have been published.[2]

Previously, we reported the transformation of 2-halo-3-hydroxyesters or amides into 2,3-dideuterioesters or amides, respectively, by using samarium diiodide and D_2O.[3] This methodology is good, but SmI_2 is expensive, and is also moisture- and air-sensitive. As an alternative, this reagent can be prepared in situ (for example from diiodomethane and powder metallic samarium)[4] in the presence of the starting organic compound. Moreover, this methodology is simpler, easier and the total reaction time (generation of SmI_2+reaction of SmI_2) is shorter than using pre-formed SmI_2.

Several synthetic applications of in situ generated samarium diiodide have been published, and in this respect the following reactions have been described from samarium metal and catalytic amounts of iodine: reduction of nitrocompounds,[5] imines[6] or azides,[7] reductive coupling of imines,[8] 1,4-reduction of α,β-unsaturated esters or amides,[9] alkylation of imines,[10] deacylation of alcohols or lactams[11] and the Barbier-type of carbonyl compounds.[12] In addition, Imamoto described the first reaction in which SmI_2 was in situ generated from metallic samarium and diiodomethane[13] and later we have published a total or high diastereoselective synthesis of (*Z*)-vinyl halides and (*E*)-α,β-unsaturated esters by using Sm/CH_2I_2.[14] However, to the best of our knowledge, no sequenced reactions promoted by in situ generated SmI_2 have been described.

In the present communication we describe a novel way of obtaining 2,3-dideuterioesters **3** by an efficient sequenced process by using the cheaper metallic samarium and diiodomethane. Thus, a β-elimination reaction of 2-chloro-3-hydroxyesters **1** promoted by in situ generated SmI_2 (from metallic samarium and diiodomethane) followed by a 1,4-reduction of the obtained α,β-unsaturated esters **2** with D_2O in the



Scheme 1.

Keywords: samarium; elimination reactions; reduction; 2,3-dideuterioesters.

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presence of in situ generated SmI_2, afforded the corresponding 2,3-dideuterioesters **3**. We understand this synthesis to be the first example of a sequenced process using metallic samarium.

So, the treatment of 2-halo-3-hydroxyesters **1** in THF at 0°C with a mixture of diiodomethane (5 equiv.) and samarium metal (5 equiv.) for 2 h, allowing the reaction mixture at room temperature, and further reaction with D_2O (2 mL) for 30 min at room temperature, afforded the corresponding 2,3-dideuterioesters **3** in high yield. This transformation took place through an efficient sequenced elimination/reduction process without the isolation of **2** (Scheme 1).

The starting compounds **1** were easily prepared by reaction of the corresponding lithium enolates of α-haloesters (generated by treatment of α-haloesters with LDA at −85°C) with aldehydes at −78°C.

The reaction time for this sequential process promoted by Sm/CH_2I_2 was shorter (2.5 h) than using preformed SmI_2 (3 h to generate SmI_2+1 h of reaction with SmI_2).[3]

Table 1 summarizes the results. The yields of the obtained 2,3-dideuterioesters **3** by using Sm/CH_2I_2 are higher than by using preformed SmI_2.[3] R^1, R^2, and R^3 can be varied widely: R^1 can be aliphatic (linear, branched, or cyclic), unsaturated, or aromatic groups, while R^2 can be aliphatic and aromatic. Moreover, the sequenced reaction was unaffected by the presence of bulky groups R^3 on the carboxyl ester (Table 1, entry 4).

The position of deuteration was established by ^{1}H and ^{13}C NMR spectrometry of the 2,3-dideuterioesters **3**, while complete deuterium incorporation (>99%) was determined by mass spectroscopy.[15] The obtained 2,3-dideuterioesters **3** were isolated as mixture of diastereoisomers since the incorporation of deuterium generates two stereogenic centres.

This sequenced process is both convenient and efficient, and taking into account that D_2O is the cheapest deuteration reagent available for obtaining organic compounds isotopically labeled with deuterium, the described methodology can be chosen to prepare 2,3-dideuterioesters.

In a typical procedure, a solution of 2-halo-3-hydroxyester **1** (0.4 mmol) in THF (4 mL) and diiodomethane (2 mmol, 0.16 mL) were successively added to a suspension of samarium powder (2 mmol, 0.344 g) in THF (24 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 h and then D_2O (2 mL) was added at the same temperature. After stirring for 30 min, the reaction mixture was quenched with 0.1 M aqueous HCl (5 mL). Usual workup provided crude 2,3-dideuterioesters **3**, which were purified by column flash chromatography over silica gel (hexane:ethyl acetate, 5:1) provided pure compounds **3**.

When the reaction was carried out by using H_2O instead of D_2O, saturated esters **4** were obtained and no important differences were observed (Table 1, entry 7).

3-Deuterioesters **5** can be prepared by the successive treatment of the obtained 2,3-dideuterioesters **3** with LDA and H_2O (Scheme 2). Thus, the reaction of **3e** with LDA and further hydrolysis afforded the corresponding 3-deuterioester **5e** in 91% yield.

The transformation of the starting compounds **1** into 3-hydroxyesters **6** can be achieved by modifying the proposed methodology. Treatment of **1f** with $Sm/CH_2I_2/MeOH$ gave the corresponding 3-hydroxyester **6f**

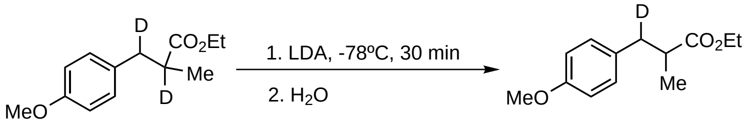
Table 1. Synthesis of 2,3-dideuterioesters **3** or saturated esters **4**

Entry	Product[a]	R^1	R^2	R^3	X	Yield[b]
1	**3a**	C_7H_{15}	Me	Et	Cl	95
2	**3b**	Cyclohexyl	Me	Et	Cl	87
3	**3c**	PhCH(Me)	C_4H_9	Et	Br	80
4	**3d**	$Me_2C{=}CH(CH_2)_2CH(Me)CH_2$	Ph	^{i}Pr	Cl	98
5	**3e**	*p*-MeO-C_6H_4	Me	Et	Cl	99
6	**3f**	Ph	C_4H_9	Et	Br	60
7	**4f**[c]	Ph	C_4H_9	Et	Br	65

[a] All products were fully characterized by spectroscopic methods (IR, NMR and MS).

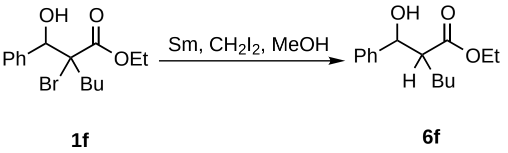
[b] Isolated yield after column chromatography based on compound **1**.

[c] In this case, H_2O was added instead of D_2O, obtaining the saturated ester **4f**, without deuterium.

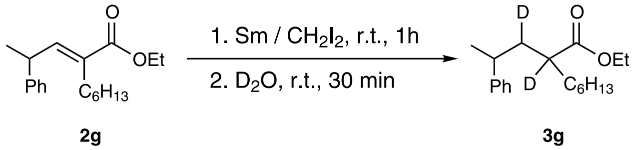


3e **5e**

Scheme 2.



Scheme 3.



Scheme 5.

in 52% yield (Scheme 3). When the reaction was carried out by using H_2O instead of MeOH, **6f** was not obtained and compound **1f** was recovered. SmI_2 can probably not be generated in situ from Sm/CH_2I_2 in the presence of H_2O.

Synthesis of **3** may be explained by assuming that the metallic samarium reacts with diiodomethane affording samarium diiodide. Reaction of the in situ generated SmI_2 with **1** gives the enolate intermediate **7**, which (in absence of MeOH) eliminates affording the (*E*)-α,β-unsaturated ester **2** with total or high diastereoselection.[14] When the reaction of **1** with SmI_2 is carried out in the presence of MeOH the corresponding 3-hydroxyester **6** is isolated. The obtained α,β-unsaturated ester **2** is reduced by SmI_2 generating the enolate radical **8**,[16] which, after a second electron transfer from SmI_2 and hydrolysis with D_2O or H_2O, afforded the corresponding compound **3** or **4** (Scheme 4).

The proposed mechanism is supported by the fact that the synthesis of dideuterated compounds **3** can also be carried out starting from the corresponding α,β-unsaturated ester **2**. Thus, treatment of ethyl (*E*)-2-hexyl-4-phenylpent-2-enoate **2g** with Sm (2.5 equiv.) and CH_2I_2 (2.5 equiv.) for 1 h at room temperature, and further addition of 2 mL of D_2O, affords **3g** in 81% yield (Scheme 5).

In conclusion, we have described a simple, easy, and convenient synthesis of 2,3-dideuterioesters and other deuterated esters from the easily available 2-chloro-3-hydroxyesters **1** and metal samarium, the synthesis being the first sequenced reaction promoted by samarium metallic.

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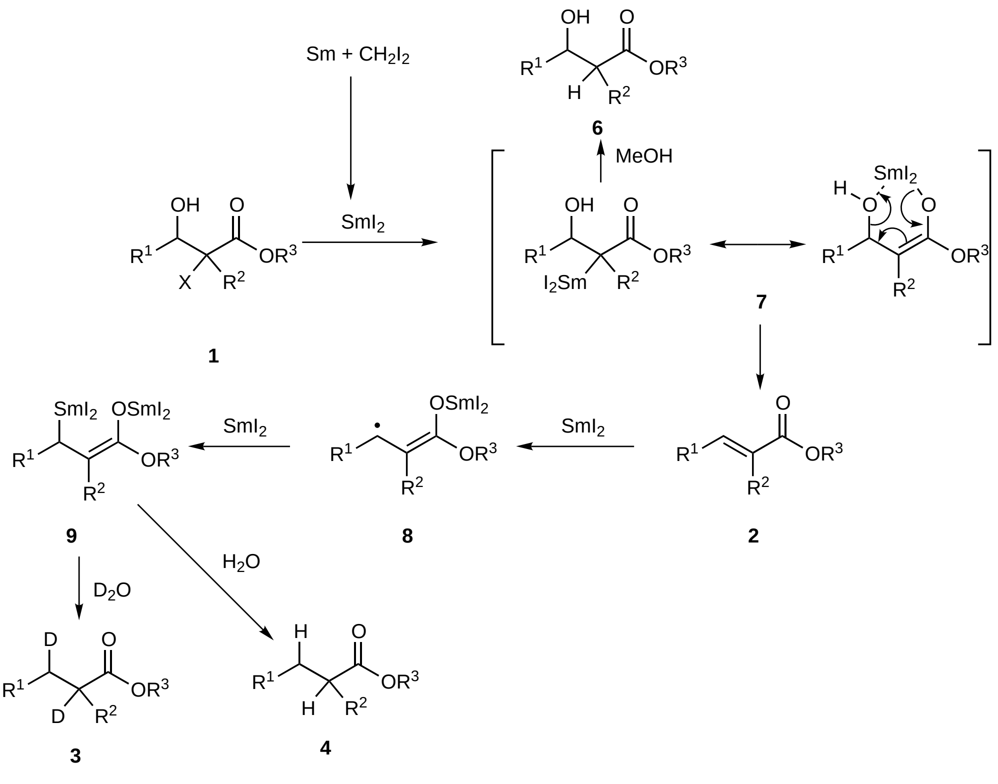

Scheme 4.

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