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Deuteration of α,β-acetylenic esters, amides, or carboxylic acids without using deuterium gas: synthesis of 2,2,3,3-tetradeuterioesters, amides, or acids

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Abstract—An easy, simple, rapid, and nonhazardous deuteration of the C–C triple bond of α, β-acetylenic esters, amides, or acids by means of samarium diiodide in the presence of D_2O, provides an efficient method for synthesizing 2,2,3,3-tetradeuterioesters, amides, or carboxylic acids, respectively. When H_2O is used instead of D_2O, saturated carboxylic esters, amides, or acids were isolated. A mechanism to explain these reduction reactions has been proposed.

Isotopically labeled compounds are very useful to establish the mechanism of organic reactions and the biosynthesis of many natural compounds.[1] However, there is only a methodology describing the conjugated reduction, employing a deuterium source, of α,β-acetylenic acid derivatives. Specifically, α,β-acetylenic esters have been deuterated by using methanol-D and magnesium,[2] and the same methodology has been used to prepare 2,2,3,3-tetradeuterioacids in two steps (deuteration of α,β-acetylenic esters and further hydrolysis).[3] This methodology is hazardous due to generation of D_2 gas and when methyl α,β-acetylenic esters are not used, transesterification reaction takes place and a mixture of different esters can be isolated.[3]

Although catalytic deuteration may be possible to use, to the best of our knowledge, no reduction of α,β-acetylenic esters, amides, or acids with deuterium gas have been described. This lack of examples may be due to the fact that D_2 gas is hazardous, its availability may be affected by regulations, and, in general, methodologies involving the use of gas are tedious or must be performed under pressure. For all these reasons, the development of a simple alternative method for the synthesis of 2,2,3,3-tetradeuterioesters, amides, or acids by using the nonhazardous SmI_2/D_2O system would be of significant value.

With regard to the synthetic application of samarium diiodide in organic synthesis,[4] only two papers have been published concerning its use in selective reduction of alkynes. In the first, *cis*- or *trans*-olefins are obtained by using different alcohols or acetic acid as proton donors in the presence of transition metal catalysts.[5] In the second phenylacetylene and diphenylacetylene are reduced to ethylbenzene and dibenzyl, respectively, it is necessary for H_2O and pentamethylethylene triamine to be present for these reactions to occur.[6]

Previously we described a practical methodology for the synthesis of various deuterated compounds such as 2,3-dideuterioesters or amides,[7] (*E*)-α,δ-dideuterio-β,γ-unsaturated esters,[8] and 2,3-dideuterioacids.[9]

In the present contribution we describe a novel and rapid method to obtain 2,2,3,3-tetradeuterioesters, amides, or carboxylic acids by an efficient, simple, and nonhazardous reduction of the C–C triple bond of α,β-acetylenic esters, amides, or carboxylic acids, the reaction being promoted by SmI_2 in the presence of D_2O. This reduction can be also carried out by using H_2O instead of D_2O, obtaining the corresponding saturated esters, amides, or carboxylic acids **2**. A mechanism to explain these reduction reactions has been proposed.

Keywords: Deuterium; Reductions; Samarium diiodide.

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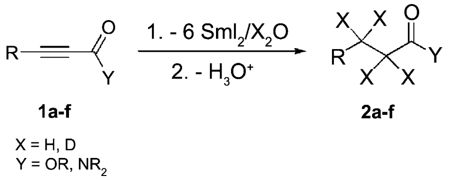


Scheme 1. Synthesis of 2,2,3,3-tetradeuterioesters and amides (X=D).

Our first attempts involved the preparation of 2,2,3,3-tetradeuterioesters or amides. Thus, a solution of the starting acetylenic esters or amides (1 equiv) in THF and D_2O was stirred with a solution of SmI_2[10] (6 equiv) in THF for 30 min at room temperature, affording after acidification with HCl 0.1 M the corresponding 2,2,3,3-tetradeuterioesters or amides **2** in high yield (Scheme 1).

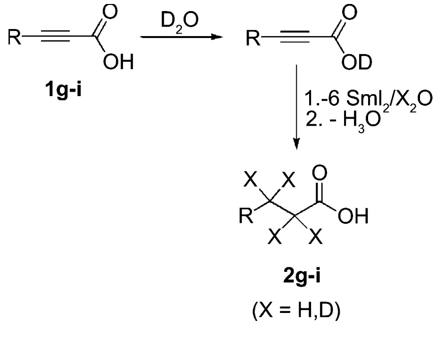
We also carried out the direct reduction of acetylenic acids. In this case, a pre-treatment of the corresponding acetylenic carboxylic acid with D_2O for 1 h at room temperature was performed. The reaction of the O–D acetylenic carboxylic acids with D_2O for 30 min and with a solution of SmI_2 (6 equiv) in THF at room temperature afforded the corresponding 2,2,3,3-tetradeuteriocarboxylic acid (Scheme 2).

When the acetylenic carboxylic acids were not pre-treated with D_2O, no complete deuterium incorporation takes place, affording a mixture of carboxylic acids bearing different number of deuterium atoms.[11]

The starting acetylenic esters[12] (Y = OEt), amides[13] (Y = NEt_2, NMe_2), or acids[14] (Y = OH) **1** were easily prepared by reaction of the corresponding lithium acetylides (generated by treatment of alkynes with BuLi at −78 °C) with ethyl chloroformiate, diethylcarbamylchloride, or dimethylcarbamylchloride at −30 °C, and solid CO_2 at −78 °C, respectively.[15]

The reduction described, seems to be general and aliphatic or aromatic acetylenic carboxylic acids and their derivatives can be reduced. Deuterated esters, amides, and acids were obtained in similar, high, or very high yields (Table 1).

The position of deuteration was established by ^1H and ^{13}C NMR spectrometry of compounds **2**. The complete deuterium incorporation was determined by ^1H, ^{13}C NMR spectrometry of products **2a–i**, and was found to be >95%. Moreover, ^1H, ^{13}C NMR of compounds **2c**,**f**,**i**, have been compared with the corresponding nondeuterated products.



Scheme 2. Synthesis of 2,2,3,3-tetradeuterioacids (X = D).

Table 1. Synthesis of 2,2,3,3-tetradeuterioesters, amides and acids (X = D)

Entry	2	R	Y	Yield (%)[a]
1	**2a**	Ph	OEt	84
2	**2b**	C_5H_{11}	OEt	83
3	**2c**	C_6H_{13}	OEt	90
4	**2d**	Ph	NEt_2	81
5	**2e**	C_5H_{11}	NMe_2	86
6	**2f**	C_6H_{13}	NMe_2	91
7	**2g**	Ph	OH	71
8	**2h**	C_5H_{11}	OH	75
9	**2i**	C_6H_{13}	OH	79

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

When H_2O was used instead of D_2O, no important differences were observed in the reduction reaction and saturated ester amide or acids were also prepared (Table 2).

It is noteworthy that D_2O is the most widely available deuteration reagent for obtaining organic compounds isotopically labeled with deuterium.

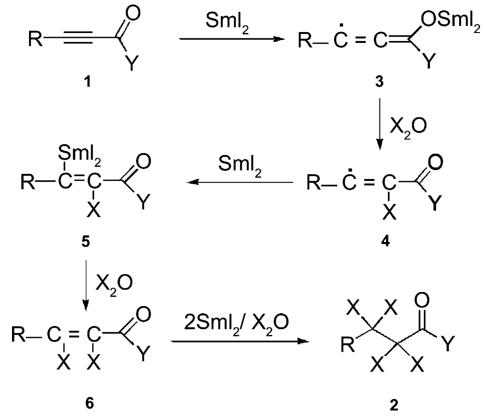
Synthesis of labeled compounds **2** may be explained by assuming that the SmI_2-promoted reduction of **1** is initiated by a single electron transfer from SmI_2 to generate the anion radical **3**, which is hydrolyzed by the protic medium (X = D, H), affording the corresponding alkene radical **4**.[16] After a second electron transfer from SmI_2 the radical generated the anion **5**, this being hydrolyzed by D_2O to afford the corresponding α,β-unsaturated carboxylic compound **6**.[17] After other successive electron-transfer and proton-transfer steps the corresponding tetradeuterated ester, amide, or acid **2** is obtained. When the acetylenic acids were not pre-treated with D_2O, a competitive hydrolysis of **3** and/or **5** produced by the acid proton of the carboxylic group and D_2O, affording a mixture of carboxylic acids with differing numbers of deuterium atoms (Scheme 3).

In conclusion, a SmI_2-promoted reduction of α,β-acetylenic esters, amides, or acids, in the presence of D_2O, provides an easy, rapid, nonhazardous, and efficient method for synthesizing aromatic or aliphatic 2,2,3,3-tetradeuterioesters, amides, or acids in high, or very high yields. When H_2O was used instead of D_2O, saturated carboxylic acids and derivatives were isolated. A mechanism to explain these syntheses has been proposed. The application of samarium diiodide-based C–C

Table 2. Synthesis of saturated esters, amides, and acids (X = H)

Entry	2	R	Y	Yield (%)[a]
1	**2j**	C_6H_{13}	OEt	87
2	**2k**	C_6H_{13}	NMe_2	87
3	**2l**	C_6H_{13}	OH	80

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



Scheme 3. Mechanistic proposal for the conversion of **1** into **2**.

triple bond partial reductions for generating olefins is currently under investigation within our laboratory.

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References and notes

1. Mann, J. *Secondary Metabolism*; Oxford University Press: Oxford, 1986; p 23.
2. Hutchins, R. O.; Suchismita, X. X.; Zipkin, R. E.; Taffer, I. M.; Sivakumar, R.; Monaghan, A.; Elisseou, E. M. *Tetrahedron Lett.* **1989**, *30*, 55.
3. Rodríguez, S.; Clapés, P.; Camps, F.; Fabriàs, G. *J. Org. Chem.* **2002**, *67*, 2228.
4. SmI_2 has been used to carry out the conjugated reduction of α,β-carbonyl compounds: (a) Inanaga, J.; Sakai, S.; Handa, Y.; Yamaguchi, M.; Yokoyama, Y. *Chem. Lett.* **1991**, 2117; (b) Cabrera, A.; Alper, H. *Tetrahedron Lett.* **1992**, *33*, 5007; (c) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5; (d) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
5. Inanaga, J.; Yokoyama, Y.; Baba, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 5559.
6. Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2003**, *44*, 2661.
7. (a) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 4266; (b) Concellón, J. M.; Bardales, E.; Llavona, R. *J. Org. Chem.* **2003**, *68*, 1585.
8. Concellón, J. M.; Bernad, P. L.; Rodríguez-Solla, H. *Angew. Chem.* **2001**, *113*, 4015; *Angew. Chem., Int. Ed.* **2001**, *40*, 3897.
9. Concellón, J. M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2002**, *8*, 4493.
10. A solution of SmI_2 in THF was very rapidly generated by the reaction of diiodomethane with samarium powder in the presence of sonic waves: Concellón, J. M.; Rodríguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775.
11. General procedure for the synthesis of 2,2,3,3-tetradeuterio or saturated esters, amides, or carboxylic acids (**2**): Under nitrogen, a solution of SmI_2 (6 equiv, 2.75 mmol) in THF (29 mL) was added dropwise to a stirred solution of the appropriate starting material **1** (1 equiv, 0.4 mmol) in D_2O (2 mL) and THF (2 mL) at room temperature. The reaction mixture was stirred for 30 min and then treated with 0.1 M aqueous HCl (5 mL). Standard work-up afforded the crude tetradeuterio esters or amides **2**, which were purified by flash column chromatography on silica gel (hexane/ethyl acetate). When the reaction was performed starting from acid carboxylic, the corresponding acid was treated with 3 mL of D_2O for 1 h. Then, the mixture was allowed to react with SmI_2 as was indicated above. When H_2O was used instead of D_2O, saturated esters, amides, or carboxylic acids were isolated.
12. (a) Goerger, M. M.; Hudson, B. S. *J. Org. Chem.* **1988**, *53*, 3148; (b) Koenig, B.; Pitsch, W.; Klein, M.; Vasold, R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2001**, *66*, 1742.
13. (a) Hartke, K.; Gerber, H. D.; Roesrath, U. *Tetrahedron* **1989**, *30*, 1073; (b) Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron* **1985**, *26*, 6265.
14. Barker, S. A.; Foster, A. B.; Lamb, D. C. *Tetrahedron* **1962**, *18*, 177.
15. General procedure for the synthesis of acetylenic esters, amides, or acids (**1**): Under nitrogen, a solution of BuLi (100 mmol) was added dropwise to a stirred solution of the requisite alkyne (110 mmol) in THF (40 mL) at −78 °C. The reaction mixture was warmed from −78 to −30 °C and then treated with ethyl chloroformiate (150 mmol) or diethylcarbamylchloride (150 mmol) or dimethylcarbamylchloride (150 mmol) at −30 °C. In the case of acetylenic acids, the reaction was performed with carbon dioxide generated from dry ice (1.2 mol) at −78 °C. The mixture was allowed to warm to room temperature and then, 20% aqueous hydrochloric acid (20 mL) was added slowly. Standard work-up afforded the crude esters, amides, or acids **1**, which were purified by distillation. Compounds **1a**,**g**, and **h** were commercially available.
16. Generally, vinyl radicals abstract hydrogen from THF see: Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Syntlett* **1992**, *23*, 943, However, in this case, **4** appears to be reduced to a vinyl organosamarium species due to complete deuteration observed in products **2** after deuterolysis.
17. Intermediate alkenes have been previously proposed in the mechanism of the reduction reaction of the C–C triple bond promoted by SmI_2 (see Refs. 5 and 6).