Synthesis and Synthetic Applications of α,β-Dideuterio-α-amino Esters Promoted by Samarium Diiodide

José M. Concellón,* Humberto Rodríguez-Solla,* Carmen Concellón, Paula Tuya

Departamento Química Orgánica e Inorgánica, Universidad de Oviedo, C/ Julián Clavería 8, 33006 Oviedo, Spain
E-mail: jmcg@uniovi.es

Received 11 October 2007

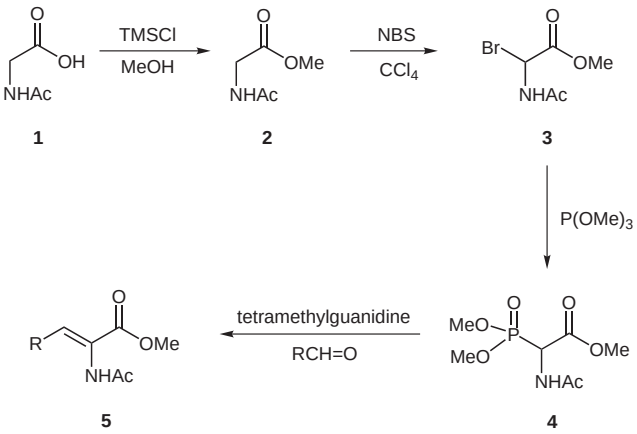
Abstract: A new, easy, and high-yielded route to isotopically labeled amino acid derivatives is reported. This process takes place through a SmI_2-promoted 1,4-reduction of a variety of dehydroamino esters in the presence of D_2O. The dideuterio amino esters were transformed into other dideuterated compounds such as α-amino acids and 1,2-amino alcohols. A mechanism to explain the 1,4-reduction process is also proposed.

Key words: amino acids, deuteration, reductions, samarium

Isotopically labeled compounds are very useful to establish the mechanism of organic reactions and the biosynthesis of many natural compounds.[1] The incorporation of isotopically labeled α-amino acid residues into proteins has become a vital tool in the determination of protein structure by NMR techniques. The indiscriminate incorporation of the NMR active isotopes ^{15}N and ^{13}C enables the effective employment of heteronuclear correlation experiments, while the incorporation of deuterium simplifies the assignment of the residual ^1H resonances, facilitating structural determination through the interpretation of NOE data. In this context, the incorporation of deuterated α-amino acids into polypeptides is a powerful tool in the structural determination of large biomolecules.[2] In addition, α-amino acids isotopically labeled on the side-chain have also found utility as valuable probes into biosynthetic pathways.[3]

Pioneered by Kagan in 1977,[4] samarium diiodide has rapidly become an important reagent in organic chemistry because of its versatility in one- and two-electron-transfer reactions. Since then, SmI_2 has emerged as one of the more useful reducing agents in synthetic organic chemistry. As a consequence of its increasing importance, several reviews have appeared that focus the utility of samarium diiodide to promote C–C bond-formation reactions,[5] and different reduction processes[6] including the reduction of multiple bonds.[6c]

Previously, we have reported the use of samarium diiodide in a range of practical methods for the synthesis of various deuterated compounds such as 2,3-dideuterio esters,[7] amides[7] or acids,[8] 2-deuterio-3-hydroxyesters,[7] (*E*)-α,δ-dideuterio-β,γ-unsaturated esters[9] or acids,[8] 3-aryl-3-deuterio-2-hydroxyamides,[10] and 2,2,3,3-tetradeuterio esters, amides, and acids.[11]



Scheme 1 Synthesis of starting materials **5**

As part of our program concerned with the development of new reduction processes mediated by SmI_2, towards the synthesis of various deuterated compounds we wish to report herein a new and easy route to access α,β-dideuterio-α-amino esters, by treatment of dehydroamino acids mediated by a SmI_2 and D_2O system, in high yields. A mechanism to explain this process is also proposed.

The starting (*Z*)-*N*-acetyldehydroamino esters **5** were easily prepared in four steps from commercially available *N*-acetylglycine (**1**) after an esterification, bromination, and a Horner–Wadsworth–Emmons protocol (Scheme 1).[12]

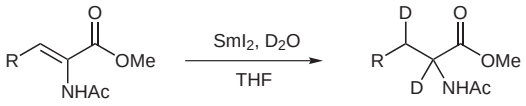
The reaction of various (*Z*)-*N*-acetyldehydroamino esters **5** in THF with SmI_2 and D_2O[13] at room temperature for 30 minutes afforded the corresponding dideuterio amino esters **6** in moderate or high yields (Table 1).[14]

This proposed methodology for obtaining isotopically labeled α-amino acid derivatives is general and the R group can be varied. Thus, aliphatic (linear, branched, or cyclic), unsaturated, or aromatic aldehydes may be used to introduce different R groups. It is noteworthy that the deuteration of the C–C double bond was completely chemoselective. Thus, employing compound **5f** (Table 1, entry 6), only the C=C conjugated with the carbonyl group was deuterated remaining the nonconjugated C–C double bond unaltered.

The position of deuteration was established by ^1H NMR and ^{13}C NMR spectroscopy of compounds **6**, while the complete deuterium incorporation (>99%) was verified

SYNLETT 2008, No. 3, pp 0402–0404
Advanced online publication: 23.01.2008
DOI: 10.1055/s-2008-1032063; Art ID: G31007ST

Table 1 Synthesis of Isotopically Labeled α-Amino Esters **6**



5 **6**

Entry	**6**	R	Yield (%)[a]
1	**6a**	*n*-C_7H_{15}	82
2	**6b**	$PhCH_2CH_2$	72
3	**6c**	*i*-Pr	80
4	**6d**	*s*-Bu	65
5	**6e**	Cy	85
6	**6f**	(*Z*)-EtCH=CH$(CH_2)_5$	65
7	**6g**	Ph[b]	75

[a] Isolated yield of pure compounds **6** after column chromatography based on compounds **5**.
[b] In this case the reaction was performed on the ethyl ester rather than the methyl ester.

by mass spectrometry.[15] These α,β-dideuterio-α-amino acid derivatives were isolated as mixtures of stereoisomers (approx. 1:1 by ^1H NMR spectroscopy and GC-MS) this fact being in agreement with the observed results of the SmI_2 and D_2O promoted synthesis of other deuterated compounds.[7–9]

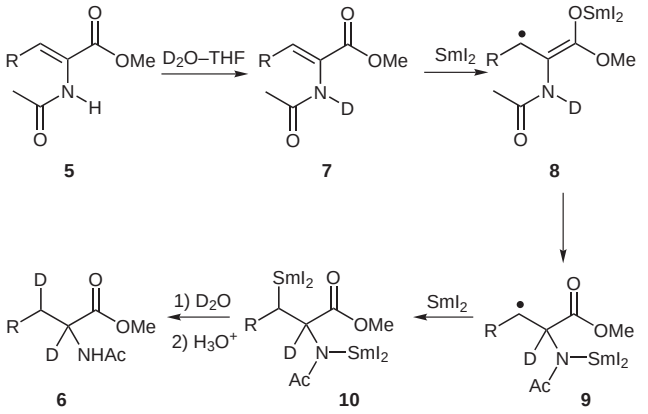
It is noteworthy that D_2O is the cheapest deuteration reagent available for obtaining organic compounds isotopically labeled with deuterium.

The synthesis of products **6** might be explained by assuming that the SmI_2-promoted 1,4-reduction of **5** is initiated by single-electron transfer of SmI_2 to generate the enolate **8**; this radical is then hydrolyzed by the acidic deuterium from the N–D bond and afford the corresponding radical **9**. After a second electron transfer from SmI_2 the radical generated the dianion **10**, this being hydrolyzed by D_2O to afford the corresponding compound **6** (Scheme 2). When the starting compounds **5** were not pretreated with D_2O, a competitive hydrolysis of **8** and **10** produced by the acidic proton of the N–H amide group and D_2O afforded a mixture of mono-, di-, and nondeuterated compounds.[16]

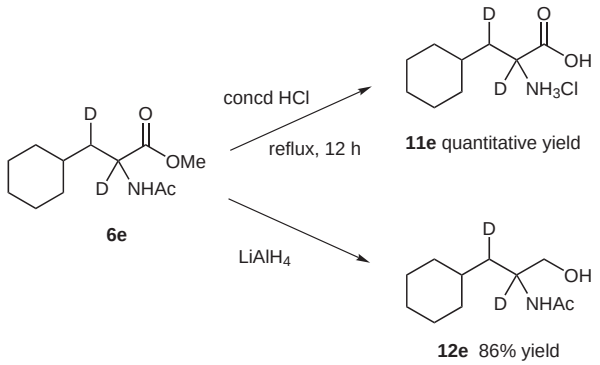
To demonstrate some synthetic applications of the obtained α-amino esters **6**, a selected example was readily transformed into isotopically labeled α-amino acids[2,3] **11** and dideuterated 1,2-amino alcohols **12**[17] (Scheme 3).[18]

These reactions took place in very high yields and no loss of the deuterium atoms were observed in both cases.

In conclusion, we have described a general synthesis of isotopically labeled α-amino acid derivatives in good yields through a SmI_2-promoted 1,4-reduction process on readily available dehydroamino esters. Other different isotopically labeled compounds such as α-amino acids and 1,2-amino alcohols were accessed.



Scheme 2 Mechanistic proposal for the conversion of **5** into **6**



Scheme 3 Conversion of **6e** into **11e** and **12e**

Acknowledgment

We thank the Ministerio de Educación y Ciencia (CTQ2004-1191/BQU) for financial support. J.M.C. thanks Carmen Fernández-Flórez for her time. H.R.S. thanks the Ministerio de Educación y Ciencia for a Ramón y Cajal Contract (Fondo Social Europeo). Our thanks to Euan C. Goddard for his revision of the English.

References and Notes

(1) Mann, J. In *Secondary Metabolism*; Oxford University Press: Oxford, **1991**, Chap. 3, 417.
(2) For a review on the application of isotopic labeling in protein-structure determination, see: Lian, L.-Y.; Middleton, D. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **2001**, *39*, 171.
(3) For example, see: (a) Baldwin, J. E.; Adlington, R. M.; Marquess, D. G.; Pitt, A. R.; Porter, M. J.; Russell, A. T. *Tetrahedron* **1996**, *52*, 2515. (b) Church, N. J.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, *52*, 1475. (c) Pirrung, M. C. *Acc. Chem. Res.* **1999**, *32*, 711.
(4) (a) Namy, J.-L.; Girard, P.; Kagan, H. B. *New J. Chem.* **1977**, *1*, 5. (b) Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
(5) (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (b) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (c) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745. (d) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (e) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (f) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Soc. Rev.* **2004**, *33*, 599.

(6) (a) Molander, G. A. In *Organic Reactions*, Vol. 46; Paquette, L. A., Ed.; John Wiley: New York, **1994**, 211. (b) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (c) Concellón, J. M.; Rodríguez-Solla, H. *Eur. J. Org. Chem.* **2006**, 1613.
(7) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 4266.
(8) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2002**, *8*, 4493.
(9) Concellón, J. M.; Bernad, P. L.; Rodríguez-Solla, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3897.
(10) Concellón, J. M.; Bardales, E.; Gómez, C. *Tetrahedron Lett.* **2003**, *44*, 5323.
(11) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C. *Tetrahedron Lett.* **2004**, *45*, 2129.
(12) (a) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534. (b) Daumas, M.; Vo-Quang, L.; Le Goffic, F. *Synth. Commun.* **1990**, *20*, 3395. (c) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, *20*, 53.
(13) The solution of SmI_2 in THF was rapidly obtained by 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.
(14) **General Procedure for Compound 6a**
Under nitrogen, a solution of SmI_2 (1.2 mmol) in THF (15 mL) was added dropwise to a stirred solution of the starting material **5a** in D_2O (2 mL) and THF (2 mL) at r.t. The reaction mixture was stirred for 30 min and then treated with 0.1 M aq HCl (5 mL). Standard workup afforded the crude 2,3-dideuterio-2-amino ester **6a**, which was purified by flash column chromatography on SiO_2 (hexane–EtOAc, 5:1):
Methyl 2-Acetylamino-2,3-dideuteriodecanoate (6a)
R_f = 0.26 (hexane–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16 (br s, 1 H), 3.70 (s, 3 H), 1.99 (s, 3 H), 1.65–1.51 (m, 1 H), 1.33–1.10 (m, 12 H), 0.84 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (C), 169.8 (C), 52.1 (CH_3), 51.7 (t, *J* = 21.8 Hz, CD), 31.8 (t, *J* = 19.6 Hz, CHD), 31.6 (CH_2), 29.2 (CH_2), 29.0 (2 × CH_2), 24.9 (CH_2), 22.9 (CH_3), 22.5 (CH_2), 13.9 (CH_3). MS (70 eV): *m/z* (%) = 245 (5) [M^+], 186 (55), 144 (100). HRMS: *m/z* calcd for $C_{13}H_{23}D_2NO_3$: 245.1960; found: 245.1944. IR (neat): 3263, 3063, 2922, 1742, 1652, 1374 cm^{-1}.
(15) In the mass spectra (MS and HRMS) of deuterated compounds **6a**,**c**,**e**,**g**, the $[M]^+$ peaks of the corresponding nondeuterated compounds are either absent or very weak, indicating that these species are present to an extent of <2%.
(16) However, the deuteration of **8** to give **9** produced by D_2O could not be rejected.
(17) β-Amino alkanols are important building blocks and have been used to prepare a large number of biologically active natural and synthetic compounds, including unnatural amino acids: (a) Corey, E. J.; Zhang, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 1931. (b) O'Brien, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 326. (c) Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340. (d) Chang, B. L.; Ganesan, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1511. (e) Li, G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 451. (f) Rogers, G. A.; Parsons, S. M.; Anderson, D. S.; Nilson, L. M.; Bahr, B. A.; Kornreich, W. D.; Kaufman, R.; Jacobs, R. S.; Kirtman, B. *J. Med. Chem.* **1989**, *32*, 1217.
(18) **General Procedure for the Synthesis of Compound 11e**
2-Acetylamino-3-cyclohexyl-2,3-dideuteriopropanoic acid methyl ester (**6e**, 100 mg, 0.43 mmol) was refluxed in concd HCl for 12 h. Then, aq HCl was evaporated at low pressure and 2-amino-3-cyclohexyl-2,3-dideuteriopropanoic acid hydrochloride was recovered as a colorless solid; quant. yield. ^{1}H NMR (300 MHz, D_2O): δ = 1.68 (d, *J* = 7.9 Hz, 1 H), 1.63–1.40 (m, 5 H), 1.35–1.21 (m, 1 H), 1.10–1.01 (m, 3 H), 0.98–0.72 (m, 2 H). ^{13}C NMR (75 MHz, D_2O): δ = 175.3 (C), 52.8 (CD, *J* = 20.5 Hz), 39.3 (CHD, *J* = 19.0 Hz), 35.2 (CH), 34.9 (CH_2), 34.1 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 27.7 (CH_2). IR (neat): = 3425, 2926, 1652, 1265 cm^{-1}.
General Procedure for the Synthesis of Compound 12e
To a solution of 2-acetylamino-3-cyclohexyl-2,3-dideuteriopropanoic acid methyl ester (**6e**, 57 mg, 0.25 mmol) in THF (5 mL), a 1.0 M in THF solution of $LiAlH_4$ (0.28 mL, 0.28 mmol) was added dropwise at 0 °C under nitrogen. The resulting solution was stirred at r.t. for 12 h, then quenched with ice water and filtered through a pad of Celite®. The aqueous layer was extracted with Et_2O, dried over Na_2SO_4 and finally the solvents were removed under vacuum, to afford 2-acetylamino-3-cyclohexyl-2,3-dideuteriopropan-1-ol as a white solid; 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.63 (br s, 1 H), 3.66 (d, *J* = 11.1 Hz, 1 H), 3.50 (d, *J* = 11.1 Hz, 1 H), 2.01 (s, 3 H), 1.79–0.84 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (C), 66.3 (CH_2), 49.1 (t, *J* = 20.0 Hz, CD), 38.2 (t, *J* = 19.5 Hz, CHD), 34.1 (CH), 33.6 (CH_2), 32.8 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 23.4 (CH_3). IR (neat): 1653, 1636, 1558, 1540 cm^{-1}.