Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5323–5326

TETRAHEDRON LETTERS

Unusual reductive cleavage of 3-aryl-2,3-epoxyamides by using samarium diiodide. Synthesis of 3-aryl-3-deuterio-2-hydroxyamides with total regioselectivity

José M. Concellón,[a,*] Eva Bardales[a] and Cecilia Gómez[b]

[a]*Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, Julián Clavería, 8, 33071 Oviedo, Spain*

[b]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, 03080 Alicante, Spain*

Received 29 April 2003; revised 5 May 2003; accepted 9 May 2003

Abstract—Ring-opening of 3-aryl-2,3-epoxyamides **1** was achieved by using samarium diiodide and D_2O, yielding 3-aryl-3-deuterio-2-hydroxyamides **2** with total regioselectivity. The starting compounds **1** were easily prepared by reaction of the corresponding lithium or potassium enolates of α-chloroamides with aldehydes or ketones. When the reaction was carried out in the presence of H_2O instead of D_2O, the corresponding 3-aryl-2-hydroxyamides were isolated. The treatment of enantiopure 3-aryl-2,3-epoxyamides afforded optically active 3-aryl-2-hydroxyamides.

Racemic and optically active α,β-epoxycarbonyl compounds, such as aldehydes, ketones and acid derivatives, are versatile building blocks in organic synthesis,[1] due to both carbonyl and epoxide moieties can be subsequently functionalized and have been used as starting compounds for the synthesis of natural products.[2]

In particular, several methodologies[3] have been described to transform α,β-epoxycarbonyl compounds into the corresponding β-hydroxycarbonyl compounds (aldol-type products) through a reductive cleavage of the C_α–O bond of the oxirane ring. Probably the most effective methodology makes use of SmI_2, which in the presence of a proton source promotes the reductive cleavage affording 3-hydroxyketones[4] or 3-hydroxyesters.[5] However, to the best of our knowledge, only a paper describing the transformation of α,β-epoxyacid derivatives into the synthetically highly interesting α-hydroxyacid derivatives has been described.[6] In this respect, methodologies to obtain α-hydroxycarbonyl compounds by reduction of the C_β–O bond of α,β-epoxycarbonyl compounds would be synthetically attractive, due to the difficult preparation of the latter by other synthetic routes.[7] In addition, α-hydroxyacid derivatives are frequently encountered as parts of natural products,[8] and also serve as useful intermediates in organic synthesis,[9] whilst certain derivatives possess anticancer properties.[10]

Recently, we have reported the transformation of α,β-epoxyesters into α,β-unsaturated esters promoted by SmI_2,[11] or into 2,3-dideuterioesters by successive treatment with SmI_2 and D_2O,[12] respectively. In this last paper, treatment of aliphatic and aromatic α,β-epoxyesters with SmI_2 in the presence of D_2O afforded 2-deuterio-3-hydroxyesters.

Here we report the synthesis of 3-aryl-*2*-hydroxyamides **2** with total regioselectivity by a reductive cleavage of the C_β–O bond of 3-aryl-2,3-epoxyamides **1**,[13] promoted by SmI_2 in the presence of H_2O. When the reaction of aromatic compounds **1** was carried out with D_2O instead of H_2O, the corresponding 3-aryl-3-deuterio-2-hydroxyamides **2** were obtained. When the reaction of 3-alkyl-2,3-epoxyamides **3** was performed in the presence of H_2O or D_2O, reductive cleavage of the C_α–O bond instead of C_β–O of **3** took place and the corresponding regioisomers 3-alkyl-3-hydroxyamides or 3-alkyl-2-deuterio-3-hydroxyamides **4** were isolated. Finally, starting from enantiomerically enriched 3-aryl-2,3-epoxyamides, this process provided an excellent means to generate enantiomerically enriched 3-aryl-2-hydroxyamides.

Disubstituted epoxyamides (**1b** and **1c**) were prepared by reaction of lithium enolate of chloroacetamide (gen-

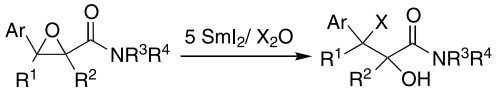
* Corresponding author.

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01201-2

erated by treatment of α-chloroacetamide with LDA at −78°C) with benzaldehyde and further treatment with sodium hydride.[14] Trisubstituted epoxyamides (**1d–j** and **3**) were obtained by reaction of the corresponding potassium enolates of α-chloroamides (generated by treatment of α-chloroamides with potassium hexamethyldisilazide at −78°C) with different aldehydes at temperatures ranging from −78 to 25°C. Tetrasubstituted epoxyamides (**1k** and **1l**) were obtained by reaction of lithium enolate of chloropropanamide with different ketones at temperatures ranging from −78 to 25°C.

With the starting 3-aryl-2,3-epoxyamides **1** in hand, we first investigated the reductive cleavage of 2,3-epoxy-*N*,*N*-diisopropyl-3-[4-(methoxy)phenyl]-2-methylpropanamide **1g** by using SmI_2[15] in the presence of H_2O, to determine the optimum reaction conditions of this transformation. The best results were obtained by treatment of **1g** with 5 equiv. of SmI_2 (long or very long reaction times were necessary by using less than 5 equiv. of SmI_2), in the presence of H_2O, for 5 h at −78°C.[16] These reaction conditions were applied to different 3-aryl-2,3-epoxyamides **1** using D_2O[17] instead of H_2O, and 3-aryl-3-deuterio-2-hydroxyamides were isolated with total regioselectivity (Scheme 1 and Table 1).[18]

The proposed methodology to obtain 3-aryl-3-deuterio-2-hydroxyamides is general. Thus, the reaction was carried out with electron rich or deficient groups at the aromatic ring, was unaffected by the presence of bulky groups or H (R^3,R^4) on nitrogen (Table 1, compounds **2a**,**c**,**2g–2i**) and can be performed starting from 3-aryl-2,3-epoxyamides in which the oxirane ring is di, tri or tetrasubstituted.[19]



1 **2**

X = H, D

Scheme 1. Synthesis of 3-aryl-3-deuterio-2-hydroxyamides **2**.

Table 1. Synthesis of 3-aryl-3-deuterio-2-hydroxyamides **2**

2[a]	Ar	R^1	R^2	R^{3b}	X	Yield (%)[c]
2a	Ph	H	H	Me	H	71
2b	Ph	H	H	Et	D	60
2c	Ph	H	H	*i*-Pr	D	80
2d	Ph	H	Me	Et	D	64
2e	Ph	H	Bu	Et	D	73[d]
2f	*p*-$MeOC_6H_4$	H	Me	Et	D	50[d]
2g	*p*-$MeOC_6H_4$	H	Me	*i*-Pr	H	70[d]
2h	*p*-$MeOC_6H_4$	H	Me	*i*-Pr	D	73[d]
2i	*p*-ClC_6H_4	H	Bu	*i*-Pr	D	67[d]
2j	*p*-CNC_6H_4	H	Me	Et	D	69[d]
2k	Ph	Me	Me	Et	D	79
2l	Ph	Et	Me	Et	H	76

[a] All products were fully characterized by spectroscopic methods [IR, NMR, MS and mp (**2a**,**c**,**e**, **2g–2j**)].

[b] In all cases $R^3 = R^4$, except compound **2a** wherein R^3 = Me and R^4 = H.

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

[d] Isolated yield after vacuum distillation based on compound **1**.

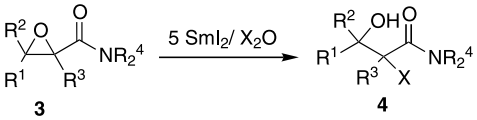
The regiochemistry (>98%) of the opening of the oxirane ring was established by analysis of ^{13}C NMR spectra and DEPT experiments of compounds **2d–j**, showing that the hydroxy group is bonded to a quaternary carbon atom. The structures of compounds **2a–c** and **2k–l** were established based on analysis of their mass spectrum. To corroborate the structures of **2a** and **2l**, a condensation of corresponding aldehyde or ketone and the lithium enolate of acetamide or propanamide, was carried out, respectively; ^{13}C NMR spectra of these aldol-type products were different to ^{13}C NMR spectra of **2a** and **2l**.

Complete deuterium incorporation was determined by mass spectroscopy, and was found to be > 98%.[20] These 3-aryl-3-deuterio-2-hydroxyamides were isolated as a mixture of diastereoisomers, roughly 1:1. Signals of the diastereoisomers could not be detected in the ^1H and ^{13}C NMR spectra of compounds **2a–j**. However, ^{13}C NMR spectrum of compound **2c** *O*-acetylated shown all signals corresponding to both diastereoisomers (roughly 1:1).

Several facts can be emphasized: (a) D_2O is the cheapest deuteration reagent to obtain organic compounds isotopically labeled with deuterium; (b) C-3 deuteration of acid derivatives is difficult to achieve by using other methodologies and (c) to the best of our knowledge, no synthesis of 3-deuterio-2-hydroxyamides has been reported.

When similar reaction conditions were applied to 3-alkyl-2,3-epoxyamides **3** (Scheme 2), the opening of the oxirane ring took place by cleavage of C_α–O bond (DEPT experiments, mass spectra), following the same regiochemistry of the α,β-epoxyesters.[5,12] Thus, 3-alkyl-3-hydroxyamides (with H_2O) or 3-alkyl-2-deuterio-3-hydroxyamides (with D_2O) were isolated, respectively (Table 2).[21]

Ideally, a proposed mechanism for this reaction should also explain the opposite regiochemistry of the opening of the oxirane ring in amides with respect to the esters. In this sense, the synthesis of products **2** may be explained (Scheme 3) by assuming the initial double coordination of samarium with both oxygen atoms, the carbonyl of the amide group and the oxirane ring. This initial quelation is not possible with α,β-epoxyesters



3 **4**

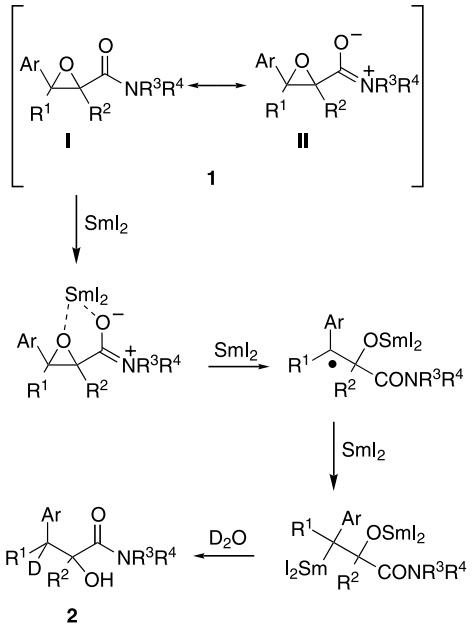
X = H, D

Scheme 2. Synthesis of 3-alkyl-2-deuterio-3-hydroxyamides **4**.

Table 2. Synthesis of 3-alkyl-2-deuterio-3-hydroxyamides **4**

4[a]	R^1	R^2	R^3	R^4	X	Yield (%)[b]
4a	C_7H_{15}	H	Me	Et	H	63
4b	MeCH(Ph)	H	Me	Et	D	61
4c	*n*-Bu	H	Ph	Et	D	64

[a] All products were fully characterized by spectroscopic methods [IR, NMR, MS and mp (**4c**)].
[b] Isolated yield after column chromatography based on compound **3**.

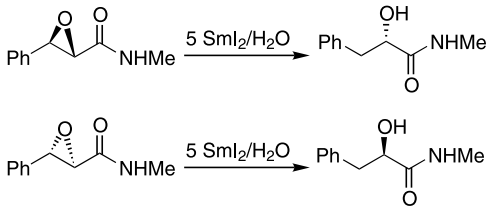


Scheme 3. Mechanistic proposal for the synthesis of 3-aryl-3-deuterio-2-hydroxyamides **2**.

since the resonance structure **II** is more favored in amides than esters (due to the electron-donating capacity of the nitrogen). The coordination of samarium with the oxirane ring produces a similar effect to that of a Lewis acid, and can evolve according to two pathways: (a) reduction of the C_α–O or (b) reduction of the C_β–O bond. In the case of α,β-epoxyesters the reduction of the C_α–O bond is favored, the obtained radical being efficiently stabilized by resonance, in contrast to α,β-epoxyamides. In addition, the cleavage of the C_β–O bond in 3-aryl-2,3-epoxyamides is favored as a result of a benzylic radical (stabilized by resonance) being obtained. A very fast second reduction with another equivalent of SmI_2 affords the corresponding anion, which is hydrolyzed by D_2O to yield 3-aryl-3-deuterio-2-hydroxyamides.

When the reaction was performed with 3-alkyl-2,3-epoxamides by using similar reaction conditions (in the presence of H_2O or D_2O), 3-alkyl-3-hydroxyamides were obtained. In this case, this is because the radical cannot be stabilized by resonance, and the C_α–O bond is reduced instead of the C_β–O bond.

This methodology is also useful to obtain enantiomerically enriched 3-aryl-2-hydroxyamides. Thus, (2*S*,3*R*)-



Scheme 4. Synthesis of enantiomerically enriched 3-aryl-2-hydroxyamides (**2a**).

and (2*R*,3*S*)-2,3-epoxy-*N*-methyl-3-phenylpropanamide (from Sharpless epoxidation of (*E*)-3-phenylprop-2-en-1-ol,[22] further oxidation[23] and conversion into the amide[24]) were transformed into enantiopure (2*S*)- or (2*R*)-2-hydroxy-*N*-methyl-3-phenylpropanamide, respectively (Scheme 4), with complete retention of configuration at α-carbon atom.

Starting from the enantiomer (2*R*,3*S*) with a >99% ee, the (2*R*)-hydroxyamide was obtained with a >99% ee, determined by comparison of their [α] with those previously described.[6] In the case of the other enantiomer, a similar result was obtained. Thus, the combination of the present method with the Sharpless process is considered to provide an efficient route to optically active 3-aryl-2-hydroxyamides.

In conclusion, an easy and general methodology has been developed to synthesize aromatic 3-aryl-3-deuterio-2-hydroxyamides, 3-alkyl-2-deuterio-3-hydroxyamides or enantiopure 3-aryl-2-hydroxyamides with total regioselectivity from the easily available 2,3-epoxyamides, the reaction being promoted by samarium diiodide. A mechanism has been proposed to explain this reaction, as well as the different regiochemistries observed with respect α,β-epoxyesters.

Acknowledgements

We thank II Plan Regional de Investigación del Principado de Asturias (PB-EXP01-11) and Ministerio de Ciencia y Tecnología (BQU2001-3807) for financial support. J.M.C. thanks Carmen Fernández-Flórez for her time and E.B to Principado de Asturias for a predoctoral fellowship. Thanks to Robin Walker for his revision of the English.

References

1. Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359–2383.
2. (a) Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251–4254; (b) Fernández, M. V.; Durante-Lanes, P.; López-Herrera, F. J. *Tetrahedron* **1990**, *23*, 7911–7922; (c) López-Herrera, F. J.; Sarabia-Garcia, F.; Pino-González, M. S. *Tetrahedron Lett.* **1994**, *35*, 2933–2936.
3. (a) Mohrig, J. R.; Vreede, J. P.; Schultz, S. C.; Fierke, C. A. *J. Org. Chem.* **1981**, *46*, 4655–4658; (b) Chong, J. M.;

Sharpless, K. B. *Tetrahedron Lett*. **1985**, *26*, 4683–4686; (c) Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshokoshi, A. *Chem. Lett*. **1988**, 507–508; (d) Torii, S.; Okumoto, H.; Nakayuso, S.; Kotani, T. *Chem. Lett*. **1989**, 1975–1978; (e) Fabio, R.; Sotgiu, G.; Cavagnero, S. *Tetrahedron* **1989**, *45*, 2895–2904; (f) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469–12486; (g) Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359–2383.

4. Molander, G. A.; Hahn, G. *J. Org. Chem*. **1986**, *51*, 2596–2599.
5. (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett*. **1987**, *28*, 4437–4440; (b) Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem*. **1986**, *51*, 5259–5259; (c) Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett*. **1991**, *32*, 4477–4480.
6. While this communication was being written, a synthesis of α-hydroxyamides from α,β-epoxyamides was described: Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc*. **2002**, *124*, 14544–14545.
7. (a) Johnson, H. E.; Grosby, D. *J. Org. Chem*. **1963**, *28*, 3255–3256; (b) Grison, C.; Coutrot, F.; Comoy, C.; Lemilbeau, C.; Coutrot, P. *Tetrahedron Lett*. **2000**, *41*, 6571–6574.
8. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, 1988; Vol. 2, p. 680.
9. α-*Hydroxy Acids in Enantioselective Syntheses*; Coppola, G. M.; Schuster, H. F., Eds.; VCH: Weinheim, 1997.
10. Markaverich, B. M.; Gregory, R. R.; Alejandro, M. A.; Kittrell, K. S.; Medina, D.; Clark, J. H.; Varma, M.; Varma, R. S. *Cancer Res*. **1990**, *50*, 1470–1478.
11. Concellón, J. M.; Bardales, E. *Org. Lett*. **2002**, *4*, 189–191.
12. Concellón, J. M.; Bardales, E. *J. Org. Chem*. **2003**, *68*, 1585–1588.
13. To the best of our knowledge treatment of α,β-epoxyamides with SmI_2 has not been described to date.
14. Compound **1a** was prepared by reaction of potassium enolate of ethyl chloroacetate with benzaldehyde[10] and further conversion into the amide.[21]
15. SmI_2 was prepared very rapidly by sonication of a mixture of samarium powder and diiodomethane in THF: Concellón, J. M.; Rodriguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem*. **2003**, 1775–1778.
16. When the reaction was carried out at a higher temperature, the corresponding α,β-unsaturated amide was obtained. Reactions are in course in order to study this β-elimination reaction.
17. Isotopic labeled compounds are very usefulness to establish the mechanism of the organic reactions and the biosynthesis of many natural compounds: Mann, J. *Secondary Metabolism*; Oxford University Press: Oxford, 1986; p. 23.
18. General procedure for the synthesis of compounds **2**: A solution of SmI_2 (2.3 mmol) and H_2O (0.4 mL) or D_2O (0.4 mL) in THF (24 mL) was added under a nitrogen atmosphere, to a stirred solution of aromatic α,β-epoxyamide **1** (0.4 mmol) in THF (2 mL) at −78°C. The mixture was stirred for 5 h at this temperature and then quenched with aqueous HCl (0.1 M, 15 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford crude 3-aryl-2-hydroxyamides or 3-aryl-3-deuterio-2-hydroxyamides **2**, which were purified by flash column chromatography on silica gel (hexane/AcOEt 3:1) or vacuum distillation (see Table 1).
19. In the case of aromatic tetrasubstituted α,β-epoxyamides, the reaction was carried out at −25°C during 3.5 h.
20. MS and HRMS spectra of the deuterated compounds **2**, show lack or a very weak peak of the M^+ of the corresponding undeuterated compounds, indicating a presence of the no deuterated compound <1%.
21. General procedure for the synthesis of compounds **4**: A solution of SmI_2 (2.3 mmol) and H_2O (0.4 mL) or D_2O (0.4 mL) in THF (24 mL) was added under a nitrogen atmosphere, to a stirred solution of **3** (0.4 mmol) in THF (2 mL) at −25°C. The mixture was stirred for 2.5 h at this temperature and then quenched with aqueous HCl (0.1 M, 15 mL). The same workup used for isolated compounds **2** afforded crude 2-deuterio-3-hydroxyamides **4**, which were purified by flash column chromatography on silica gel (hexane/AcOEt, 3:1).
22. Gau, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *65*, 5765–5779.
23. Huang, D. F.; Huang, L. *Tetrahedron* **1990**, *46*, 3135–3142.
24. Estiarte, M. A.; Rubiralta, M.; Diez, A. *J. Org. Chem*. **2002**, *67*, 6992–6999.