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The First Transformation of Aliphatic α,β-Epoxyamides into α-Hydroxyamides

José M. Concellón* and Eva Bardales

Departamento de Química Orgánica e Inorgánica, Facultad de Química Universidad de Oviedo, Julián Clavería, 8, 33071 Oviedo, Spain

jmcg@sauron.quimica.uniovi.es

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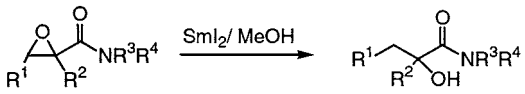
ABSTRACT



A general synthesis of aliphatic α-hydroxyamides with total regioselectivity by a reductive cleaveage of the C_β-O bond of aliphatic α,β-epoxyamides, promoted by samarium diiodide and MeOH, is described. The treatment of enantiopure aliphatic α,β-epoxyamides afforded enantiomerically enriched aliphatic α-hydroxyamides. A radical mechanism has been proposed to explain this reaction.

α-Hydroxy acid derivatives are frequently encountered as parts of natural products.[1] Some of these products (or their derivatives) possess anticancer properties,[2] while also being versatile building blocks in organic synthesis.[3]

Despite this, the synthesis of α-hydroxy acid derivatives has been scarcely reported.[4] Taking into account the easy preparation of α,β-epoxy acid derivatives, their transformation into α-hydroxy acid derivatives would be synthetically very attractive. In this sense, only a paper showing the transformation of aromatic α,β-epoxyamides into α-hydroxyamides has been described.[5] In relation to the synthetic application of samarium diiodide, transformation of α,β-epoxy carbonyl compounds into β-hydroxyketones[6] or β-hydroxyesters[7] by using SmI_2 in the presence of a proton source has been described. To the best of our knowledge, no general transformation of aliphatic α,β-epoxycarbonyl compounds into α-hydroxycarbonyl compounds has been decribed.

Recently, we have reported the transformation, with total regioselectivity, of aromatic α,β-epoxyamides into α-hydroxycarboxamide or β-deuterio-α-hydroxycarboxamides, promoted by SmI_2 in the presence of H_2O or D_2O, respectively. However, this transformation was limited to aromatic amides, and when aliphatic epoxyamides were used as starting compounds, β-hydroxycarboxamides or α-deuterio-β-hydroxycarboxamides were isolated by using H_2O or D_2O, respectively. In the previous paper,[8] an anionic mechanism is proposed to explain these transformations.

Herein, we report a general synthesis of aliphatic α-hydroxycarboxamides **2** with total regioselectivity by reductive cleavage of the C_β-O bond of aliphatic α,β-epoxycarboxamides **1**, promoted by SmI_2. The reaction conditions to obtain aliphatic α-hydroxyamides are different from those previously described to prepare aromatic α-hydroxyamides, using methanol as the protic medium instead of H_2O or D_2O. A radical mechanism is proposed to justify this transformation (from aliphatic α,β-epoxyamides) in contrast to the anionic mechanism proposed for the synthesis of aromatic α-hydroxyamides. Enantiomerically enriched α-hydroxycarboxamides can be obtained starting from enantiomerically enriched α,β-epoxycarboxamides, this being an excellent means to generate these synthetically important compounds.

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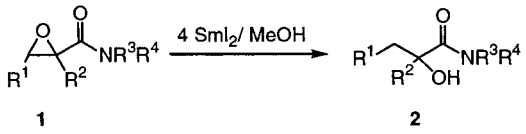
Scheme 1. Synthesis of Aliphatic α-Hydroxyamides **2**



Treatment of different aliphatic α,β-epoxyamides **1** with a mixture of a solution of 4 equiv[9] of SmI_2 in THF[10] and methanol over 3 h at room temperature afforded α-hydroxyamides with total regioselectivity (Scheme 1 and Table 1).[11]

Table 1. Synthesis of Aliphatic α-Hydroxyamides **2**.

entry	2[a]	R^1	R^2	R^3	yield[b]
1	**2a**	C_7H_{15}	H	Me	71%
2	**2b**	C_7H_{15}	H	Et	70%
3	**2c**	cyclohexyl	H	*i*-Pr	80%
4	**2d**	$Me_2C{=}CH(CH_2)_2CHMeCH_2$	H	Et	68%
5	**2e**	*i*-Bu	Me	Et	68%
6	**2f**	C_7H_{15}	Me	Et	72%
7	**2g**	cyclohexyl	Me	Et	63%
8	**2h**	cyclohexyl	Bu	Et	70%
9	**2i**	$Me_2C{=}CH(CH_2)_2CHMeCH_2$	Me	Et	62%

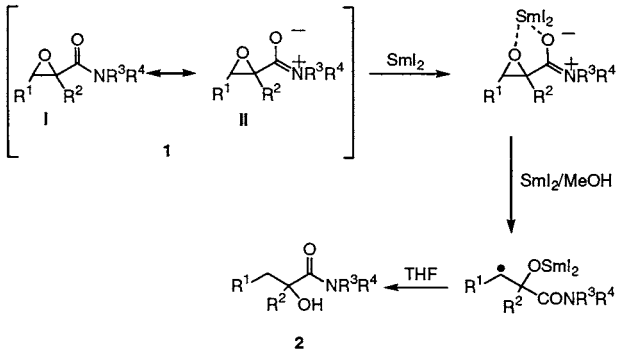
[a] In all cases, $R^3 = R^4$, except compound **2a,** wherein R^3 = Me and R^4 = H. [b] Isolated yield after column chromatography based on compound **1**.

Starting compounds **1** were easily obtained by treatment of potassium enolates derived from 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.[12]

This transformation seems to be general and can be performed starting from aliphatic amides bearing bulky groups R^3 on the nitrogen (Table 1, entry 3), with the oxirane ring di- or trisubstituted, and with R^1 linear, branched, or cyclic.

Analysis of ^{13}C NMR spectra and DEPT experiments of these compounds was performed to establish the structures of compounds **2e**−**i**, and consequently the regiochemistry of the ring opening of the oxirane, showing that the hydroxy group is bonded to a tertiary carbon atom. The structures of **2a**−**d** were established on the basis of analysis of their mass spectra. In addition, NMR spectra of **2c** and NMR spectra of the product obtained from the condensation of cyclohexanecarboxaldehyde and the lithium enolate of acetamide were different, confirming the proposed structure of **2c**. This described method complements the previously described reduction of aliphatic α,β-epoxyamides by using SmI_2 and H_2O.[8] Thus, using MeOH or H_2O as the protic medium allows aliphatic α- or β-hydroxyamides to be isolated.

Scheme 2. Mechanistic Proposal for the Synthesis of Aliphatic α-Hydroxyamides **2**



Taking into account the usefulness of deuterated compounds,[13] the same reaction was performed by using MeOD or CD_3OD instead of MeOH. However, deuterium incorporation, determined by mass and ^{13}C NMR spectroscopy, was not observed. This suggests a radical rather than an anionic mechanism. Additional support for a radical mechanism was provided by the detection of dimerization products when THF was substituted by THF-d_8.[14] In contrast to the reaction in THF, when the THF-d_8 is used as a solvent, dimerization of radical species should be faster than deuterium abstraction from THF-d_8 (isotope effect).[15]

It is noteworthy that this C-3 ring-opening reaction of α,β-epoxyamides promoted by SmI_2 has not been previously observed (α,β-epoxy esters afford β-hydroxy esters). The opposite regiochemistry of the opening of the oxirane ring in amides with respect to esters may be explained (Scheme 2) by assuming the initial double coordination of samarium with both oxygen atoms, the carbonyl of the amide group, and the oxirane ring. This initial chelation of SmI_2 to the α,β-epoxyamides is stronger than chelation to a α,β-epoxy esters since the resonance structure **II** is more favored in amides than in esters due to the electron-donating capacity of the nitrogen. The coordination of samarium with the oxirane ring produces an effect similar to that of a Lewis acid. Under the reaction conditions used, reduction of the C_β-O bond takes place, affording the more stable radical

(9) When minor amounts of SmI_2 were used, the α-hydroxyamides obtained were contaminated with other products of radical coupling.

(10) A 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.; Rodriguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775−1778.

(11) **Representative Procedure for the Synthesis of 2.** A solution of SmI_2 (1.6 mmol) and MeOH (0.5 mL) in THF (19 mL) was added, under a nitrogen atmosphere, to a stirred solution of aliphatic α,β-epoxyamide **1** (0.4 mmol) in THF (2 mL) at 25 °C. The mixture was stirred for 3 h at this temperature and then quenched with aqueous HCl (0.1 M, 15 mL). Usual workup afforded crude 2-hydroxyamides **2**, which were purified by flash column chromatography on silica gel (hexane/AcOEt).

(12) Disubstituted epoxyamide compounds **1a**−**c** were prepared by reaction of the lithium enolate of chloroacetamide with the correspondig aldehyde and further treatment with sodium hydride. See Supporting Information.

(13) Isotope-labeled compounds are very useful for establishing the mechanism of organic reactions and the biosynthesis of many natural compounds: Mann, J. *Secondary Metabolism*; Oxford University Press: Oxford, 1986; p 23.

(14) Results of the synthesis of dimerization products are being studied.

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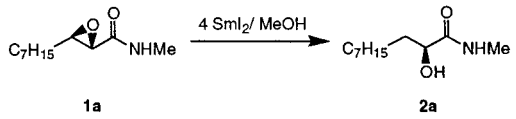
Scheme 3. Synthesis of Enantiomerically Enriched α-Hydroxyamide **2a**



(Scheme 3).[16] This radical abstracts one H from THF to afford α-hydroxyamides **2**.

Enantiomerically enriched α-hydroxyamides can also be prepared. Thus, optically pure α,*β*-epoxyamide **1a** (obtained from Sharpless epoxidation of the corresponding allyl alcohol,[17] further oxidation,[18] and conversion into the amide[19]) was transformed into the enantiopure α-hydroxyamide **2a**, with complete retention of configuration at the α-carbon atom (Scheme 3). Thus, the combination of the present method with the Sharpless process is considered to provide an efficient route to optically active α-hydroxy amides.

In conclusion, we have described the first method for synthesizing aliphatic α-hydroxyamides with total regioselectivity from the easily available α,*β*-epoxyamides, the reaction being promoted by samarium diiodide. A radical mechanism has been proposed to explain this reaction.

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Supporting Information Available: Experimental procedure of **1**, spectroscopic data of **1** and **2**, and ^{13}C NMR spectra of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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