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Sequential Elimination−Cyclopropanation Reactions Promoted by Samarium: Highly Diastereoselective Synthesis of Cyclopropylamides

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Abstract: *trans*-Cyclopropanamides were obtained, in high yield, from 2-chloro-3-hydroxyamides by a sequenced elimination−cyclopropanation process promoted by Samarium/diiodomethane or Samarium diiodide and Samarium/diiodomethane.

The cyclopropyl group is unique among carbocycles in both its properties and reactions.[1] This structural unit is found in a number of significant natural products,[2] as well as in synthetic compounds of importance in biological studies.[3] In addition, cyclopropane derivatives provide building blocks of unprecedented synthetic potential.[4]

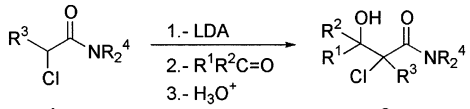
Recently, we reported a new methodology for stereospecific cyclopropanation of (*Z*)- or (*E*)-α,*β*-unsaturated amides, in which the cyclopropane ring is di-, tri-, or tetrasubstituted, by using samarium and diiodomethane.[5]

Here we describe an easy and general methodology for obtaining *trans*-cyclopropanamides in high yield starting from 2-chloro-3-hydroxyamides through a sequenced elimination−cyclopropanation process in which the elimination is promoted by a mixture of samarium and diiodomethane or by SmI_2 and the cyclopropanation is carried out by using Sm/CH_2I_2.

The starting 2-chloro-3-hydroxyamides **2** were easily prepared in high yield by reaction of the corresponding lithium enolates of α-chloroamides[6] (generated by reaction of α-chloroamides **1** with LDA at −85 °C) with aldehydes or ketones at −78 °C (Scheme 1).

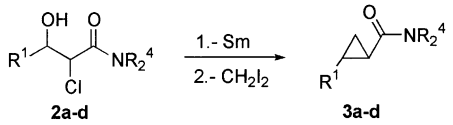
With the starting compounds **2** in hand, studies were first performed to obtain disubstituted cyclopropanamides. Treatment of 2-chloro-3-hydroxyamides **2a**−**d** with Samarium metal and diiodomethane at 0 °C gave the corresponding *trans*-cyclopropylamides **3a**−**d**, after hydrolysis, with total diastereoselectivity and in high yield (see Scheme 2 and Table 1).

SCHEME 1. Synthesis of Starting Compounds 2



1 **2**

SCHEME 2. Synthesis of Disubstituted Cyclopropanecarboxamides 3



2a-d **3a-d**

TABLE 1. Synthesis of Disubstituted Cyclopropylamides 3 ($R^2 = R^3 = H$)

entry	3[a]	R^1	R^4	yield (%)[b]
1	**3a**	C_7H_{15}	*i*-Pr	96
2	**3b**	MeCH(Ph)	Et	81
3	**3c**	C_6H_{11}	Et	94
4	**3d**	Ph	Et	80

[a] All products were obtained with complete stereospecificity (see text). Diastereoisomeric purity was determined by GC-MS and ^1H and ^{13}C NMR. [b] Isolated yield after column chromatography based on compound **2**.

The diastereoisomeric excess of compounds **3a**−**d** was determined on the crude reaction products by ^1H NMR spectroscopy (300 MHz) and GC-MS, showing the presence of a single diastereoisomer. The relative trans configuration in the cyclopropane ring was established by analysis of ^1H NMR coupling constants between the cyclopropane protons of compounds **3a**−**d**[7] and by comparison with authentic samples.[5]

Results in Table 1 show that this cyclopropanation reaction (a) is general and can be carried out starting from aliphatic (lineal, branched or cyclic) or aromatic compounds and (b) is unaffected by the presence of bulky groups R^4 on the carbonyl amide (Table 1, entry 1).

To explain this transformation, a sequential process is proposed. In the first step a *β*-elimination reaction promoted by in situ-generated SmI_2[8] takes place, affording (*E*)-α,*β*-unsaturated amide **4** with total diastereoselectivity.[9] In the second step of this process, a cyclopropanation reaction of the obtained **4** is produced by a samarium carbenoid. This cyclopropanation reaction takes place with complete stereospecificity[5] (Scheme 3).

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(2) (a) Liu, H. W.; Walsh, C. T. Biochemistry of the Cyclopropyl Group. In *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; Wiley and Sons: New York, 1987; Chapter 16. (b) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2252−2253. (c) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589−8627. (d) Solaün, J. *Top. Curr. Chem.* **2000**, *207*, 1−67. (e) Beumer, R.; Reiser, O. *Tetrahedron* **2001**, *57*, 6497−6503. (f) Alami, A.; Calnes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5−24.

(3) (a) Breckenridge, R. J.; Suckling, C. J. *Tetrahedron* **1986**, *42*, 5665−5677. (b) Arai, Y.; Konno, M.; Shimoji, K.; Konishi, Y.; Niwa, H.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1982**, *30*, 379−382.

(4) Carbocyclic Three- and Four-Membered Ring Systems. In *Houben-Weyl Methods of Organic Chemistry*; De Meijere, A., Ed.; 1997; Vol. E17a−f.

(5) Concellón, J. M.; Rodríguez-Solla, H.; Gómez, C. *Angew. Chem.* **2002**, *114*, 1997−1999; *Angew. Chem., Int. Ed.* **2002**, *41*, 1917−1919.

(6) Chloroamides **1** were prepared by treatment of 2-chloroacid chlorides with amines.

(7) Morris, D. G. Nuclear Magnetic Resonance and Infrared Spectra of Cyclopropanes and Cyclopropenes. In *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; Wiley and Sons: New York, 1987; Chapter 3.

(8) When the metalation reaction of **2** was carried out, at room temperature or at reflux, by using samarium metal without of diiodomethane, no reaction was observed.

(9) (a) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem.* **2000**, *112*, 2866−2868; *Angew. Chem., Int. Ed.* **2000**, *39*, 2773−2775. (b) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 3062−3068

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SCHEME 3. Proposed Sequential Reactions for the Conversion of 2 into 3

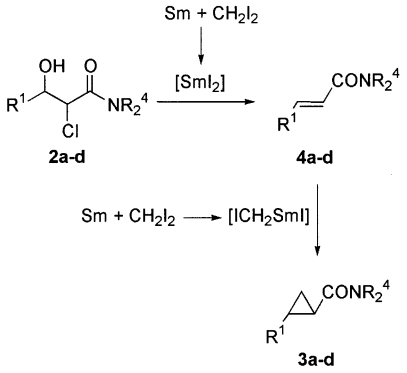


TABLE 2. Synthesis of Tri- and Tetrasubstituted Cyclopropanocarboxamides 3

entry	**3**[a]	R^1	R^2	R^3	de[b]	yield (%)[c]
1	**3e**	Bu	H	Et	93	85
2	**3f**	C_6H_{11}	H	Me	>98	95
3	**3g**[d]	*p*MeO−C_6H_4	H	Me	76[e]	63
4	**3g**[d]	*p*MeO−C_6H_4	H	Me	91	59
5	**3h**	−$(CH_2)_5$−		Me		90
6	**3i**	$PhCH_2$	Me	Me	>98	91
7	**3j**	Ph	Et	Me	91	78

[a] Unless otherwise noted, R^4 = Et. [b] Diastereoisomeric excess was determined by GC-MS and ^1H and ^{13}C NMR. [c] Isolated yield after column chromatography based on compound **2**. [d] R^4 = *i*-Pr. [e] Elimination−cyclopropanation reaction was carried out using Sm/CH_2I_2 at 0 °C.

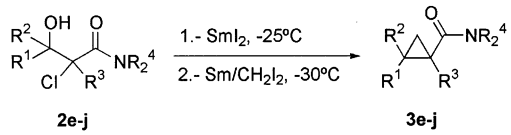
When the same reaction conditions (Sm/CH_2I_2, 0 °C) were used to prepare tri- or tetrasubstituted cyclopropanamides, a mixture of *cis*- and *trans*-cyclopropanamides was obtained (Table 2, entry 3). Taking into account that the cyclopropanation reaction is diastereospecific,[5] the loss of diastereoselectivity in the total sequenced process could be due to the low diastereoselectivity in the generation of tri- or tetrasubstituted α,*β*-unsaturated amides from **2**.[10] To increase the diastereoselectivity of the first step (*β*-elimination reaction), the reaction was performed at a lower temperature (−25 °C). However, satisfactory results were not obtained because the *β*-elimination reaction was incomplete, and a mixture of the corresponding cyclopropanamide **3** (with total or high diastereoselectivity) and starting compound **2** was isolated. To complete the first step, SmI_2 was used to promote the elimination instead of a mixture of metallic Sm and CH_2I_2. Thus, the successive treatment of 2-chloro-3-hydroxyamides **2e**−**j** with Samarium diiodide at −25 °C for 12 h and then with Sm metal and diiodomethane for 10 h gave the corresponding *trans*-cyclopropylamides **3d**−**j**, after hydrolysis, with total or high diastereoselectivity and in high yield (see Scheme 4 and Table 2).

Under these reaction conditions, the synthesis of tri- or tetrasubstituted cyclopropylamides is general and no important differences were observed upon changing R^1, R^2, R^3, or R.[4]

The diastereoisomeric excess of compounds **3e**−**j** was determined on the crude reaction products by ^1H NMR spectroscopy (300 MHz) and GC-MS. The relative trans configuration in the cyclopropane ring of compounds **3e**−**j** was established by NOE experiments (**3g** and **3j**) and by comparison with authentic samples.[5]

(10) Comparatively, the elimination reaction from compounds **2**, promoted by SmI_2, afforded tri- or tetrasubstituted α,*β*-unsaturated amides, with lower diastereoselectivity than that of disubstituted α,*β*-unsaturated amides; see ref 9b.

SCHEME 4. Synthesis of Tri- and Tetrasubstituted Cyclopropanecarboxamides 3



In conclusion, an easy, simple, and general transformation of 2-chloro-3-hydroxyamides into cyclopropylamides with very high or total diastereoselectivity has been developed. This sequenced elimination−cyclopropanation process was carried out by using Samarium/diiodomethane, in the case of disubstituted cyclopropanamides, and by successive addition of SmI_2 and a mixture of Sm/CH_2I_2, in the case of tri- or tetrasubstituted cyclopropanamides.

Experimental Section

General. Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased in the higher quality available and used without further purification. ^1H NMR spectra were recorded at 200, 300, or 400 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50, 75, or 100 MHz. GC-MS and HRMS were measured at 70 eV. A general procedure for the synthesis of α-chloro-*β*-hydroxyamides **1** and spectroscopic data have previously been described.[9b]

General Procedure for the Synthesis of Disubstituted Cyclopropanocarboxamides 3a−d and 3h. A solution of the corresponding 2-chloro-3-hydroxyamide (0.4 mmol) in THF (2 mL) was added to a suspension of samarium powder (2.4 mmol) in THF (24 mL). The mixture was cooled to 0 °C, and diiodomethane (2.4 mmol) was added dropwise. After the mixture was stirred at room temperature for 4 h, the reaction was quenched by the addition of 0.1 M aqueous HCl. Standard workup afforded the crude cyclopropanecarboxamides **3a**−**d** or the tetrasubstituted cyclopropylamide **3h**, which were purified by flash column chromatography on silica gel (5/1 hexane/ethyl acetate).

General Procedure for the Synthesis of Tri- or Tetrasubstituted Cyclopropanocarboxamides 3e−j. A solution of SmI_2 (1.6 mmol) in THF (12 mL) was added very slowly dropwise, under a nitrogen atmosphere, to a stirred solution of the corresponding 2-cloro-3-hydroxyamides **2e**−**j** (0.4 mmol) in THF (2 mL) at −25 °C. After 12 h, the mixture was cooled to −30 °C and metallic samarium (2.4 mmol), diiodomethane (2.4 mmol), and THF (16 mL) were added. The reaction mixture was stirred for 10 h, and then the reaction was quenched by the addition of 0.1 M aqueous HCl. Standard workup afforded the crude cyclopropanecarboxamides **3e**−**j**, which were purified by flash column chromatography on silica gel (5/1 hexane/ethyl acetate).

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Supporting Information Available: Spectral data and copies of ^{13}C NMR spectra of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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