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Novel Synthesis of 4-Carboxymethyl 5-Alkyl/Aryl Oxazolidin-2-ones by Rearrangement of 2-Carboxymethyl 3-Alkyl/Aryl *N-tert*-Butoxycarbonyl Aziridines

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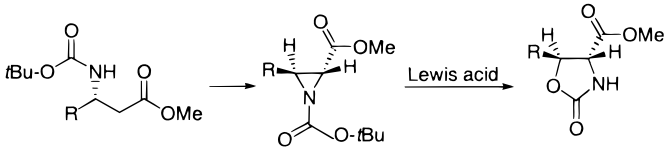
ABSTRACT



A two-step approach for the diastereoselective synthesis of 4-carboxymethyl 5-alkyl/aryl oxazolidin-2-ones is described, which proceeds via the intermediate formation of 2-carboxymethyl 3-alkyl/aryl *N-tert*-butoxycarbonyl (*N*-Boc) aziridines. By reaction of *N*-Boc *β*-amino methyl esters with LiHMDS and iodine, *trans* 2,3-disubstituted *N*-Boc aziridines are obtained with high stereoselectivities and yields. The final rearrangement to oxazolidin-2-ones is achieved by treatment with a catalytic amount of a Lewis acid and proceeds with high yield and complete regio- and stereoselectivity.

Polypeptides containing unusual amino acids are among the new interesting compounds which show high antibacterial or anticancer activity. In particular, *β*-hydroxy α-amino acids are widely present in macrocyclic polypeptides such as Lysobactin,[1] Vancomicin,[2] and Luzopeptidin E_2.[3]

A number of elegant approaches have been described for the synthesis of nonproteogenic *syn* and *anti* *β*-hydroxy α-amino acids.[4] Many of these methods involve derivatization of glycine equivalents attached to a chiral template, a difficult problem since they are rarely easily removable.

We propose here a novel synthesis of *trans* 4-alkyl/aryl 5-carboxymethyl oxazolidin-2-ones, which are the protected forms of *syn* *β*-hydroxy α-amino acids. These heterocycles are excellent protecting groups for amino alcohols and allow the derivatization of the nitrogen, so that polypeptide chains can be obtained without the hydrolysis of the heterocycle.[5]

The starting *N*-Boc *β*-amino methyl esters **1a**−**c** are easily obtained in good yields from the corresponding *β*-amino acids[6] by esterification with MeOH/$SOCl_2$ and reaction with Boc-anhydride and sodium carbonate.[7] By treatment with LiHMDS and iodine at low temperature, these substrates undergo cyclization with the formation of the corresponding 2-carboxymethyl 3-alkyl/aryl aziridines, with high diaste-

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(2) (a) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364. (b) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915. (c) Nagarajan, R.; Schabel, A. A.; Occolowitz, J. L.; Counter, F. T.; Ott, J. L. *J. Antibiot.* **1988**, *41*, 1431.

(3) (a) Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Am. Chem. Soc.* **1981**, *103*, 1241. (b) Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 1243.

(4) See for example: (a) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 6361 and references therein. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(5) Xi, N.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 6595.

(6) Racemic 3-aminobutanoic acid is commercially available. Racemic 3-amino-5-methylbutanoic acid was obtained according to: Lazar, L.; Martinek, T.; Bernath, G.; Fulop, F. *Synth. Commun.* **1998**, *28*, 219. Racemic 3-amino-3-phenylpropanoic acid was obtained according to: Rodionow, W. M.; Postovskaja, E. A. *J. Am. Chem. Soc.* **1929**, *51*, 841.

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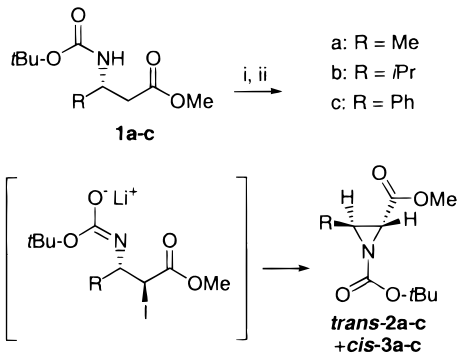
Scheme 1



Reagents and conditions: i) LiHMDS (2.2 equiv.), dry THF, -60 °C, 1 h; ii) I_2 (1.2 equiv.), -60° C, 30 min

Table 1. Chemical Yields and Diastereomeric Product Ratios for the Cyclization of Amidoesters **1a**−**c**

entry	R	yield (%)	*trans*/*cis* ratio
1	Me	80	87:13
2	*i*Pr	90	90:10
3	Ph	85	98:2

reoselectivity (Scheme 1 and Table 1).[8] As was previously observed by Seebach[9] and by us,[10] the reaction of the lithium dianion of N-protected β-amino esters with an electrophile affords the 2,3-*anti* adducts with both high yields and high stereoselectivities. When the electrophile is a good leaving group (as in the case of halogens), the direct formation of the corresponding aziridine is observed, since the halogen is substituted by the neighboring nitrogen.[11]

(7) Although these compounds have been used in the racemic form, it is well-known that β-amino acids can be obtained in the enantiomerically pure form by kinetic resolution of the corresponding phenylacetylamides by reaction with enzyme PGA, which selectively hydrolyzes amides of α- and β-amino acids of the *L* series. See: (a) Rossi, D.; Lucente, G.; Romeo, A. *Experientia* **1977**, *33*, 1557. (b) Soloshonok, V. A.; Svedas, V. K.; Kukhlar, V. P.; Kirilenko, A. G.; Rybakova, A. V.; Solodenko, V. A.; Fokina, N. A.; Kogut, O. V.; Galaev, I. Y.; Kozlova, E. V.; Shishkina, I. P.; Galushko, S. V. *Synlett* **1993**, 339. (c) Soloshonok, V. A.; Fokina, N. A.; Rybakova, A. V.; Shishkina, I. P.; Galushko, S. V.; Sorochinsky, A. E.; Kukhlar, V. P.; Savchenko, M. V.; Svedas, K. V.; *Tetrahedron: Asymmetry* **1995**, *7*, 1601. (d) Cardillo, G.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1996**, *61*, 8651. For general reviews reporting the asymmetric synthesis of β-amino acids, see: (e) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (f) Cole, D. C. *Tetrahedron* **1989**, *50*, 9517. (g) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. (g) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.

(8) (a) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (b) Zwanenburg, B.; Thjis, L. *Pure Appl. Chem.* **1196**, *68*, 735. (c) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (d) Fanta, P. E. In *Heterocyclic Compounds with Three- and Four-membered Rings*; Weissberg, A., Ed.; Wiley-Interscience: New York, 1964; Part 1, p 524.

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(11) In similar substrates, when the amine is protected with a benzoyl group, the exclusive formation of the oxazoline is observed.[10]

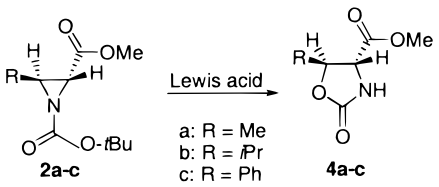
The results reported in Table 1 show that high yields and satisfactory diastereoselectivities are always achieved. The reported *trans*/*cis* ratio may be rationalized by the intermediate α-iodo derivative undergoing a competing Filkenstein reaction by some iodide ion prior to ring closure. This would account for the formation of a small amount of *cis* aziridine.

The products are obtained pure by flash chromatography and have been characterized by IR and NMR spectroscopy.[12]

Both the ring opening of N-acyl aziridines by means of an external nucleophile and their ring expansion by means of an internal nucleophile with formation of oxazolines are well-known.[13] The reactions proceed with high stereocontrol. The ring expansion of *N*-carboxyaziridines is usually catalyzed by a Lewis acid such as boron trifluoride, while the reaction of *N*-Boc aziridines with Brønsted acids has been reported in the past[14] and affords mixtures of products that also contain oxazolidin-2-ones.

The treatment of *N*-Boc aziridines *trans*-**2a**−**c** and *cis*-**3a**,**b** with $BF_3{\cdot}Et_2O$ or $BF_3{\cdot}2H_2O$ afforded the corresponding 4-carboxymethyl oxazolidin-2-ones *trans*-**4a**−**c** and *cis*-**5a**,**b**, respectively (Scheme 2). The rearrangement proceeds with

Scheme 2



complete regio- and stereoselectivity. Indeed, only 4-carboxymethyl oxazolidin-2-ones are obtained, thus showing that the oxygen always migrates away from the carboxymethyl group. Moreover, the rearrangement is totally stereoselective, because both *cis* and *trans* disubstituted *N*-Boc aziridines afford exclusively *cis* and *trans* oxazolidin-2-ones, respectively.[15]

Satisfactory yields were obtained only by starting from aziridine **2c** (Table 2, entries 8−11). When R is a methyl or

Table 2. Chemical Yields for the Rearrangement of *N*-Boc Aziridines **2a**−**c** with BF_3

entry	R	Lewis acid (amt (equiv))	yield (%)
1	Me	$BF_3{\cdot}Et_2O$ (3)	*a*
2	Me	$BF_3{\cdot}H_2O$ (3)	*a*
4	Me	$BF_3{\cdot}Et_2O$ (0.5)	15[a]
5	Me	$BF_3{\cdot}H_2O$ (0.5)	15[a]
6	*i*Pr	$BF_3{\cdot}H_2O$ (0.5)	10[a]
7	*i*Pr	$BF_3{\cdot}Et_2O$ (0.5)	30[a]
8	Ph	$BF_3{\cdot}Et_2O$ (3)	90
9	Ph	$BF_3{\cdot}H_2O$ (3)	90
10	Ph	$BF_3{\cdot}H_2O$ (0.5)	98
11	Ph	$BF_3{\cdot}Et_2O$ (0.5)	92

[a] The remaining starting material was transformed into a complex mixture of products.

an isopropyl group, complex mixtures of ring-opening products together with small amounts of oxazolidin-2-ones were obtained. This behavior can be explained by analyzing the probable reaction mechanism (Figure 1). The Lewis acid

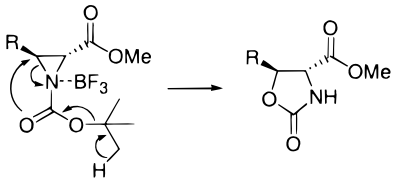


Figure 1. Mechanism for the rearrangement of *N*-Boc aziridine catalyzed by BF_3.

catalyzes the formation of an incipient carbocation on C-3, which is the driving force for the rearrangement that proceeds with the elimination of a molecule of isobutene. This process is certainly easier when an electron-donating group is connected to C-3. This explains the excellent results obtained with the phenyl group and the low yields of methyl and isopropyl groups.

In contrast, very good results were obtained when the reaction was performed with catalytic amounts of chelating Lewis acids (Table 3). Recently Leckta[16] highlighted the ring

Table 3. Chemical Yields for the Rearrangement of *N*-Boc Aziridines 2a−c with Various Lewis Acids

entry	R	Lewis acid (amt (equiv))	solvent	time (h)	yield (%)
1	Me	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	40	99
2	Me	$Zn(OTf)_2$ (0.1)	CH_2Cl_2	40	90
3	Me	$Sn(OTf)_2$ (0.1)	CH_2Cl_2	40	99
4	*i*Pr	$Cu(OTf)_2$ (0.1)	DME/THF	6	*a*
5	*i*Pr	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	8	20[a]
6	*i*Pr	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	40	65
7	*i*Pr	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	70	85
8	*i*Pr	$Zn(OTf)_2$ (0.1)	CH_2Cl_2	40	20[a]
9	*i*Pr	$Sn(OTf)_2$ (0.1)	CH_2Cl_2	40	98
10	Ph	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	40	98
11	Ph	$Zn(OTf)_2$ (0.1)	CH_2Cl_2	40	98
12	Ph	$Sn(OTf)_2$ (0.1)	CH_2Cl_2	40	96

[a] The starting material was recovered.

expansion of *N*-benzoyl aziridines to oxazolines by reaction with catalytic amounts of azaphilic Lewis acids, such as $Cu(OTf)_2$, $Sn(OTf)_2$, and $Zn(OTf)_2$. The best results were obtained with $Cu(OTf)_2$, and the reaction rate could be greatly accelerated by the use of a chelating solvent, such as THF/DME, which promotes the full conversion of the aziridine to oxazoline.

In our hands, when *N*-Boc aziridines **2a**−**c** and **3a**,**b** were treated with a catalytic amount of $Cu(OTf)_2$, $Sn(OTf)_2$, and $Zn(OTf)_2$, they afforded the desired oxazolidin-2-ones in good to excellent yields.[17] Surprisingly, when the reaction was carried out in a mixture of THF/DME as described by Leckta (entry 4), only the starting material was recovered, while high yields were obtained in methylene chloride. This discrepancy can be attributed to the carboxymethyl group present near the aziridine ring, which chelates the metal ion (Figure 2).

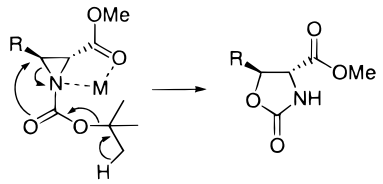
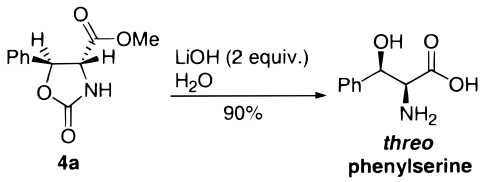


Figure 2. Mechanism for the rearrangement of *N*-Boc aziridine catalyzed by azaphilic Lewis acids.

The oxazolidin-2-ones **4a**−**c** and **5a**,**b** can be easily transformed into the corresponding β-hydroxy α-amino acids.[18] Indeed, the hydrolysis of *trans* 4-carboxymethyl 5-phenyl oxazolidin-2-one **4c** with LiOH in water afforded *threo* phenylserine in high yield (Scheme 3).

Scheme 3



In conclusion, we have demonstrated an efficient method for the preparation of *trans* 4-carboxymethyl 5-alkyl/aryl oxazolidin-2-ones, the protected forms of β-hydroxy α-amino acids. These substrates have been obtained by means of a new rearrangement which allows us to transform *N*-Boc aziridines into oxazolidin-2-ones by reaction with a catalytic

(12) All new compounds have been fully characterized.

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(15) As the reaction is totally stereoselective, only the results regarding the *trans* aziridines **2a**−**c** are reported.

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amount of Lewis acid and are efficient starting materials for the synthesis of polypeptides.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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