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Regioselective and stereoselective glycidic oxirane ring opening: a new entry to optically pure α-alkyl α-hydroxy β-amino acid derivatives

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Abstract

The $BF_3{\cdot}OEt_2$ catalyzed oxirane ring opening of glycidic esters or amides with acetonitrile afforded the corresponding 2-oxazolines under very mild conditions in good yields. The reactions are completely regioselective (the nitrogen attacks the β-carbon) and stereoselective (with inversion of configuration) starting from 2-alkyl or 2,3-dialkyl glycidic derivatives, but the stereoselectivity is lost and the regioselectivity is completely inverted from 2-aryl derivatives. The 2-oxazolines obtained are readily hydrolyzed into β-amino, α-hydroxy esters or amides.

β-Amino, α-hydroxy amide residues seem to be involved in the marked inhibition of aminopeptidases shown by some natural products.[1] Efficient methods for the synthesis of these compounds in their enantiomerically pure form involve Sharpless asymmetric aminohydroxylation of α,β-unsaturated amides,[2] Ojima's β-lactam ring-opening procedure,[3] stereoselective reduction of α-keto carboxylic acid derivatives,[4] and homologation reactions of aldehydes or amides.[5] Special attention is deserved by two recent papers from Tomasini et al. on the synthesis of the *syn*[6] and *anti*[7] α-alkylderivatives of these compounds, of great importance in the design and preparation of unnatural polypeptides of constrained conformation.[8] In this paper we report a new method to prepare α-alkylsubstituted β-acylamino α-hydroxy amides from the corresponding glycidic derivatives in a two-step sequence. The first step involves the regio and stereoselective transformation of the oxirane ring into a 2-oxazoline ring by reaction with acetonitrile in the presence of $BF_3{\cdot}OEt_2$. The second step is the spontaneous or induced hydrolysis of the oxazoline to give the target derivatives. Glycidic esters and amides afford similar results (Scheme 1).

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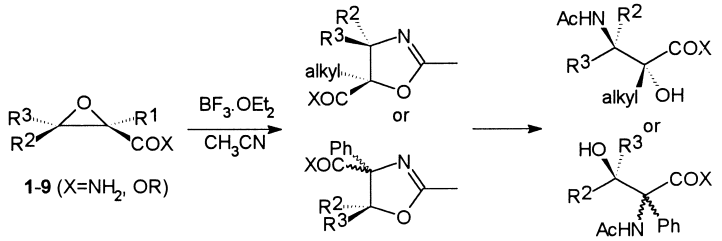


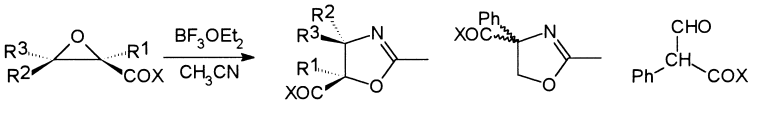
Scheme 1.

In the course of our studies focused on the synthesis of enantiomerically pure α-alkyl glycidamides[9] by reaction of α-hydroxy β-tolylsulfenylamides with $(Me_3O)^+BF_4^-$ and subsequent treatment with Na_2CO_3, we observed the formation of a small amount of only one regioisomeric 2-oxazoline when acetonitrile was used as the solvent. The interest of 2-oxazolines in modern organic synthesis[10,11] and the rather limited number of methods of preparation (the reaction of carboxylic acid derivatives with different β-aminoalcohols or β-haloamines is the most widely used,[12] whereas the development of alternative methods[13] is limited by the low number of available difunctionalized precursors), prompted us to investigate the behaviour of the glycidic oxirane rings in the presence of acetonitrile under the influence of different Lewis acids.[14] The resulting 2-oxazolines were transformed into β-aminoalcohols, thus offering an alternative method to the known opening of the oxirane rings with sodium azide[15] or with an excess of amine under high temperatures or in the presence of different activators.[16] These methods usually yield mixtures of regioisomers and have some limitations derived from the reaction conditions, which are too strong in some of the latter cases.[17]

Optically pure glycidic amides **1**–**5** were prepared as previously described.[9] When these compounds were dissolved in acetonitrile at rt and treated with $BF_3{\cdot}OEt_2$,[18] 2-methyl oxazolines **10**–**14** were obtained (Table 1). The regioselectivity of the reactions was complete in all cases but opposite for α-alkyl derivatives **1**–**4** and α-phenyl derivative **5**. In the first cases the attack of the nitrogen takes place at the β-carbon of the glycidic systems yielding the regioisomers A (Table 1), whereas starting from **5** the reaction occurs at the benzylic α-position affording the regioisomer B along with aldehyde **19**. Concerning the stereoselectivity, the exclusive transformation of the substrates **1**–**4** into **10**–**13**, respectively, suggests that the nucleophilic attack at β-carbon of the oxirane rings takes place according to a S_N2 process with complete inversion of the configuration and reveals that configurational integrity of the α-carbon is not affected under the reaction conditions. By contrast, compound **5** affords almost racemic **14** suggesting a benzylic carbocation acting as an intermediate.

The obtained results suggest the mechanism shown in Scheme 2. After association of the oxirane oxygen to the Lewis acid (2 equiv.),[19] the nitrogen of the solvent opens the epoxide yielding a very reactive intermediate collapsing into oxazoline.[20] Steric and electronic factors can be invoked to explain the regioselectivity. As we can see, the most congested α-carbon bears a carboxamide group unstabilizing the positive charge, which justifies the nucleophilic preferential attack to the less hindered and more positively charged β-carbon. The formation of a carbocation must be disregarded because of the complete stereoselectivity of the reactions (only one diastereoisomer was formed from **1**–**4**) and the absence of carbonyl compounds (usually formed as a consequence of rearrangement processes of the carbocations generated from epoxides[21] in the presence of $BF_3{\cdot}OEt_2$). The ability of the aromatic ring in **5** to stabilize benzylic carbocation determines a

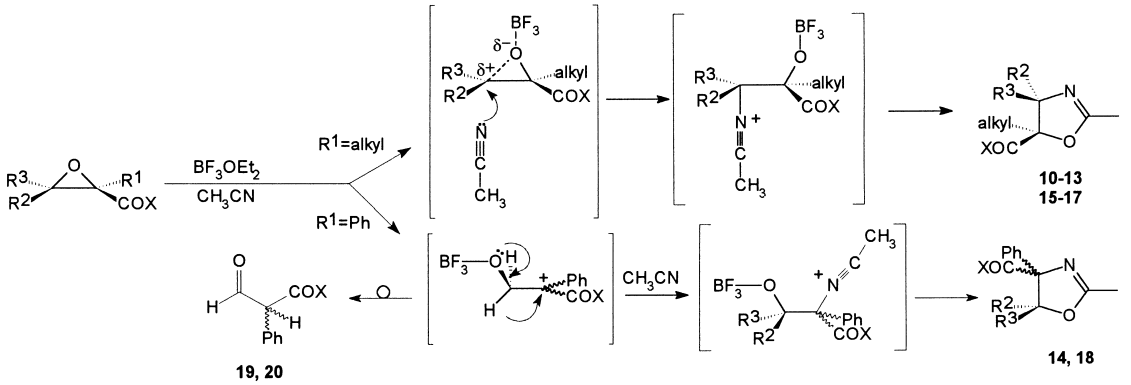
Table 1
Reaction of glycidic esters and amides with CH_3CN in the presence of $BF_3{\cdot}OEt_2$



Epoxide	R^1	R^2	R^3	X	Time	A (% yield)	B (%yield)	C (%yield)
1	CH_3	H	CH_3	NH_2	15 min	**10** (86)		
2	*n*-Pr	H	CH_3	NH_2	15 min	**11** (65)		
3	*i*-Pr	H	CH_3	NH_2	15 min	**12** (60)		
4	*i*-Pr	CH_3	H	NH_2	15 min	**13** (83)		
5	Ph	H	H	NH_2	15 min	-	**14** (30)	**19** (25)
6	CH_3	H	H	OMe	5 min	**15** (90)		
7	H	CH_3	CH_3	OMe	5 min	**16** (85)		
8	H	H	CH_3	OEt	5 min	**17** (92)		
9*	Ph	H	H	OMe	5 min	-	**18** (32)	**20** (34)

*Reaction performed in the presence of TMSOTf.

substantial increase in the positive charge at C-α of the oxirane ring, which is the preferred one for the nucleophilic attack of the nitrile thus inverting the regioselectivity. Moreover, the low enantiomeric purity of **14** (<10% ee) suggests that a carbocation must be involved in its formation, which is reinforced by the isolation of the rearrangement compound **19**. These results suggest that the influence of the carboxamide group destabilizing the positive charge at C-α is favourably counterbalanced by the mesomeric effect of the phenyl group in **5**, but not by the inductive effect of the alkyl groups in **1**–**4**.



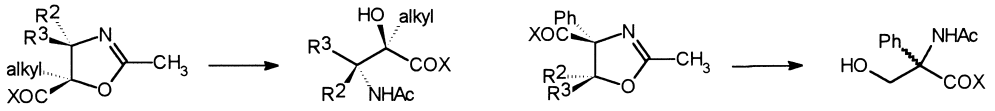
Scheme 2.

A similar completely regio and stereoselective evolution was observed from glycidic esters **6**–**8**[22] in the presence of $BF_3{\cdot}OEt_2$ (1 equiv. 0°C). Reactivity of the esters seems to be slightly higher than that of the amides, maybe due to the easier association of the BF_3 to epoxidic oxygen of the first compounds (the $CONH_2$ group of amides competes for the Lewis acid). The observed

regioselectivity in the reactions yielding oxazolines **15**–**17** is identical to that indicated for amides **1**–**4**. The exclusive transformation of compound **7** through nucleophilic attack at the much more congested β-carbon, suggests that electronic effects are clearly predominant with respect to the steric ones in the regioselectivity control of these S_N2 reactions. This was not unexpected taking into account the linear structure of the nucleophile with low sensitivity towards steric factors.

In the presence of $BF_3{\cdot}OEt_2$, enantiomerically pure **9** yielded a mixture of compounds, the aldehyde **20** being predominant. As in the case of **19**, **20** must be formed by rearrangement of a benzylic carbocation formed by oxirane ring opening. When compound **9** was treated with TMSOTf in acetonitrile a 1:1 mixture of compounds **18** and **20** was obtained. The enantiomeric purity of **18** (<10% ee) suggests a mechanism similar for **9** and **5** (Scheme 2).

Hydrolysis of the reaction mixtures with saturated $NaHCO_3$ allowed the isolation of the corresponding 2-oxazolines, whereas hydrolysis with H_2O overnight afforded in quantitative yields the corresponding *N*-acetylamino hydroxy derivatives.[23] Starting from **10**–**13** and **15**–**17** 2-alkyl, 2-hydroxy, 3-amino acid derivatives **21**–**24** and **26**–**28** were obtained, whereas **14** and **18** afforded compounds **25** and **29**, respectively (Scheme 3).[24]



10-13 X=NH_2
15-17 X=OR

21-24 X=NH_2
26-28 X=OR

14 X=NH_2
18 X=OMe

25 X=NH_2
29 X=OMe

Scheme 3.

In summary, we have reported a very efficient method to obtain oxazolines starting from the readily available glycidic acid derivatives in a completely stereoselective and regioselective manner. It is based on the nucleophilic opening of the oxiranic ring, activated by Lewis acids, acetonitrile acting as the nucleophile and solvent. The most relevant features of these opening reactions are their complete regioselectivity (mainly controlled by electronic grounds) and stereoselectivity, which determines some interesting advantages with respect to other opening reactions of epoxides. These reactions have allowed us the synthesis of optically pure 2-alkyl, 2-hydroxy, 3-*N*-acylamino amides.

Acknowledgements

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22. Racemic glycidic esters **6**–**8** were obtained from the corresponding olefins by epoxidation with MCPBA and the optically pure **9** was prepared as indicated in Ref. 9.
23. Chloroform solutions of the oxazolines spontaneously evolved into the *N*-acetylamino hydroxy derivatives in one week at rt.
24. New compounds were completely characterized and gave satisfactory spectral and analytical data. Selected data: Compound **10** $[\alpha]_D^{20}=+135$ (*c* 0.2, acetone). ^{1}H NMR δ: 6.34 (s_{br}, 1H), 5.74 (s_{br}, 1H), 3.93 (qq, J = 1.4, 6.8 Hz, 1H), 2.01 (d, J = 1.4 Hz, 3H), 1.54 (s, 3H), 1.18 (d, J = 6.8 Hz, 3H). Compound **11** $[\alpha]_D^{20}=+15$ (*c* 0.64, $CHCl_3$). ^{1}H NMR δ: 6.36 (s_{br}, 1H), 5.77 (s_{br}, 1H), 4.24 (qq, J = 7.2, 1.5 Hz, 1H), 2.03 (d, J = 1.8 Hz, 3H), 1.84 (m, 1H), 1.55 (m, 1H), 1.33 (m, 2H), 1.27 (d, J = 7.2 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H). Compound **12** $[\alpha]_D^{20}=+261$ (*c* 0.93, $CHCl_3$). ^{1}H NMR δ: 6.39 (s_{br}, 1H), 5.92 (s_{br}, 1H), 4.05 (qq, J = 6.8, 1.2 Hz, 1H), 2.18 (sep, J = 6.8 Hz, 1H), 2.01 (d, J = 1.2 Hz, 1H), 1.21 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H). Compound **13** $[\alpha]_D=+66$ (*c* 0.7, $CHCl_3$). ^{1}H NMR δ: 6.30 (s_{br}, 1H), 5.77 (s_{br}, 1H), 4.24 (qq, J = 7.3, 1.6 Hz, 1H), 2.27 (sep, J = 6.8 Hz, 1H), 2.01 (d, J = 1.6 Hz, 1H), 1.40 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H). Compound **21** ^{1}H NMR (D_2O) δ: 4.0 (q, J = 6.6 Hz, 1H), 2.04 (s, 3H), 1.21 (s, 3H), 0.93 (d, J = 6.9 Hz, 3H). Compound **22** ^{1}H NMR δ: 6.87 (s_{br}, 1H), 6.65 (s_{br}, 1H), 5.60 (s_{br}, 1H), 4.80 (s_{br}, 1H), 4.03 (m, 1H), 1.99 (s, 3H), 1.9 (m, 1H), 1.8–1.2 (m, 3H), 1.25 (d, J = 7.2 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H). Compound **23** ^{1}H NMR δ: 7.03 (s_{br}, 1H), 5.76 (s_{br}, 2H), 5.41 (s_{br}, 1H), 4.10 (q, J = 7.1 Hz, 1H), 2.10 (sep, J = 6.6 Hz, 1H), 2.02 (s, 3H), 1.41 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H) 0.90 (d, J = 6.8 Hz, 3H). Compound **24** $[\alpha]_D^{20}=+17$ (*c* 0.55, $CHCl_3$). ^{1}H NMR δ: 6.91 (s_{br}, 2H), 5.79 (s_{br}, 2H), 4.20 (dq, J = 6.8, 9.3 Hz, 1H), 2.24 (sep, J = 6.5 Hz, 1H), 2.16 (s, 1H), 1.17 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H).