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Ring Expansion of *N*-Acyl Aziridine-2-imides to Oxazoline-4-imides, Useful Precursors of Pure β-Hydroxy α-Aminoacids.

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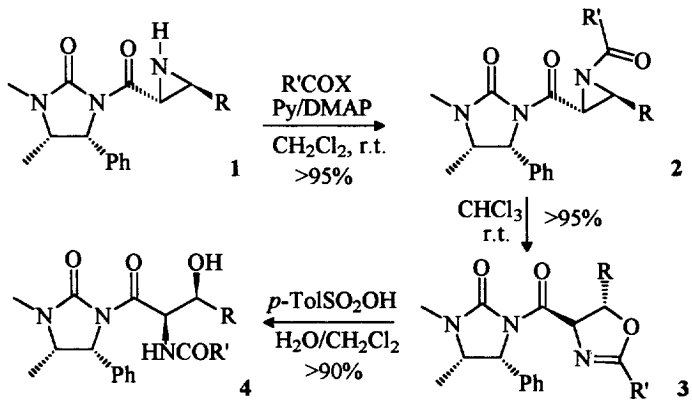
Abstract. Optically active *N*-acyl aziridine 2-imides or 2-carboxylates rearrange to oxazoline-4-imides or 4-carboxylates with high regio and stereo control. This ring expansion followed by mild hydrolisis allows the synthesis of enantiomerically pure β-hydroxy α-aminoacid precursors.

The prepararation of stereodefined β-hydroxy α-amino acids is an important area of research because of their presence in natural peptides antibiotics; indeed, a number of hydroxy amino acids are crucial components of pharmaceuticals and many protease inhibitors.[1]

Substituted and unsubtituted aziridine-2-carboxylates have attracted much attention as starting material in many important transformations.[2] The ring strain renders the *N*-activated aziridines susceptible to nucleophilic ring opening, which can occur regioselectively in the α or β position thus affording α-substituted β-amino acids or β-substituted α-amino acids.[3] Furthermore, aziridines bearing unsaturations on nitrogen rearrange under a variety of conditions; in particular, *N*-acyl derivatives are readily converted via thermal,[4] acid,[5] or nucleophilic[3a,6] assistance to oxazolines.

We wish to describe here the regioselective ring expansions of *N*-acyl aziridine-2-imides to afford the corresponding oxazoline-4-imides, useful precursors of β-hydroxy-α-amino acid derivatives in enantiomerically pure form.

Scheme 1



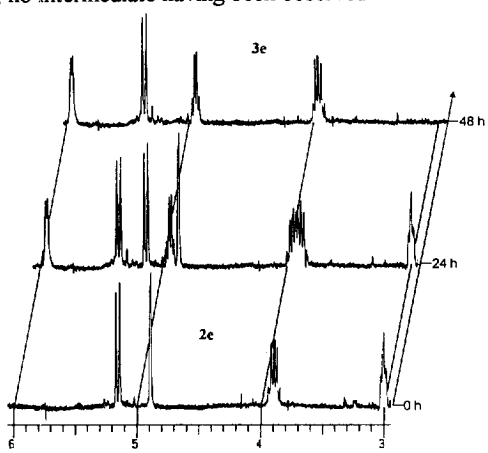
a: R = Me, R' = Me
b: R = Et, R' = Me
c: R = *n*-Pr, R' = Me
d: R = Me, R' = Ph
e: R = Et, R' = Ph
f: R = *n*-Pr, R' = Ph

The *N*-acetyl aziridines **2a-c** are easily obtained in 1 h by treatment of aziridine-2-imides **1a-c**[7] with 1.2 equiv of acetic anhydride in the presence of 1.2 equiv of pyridine and a catalitic amount of DMAP in CH_2Cl_2 at

room temperature. The *N*-benzoyl aziridines **2d-f** are obtained under the same conditions by treatment of **1d-f**[7] with 1.1 equiv of benzoyl chloride. After purification by crystallization from cyclohexane/ether, **2**[8] spontaneously rearrange in $CHCl_3$, affording quantitatively the *trans* 2-methyl oxazolines **3**[9] under complete regio and stereo-control (Scheme 1).

The *trans* stereochemistry is determined by comparison of the ^{1}H-NMR coupling constants of the oxazoline H4-H5 protons with the values reported in the literature.[10] This ring expansion may be followed on recording ^{1}H NMR spectrum in $CDCl_3$ (Figure 1): the ^{1}H-NMR shows a slow decrease of the signals relative to reagent **2** and the corresponding increase of the signals of *trans* oxazoline **3**. The reaction is complete within two days, and only **2** and **3** are detected, no intermediate having been observed in the reaction mixture.

Figure 1

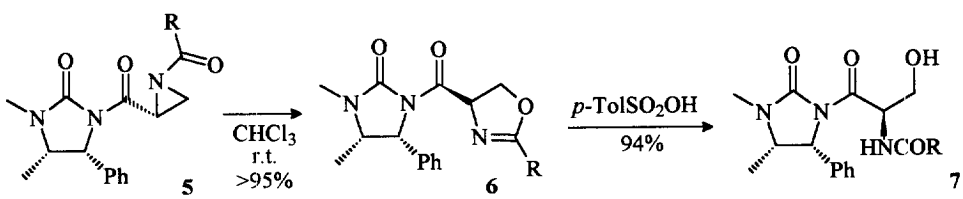


The oxazoline hydrolysis can be performed under very mild conditions. The treatment of **3** with a catalytic amount of *p*-toluensulfonic acid and traces of water in dichloromethane at room temperature for 2-4 h gives 2'-acylamino 3'-hydroxy **4**[11] in high yield as a single isomer.

In order to obtain further informations[12] and to define the better conditions for the ring expansion, the *N*-acyl 3'-unsubstituted aziridines **5**[7b] are treated under a variety of conditions, including solvents, temperatures, and acid catalysis. Depending on these parameters, **5** are regioselectively converted into the corresponding oxazolines **6**, as confirmed by ^{1}H-NMR and GC-MS analysis of the reaction mixture (Scheme 2). The presence of water traces caused also the formation of variable amounts of the β-hydroxy α-aminoacids **7**.

Scheme 2

a: R = Me
b: R = Ph



Representative results are reported in Table 1. **5a** Rearranges to **6a** in 95% yield in $CHCl_3$ at room temperature after 20 h (Entry 1). The hydrolysis of **6a** was performed under the above reported mild conditions to give almost quantitatively the β-hydroxy α-amino derivative **7a** (Scheme 2).

By refluxing **5a** in $CHCl_3$, the rearrangement to **6a** is quantitative in 2 h, althought traces of **7a** are observed (Entry 2). On the other hand, by treatment of **5a** in THF, CH_2Cl_2, or toluene at reflux only poor convertions are observed (Entries 3, 4, and 5). When a catalytic amount of Amberlyst H-15 is added to a solution of **5a** in toluene at reflux, a complete conversion is obtained (Entry 6), but a considerable amount of **7a**

is also formed. Similar results can be observed when a catalytic amount of $BF_3{\cdot}Et_2O$ is added at -78 C to a solution of **5a** in CH_2Cl_2 (Entry 7).

Table 1. Ring Expansion of **5** to **6** in Function of Solvent, Temperature and Acidity.

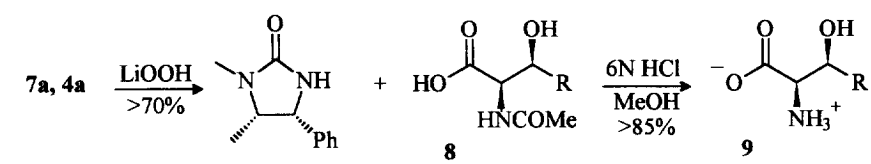
Entry	5	Solvent	Acid	Temp (°C)	Time (h)	5[a] (%)	6[a] (%)	7[a] (%)
1	**a**	$CHCl_3$	-	r.t.	20	traces	>95	-
2	**a**	$CHCl_3$	-	Δ[b]	2	-	>95	traces
3	**a**	THF	-	Δ[b]	20	90	6	4
4	**a**	CH_2Cl_2	-	Δ[b]	18	86	7	7
5	**a**	$C_6H_5CH_3$	-	Δ[b]	20	>95	-	traces
6	**a**	$C_6H_5CH_3$	Amberlyst H-15	Δ[b]	6	8	71	21
7	**a**	CH_2Cl_2	$BF_3{\cdot}Et_2O$	-78	4	5	85	10
8	**b**	$CHCl_3$	-	r.t.	10	-	>95	-

[a] Calculated on the basis of ^1H NMR and GC-MS analysis of crude reaction mixtures. [b] Reflux.

A faster ring expansion occurs when the aziridine is activated with a benzoyl group. The *N*-benzoyl aziridine **5b** rearranges in $CHCl_3$ in 10 h at room temperature affording quantitavely the 2-phenyl oxazoline **6b**, again with complete regio-control (Entry 8).

The non-destructive removal of the chiral auxiliary is easily achieved under the conditions reported by Evans[13] (Scheme 3). Treatment of **4a** with $LiOH/H_2O_2$ in THF/H_2O at 0°C affords the chiral imidazolidin-2-one and D-*N*-acetyl threonine **8a**,[14] confirming that the ring expansion occurs with retention of the configuration. Further hydrolysis of **8a** with 6N HCl/methanol at reflux gives free D-threonine **9a**,[15] which is purified on cation-excange resin using NH_4OH as eluant. Following the same procedure, after complete deprotection of **7a** free D-serine **9b**[15] is obtained.

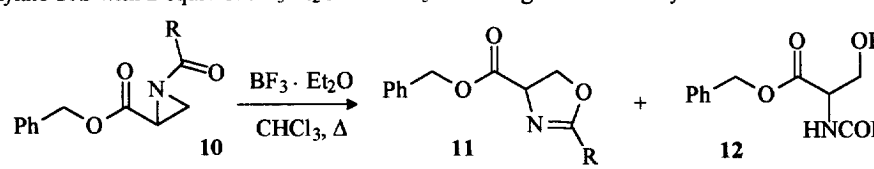
Scheme 3



In order to control the effect of the substituent in position 2 of the aziridine, the ring expansion is studied on racemic *N*-acyl benzyl aziridine-2-carboxylate **10**[16] (Scheme 4).

By stirring a solution of **10a** in $CHCl_3$ both at room temperature and at reflux, no traces of oxazoline **11a** or 2'-acetylamino 3'-hydroxy derivative **12a** are obtained after 20 h. On the contrary, in the presence of $BF_3{\cdot}Et_2O$ (2 equiv), **12a** is isolated after 12 h in quantitative yield. On the other hand, treatment of *N*-benzoyl benzyl 2-carboxylate **10b** with 2 equiv of $BF_3{\cdot}Et_2O$ in $CHCl_3$ at reflux gives exclusively the oxazoline **11b**.

Scheme 4



In conclusion, chiral oxazoline-4-imides **3** are excellent precursors of optically pure β-hydroxy α-aminoacid derivatives **4**, which are obtained by mild hydrolysis in high yield and with retention of the configuration. The oxazoline-4-imides **3** are simply prepared by regio and stereoselective rearrangement of the

corresponding chiral *N*-acyl aziridine-2-imides **2**. The ring expansion occurs quantitatively in chloroform, while it is very slow in other solvents, in which its rate is enhanced by the presence of acids. The *N*-acyl aziridine-2-carboxylates **10** show a slightly different behaviour, being the ring expansion more difficult.

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8. Analytical data for **2e**: ^{1}H-NMR ($CDCl_3$) δ 0.73 (d, *J* = 6.6 Hz, 3H, CH_3), 1.09 (t, *J* = 7.4 Hz, 3H, CH_3), 1.58-1.86 (m, 2H, CH_2), 2.84 (s, 3H, NCH_3), 2.99 (dt, *J* = 2.7, 5.7 Hz, 1H, C*H*CH_2), 3.90 (dq, *J* = 6.6, 8.7 Hz, 1H, CHMe), 4.89 (d, *J* = 2.7 Hz, 1H, COCH), 5.15 (d, *J* = 8.7 Hz, 1H, CHPh), 7.00-8.10 (m, 10H, Ph).
9. Analytical data for **3e**: IR ν 1720, 1660, 1420 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.83 (d, *J* = 6.6 Hz, 3H, CH_3), 1.03 (t, *J* = 7.3 Hz, 3H, CH_3), 1.74-1.88 (m, 2H, CH_2), 2.89 (s, 3H, NCH_3), 3.96 (dq, *J* = 6.6, 8.8 Hz, 1H, CHMe), 4.95 (q, *J* = 5.0 Hz, 1H, C*H*CH_2), 5.37 (d, *J* = 8.8 Hz, 1H, CHPh), 5.95 (d, *J* = 5.0 Hz, 1H, COCH), 7.10-8.20 (m, 10H, Ph).
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11. Analytical data for **4e**: IR ν 3400, 1729, 1654, 1648, 1424, 1378 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.84 (d, *J* = 6.5 Hz, 3H, CH_3), 1.07 (t, *J* = 7.4 Hz, 3H, CH_3), 1.40-1.85 (m, 2H, CH_2), 2.87 (s, 3H, NCH_3), 3.98 (dq, *J* = 6.5, 8.7 Hz, 1H, CHMe), 4.11 (ddd, *J* = 1.8, 5.8, 7.4 Hz, 1H, C*H*CH_2), 5.31 (d, *J* = 8.7 Hz, 1H, CHPh), 6.31 (dd, *J* = 1.8, 8.6 Hz, 1H, COCH), 7.10-8.15 (m, 11H, NH + Ph); $[\alpha]_D$ = -82 (*c* 0.2, $CHCl_3$).
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14. For **8a**: $[\alpha]_D$ = -10 (*c* 3.0, MeOH). The absolute stereochemistry of **8a** was assigned by comparison with *N*-acetyl threonine prepared from commercially available L-threonine: $[\alpha]_D$ = +12 (*c* 4.7, MeOH).
15. For **9a**: $[\alpha]_D$ = +27 (*c* 1.0, H_2O), in good agreement with a typically reported value: $[\alpha]_D$ = +29 (*c* 5.0, H_2O). For **9b**: $[\alpha]_D$ = -12 (*c* 1.4, 5N HCl), in good agreement with a typically reported value: $[\alpha]_D$ = -13 (*c* 5.0, 5N HCl).
16. Prepared by acylation under the above reported conditions of the racemic benzyl aziridine-2-carboxylate obtained by Gabriel-Cromwell procedure.[7a]

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