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Regioselective Opening of 3-Substituted N-Ethoxycarbonyl Aziridine-2-Carboxylates with Metal Halides toward the Preparation of α and β-Amino Acids

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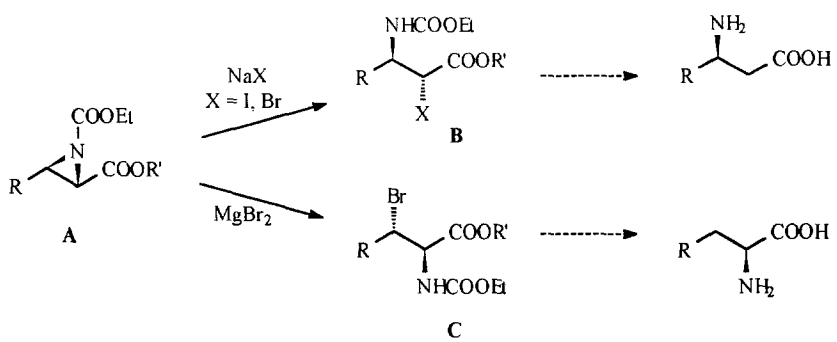
Abstract: 3-Substituted N-Ethoxycarbonyl aziridine-2-carboxylates are opened in a regio and stereoselective fashion whether in C-2 position by NaX (X = I, Br) or in C-3 by $MgBr_2$

Chiral aziridines are attractive building blocks for the synthesis of natural products such as alkaloids, amino sugars, amino acids and β-lactams antibiotics.[1] In particular chiral α,β-aziridino alcohols have been used for the enantioselective synthesis of important carbapenem antibiotics.[2]

Also aziridine-2-carboxylates, available in optical active form,[3] could be potentially useful synthetic intermediates. It is thus important to search for simple methods to open the three membered aziridine ring in regio and stereoselective fashion.

Heteroatom and carbon nucleophiles were shown to attack preferentially the C-3 position of aziridine-2-carboxylates.[1,4] So far halogen nucleophiles were introduced only by HCl[4] or in a particular case of C-2-symmetric aziridine dicarboxylate;[5] no examples of a more general C-2 or C-3 regioselective opening of 3-substituted- aziridine-2-carboxylates by halogen nucleophiles were reported.

Scheme 1

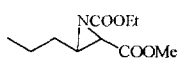
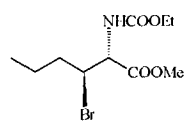
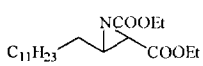
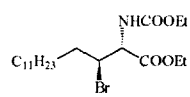
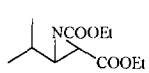
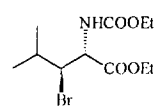
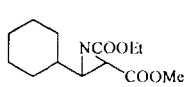
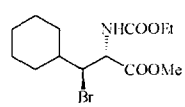
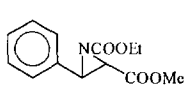
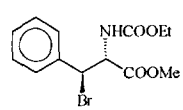


This paper reports a simple conversion of 3-substituted-N-ethoxycarbonyl aziridine-2-carboxylates **A** to α-halo-β-amino esters **B** or to β-bromo-α-amino esters **C** using metal halides, as shown in scheme 1; successively the halogen can be eventually removed via radical reduction to afford, after hydrolysis, α or β-amino esters (see below).

Our recent studies on the regioselective opening of α,β-epoxy esters [6, 7] were helpful for the proper choice of the reaction conditions; after several attempts the regioselective C-3 attack was performed with $MgBr_2$ or MgI_2, whereas, for the C-2 attack, NaX / Amberlyst 15 (X=I, Br) was proved to be the best reagent.

We have always used aziridines (racemic) bearing a strong electron withdrawing group on the nitrogen, (COOEt), because non activated aziridines did not react to our conditions; moreover the former can be easier purified.[8] As shown in Table 1 several *trans* 3-substituted-N-ethoxycarbonyl aziridine-2-carboxylates, treated with $MgBr_2$ in Et_2O,[9] provided diastereomerically pure β-bromo derivatives in almost quantitative yield, mild conditions and with short reaction time (about 2 h).

Table 1. C-3 regioselective cleavage of 3-substituted-N-ethoxycarbonyl aziridine-2-carboxylates with $MgBr_2$

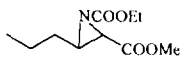
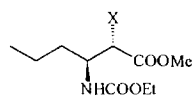
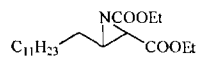
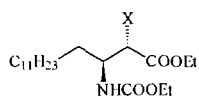
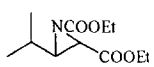
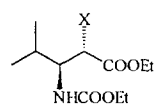
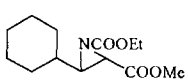
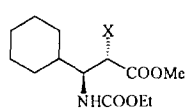
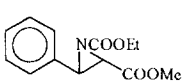
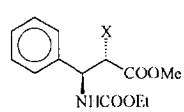
N-Ethoxycarbonyl Aziridine-2-Carboxylate [8]	Main product	C-3 / C-2 ratio [a, b]
 **1**		> 99 / 1
 **2**		> 99 / 1
 **3**		> 99 / 1
 **4**		> 99 / 1
 **5**		> 99 / 1

[a] Chemicals yields of the isolated products are nearly quantitative [b] The ratio has been determined by ^{1}H-NMR analysis

Also MgI_2 was employed to afford efficiently 3-iodo derivatives, but $MgBr_2$ (commercially available) can be more conveniently used.

The use of NaX / Amberlyst 15 [10] reagent in acetone gave preferentially the C-2 attack; as shown in Table 2; the best results were obtained (ratio C-2 / C-3, 99/1) with compounds **3** and **4**, bearing a bulky group, while for compounds **1** and **2** the ratio C-2 / C-3 decreased to 75 / 25. The lack of regioselectivity for compound **5** resembles the behaviour of other phenyl substituted three membered ring.[11]

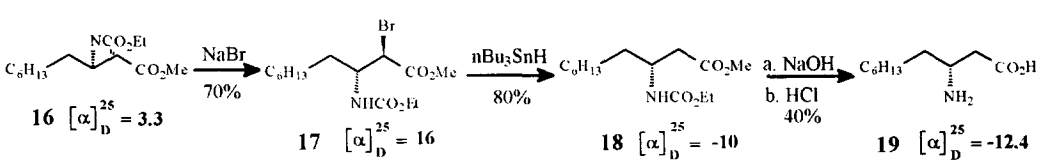
Table 2. C-2 regioselective cleavage of 3-substituted-N-ethoxycarbonyl aziridine-2-carboxylates with NaX

N-Ethoxycarbonyl Aziridine-2-Carboxylate [8]	Main product	X	C-2 / C-3 ratio [a, b]
 **1**		**6** I	75 / 25
		7 Br	77 / 23
 **2**		**8** I	70 / 30
		9 Br	75 / 25
 **3**		**10** I	99 / 1
		11 Br	99 / 1
 **4**		**12** I	99 / 1
		13 Br	99 / 1
 **5**		**14** I	50 / 50
		15 Br	50 / 50

[a] Chemicals yields of the isolated products are nearly quantitative [b] The ratio has been determined by ^{1}H-NMR analysis

As already point out the obtained α or β halogen derivatives can be considered straight precursors of the corresponding amino acids. Scheme 2 shows an overall reaction sequence (non optimized) [12] applied to the chiral aziridine-2-carboxylate **16** (prepared from the corresponding chiral epoxy alcohol).[13] The regioselective opening to the bromo derivatives **17** was followed by radical reduction, already extensively used on our previous studies. [6, 11] Finally hydrolysis of **18** afforded the known (3R)-3-Aminodecanoic acid **19**, an inhibitor of germination of sasanqua pollen.[14]

Scheme 2



The overall sequence from 3-substituted-aziridine 2-carboxylates to α or β-amino acids represents an attractive alternative to the direct reductive opening of the aziridine ring. In fact, although recent papers describe the catalytic hydrogenation [15] of 3-unsubstituted or 3-phenyl aziridine 2-carboxylates to the corresponding α-amino acids, these methodologies were not reported to give good results on more generally C-3 substituted aziridine 2-carboxylates. Therefore we believe that the described approach represents an important example of regioselective opening of the aziridine 3-substituted-2-carboxylates, with a wide range of applicability.

Studies on other possible applications of our methodologies in organic synthesis are in progress.

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8. Aziridines-2-carboxylate have been prepared according to ref.3 ; the aziridine-2-carboxylates were obtained only after a difficult column-chromatography separation. More advantageously, the crude reaction mixture containing the aziridine and $POPh_3$ was treated with ClCOOEt and Et_3N affording the corresponding N-ethoxycarbonyl derivative, easily separable from $POPh_3$ by flash-chromatography.
9. *General preparation of α-amino-β-bromo esters:* To a solution of N-ethoxycarbonyl aziridine-2-carboxylate (1 mmol) in Et_2O (6 mL) $MgBr_2{\cdot}Et_2O$ (193 mg, 1.5 meq) was added. The solution was stirred at room temperature for 2h (TLC monitoring), washed with brine. and the organic layers were dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was checked by ^{1}H-NMR analysis.
10. *General preparation of the α-halo-β-amino esters* :To a cold (-40°C), stirred solution of N-ethoxycarbonyl aziridine-2-carboxylate (1 mmol) in acetone (10 mL), NaX (150 mg, 1 mmol for X = I and 154 mg, 1.5 mmol for X = Br) and Amberlyst 15 (217 mg, 1 mmol) were added. The mixture was stirred for 6 h (TLC monitoring) and filtered. The filtrate solution, diluted with EtOAc, was washed with saturated $Na_2S_2O_3$; the organic layer, dried over Na_2SO_4, was evaporated in vacuo, affording the crude mixture of haloderivatives, which was checked by ^{1}H-NMR analysis.
11. See review Bonini, C. ; Righi, G. *Synthesis* **1994**, 225-238.
12. Details of the radical reduction and subsequent hydrolysis to the amino acids will be given in a forthcoming full paper.
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