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Regiospecific and Enantiospecific Ring Opening of Methyl (+)-(1'R, 2R)- and (-)-(1'R, 2S)-1-(2-phenylethanol) Aziridine-2-carboxylates

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Abstract: The acid-catalyzed ring-opening of methyl (+)-(1'R, 2R) and (-)-(1'R, 2S)-1-(2-phenylethanol) aziridine-2-carboxylates (**1**) and (**2**) lead quantitatively to the corresponding 2(S)-(-)-chloro-3-[2'-hydroxy-1'(R)-phenyl-ethylamino] propionic acid methyl ester (**3**) and 2(R)-(-)-chloro-3-[2'-hydroxy-1'(R)-phenyl-ethylamino] propionic acid methyl ester (**4**) hydrochlorides.
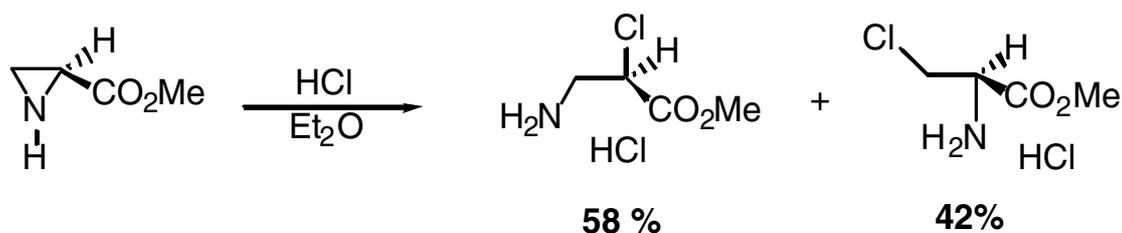
Keywords: aziridine-ring opening, regiospecificity, enantiospecificity.

Introduction

The ring-opening reactions of aziridines by hydrogen halides, water and other nucleophiles are among the oldest known reactions of aziridines and have been studied extensively [1-3]. The ring-opening of aziridines provides a route for the synthesis of haloamines.

The strain associated with the three member ring of aziridine accounts for its reactivity towards ring opening, while additional regio- and stereochemical control on the ring opening reaction can be gained by the presence of specific substituents. We are concerned with the stereochemical control of such ring-opening reactions, which becomes very important in regard to making these reactions synthetically useful.

The mechanism and regioselectivity of the acid catalyzed ring-opening of the nonactivated aziridine-2-carboxylates may exhibit important differences, depending on the conditions used, as it was demonstrated by E. Kyburz et al. [4], Scheme 1.

Scheme 1.

To the present, the mentioned reaction shows more often poor regioselectivity and it is less common to find reports where the ring-opening of aziridines occurs with high regio- and stereospecificity. [5-8].

Results and Discussion

Methyl (+)-(1'R, 2R) and (-)-(1'R, 2S)-1-(2-phenylethanol)aziridine-2-carboxylates (**1**) and (**2**) were obtained in good yield after reaction of racemic methyl 2, 3-dibromopropionate [9] with (R)-(-)-2-phenylglycinol [10]. Flash chromatography readily afforded each diasteromer in pure form [11].

2(S)-(-)-Chloro-3-[2'-hydroxy-1'(R)-phenylethylamino]propionic acid methyl ester (**3**) and 2(R)-(-)-chloro-3-[2'-hydroxy-1'(R)-phenylethylamino]propionic acid methyl ester (**4**) hydrochlorides, were obtained in quantitative yield from enantiopure aziridines (**1**) and (**2**) respectively by treatment with a solution of acetone/2N hydro-chloric acid at pH *ca*. 4 at room temperature.

The reactions were monitored by TLC (silicagel, ethylacetate or dichloromethane/methanol 95:5). Aside from the products (**3**HCl) or (**4**HCl), no spots correpsonding to the starting materials were detected.

The ^{1}H and ^{13}C NMR spectral data for each crude reaction showed only one product. These results were consistent with the single spots observed by TLC. Finally, the solvent was removed *in vacuo* affording the corresponding (**3**HCl) and (**4**HCl) in quantitative yields respectively.
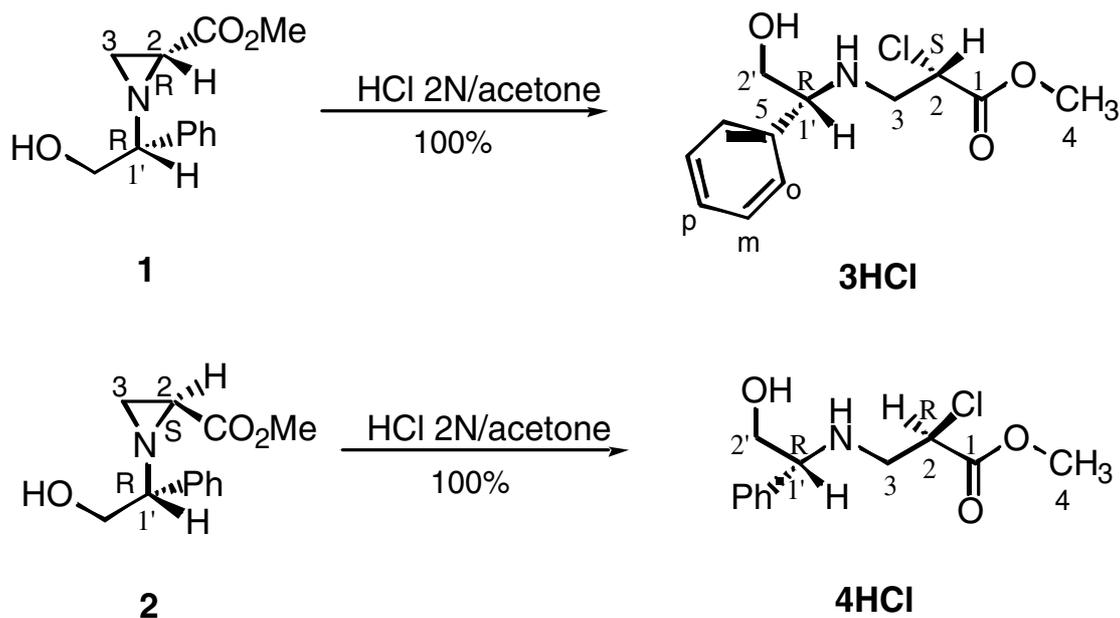
Scheme 2.

Two sets of ^{1}H NMR spectra were performed for compound (**3**HCl); a dramatic improvement in resolution was achieved after addition of a small amount of DMSO-d_6. In addition, this allowed the precise measurement of coupling constants. Important differences in chemical shifts were found in the ^{1}H NMR spectra for (**3**HCl) and (**4**HCl) hydrochlorides after addition of DMSO-d_6. These results confirm that each diasteromer was obtained in pure form and has a particular ^{1}H NMR spectrum that can be clearly identified (Scheme 2. See Experimental).

Next, a single crystal of (**4**HCl) was obtained and X-ray diffraction analysis performed. The absolute configuration for C-4(R) and C-2(R) was established from the known configuration of (R)-(-)-2-phenylglycinol. Based on X-ray diffraction analysis of (**4**HCl) and the NMR of (**3**HCl) and (**4**HCl), we concluded that the stereochemical configuration of (**3**HCl) was C-4(R) and C-2 (S) (Figure 1).
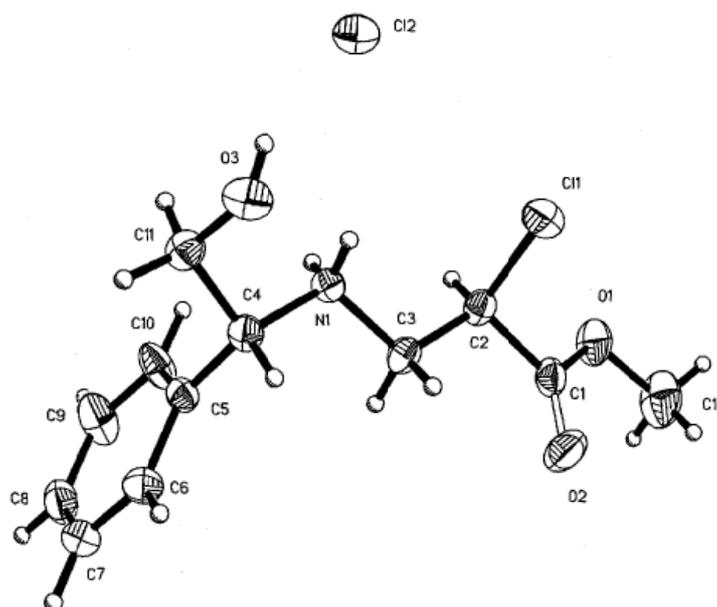

Figure 1.

In a different experiment, a mixture 1:1 of α and β-chloroaminoesters was obtained in quantitative yield from methyl (-)-(1'S,2R)-(phenylethyl)aziridine-2-carboxylate by treatment with a solution of acetone/2N hydrochloric acid at pH *ca*. 4 at room temperature. The proportions were established by NMR.

Conclusions

Pure diastereisomers of 2(S)-(-)-chloro-3-[2'-hydroxy-1' (R)-phenylethylamino]propionic acid methyl ester (**3**HCl) and 2(R)-(-)-chloro-3-[2'-hydroxy-1' (R)-phenylethylamino]propionic acid methyl ester (**4**HCl) were easily obtainable in quantitative yields from (**1**) and (**2**) respectively. Each diasteromer has a distinctive ^{1}H NMR spectrum that can be unambiguously assigned. The spectroscopic data reported for (**3**) and (**4**) hydrochlorides were consistent with the chemical and optical purity of these compounds.

Finally, based on these results, we concluded that the ring-opening was enantiospecific [12]. This can be explained by an SN_2 mechanism in which chloride ion attacks C-2 with total inversion [13]. An SN_1 mechanism is not possible because C-2 is α to a carbonyl group which is not capable of stabilizing a positive charge.

The regiospecific ring-opening by the chloride ion could be explained by the increasing of the electrophylicity in C-2, via intramolecular hydrogen bonding between the carboxyl methyl ester and the hydroxyl group.

The participation of the hydroxyl group in the regiospecific ring-opening was confirmed by the ring-opening of methyl (-)-(1'S, 2R) (phenylethyl)aziridine-2-carboxylate, carried out in the conditions previous described, affording the corresponding (**3**HCl) and (**4**HCl) in quantitative yields respectively.

To the best of our knowledge, this is the first report of the regio- and enantiospecific ring-opening of nonactivated enantiopure aziridine-2-carboxylates derivatives of (R)-(-)-2-phenylglycinol.

Experimental

General

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr disks on a Nicolet Magna-750 spectrophotometer. NMR spectra were measured on Varian Unity 300 and 500 MHz. Spectrometers, using TMS as internal standard. Optical rotations were measured on a Perkin-Elmer Polarimeter M241. The X-ray structure was determined on a Siemens P4/PC diffractometer. Elemental analysis was carried out on a Perkin-Elmer 2400 CHN analyzer.

Preparation of α-chloro-β-aminoester (**3**) or (**4**) hydrochloride

Aziridines (**1**) or (**2**) were stirred for 20 minutes at room temperature in acetone/HCl 2N maintaining acidic conditions (a pH of *ca*. 4). After some 10 minutes the reaction was complete, as monitored by (Silicagel, ethylacetate or dichloromethane/methanol 95:5). Not starting materials or products aside from compounds (**3**HCl) or (**4**HCl) were detected. The solvent was removed *in vacuo* and the corresponding α-chloro-β-aminoester hydrochloride was obtained in quantitative yields.

Spectral Data

2(S)-(-)-Chloro-3-[2'-hydroxy-1' (R)-phenyl-ethylamino] propionic acid methyl ester hydrochloride (**3**HCl): m.p. = 112ºC. $[\alpha]_D$= -58.3 (c=10, CH_2Cl_2); IR (KBr, cm^{-1}): 1764. ^{1}H NMR: δ (ppm, CDCl$_3$, JHz): 3.18 (H-3, dd, 8.1, 13.3), 3.73 (H-3, dd, 5.5, 13.3); 3.77 (CH$_3$-O, s); 4.00 (H-2', dd, 3.8, 12.3), 4.46 (H-2', dd, 8.9, 12.3); 4.62 (H-1', dd, 3.8, 8.9); 5.18 (H-2, dd, 5.5, 8.1); 7.24-7.70 (5H, m, aromatic); 9.41 and 10.15 ([HNH]$^+$ Cl$^-$, two broad signals).
^{1}H NMR of (**3**HCl): δ (ppm, CDCl$_3$ + 2% (CD$_3$)$_2$SO, JHz): 3.12 (H-3, dd, 8.1, 13.3), 3.54 (H-3, dd, 5.5, 13.3); 3.77 (CH$_3$-O, s); 3.95 (H-2', dd, 3.8, 12.3), 4.22 (H-2', dd, 8.9, 12.3); 4.41 (H-1', dd, 3.8, 8.9); 5.20 (H-2, dd, 5.5, 8.1); 7.43-7.70 (5H, m, aromatic); 9.42-10.05 ([HNH]$^+$ Cl$^-$, very broad signal); ^{13}C NMR: δ (ppm, CDCl$_3$): C-3, 48.80; C-2, 50.90; C-4, 53.90; C-2', 63.23; C-1', 66.69; C-5, 131.00; ϕ-C $_{o, m, p}$ 128-130; C=O, 167.69. Anal. Calcd. for C$_{12}$H$_{17}$Cl$_2$NO$_3$: C, 49.0; H, 5.8; N, 4.8; O, 16.3; Cl, 24.1. Found: C, 48.24; H, 5.85; N, 4.41; O, 16.29; Cl, 25.21.

2(R)-(-)-Chloro-3-[2'-hydroxy-1' (R)-phenyl-ethylamino] propionic acid methyl ester hydrochloride (**4**HCl): m.p. = 106-108ºC. $[\alpha]_D$= -29.4 (c=10, CH_2Cl_2); IR (KBr, cm^{-1}): 1747. ^{1}H NMR: δ (ppm, CDCl$_3$, JH$_z$): 3.33 (H-3, broad), 3.49 (H-3, dd, 6.95, 11.72); 3.79 (CH$_3$-O, s); 4.04 (H-2', d, 10.25), 4.32 (H-2', dd, 9.51, 11.72); 4.66 (H-1', broad); 5.23 (H-2, t, 6.95); 7.3-7.7 (5H, aromatic, m); 9.40-

10.10 (HNH$^+$ Cl$^-$, two broad signals). ^{13}C NMR: δ (ppm, CDCl$_3$): C-3, 47.92; C-2, 50.51; C-4, 53.95; C-2', 63.28; C-1', 66.37; C-5, 130.75; φ-C $_{o, m, p}$, 128-130; C=O, 167.55. Anal. Calcd. for C$_{12}$H$_{17}$Cl$_2$NO$_3$: C, 49.0; H, 5.8; N, 4.8; O, 16.3; Cl, 24.1. Found: C, 48.33; H, 5.84; N, 4.51; O, 16.15; Cl, 25.17.

X-ray structure of (**4**HCl). The compound (**4**HCl) was crystallized from dichloromethane. Crystal data C$_{12}$H$_{17}$Cl$_2$N O$_3$, Mw = 294.17, monoclinic, space group C2, Z= 4, a= 22.001 (2) Å, b= 7.25 (1) Å, c= 9.401 (2) Å, α= 90, β=105.28 (1)$^{\circ}$, γ= 90, V=1446.5 (4) Å^3, D$_{calc}$= 1.355 mg/m^3, F(000)= 616, λ(MoKα)= 0.71073 Å, μ= 0.4448mm^{-1}; 2838 measured intensities, 2557 unique. Intensity data measured on a Siemens P4/PC diffractometer using θ-2θ scan technique up to 2θ= 25°. The structure was solved by direct methods using SIR92 and refined by full matrix least-squares treatment using SHELXL97, minimizing the function $\Sigma(F_0^2 - F_c^2)^2$. Final discrepancy factors: R= 5.72 (on F), wR= 15.31% (on F^2). The determination of the absolute configuration was possible from the known configuration (R)-(-)-2-phenylglycinol as starting material.

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10. Using the general procedure [9] for obtaining of (**1**) and (**2**), we prepared the methyl (+)-(1'S, 2R)-1-(2-phenylethanol)aziridine-2-carboxylate and methyl (+)-(1'S, 2S)-1-(2-phenylethanol) aziridine-2-carboxylate from (S)-(+)-2-phenylglycinol. The acid-catalyzed ring opening of methyl (+)-(1'S, 2R)-1-(2-phenylethanol) aziridine-2-carboxylate lead quantitatively to the enantiopure (+)-(1'S, 2S) α-chloro-β-aminoester hydrochloride: m.p.=105-107ºC. [α]$_D$ = + 30.0 (c=10, CH$_2$Cl$_2$). The (+)-(1'S, 2S)-1-(2-phenylethanol) aziridine-2-carboxylates afforded quantitatively to the enantiopure (+)-(1'S, 2R) α-chloro-β-aminoester hydrochloride: m.p. =111-113ºC. [α]$_D$ = +57.9 (c=10, CH$_2$Cl$_2$). The magnitude of [α]$_D$ and m.p. found for these products are comparable with the corresponding enantiomers (**4**HCl) and (**3**HCl) respectively and the NMR spectral data are identical.

11. Aziridine (**1**) (1´R, 2R*):* yield 70%; m.p. =58-60°C. [α]$_D$ = +36.96 (c = 26, CH$_2$Cl$_2$); IR (KBr): 3600-3300, 2953, 1740, 1201 cm^{-1}. NMR ^{1}H: δ (ppm, CDCl$_3$, JHz): 7.30-7.35 (5H, m, aromatic);

3.93 (1H-4, dd, 11.32, 6.96); 3.83 (1H-4´, dd, 11.32, 4.76); 3.70 (3H, s); 2.74 (1H-1´, dd, 6.9, 4.8); 2.44 (1H-3´, dd, 3.0, 1.1); 2.06 (1H-3, dd, 6.5, 1.1); OH, 2.07 Br s; 2.08 (1H-2, dd, 6.5, 3.0). NMR ^{13}C: δ (ppm, CDCl$_3$): C-**i**, 139.04; 2C-**o**, 127.35; 2C-**m**, 127.90; C-**p**, 128.63; C-2, 36.42; C-3, 34.69; C-1', 75.20; C-4, 67.74; C-6, 52.31; C-5, 171.23.

Aziridine (**2**) (1´R, 2S*): yield 30%; m.p. =105-106°C; [α]$_D$ = -126.20 (c = 10, CH$_2$Cl$_2$). IR (KBr): 3500-3400, 2930, 1730, 1245 cm.$^{-1}$. NMR ^{1}H: δ (ppm, CDCl$_3$, J Hz): 7.31-740 (5H, m, aromatic); 3.92 (H-4, dd, 11.40, 6.80); 3.80 (H-4´, dd, 11.40, 4.80); 3.78 (3H, s); 2.75 (1H-1´, dd, 6.8, 4.2); 2.49 (H-2, dd, 6.5, 3.2); 2.14 (H-3, d, 3.2); OH, 2.28 Broad singlet; 1.58 (1H-3´, d, 6.5). ^{13}C NMR: δ (ppm, CDCl$_3$): C$_i$, 138.99; 2C-*o*, 127.73; 2C$_m$, 128.50; C-*p*, 127.90; C-2, 39.21; C-3, 31.49; C-1', 74.91; C-4, 67.52; C-6, 52.44; C-5, 171.07.

12. When (**3**HCl) or (**4**HCl) was refluxed in Et$_3$N/Acetone, we obtained quantitatively the corresponding enantiopure aziridines (**1**) and (**2**) respectively. These results can be explained by an SN$_2$ mechanism.

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Sample Availability: Available from the authors.