Pergamon

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Tetrahedron Letters 44 (2003) 3259–3261

TETRAHEDRON LETTERS

Easy access to β-halo amino esters and aziridine 2-carboxylic esters from halohydrins

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Received 9 January 2003; revised 28 February 2003; accepted 6 March 2003

Abstract—The halohydrins prepared from epoxide esters, were treated with hydroxylamine derivatives. In subsequent reaction with $NaOH/K_2CO_3/Bu_4NHSO_4$ the *N*-protected β-halo α-aminoesters thus obtained were converted into *N*-hydroxy ariridine 2-carboxylic esters in good yields.

Aziridines are useful chiral building blocks for the synthesis of modified amino acids[1] and nitrogen-containing functional compounds via ring opening and ring expansion reactions.[2–4] They are also found in some natural products as well as biologically active compounds such as mitomycins and azinomycins.[3,5] In addition, aziridines have also found applications as chiral auxiliaries[1] and lately as chiral ligands in asymmetric catalysis.[3b] However, the aziridine 2-carboxylic acids (esters) represent an interesting class of compounds since they may be considered simultaneously as α- or β-amino acid derivatives. Although a variety of routes leading to aziridines have been developed to date,[6] little attention has been devoted so far to these carboxylic acids. A commonly used strategy for the synthesis of these compounds involves the so-called Gabriel–Cromwell reaction of 2,3-dihalopropionic (or 2-bromo acrylic) acid derivatives with primary amines.[7] Moreover, stereo-controlled synthetic access to this class of compounds is generally restricted to dehydrative ring closure of β-hydroxy α-amino acid derivatives[8] or double SN_2 displacement of oxirane-carboxylates with an ammonia equivalent.[9]

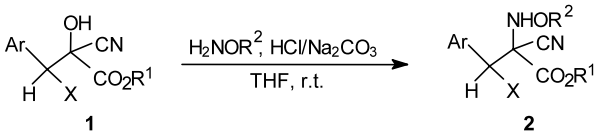
In connection with a research program aimed at the synthesis of new α-amino acids, we discovered a simple and general route for the preparation of *N*-hydroxy α-amino esters **2** starting from the corresponding halohydrins **1**.[10] These latter are readily accessible in regioselective form, employing the ring opening reaction of epoxide esters.[11]

Indeed, a substantial number of natural products containing one or more oxidized peptide bonds -C(O)-N(OH)- have been found in nature. These compounds act variously as potent growth factors, antibiotics, antibiotic antagonists or tumour inhibitors.[12] In addition, it has been suggested that *N*-hydroxy peptides play an important role in the biosynthesis of β-lactam antibiotics.[13]

When a variety of halohydrins **1** were treated with a mixture of hydroxylamine hydrochloride/sodium carbonate, good yields of β-halo α-amino esters **2** were generally obtained according to the Strecker-type reaction (Scheme 1).[14] The typical laboratory procedure is outlined in Ref. 15. The yields of these reactions are collected in the Table 1.

In this letter we also report a convenient method for the synthesis of new *N*-hydroxy aziridine 2-cyano 2-carboxylic acids (esters) **3**. Although the synthetic method of aziridines are well documented, the method for the synthesis of *N*-hydroxy aziridine carboxylic acids are limited.

Our route to the aziridines **3** is shown in the Scheme 2, a key intermediate being the β-halo amino esters **2**. The



1 **2**

Scheme 1.

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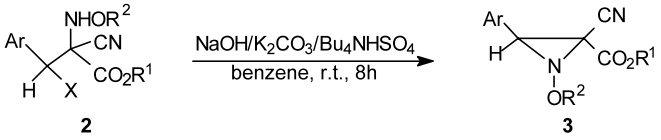
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00631-2

Table 1. Conversion of halohydrins **1** into β-halo α-amino esters **2**

Substrate	Ar	R^1	X	R^2	Products (yield %, mp °C)
1a	4-MeC_6H_4	Et	Cl	H	**2a** (86, oil)
1b	4-ClC_6H_4	Et	Cl	H	**2b** (88, oil)
1c	4-$NO_2C_6H_4$	Et	Cl	H	**2c** (74, oil)
1d	C_6H_5	Et	Cl	H	**2d** (89, oil)
1e	4-MeC_6H_4	Et	Br	H	**2e** (87, 123–4)
1f	4-ClC_6H_4	Et	Br	H	**2f** (85, 112–3)
1g	4-MeC_6H_4	Me	Cl	H	**2g** (90, 117–8)
1h	4-ClC_6H_4	Me	Cl	H	**2h** (86, 114–5)
1i	C_6H_5	Me	Cl	H	**2i** (87, 111–2)
1j	4-$NO_2C_6H_4$	Me	Cl	H	**2g** (82, 130–1)
1k	4-MeC_6H_4	Me	Br	H	**2k** (88, 132–3)
1l	4-ClC_6H	Me	Br	H	**2l** (87, 154–5)
1m	4-MeC_6H_4	Et	Cl	Me	**2m** (86, oil)
1n	4-MeC_6H_4	Et	Br	Me	**2n** (85, oil)
1o	4-MeC_6H_4	Me	Cl	Me	**2o** (86, 142–3)
1p	4-MeC_6H_4	Me	Br	Me	**2p** (87, 167–8)

direct aziridination of the latter was then examined. We were not able to achieve practical yields of the aziridines **3** using the traditional procedure by treating the β-halo α-amino esters **2** with triethylamine. To circumvent this potential problem, we examined several other activating agents. A marginal improvement in the yield of aziridines was obtained using NaH, but a mixture of $NaOH/K_2CO_3/Bu_4NHSO_4$ proved to be the best agent.

Thus, β-halo α-amino esters **2** formed in excellent yields were subjected to cyclization in a solid-liquid two-phase system consisting of benzene and a mixture of solid powdered sodium hydroxide/potassium carbonate. The reaction proceeded smoothly at room temperature and in the presence of tetrabutylammonium hydrogen sulfate it was completed after 8 h affording aziridines **3**[16] in moderate yields (Scheme 2, Table 2).



2 **3**

Scheme 2.

Table 2. *N*-Hydroxy aziridines **3** prepared

Product	Ar	R^1	R^2	Yield (%)[a]
3a	4-MeC_6H_4	Me	H	64
3b	4-ClC_6H_4	Me	H	62
3c	4-$NO_2C_6H_4$	Me	H	60
3d	C_6H_5	Me	H	58
3e	4-MeC_6H_4	Et	H	65
3f	4-ClC_6H_4	Et	H	63
3g	4-$NO_2C_6H_4$	Et	H	62
3h	C_6H_5	Et	H	60
3i	4-MeC_6H_4	Me	Me	64
3j	4-ClC_6H_4	Me	Me	62
3k	4-MeC_6H_4	Et	Me	62
3l	4-ClC_6H_4	Et	Me	64

[a] Isolated yields, after flash chromatography on silica gel. Ethyl acetate/petroleum ether 3:2 as eluent.

It was found that in the absence of PTC catalyst cyclization is extremely slow, and far from completion after 24 h, at room temperature.

All aziridines **3** were characterized by satisfactory HRMS and by NMR spectroscopy. Only one regioisomer was obtained.

In conclusion, we have described a new convenient one-pot synthesis of *N*-hydroxy β-halo α-amino esters. We have also shown that the β-halo α-amino esters react in basic media to give *N*-hydroxy aziridine carboxylic acids (esters) which, at the moment, is limited to access. The easy removal of the *N*-hydroxy aziridines makes this method competitive with other direct aziridination procedures. Further studies of these reactions are under investigation.

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15. To a solution of the hydroxylamine chlorhydrate (10 mmol) and sodium carbonate (10 mmol) in THF/H_2O (20/5 mL), under N_2, was added a solution of halohydrine **1** (10 mmol) in THF (20 mL). The solution was then stirred at 0°C for 1 h and at room temperature for 6 h. The solution was partitioned between H_2O and CH_2Cl_2, the aqueous layer extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered and the solvent removed in vacuo. The residue was directly subjected to silica gel column chromatography (EtOAc–petroleum ether 3:2 as eluent) to afford β-halo α-amino esters **2** ($R_1 = Me$) as a white solid or **2** ($R_1 = Et$) as a yellow oil.
For example: **2g**: IR (Nujol): *v*: 3210–3430, 2230, 1720 cm^{-1}. ^1H NMR ($CDCl_3$+TFA/250 MHz) δ ppm: 7.40–7.56 (m, 4H, Ar); 3.84 (s, 3H, $CO_2\underline{CH_3}$); 2.30 (s, 3H, CH_3); 5.42 (s, 1H, CH). ^{13}C NMR: 128.5, 132.3, 136.5, 139.0 (Ar-ring C); 62.0 (d, $^1J = 157.4$ Hz, CH); 53.8 (q, $^1J = 147.4$ Hz, $CO_2\underline{CH_3}$); 75.0 (dd, $^2J = 5.0$ Hz, $\underline{C}$(NH)); 167.3 (s, CO); 115.5 (s, CN), 20.6 (q, $^1J = 126.1$ Hz, CH_3). HMRS calcd for $C_{11}H_{12}NO_3Cl$ $(M-HCN)^{+\bullet}$: 241.0505 found 241.048. Anal. calcd: C, 53.58; H, 4.91; N, 10.38; Cl, 13.17; found: C, 53.62; H, 4.88; N, 10.35; Cl, 13.22.
Compound **2k**: IR (Nujol): *v*: 3210–3420, 2220, 1725 cm^{-1}. ^1H NMR ($CDCl_3$+TFA/250 MHz) δ ppm: 7.28–7.44 (m, 4H, Ar); 3.82 (s, 3H, $CO_2\underline{CH_3}$); 2.28 (s, 3H, CH_3); 5.45 (s, 1H, CH)). ^{13}C NMR: 128.7, 130.3, 134.5, 138.2 (Ar-ring C); 62.2 (d, $^1J = 157.1$ Hz, CH); 53.6 (q $^1J = 147.3$ Hz, $CO_2\underline{CH_3}$); 75.2 (dd, $^2J = 5.1$ Hz, $\underline{C}$(NH)); 167.1 (s, CO); 115.2 (s, CN), 20.4 (q, $^1J = 126.0$ Hz, CH_3). HMRS calcd for $C_{11}H_{12}NO_3Br$ $(M-HCN)^{+\bullet}$: 285.0001 found 284.998. Anal. calcd: C, 45.99; H, 4.20; N, 8.98; Br, 25.50; found: C, 45.96; H, 4.18; N, 9.01; Br, 25.47.
16. A mixture of β-halo-α-amino esters **2** (10 mmol), powdered NaOH (5 mmol), finely powdered K_2CO_3 (5 mmol), Bu_4NHSO_4 (0.25 mmol) and benzene (60 mL) was stirred efficiently at rt for 8 h. Solid inorganic salts were filtered off, washed with benzene and the solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford aziridine esters **3** as a colourless oils.
For example: **3a**: IR (Nujol): *v*: 3430, 2240, 1750 cm^{-1}. ^1H NMR ($CDCl_3$/250 MHz) δ ppm: 7.15–7.38 (m, 4H, Ar); 3.92 (s, 3H, $CO_2\underline{CH_3}$); 2.32 (s, 3H, CH_3); 4.32 (s, 1H, CH). ^{13}C NMR: 128.5, 131.1, 135.2, 139.0 (Ar-ring C); 64.0 (d, $^1J = 157.4$ Hz, CH); 53.6 (q, $^1J = 147.4$ Hz, $CO_2\underline{CH_3}$); 53.0 (d, $^2J = 5.0$ Hz, $\underline{C}$(NH)); 163.8 (s, CO); 114.1 (s, CN), 20.6 (q, $^1J = 126.2$ Hz, CH_3). HMRS calcd for $C_{12}H_{12}N_2O_3$ $(M^{+\bullet})$: 232.0847 found 232.082. Anal. calcd: C, 62.08; H, 5.21; N, 12.12; found: C, 62.11; H, 5.18; N, 12.09. Compound **3i**: IR (Nujol): *v*: 3400, 2230, 1740 cm^{-1}. ^1H NMR ($CDCl_3$/250 MHz) δ ppm: 7.25–7.45 (m, 4H, Ar); 3.88 (s, 3H, $CO_2\underline{CH_3}$); 2.32 (s, 3H, CH_3); 4.33 (s, 1H, CH), 3.45 (s, 3H, OCH_3). HMRS calcd for $C_{13}H_{14}N_2O_3$ $(M^{+\bullet})$: 246.1004 found 246.098; $(M^{+\bullet}-H_2O)$: 228.0898 found 228.088.