Pergamon

Tetrahedron Letters 43 (2002) 5867–5869

TETRAHEDRON LETTERS

Stereo- and regioselective ring opening of alkenyl aziridines with metal halides

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Received 15 March 2002; revised 10 June 2002; accepted 13 June 2002

Abstract—The reaction of *N*-Boc-alkenyl aziridines with lithium halides in presence of Amberlyst 15 afforded the stereo- and regioselective ring-opened products in high yields. The following treatment of the bromo- and iododerivatives with silica gel produced the corresponding oxazolidin-2-ones.

The transformation of chiral aziridines has received great attention in the last years both for their occurrence in natural products and for the possibility to control the opening of the strained heterocyclic ring, useful in the synthesis of biological interesting compounds.[1]

In this context, alkenyl aziridines are of particular interest since the olefinic moiety allows an efficient control of the regioselectivity of the ring opening and can be further elaborated.

Only in the last years, these substrates have been utilised in organic synthesis. Ring expansion to four-, five-, six-, or seven-membered heterocycles, frequently present in naturally occurring compounds[2] and regiospecific ring-opening reactions applied to the stereoselective synthesis of *E*-alkene dipeptide isosters,[3] are the most significant examples recently appeared in the literature.

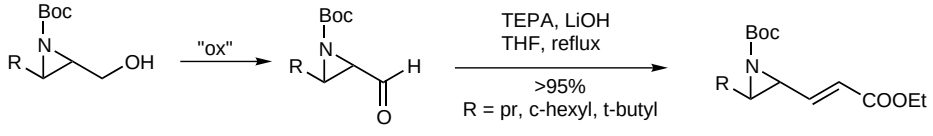
As we are interested in synthetic methodologies to prepare highly functionalised chiral fragments by stereo- and regioselective ring opening of functionalised three-membered ring heterocycles,[4,5] we planned to extend our studies on these particular substrates.

In the light of the excellent results obtained with vinyloxiranes,[6] we decided to employ the LiX/Amb15 system to attempt the regio- and stereoselective opening of the aziridine ring of the alkenyl aziridines.

Aziridines bearing an α,β-unsaturated ester group were prepared by a Horner–Emmonds reaction,[7] from α,β-aziridine aldehydes, these last easily obtained from the corresponding aziridine alcohols by an oxidation by the pyridine/SO_3 complex (Scheme 1).[8]

To study the reactivity of these substrates we prepared compounds with various R groups to investigate the influence of the steric hindrance on the course of the reaction.

All substrates were submitted to the reaction with LiX/Amb15 in acetone at −20°C. At higher or lower temperatures, regioselectivities or conversions



Scheme 1.

Keywords: alkenyl aziridines; aminohalides; oxazolidin-2-ones.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)01118-8

decreased. Moreover, the presence of Amb15 was necessary because in its absence the starting material was completely recovered.

Under these conditions, in a few hours, the aziridine ring was opened in a regio- and diastereoselective fashion to give the corresponding *anti* allyl haloderivative in a nearly quantitative yield. The regiochemistry of the reaction products was established by spin–spin decoupling experiments and the *anti* configuration was assigned based on a S_N2 mechanism, since only one diastereomer was detected.

As reported in Table 1, the regio- and stereoselectivity of the aziridine ring opening with LiX/Amb15 did not depend from the R hindrance. The known high reactivity of the allylic position[10] could be responsible for the complete regioselectivity observed, especially when an electron-withdrawing substituent on the double bond makes this position more electron-poor. In fact, when an alkyl group was present in place of the carboxyl, the reaction led to a complex mixture of products.

The chloro- and bromoderivatives did not need any purification and were characterised in the crude. The iododerivatives, instead, underwent a rearrangement during the purification on silica gel, giving in every case an unexpected product in almost quantitative yield. When treated with silica gel, the bromoderivatives showed the same behaviour, meanwhile the chloroderivatives did not change.

The physical data of these new compounds were in agreement with a 2-oxazolidinone structure, which should be derived from a silica gel induced rearrangement through an intramolecular nucleophilic substitution of the bromine or iodine (Fig. 1, Table 2). In fact, with chloride, the worst leaving group, the reaction did not occur.

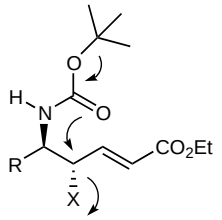
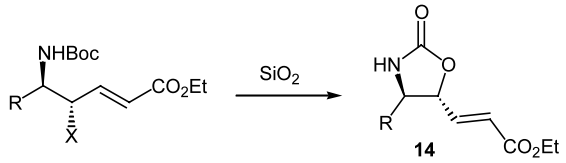


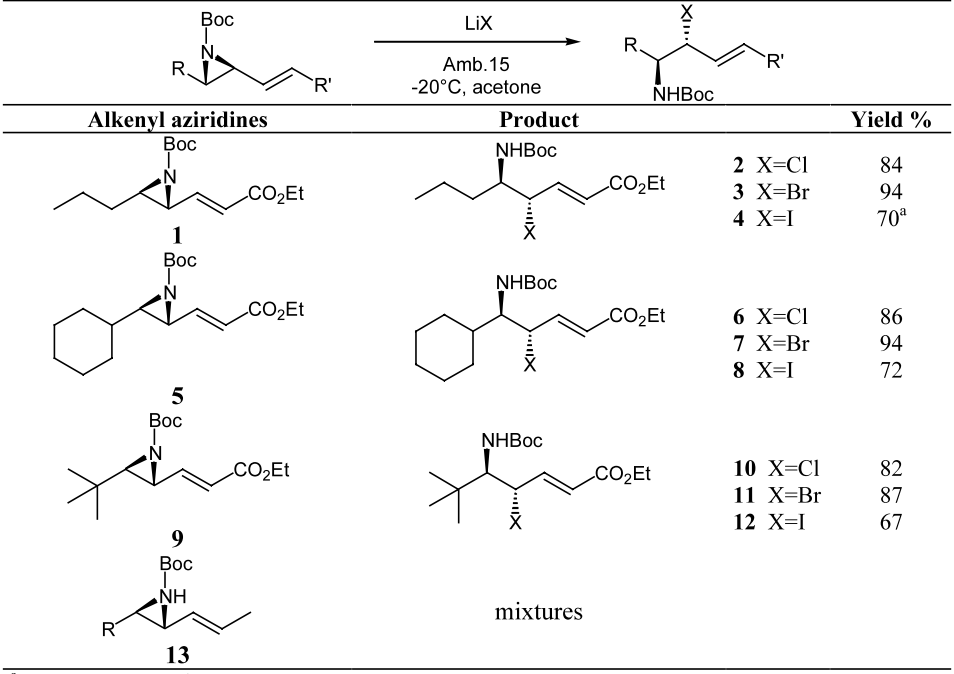
Figure 1.

Table 2. Formation of oxazolidinones[11]



R	X	Yield (%)
C_3H_7	I	66
C_3H_7	Br	>95
c-Hexyl	I	60
c-Hexyl	Br	>95
t-Butyl	I	50
t-Butyl	Br	>95

Table 1. Ring opening of alkenyl aziridines by LiX/Amb15[9]



Alkenyl aziridines	Product		Yield %
1		**2** X=Cl	84
		3 X=Br	94
		4 X=I	70[a]
5		**6** X=Cl	86
		7 X=Br	94
		8 X=I	72
9		**10** X=Cl	82
		11 X=Br	87
		12 X=I	67
13	mixtures		

[a] Yields calculated by ^{1}H-NMR analysis

The method appears of general value and the obtained products are promising intermediates for the possibility to substitute the halide and to further functionalise the double bond. Moreover, considering that oxazolidinones have been extensively used as chiral auxiliaries in a wide range of reactions in the stereoselective synthesis of natural products, antibiotics and pharmaceuticals,[12] the application of these results could be varied.

The employment of these methodologies to the synthesis of polyfunctionalised fragments, usually present in many naturally occurring compounds, is currently under investigation.

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9. NMR data for representative compounds. Compound **1**: ^{1}H NMR: δ 0.95 (3H, t, $J=7.3$ Hz), 1.29 (3H, t, $J=7.3$ Hz), 1.45 (9H, s, Boc), 1.25–1.70 (4H, m), 2.50 (1H, ddd, $J=3.0$, 5.8, 5.8 Hz, CHN), 2.82 (1H, dd, $J=3$, 8.8 Hz, CHN), 4.19 (2H, q, $J=7.3$ Hz), 6.13 (1H, d, $J=15.4$ Hz, C=CH), 6.42 (1H, dd, $J=8.8$, 15.4 Hz, C=CH); ^{13}C NMR: δ 13.4, 14.0, 19.9, 27.6, 32.9, 43.4, 45.3, 60.2, 81.3, 123.9, 143.9, 159.8, 165.2. Compound **2**: ^{1}H NMR: δ 0.88 (3H, t, $J=6.8$ Hz), 1.26 (3H, t, $J=7.1$ Hz), 1.26–1.55 (4H, m), 1.45 (9H, s), 3.80–3.97 (1H, m, CHN), 4.17 (2H, q, $J=7.1$ Hz), 4.61–4.75 (2H, m, CHCl, NH), 6.09 (1H, dd, $J=1.3$, 15.4 Hz, C=CH), 6.88 (1H, dd, $J=6.8$, 15.4 Hz, C=CH); ^{13}C NMR 13.6, 14.1, 18.9, 28.2, 31.6, 54.3, 60.6, 64.1, 79.7, 124.2, 142.9, 155.3, 165.4. Compound **3**: ^{1}H NMR: δ 0.90 (3H, t, $J=6.6$ Hz), 1.3 (3H, t, $J=6.6$ Hz), 1.20–1.65 (4H, m), 1.45 (9H, s), 3.78–3.80 (1H, m, CHN), 4.2 (2H, q, $J=6.6$ Hz), 4.65 (1H, bd, $J=8.8$ Hz, NH), 4.75 (1H, dd, $J=4.4$, 8.8 Hz, CHBr), 6.02 (1H, d, $J=15.4$ Hz, C=CH), 6.95 (1H, dd, $J=8.8$, 15.4 Hz, C=CH); ^{13}C NMR: δ 13.6, 14.1, 18.9, 28.2, 54.1, 56.9, 60.7, 79.7, 124.2, 143.1, 155.2, 165.4. Compound **4**: ^{1}H NMR: δ 0.90 (3H, t, $J=7.0$ Hz), 1.28 (3H, t, $J=7.1$ Hz), 1.25–1.48 (4H, m), 1.45 (9H, s), 3.25–3.41 (1H, m, CHN), 4.15 (2H, q, $J=7.1$ Hz), 4.58 (1H, bd, $J=9.1$ Hz, NH), 4.88 (1H, ddd, $J=3.9$, 3.9, 10.6 Hz, CHI), 5.88 (1H, dd, $J=3.9$, 15.4 Hz, C=CH), 7.02 (1H, dd, $J=10.6$, 15.4 Hz, C=CH).
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11. Compound **14** (R = Pr): ^{1}H NMR: δ 0.96 (3H, t, $J=7.3$ Hz), 1.42 (3H, t, $J=7.3$ Hz), 1.43–1.96 (4H, m), 3.54 (1H, dd, $J=6.6$ Hz, CHN), 4.08 (2H, q, $J=7.3$ Hz), 4.74 (1H, ddd, $J=1.5$, 6.6 Hz, CHO), 6.06 (1H, dd, $J=1.5$, 15.4 Hz, C=CH), 6.42 (1H, s, NH), 6.96 (1H, dd, $J=5.1$, 15.4 Hz, C=CH); ^{13}C NMR: δ 13.7, 14.1, 18.6, 28.2, 37.0, 57.7, 60.9, 80.2, 123.2, 141.8, 158.4, 165.5.
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