Lewis acid-catalyzed stereospecific ring expansion of aziridine-2-carboxylates to imidazolidin-2-ones†

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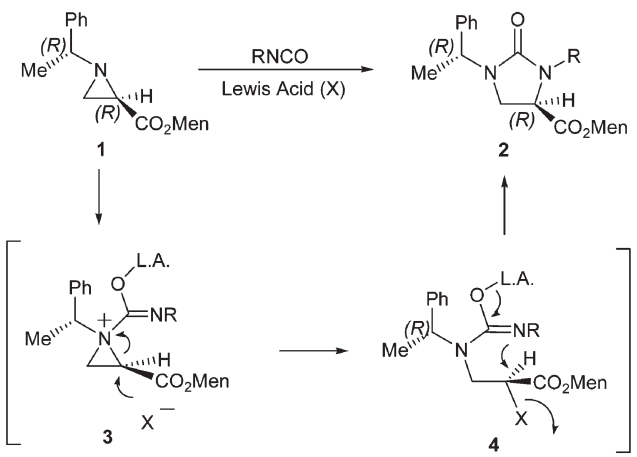
Lewis acid-catalyzed ring expansion reaction of chiral aziridine-2-carboxylate proceeds regio- and stereospecifically to yield enantiomerically pure 4-functionalized imidazolidin-2-ones in high yields.

Cycloaddition of three-membered ring heterocycles with hetero-cumulenes attracts a great deal of attention due to the potential biological activity of the products.[1] However, few successes with activated aziridine have been reported with proper control of the regio- and stereochemistry utilizing metals as catalysts.[1k,l] In this report we would like to describe the first Lewis acid-catalyzed regio- and stereospecific cycloaddition reaction involving aziridines with isocyanates as a new simple stereospecific approach to 4-functionalized imidazolidin-2-one ring systems. Functionalized imidazolidin-2-ones have been used not only as chiral synthons in asymmetric syntheses of biologically active compounds or their synthetic intermediates,[2] but also as chiral auxiliaries in asymmetric transformations.[3] Moreover, some suitably substituted chiral imidazolidin-2-ones are also being used as biologically active compounds.[4] In spite of their great variety of applicability, only a few preparative methods exist for the target compounds starting from β-keto esters,[5] 1,2-amino alcohols,[6] oxime ethers,[7] resin-bound amino acids,[8] halocyclization,[9] and aziridines.[10] This Lewis acid-catalyzed cycloaddition reaction of aziridine-2-carboxylates with isocyanates will serve as a facile and asymmetric route to access functionalized imidazolidin-2-ones.

We reported the possibilities of the chiral aziridine as a three-carbon chiral building block for the preparation of various amino acid derivatives and biologically active natural products.[11] We also reported the preparation of enantiomerically pure functionalized oxazolidin-2-ones starting from the commercially available chiral aziridine using a single step ring expansion reaction.[12] Throughout our earlier studies we found that the nitrogen of the aziridine was quite basic and also nucleophilic enough to participate in various reactions. Therefore, we learned that the ring-opening reaction of the aziridine was initiated by the formation of the aziridinium ion intermediate. These results motivated us to explore a new efficient method to obtain new ring expansion products, imidazolidin-2-ones, from the reactions of the chiral aziridine-2-carboxylate with various isocyanates.

An initial experiment was performed with the commercially available *N*-[(*R*)-(+)-α-methylbenzyl]-2(*R*)-carboxylic acid (−)-menthol ester **1** with 1.01 equiv. of phenyl isocyanate in DMF at room temperature or under reflux but resulted in no addition product. We realized that the isocyanate was not electrophilic enough to form the aziridinium ion intermediate. Therefore, we introduced $Ti(OiPr)_4$ as a Lewis acid to activate the isocyanate to become more electrophilic so that the aziridine ring nitrogen can attack easily. This introduction of a Lewis acid still did not provide the expected product leaving all the starting material unreacted.

All those repeated failures reminded us of our previous one-step transformation of aziridine-2-carboxylates into the corresponding 5-functionalized oxazolidin-2-ones.[12a] This previous work gave us a new insight and led us to introduce Lewis acids containing halide that could serve as both a nucleophile and a leaving group. The reaction of the chiral aziridine **1** with 1.1 equiv of phenyl isocyanate and 3.0 equiv. of TMSCl in DMF at an ambient temperature proceeded smoothly to provide 89% yield of imidazolidin-2-one-4(*R*)-carboxylic acid (−)-menthol ester **2a** (Scheme 1). After optimization of Lewis acids, solvents, concentrations, and temperature, we found that different reaction conditions were needed for different isocyanates. Furthermore, we realized that the introduction of a Lewis acid involving halide makes the reactions proceed smoothly to afford the corresponding imidazolidin-2-one **2a**. We therefore proposed a plausible mechanistic pathway with retention of the configuration at C-2 of the aziridine *via* a double inversion process at the C-2 position of the chiral aziridine. The C(2)–N bond is regiospecifically cleaved by the bromide ion from $MgBr_2$ or $MgBr_2{\cdot}Et_2O$ or by the chloride ion from TMSCl *via* an S_N2 process as in **3**, and then the following



Scheme 1 Preparation of imidazolidin-2-ones with isocyanates and its plausible mechanism.

† Electronic Supplementary Information (ESI) available: Synthetic procedure and characterisation of all new compounds. See http://www.rsc.org/suppdata/cc/b5/b503750f/

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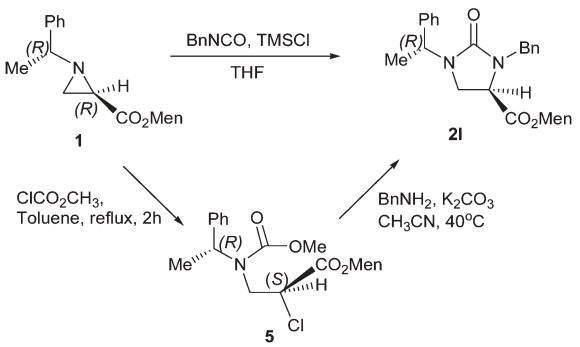
intramolecular cyclization by the urea amide nitrogen of **4** gives the corresponding imidazolidinone **2** with retention of the configuration at C-2 of the aziridine **1**. Therefore, the presence of a suitable Lewis acid is necessary and the same reaction without the Lewis acid does not proceed at all.

To confirm the absolute configuration at C-4 of the imidazolidin-2-one **2**, we carried out two additional experiments. *N*-[(*R*)-(+)-α-methylbenzyl]-*N*′-benzylimidazolidin-2-one-4(*R*)-carboxylic acid (−)-menthol ester **2l** was obtained from the chiral aziridine **1** by the optimized reaction conditions using benzyl isocyanate. The same compound imidazolidin-2-one **2l** was obtained from the compound **5**, the intermediate of our previous work,[12a] by the reaction with benzylamine with potassium carbonate in CH_3CN followed by intramolecular cyclization (Scheme 2). We also obtained *N*-[(*R*)-(+)-α-methylbenzyl]-*N*′-tosyl-imidazolidin-2-one-4-(*R*)-carboxylic acid (−)-menthol ester **2o** from the chiral aziridine **1** with tosyl isocyanate through the same reaction conditions. Imidazolidin-2-one-4(*R*)-carboxylate **2o** was reduced to provide 4(*R*)-hydroxymethyl substituted imidazolidin-2-one **6o** in high optical purity with $[\alpha]_D = +169$ ($c = 0.16$ in $CHCl_3$) [lit.[10b] $[\alpha]_D = -165$ ($c = 0.7$ in $CHCl_3$) for its enantiomer] whose configuration was confirmed as stated.

The above mentioned stereospecific transformation of the aziridine-2-carboxylic acid (−)-menthol ester **1** with phenyl isocyanate proceeded well to give the corresponding enantiomerically pure imidazolidin-2-one-4(*R*)-carboxylic acid (−)-menthol ester **2a** as a white solid in 89% yield. We also confirmed the retention of the configuration at C-2 of the aziridine by using 2(*S*)-stereoisomer $\mathbf{1_d}$ to obtain the corresponding 4(*S*)-imidazolidin-2-one $\mathbf{2a_d}$ as an oil in 83% yield under the same reaction conditions. This shows that the absolute configuration at C-4 of the imidazolidin-2-one is controlled by that of the C-2 position of the chiral aziridines. As a result, enantiomerically pure imidazolidin-2-one-4-carboxylates are available efficiently from the corresponding aziridine-2-carboxylate using a ring expansion reaction with various isocyanates with retention of the configuration at the C-2 position of the aziridine-2-carboxylates (Table 1). We used isocyanates with various substituents such as aryl (entries 1–11), alkyl (entries 12–14), tosyl (entry 15) and trichloromethylcarbonyl (entry 16) to provide a variety of structurally modified enantiomerically pure imidazolidin-2-one-4-carboxylates in high yields. We also functionalized imidazolidin-2-one-4-carboxylates **2** to the corresponding 4-hydroxylmethyl imidazolidin-2-ones **6**, and also to the corresponding amides **7** in high yields.



Scheme 2 Stereochemical identification of the reaction product.

Table 1 Preparation of imidazolidin-2-ones with isocyanate[a]

Entry	R	Product	Yield (%)[e]
1	Ph	**2a**	89
2	4-Biphenyl	**2b**	86
3	1-Naphthyl	**2c**	89
4	*o*-Tolyl	**2d**	80
5	4-FPh	**2e**	91
6	4-ClPh	**2f**	89
7	3-MeOPh	**2g**	87
8	4-MeOPh	**2h**	95
9	2-NO_2Ph	**2i**	93
10	2,4-DiMeOPh	**2j**	77
11	1,4-DiNCOPh	**2k**	76
12[b]	Bn	**2l**	88
13[b]	Et	**2m**	77
14[c]	Cyclohexyl	**2n**	65
15[d]	Ts	**2o**	93
16[d]	C(O)CCl_3	**2p**	75

[a] Reactions were conducted with aziridine, 10 mol% $MgBr_2$, 0.2 M in dioxane and 1.01 equiv. of RNCO at room temperature, 12–48 h. [b] Reactions were conducted with aziridine, 10 mol% $MgBr_2 \cdot Et_2O$, 0.2 M in THF and 1.01 equiv. of RNCO at room temperature, 1 h. [c] Reactions were conducted with aziridine, 2.0 equiv. TMSCl, 0.2 M in THF and 2.0 equiv. of RNCO at room temperature, 10 min. [d] Reactions were conducted with aziridine, 3.0 equiv. TMSCl, 0.2 M in THF and 2.0 equiv. of RNCO at room temperature, 10 min. [e] Isolated yield.

In conclusion, the enantiomerically pure *N*,*N*′-disubstituted imidazolidin-2-one-4-carboxylates can be obtained in a one-step, simple and highly efficient manner using a Lewis acid-catalyzed ring expansion reaction of the commercially available chiral aziridines with isocyanates. These reactions proceed both regio- and stereospecifically with retention of the configuration at the C-2 of the chiral aziridines.‡

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Notes and references

‡ General procedure for the synthesis of imidazolidin-2-one-4-carboxylates *via* $MgBr_2$-catalyzed reaction: preparation of *N*-[(*R*)-(+)- α-methylbenzyl]-*N*′-(*R*)-imidazolidin-2-one-4-carboxylates (**2a**). To a solution of **1** (100 mg, 0.30 mmol) in 1.80 mL of dioxane was added PhNCO (37 μL, 0.30 mmol) and magnesium bromide (9 mg, 0.03 mmol) successively under nitrogen with stirring at room temperature. The mixture was stirred for 12 h at the same temperature. The mixture was filtered and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc–*n*-hexane, 5 : 95) provided 89% of **2a** as a white solid. (R = Ph): Yield 89% (white solid); mp 92—94 °C; $[\alpha]_D^{24} = +307.4$ (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.44 (d, $J = 7.5$ Hz, 2H), 7.39–7.36 (m, 2H), 7.33–7.29 (m, 1H), 7.28–7.24 (m, 2H), 7.18–7.16 (dd, $J = 8.5$, 1.5 Hz, 2H), 7.00–6.96 (tt, $J = 7.0$, 1.5 Hz, 1H), 5.52 (q, $J = 7.0$ Hz, 1H), 4.81 (dt, $J = 9.0$, 4.5 Hz, 1H) 4.77 (dd, $J = 9.0$, 5.0 Hz, 1H), 3.47 (dd, $J = 9.0$, 5.0 Hz, 1H)), 3.35 (t, $J = 9.0$ Hz, 1H), 2.04–2.00 (m, 1H), 1.91–1.85 (m, 1H), 1.74–1.72 (m, 1H), 1.71–1.69 (m, 1H), 1.58 (d, $J = 7.5$ Hz, 3H), 1.59–1.45 (m, 2H), 1.12–1.01

(m, 3H), 0.93 (dd, J = 5.0, 2.0 Hz, 6H), 0.76 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 150.9, 147.4, 139.5, 128.6, 128.4, 127.7, 127.3, 123.5, 122.2, 76.7, 76.3, 72.7, 51.3, 46.9, 44.3, 44.3, 40.6, 34.0, 31.4, 26.1, 23.1, 21.9, 20.8, 16.2, 16.0; IR (CH_2Cl_2) ν(C=O) 1746 cm−1, ν(C=O) 1684 cm−1; Anal. Calcd for $C_{28}H_{36}N_2O_3$: C, 74.95; H, 7.98; N, 6.41. Found: C, 74.97; H, 8.09; N, 6.24%; HRMS (EI) *m*/*z* exact mass calcd for $C_{28}H_{36}N_2O_3$: 448.2726, found 448.2719.

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