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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7713–7716

An easy one-pot stereoselective synthesis of 4-substituted and 4,5-disubstituted oxazolidin-2-ones from *N*-Boc-2,3-aziridino alcohols

Giuliana Righi,* Simona Ciambrone, Alessandra Pompili and Francesco Caruso

Istituto di Chimica Biomolecolare—Sezione di Roma, c/o Dipartimento di Chimica, Università 'La Sapienza', P.le A. Moro 5, 00185 Roma, Italy

Received 28 June 2007; revised 2 August 2007; accepted 6 August 2007
Available online 10 August 2007

Abstract—A novel and efficient one-pot stereoselective transformation of *N*-(*t*-butoxycarbonyl)-2,3-aziridino alcohols into 4-substituted and 4,5-disubstituted oxazolidin-2-ones has been developed; these functionalized products are amenable to other elaborations, some of which are described.

Chiral oxazolidin-2-ones are without any doubt one of the most important classes of five-membered heterocycles in organic chemistry.[1] They have been used as chiral synthons in asymmetric syntheses of various biologically active compounds and also, extensively, as chiral auxiliaries (Evan's auxiliaries) in a wide range of asymmetric reactions, such as aldol condensation, alkylation and Diels–Alder reactions.[2] Moreover, some substituted oxazolidin-2-ones show remarkable antibacterial activity;[3] for example, the antibiotic Linezolid, having a 5-functionalized chiral oxazolidin-2-one as a key structural unit, has continued to be a leading agent of its class of antibiotics (for over three decades) and has been demonstrated recently as a protein synthesis inhibitor in bacteria.[4] Furthermore, the novel cytokine modulator Cytoxazone, produced by *Streptomyces* sp., possesses a 4,5-disubstitued oxazolidin-2-one moiety.[5]

Consequently, the stereoselective synthesis of this heterocyclic system is of much interest and a number of procedures have been developed. The first method employed the condensation of chiral 1,2-amino alcohols with toxic carbonyl derivatives (e.g., phosgene, diphosgene, triphosgene and isocyanates),[2a] while more recent methods use electrochemically generated carbonates,[6] enzymatic desymmetrization of achiral compounds,[7] intramolecular cyclizations onto allyl sulfonates[8] or chiral aziridines.[9]

In recent years we have focused our attention on the use of the aziridine ring to prepare functionalized fragments through regio- and stereo-controlled ring-opening reactions;[10] during these studies, we observed a very interesting reactivity of *N*-(*t*-butoxycarbonyl)-2,3-aziridine alcohols, which allowed us to develop a straightforward method for the synthesis of 4-substituted and 4,5-disubstituted oxazolidin-2-ones.

When NaN_3 was added to 3-propyl-2,3-aziridino alcohol in DMF, at about 70 °C, a single product was obtained in nearly quantitative yield (Scheme 1). The spectroscopic data of this compound were in agreement with an oxazolidin-2-one structure, which could be explained through regio- and stereoselective nucleophilic attack of N_3^- at C-3 ring of the aziridine followed by intramolecular cyclization, with C-3 inversion and C-2 retention of configuration. The same result was obtained by heating the substrate in DMSO instead of DMF, and also by using the $NaN_3/LiClO_4$ system,[11] while the reaction did not proceed when carried out at room temperature.

The importance of functionalized chiral oxazolidin-2-ones emphasized above prompted us to further investigate this reaction, testing the possibility to extend the method to other substrates. To this end we synthesized 2,3-aziridino alcohols of type **A**[12] and *syn*-2,3-aziridino

* Corresponding author. Tel.: +39 6490422; fax: +39 649913628; e-mail: giuliana.righi@uniroma1.it

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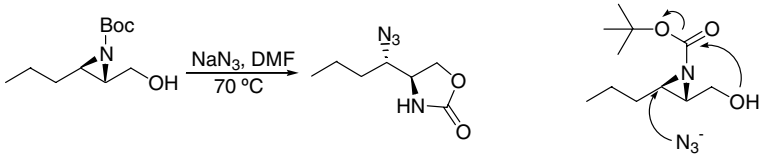
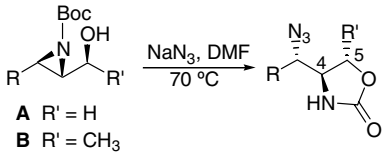
doi:10.1016/j.tetlet.2007.08.021



Scheme 1. 4-Substituted oxazolidin-2-one from *N*-Boc-2,3-aziridino alcohol.

Table 1. (1′-Azido)-oxazolidinones from 2,3-aziridino alcohols[14]



A R' = H
B R' = CH_3

2,3-Aziridino alcohol	R	R′	Oxazolidinone	Yield (%)
1	Pr	H	**7**	82
2		CH_3	**8**	80
3	*c*-Hexyl	H	**9**	94
4		CH_3	**10**	82
5	*t*-Butyl	H	**11**	77
6		CH_3	**12**	72

alcohols of type **B**[13] having different sterically demanding substituents at the C-3 ring position.

As shown in Table 1, the reaction afforded very good yields of products, independent of the steric hindrance of substituent R present on the 2,3-aziridino alcohols. Type **A** reagents led to 4-substituted oxazolidinones, and 2,3-aziridino alcohols of type **B** to *trans*-4,5-disubstituted oxazolidinones. In the latter, the expected *trans* stereochemistry was established from the value of the coupling constant $J_{4,5}$, which was always in accordance with *trans* stereochemistry ($J_{4,5} \approx 4.4$ Hz).[15]

The molecular structure of compound **9** was studied by X-ray diffraction. The crystallographic data† are consistent with the structure shown in Figure 1, or the inverted one. Both confirm the *anti* stereochemistry of the N_3–C1′–C4–NH fragment.

Also remarkable is the presence, in the C-4 chain, of a controlled chiral centre, susceptible to further elaboration, such as reduction to an amino group to give *anti* diamino vicinal systems, which are important and versatile structural units present in a wide variety of natural products[16] and drugs.[17] As expected, catalytic hydrogenation in the presence of di-*tert*-butyl carbonate[18] followed by hydrolysis of the *N*-Boc-protected oxazolidinone **13**, afforded **15** in a satisfactory overall yield (Scheme 2). However, it was also possible to obtain the free amino group by treating the oxazolidinone with LiOH in EtOH, as demonstrated by the hydrolysis of **10** (Scheme 3).

†The crystal structure **9** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 659180.

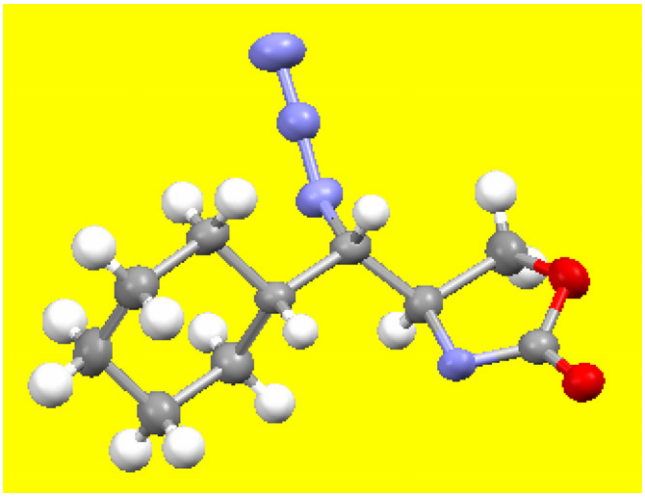
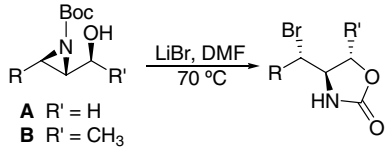


Figure 1. The *trans* arrangement of the N_3–C1′–C4–NH grouping in compound **9** obtained from X-ray diffraction.

Table 2. (1′-Bromo)-oxazolidinones from 2,3-aziridino alcohols[14]



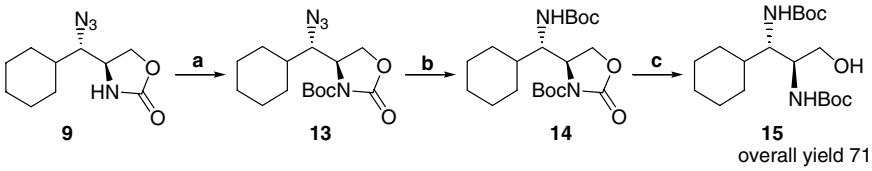
A R' = H
B R' = CH_3

2,3-Aziridino alcohol	R	R′	Oxazolidinone	Yield (%)
1	Pr	H	**17**	78
2		CH_3	**18**	74
3	*c*-Hexyl	H	**19**	84
4		CH_3	**20**	85
5	*t*-Butyl	H	**21**	77
6		CH_3	**22**	76

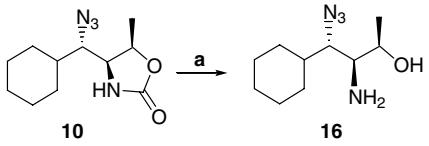
In order to test the possibility of using a different nucleophile to generate the oxazolidinone, we treated 2,3-aziridino alcohols **1**–**6** with LiBr in DMF at 70 °C and obtained only a single product in good yield in each case, which was identified as the corresponding bromo-substituted oxazolidinone (Table 2).[19]

These bromo-oxazolidinones can be further elaborated, as shown by the reduction of **17** to **23**. The easy removal of bromine via radical reduction with Bu_3SnH or TTSS afforded dehalogenated derivatives (Scheme 4), that is, structures found as antipenetrant agents in cosmetic and/or dermatological compositions.[20]

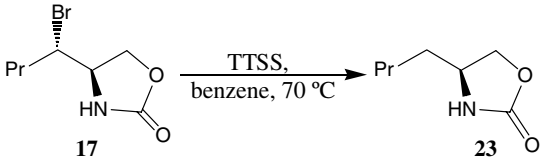
In summary, we have developed a novel, efficient, one-pot stereoselective transformation of *N*-Boc-2,3-aziridine alcohols into 4-substituted and 4,5-disubstituted oxazolidin-2-ones;[21] the mild reaction conditions used



Scheme 2. Preparation of an *anti* diamino vicinal system. Reagents and conditions: (a) Boc_2O, DMAP, CH_2Cl_2, rt; (b) H_2, Pd/C, Boc_2O, EtOAc, rt; (c) Cs_2CO_3, MeOH, rt.



Scheme 3. Hydrolysis of oxazolidin-2-one **10**. Reagents and conditions: (a) LiOH, $EtOH/H_2O$, reflux, >95%.



Scheme 4. Radical reduction of halo derivatives.

are compatible with the presence of numerous functional groups. As shown, this method allows the direct access to precursors of important biologically active molecules; studies in this sense are currently underway.

Acknowledgements

We thank MIUR (Ministry of University and Research—Rome) for partial financial support (PRIN 2005) and Joseph Tanski at Columbia University for use of a diffractometer.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.021.

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14. Representative procedure for the one-pot preparation of oxazolidin-2-ones. NaN_3 (2.5 mmol) or LiBr (3 mmol) was added to a solution of 2,3-aziridino alcohol of type **A** or **B** (1 mmol) in dry DMF (2.5 mL) at room temperature. The reaction was stirred at 70 °C for 8–10 h (TLC monitoring). After cooling, the product was diluted with EtOAc (10 mL) and washed with saturated aq NH_4Cl; the organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 1:1).
(1′S,4S*)-4-(1′-azidobutyl) oxazolidin-2-one*, **7**: This was obtained as colourless viscous oil. ^{1}H NMR: δ 6.64 (br s, 1H, N*H*), 4.45 (pseudo t, 1H, *J* 8.8 Hz, CH_aO), 4.29 (dd, 1H, *J* 8.8, 5.1 Hz, CH_bO), 3.85 (dt, 1H, *J* 10.2 5.1 Hz, C*H*NH), 3.45 (m, 1H, C*H*N_3), 1.78–1.21 (m, 4H), 0.97 (t, 3H, *J* 6.6 Hz, CH_3).^{13}C NMR: δ 160.1, 66.6, 64.9, 55.5, 32.6, 18.9, 13.8. $C_7H_{12}N_4O_2$ (184.20): C, 45.64; H, 6.57; N, 30.42. Found: C, 45.60; H, 6.54; N, 30.39.
(1′S,4R*)-4-(1′-bromobutyl)oxazolidin-2-one*, **17**: This was obtained as a yellow viscous oil. ^{1}H NMR: δ 6.78 (br s, 1H, N*H*), 4.52 (pseudo t, 1H, *J* 8.8 Hz, CH_aO), 4.30 (dd, 1H, *J* 8.8, 5.1 Hz, CH_bO), 4.19–4.01 (m, 1H, C*H*Br), 4.01–3.84 (m, 1H, C*H*NH), 1.92–1.34 (m, 4H), 0.95 (t, 3H, *J* 6.6 Hz, CH_3). ^{13}C NMR: δ 159.5, 69.1, 57.4, 57.3, 36.0, 20.3, 13.2. $C_7H_{12}BrNO_2$ (222.08): C, 37.86; H, 5.45; N, 6.31. Found: C, 37.81; H, 5.41; N, 6.25.
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21. On using optically active 2,3-aziridine alcohols (Ref. 12) the corresponding chiral oxazolidin-2-ones could be readily obtained.