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Stereoselective synthesis of novel (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinones from (*S*)-epichlorohydrin: a key precursor for the oxazolidinone class of antibacterial agents ☆

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Abstract

A facile synthesis of novel (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinones starting from (*S*)-epichlorohydrin is described. The (*R*)-azide was utilized for the preparation of Linezolid.

Oxazolidinones have shown various pharmacological activities in the areas of drug development, antibacterials,[1] inhibitors of monoamine oxidase,[2] cytokine modulators,[3] sigma receptors,[4] pschyotropics,[5] antiallergy agents,[6] antibiotics,[7] intermediates in the synthesis of renin inhibitors,[8] β-lactam and macrolide antibiotics,[9] immunosuppressants[10] and in many other applications.[11]

Oxazolidinones are the first new class of synthetic antibacterial agents introduced since the discovery of quinolones more than 30 years ago. Linezolid[1] was the first drug of this class possessing antibacterial activity, having an *N*-aryl-5-aminomethyl-2-oxazolidinone moiety.

To access a large number of derivatives to be screened in biological assays, we required a general and efficient method for the synthesis of analogues containing *N*-aryl-5-aminomethyl-2-oxazolidinone without using (*n*-BuLi), epoxides and phenylisocyanates which are used in the classical synthesis of this class of compounds.[3,4] The preparation of aryl isocyanates is cumbersome from multi-substituted aryl amines. Moreover, these strategies require further steps to convert the 5-hydroxymethyl group into a 5-aminomethyl functionality. The latest analogues have common functionalities on the 5-aminomethyl group such as acetamides carbamates, thiocarbamates, ureas and thioureas.[12] During the conversion of amines to carbamates, thiocarbamates, ureas and thioureas, there is a higher chance of obtaining the corresponding symmetrical derivatives. In view of these limitations, we focused our attention to prepare the useful chiral synthons (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinone starting from commercially available (*S*)-epichlorohydrin using a new methodology. These moieties can be derivatized on both ends to develop new oxazolidinone antibacterial analogues, as well as MAO-B inhibitors used in the treatment of Parkinson's disease.[13] In the present synthetic strategy, we have developed facile conditions for the one-pot synthesis of 2-oxazolidinones from azido alcohols using Ph_3P/CO_2 via the generation of an intermediate isocyanate followed by cyclization. This is an attractive application of aza-Wittig reactions of iminophosphoranes[14] and should find general utility in the synthesis of 2-oxazolidinones (Fig. 1).

(*S*)-Epichlorohydrin **1** was stereoselectively ring-opened with NaN_3 in a mixture of H_2O/EtOH, whilst maintaining mild acidic conditions using NH_4Cl, to give (2*S*)-1-azido-3-chloropropan-2-ol **2** without racemization. The azido

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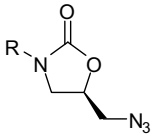
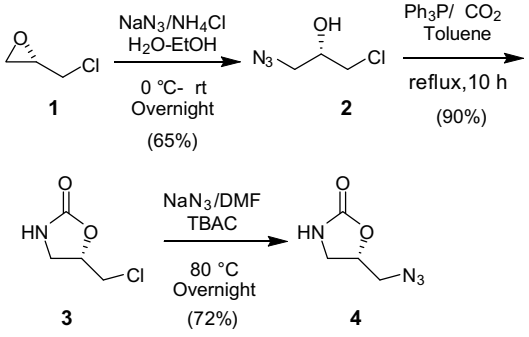


Fig. 1. 5-Azidomethyl-2-oxazolidinones.

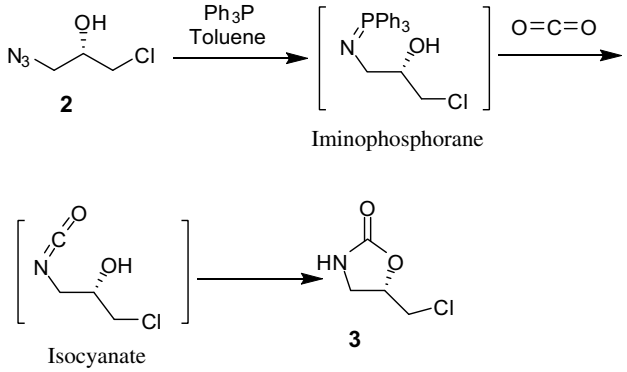
alcohol **2** on treatment with Ph_3P and carbon dioxide in toluene under reflux gave (*S*)-5-chloromethyl-2-oxazolidinone **3**,[15] which was further treated with NaN_3 under PTC conditions to give the desired compound **4** (Scheme 1). The reaction mechanism for the formation of compound **3** can be explained via an intermediate iminophosphorane. The iminophosphorane reacts with carbon dioxide to generate an intermediate isocyanate, which reacts further with the vicinal hydroxyl group to afford the corresponding oxazolidinone (Scheme 2).

The epimer **7** (*R* isomer) was obtained by converting compound **2** into *tert*-butyl carbamate derivative **5** by reductive protection with Boc using Pd/C. The specific rotation value obtained for **5** is −21.5 (*c* 1, $CHCl_3$) and this matched with the literature result.[16] Compound **5** was further reacted with NaN_3 using tetrabutylammonium chloride (TBAC) to give azido compound **6**. This azide **6** was cyclized with S_N2 inversion in Ph_3P–CCl_4–Et_3N[17] to (*R*)-oxazolidinone **7** (Scheme 3).

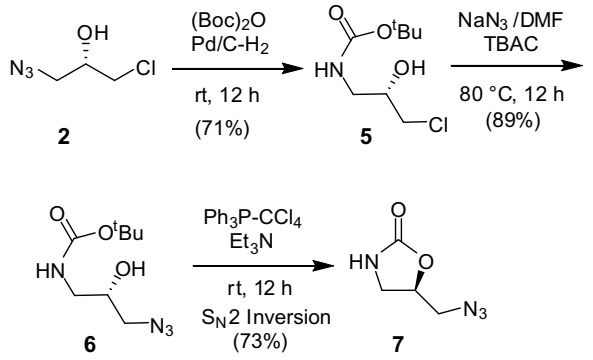
Oxazolidinone **7** provides access for derivatization on both nitrogens. The ring nitrogen can be alkylated and



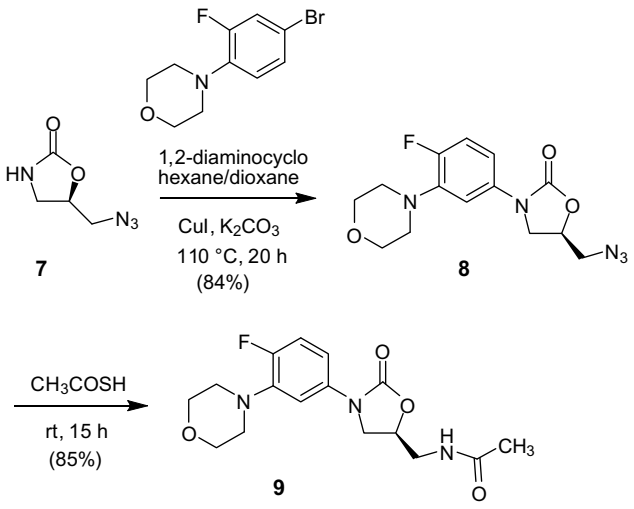
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

should also be a good candidate for arylation. The azide functionality provides the required site for preparing different analogues of the oxazolidinone. Many established procedures are available for reductive conversion of azides to acetamides[18] and carbamates.[19] The azide functionality can also be converted to carbamates, ureas, thiocarbamates and thioureas via iminophosphorane[14] and isocyanate or thiocyanate[20] intermediates, respectively. The utility of these intermediates has been exemplified by the synthesis of Linezolid as shown in Scheme 4. The required aryl bromide was coupled with azide **7** using established conditions[21] to afford compound **8** of which reductive acylation gave Linezolid **9**.[18b]

In conclusion, an efficient method has been developed for the preparation of novel chiral synthons (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinones, which are precursors for further transformations into potential antibacterial agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.061.

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15. (a) *General procedure for the one-pot conversion of azido alcohols to 2-oxazolidinones*: A solution of the azido alcohol (0.074 mol) and Ph_3P (0.081 mol) in toluene (100 mL) was taken under CO_2 (pressure 2–5 psi) at 0 °C. Then the reaction mass was slowly warmed and refluxed for 7–12 h. The reaction mixture was concentrated and the crude product obtained was purified by flash column chromatography using ethylacetate in petroleum ether system as eluent, to yield the corresponding 2-oxazolidinone. *Compound* **3**: $[\alpha]_D$ +16.42 (*c* 0.7, CH_2Cl_2), IR (Neat): 3369, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.3 (s, 1H), 4.79–4.80 (m, 1H), 3.8–3.45 (m, 4H), MS (*m*/*z*): 136, 138; (b) Madhusudhan, G.; Om Reddy, G.; Ramanatham, J.; Dubey, P. K. *Indian J. Chem., Sect. B* **2006**, *45B*, 1264–1268.
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