September 2009 *Volume 5 Issue 3*

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 5(3), 2009 [330-333]

A facile KOCN-TBAC/DMF mediated, one-pot synthesis of (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinone from corresponding β-chlorohydrin: A key precursor for the oxazolidinone class of antibacterial agents

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Received: 20th May, 2009 ; Accepted: 30th May, 2009

ABSTRACT

Synthesis of (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinones in single step from corresponding β-chlorohydrin by reacting with potassium cyanate (KOCN) in the presence of tetrabutylammonium chloride (TBAC) in DMF at 120°C is reported. Along with 2-oxazolidinones, also described the formation of (*R*)- and (*S*)-4-(azidomethyl)-1,3-dioxolan-2-one.

KEYWORDS

Linezolid;
5-azidomethyl-2-oxazolidinone;
Epichlorohydrin;
Potassium cyanate;
Antibacterial agent.

INTRODUCTION

Oxazolidinone antibacterial agents represented by linezolid[1] (**(1)**; Figure 1) (Zyvox™), approved for use in humans in April 2000, emerged as the first totally synthetic, structurally distinct, and mechanistically novel class of antibacterial agents since the discovery of trimethoprim in 1968. Linezolid exhibits its antibacterial activity by inhibiting bacterial protein synthesis via binding to the 50S ribosomal subunit and interfering with the fMet-tRNA binding to the P-site of the ribosomal peptidyltransferase center[2].

Small chiral molecules are very important building blocks for pharmaceutical compounds. Chiral 5-substituted-2-oxazolidinones are important core structures in many drug molecules and useful intermediates in the synthesis of chiral amino alcohols. The 5-azidomethyl- and 5-hydroxymethyl-2-oxazolidinones (**(2)** and **(3)**; Figure 1) are important in the preparation of oxazolidinone antibacterial agents[3]. Oxazolidinones have been used in the synthesis of chiral amino alcohols such as the betablocker carvedilol[4]. There has been great interest in developing efficient syntheses toward 2-oxazolidinones[5,6]. We and others have developed several efficient synthetic methods toward the synthesis of chiral 5-substituted 2-oxazolidinones[7-9,14].

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 5-aminomethyl-3-aryl-2-oxazolidinone without using (*n*-BuLi), epoxides and phenylisocyanates which are used in the classical synthesis of this class of compounds[10,11]. 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 5-aminomethyl functionality. The latest analogs have common functionalities on the 5-aminomethyl group, such as acetamides carbamates, thio carbamates, 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, (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinone moieties are useful to derivatize on both ends to develop new oxazolidinone antibacterial analogs, as well as MAO-B inhibitors used in the treatment of Parkinson's disease[13].

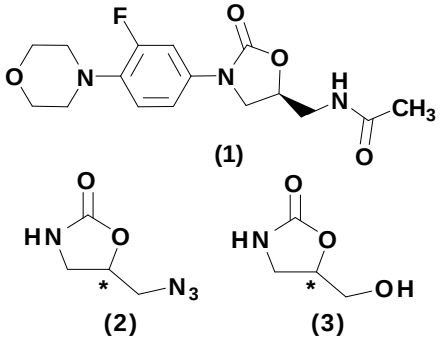
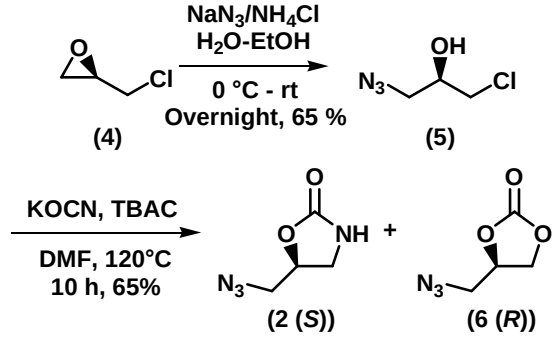


Figure 1 : Structures of Linezolid (1), 5-azidomethyl-2-oxazolidinone (2) and 5-hydroxymethyl-2-oxazolidinone (3)

RESULTS AND DISCUSSION

Earlier[14], (*R*)- and (*S*)-5-azidomethyl-2-oxazolidinones are synthesized by our research group using commercially available (*S*)-epichloro hydrin. (*S*)-Epichlorohydrin was stereoselectively ring-opened with NaN_3/ NH_4Cl, to give (2*S*)-1-azido-3-chloropropan-2-ol with out racemization. This azido alcohol was converted to (*S*)-5-chloromethyl-2-oxazolidinone, which was further treated with NaN_3 to give the desired (*S*)-5-(azidomethyl)oxazolidin-2-one. The other isomer (*R* isomer) was also obtained by converting (2*S*)-1-azido-3-chloropropan-2-ol into *tert*-butyl carbamate derivative by reductive protection with Boc using Pd/C followed by further reaction with NaN_3 to give azido compound. This azide was cyclized with S_N2 inversion in Ph_3P-CCl_4-Et_3N to (*R*)-oxazolidinone. This (*R*)-oxazolidinone was utilized previously by us for the preparation of Linezolid[14] and these two chiral oxazolidinones can be utilized for the preparation of various antimicrobial agents containing oxazolidinone ring system by simple arylation of the oxazolidinone ring[15]. While executing this research work[14], to reduce the synthetic stages we attempted the preparation of compound **(2)** from **(5)** in single step by the known method[16].

The (*R*)-1-azido-3-chloropropan-2-ol **(5)**, prepared from (*R*)-epichlorohydrin, was converted to (*S*)-5-(azidomethyl)oxazolidin-2-one **(2)** on reaction with KOCN in the presence of tetrabutylammonium chloride (TBAC) in DMF at 80°C. In this reaction, we observed the formation of a major impurity along with the product (by TLC). This impurity was separated by flash column chromatography and characterized as (*R*)-4-(azidomethyl)-1,3-dioxolan-2-one, **(6)** (Scheme 1).



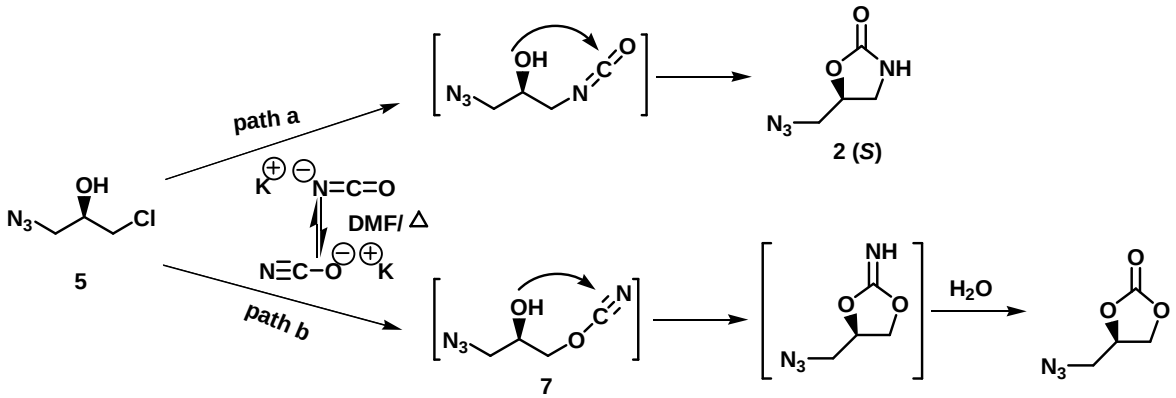
Scheme 1

The formation of these two products explained by the ambident nature of the OCN^-, the nucleophillic attack can proceed *via* nitrogen (path a, Scheme II) or oxygen (path b, Scheme II). The formation of (*S*)-5-(azidomethyl) oxazolidin-2-one, **(2)** because of the reaction of nitrogen terminus of KOCN with chloro compound **(5)** leading to the formation of intermediate isocyanate, in which the isocyanate group further reacts with the vicinal hydroxyl group. The unexpected formation of (*R*)-4-(azidomethyl)-1,3-dioxolan-2-one **(6)** due to the reaction of oxygen terminus of KOCN with compound **(5)** leading to the formation of intermediate (*R*)-1-azido-3-cyanatopropan-2-ol **(7)**, which on further cyclization forms imine. The obtained imine undergoes hydrolysis while work up lead to the formation of impurity **(6)** (Scheme II). The formation of oxazolidinone, **(2)** is about 30% only when the reaction was performed at 80°C and this was proportionally increased to 62-65% by increasing the temperature of the reaction from 80°C to 120°C. The (*R*)-5-(azidomethyl) oxazolidin-2-one is also prepared along with the (*S*)-4-(azidomethyl)-1,3-dioxolan-2-one by reacting (*S*)-1-azido-3-chloropropan-2-ol with KOCN by using the

same reaction conditions.

Finally, in the present synthetic strategy, developed a simple condition for the one-pot synthesis of 2-oxazolidinones from β-chloro hydrin using KOCN/DMF at elevated temperature under phase transfer catalyst (PTC) such as TBAC *via* generation of a β-hydroxy isocyanate intermediate, which readily converts into 2-oxazolidinone through intramolecular cyclization. This is an attractive application for the conversion of β-halohydrins to 2-oxazolidinones and should find general utility in the synthesis of 2-oxazolidinones.

As a conclusion, a short and simpler synthesis of (*R*)- and (*S*)-5-(azidomethyl) oxazolidin-2-one is described. These chiral synthons are useful for the preparation of oxazolidinone class of antibacterial agents.



Scheme 2

EXPERIMENTAL SECTION

Melting points were determined on a Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), ^1H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 and $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under N_2 atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on pre coated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

General procedure for the preparation of β-chlorohydrins

To a cooled solution of sodium azide (16.86 g, 0.259 mole) and ammonium chloride (13.87 g, 0.259 mole) in water (80 mL), a solution of (*R*)- or (*S*)-epichlorohydrin (0.216 mole) in ethanol (20 mL) was added. The reaction mixture was stirred at 0°C for 1 hr then allowed to RT and maintained for overnight. The reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with water (3 × 75 mL) and concentrated to get crude compound, which was purified by flash column chromatography to obtain the required compound as an oily liquid; 65% yield.

(*R*)-1-azido-3-chloropropan-2-ol, (5)

^1H NMR ($CDCl_3$): δ 2.45 (s, 1H, -OH, D_2O exchangeable), 3.4-3.65 (m, 4H, $-CH_2N_3$ and $-CH_2Cl$), 4.0 (m, 1H, -CHOH); IR (film, KBr) 3400, 2118 cm^{-1}; MS: *m/z* (M^++1) 136;

(*S*)-1-azido-3-chloropropan-2-ol

^1H NMR ($CDCl_3$): δ 2.45 (s, 1H, -OH, D_2O exchangeable), 3.4-3.65 (m, 4H, $-CH_2N_3$ and $-CH_2Cl$), 4.0 (m, 1H, -CHOH); IR (film, KBr) 3400, 2109 cm^{-1}; MS: *m/z* (M^++1) 136;

General procedure for the preparation of 2-oxazolidinones from β-chlorohydrins.

To a solution of (*R*) or (*S*)- 1-azido-3-chloropropan-2-ol, **(2)** (5 g, 0.0369 mole) in DMF (15

mL), KOCN (5.98 g, 0.074 mole) and catalytic amount of tetrabutylammonium chloride were added. The reaction mixture was stirred at 120°C for 10 hr. Then the reaction mixture was cooled to RT and poured into water (100 mL). Reaction mass was extracted with ethyl acetate (3 × 40 mL) and combined organic layer was washed with water (3 × 30 mL). The solvent was removed by evaporation under vacuum to give mixture of crude compound. This crude was subjected to flash column chromatography to get corresponding oxazolidinone and 1,3-dioxolan-2-one.

(*S*)-5-(azidomethyl)oxazolidin-2-one, (2)

65% yield; ^{1}H NMR ($CDCl_3$): δ 3.4-3.8 (m, 4H, -CH_2NH- and -CH_2N_3), 4.8 (m, 1H, -CHO-), 6.15 (s, 1H, -NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 159.36, 74.52, 52.86, 42.66; IR (film, KBr) 3306, 2109, 1760 cm^{-1}; MS: *m/z* (M^++1) 143; $[\alpha]^{25}_D$ = +48.2° (*c* = 1 in $CHCl_3$).

(*R*)-4-(azidomethyl)-1,3-dioxolan-2-one, (6)

25% yield; ^{1}H NMR ($CDCl_3$): δ 3.55-3.65 (dd, 1H, -CH-H-N_3, *J*= 4.2, 13.4 Hz), 3.7-3.8 (dd, 1H, -CH-H-N_3, *J*= 3.9, 13.4 Hz), 4.3-4.6 (m, 2H, -CH_2O-), 4.85 (m, 1H, -CHO-); ^{13}C NMR ($CDCl_3$): δ 154.36, 74.37, 66.23, 51.77; IR (film, KBr) 2114, 1801 cm^{-1}; MS: *m/z* (M^++1) 144; $[\alpha]^{25}_D$ = +79.0° (*c* = 1 in $CHCl_3$).

(*R*)-5-(azidomethyl)oxazolidin-2-one

63% yield; ^{1}H NMR ($CDCl_3$): δ 3.4-3.8 (m, 4H, -CH_2NH- and -CH_2N_3), 4.8 (m, 1H, -CHO-), 6.15 (s, 1H, -NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 159.36, 74.52, 52.86, 42.66; IR (film, KBr) 3307, 2109 cm^{-1}; MS: *m/z* (M^++1) 143; $[\alpha]^{25}_D$ = –62.0° (*c* = 1 in $CHCl_3$).

(*S*)-4-(azidomethyl)-1,3-dioxolan-2-one

27% yield; ^{1}H NMR ($CDCl_3$): δ 3.55-3.65 (dd, 1H, -CH-H-N_3, *J*= 4.2, 13.4), 3.7-3.8 (dd, 1H, -CH-H-N_3, *J*= 3.9, 13.4), 4.3-4.6 (m, 2H, -CH_2O-), 4.85 (m, 1H, -CHO-); IR (film, KBr) 2113, 1801 cm^{-1}; MS: *m/z* (M^++1) 144; $[\alpha]^{25}_D$ = -79.5° (*c* = 1 in $CHCl_3$).

ACKNOWLEDGEMENT

The authors thank Inogent Laboratories Private Limited (A GVK BIO Company) for the financial support and encouragement.

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