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A new route for the synthesis of (R)- & (S)- 2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione: A key chiral building block

G. Ravi Babu[§†], P. Venkateshwarlu[§], S. Yellamanda Rao[§], G. Madhusudhan[*§] and K. Mukkanti[†]

[§]*Research & Development, Inogent Laboratories Private Limited, A GVK BIO Company, 28A, IDA, Nacharam, Hyderabad, India*
[†]*Centre for Pharmaceutical Sciences, J.N.T. University, Kukkatpally, Hyderabad, India*

ABSTRACT

A new and efficient route for the synthesis of (R)- & (S)-2-((2-oxooxazolidin-5-yl)methyl) isoindoline-1,3-dione is described. The enantiopurity of the synthesized two stereoisomers of 2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione, is established using chiral high performance liquid chromatography (HPLC) i.e. enantiomeric excess (ee) of R & S isomers are 99.5% and 99.6% respectively. This route also involves the synthesis of a key chiral constituent, (R)- & (S)5-(chloromethyl) oxazolidin-2-one.

Keywords: (*R*)- & (*S*)-2-((2-Oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione, enantiomeric excess, chiral HPLC, 5-(chloromethyl)oxazolidin-2-one, 2-oxazolidinones.

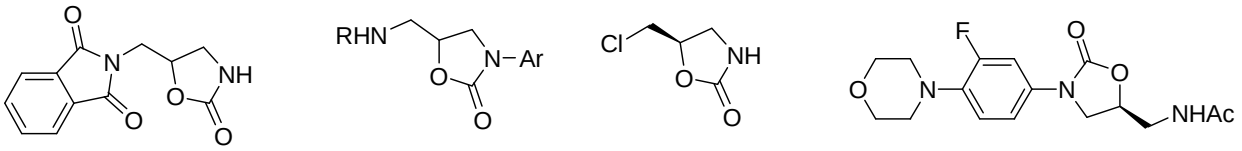
INTRODUCTION

Enantiomerically pure 5-substituted 2-oxazolidinones are important target molecules in organic synthesis because of their pharmacological properties. This is not only true of the oxazolidinones themselves, which can act as antibiotics against highly resistant Gram-positive bacteria [1], but even more of β-amino alcohols, which can be obtained from 2-oxazolidinones by base hydrolysis. The β-amino alcohol subunit is an important structural element in a number of different enzyme inhibitors [2] and β-blockers [3]. In addition, ring-annulated 2-oxazolidinones are precursors of azasugar structures [4], which can act as glycosidase inhibitors [5].

For these reasons, many publications deal with the use of chiral oxazolidinones [6] in organic synthesis, especially for the formation of chiral β-amino alcohols [7]. Important strategies for their synthesis make use, for example, of amino acids [8], amino aldehydes, amino ketones [9] or cyclic sulfates [10] as starting materials. However, most of these methods are not very flexible in the choice of substituent allowed. It was therefore our goal to develop a strategy for a very flexible and efficient synthesis of a whole class of enantiomerically pure 2-oxazolidinones, with

scope for a large structural variety of functionalities in the 5-position, starting from readily available building blocks.

In this class of 5-substituted-2-oxazolidinones, 2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione **1** is a very important chemical entity in the synthesis of several 5-subtitutedmethyl-3-aryl-2-oxazolidinones such as Linezolid [11] (**Figure 1**). The deprotection of the phthalimide group (amino protecting group) in **1** could be performed effortlessly using aqueous methylamine or hydrazine hence research scientists utilize the compound **1** to build numerous chiral 5-substituted methyl-3-aryl-2-oxazolidinones, **2**. The key chiral intermediate, 5-(chloromethyl)oxazolidin-2-one **3** is also a versatile compound to synthesize the 5-subtitutedmethyl 2-oxazolidinones since derivatization is possible on both sides, nitrogen site and chlorine site [12].



1 **2** **3** **Linezolid**

Figure 1. Chemical Structures of 2-((2-oxooxazolidin-5-yl) methyl)isoindoline, 3-dione (1), 3-Aryl-5-substituedmethylamino-2-oxazolidinone (2), (*R*)-5-(chloromethyl) oxazolidin-2-one (3) and Linezolid

Firstly, Piper *et al* have reported the preparation of racemic 2-((2-oxooxazolidin-5-yl)methyl) isoindoline-1,3-dione **1** starting from 2-((oxiran-2-yl)methyl)isoindoline-1,3-dione using urethane in low yield and also prepared using 2-(3-chloro-2-hydroxypropyl)isoindoline-1,3-dione on reaction with potassium cyanate (KOCN), sodium iodide (NaI), *N*,*N*-dimethylformamide (DMF) at 100°C in 27% yield [13]. Recently, our research group improved the yield of this reaction to 65% by transforming the conditions to KOCN, *N*,*N*-dimethylaminopyridine (DMAP) in DMF at 120°C [14]. The (*R*)-2-((2-oxo oxazolidin-5-yl)methyl)isoindoline-1,3-dione was prepared previously from (*R*)-hydroxymethyl-2-oxazolidinones [15], which was prepared in a multi step synthesis from D-malic acid [16]. The (*R*)-compound was also prepared previously by our research group from (*R*)-2-(chloromethyl)oxirane in four steps [17]. In all these research reports, there is no discussion regarding the enantiopurity of the targeted compound.

MATERIALS AND METHODS

Melting points were determined on 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), ^{1}H 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 anhydrous sodium sulfate after work-up.

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

Preparation of 1-amino-3-chloropropan-2-ol hydrochloride, 6. To a solution of benzaldehyde (3.7 g, 0.035 mol) in 18.5 mL of ethanol was added with stirring 3.7 mL of ammonium hydroxide (28%) and stirred at RT for 10 min. Epichlorohydrin (3.22 g, 0.35 mol) was added slowly drop wise to the

reaction mixture over a period of 1 h while maintaining the temperature between 25-30°C. The reaction mixture was allowed to stir overnight at RT and was then heated to 45°C for 20 min to complete the reaction conversion. Ethanol and ammonia were removed under vacuum and the obtained residual yellow syrup was poured into 200 mL of ice cold water. The mixture was cooled to 0°C and stirred for 4 h at the same temperature. The precipitated solids were filtered and washed with excess amount of water. The obtained white colored solid was recrystallized using *n*-hexane (177 mL) and yielded 10 g of benzylidene derivative **5**. To this benzylidene derivative (10 g, 0.05 mol), 6 N HCl (30 mL) was added and this reaction mixture was refluxed for 5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, water was distilled off completely under vacuum. The residual water was also removed by azeotropic distillation using toluene (50 mL). The obtained residue was triturated with ethyl acetate (15 mL), filtered and washed with ethyl acetate (5 mL) to gave 6 g of 1-amino-3-chloropropan-2-ol hydrochloride; 60 % yield; m.p. 101-102°C (lit.[19] 103-104°C); ^{1}H NMR (D_2O): δ 3.0-3.1 (m, 1H), 3.2-3.3 (m, 1H), 3.6-3.8 (m, 2H), 4.0-4.2 (m, 1H); MS: *m/z* (M^++1) 110.

Preparation of 5-(chloromethyl)oxazolidin-2-one, 3. To a cold solution of 1-amino-3-chloropropan-2-ol hydrochloride (5 g, 0.03 mol) in 50 mL dichloromethane, was added carbonyl diimidazole (5.84 g, 0.036 mol) at 0°C under nitrogen atmosphere. The reaction mixture was allowed to RT and stirred at the same temperature for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was washed with water (2 x 20 mL) and the organic layer was dried over sodium sulphate. The organic layer was distilled under reduced pressure and the obtained residue was purified using column chromatography (ethyl acetate: hexanes, 30:70) to gave 3.2 g of 5-chloro methyloxazolidine-2-one, **3**; 69.6 % yield; ^{1}H NMR ($CDCl_3$): δ 3.5-3.8 (m, 4H), 4.8 (m,1H), 5.8 (br, s); ^{13}C NMR (DMSO-d_6): δ 42.5, 46.2, 73.9, 158.2; MS: *m/z* (M^++1) 136.5; IR (KBr): 3363, 1746 cm^{-1}. OR: $[\alpha]_D^{25}$= -16.0 (c=0.7, CH_2Cl_2, (*R*)-**3**); $[\alpha]_D^{25}$= +16.1 (c=0.7, CH_2Cl_2, (*S*)-**1**)

Preparation of 2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione, 1. The solution of 5-chloro methyloxazolidine-2-one (1 g 0.007 mol) in *N*,*N*-dimethylformamide (10 mL), potassium phthalimide (1.51 g 0.008 mol) and catalytic amount of benzyltributylammonium chloride (0.21 g, 0.1 equivalents) were added at RT. The reaction mixture was heated to 80°C and maintained at same temperature for 12 h. After completion of the reaction, the solvent was distilled under reduced pressure and obtained residue was diluted with water (10 mL). The residue was extracted with ethyl acetate (3 x 20 mL), combined organic layer was washed with water (2 x 10 mL) and the solvent was distilled under reduced pressure. The obtained crude compound was purified using column chromatography (ethyl acetate: hexanes) to gave 1.4 g of 2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione;75.1% yield; ^{1}H NMR ($CDCl_3$): δ 3.3 (m, 1H), 3.5-3.9 (m, 1H), 3.8-4.0 (m, 2H), 4.7 (m, 1H), 7.5 (s, 1H, D_2O exchangeable), 7.7-8.0 (m, 4H); ^{13}C NMR ($DMSOd_6$): δ 40.57, 42.94, 72.48, 123.16, 131.39, 134.53, 158.22, 167.7; MS: *m/z* (M^++1) 247.1. *ee* by Chiral HPLC: (*R*)-**1**: 99.5% ee; (*S*)-1: 99.6% ee.

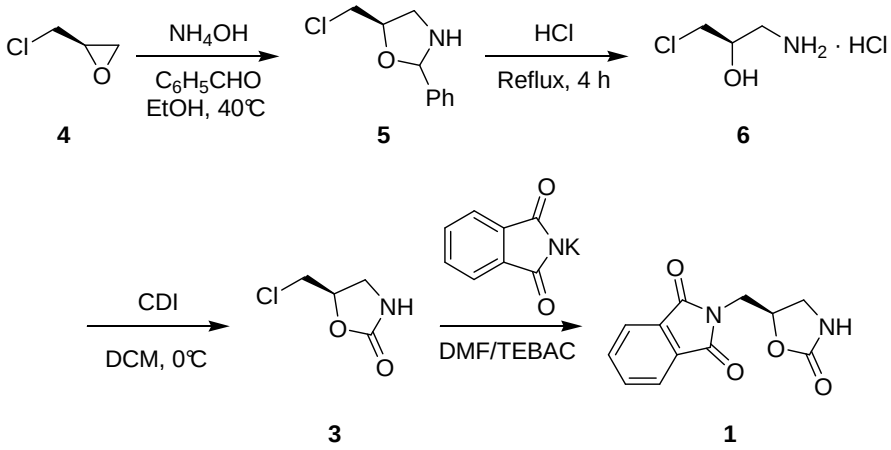
RESULTS AND DISCUSSION

Herein is reported a new synthesis of (*R*)- & (*S*)-2-((2-oxooxazolidin-5-yl)methyl) isoindoline-1,3-dione **1**, using commercially available starting material, corresponding chiral 2-(chloromethyl)oxirane (epichlorohydrin) (**Scheme 1**). Accordingly, (*R*)-2-(chloromethyl)oxirane, **4** was directly condensed with benzaldehyde and ammonium hydroxide by following a literature procedure [18] gave the corresponding (*R*)-benzylidene derivative, **5**. The resulted benzylidene derivative **5** on reaction with hydrochloric acid under reflux conditions yielded (*R*)-1-amino-3-chloropropan-2-ol hydrochloride, **6** as a white crystalline solid. A dispute in international scientific community about the structural assignment of **5** as either open form (imine form) or closed form

(benzlydine form), however irrespective of it's structural assignment *in-situ* cleavage of the benzyl moiety results corresponding chiral aminoalcohol [19].

This amino alcohol **6**, was converted to (*R*)-5-(chloromethyl)oxazolidin-2-one **3**, on the reaction with *N*,*N*′-carbonyldiimidazole (CDI) in dichloromethane at 0 °C. Finally, compound (*R*)-**3** was reacted with potassium phthalimide in DMF under PTC conditions to obtain the desired (*R*)-2-((-2-oxo oxazolidin-5-yl)methyl) isoindoline-1,3-dione ((*R*)-**1**) (**Scheme 1**).

Initially, the sequence of reactions has been illustrated on racemic version using racemic 2-(chloromethyl)oxirane. Starting from enantio pure (*S*)-epichlorohydrin followed by optimized reaction conditions yielded corresponding (*S*)-5-(chloromethyl)oxazolidin-2-one and another enantiomer (*R*)-5-(chloromethyl)oxazolidin-2-one was synthesized from (*R*)-epichlorohydrin. Both the chiral sequences were ended with about 32 % overall yield. This entire process demonstrates that important chiral entity (*R*)- & (*S*)-**1** has been prepared from commercially available cost effective starting material and reagents without racemization as depicted in



Scheme 1. **Synthesis of 2-((2-oxooxazolidin-5-yl) methyl) isoindoline (1)**

To establish the enantiopurity of the prepared stereoisomers, chiral HPLC method has been developed using standard racemic, (*R*)- & (*S*)-2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione **1**. The description of chiral HPLC method is "A Shimadzu CLASS-VP V6.14SP1 separation module equipped with Shimadzu UV detector was used. The analysis was carried out on chiral pack ASH, 250 x 4.6, 5 µ with mobile phase n-hexane and ethanol in the ratio of 30:70 (filter and degas through 0.45 µ membrane filter paper) Program; isocratic elution was used with UV detection at 200 nm at flow rate of 1.0 mL/min. The column temperature was maintained as ambient. The data was recorded using Shimadzu Class-VP software (run time-30 min). The chiral HPLC indicates the enantiomeric excess of the synthesized (*R*)- & (*S*)- 2-((2-oxooxazolidin-5-yl) methyl)isoindoline-1,3-dione are 99.5% and 99.6%.

Previously our research group prepared (*R*)-2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione (*R*)-**1**, using (*R*)- 2-(chloromethyl)oxirane in four steps. To establish the enantiopurity of the (*R*)-2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione which is prepared previously by our research group [17], preparation of the compound **1** was repeated and examined *ee* using chiral HPLC and indicates as 99.1% *ee*.

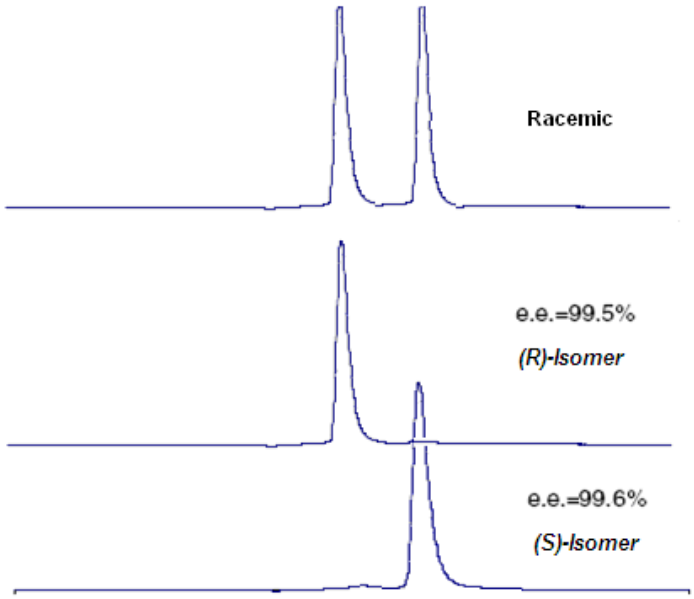


Figure 2. HPLC chromatogram showing separation of racemic, (*R*)- and (*S*)-2-((2-oxooxazolidin-5-yl) methyl)isoindoline-1,3-dione on the chiral pack ASH, 250 x 4.6, 5 µ HPLC column. Mobile phase n-hexane and ethanol in the ratio of 30:70 flow rate of 1.0 ml/min and detection wavelength 200 nm.

CONCLUSION

In conclusion, developed a new and efficient synthetic route for the preparation of (*R*)- & (*S*)- 2-((2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione 1, *via* a key chiral 5-(chloromethyl) oxazolidin-2-one 3, starting from corresponding 2-(chloromethyl)oxiranes.

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REFERENCES

[1](a) Brickner S J, Hutchinson D K, Barbachyn M R, Manninen P R, Ulanowicz D A, Garmon St A, Grega K C, Hendges S K, Toops D S, Ford C W & Zurenko G E, *J Med Chem*, **1996**, *36*, 460. (b) Glaeve D M, & Brickner S J, *J Org Chem*, 61, **1996**, 6470. (c) Brickner S J, *Curr Pharm Design*, **1996**, *2*, 175. (d) Riedl B & Endermann R, *Exp Opin Ther Patents*, **1999**, *9 (5)*, 625.
[2](a) Gante J, *Angew Chem*, **1994**, *106*, 1780; *Angew Chem Int Ed (Eng)*, **1994**, *33*, 699. (b) Dorsch D, Raddatz P, Schmitges C J, Von der Helm K & Rippmann F, *Kontakte (Darmstadt)*, **1993**, *2*, 48256.
[3](a) Warmerdam E G J C, Brussee J & Van der Geen A, *Helv Chim Acta*, **1994**, *77*, 252. (b) Sasai H, Itoh N, Suzuki T & Shibaski M, *Tetrahedron Lett*, **1993**, *34*, 855. (c) Sasai H, Yamada Y M A, Suzuki T & Shibasaki M, *Tetrahedron*, **1994**, *50*, 12313.
[4]Schierle K, Vahle R & Steckhan E, *Eur J Org Chem*, **1998**, 509.
[5](a) Elbein A D, *Ann Rev Biochem*, **1987**, *56*, 497. (b) Elbein A D, *FASEB J*, **1991**, *5*, 3055.
[6](a) Laı¨b T, Chastanet J & Zhu J, *Tetrahedron Lett*, **1997**, *38*, 1771. (b) Lucet D, Toupet L, Le Gall T & Mioskowski C, *J Org Chem*, **1997**, *62*, 2682. (c) Hirai Y, Watanabe J, Nozaki T, Yokoyama H & Yamagchi S, *J Org Chem*, **1997**, *62*, 776. (d) Ishibashi H, Uegaki M & Sakai M, *Synlett*, **1997**, 915. (e) Van Delft F L, Timmers C M, Van der Marel G A, Van Boom J H, *Synthesis* **1997**, 450. (f) Marco J A, Carda M, Murga J, Gonza´lez F & Falomir E, *Tetrahedron Lett*, **1997**, *38*, 1841.
[7](a) Shibata N, Katoh T & Terashima S, *Tetrahedron Lett*, **1997**, 38, 6192620. (b) Remuzon P, Dussy C, Jacquet J P, Roty P & Bouzard D, *Tetrahedron: Asymmetry*, **1996**, 7, 1181. (c) Matsunaga H, Ishizuka T & Kunieda T, *Tetrahedron*, **1997**, *53*, 1275.

[8](a) McKennon M J & Meyers A I, *J Org Chem*, **1993**, *58*, 3568. (b) Delaunay D & Le Corre M J, *J Chem Soc, Perkin Trans 1*, **1994**, 3041.
[9](a) Beaulieu P L, Wernic D, Duceppe J S, Guindon Y, *Tetrahedron Lett*, **1995**, *36*,3317. (b) Tillyer R D, Boudreau C, Tschaen D, Dolling U H & Reider P J, *Tetrahedron Lett*, **1995**, *36*, 4337.
[10] Kim B M & Sharpless K B, *Tetrahedron Lett*, **1989**, *30*, 655.
[11] (a) Brickner S J, Hutchinson D K, Barbachyn M R, Garmon S A, Grega K C, Hendges S K, Manninen P R, Toops D S, Ulanowicz D A, Kilburn J O, Glickman S, Zurenko G E & Ford C, 35th *Interscienc Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, September **1995**, *F 208*, 149. (b) Brickner S J, Hutchinson D K, Barbachyn M R, Manninen P R, Ulanowicz D A, Garmon S A, Grega K C, Hendges S K, Toops D S, Ford C Z & Zurenko G E, *J Med Chem*, **1996**, *39*, 673.
[12] Madhusudhan G, Om Reddy G, Rajesh T, Ramanatham J & Dubey P K, *Tetrahedron Lett*, **2008**, *49*, 3060.
[13] Piper J R, Rose L M, Johnston T P & Grenan M M, *J Med Chem*, **1979**, *22*, 631.
[14] Chinnam Naidu K, Ravi Babu G, Gangaiah L, Mukkanti K & Madhusudhan G, *Tetrahedron Lett*, **2010**, *51*, 1226.
[15] (a) Madar D J, Kopecka H, Pireh D, Pease J, Pliushchev M, Sciotti R J, Wiedeman P E & Djuric S W, *Tetrahedron Lett*, **2001**, *42*, 3681. (b) Sciotti R, Pliushchev M, Wiedeman P E, Balli D, Flamm R, Nilius A M, Marsh K, Stolarik D, Olly R, Ulrich R & Djuric S W, *Bioorg Med Chem Lett*, **2002**, *12*, 2121.
[16] Danielmeier K & Steckhen E, *Tetrahedron: Asymmetry*, **1995**, *6*, 1181.
[17] Madhusudhan G, Om Reddy G, Ramanatham J & Dubey P K, *Indian J Chem*, **2006**, *45B*, 1264.
[18] Perrault W R, Pearlman B A, Godrej D B, Jeganathan A, Yamagata, Chen J J, Lu C V, Herrinton P M, Gadwood R C, Chan L, Lyster M A, Maloney M T, Moeslein J A, Greene M L & Barbachyn M R, *Org Proc Res Dev*, **2003**, *7*, 533.
[19] Paul R, Williams R P & Cohen E, *J Org Chem*, **1975**, *40*,1653.