An efficient and practical synthesis of antibacterial linezolid

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A convergent and efficient synthesis of linezolid was developed using the cycloaddition of commercially available (*R*)-epichlorohydrin with morpholine substituted phenylisocyanate catalysed by MgI_2 or $MgBr_2$ etherate as the key step in the 50% overall yield.

Keywords: (*R*)-epichlorohydrin, isocyanate, MgI_2 etherate, linezolid

Oxazolidinones,a new class of synthetic antibacterial agents, exhibit activity against a large number of Gram-positive organisms and vancomycin-resistant enterococcus.[1,2] Their mode of action is by inhibition of protein synthesis at an early step.[3,4] Linezolid (**1**), the only oxazolidinone approved by the FDA, became the first compound commercialised worldwide from the oxazolidinone class of antibacterials.[5-8] Linezolid (Zyvox) was introduced into the market which led to the need for a high-yielding, economical and environmentally sound process.

The first synthesis of linezolid from (5*S*)-5-(hydroxymethyl) oxazolidin-2-one, which was obtained by the reaction of aryl carbamate with (*R*)-glycidyl butyrate in the presence of butyllithium, was reported by Manninen.[1] A modified synthetic method via (2*S*)-1-amino-3-chloropropan-2-ol coupling with aryl carbamates to give (5*S*)-N-aryl-5-(aminomethyl)oxazolidin-2-one promoted by lithium *tert*-butoxide has been developed.[9] Very recently, BF_3•Et_2O-promoted regioselective and stereospecific intramolecular ring opening of 2-(boc-aminomethyl)aziridines was applied to the preparation of enantiopure linezolid.[10] However, not all methods are practical on a large scale, due primarily to the overall low yields, high costs of reagents, large number of steps involved, or poor conversion of the oxazolidinone cyclisation. Thus, development of a more convergent, practical and rapid preparation of linezolid was highly desirable.

As shown in Scheme 1, treatment of morpholine with 3,4-difluoronitrobenzene in ethanol under reflux produced compound **2,** which was followed by hydrogenation. Amine **3** reacted with bis(trichloromethyl)carbonate (triphosgene, BTC) to give isocyanate **4**. Cycloaddition of isocyanate **4** with (*R*)-epichlorohydrin catalysed by 50 mol% MgI_2 etherate or $MgBr_2$ etherate at 65 °C in THF exclusively afforded the desired enantiopure cycloadduct **5** in 96% yield. Then **5** was transformed into azide **6** under treatment of sodium azide in 86% yield. Azide **6** was subjected to hydrogenation and acetylation to provide linezolid **1** in 90% yield over two steps.

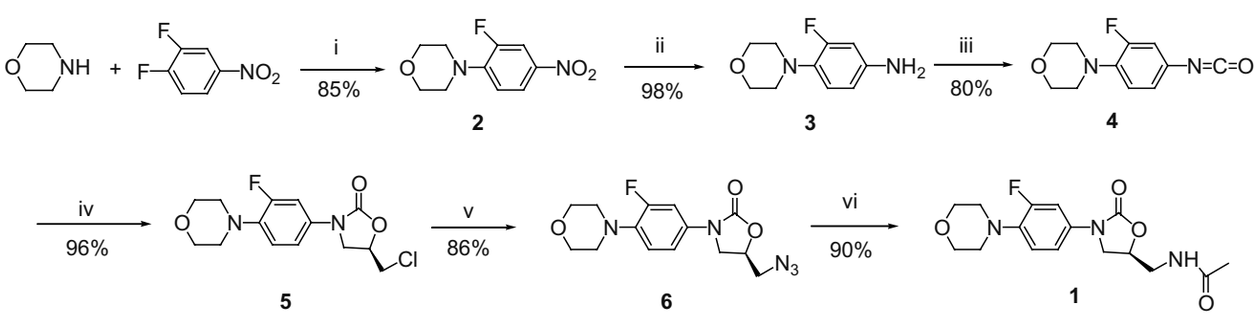
In conclusion, we have described a highly-efficient and gentle method for the preparation of antibacterial linezolid using the cycloaddition of (*R*)-epichlorohydrin with substituted phenylisocyanate **4** catalysed by MgI_2 or $MgBr_2$ etherate as the key step. Further synthetic application of MgI_2 or $MgBr_2$ etherate-catalysed cycloaddition of epoxide with isocyanate into natural producuts and drugs is ongoing in our lab.

Experimental

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90 °C) were used. ^{1}H NMR spectra were taken on a Bruker Avance-500 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. The reactions monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. Melting points were measured on BUCHI B-540 and uncorrected. FT-IR was recorded on a Bruker Tensor 27 spectrometer. All compounds were identified by ^{1}H NMR and are in good agreement with those reported.

3-fluoro-4-(morpholin-4-yl)phenylisocyanate (**4**):[11] To a solution of 3-fluoro-4-(morpholin-4-yl-aniline **3** (30 mmol, 5.88 g) in toluene (150 mL) was added dropwise a solution of *bis*(trichloromethyl) carbonate (16.5 mmol, 4.9 g) in 50 mL toluene at room temperature. Then the reaction mixture was refluxed for 4 h. After removal of the solvent, the residue was distilled to give the desired product **4** (5.35 g) under reduced pressure in 80% yield. IR (film) υ (cm^{-1}) 3072, 2970, 2837, 2321(N=C=O), 1648 (C=O), 1518, 1451, 1239(C–O), 1115 (C–F).

(5R)-5-(chloromethyl)-3-(3-fluoro-4-(morpholin-4-yl)phenyl) oxazolidin-2-one (**5**):[12] To a stirred solution of freshly prepared MgI_2 etherate (2.5 mmol) in THF (10 mL) was added dropwise (*R*)-epichlorohydrin (508 mg, 5.5 mmol) followed by addition of substituted phenylisocyanate **4** (1.11 g, 5 mmol) at room temperature under nitrogen. After addition, the reaction mixture was allowed to warm to 65 °C and continued to be stirred for 4 h. The resulting homogeneous reaction mixture was quenched with saturated Na_2SO_3 aqueous solution. Extractive workup with CH_2Cl_2 and flash chromatographic purification of the crude product on silica gel gave the compound **5** (931 mg) in 96% yield. White solid, m.p. 117.3–118.3 °C. δ_H 3.06 (t, *J* = 5.0 Hz, 4H), 3.73–3.81 (m, 2H), 3.87 (t, *J* = 5.0 Hz, 4H), 3.91 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.12 (t, *J* = 9.0 Hz, 1H), 4.84–4.89 (m, 1H), 6.94 (t, *J* = 9.0 Hz, 1H), 7.14 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.44 (dd, *J* = 2.5, 14.5 Hz, 1H). *m/z* (EI): 314 ($[M]^+$, 100), 316 ($[M + 2]^+$, 33), 256 (67), 177 (52), 149 (51). HRMS (EI) Calcd for $C_{14}H_{16}ClFN_2O_3$: 314.0833, found for $[M]^+$: 314.0816.



Scheme 1 *Reagents and conditons*: i, EtOH, reflux; ii, H_2, 5%Pd-C, EtOH, room temperature; iii, BTC, toluene, reflux; iv, (*R*)-epichlorohydrin, MgI_2 etherate or $MgBr_2$ etherate, THF, 65 °C; v. NaN_3, DMF, 85 °C; vi, (1) H_2, 5%Pd–C, EtOAc; (2) Ac_2O, Et_3N, room temperature.

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(5S)-5-(azidomethyl)-3-(3-fluoro-4-(morpholin-4-yl)phenyl)-oxazolidin-2-one (**6**):[1] Sodium azide (520 mg, 8 mmol) was added into the solution of compound **5** (2.52 g, 4 mmol) in DMF (8 mL) under stirring. The reaction mixture was allowed to warm to 85 °C and continued to be stirred for 12 h. After completion monitored by TLC, the reaction mixture was diluted with ethyl acetate and washed with water. The crude product was purified by flash chromatography on silica gel to give the compound **6** (1.06 g) in 86% yield. White solid, m.p. 102.5–103.5 °C. δ_H 3.06 (t, J = 5.0 Hz, 4H), 3.59 (dd, J = 4.5, 8.5 Hz, 1H), 3.70 (dd, J = 4.5, 8.0 Hz, 1H), 3.82 (dd, J = 6.0, 9.0 Hz, 1H), 3.87 (t, J = 4.5 Hz, 4H), 4.05 (t, J = 9.0 Hz, 1H), 4.75–4.80 (m, 1H), 6.95 (t, J = 9.0 Hz, 1H), 7.11–7.14 (m, 1H), 7.44 (dd, J = 2.5, 14.5 Hz, 1H). *m/z* (EI): 321 ($[M]^+$, 43), 293 (100), 249 (72), 222 (91), 208 (83), 190 (62), 164 (65), 150 (55). HRMS (ESI) Calcd for $C_{14}H_{16}FN_5NaO_3$: 344.1135, found for $[M + Na]^+$: 344.1135.

N-{[(5S)-3-(3-fluoro-4-(morpholin-4-yl)phenyl)-2-oxo-5-oxazolidinyl]methyl}-acetamide (linezolid) (**1**):[1] A solution of compound **6** (963 mg, 3 mmol) in ethyl acetate (15 mL) was hydrogenated over 5% palladium on carbon (192 mg) under H_2 for 12 h. Then the reaction mixture was filtered through the celite. To this filtration was added triethylamine (365 mg, 3.6 mmol) and acetic anhydride (946 mg, 9 mmol) at ambient temperature. Then the reaction mixture continued to be stirred for 3 h. After completion monitored by TLC, the reaction mixture was quenched by saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate. The crude product was purified by flash chromatography on silica gel to give the linezolid **1** (910 mg) in 90% yield. White solid, m.p. 178.8–179.0 °C (lit.[1], 181.5–182.5 °C), δ_H 2.02 (s, 3H), 3.06 (t, J = 4.5 Hz, 4H), 3.65 (s, 2H), 3.77 (t, J = 7.5 Hz, 1H), 3.88 (t, J = 4.5 Hz, 4H), 4.02 (t, J = 9.0 Hz, 1H), 4.78 (s, 1H), 6.64 (s, 1H), 6.96 (t, J = 8.5 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.43 (dd, J = 1.5, 14.0 Hz, 1H).

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