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Original article

A facile synthesis of the oxazolidinone antibacterial agent linezolid

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ABSTRACT

A facile synthetic route of linezolid **1** has been developed. Using commercially available (*R*)-epichlorohydrin as the starting material, **1** was obtained through a sequence of cyclization, substitution, a Goldberg coupling, aminolysis and acetylation reactions. The synthetic route is easy to perform and can be scaled up.

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1. Introduction

The alarming rate of emerging and reemerging microbial threats coupled with the increasing antibacterial resistance in hospitals is major concerns to the public health and scientific communities worldwide, especially with regard to the multidrug-resistant Gram-positive bacteria [1–3]. The *N*-aryloxazolidinones represent a latest class of antibacterials that emerged in the last four decades, having potent activity against multidrug-resistant Gram-positive bacteria [4,5]. Linezolid (**1**) is an important representative of the *N*-aryloxazolidinones. Extensive research efforts led to the discovery and introduction of linezolid (**1**) (Fig. 1) in clinical use against hospital- and community-acquired pneumonia, skin infections and diabetic foot infections caused by Gram-positive bacterial strains [6]. For these reasons, much attention has been given to the synthesis of linezolid and several synthetic methods for linezolid were developed.

Most methods reported involve the construction of the oxazolidinone as a key step in the synthesis of 5-substituted 3-aryloxazolidinones [7–12]. A common strategy for the preparation of 5-aminomethyl-3-aryl oxazolidinone in the linezolid is to deprotonate the aryl carbamate (**2**) with BuLi and react the resulting anion with (*R*)-glycidylbutyrate (**3**) to give the corresponding 5(*S*)-hydroxymethyl oxazolidinone. The lithium anion of the carbamate was necessary to obtain a useful yield of the desired oxazolidinone. In an alternative strategy, the aryl oxazolidinone could be obtained from aryl isocyanides (**4**) and (*R*)-glycidylbutyrate (**3**). The preparation of aryl isocyanate is cumbersome from aryl amines. Other methods reported in literature [13,14] involve metal-catalyzed coupling reactions between aryl halides (**5**) and oxazolidinone (**6**). This strategy took advantage of the pioneering work by Buchwald and Hartwig [15,16]. Recently, Buchwald reported a landmark development in the Goldberg coupling reaction using CuI for the amidation of aryl halides [17,18]. The procedure, in addition to being cost-effective, could also tolerate some functional groups that would be otherwise problematic in palladium-catalyzed coupling reactions. But the reactions reported in which oxazolidinone were coupled with aryl iodides using CuI gave only modest yields [19]. To generalize the Goldberg coupling reaction using CuI for the amidation of aryl halides, Trehan has developed an efficient and higher yielding CuI-mediated *N* arylation of oxazolidinone using the Buchwald protocol [20]. To overcome these limitations, a convenient synthetic method of linezolid by the Goldberg coupling reaction from commercially available (*R*)-epichlorohydrin and aryl bromide as the key step is reported in this paper (Scheme 1).

2. Experimental

(R)-5-(Chloromethyl)oxazolidin-2-one (**8**): A mixture of 120 g (0.1 mol) of magnesium sulfate and 1 g (1 mmol) of sodium cyanate in 500 mL water at 60 °C was added 46.3 g (0.5 mol) of (*R*)-epichlorohydrin dropwise over 30 min, keep the warm for 1 h, the water was removed under reduced pressure and then added ethyl acetate (500 mL), the mixture was filtered and the filter cake was washed with ethyl acetate (2× 200 mL), the combined ethyl

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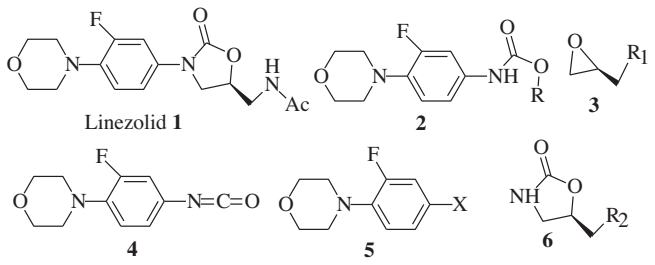


Fig. 1. Structures of linezolid and compounds **2**–**6**.

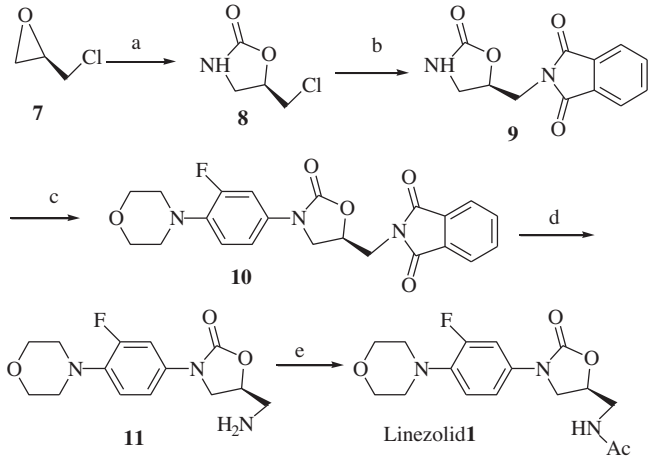
acetate were dried (Na_2SO_4) and concentrated to give a yellow liquid, which was cooled to 0 °C and crystallized of **8** as a white solid, the obtained solid was recrystallized from ethyl acetate to give 46 g (67.8%). mp 64–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48 (dd, 1H, J_1 = 6.6 Hz, J_2 = 4.6 Hz), 3.56 (t, 1H, J = 6.6 Hz), 3.80 (dd, 1H, J_1 = 8.9 Hz, J_2 = 3.7 Hz), 3.89 (dd, 1H, J_1 = 8.9 Hz, J_2 = 3 Hz), 4.84 (m, 1H), 7.62 (s, 1H), 7.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.8, 43.8, 73.4, 168.1.

*(R)-2-((2-Oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione (***9***)*: A solution of 27 g (0.2 mol) of **8** in 500 mL DMF was treated with 40.8 g (0.22 mol) of potassium phthalimide, the mixture was heated to 80 °C for 12 h, the reaction was cooled to ambient temperature, diluted with 2 L of water and extracted with methylene dichloride (3× 200 mL), the combined organic layer was washed with saturated sodium chloride solution followed and then dried (Na_2SO_4), the solution was evaporated in vacuo to obtained a white solid, which was stirred with ethyl acetate and petroleum ether to get product 34.4 g (70%) of **9** as a white solid, mp 195–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.2 (dd, 1H, J_1 = 6.6 Hz, J_2 = 4.3 Hz), 3.72 (t, 1H, J = 6.6 Hz), 3.91 (dd, 1H, J_1 = 10.6 Hz, J_2 = 4.2 Hz), 4.10 (dd, 1H, J_1 = 10.6 Hz, J_2 = 5.2 Hz), 4.97 (m, 1H), 7.75 (m, 2H), 7.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.6, 46.3, 73.9, 158.2.

*(S)-2-((3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione (***10***)*: A mixture of 14.8 g (60 mmol) of **9** in 300 mL of anhydrous dioxane under nitrogen was added 13 g (50 mmol) of 4-(4-bromo-2-fluorophenyl)-morpholine, 0.48 g (2.5 mmol) of CuI, 0.58 g (5 mmol) of (+)-*trans*-1,2-diaminocyclohexane and 13.9 g (0.1 mol) anhydrous potassium carbonate, the mixture was allowed to stir at reflux for 20 h. The solution was cooled to ambient temperature, which was filtered and the filtrate concentrated in vacuo, diluted with water (100 mL) and extracted with ethyl acetate (3× 40 mL), the combined organic layers were dried (Na_2SO_4) and the concentrate was purified by chromatography on silica gel column (ethyl acetate:hexane = 1:2) to give 16.2 g (76%) of **10**, mp 204–206 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05 (t, 4H, J = 3.4 Hz), 3.85–3.89 (m, 5H), 3.98 (dd, 1H, J_1 = 10.6 Hz, J_2 = 4.3 Hz), 4.09 (t, 1H, J = 6.6 Hz), 4.14 (dd, 1H, J_1 = 10.6 Hz, J_2 = 5.0 Hz), 4.98 (m, 1H), 6.92 (t, 1H, J = 6.8 Hz), 7.11 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.9 Hz), 7.41 (dd, 1H, J_1 = 10.6 Hz, J_2 = 1.9 Hz), 7.78 (m, 2H), 7.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.8, 48.5, 51.1, 67.1, 69.7, 107.6 (d, J = 19.5 Hz), 114.1 (d, J = 2.3 Hz), 118.9 (d, J = 3 Hz), 123.8, 131.8, 133.1 (d, J = 8.2 Hz), 134.6, 136.6 (d, J = 6.7 Hz), 153.9, 155.5 (d, J = 183.7 Hz), 168.1.

*(S)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (***11***)*: A solution of 8.5 g (0.02 mol) of **10** in 100 mL methanol was added 6.9 g (0.11 mol) of 80% hydrazinium hydroxide, the mixture was heated at reflux temperature for 1 h and cooled to ambient temperature (the reaction produced a large white byproduct). The mixture was filtered and the filtrate removed the methanol in vacuo, extracted with methylene dichloride (3× 30 mL) and water (50 mL). The combined organic layers were dried (Na_2SO_4) and the concentrate was purified by chromatography on silica gel column (ethyl acetate:methanol = 10:1) to give 4.2 g (71%) of **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 2H), 2.98 (dd, 1H, J_1 = 10.3 Hz, J_2 = 4.3 Hz), 3.05 (t, 4H, J = 3.5 Hz), 3.11 (dd, 1H, J_1 = 10.3 Hz, J_2 = 3 Hz), 3.82 (t, 1H, J = 6.1 Hz), 3.87 (t, 4H, J = 3.5 Hz), 4.01 (t, 1H, J = 6.1 Hz), 4.68 (m, 1H), 6.93 (t, 1H, J = 6.8 Hz), 7.14 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.8 Hz), 7.45 (dd, 1H, J_1 = 10.1 Hz, J_2 = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.1, 47.8, 51.1, 67.1, 73.9, 107.4 (d, J = 20.2 Hz), 113.8 (d, J = 3 Hz), 118.9 (d, J = 3 Hz), 133.5 (d, J = 22.5 Hz), 136.4 (d, J = 3.7 Hz), 154.7, 155.6 (d, J = 183.7 Hz), 171.4.

*(S)-N-((3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (***1***)*: A mixture of 2.95 g (10 mmol) of **11** and 2 g (20 mmol) of triethylamine in 50 mL methylene dichloride was added slowly 0.95 g (12 mmol) of acetyl chloride at 0 °C, the reaction remove the room temperature for 1 h. The mixture was washed with water (50 mL) and dried (Na_2SO_4). The concentrate was purified by chromatography on silica gel column (ethyl acetate:methanol = 10:1) to give 2.86 g (85%) of **1** as a white solid, mp 181–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (s, 3H), 3.05 (t, 4H, J = 3.4 Hz), 3.59–3.69 (m, 2H), 3.75 (dd, 1H, J = 6.7 Hz, J = 1.7 Hz), 3.87 (t, 4H, J = 3.4 Hz), 4.02 (t, J = 6.7 Hz, 1H), 4.48 (m, 1H), 6.36 (t, 1H, J = 4.6 Hz), 6.92 (t, 1H, J = 6.8 Hz), 7.06 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.8 Hz), 7.42 (dd, 1H, J_1 = 10.7 Hz, J_2 = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 41.9, 47.7, 51.0, 67.1, 72.1, 107.6 (d, J = 20.2 Hz), 114.0 (d, J = 3 Hz), 118.9 (d, J = 3.7 Hz), 133.0 (d, J = 7.5 Hz), 136.6 (d, J = 6.7 Hz), 154.4, 155.5 (d, J = 183.8 Hz), 171.4.



Scheme 1. (a) NaOCN, 60 °C; (b) potassium phthalimide, DMF, 80 °C; (c) 4-(4-bromo-2-fluorophenyl)morpholine, CuI (5 mmol%), (*Z*)-1,2-diaminocyclo-hexane (10 mol%), dioxane, K_2CO_3, 110 °C; (d) hydrazine hydrate (80%), MeOH, reflux; (e) methylene dichloride, Et_3N, DCM, r.t.

3. Results and discussion

After a detailed survey of the previous results, we chose commercially available chiral (*R*)-epichlorohydrin (**7**) as a starting material (Scheme 1), which was reacted with NaOCN to afford (*R*)-chloromethyl-2-oxazolidinone (**8**) as a key intermediate. Following a classical method [21] for the introduction of amino groups, the compound (**8**) was reacted with potassium phthalimide by an S_N2 nucleophile substitution reaction to produce the corresponding phthalimide (**9**). A Goldberg coupling reaction between amide (**9**) and aryl halide (4-(4-bromo-2-fluorophenyl)morpholine) using CuI as a catalyst afforded the coupled product (**10**). Amine (**11**) was obtained by the deprotection of the phthalimide (**10**) using aqueous NH_2NH_2. Finally, treatment of the amine (**11**) with Ac_2O in the presence of pyridine provided linezolid (**1**). The physical and spectroscopic data of linezolid (**1**) were in complete agreement with the reported values.

4. Conclusion

In conclusion, we have developed an efficient and facile synthetic method to synthesize linezolid **1** using the Goldberg coupling reaction as a key step from (*R*)-2-(chloromethyl)oxirane in five steps in a total yield of 22%. Compared to the known methods, this route is more straightforward to operate with a lower cost of goods.

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