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A facile construction of 5-methylazido-3-aryl 2-oxazolidinone: A key precursor for the synthesis of Linezolid

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ABSTRACT

A facile construction of 5-methylazido-3-Aryl 2-Oxazolidinone is derived from various 1-azido-3-chloro-2-aryl/alkyl carbonates derivative and this extended to syntheses of Linezolid, an antibacterial agent are reported. The key step in the approached involves addition of 3-fluoro-4-morpholinobenzenamine with respective compounds by changing the leaving functionalities carbamate followed by formation of 2-oxazolidnone on other end and followed by functional group transformations yielded an antibacterial agent Linezolid. Process and less number of steps.

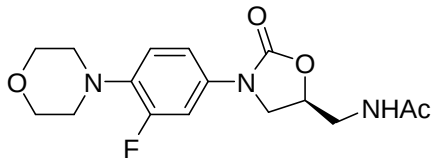
Keywords: Various carbamates, 5-methylazido-3-Aryl 2-Oxazolidinone, Linezolid, antibacterial agent.

INTRODUCTION

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] immune suppressants [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.Several methods are reported in the literature for the synthesis of linezolid. Brickner S J reported a route to linezolid with good yield [12]. However, in this method for the synthetic key step to form 2-oxazolidinone ring, severe typical conditions including cryogenic conditions (–78 °C) and air-sensitive base (*n*-BuLi) were used which limit industrial preparation. Lohray presented another possibility to linezolid *via* asymmetric bis-epoxide using D-mannitol as a starting material [13]. However, the synthetic route was very long.

With the aim of searching for efficient method to build the phenoxyoxazolidinone moiety without using *n*-BuLi, epoxides and phenyl isocynides that are required in the classical synthesis of this class of compounds. A systematic study on the synthesis of 1-azido-3-chlor-2-aryl/alkyl carbonates (2) derivative using various conditions by changing solvents and bases to identify better carbamate followed by formation of 2-oxazolidnone[14]. In this context, the synthesis of Linezolid (3-aryl-5-substitutedmethyl-2-oxazolidinone) described in research articles need to be mentioned. Among the various carbamates better one proceeded upto Linezolid and obtained in 99% purity and better yields. For instance, the classical method involves conversion of 3-fluoro-4-morpholinobenzenamine ($ArNH_2$) to corresponding carbamate which is deprotonated with *n*-BuLi or lithiumdiisopropyl amide (LDA) in THF followed by reaction with 2-substitutedoxirane at −78°C or in another method, the aryl carbamate was reacted with 1-substituted-3-chloropropan-2-ol (halohydrin) using lithium *t*-butoxide (Li*O*t*Bu*) or *n*-BuLi to generate (*R*)-3-aryl-5-(hydroxylmethyl)-2-oxazolidinones. These 3-aryl-5-(hydroxylmethyl)-2-oxazolidinone intermediates are elaborated to final products [15, 16].



LINEZOLID, 1

Figure 1

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), ^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 nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated 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.

Procedure for the preapration of (2R)-1-azido-3-chloropropane-2-ol

Sodium azide solution (91.3 g, 1.405 mole) was added to the solution of (R)- Epichlorohydrin (25.0 g, 0.270 mol) dissolved in water (125 ml), 200 ml of acetic acid was added slowly and the resulting solution was stirred for 5 hr at room temperature. The reaction mixture was extracted with ethyl acetate and dried over sodium sulfate. Ethyl acetate concentrated under reduced pressure and purified by column chromatography to get (S)-1-azido-3-chloropropan-2-ol (28.0 g) as a liquid; Yield 76 %;, [α]20D = +1.7 (c = 1.0, CHCl3); 1H NMR (CDCl3): δ2.4(S, 1H,-OHD2Oexangble), 3.28-3.45(m, 4H,-CH2-N3&-CH2Cl),4.0(m, 1H-CH-OH); ^{13}CNMR(DMSO-d_6): δ46.02, 53.28, 70.11; ESI-MS: *m*/*z* (%) 136 (M^++1).

General procedure for the preparation of 1-azido-3-chlor-2-aryl/alkyl carbonates derivative (Compound 2a to 2g)

Method –A:

To a solution of azido alcohol (0.073 moles), pyridine (2.0 mole ratio) and DCM (100mL), alkyl/aryl chloroformate (1.5 mole ratio) was added drop wise at 0^{o}C. After stirring at 0^{o}C to 35 ^{o}C for 1-4 h, the reaction mixture was poured into water and the DCM layer was separated. The aqueous layer was extracted with DCM and the combined organic extract was washed with citric acid solution followed by water and then concentrated and after flash column chromatography to give corresponding 1-azido-3-chlor-2-alkyl\aryl carbonates derivative. The yield and condition data for carbonates derivative are given in **Table- 1(scheme1).**

Method –B:

To a solution of azido alcohol (0.073 moles), Tri ethyl amine (3.0 mole ratio) and THF (75mL) Methanol (25mL) mixture, alkyl/aryl chloroformate (1.5 mole ratio) was added drop wise at 0^{o}C. After stirring at 0^{o}C to 35 ^{o}C for 1-4 h, the reaction mixture was poured into water and the THF layer was separated. The aqueous layer was extracted with THF and the combined organic extract was washed with citric acid solution followed by water and then concentrated and after flash column chromatography to give corresponding 1-azido-3-chlor-2-aryl/alkyl carbonates derivative are given in **Table- 1(scheme1)**

The (*R*)-1-azido-3-chloropropan-2-yl phenyl carbonate, (2a) was prepared using Method-A and obtained (2a) as a syrup; yield 91%; $[\alpha]^{20}_{D}$ = -19.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.65-3.8 (m,4H),5.05(m,1H),7.15-7.45 (m,5H);^{13}CNMR(DMSO-d_6): δ 41.87,50.53,75.63,120.69,126.21,129.42,150.69,152.59; ESI-MS: *m*/*z* (%) 256 (M^{+}+1).

The (R)-1-azido-3-chloropropan-2-yl 4-nitrophenyl carbonate (2b) was prepared using Method-A and obtained (2b) yield 95%;$[\alpha]^{20}_{D}$ = -21.6 (*c* = 1.0, $CHCl_3$); mp 98-102 °C; ^{1}H NMR ($CDCl_3$): δ 3.62-3.82 (m, 4H), 5.02(m, 1H), 7.14-7.46 (m, 2H); 8.15-8.25 (m, 2H); ESI-MS: *m*/*z* (%) 301 (M^{+}+1).

The (R)-1-azido-3-chloropropan-2-yl ethyl carbonate (2c) was prepared using Method-A and obtained (2c) yield 60%; syrup; ^{1}H NMR ($CDCl_3$): 1.26-1.29(t, 3H), 3.27-3.46(m, 4H), 4.88(m, 1H) 4.23-4.28(m,2H) ; ESI-MS: m/z (%) 208 (M^{+}+1).

The (R)-1-azido-3-chloropropan-2-yl benzyl carbonate (2d) was prepared using Method-B and obtained (2d) yield 28%; syrup; ^{1}H NMR ($CDCl_3$): δ 3.65-3.81 (m, 4H), 4.76(s, 2H) 5.02(m, 1H), 7.15-7.46 (m, 5H) ; ESI-MS: m/z (%) 270 (M^{+}+1).

The (R)-1-azido-3-chloropropan-2-yl 4-nitrobenzyl carbonate (2e) was prepared using Method-B and obtained (2e) yield 36%; mp 72-75°C; ^{1}H NMR ($CDCl_3$): 3.64-3.82 (m, 4H), 4.67(s, 2H), 5.03(m, 1H), 7.50 (2H, d, J=9.0Hz) 2H); 8.21 (2H, d, J=8.8Hz); ESI-MS: *m*/*z* (%) 315 (M^{+}+1).

The (R)-1-azido-3-chloropropan-2-yl tert-butyl carbonate (2f) was prepared using Method-A and obtained (2f) yield 95%; syrup; ^{1}H NMR ($CDCl_3$): δ 3.26-3.46(m, 4H), 4.86 (m, 1H), 1.52(s, 9H) ; ESI-MS: m/z (%) 236 (M^{+}+1).

The (R)-1-azido-3-chloropropan-2-yl isobutyl carbonate (2g) was prepared using Method-A and obtained (2g) yield 94%; syrup; ^{1}H NMR ($CDCl_3$): δ0.98(m, 6H), 2.09(m, 1H), 3.27-3.48(m, 4H), 4.98 (m, 1H) ; ESI-MS: m/z (%) 236 (M^{+}+1).

General procedure for the preparation of 2-oxazolidnone from various azido chloro carbonates

Method –A

To a solution of nitro phenyl chlorocarbonate (2g, 0.012 moles) and aryl amine (0.009 mole), DMF (10 mL), cesium cabonate (6.35g, 0.0195mole) and catalytic amount of triethylbenzylammonium bromide were added and stirred at 80°c for 12hr. The reaction mixture was poured into water (20ml) and extracted with ethyl acetate (3x 30 ml). The combined organic extract was washed with water (2x 20ml) and evaporated to get crude azido compound, which was purified by flash column chromatography (ethylacetate-hexane 0.5:9.5) to obtain 2-oxazolidnone

Method-B

To a solution of nitro phenyl chlorocarbonate (2g, 0.012 moles) and aryl amine (0.009 mole), DMF (10mL), potassium carbonate (2.7g, 0.0195mole) and catalytic amount of triethylbenzylammonium bromide were added and stirred at 80°c for 12hr. The reaction mixture was poured into water (20ml) and extracted with ethyl acetate (3x 30 ml). The combined organic extract was washed with water (2x 20ml) and evaporated to get crude azido compound, which was purified by flash column chromatography (ethylacetate-hexane 0.5:9.5) to obtain 2-oxazolidnone

Method-C

To a solution of a nitro phenyl chlorocarbonate (2g, 0.012 moles) and aryl amine (0.009 mole), Acetone (10 mL), potassium carbonate (2.7g, 0.0195mole) and catalytic amount of triethylbenzylammonium bromide were added and stirred at 80°c for 12hr. The reaction mixture was poured into water (20ml) and extracted with ethyl acetate (3x 30 ml). The combined organic extract was washed with water (2x20ml) and evaporated to get crude azido compound, which was purified by flash column chromatography (ethyl acetate-hexane 0.5:9.5) to obtain 2-oxazolidnone

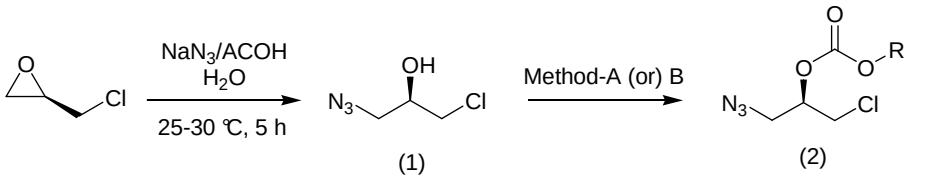
Method-D

To a solution of Nitro phenyl chlorocarbonate (2g, 0.012 moles) and aryl amine (0.009 mole), Ethanol (10 mL), Triethylamine (2.6mL, 0.0195mole) were added and stirred at 80°c for 12hr. The reaction mixture was poured into water (20ml) and extracted with ethyl acetate (3x 30 ml). The combined organic extract was washed with water (2x 20ml) and evaporated to get crude azido compound, which was purified by flash column chromatography (ethyl acetate-hexane 0.5:9.5) to obtain 2-oxazolidnone.

Preparation of (S)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one.

10% Pd/C (3.9 g, 0.077 mol) was added to a stirred solution of 2-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione (6.0 g, 0.014 mol) and methanol (50 mL). The mixture was stirred at reflux temperature for 1 h. The reaction progress can be monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature, water was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combine organic extracts were washed with water, dried over Na_2SO_4 and concentrated in vacuum to give (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one as a white colored solid in 88 % yield (3.66 g); ^{1}H NMR ($CDCl_3$): δ 7.44-7.49 (dd, 1H), 7.12-7.15 (dd, 1H), 6.90-6.96 (t , 1H), 4.04 - 4.69 (m, 1H), 3.98-4.04 (t, 1H), 3.85-3.89 (t, 4H), 3.79 -3.84 (dd, 1H), 3.09-3.14 (dd, 1H), 3.03-3.06 (t, 4H), 2.94-3.0 (dd, 1H), 1.49 (br s, 2H); IR (KBr): 3404, 2958, 1726, 1229 cm^{-1}; ESI-MS: *m/z* (%) 296 (100, M^++1).

Scheme-1



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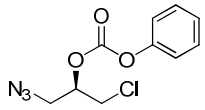
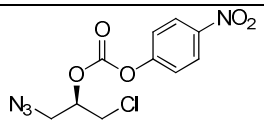
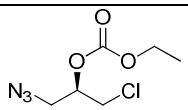
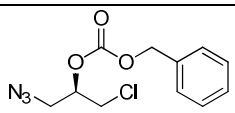
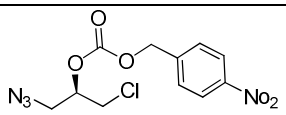
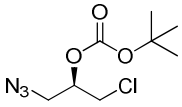
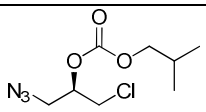
1	Method-A	 (2a)	91%
2	Method-A	 (2b)	95%
3	Method-A	 (2c)	60%
4	Method-B	 (2d)	28%
5	Method-B	 (2e)	36%
6	Method-A	 (2f)	95%
7	Method-A	 (2g)	94%

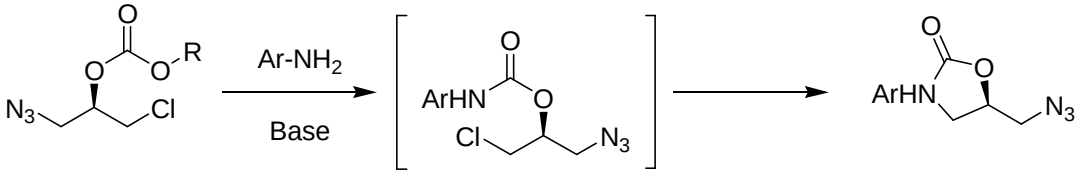
Scheme 1. Synthesis of 1-azido-3-chlor-2-aryl/alkyl carbonates derivative

Preparation of *N*-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) acetamide (Linezolid).

Acetic anhydride (3.11 g, 0.030 mol) was added dropwise to a stirred solution of (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (3.0 g, 0.010 mol) and toluene (30 mL) by maintaining the temperature at below 35 °C. The mixture was stirred at room temperature for 1 h. The reaction progress can be monitored by TLC. After completion ofreaction, the reaction mixture was allowed to cool to 0°C and the obtained solids were filtrated to give *N*-(((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) acetamide **1** as white colored solid (2.74 g); Yield: 80 % (2.74 g); chiral HPLC purity: 99.98 % (% of *ee* = 99.6 %); mp 181.5-182.5 °C; IR (KBr): ν 3342 (NH), 3075 (ArH), 2967 (CH), 1741, 1660 (C=O) cm^{-}

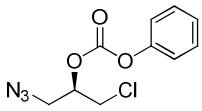
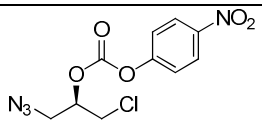
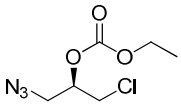
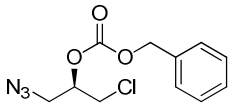
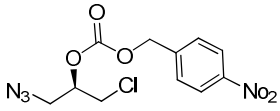
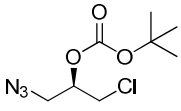
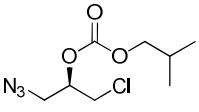
[1]; [1]H NMR ($CDCl_3$): δ 2.07 (s, 3H), 3.03-3.07 (t, 4H), δ 3.55-3.76 (m, 3H), 3.85-3.89 (t, 4H), 3.99-4.05 (t, 1H), 4.74-4.79 (m, 1H), 5.96 (s, 1H), 6.89-6.95 (t, 1H), 7.00-7.10 (d, 1H), 7.42-7.48 (d, 1H). [13]C NMR (DMSO): δ 22.4, 47.2, 50.6, 66.1, 71.5, 106.4, 114.0, 119.1, 113.3, 113.5, 152.9, 154.0, 156.1, 170.0; ESI-MS: *m/z* (%) 338.18 (100, M^++1).

Scheme 2



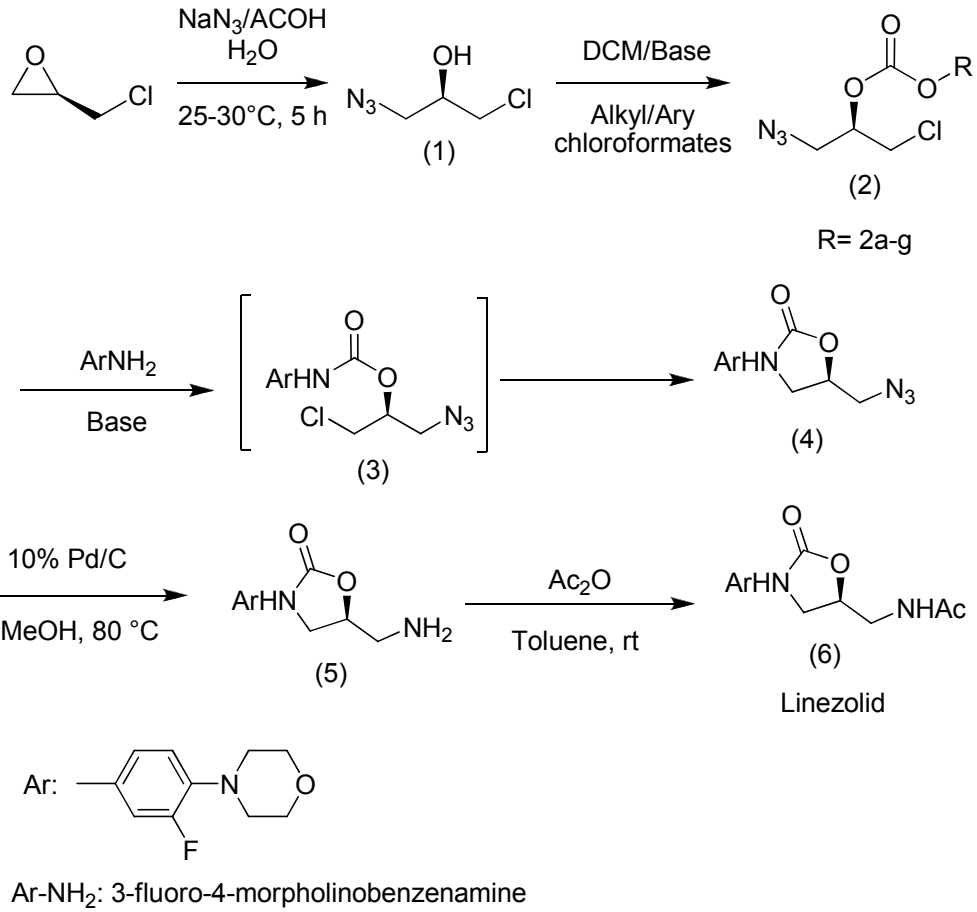
(2) (3) (4)

R= Alky;/Aryl carbonates Carbamate 2-Oxazolidinone

Entry no	Product	2-Oxazolidinone Method	Yield (%)
1	 (2a)	A	90%
		B	70%
		C	68%
		D	86%
2	 (2b)	A	96%
		B	75%
		C	70%
		D	92%
3	 (2c)	A	36%
		B	20%
		C	10%
		D	15%
4	 (2d)	A	45%
		B	30%
		C	28%
		D	50%
5	 (2e)	A	52%
		B	30%
		C	40%
		D	50%
6	 (2f)	A	95%
		B	65%
		C	30%
		D	78%
7	 (2g)	A	92%
		B	36%
		C	20%
		D	74%

Scheme 2. Synthesis of 2-oxazolidnone from various azido chloro carbonates

Scheme -3



Scheme- 3 Synthesis of linezolid by using various azido chloro carbonates

RESULTS AND DISCUSSION

Previously, our research team synthesized 3-chloro-2-((phenoxycarbonyl)oxy)propyl azide starting from epichlorohydrin in two steps and utilized this compound in the synthesis of 2-oxazolidinone antibacterial such as Linezolid and Dup-721.

Herein we reported various carbonate derivatives analogues to 3-chloro-2-((phenoxy carbonyl)oxy)propyl azide by altering phenyl group with others. Also, the leaving group effect was studied during the reaction of these carbonate derivatives with aryl amine in view of yield and quality of the final targets. These chiral carbonate derivatives require to the scientific team to prepare various analogues 5-methylazido-3-aryl 2-oxazolidinones. Later these 5-methylazido-3-aryl 2-oxazolidinones converted to required targets.

In preparation of these carbonate derivatives, chosen 4-nitro (aryl), benzyl (aralkyl), 4-nitrobenzyl (aralkyl), ethyl, *t*-butyl, *iso*-butyl (alkyl) groups instead of phenyl group. Except aralkyl carbonate derivatives, all are synthesized starting from 1-chloro-3-azido-propan-2-ol using pyridine in dichloromethane (Method A). However, this method was not able to produce required aralkyl carbonate derivatives and these aralkyl compounds were prepared starting from 1-chloro-3-azido-propan-2-ol using triethylamine in methanol and THF (Method B). Moreover, we observed low yield while preparing aralkyl carbonate derivatives.

During the reaction of these carbonate derivatives with aryl amine, screened various reaction conditions using organic and inorganic bases and solvents. Among screened reaction conditions, Cs_2CO_3, DMF (Method C), K_2CO_3, DMF (Method D), K_2CO_3, acetone (Method E) and triethylamine and ethanol (Method F) gave better results with respect to yield which tabulated in table 1. In comparison to these four methods (C-F), method C was superior to prepare corresponding 2-oxazolidinone compound.

CONCLUSION

In conclusion, highly efficient method **(Scheme-3)** has been developed to prepare Linezolid, by using various azido chloro carbonates higher overall yield. This method overcomes many of the drawbacks associated with previously reported syntheses and offers an industrial viable procedure for the synthesis of Linezolid and exploration of this method for the preparation of similar molecules is currently underway in our laboratory.

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