A Facile Solvent-Free Synthesis of Chiral Oxazolidinone Derivatives Catalyzed by MgI_2 Etherate: An Approach to Enantiopure Synthesis of Linezolid

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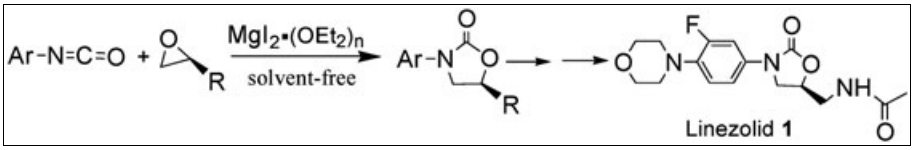

A highly efficient and stereoselective cycloaddition of aryl isocyanates with chiral oxiranes catalyzed by MgI_2 etherate under solvent-free conditions was developed to prepare the chiral oxazolidinone derivatives. This methodology has been applied into the practical synthesis of antibacterial drug linezolid.

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INTRODUCTION

The *5S*-aryloxazolidin-2-one moiety is present in a number of compounds which show diverse biological activities. Oxazolidinones are a new class of antibacterial agent that show good activity against Gram-positive bacteria. Some of these activities include monoamine oxidase (MAO) inhibition [1], GP IIb/IIIa antagonism [2], neuroleptic activity [3], and antibacterial activity [4]. Oxazolidinones, exemplied by linezolid (**1**), eperezolid (**2**), and AZD2563 (**3**) (Fig. 1), represent an exciting new class of linezolid totally synthetic antibacterial agents [5]. Because of this medicinal importance, methods for generating libraries of these compounds have received significant interest [6].

The development of sustainable methods for the synthesis of complex molecules is nowadays a main goal in synthetic chemistry and the application of solvent-free reaction conditions meets the established principles for Green Chemistry [7]. Great efforts have been made on developing chemical technologies that can intrinsically reduce or eliminate the use or generation of hazardous substances during the design, manufacture, and use of chemical products and processes [8]. Organic reactions under solvent-free conditions are especially important and have attracted much attention in recent years [9]. This is because no-solvent reactions usually need shorter reaction times and simpler reactors and result in simple and efficient workup procedures.

Recent research from our group has shown that MgI_2 etherate can function as a Lewis acid for many carbon–carbon bond formation reactions, such as allylation, halo-aldol reaction, and cycloaddition [10]. Herein, we will report the cycloaddition of aryl isocyanate with chiral oxirane promoted by MgI_2 etherate under solvent-free conditions.

RESULTS AND DISCUSSIONS

Initially, we studied the effect of amounts of MgI_2 etherate on the reaction yields with a model reaction of phenyl isocyanate with *R*-epichlorohydrin (Table 1, entries 1–5). It has been found that the reaction gave low yields of the desired product using less than 10 mol% of MgI_2 etherate (Table 1, entry 1). By increasing the amount of MgI_2 etherate, the yield of cycloadduct was obviously improved. The reaction gave the desired product in 94% yield in the presence of 30 mol % of MgI_2 etherate without any side-products (Table 1, entry 4). However, the similar reaction gave 71% yield when it was conducted in THF for 3.0 h using 30 mol % of MgI_2 etherate. Furthermore, the cycloaddition of a variety of aryl isocyanates with *R*-epichlorohydrin has been investigated (Table 1, entries 6–12) and proceeded smoothly at 65°C to provide the desired products in excellent yields. The electronic effect of substituted groups on the aromatic ring of isocyanates has no obvious effect on the yield of the cycloaddition product. It is worthy to be noted that MgI_2 etherate could efficiently promote the reaction of more sterically hindred 2,6-diisopropylphenyl isocyanate with *R*-epichlorohydrin and gave the product in 90% yield (Table 1, entry 9). Moreover, the cycloaddition of 2*R*-phenoxymethyl oxirane with aryl isocyanates underwent effectively catalyzed by 30 mol % of MgI_2 etherate to give the desired product in 88%–92% yield (Table 1, entries 13–15).

The key question in the synthesis of linezolid **1** is the access to the oxazolidin-2-one ring with the appropriate *S*-conguration at its C-5 position, a goal which has been achieved in different ways. Manninen reported the first synthesis of linezolid by the reaction of aryl carbamate with (*R*)-glycidyl butyrate in the presence of butyllithium

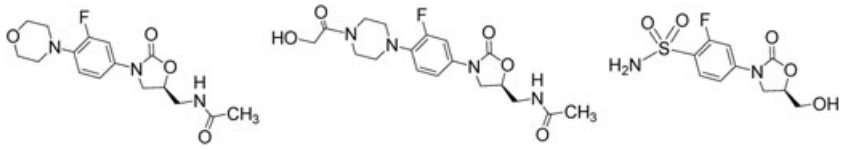
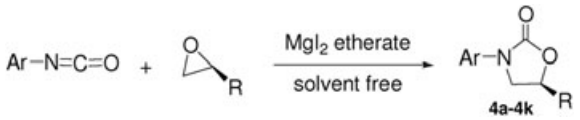


Figure 1. The typical chiral oxazolidinone drugs.

Table 1

MgI_2 etherate-catalyzed cycloaddition of various aryl isocyanates with chiral oxiranes under solvent-free conditions.[a]



Entry	Ar	R	Loading (mol%)[b]	Time (h)	Product	Yield (%)[c]
1	C_6H_5	CH_2Cl	5	5	**4a**	62
2	C_6H_5	CH_2Cl	10	5	**4a**	70
3	C_6H_5	CH_2Cl	20	3	**4a**	84
4	C_6H_5	CH_2Cl	30	1	**4a**	94
5	C_6H_5	CH_2Cl	40	1	**4a**	93
6	2-MeC_6H_4	CH_2Cl	30	2	**4b**	91
7	2,3-$Me_2C_6H_3$	CH_2Cl	30	2	**4c**	92
8	4-MeC_6H_4	CH_2Cl	30	1	**4d**	93
9	2,6-(^{i}Pr)$_2C_6H_3$	CH_2Cl	30	3	**4e**	90
10	2-Me-5-ClC_6H_3	CH_2Cl	30	3	**4f**	91
11	4-$NO_2C_6H_4$	CH_2Cl	30	0.5	**4g**	93
12	4-BrC_6H_4	CH_2Cl	30	3	**4h**	93
13	C_6H_5	CH_2OPh	30	2	**4i**	88
14	4-MeC_6H_4	CH_2OPh	30	1	**4j**	92
15	2,3,4-$F_3C_6H_2$	CH_2OPh	30	1	**4k**	88

[a]Reactions were run with a mixture of 5 mmol of aryl isocyanate, 10 mmol of oxirane, and 30 mol % of MgI_2 etherate under solvent-free condition.
[b]Relative to aryl isocyanate.
[c]Isolated yield by silica gel flash chromatography.

[11]. A modified synthetic method via (2*S*)-1-amino-3-chloropropan-2-ol coupling with aryl carbamates promoted by lithium *tert*-butoxide was developed [12]. Recently, $BF_3{\cdot}Et_2O$-promoted stereospecific intramolecular ring opening of 2-(Boc-aminomethyl)aziridines was applied into the preparation of enantiopure linezolid [13]. The structural core of linezolid **1** is its (5*S*)-(aminomethyl)-1,3-oxazolidin-2-one unit, which is easily prepared from our (5*R*)-5-(chloromethyl)-3-phenyl-oxazolidin-2-one, we therefore started from 3-fluoro-4-morpholinyl-phenyl isocyanate **7** in the subsequent synthetic approach to **1**. The synthesis of linezolid from **7** with an overall yield of 52% is outlined in Scheme 1. Firstly, we prepared 3-fluoro-4-morpholinoaniline **6** from morpholine and 3,4-difluoronitrobenzene reported by literature [11]. Then, the amine **6** reacted with *bis*-(trichloromethyl)-carbonate (triphosgene, BTC) to give isocyanate **7** [14]. Cycloaddition of isocyanate **7** with (*R*)-epichlorohydrin catalyzed by 30 mol % of MgI_2 etherate at 65°C under solvent-free conditions exclusively afforded the desired enantiopure cycloadduct **8** in 97% yield. We thereby easily prepared the key intermediate azide **9**, which was finally converted into linezolid **1** after hydrogenolysis and further acetylation in 91% yield over two steps.

CONCLUSIONS

In summary, we have described a highly-efficient and gentle method for the preparation of enantiopure 5-(chloromethyl)-1,3-oxazolidin-2-ones using MgI_2 etherate-catalyzed cycloaddition of (*R*)-epichlorohydrin with substituted phenylisocyanate. One of these oxazolidinones was conveniently transformed into the antibiotic linezolid. Further synthetic application of MgI_2 etherate-catalyzed cyclization into natural products and drugs is ongoing in our lab.

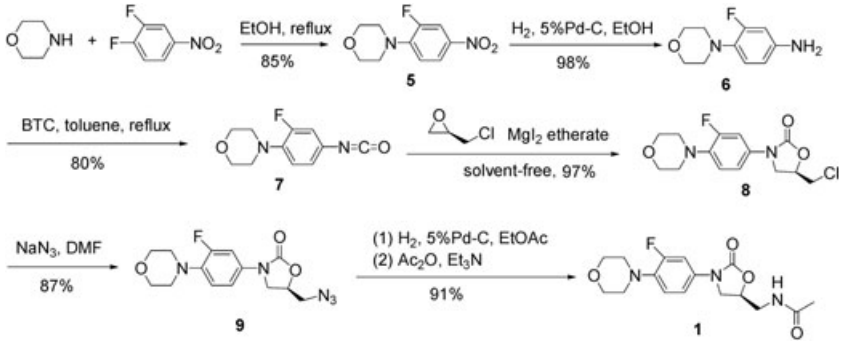
EXPERIMENTAL

R-Epichlorohydrin was purchased from Aldrich. 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. FT-IR was recorded on a Bruker Tensor 27 spectrometer. Melting points were measured on BUCHI B-540 and uncorrected. Elemental analysis was performed on a VarioEL-3 instrument.

The representative procedure for the preparation of aryl oxazolidin-2-ones. To a stirred solution of freshly prepared MgI_2 etherate (1.5 mmol) was added dropwise phenyl isocyanate (5 mmol) and *R*-epichlorohydrin (10.0 mmol) at room temperature. After addition, the reaction mixture was allowed to warm to 65°C and continued to be stirred for 30 minutes. The resulting homogeneous reaction mixture was quenched with saturated Na_2SO_3 aqueous solution. Extractive workup with dichloromethane and flash chromatographic purification of the crude product on silica gel gave the desired compound **4a** in 94% yield.

5-Chloromethyl-3-phenyl-oxazolidin-2-one (4a) [15]. White solid; mp 130.4–131.3°C (lit, 132°C); ir: 2960, CO 1739, 1592, 1493 cm^{-1}; ^{1}H nmr: δ 3.73–3.81 (*m*, 2H), 3.96 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.17 (t, *J* = 9.0 Hz, 1H), 4.85–4.88 (*m*, 1H), 7.14–7.18 (*m*, 1H), 7.37–7.40 (*m*, 2H), 7.54 (dd, *J* = 1.0, 8.5 Hz, 2H) ppm.

Scheme 1. An approach to synthesis of linezolid **1**.



5-Chloromethyl-3-(2-methyl-phenyl)-oxazolidin-2-one (4b). Yellowish solid, mp 56.8–57.8°C; ir: 2967, CO 1731, 1493 cm^{-1}; ^1H nmr: δ 2.32 (s, 3H), 3.77 (dd, *J* = 3.5, 11.5 Hz, 1H), 3.81–3.86 (*m*, 2H), 4.06 (*t*, *J* = 9.0 Hz, 1H), 4.90–4.94 (*m*, 1H), 7.22–7.29 (*m*, 4H) ppm. Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.65; H, 5.45; N, 6.32.

5-Chloromethyl-3-(2,3-dimethyl-phenyl)-oxazolidin-2-one (4c). White solid. mp 121.7–122.3°C; ir: 2945, CO 1735, 1477 cm^{-1}; ^1H nmr: δ 2.19 (s, 3H), 2.30 (s, 3H), 3.75–3.82 (*m*, 1H), 3.83 (dd, *J* = 2.0, 6.0 Hz, 2H), 4.03 (t, *J* = 9.0 Hz, 1H), 4.89–4.94 (*m*, 1H), 7.09 (dd, *J* = 2.5, 6.5 Hz, 1H), 7.12–7.16 (*m*, 2H) ppm. Anal. Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.26; H, 5.98; N, 5.68.

5-Chloromethyl-3-(4-methyl-phenyl)-oxazolidin-2-one (4d) [16]. White solid; mp 100.1–101.1°C; ir: 2970, CO 1736, 1542 cm^{-1}; ^1H nmr: δ 2.33 (*s*, 3H), 3.72–3.80 (*m*, 2H), 3.94 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.15(t, *J* = 9.0 Hz, 1H), 4.83–4.87 (*m*, 1H), 7.19 (*d*, *J* = 8.0 Hz, 2H), 7.40–7.42 (*m*, 2H) ppm. Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.65; H, 5.48; N, 6.37.

5-Chloromethyl-3-(2,6-diisopropyl-phenyl)-oxazolidin-2-one (4e). White solid; mp 90.2–91.3°C; ir: 3068, CO 1739, 1641, 1548, 1463 cm^{-1}; ^1H nmr: δ 1.24–1.28 (*m*, 12H), 2.93–2.98 (*m*, 1H), 3.01–3.07 (*m*, 1H), 3.76–3.86 (*m*, 3H), 3.90 (*t*, *J* = 9.0 Hz, 1H), 4.95–5.00 (*m*, 1H), 7.20–7.22 (*m*, 2H), 7.36 (t, *J* = 8.0 Hz, 1H) ppm; Anal. Calcd. for $C_{16}H_{22}ClNO_2$: C, 64.97; H, 7.50; N, 4.74. Found: C, 65.11; H, 7.62; N, 4.88.

5-Chloromethyl-3-(5-chloro-2-methyl-phenyl)-oxazolidin-2-one (4f). White solid; mp 108.6–109.5 °C; ir: 2961, CO 1748, 1580, 1487 cm^{-1}; ^1H nmr: δ 2.25 (s, 3H), 3.72 (dd, *J* = 3.5, 12.0 Hz, 1H), 3.77 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.82 (dd, *J* = 5.0, 12.0 Hz, 1H), 4.00 (t, *J* = 9.0 Hz, 1 H), 4.89–4.94 (m, 1 H), 7.19 (dd, *J* = 8.5, 9.5 Hz, 2H), 7.23 (s, 1H) ppm; Anal. Calcd. for $C_{11}H_{11}Cl_2NO_2$: C, 50.79; H, 4.26; N, 5.38. Found: C, 50.90; H, 4.37; N, 5.54.

5-Chloromethyl-3-(4-nitro-phenyl)-oxazolidin-2-one (4g) [17]. Yellowish solid; mp 141.0–141.9 °C; ir: 2959, CO 1759, 1597, 1519, 1473, 1431 cm^{-1}; ^1H nmr: δ 3.82–3.84 (*m*, 2H), 4.05 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.26 (*t*, *J* = 9.0 Hz, 1H), 4.96–5.01 (*m*, 1H), 7.75 (dd, *J* = 2.0, 7.0 Hz, 2H), 8.28 (dd, *J* = 2.0, 7.0 Hz, 2H) ppm.

5-Chloromethyl-3-(4-bromo-phenyl)-oxazolidin-2-one (4h). White solid; mp 90.6–91.6°C; ir: 2960, CO 1738, 1591, 1490 cm^{-1}; ^1H nmr: δ 3.74–3.80 (*m*, 2H), 3.91 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.13 (*t*, *J* = 9.0 Hz, 1H), 4.85–4.90 (*m*, 1H), 7.41–7.44 (*m*, 2H), 7.46–7.49 (*m*, 2H) ppm; Anal. Calcd. for $C_{10}H_9BrClNO_2$: C, 41.34; H, 3.12; N, 4.82. Found: C, 41.47; H, 3.21; N, 4.74.

5-Phenoxymethyl-3-phenyl-oxazolidin-2-one (4i) [18]. White solid; mp 139.0–139.7°C (lit, 139°C); ir: 3062, CO 1739, 1599, 1502, 1445 cm^{-1}; ^1H nmr: δ 4.08 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.19–4.25 (*m*, 3H), 4.97–5.01 (*m*, 1H), 6.91–6.92 (*m*, 2H), 7.00 (*t*, *J* = 7.5 Hz, 1H), 7.16 (*t*, *J* = 7.5 Hz, 1H), 7.29–7.32 (*m*, 2H), 7.38–7.41 (*m*, 2H), 7.57–7.59 (*m*, 2H) ppm.

5-Phenoxymethyl-3-(5-chloro-2-methyl-phenyl)-oxazolidin-2-one (4j) [19]. White solid; mp 126.5–127.5°C; ir: CO 1745, 1594, 1512, 1455 cm^{-1}; ^1H nmr: δ 2.33 (*s*, 3H), 4.03 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.14–4.23 (*m*, 3H), 4.95 (dd, *J* = 4.5, 9.0 Hz, 1H), 6.90 (*d*, *J* = 8.0 Hz, 2H), 6.99 (*t*, *J* = 7.5 Hz, 1H), 7.18 (*d*, *J* = 8.5 Hz, 2H), 7.29 (dd, *J* = 7.5, 8.0 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H) ppm.

5-Phenoxymethyl-3-(2,3,4-trifluoro-phenyl)-oxazolidin-2-one (4k). White solid; mp 104.8–105.5°C; ir: CO 1736, 1610, 1507, 1442 cm^{-1}; ^1H nmr: δ 4.05 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.19–4.23 (*m*, 2H), 4.27 (dd, *J* = 4.5, 11.5 Hz, 1H), 5.03 (dd, *J* = 4.5, 9.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 7.00–7.05 (*m*, 2H), 7.31 (*t*, *J* = 8.0 Hz, 3H) ppm; Anal. Calcd. for $C_{16}H_{12}F_3NO_3$: C, 59.45; H, 3.74; N, 4.33. Found: C, 59.56; H, 3.67; N, 4.45.

Procedure for 8 from 7. To a stirred solution of (*R*)-epichlorohydrin (923 mg, 10.0 mmol) and 3-fluoro-4-morpholinyl-phenyl isocyanate **7** (1.11 g, 5 mmol) was added MgI_2 etherate (1.5 mmol) at room temperature. After addition, the reaction mixture was allowed to warm to 65°C and continued to be stirred for 3.0 h. The resulting reaction mixture was quenched with saturated Na_2SO_3 aqueous solution. Extractive workup with EtOAc and flash chromatographic purification of the crude product on silica gel gave the compound **8** (941 mg) in 97% yield.

5-(Chloromethyl)-3-(3-fluoro-morpholin-4-yl-phenyl) oxazolidin-2-one (8). This compound was obtained as white solid; mp 117.3–118.3°C; ^1H nmr: δ 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); ms: *m/z* 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.

Procedure for 9 from 8. Sodium azide (390 mg, 6 mmol) was added into the solution of 5-(chloromethyl)-3-(3-fluoro-morpholin-4-yl-phenyl)oxazolidin-2-one **8** (1.90 g, 3 mmol) in DMF (5 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 **9** (837 mg) in 87% yield.

5-(Azidomethyl)-3-(3-fluoro-morpholin-4-yl-phenyl)-oxazolidin-2-one (9). This compound was obtained as white solid; mp 102.5–103.5°C; ^{1}H nmr: 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, 4HHHHHhhhhH), 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) ppm; ms: *m/z* 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.

Procedure for 1 from 9. A solution of compound **9** (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** (920 mg) in 91% yield.

***N*-[[3-(3-Fluoro-morpholin-4-yl-phenyl)-2-oxo-5-oxazolidinyl] methyl]-acetamide (linezolid, 1).** This compound was obtained as white solid; mp 178.8–179.0°C (lit[5], 181.5–182.5°C); ^{1}H nmr: δ 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) ppm.

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