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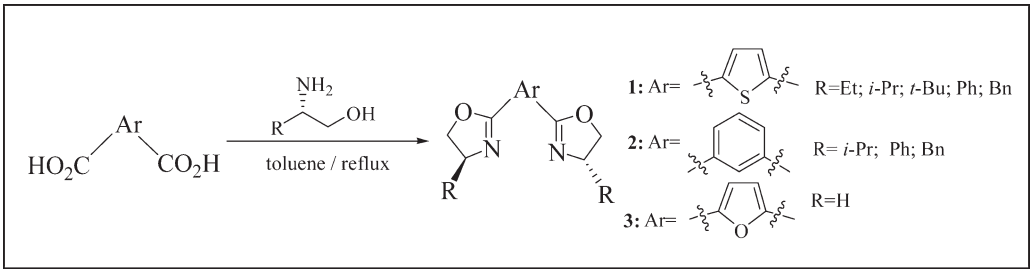

Thiophene-2,5-dicarboxylic acid, benzene-1,3-dicarboxylic acid, or furan-2,5-di-carboxylic acid, respectively, reacted with various β-amino alcohols in toluene under reflux within 24 h, to form nine bis(oxazoline)s (**1**–**3**) in good yields through water deprivation *via* a one-pot reaction. The synthetic method is facile and efficient and deserves great application potentials in the research and development in the area of bis(oxazoline)s.

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INTRODUCTION

Since Butula *et al*. prepared the first optically active bis(oxazoline) in 1976, the design and development of effective chiral bis(oxazoline) ligands have played a significant role in advancement of asymmetric catalysis and have attracted a great deal of attention because they hold special structural characters and provide high enantioselectivities in a variety of asymmetric catalytic reactions [1–6]. Chiral bis(oxazoline) ligands have widespread uses in asymmetric hydrosilylation [7], cyclopropantion reaction [8], Friedel-Crafts reaction [9], Diels-Alder reaction [10], Aldol addition [11], Michael reaction [12], Henry reaction [13], allylic oxidation [14], 1,3-dipolar cycloaddition [15], and so on.

Chiral bis(oxazoline)s have various structures, which determine the diversity of their synthetic methods. At present, two general synthetic routes are summarized from various synthesis [2,3,16]: (a) Reaction of dintriles with chiral amino alcohol or diols afford the target compound *via* a one or multiple-step reaction in the presence of Lewis acid or base. (b) Dicarboxylic acids or their derivatives (diacyl halide, diacylamide or diesters) react with chiral amino alcohol, *via* the corresponding bis(β-hydroxylamide)s as the successive intermediates, that cyclize to produce the target compounds. The latter method requires activating agents, with thionyl chloride, also cyclizing agent being the most commonly used, which results in more side reactions and low yields. Therefore, a simpler and more efficient synthesis approach should be explored to meet the needs of bis(oxazoline) ligands.

In this article, we report the results of the reaction of dicarboxylic acids with β-amino alcohols under reflux through water deprivation to obtain chrial bis(oxazoline)s **1a**–**1e**, **2a**–**2c**, and a novel achiral bisoxazoline **3** (Fig. 1 and Scheme 1–3) *via* a one-pot reaction. This method afforded high yields with simple workup procedure.

RESULTS AND DISCUSSION

Gao *et al*. reported that chiral bis(oxazoline)s **1a**–**1e** were synthesized from thiophene-2,5-dicarboxylic acid by sequential amidation with a chiral ethanolamine, conversion of hydroxyl to chloro group, and base-promoted oxazoline ring formation [17,18]. Kanazawa *et al*. described the synthetic procedure of chiral 1,3-bis[4′-substitutedoxazolin-2′-yl]benzene including bis(oxazoline)s **2a**–**2c**, which isophthaloyl dichloride reacted with chiral β-amino alcohols at 0°C to form the corresponding diamide-dialcohols as the successive intermediates and then cyclized to obtain the target compounds in the presence of methanesulfonyl chloride at 0°C [19]. As described above, the syntheses of chiral bis(oxazoline)s involve multistep reactions, which result in more side reactions and low yields.

To address above issues, we successfully developed a new, facile, and efficient method for the synthesis of

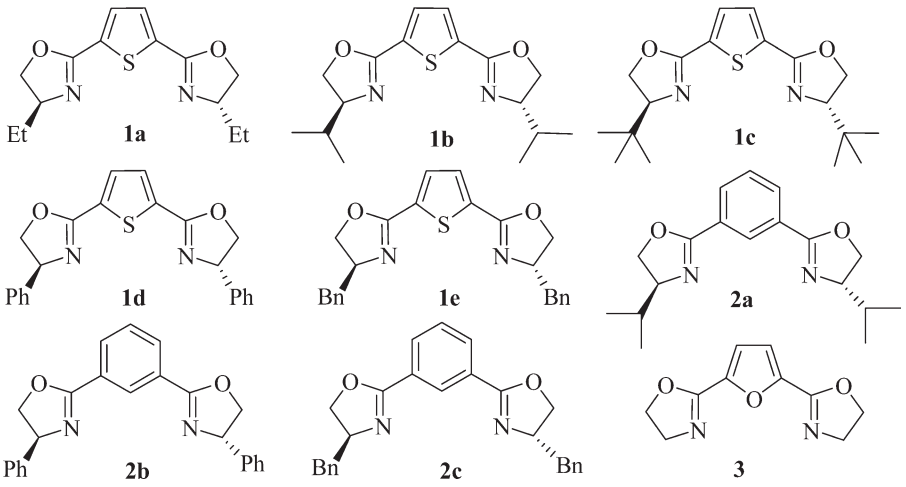


Figure 1. Chemical structures of bis(oxazoline)s.

bis(oxazoline)s starting from dicarboxylic acids. With this convenient method, bis(oxazoline)s **1** or **2** were readily synthesized in high yields from thiophene-2,5-dicarboxylic acid (TDA) or benzene-1,3-dicarboxylic acid (BDA) and β-amino alcohols (Scheme 1 and 2). Briefly, a mixture of dicarboxylic acid and β-amino alcohol was refluxed in toluene through water deprivation for 24 h. After cooling to ambient temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the desired product in high yield. The conditions and results of reaction of carboxylic acids with β-amino alcohols have been listed in Table 1 (entries 1–8).

Instead of thiophene-2,5-dicarboxylic acid (TDA) or benzene-1,3-dicarboxylic acid (BDA), furan-2,5-dicarboxylic acid (FDA) reacted with 2-aminoethanol to afford a new achiral bis(oxazoline) **3** in high yield under the same reaction condition (Scheme 3 and Table 1, entry 9).

In conclusion, a facile one-pot synthetic method of bis(oxazoline)s (**1**–**3**) was described, which is simple and efficient, deserving great application potentials in the research and development in the area of bis(oxazoline)s.

EXPERIMENTAL

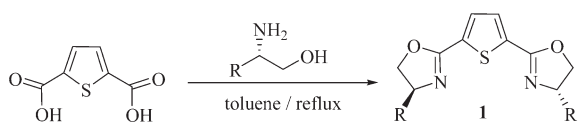
General. Melting points were determined by the capillary method and are uncorrected. ^{1}H-NMR spectra were measured on a Varian UNITY INOVI-500 NMR spectrometer, a Bruker Avance DPX300 NMR spectrometer or a Bruker DRX-400 NMR spectrometer, using TMS as internal standard. Mass spectra were taken on a MDS Sciex API 2000 LC/GC/MS instrument. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer. Optical rotation values were measured on a POLARTRONIC HNQW 5 polarimeter.

All solvents used for the synthesis were of analytical grade and were dried and freshly distilled under a nitrogen atmosphere prior to use. Chiral β-amino alcohols, furan-2,5-dicarboxylic acid, and benzene-1,3-dicarboxylic acid were purchased from Fluka Chemical Co. Thiophene-2,5-dicarboxylic acid was synthesized in our own laboratory. Other reagents were all of analytical grade.

General procedure for the synthesis of 2,5-bis[4′(*S*)-substituted-oxazolin-2′-yl]thiophene (1a–1e). Thio-phene-2,5-dicarboxylic acid (100.0 mg, 0.58 mmol), chiral β-amino alcohol (1.16 mmol), and toluene (20 mL) were added to a three-neck flask with a water segregator, a reflux condenser, and a magnetic stirring bar. The mixture was refluxed and dehydrated for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with dichloromethane and ethanol (50:1) as eluent to give the pure title compound.

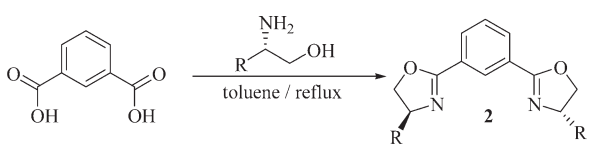
(−)-2,5-Bis[4′(S)-ethyloxazolin-2′-yl]thiophene(1a). This compound was obtained as colorless solid; yield 96%; mp 90–91°C ([18] 89–90°C); $[\alpha]_D^{20} = -95.3$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.99 (t, J = 7.4Hz, 6H, CH_3), 1.58–1.65 (m, 2H, CH_2), 1.67–1.74 (m, 2H, CH_2), 4.06 (dd, J = 7.4, 10.2 Hz, 2H, OCH_2), 4.19–4.28 (m, 2H, NCH), 4.50 (dd, J = 8.4, 10.2 Hz, 2H, OCH_2), 7.56 (s, 2H, thiophene-H).

Scheme 1



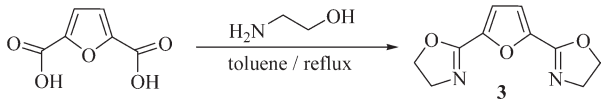
a: R=Et; b: R=*i*-Pr; c: R=*t*-Bu
d: R=Ph; e: R=Bn

Scheme 2



a: R= *i*-Pr; b: R=Ph; c: R=Bn

Scheme 3



ESI-MS: *m/z* (MH^+) 279. Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.23; H, 6.54; N, 10.02.

(−)-2,5-Bis[4′(S)-isopropyloxazolin-2′-yl]thiophene(1b). This compound was obtained as colorless solid; yield 91; mp 66–67°C ([18] 66–68°C); $[\alpha]_D^{20} = -29.7$ (*c* 0.5, CH_3COCH_3); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.91 (d, *J* = 7.0 Hz, 6H, CH_3), 1.15 (d, *J* = 7.0 Hz, 6H, CH_3), 1.84–1.91 (m, 2H, CH), 4.08–4.15 (m, 4H, OCH_2), 4.39 (dd, *J* = 8.0, 9.0 Hz, 2H, NCH), 7.57 (s, 2H, thiophene-H). ESI-MS: *m/z* (MH^+) 307. Anal. Calcd. for $C_{16}H_{22}N_2O_2S$: C, 62.71; H, 7.24; N, 9.14. Found: C, 62.55; H, 7.26; N, 9.11.

(+)-2,5-Bis[4′(S)-tert-butyloxazolin-2′-yl]thiophene(1c). This compound was obtained as colorless solid; yield 89%; mp 119–120°C ([17] 120–121°C); $[\alpha]_D^{20} = +5.9$ (*c* 0.6, CH_3COCH_3); ^{1} H-NMR (500 MHz, $CDCl_3$): δ 0.98 (s, 18H, CH_3), 4.02 (dd, *J* = 7.5, 10.0 Hz, 2H, OCH_2), 4.24 (dd, *J* = 8.0, 8.5 Hz, 2H, NCH), 4.35 (dd, *J* = 8.5, 10.0 Hz, 2H, OCH_2), 7.53 (s, 2H, thiophene-H). ESI-MS: *m/z* (MH^+) 335. Anal. Calcd. for $C_{18}H_{24}N_2O_2S$: C, 64.64; H, 7.84; N, 8.38. Found: C, 64.41; H, 7.86; N, 8.35.

(+)-2,5-Bis[4′(S)-phenyloxazolin-2′-yl]thiophene(1d). This compound was obtained as colorless solid; yield 93%; mp 127–128°C; $[\alpha]_D^{20} = +59.5$ (*c* 0.4, CH_2Cl_2); ^{1} H-NMR (500 MHz, $CDCl_3$): δ 4.32 (dd, *J* = 8.0, 16.0 Hz, 2H, NCH), 4.78 (dd, *J* = 8.5, 10.0 Hz, 2H, OCH_2), 5.39 (dd, *J* = 8.0, 10.0 Hz, 2H, OCH_2), 7.27–7.36 (m, 10H, Ph-H), 7.68 (s, 2H, thiophene-H). ESI-MS: *m/z* (MH^+) 375. Anal. Calcd. for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.46; H, 4.84; N, 7.46.

(+)-2,5-Bis[4′(S)-benzyloxazolin-2′-yl]thiophene(1e). This compound was obtained as colorless solid; yield 93%; mp 108–110°C ([18] 107–109°C); $[\alpha]_D^{20} = +91.5$ (*c* 0.3, CH_3COCH_3); ^{1} H-NMR (500 MHz, $CDCl_3$): δ 2.74 (dd, *J* = 8.5, 13.5 Hz, 2H, CH_2-Ph), 3.21 (dd, *J* = 5.0, 13.5 Hz, 2H, CH_2-Ph), 4.14 (dd, *J* = 7.0, 9.0 Hz, 2H, OCH_2), 4.37 (dd, *J* = 8.5, 9.0 Hz, 2H, OCH_2), 4.58–4.61 (m, 2H, NCH), 7.22–7.31 (m, 10H, Ph-H), 7.52 (s, 2H, thiophene-H). ESI-MS: *m/z* (MH^+) 403. Anal. Calcd. for $C_{24}H_{22}N_2O_2S$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.34; H, 5.53; N, 6.94.

General procedure for the synthesis of 1,3-bis[4′(*S*)-substitutedoxazolin-2′-yl]benzene (2a–2c). Benzene-1,3-dicarboxylic acid (100.0 mg, 0.60 mmol), chiral β-amino alcohol (1.20 mmol), and toluene (20 mL) were added to a three-neck flask with a water segregator, a reflux condenser, and a magnetic stirring bar. The mixture was refluxed and dehydrated for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with dichloromethane and ethanol (50:1) as eluent to give the pure title compound.

(−)-1,3-Bis[4′(S)-isopropyloxazolin-2′-yl]benzene(2a). This compound was obtained as colorless solid; yield 93%; mp 58–60°C; $[\alpha]_D^{20} = -141.5$ (*c* 0.3, $CHCl_3$); ^{1} H-NMR (500 MHz, $CDCl_3$): δ 0.94 (d, *J* = 7.0 Hz, 6H, CH_3), 1.06 (d, *J* = 7.0 Hz, 6H, CH_3), 1.87–1.94 (m, 2H, CH), 4.11–4.19 (m, 4H, OCH_2), 4.38–4.45 (m, 2H, NCH), 7.45–8.51 (m, 4H, benzene-H). ESI-MS: *m/z* (MH^+) 301. Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.75; H, 8.08; N, 9.31.

(−)-1,3-Bis[4′(S)-phenyloxazolin-2′-yl]benzene(2b). This compound was obtained as colorless solid; yield 94%; mp 122–124°C ([19] 120–124°C); $[\alpha]_D^{20} = -73.1$ (*c* 0.3, CH_2Cl_2); ^{1} H-NMR (500 MHz, $CDCl_3$): δ 4.42 (dd, *J* = 8.0, 8.5 Hz, 2H, OCH_2), 4.92 (dd, *J* = 8.0, 10.0 Hz, 2H, OCH_2), 5.48 (dd, *J* = 7.0, 10.0 Hz, NCH), 7.27–7.41 (m, 10H, Ph-H), 7.57 (t, *J* = 7.5 Hz, 1H, benzene-H), 8.39 (dd, *J* = 1.5, 7.5 Hz, 2H, benzene-H), 8.76 (t, *J* = 1.5 Hz, 1H, benzene-H). ESI-MS: *m/z* (MH^+) 369. Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.01; H, 5.49; N, 7.58.

(−)-1,3-Bis[4′(S)-benzyloxazolin-2′-yl]benzene(2c). This compound was obtained as colorless solid; yield 94%; mp 105–107°C ([19] 106–107°C); $[\alpha]_D^{20} = -4.1$ (*c* 0.5, $CHCl_3$); ^{1} H-NMR (300 MHz, $CDCl_3$): δ 2.73–3.28 (m, 4H, CH_2Ph), 4.17 (dd, *J* = 7.5, 8.5Hz, 2H, OCH_2), 4.37–4.41 (m, 2H, OCH_2), 4.58–4.63 (m, 2H, NCH), 7.10–7.36 (m, 10H, Ph-H), 7.50–8.49 (m, 4H, benzene-H). ESI-MS: *m/z* (MH^+) 397. Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.52; H, 6.12; N, 7.05.

Synthesis of 2,5-bis(oxazolin-2′-yl) furan (3). Furan-2,5-dicarboxylic acid (100.0 mg, 0.64 mmol), 2-aminoethanol (78.3 mg, 1.28 mmol), and toluene (20 mL) were added to a three-neck flask with a water segregator, a reflux condenser, and a magnetic stirring bar. The mixture was refluxed and dehydrated for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with

Table 1

The conditions and results of dicarboxylic acid reacted with β-amino alcohol in toluene through water deprivation.[a]

Entry	Dicarboxylic acid	β-Amino alcohol	Bis(oxazoline)	Yield (%)
1	TDA	(*S*)-2-aminobutan-1-ol	**1a**	96
2	TDA	L-leucinol	**1b**	91
3	TDA	L-tert-leucinol	**1c**	89
4	TDA	L-phenylglycinol	**1d**	93
5	TDA	L-phenylalaninol	**1e**	93
6	BDA	L-leucinol	**2a**	93
7	BDA	L-phenylglycinol	**2b**	94
8	BDA	L-phenylalaninol	**2c**	94
9	FDA	2-aminoethanol	**3**	88

[a] Dicarboxylic acid/β-amino alcohol = 1/2 (mole ratio). Reaction time: 24 h.

dichloromethane and ethanol (50:1) as eluent to give the pure title compound as colorless liquid; yield 88%; ^{1} H-NMR (400 MHz, DMSO-d_6): δ 2.94 (t, J = 5.2 Hz, 4H, NCH_2), 3.62 (t, J = 5.2 Hz, 4H, OCH_2), 6.73 (s, 2H, furan-H). ^{13} C-NMR (400 MHz, DMSO-d_6): 41.5, 57.9, 113.5, 151.1, 163.3. ESI-MS: m/z (MK^+) 245. Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.14; H, 4.91; N, 13.57.

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